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SYNTHESIS AND DECOMPOSITION OF OPTICALLY ACTIVE AZOALKANES

BY

© THOMAS GILLAN

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

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SPRING, 1969

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled

SYNTHESIS AND DECOMPOSITION OF

OPTICALLY ACTIVE AZOALKANES

submitted by Thomas Gillan, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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TO MY MOTHER

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ABSTRACT

The azo compound, 1,1'-diphenyl-1-methylazomethane, 7, was synthesized and resolved to optical purity. Its absolute configuration was determined by a stereospecific synthesis of (-)-7 from (-)-α-phenylethylamine. Optically active 1,1'-diphenyl-1-ethyl-1-methylazomethane, 29, was also synthesized.

The cage products from the decomposition of 7 and 29, 1,2-diphenylpropane, 13, and 1,2-diphenyl-2-methylbutane, 35, respectively, were synthesized from optically active precursors and their maximum specific rotations and absolute configurations determined.

Decomposition of (-)-7 and (+)- and (-)-29 were carried out in a variety of solvents in absence and presence of a scavenger. The cage coupling products, 13 and 35, were isolated and their rotations measured. In each case these products were shown to have been formed from the parent azo compound with net retention of configuration.

The cage effects in the decomposition of 7 and 29 were determined in benzene in the absence of scavenger from the product distribution. They were also measured in a variety of solvents in the presence of a scavenger from the product distribution.

The net retention of configuration was 10-15% and the cage effects varied from 15% to 35% depending on the solvent used. From the values for net retention of configuration and the cage effects, the ratio of the rate of coupling of the asymmetric radical with the counter radical to its rate of rotation, k_c/k_r, was calculated and was found to have values in the range 0.05 - 0.1. No significant difference in the value of k_c/k_r was found for the two systems studied.

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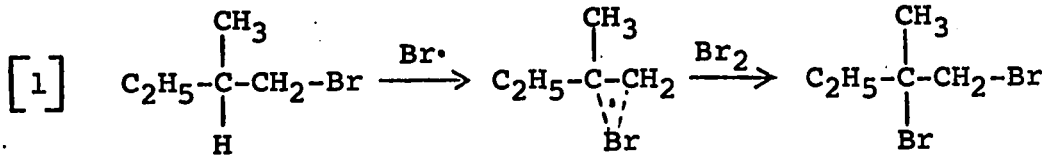
I N T R O D U C T I O N

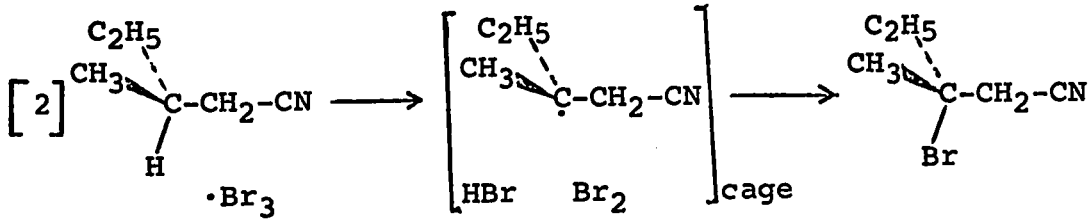
The stereochemistry of breaking and making of bonds to an asymmetric carbon atom has been intensively studied in cases where the mechanism of the process has been ionic in character. However, less attention has been paid to corresponding radical reactions.

Of attempts to study this phenomenon, the earliest reported was that of Brown, Kharasch and Chao (1), who generated a radical at an asymmetric centre by the photochlorination of optically active 1-chloro-2-methylbutane. The product, 1,2-dichloro-2-methylbutane, was found to be completely racemized.

Skell and coworkers (2) found that the photochemical bromination of 1-bromo-2-methylbutane gave 1,2-dibromo-2-methylbutane as product and this had retained optical activity. However, since neither the absolute configuration of the product nor its optical purity had been determined, it is not known whether the reaction proceeded with inversion or retention of configuration. The retention of optical activity in this case has been rationalized on the basis of a bridged bromine radical, as shown in the following equation.



An alternative explanation for retention of optical activity in the product obtained from the photobromination of 3-methylpentanoic nitrile was proposed by Haig and Heiba (3). They proposed that the abstracting species is $Br_3\cdot$ and the resulting alkyl radical undergoes a cage reaction with bromine before rotation can occur.



No data were presented concerning the degree of optical purity of the product or whether configuration was retained.

Photochemical hydrobromination of olefins at low temperature (-80°C) carried out in the presence of a large excess of hydrogen bromide results in a high degree of stereoselectivity (4,5).

The free radical decarbonylation of aldehydes might yield optically active products. However, the gas phase photolysis of 2-methylbutanal in the presence of iodine yielded racemic 2-iodobutane (6), and photolysis of 2,4-dimethyl-2-ethylpentanal in the liquid phase resulted in

racemic 2,4-dimethylbutane (7). While decarbonylation of aldehydes is a chain reaction it might be expected, particularly in the presence of scavengers, that loss of carbon monoxide from the acyl radical might block frontside attack to some extent if hydrogen abstraction were competitive with diffusion, with resulting net inversion of configuration.

The Hunsdiecker reaction apparently proceeds by a radical mechanism, since decarboxylation proceeds readily at the bridgehead position of strained bicyclic systems (8). Attempts to study the stereochemical outcome of this reaction have led to a series of confusing and conflicting results. Arcus and Kenyon (9) reported that optically active hydratropic acid yielded α-phenylethyl bromide in good yield with 35% retention of configuration. This work was repeated later by Arcus and Abbott(10) who could not isolate any bromide from the reaction despite repeated attempts. These workers, however, obtained from optically active 2-ethylpentanoic acid, the corresponding optically active bromide, but of unknown optical purity and stereochemistry. However, Bell and Smith had carried out this reaction two years earlier and obtained completely racemic product (11).

A major disadvantage to the study of the Hunsdiecker reaction is the presence of silver bromide, bromine, and inevitably, hydrogen bromide. These are capable of

racemizing the alkyl bromide formed.

It has been reported recently by Jensen and coworkers (12) that the Hunsdiecker reaction on 4-tert-butylcyclohexyl carboxylic acids yielded the corresponding bromides with 5% net retention of configuration. They envisaged this retention as arising from a fraction of the acyl hypobromite decomposing in the solvent cage while the remainder proceeded by a chain reaction, as shown in Scheme I.

Scheme I

$$R\text{-}CO_2Ag + Br_2 \longrightarrow R\text{-}CO_2Br + AgBr$$

$$R\text{-}CO_2\text{-}Br \longrightarrow RCO_2\cdot + Br\cdot$$

$$RCO_2\cdot \longrightarrow R\cdot + CO_2$$

$$R\cdot + RCO_2Br \longrightarrow R\text{-}Br + RCO_2\cdot$$

$$RCO_2Br \longrightarrow \left[RCO_2\cdot \cdot Br\right]_{cage} \longrightarrow \left[R\cdot CO_2\cdot Br\right]_{cage} \longrightarrow RBr + CO_2$$

These results differ from those obtained by Eliel and Acharya (13). They reported that the Hunsdiecker reaction on cis- and trans-4-tert-butylcyclohexanecarboxylic acid both yielded the same product mixture, 65% trans, 35% cis. While the reaction conditions used by these workers were more severe than those employed by Jensen and coworkers,

control experiments indicated that the result could not have been entirely due to product equilibration.

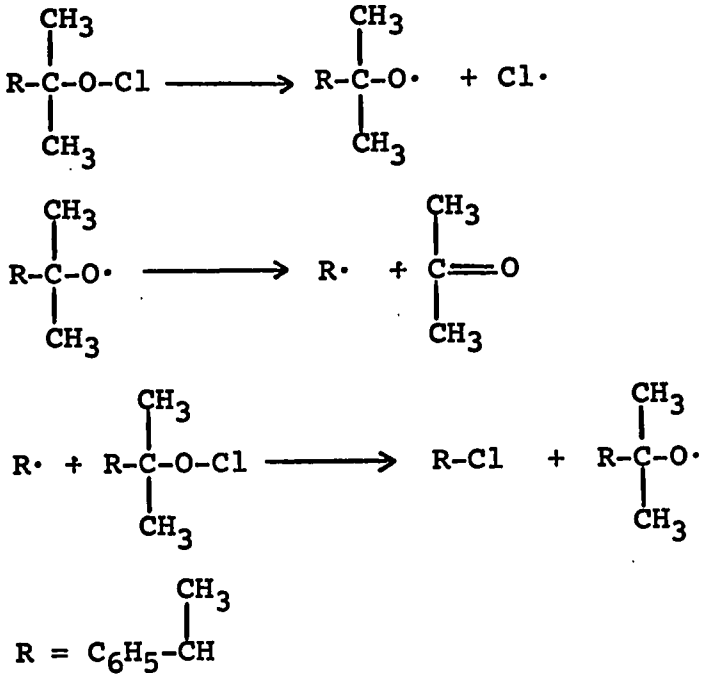
Lau and Hart (14) generated the 4-tert-butylcyclohexyl radical from decomposition of the corresponding diacyl peroxide. Product was formed by this radical abstracting a bromine atom from tetrabromoethane. Analysis of the products revealed that the trans and cis bromides were formed in relative yields of 52% and 48% respectively, regardless of whether the diacyl peroxide had cis or trans geometry.

Greene, Chu and Walia (15) also generated this radical from decomposition of dimethyl-cis- and trans-4-tert-butylcyclohexylcarbinyl hypochlorite. These workers obtained cis- and trans-4-tert-butylcyclohexyl chloride in the ratio of 2:1 in both cases.

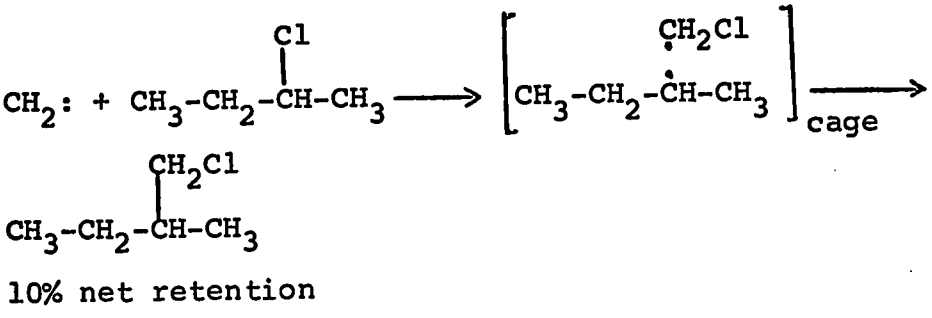
Decomposition of tertiary alkylhypochlorites yields alkyl chlorides as products (16). The mechanism of decomposition was believed to involve a chain reaction as shown in Scheme II below. However, it was possible that all or some of the product might arise by two-bond cleavage in a solvent cage.

Two groups (17,18) independently studied the decomposition of 2-methyl-3-phenyl-2-butylhypochlorite. Both obtained α-phenylethyl chloride with approximately 2% retention of configuration.

Scheme II



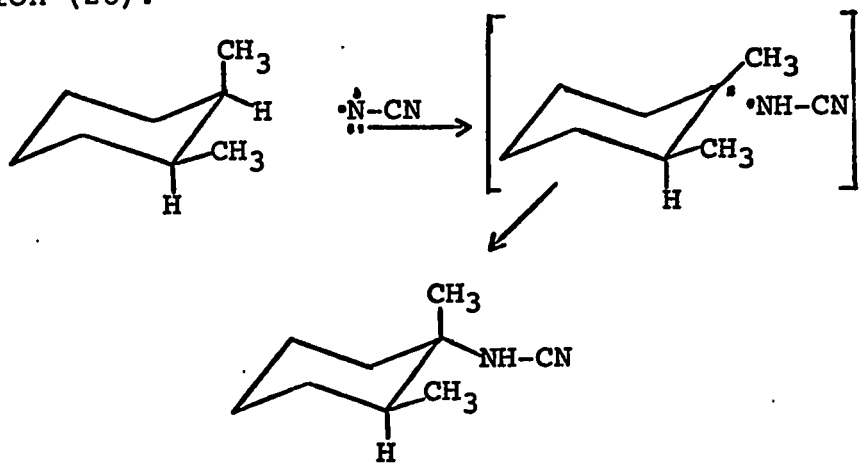
Several insertion reactions of carbenes have been proposed to involve abstraction followed by recombination of radical pairs to yield optically active products. The reaction of methylene with optically active 2-chlorobutane yielded 2-methyl-1-chlorobutane with 10% retention of configuration (19).



10% net retention

Similarly, reaction of cyanonitrene with 1,2-dimethylcyclohexane yielded product with net retention of configuration (20).

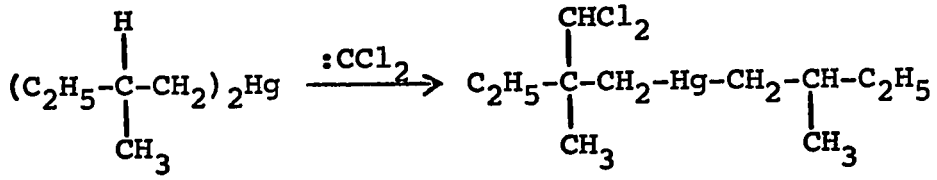
[4]



major product

Reaction of dichlorocarbene with optically active bis-2-methyl-1-butyl mercury yielded 2-methyl-1-butyl 2-methyl-2-dichloromethyl-1-butyl mercury with 10% net retention of configuration (21).

[5]

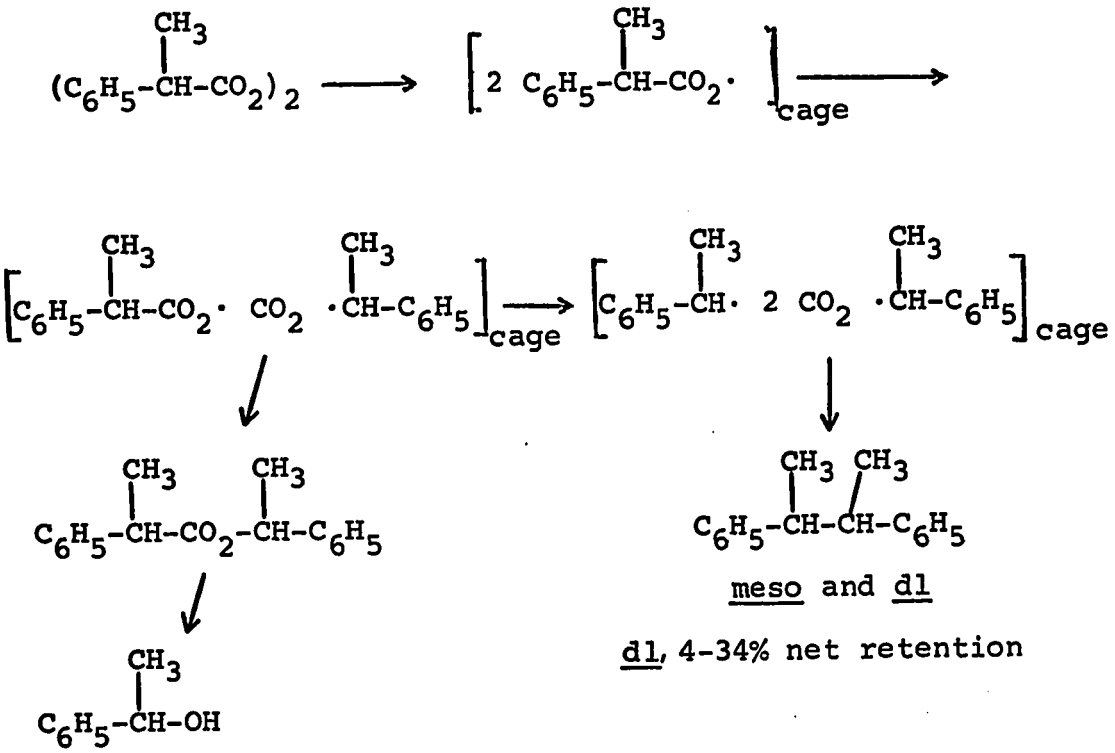


10% net retention

The systems most frequently studied in an effort to observe the stereochemistry of radical reactions have been acyl peroxides. The first study was carried out by Greene (22). This was the decomposition of optically active

hydratropoyl peroxide. Unfortunately, this compound was too unstable to be isolated, so it was generated and decomposed in solution at 0°C and at -15°C. The details are shown in Scheme III below. The run at -15°C showed higher retention of configuration.

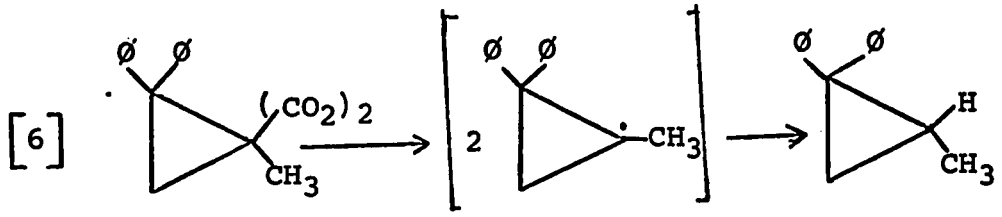
Scheme III



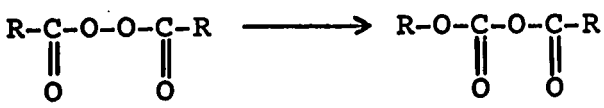
The hydrocarbon product, formed within the cage, was composed of approximately equal quantities of meso and dl isomers. Examination of the dl portion showed it to have been formed with 4-34% retention of configuration.

Kharasch and coworkers (23) found that the ester, 2-butyl 2-methylbutyrate, isolated from decomposition of optically active 2-methylbutyryl peroxide showed 78% retention of configuration in the alcohol moiety. No hydrocarbon was reported. Also, DeTar and coworkers (24) reported that the decomposition of 2-methyl-3-phenyl-propionyl peroxide to the corresponding ester proceeded with 75% retention of configuration in the alcohol portion. Again no hydrocarbon was reported in this decomposition.

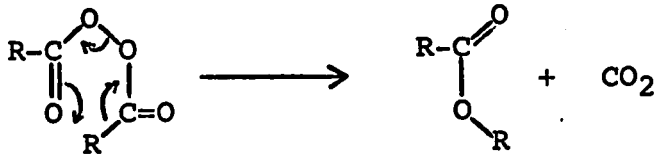
Recently, Walborsky reported that the decomposition of optically active 2,2-diphenyl-1-methylcyclopropylcarboxy peroxide in carbon tetrachloride gave a small quantity of 2,2-diphenyl-1-methylcyclopropane (25). This was interpreted as having arisen by disproportionation within the solvent cage, although the corresponding olefin was not identified. The degree of retention observed was 31-37%.



One disadvantage of experiments on acyl peroxides is that the decomposition may be occurring by more than one mechanism. It is known, for example, that rearrangement of the acyl peroxide can occur prior to decomposition (26).

[7] 

A cyclic mechanism has also been proposed for formation of ester (23) as shown in the equation below.

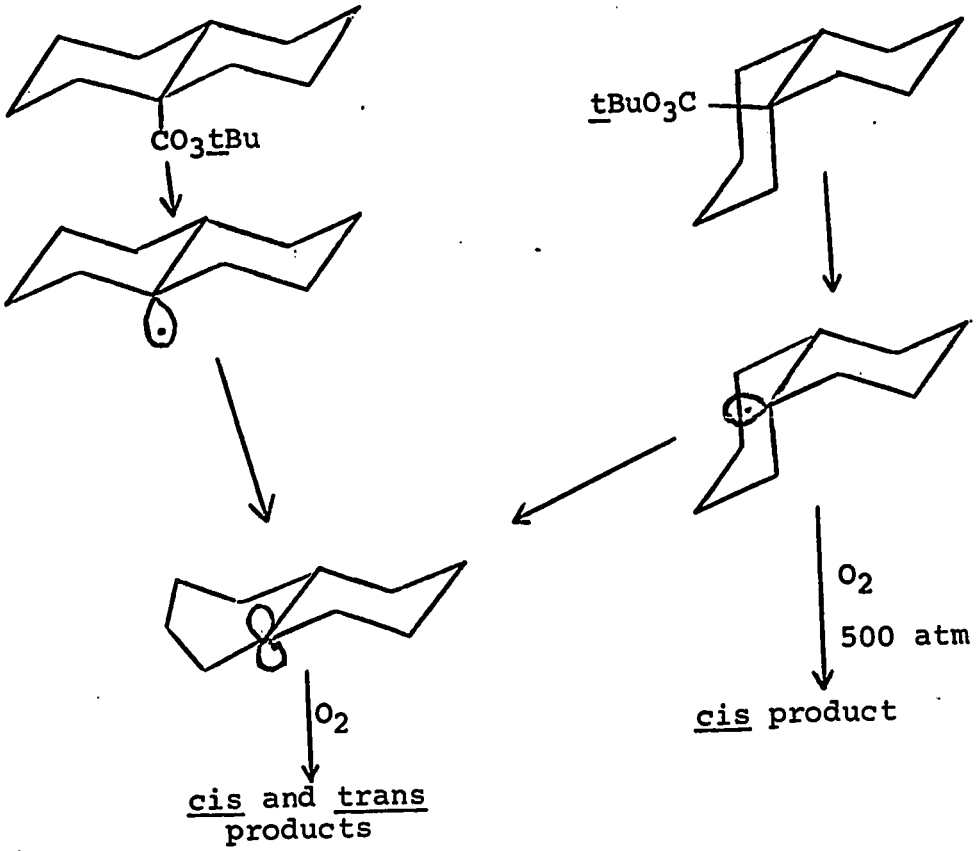
[8] 

If this were the case, no racemization at all would be expected. In the case of the optically active hydrocarbon obtained by Greene, it is difficult to envisage a mechanism by which it could arise, other than by a radical mechanism within a solvent cage.

Bartlett and coworkers have reported on the decomposition of cis- and trans- tert-butyl 9-decalylpercarboxylate (27). Reaction between the two radicals generated seemed to be entirely by disproportionation. Reaction of the decalyl radical with oxygen gave the same product mixture, 10% cis, 90% trans, starting with trans isomer at

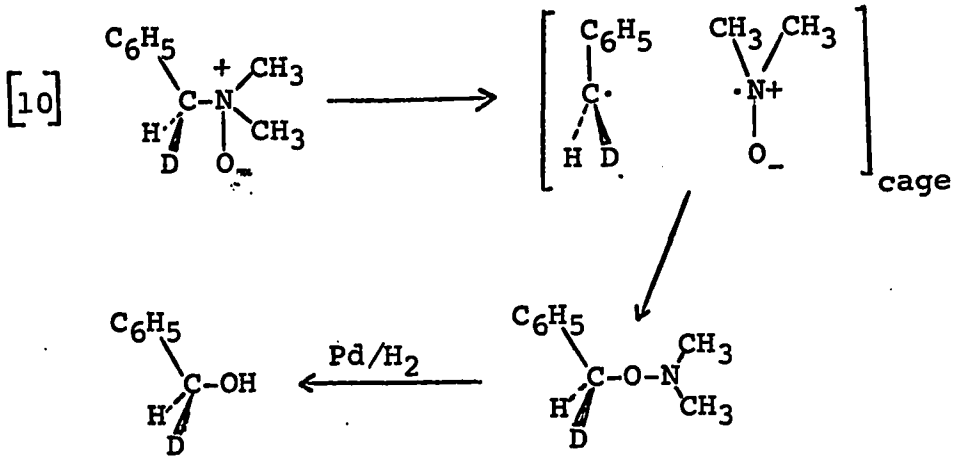
low and high pressures of oxygen and with cis isomer at low pressure of oxygen. However, at high pressures of oxygen (500 atmospheres) cis isomer gave predominantly cis oxygenated product. The authors, based on these results, argued in favor of two types of radical intermediate. The more stable one is planar so that cis and trans both attain it at low oxygen concentrations. At high oxygen concentrations, a different radical species is being captured before it can change to the more stable planar radical. These are outlined in the equation below.

[9]



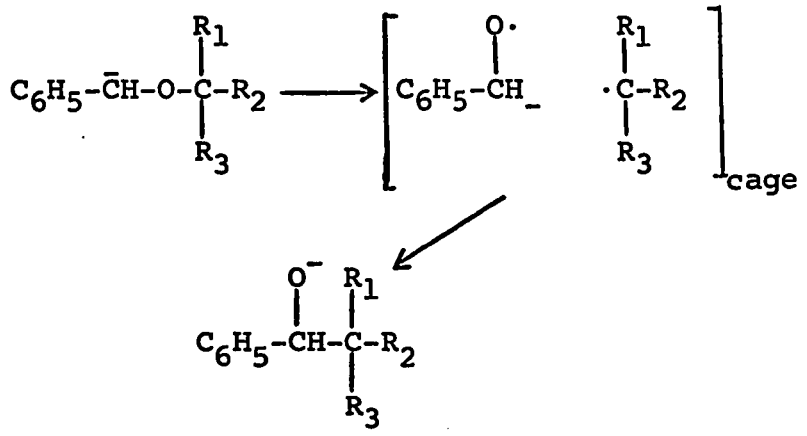
Decomposition of substituted tert-butyl percinnamates (28,29) yielded vinyl radicals which become completely equilibrated before capture by hydrogen donors can occur.

The Meisenheimer rearrangement of amine oxides to hydroxylamines has been postulated to involve cleavage to a pair of radicals, followed by recombination within the solvent cage. Schollkopf and coworkers studied this reaction using the amine oxide from N,N-dimethyl-α-deuteriobenzylamine. The hydroxylamine obtained as product was hydrogenolyzed to the corresponding alcohol which was found to have 23-38% net retention of configuration (30).

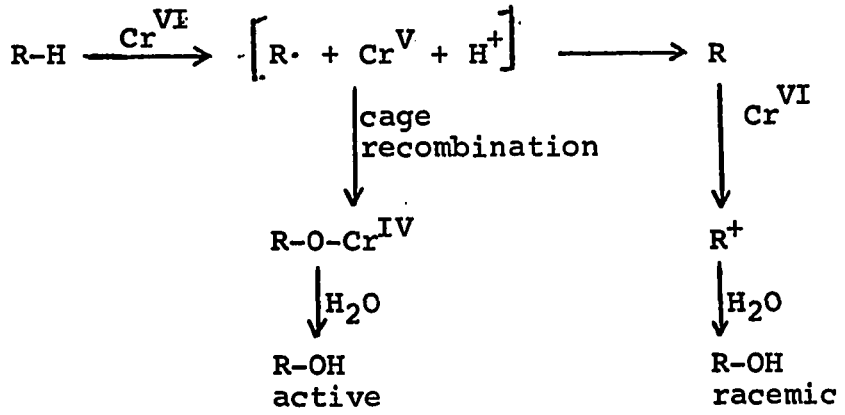


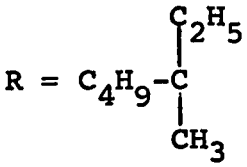
23-38% net retention

A similar rearrangement is the Wittig rearrangement of metalated benzylic ethers. Among others, a radical cleavage recombination reaction has been proposed as the mechanism. This rearrangement proceeds with 60-80% retention of configuration (31).

[11] 

The chromic acid oxidation of optically active 3-methylheptane yielded 3-methyl-3-heptanol with 70-85% retention of configuration (32). The reaction has been proposed to involve a radical mechanism.

[12] 



The authors believe the 10-15% racemization to be due to escape from the solvent cage.

Decomposition of pyrazolines to the corresponding cyclopropanes has been shown by Crawford and Mishra to involve a diradical intermediate (33). The stereochemical results, however, vary considerably from compound to compound. Thus von Auwers (34) reports almost complete retention of configuration for decomposition of cis- and trans-3,5-dicarbomethoxy-3,5-dimethyl-1-pyrazoline. Von Auken and Rinehart (35), on the other hand, report only a very small net retention of configuration for thermal decomposition of 3-carbomethoxy-cis-3,4-dimethyl-1-pyrazoline.

Crawford and Mishra (36) found that 3,5-dimethyl-pyrazoline gave net inversion of configuration. Thus, starting from the cis-pyrazoline the 1,2-dimethylcyclopropane was 66% trans, 33% cis.

Since this research programme was commenced, several reports of studies in the field of azo compounds have appeared. Bartlett and McBride reported on the decomposition of meso- and dl-azo-bis-3-methyl-2-phenyl-2-butane (37). The product of recombination of the two 3-methyl-2-phenyl-2-butyl radicals showed no stereospecificity at temperatures above 0°C. This was due to the fact that the amount of recombination within the solvent cage was extremely small - about 2%. By decomposing the azo compound photolytically in a glass matrix at 77°K, where escape from the cage was impossible, 100% stereospecificity was observed.

A preliminary account of the decomposition of optically active 1,1'-diphenylazoethane has recently been published by Greene and Berwick (39). The products isolated from the decomposition were meso-, d- and l-2,3-diphenylbutane. In the absence of a scavenger, a yield of 90% of coupling products was achieved. On analysis, the product mixture was found to be 49.3% meso. Of the non-meso coupling products, 26.8% had retained configuration and 23.4% had inverted configuration. In the presence of a scavenger, the yield of coupling product was 28%. This was composed of meso isomer, 48.1%, and non-meso, 31.3% of retained and 20.6% of inverted configuration. These figures correspond to 10% net retention of configuration for each asymmetric centre.

In contrast to the low stereoselectivity observed for the decomposition of this azo compound, recent work by Bartlett and Porter (38) on the decomposition of 3,6-dimethyl-3,6-diethyl-3,4,5,6-tetrahydropyridazine yielded the corresponding cyclobutane with 98% retention of configuration.

From the foregoing results, it becomes obvious that the chances of observing retention of configuration are extremely remote for those radical reactions which proceed by a chain reaction. Those reactions which generate a pair of radicals simultaneously in a solvent cage have the greatest chance of showing stereospecificity in the

recombination reaction.

Azo compounds, therefore, seem to fulfill this ideal, but it is necessary to examine the evidence to ensure that decomposition is truly a radical process and not open to question as in the case of acyl peroxides or the Wittig rearrangement.

Azo-nitriles such as azoisobutyronitrile (AIBN) have been known for a long time to decompose on heating, with loss of nitrogen, to yield product resulting from coupling of the two remaining fragments (68). Whether this coupling product arose by a concerted process or by recombination of two radicals generated in the decomposition was uncertain, until it was demonstrated by several groups (40) that AIBN could be used to initiate polymerization of vinyl monomers, in the same manner as other compounds, such as benzoyl peroxide, which give rise to radicals.

The radical nature of the decomposition is further supported by the bleaching of stable free radicals such as α,α-diphenylpicrylhydrazyl (DPPH)(41).

Overberger and Berenbaum showed that a radical process rather than an intramolecular process was involved in the decomposition of azonitriles by heating a mixture of azobisisobutyronitrile and 1-azobiscyclopentanenitrile and showing that a cross-product was formed as well as the two symmetrical coupling products (44).

Rates of decomposition and the energies of activation

for decomposition are dependent on the degree of substitution of the carbon atoms alpha to the nitrogen atoms of the azo compound. Azobenzene does not decompose until heated to greater than 600°C (42) while azotriphenylmethane is too unstable to be isolated (43). Therefore, it would appear that the rate of decomposition is dependent on the stability of the radicals generated. This is borne out by study of the rate of decomposition of a large variety of azo compounds and is consistent with a free radical mechanism for the decomposition. In Table I it can be seen that in the series R-=CH_3-,CH_3CH_2-, $(CH_3)_2CH$-, $(CH_3)_3C$-, there is a gradual lowering of the energy of activation, due to increasing stabilization of the incipient radicals through hyperconjugation at the transition state. By substituting a phenyl, cyano or carboxy group on the α-carbon of an azo compound, the radicals produced by decomposition are stabilized by mesomerism. This provides much greater stabilization of the radicals and as a result increases the rate considerably.

In order to observe retention of configuration in the product arising from radical recombination in the solvent cage, it is important that the two radicals should be generated simultaneously in the decomposition of optically active azo compounds. This problem has received considerable study. Seltzer and coworkers studied the secondary

TABLE I

Rates and Activation Energies for Decomposition of R-N=N-R

R	Solvent	Temp. °C	Rate x10^4	E_a	Reference
CH_3	gas	300	5.6	50.2	45, 46
CH_3CH_2	gas			49.5	47, 48
$(CH_3)_2CH$	gas	250	4.8	40.9	49
$(CH_3)_3C$	gas			44	50
$C_6H_5-CH_2$	gas			36	51
$C_6H_5-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{\displaystyle |}{\overset{\displaystyle |}{CH}}}}$	toluene	110	1.69	32.2	48, 52
$C_6H_5-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{\displaystyle |}{\overset{\displaystyle |}{C}}}}$	toluene	59.4	1.62	29	48
$(CH_3)_2-C-CN$	toluene	80	1.55	31.1	53
$(C_6H_5)_2CH$	toluene	64	3.40	26.6	54

α-deuterium isotope effects in the decomposition of the series of azo compounds shown in Table II. In the decomposition of 1,1'-diphenylazoethane-1,1'-$\underline{d}_2$ and its protio counterpart, the rate ratio k_H/k_D was found to be 1.27. This corresponds to about a 12% decrease in rate per deuterium atom and is in agreement with the results obtained elsewhere (55). This implies that both carbon-nitrogen bonds are being stretched to the same extent in the transition state. The results for α-phenylethylazoisopropane indicate that while both carbon-nitrogen bonds are being stretched at the transition state, bond cleavage of α-phenylethyl-nitrogen bond is occurring somewhat faster than the other. The results for α-phenylethylazomethane indicate that only the α-phenylethyl-nitrogen bond is being broken at the transition state.

From these results, it would seem that where the two groups have a reasonable ability to stabilize a radical both bonds break simultaneously. Arylazotriphenylmethanes would, therefore, be expected to undergo cleavage by a sequential mechanism, cleaving to a triphenylmethyl and a phenyldiazo radical which later loses nitrogen to give a phenyl radical.

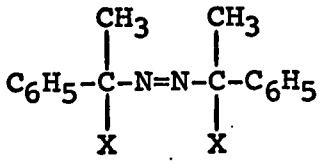
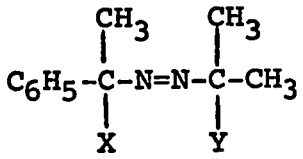
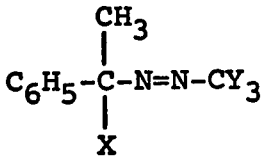
$$[13] \quad Ar_3\text{-}C\text{-}N{=}N\text{-}\phi \longrightarrow [Ar_3C\cdot \; \cdot N{=}N\text{-}\phi]_{cage} \longrightarrow Ar_3C\cdot + \cdot N{=}N\text{-}\phi$$

$$\downarrow \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \downarrow$$

$$[Ar_3C\cdot + N_2 \; \cdot\phi]_{cage} \qquad\qquad\qquad\qquad N_2{+}\cdot\phi$$

TABLE II

Isotope Effects in the Decompositions of Azo Compounds

Compound	Isotope Effect	Reference
	$\frac{k_{Ia}}{k_{Ib}} = 1.27$	55
Ia X = H		
Ib X = D		
	$\frac{k_{IIa}}{k_{IIb}} = 1.16$	56
IIa X = Y = H	$\frac{k_{IIa}}{k_{IIc}} = 1.04$	
IIb X = D, Y = H		
IIc X = H, Y = D		
	$\frac{k_{IIIa}}{k_{IIIb}} = 1.12$	57
IIIa X = Y = H	$\frac{k_{IIIa}}{k_{IIIc}} = 0.97$	
IIIb X = D Y = H		
IIIc X = H, Y = D		

This was borne out by the work of Pryor who observed a decrease in rate of decomposition of these compounds, where the decompositions were carried out in increasingly viscous solvents (58). This can be explained on the basis of a recombination of the initial radical pair to regenerate starting azo compound. In more viscous solvents, diffusion from the cage would be slowed down and recombination could compete more effectively with diffusion resulting in a decrease in the overall rate.

Use of activation energies might have been used to show that decomposition of azo compounds is a concerted process, had there been data available for the decomposition of unsymmetrically substituted azo compounds. Unfortunately, the efforts of Cohen and Wang to synthesize methylazo- and benzylazodiphenylmethane were unsuccessful (59).

The mechanism of decomposition of azo compounds is outlined in Scheme IV.

It can be seen that recombination and disproportionation of the radical pair in the solvent cage may compete with diffusion of the radical pair from the solvent cage. After diffusion, the radicals may behave in the normal manner, either coupling with each other at random or reacting with the solvent, with added species such as radical scavengers, or, for example, vinyl monomers, initiating polymerization.

Scheme IV

(1) $R\text{-}N{=}N\text{-}R \xrightarrow{k_1} [R\cdot\ N_2\ \cdot R]_{cage}$

(2) $[R\cdot\ N_2\ \cdot R]_{cage} \xrightarrow{k_2}$ R-R + disproportionation products + N_2

(3) $[R\cdot\ N_2\ \cdot R]_{cage} \xrightarrow{k_3} 2\ R\cdot + N_2$

(4) $2\ R\cdot \xrightarrow{k_4}$ R-R + disproportionation products

The fraction of the radical pairs that couple before diffusion can occur is a result of the cage effect (60).

The inefficiency in radical production resulting from the cage effect was recognised as the cause of lower than expected rate of initiation of vinyl polymerization (61).

In 1954, Noyes gave a full theoretical treatment to the phenomenon of the cage effect (62). Briefly, his theory makes the following points:-

(1) The radicals from a specific decomposing molecule may undergo "primary recombination" in the cage in which they are formed. This must happen before the two radicals have attained a molecular diameter separation and will take place within 10^{-11} seconds.

(2) If these radicals escape from the primary cage, they undergo random diffusive displacements. During these displacements these two radicals may reencounter each other

and undergo "secondary recombination". Secondary recombination will occur within 10^{-9} seconds, otherwise they will have diffused so far apart that the probability that they will reencounter each other is negligible. The sum of primary and secondary recombinations constitute the cage effect.

(3) Radicals escaping both primary and second recombinations may then couple with radicals generated in other decompositions or react with radical scavengers in the solvent. If the radical scavenger is of sufficient reactivity and present in sufficient concentration, it may react with all the radicals outside the cage to the total exclusion of radical-radical recombinations.

(4) If an extremely reactive scavenger is used, i.e. one which will react with radicals with a rate constant in excess of 10^7 M^{-1} sec^{-1}, then the scavenger is capable of competing with secondary recombinations even at relatively low concentrations of scavenger (i.e. 10^{-2} M or greater). Putting this in its mathematical form, to a first approximation, the increased efficiency due to competition with secondary recombination is proportional to the square root of the scavenger concentration.

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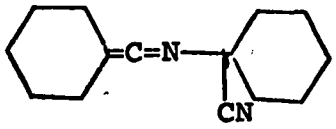
hexane and the related N-1-cyanocyclohexanepentamethylene-keteneimine,



using bromine and DPPH as scavengers (63). They found an approximately linear relationship between the square root of scavenger concentration and increased scavenging efficiency at higher scavenger concentrations, but not at 10^{-2} M as predicted by Noyes. Waits and Hammond concluded that either the cage effect is not divisible into two separate types of recombinations, or these are not distinguishable experimentally.

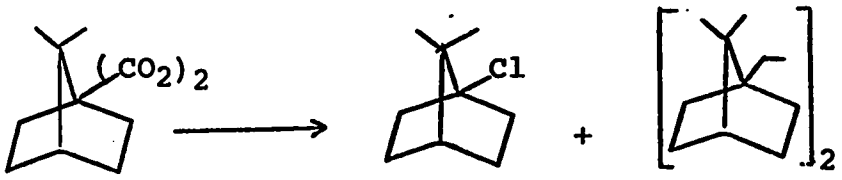
They accounted for the increased efficiency as being due to interference of scavenger molecules, which are nearest neighbors, with primary recombination.

A further consideration in the study of the stereochemistry of radicals is the conformation of the radical itself. There are a number of possibilities. The first of these is that radical bearing carbon is hybridized with the odd electron in a pure p orbital, i.e. a planar conformation. A second consideration is an sp^3 hybridized carbon with one of the sp^3 orbitals occupied by the odd electron. This is a pyramidal conformation. Something between these, namely a shallow pyramid, is also a possibility. A simple theoretical calculation based on the percentage s character of the carbon-carbon bonds would

favor a planar conformation (64), however, a more sophisticated theoretical treatment would seem to favor a pyramidal structure (65).

Direct observation of methyl radicals by both ultra violet spectroscopy and by electron paramagnetic resonance spectroscopy (e.p.r.) favors a planar or nearly planar conformation (66,67).

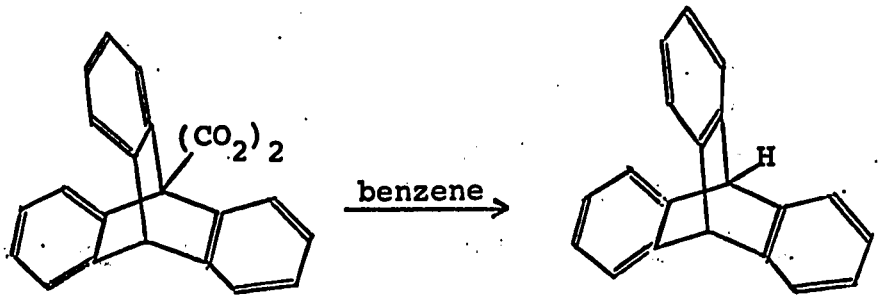
Chemical evidence would seem to indicate that both types of conformations are compatible with the generation of a free radical centre. Thus apocamphane-1-carboxylic acid (8) undergoes the Hunsdiecker reaction to yield the corresponding bromide presumably via a radical intermediate. Another strained system to behave in a similar manner is apocamphyl peroxide which decomposes in carbon tetrachloride to yield 1-chloroapocamphane together with some biapocamphyl (69).

[14] 

Similarly, another system which gives of necessity a pyramidal radical is tryptoyl peroxide (70). It decomposes in benzene to yield tryptycene presumably by abstraction of a hydrogen atom from the solvent, or iodo-tryptycene when

the decomposition is carried out in the presence of iodine.

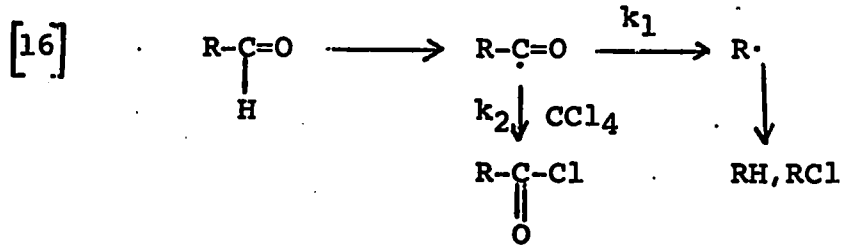
[15]



While pyramidal radicals are generated in these cases, their rates of formation tend to be slow. For example, apocamphyl and triptoyl peroxide decompose at a rate comparable to that of acetyl peroxide; other tertiary substituted peroxides decompose very rapidly. The triptycyl radical like the triphenylmethyl radical, has three phenyl groups attached to the carbon bearing the odd electron, but does not show any of the great stability of the latter. In fact, its great instability is evidenced by its ability to abstract a hydrogen atom from benzene. Neither will tryptycene undergo free radical chlorination by sulfuryl chloride in the presence of benzoyl peroxide.

On the other hand, a triphenylmethyl radical constrained to be planar by virtue of two oxygen bridges appears to be quite stable as evidenced by the high degree of dissociation of the corresponding hexaphenylethane (71).

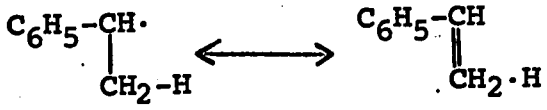
Evidence in favor of a planar radical is provided by the experiments of Applequist and Kaplan (72). They studied the decarbonylation of aldehydes in carbon tetrachloride with a view to trapping the acyl radical, as outlined in the equation below.



The crux of the experiment is that the less stable R· is, the slower the acyl radical may be in losing carbon monoxide. Hence the ratio k_1/k_2 as measured by product analysis is a guide to the stability of the R· radical. For the series 1-adamantylcarboxaldehyde, bicyclo [2,2,2] -octyl-1-carboxaldehyde and 1-norbornylcarboxaldehyde, the ratio is 28.5, 15.0 and 0.08. Hence in the highly strained bicyclic ring, where there is absolutely no chance for a planar radical, the acyl radical shows some reluctance to lose a molecule of carbon monoxide. Similarly, Humphrey, Hodgson and Pincock (85) found that the bridgehead peroxyesters of these systems decomposed with relative rates of 1.00, 0.07 and 0.001 respectively. These rates can be interpreted as a measure of the relative stabilities of the radicals formed.

Further evidence in favor of a planar conformation is

provided by a study of secondary β-deuterium isotope effects carried out by Seltzer and Hamilton (73). They studied the decomposition of azobis-α-phenylethane-β,β,β,-$\underline{d}_3$ and its protio counterpart. The observation of an isotope effect is based on stabilization of the developing radical by hyperconjugation.



A contribution from hyperconjugation therefore implies that the developing radical is approaching planarity at the transition state. A 2% reduction of rate per D atom was observed by these workers. β-Deuterium isotope effects have been measured for carbonium ion processes. In these, rate reduction is somewhat larger, $\underline{e}.\underline{g}.$, 7% reduction per deuterium was observed in the solvolysis of α-phenylethyl-β,β,β-$\underline{d}_3$ chloride (74).

That both hyperconjugation and resonance stabilization (Table I) are important in lowering the activation energy for decomposition of azo compounds is also in support of a planar conformation.

It seems that azo compounds are best suited for a systematic study of the stereochemistry of radicals in a solvent cage, on account of the fact that the two radicals are generated simultaneously in close proximity. The reaction is free from induced decomposition (75), and other

mechanisms for decomposition appear to be absent. There are, however, a number of criticisms that might be made. Use of symmetrical azo compounds as used by Bartlett (37) and Greene (39) lead to complications. Since two optically active centres are involved, the products will inevitably be a mixture of diastereomers. These can often be very difficult to separate (37). While symmetrical tertiary substituted azo compounds have the advantage of being easy to prepare, free from side reactions such as isomerization to hydrazone, and decompose at relatively low temperatures, the size of the cage product can be very small (37). There is also the problem of interconversion of product diastereomers on attempted gas liquid chromatography (g.l.c.) separation (37).

For these reasons, it seemed that an unsymmetrically disubstituted azo compound with one optically active centre would yield the best results. Only one coupling product will be formed within the solvent cage and this product will, in general, be easy to isolate from any others formed.

C H A P T E R I

SYNTHESIS AND DECOMPOSITION OF 1,1'-DIPHENYL-1-METHYLAZOMETHANE, 7

The purpose of this work is to observe the stereochemistry of the product produced in the solvent cage by the combination of the radicals generated by the decomposition of an unsymmetrical azo compound. The unsymmetrical azo compound chosen should have one asymmetric centre and should decompose to give a coupling product in the solvent cage which should also be asymmetric. A further requirement for the azo compound is that it should decompose at a convenient temperature. It should be reasonably easy to synthesize and the two alkyl groups should be sufficiently similar so that decomposition of the azo compound will take place with simultaneous fission of the two carbon-nitrogen bonds.

It seemed that 1,1'-diphenyl-1-methylazomethane possessed most of these features.

RESULTS

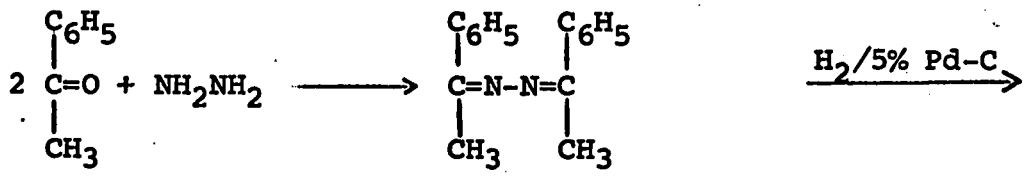
Synthesis of 1,1'-Diphenyl-1-methylazomethane, 7

This compound was synthesized by a modification of a method used by Seltzer (56). The reaction is outlined in Scheme V.

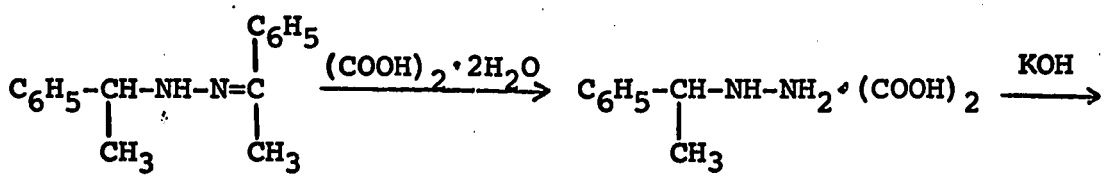
Acetophenone ketazine, 1, was synthesized by dissolving stoichiometric amounts of hydrazine hydrate and acetophenone in ethanol and adding a few millilitres of acetic acid to catalyze the condensation. The reaction is exothermic and is complete in about two hours at room temperature, depositing bright yellow crystals of 1. This compound was used directly without further recrystallization.

Catalytic hydrogenation of 1 was carried out in ethyl acetate using 5% palladium on charcoal and initial pressures of 20-30 p.s.i. of hydrogen. Uptake of hydrogen was usually very fast, one equivalent of hydrogen being taken up in ten to fifteen minutes. The resulting acetophenone α-phenylethylhydrazone, 2, was not isolated. After removal of solvent, 2 was added to a stirred solution of oxalic acid dihydrate in 95% ethanol-ether. α-Phenylethylhydrazine oxalate, 3, slowly separated as a white solid. Crude compound 3 was obtained in good yield and was used directly in the next step of the reaction sequence.

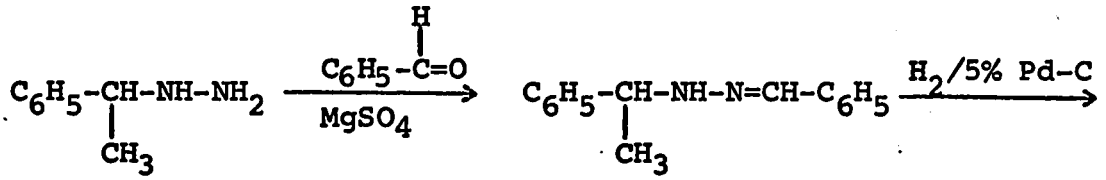
Scheme V



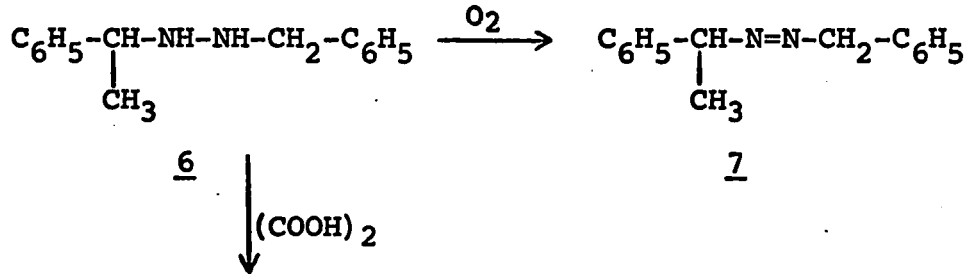
1



2 3



4 5



6 7 8

Basification of 3 was carried out by adding it slowly to a stirred 20% solution of potassium hydroxide. The reaction mixture was extracted with methylene chloride, and after removal of the solvent, the residue was distilled under reduced pressure to yield α-phenylethylhydrazine, 4, as a colorless liquid in good yield. The boiling point and refractive index were in agreement with those obtained previously for this compound (77). The n.m.r. spectrum obtained was consistent with the structure proposed for the compound.

After distillation of 4, a quantity of higher boiling material remained in the pot. Distillation of this yielded a colorless, viscous liquid, which was identified as 1,2-di-α-phenylethylhydrazine, 21, by the n.m.r. spectrum. Only a small amount of this material was obtained and this shows that hydrogenation of the first double bond of 1 proceeded at a much faster rate than the second one.

Due to the ease of oxidation of 4, all operations involving it were carried out as much as possible under an atmosphere of nitrogen.

Freshly distilled benzaldehyde was condensed with 4 simply by stirring them together in 98% ethanol or anhydrous ether in the presence of anhydrous magnesium sulfate. After filtration to remove the drying agent and evaporation of the solvent, the product benzaldehyde α-phenylethylhydrazone, 5,

was obtained as a yellow oil. Compound 5 could be crystallized with some difficulty and in low yield from Skellysolve B, m.p. 50-54°C. The n.m.r. spectrum of the oil was identical with that of the solid. This suggests that the oil is probably a mixture of syn- and anti- isomers. The n.m.r. spectrum of 5 was consistent with the structure proposed.

Compound 5 could also be obtained directly from the reaction of methyl lithium with benzalazine. The n.m.r. spectrum was identical to that obtained by the method above. This had a single advantage in that 5 is obtained in a smaller number of steps. Unfortunately, it is difficult to obtain free from benzalazine. Therefore, the former method was used in subsequent syntheses.

Compound 5, dissolved in 98% ethanol or anhydrous ether, was hydrogenated over 5% palladium on charcoal catalyst and at an initial pressure of hydrogen of 20-30 p.s.i. Hydrogen uptake was fast and the reaction was usually complete in two or three hours. However, in order to ensure complete reaction of 5, the reaction time was extended to twelve hours. The product, 1-benzyl-2-α-phenylethylhydrazine, 6, had to be handled carefully because of the ease of oxidation. Therefore, where possible, manipulations involving 6 were carried out in an atmosphere of nitrogen. Compound 6 was distilled under reduced pressure to yield a colorless viscous liquid.

Sealed in vials under nitrogen and refrigerated, 6 showed a tendency to crystallize. However, no solid could be isolated at room temperature. The n.m.r. spectrum of 6 was consistent with the structure, and showed no extraneous peaks. Compound 6 was assumed free of hydrazone on this basis. Generally, 6 was stored either by sealing in vials under vacuum or reacting it with oxalic acid to form the oxalate salt, 8.

Because of the instability of 6, no attempt was made to obtain an elemental analysis. However, an attempt was made to obtain an elemental analysis on a derivative, 1-benzyl-2-α-phenylethylhydrazine oxalate, 8. Unfortunately, after repeated recrystallizations (m.p. 183-4°C.) a satisfactory analysis could not be obtained to fit either a 1:1 base:acid or a 2:1 base:acid salt. The carbon and hydrogen analyses indicated a mixture of these two salts in the ratio of 2:1 respectively. This ratio was confirmed by the nitrogen analysis. Difficulty in obtaining a good elemental analysis for hydrazine oxalates has been experienced by earlier workers (78).

Oxidation of 6 to the corresponding azo compound, 1,1'-diphenyl-1-methylazomethane, 7, was attempted using methods employed previously (77). However, both silver nitrate and mercuric oxide gave mixtures of products. The greater part of these impurities was undoubtedly due to the

corresponding hydrazones, 5, and acetophenone benzylhydrazone, 9. Air oxidation has been used to synthesize 3,6-diphenyl-3,4,5,6-tetrahydropyridazine in a pure state (79), whereas traditional methods of oxidation yielded largely corresponding hydrazone (59).

Oxidation was therefore carried out by passing oxygen into an ethereal solution of 6. After oxidation, the ethereal solution of the azo compound, 7, was extracted with water and dried. The solvent was removed on a rotary evaporator at reduced pressure. After several hours all traces of solvent had been removed, as checked by n.m.r. spectroscopy and refractive index. The product, 7, was a yellow oil. Attempts to recrystallize this failed. Since no purification of 7 was available, it was essential to make sure that the starting material was pure. For this reason, isolated 6 was not used to generate 7. Instead 6 was generated from recrystallized 8 by treating 8 with aqueous sodium or potassium bicarbonate and extracting 6 into ether in which it was oxidized. The purity of 7 was checked by n.m.r. spectroscopy. The spectrum, which conforms to the structure proposed for 7, had no extraneous peaks, particularly in the region expected for hydrazone. The ultraviolet (u.v.) spectrum had an absorption in the expected region, namely 3600°A (ϵ=50). However, a second absorption at 2800-3000°A was observed which was attributed

to the hydrazones, 5 and 9. The expected extinction coefficient for these is in the neighborhood of 15000 (79). Based on this estimated extinction coefficient, the azo compound 7 contained less than 1% of the hydrazones. A satisfactory elemental analysis was also obtained for 7.

Compound 7 was found to be very sensitive and deteriorated rapidly, particularly at room temperature. Samples could, however, be stored for a week or longer, in the refrigerator without serious deterioration. This deterioration was believed to be due to rearrangement of 7 to the corresponding hydrazones 5 and 9. This rearrangement can be catalyzed by acid, base and light. Therefore, apparatus used during and after the oxidation step was carefully neutralized and wrapped with aluminum foil to exclude light.

Anhydrous magnesium sulfate used as a drying agent for ethereal solutions of 7 caused isomerization to hydrazone in a few minutes. Fortunately, sodium or potassium carbonate could be used for this purpose without appreciable isomerisation. Attempts to purify contaminated samples of 7 using a short column of alumina resulted in recovery of 7 of about the same degree of impurity. This contrasts with the behavior of 1-ethyl-1-phenyl-1'-methylazoethane which could be separated from the corresponding hydrazone by elution from an alumina column (81).

Resolution of 6

Resolution of 6 was achieved by formation and fractional crystallization of the camphorate salt from a solvent mixture of ethyl acetate-dioxane. After three or four recrystallizations resulting in a 15% yield of resolved salt, the specific rotation did not change appreciably and any change observed was as a result of error due to the small observed rotation. This will be appreciated if it is pointed out that the specific rotation of the salt at this stage is $[\alpha]_D^{25} = -2.5^\circ$. Hence any small amount of optically active impurity, e.g., azo compound, can effect the rotation considerably. This resulted in rotations of -2.0° to -4.5° being recorded for salt from the same recrystallization.

Synthesis of (-)-7

Optically active compound 7 was generated directly from the camphorate salt. This was done in the same manner as when racemic azo compound was obtained from oxalate salt, 8. Optical rotation of (-)-7 was taken, $[\alpha]_D^{25} = -152^\circ$ (c 5.0 benzene).

The optical rotary dispersion (o.r.d.) spectrum was measured and conformed to the typical Cotton curve.

Determination of optical purity of (-)-7

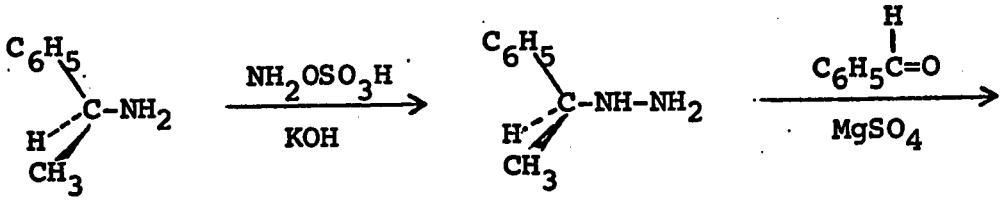
It was necessary that the optical purity of azo compound 7 be known, in order to assess the stereochemical course of its decomposition to coupling product 13.

In order to find the optical purity, an approach which is often used is to synthesize the azo compound from a precursor whose optical purity is known. This synthesis ideally should not involve any step in which racemization of the optically active centre is possible. Such a synthetic sequence for (-)-7 is outlined in Scheme VI.

α-Phenylethylamine, 10, was resolved by the method of Thielacker (86). On hydrolysis of the tartrate salt, (-)-10 was recovered 95% optically pure, $\alpha_D^{25} = -37.38^{\circ}$.

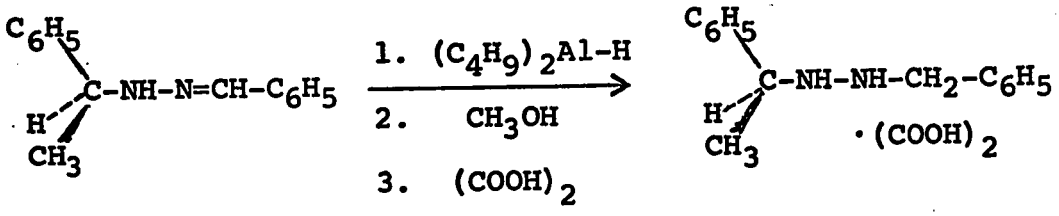
Amination of the amine was carried out by the method of Gösl and Meuwsen (82). This involved treating a three-fold excess of (-)-10 with hydroxylamine-O-sulfonic acid which yielded the α-phenylethylhydrazine, (-)-4. The reaction did not work as well as for those reported for other substrates. However, amination of benzylic amines has not been reported. Due to the fact that a large excess of amine must be used in these reactions, the unreacted (-)-10 was separated from (-)-4 by fractional distillation and subjected to the reaction again. Three cycles of the amine were required to obtain a 10% yield of (-)-4. The n.m.r. spectrum of (-)-4 was identical with that obtained

Scheme VI



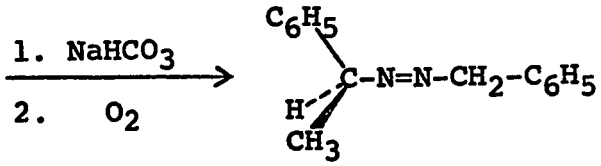
S-(-)-10 S-(-)-4

α_D^{25} = -38.2° (neat, 1 dm) $[\alpha]_D^{25}$ = -31° (c 0.9, benzene)



S-(-)-5 S-(-)-8

$[\alpha]_D^{25}$ = -69.1° (c 3.31, benzene)



S-(-)-7

$[\alpha]_D^{25}$ = -156° (c 1.06, benzene)

for racemic 4.

The hydrazone, (-)-5, was prepared as reported for racemic 5. Previously, this was hydrogenated to (-)-6. The rotation of (-)-6 was taken neat and found to be $\alpha_D^{25} = -36.34$ (neat, 1 dm). This compares with a rotation of $\alpha_D^{25} = -50.5$ obtained for (-)-6 as isolated from an optical resolution experiment. These figures must be treated cautiously, however, since 6 is very sensitive to air oxidation, so that the difference in the rotations could be due, to a large extent, to varying degrees of oxidation of 6.

Oxidation of (-)-6 resulted in an impure sample of (-)-7, which contained an estimated 7% of hydrazone based on the u.v. spectrum assuming an extinction coefficient of 15000. The rotation of the sample was taken, however, and was found to be: $[\alpha]_D^{25} = -106.7$ (c 5.7, chloroform). Even considering the impurity, this falls far short of the rotation obtained by resolution.

It was suspected that racemization might be occurring during the hydrogenation step. Therefore, the experiment was repeated using diisobutylaluminum hydride to effect the reduction of (-)-5 to (-)-6. Compound (-)-6 was not isolated, but was converted to (-)-8. The yield of (-)-8 obtained was poor (30%). Hydrolysis of (-)-8 followed by oxidation yielded (-)-7, $[\alpha]_D^{25} = -139.82$ (c 1.36, benzene).

The u.v. spectrum showed that 5 and 9 were present in negligible amounts. However, the n.m.r. spectrum showed that about 7½% of the material was (-)-4. By correcting for this and correcting for the fact that (-)-10 was not optically pure, the rotation of optically pure (-)-7 would be $[\alpha]_D^{25} = -156^o$. This is not significantly different from the optical rotation obtained by optical resolution.

A second approach was used to determine the optical purity of (-)-7. This was to degrade (-)-7 to a simpler compound, (-)-10, whose maximum optical rotation is known.

Degradation of (-)-7 to (-)-10 gave an anomalous result. (-)-7 of maximum rotation was hydrogenolyzed over Raney nickel. Uptake of the first equivalent of hydrogen was fast while it took several days for uptake of the second equivalent. The products of the hydrogenolysis were analyzed by gas liquid chromatography (g.l.c.) and were found to be mainly α-phenylethylamine and benzylamine with small amounts of two other products whose retention times corresponded to toluene and ethylbenzene. The two peaks corresponding to the amines were overlapped considerably. The best separation was achieved using an SF 96 Column. Under the best conditions with this column, two passes through the column were necessary before (-)-10 was obtained free of benzylamine. The optical rotation of (-)-10 was taken, $[\alpha]_D^{25} = -31.3^o$ (c 5.4, dioxane). This

was equivalent to about 80% optical purity for (-)-7. Since optical purity was approximately 100% as determined by synthesis, it would appear that some racemization must have occurred with this method. Racemization could have occurred by isomerization of the azo compound on the nickel catalyst to hydrazone, 9, prior to reduction to (-)-6.

The possibility of racemization of (-)-10 was investigated by subjecting it to the reaction conditions. However, the optical rotation of (-)-10 after the experiment was the same as before.

Synthesis of hydrocarbon coupling products

Decomposition of 7 was expected to give rise to a number of hydrocarbon coupling products. Since 7 decomposes to a benzyl and an α-phenylethyl radical, random coupling of radicals would give rise to bibenzyl, 1,2-diphenylpropane and meso- and dl-2,3-diphenylbutane. Bibenzyl is available commercially. However, it was necessary to have authentic samples of the other three. Their syntheses are described below.

dl-1,2-Diphenylpropane, 13

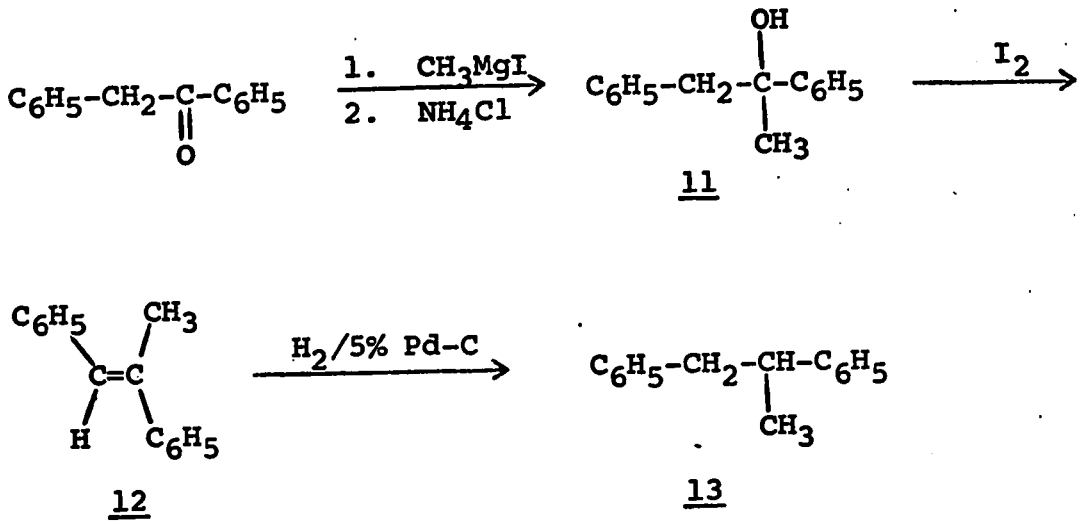
Method A

This was synthesized as shown in Scheme VII. Deoxybenzoin was treated with methyl magnesium iodide. After neutralization of the reaction mixture with ammonium

chloride solution, the crude alcohol, 1,2-diphenyl-2-propanol, 11, was distilled. On distillation, 11 eliminated the elements of water, probably due to the presence of iodine, and 1,2-diphenyl-1-propene, 12, was formed. The distillate immediately solidified and was recrystallized from methanol.

Compound 12 was hydrogenated over 5% palladium on charcoal catalyst. Uptake of hydrogen was fast and one equivalent of hydrogen was taken up in less than one hour. On evaporation of the solvent, the residue distilled over as a colorless liquid. This was identified as 1,2-diphenylpropane by its n.m.r. spectrum and by comparison of its refractive index with that reported (83).

Scheme VII



Method B

In order to obtain 13 optically pure, it was necessary to start with an optically pure precursor. This precursor was 2,3-diphenylpropionic acid, 15. The reaction sequence from this compound is outlined in Scheme VIII. The reaction sequence was tested first on racemic 15.

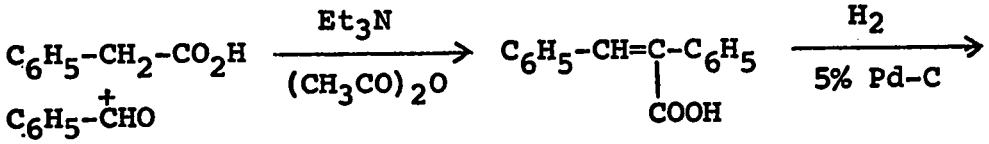
α-Phenylcinnamic acid, 14, was synthesized in good yield as a mixture of cis and trans isomers, from phenylacetic acid and benzaldehyde by the Perkin reaction (84).

Compound 14 was hydrogenated over 5% palladium on charcoal and one equivalent of hydrogen was taken up in about two hours. After removal of solvent, crude dl-2,3-diphenylpropionic acid, 15, was recrystallized from hexane. The n.m.r. spectrum of this compound was consistent with the proposed structure. Its melting point also coincided with that reported for this compound.

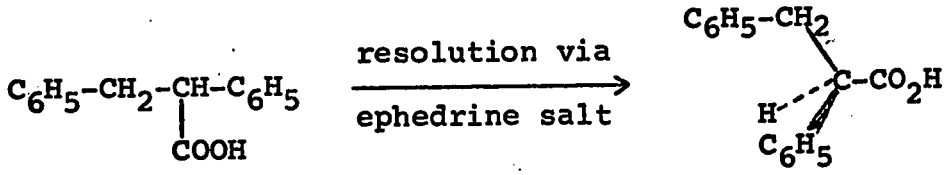
Compound 15 was reduced using lithium aluminum hydride in anhydrous ether. The reaction mixture was heated under reflux overnight. After the aluminum complex was broken up and solvent removed the crude 2,3-diphenyl-1-propanol, 16, was isolated by distillation under reduced pressure to yield a very viscous, colorless liquid.

The structure of 16 was confirmed by the n.m.r. spectrum and the coincidence of the refractive index and boiling point with those reported for this compound (85).

Scheme VIII



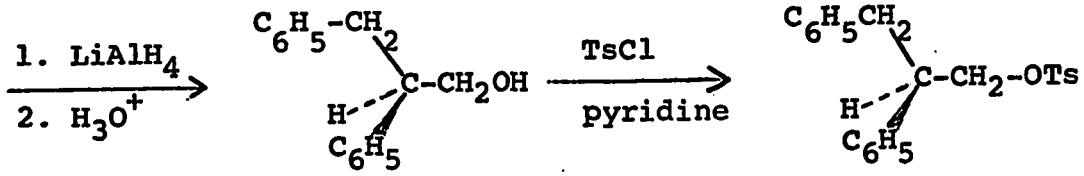
cis- and trans- 14



dl-15

R-(-)-15

$[\alpha]_D^{25} = -132.5^\circ$

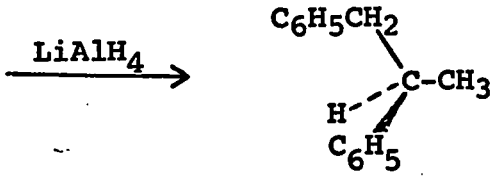


R-(-)-16

$[\alpha]_D^{25} = -88.47^\circ$

R-(-)-17

$[\alpha]_D^{25} = -42.63^\circ$



R-(-)-13

$[\alpha]_D^{25} = -80.51^\circ$

Sulfonation of 16 was carried out by addition of p-toluenesulfonyl chloride in pyridine to an ice cold solution of the alcohol in pyridine. After normal work-up, a white cyrstalline solid was obtained which was identified as 2,3-diphenyl-1-propyl p-toluenesulfonate, 17, by its n.m.r. spectrum.

An ethereal solution of the tosylate 17 was treated with excess lithium aluminum hydride and the reaction mixture was heated under reflux for a prolonged period. After destroying the excess hydride and evaporating the solvent, the residue was found to be composed entirely of 13 by g.l.c. analysis. The n.m.r. spectrum and refractive index were identical to those obtained by Method A.

Stereospecific Synthesis of R-(-)-13

The first step in the stereospecific synthesis of R-(-)-13 was the resolution of the acid 15. This was carried out by the method of Pettersson (91). From the resolution, (-)-15 was isolated optically pure as determined by Pettersson. This material had a rotation of $[\alpha]_D^{25} = -132.5^\circ$ (c 0.62, acetone). The rest of the synthesis was carried out as described for the racemic material. The optical rotations of the intermediate compounds are shown on Scheme VIII. Isolation of (-)-13 was carried out by preparative g.l.c.. The rotation of (-)-13

was $[\alpha]_D^{25} = -80.51^\circ$ (c 8.67, chloroform). A second synthesis of (-)-13 by the same route yielded material of the same rotation, $[\alpha]_D^{25} = -80.5^\circ$ (c 3.2, chloroform). (-)-13 had an identical n.m.r. spectrum to that obtained by Method A. It showed no extraneous peaks either in the n.m.r. spectrum or in g.l. chromatogram. The refractive index agreed well with those reported by Method A and by previous workers (83).

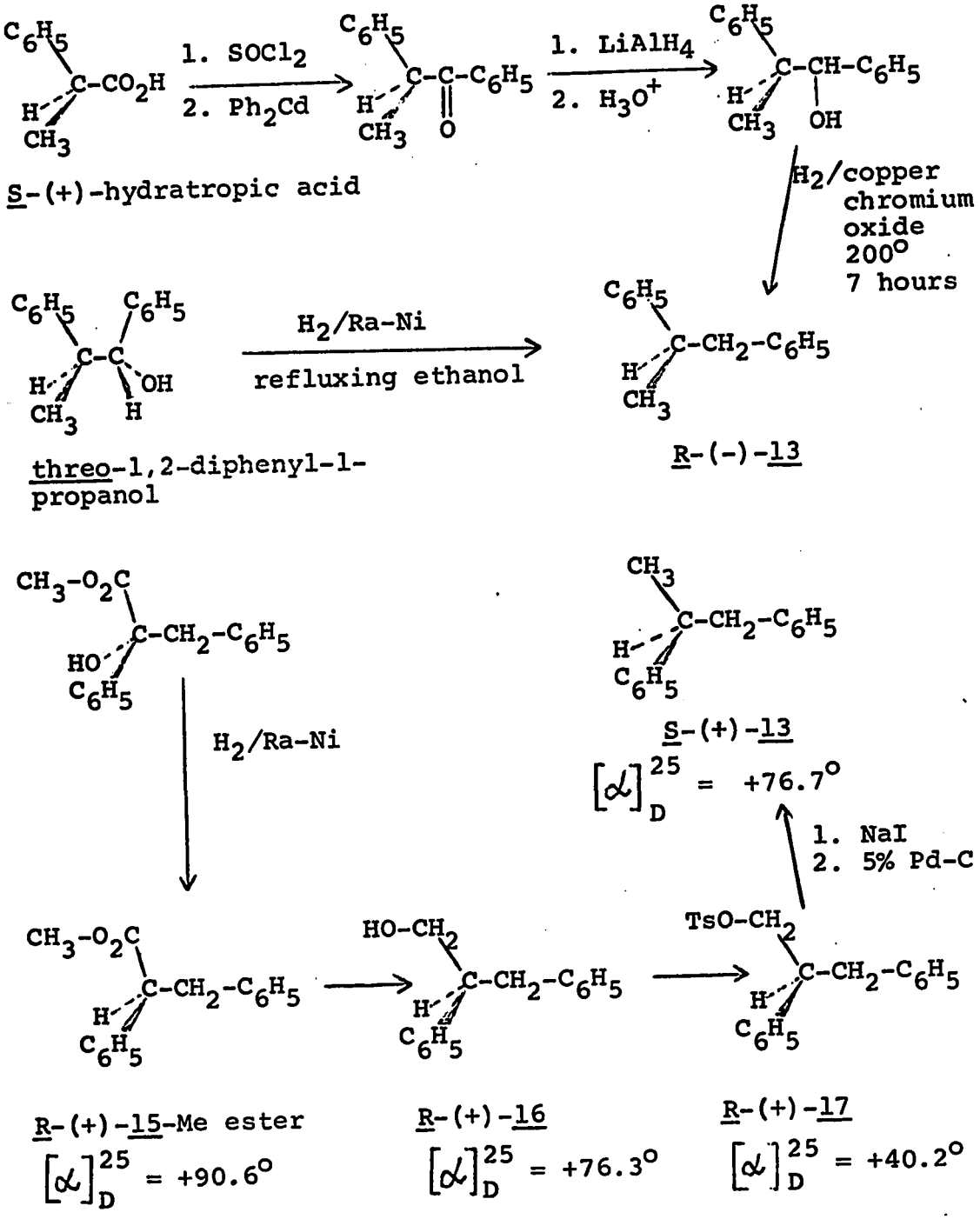
Absolute configuration of (-)-7 and (-)-13

In order to know whether decomposition of (-)-7 has taken place with retention or inversion of configuration it is necessary to know the absolute configurations of (-)-7 and of (-)-13. In Scheme VI, the absolute configuration of (-)-7 is related to that of (-)-10. The latter has been shown by Leithe (87) to have the S configuration. Therefore, (-)-7 will also have the S configuration.

The work of Barnes and Juliano (88) and Sullivan and coworkers (89) has related the configuration of (-)-13 with that of hydratropic acid. This is shown in Scheme IX. (-)-13 is shown to have the R configuration since (+)-hydratropic acid is known to have the S configuration (90).

Included also in this scheme is the synthesis of the (+)-isomer. This synthesis, after a certain point, is similar to the one employed in this work. Comparison of

Scheme IX

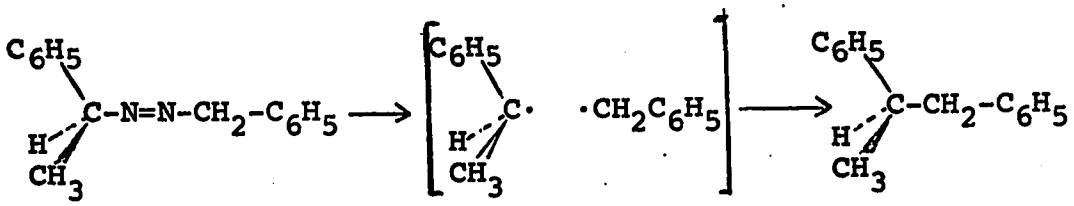

1. SOCl2
2. Ph2Cd
1. LiAlH4
2. H3O+
S-(+)-hydratropic acid
H2/copper chromium oxide 200° 7 hours
H2/Ra-Ni
refluxing ethanol
threo-1,2-diphenyl-1-propanol
R-(-)-13
H2/Ra-Ni
S-(+)-13
[α]D25 = +76.7°
1. NaI
2. 5% Pd-C
R-(+)-15-Me ester
[α]D25 = +90.6°
R-(+)-16
[α]D25 = +76.3°
R-(+)-17
[α]D25 = +40.2°

rotations for intermediate compounds, although not always in the same solvents, is of interest and will be discussed later.

The absolute configuration of (-)-15, had been assigned as R by Pettersson on the basis of the method of pseudo-racemates, and on the change of rotation with change of solvent (92). The synthesis, therefore, of (-)-13 from (-)-15 establishes the absolute configuration of (-)-15 and proves Pettersson's assignment to be correct.

Decomposition of (-)-7 is shown in Scheme X as proceeding with retention of configuration. If retention of configuration then takes place, the isolated hydrocarbon should have a negative rotation.

Scheme X



S-(-)-7 R-(-)-13

Synthesis of meso- and dl-2,3-diphenylbutanes, 19 and 20

The symmetrical coupling products resulting from the coupling of two α-phenylethyl radicals generated in the decomposition of 7 are meso- and dl-2,3-diphenylbutane, 19 and 20. The syntheses of these have been reported previously

by Barber, Stack and Woolman (93). α-Phenylethyl chloride was coupled using magnesium in anhydrous ether, and the mixture of 19 and 20 formed was separated by fractional crystallization. These two compounds gave n.m.r. spectra which were consistent with their structures.

Kinetics of decomposition of 7

The decomposition of azo compounds is known to follow first order kinetics by a large number of studies. A number of studies have shown that these compounds are also free from induced decomposition (75). However, secondary and primary azo compounds are known to rearrange as well as decompose. Cohen and Zand (94) have pointed out that 1,1'-dimethylazoethane undergoes rearrangement to acetone isopropylhydrazone and Williams and Lawrence (51) observed isomerization in the decomposition of 1,1'-diphenylazomethane. It is not surprising, therefore, that 7 should undergo a similar rearrangement under the conditions of the decomposition. The driving force for such a rearrangement must be the greater stability of the benzylic hydrazones. In actual fact, 7 was never synthesized entirely free from these hydrazones. Since there is no purification process available for this compound, the only approach that could be taken was to synthesize the azo compound as carefully as possible.

Several methods of measuring the kinetics of decomposition were attempted before one which was satisfactory was found. Measurement of the rate of decomposition was attempted using n.m.r. spectroscopy. The methylene and methine peak in the n.m.r. spectrum of 7 were well removed from the area of the spectrum where peaks due to products were expected. Disappearance of these peaks could be followed. This method of following the decomposition was abandoned because a large number of readings could not be taken due to the large time lapse, when the spectra were being run. Secondly, the accuracy with which the measurements could be made was not as high as was desired.

Disappearance of azo compound has been followed by observing the disappearance of the absorption due to the nitrogen-nitrogen double bond in the u.v. spectrum (55,56). A trial run of this method was fruitless because as hydrazone was formed, the intense absorption due to it overlapped the absorption due to the azo compound, so that little change was observed in the intensity of the absorption with time.

The method most frequently used to measure the rate of decomposition of azo compounds is to follow the rate of evolution of nitrogen. This can be done by observing either the volume change or the pressure change. Utilization of volume change with nitrogen evolution proved

the most satisfactory.

Early attempts to calculate the rate constant for decomposition by plotting log $(V_\infty - V_t)$ versus time revealed a curvature in the plot. This was particularly true at times greater than one half life. This would seem to be due to formation of the hydrazone with autocatalysis. It is essential, therefore, that the initial rate of decomposition be calculated. It is necessary that the equipment be such that thermal equilibration be fast. The apparatus had to be constructed so that "dead space" within the apparatus be eliminated as far as possible. This was achieved by using capillary tubing where possible.

Typical results obtained from these experiments are included in Tables III and IV, and graphical plots are shown in Figures I and II.

The results obtained in the measurement of the rates of decomposition at two temperatures are shown in Table V. From these results, the activation parameters were calculated in the usual way (95).

TABLE III

Rate Data for the Decomposition of

1,1'-Diphenyl-1-methylazomethane, 7

Temperature = 106.0°C Solvent: Cumene

$(V_\infty - V_o)_{calculated}$ = 16.30 ml

Time, seconds	$(V_\infty - V_t)$, millilitres	$\log \frac{(V_\infty - V_o)}{(V_\infty - V_t)}$	k_d, sec^{-1}
1000	16.15	0.0040	
2800	15.95	0.0094	
5000	15.57	0.0200	
8200	15.30	0.0275	
12000	14.85	0.0405	8.05×10^{-6}
18200	14.10	0.0630	
24000	13.47	0.0828	
30100	12.85	0.1033	
39600	11.95	0.1349	
50200	11.15	0.1649	
86800	8.85	0.2653	
92200	8.60	0.2777	
280000 (∞)	5.35		

TABLE IV

Rate Data for the Decomposition of

1,1'-Diphenyl-1-methylazomethane, 7

Temperature 127.9°C Solvent: Cumene

$(V_\infty - V_o)_{calculated}$ = 11.45 ml

Time, seconds	$(V_\infty - V_t)$, millitres	$\log \frac{(V_\infty - V_t)}{(V_\infty - V_t)}$	k_d, sec^{-1}
250	11.05	0.0155	
650	10.40	0.0418	
1050	9.70	0.0720	
1450	9.20	0.0950	
1850	8.65	0.1218	1.24×10^{-4}
2250	8.25	0.1423	
2850	7.70	0.1723	
3450	7.20	0.2015	
4050	6.65	0.2360	
4750	6.10	0.2735	
5450	5.60	0.3106	
6550	4.90	0.3686	
7650	4.30	0.4253	
8750	3.85	0.4733	
10050	3.45	0.5210	
11450	2.90	0.5964	
35000 (∞)	1.10		

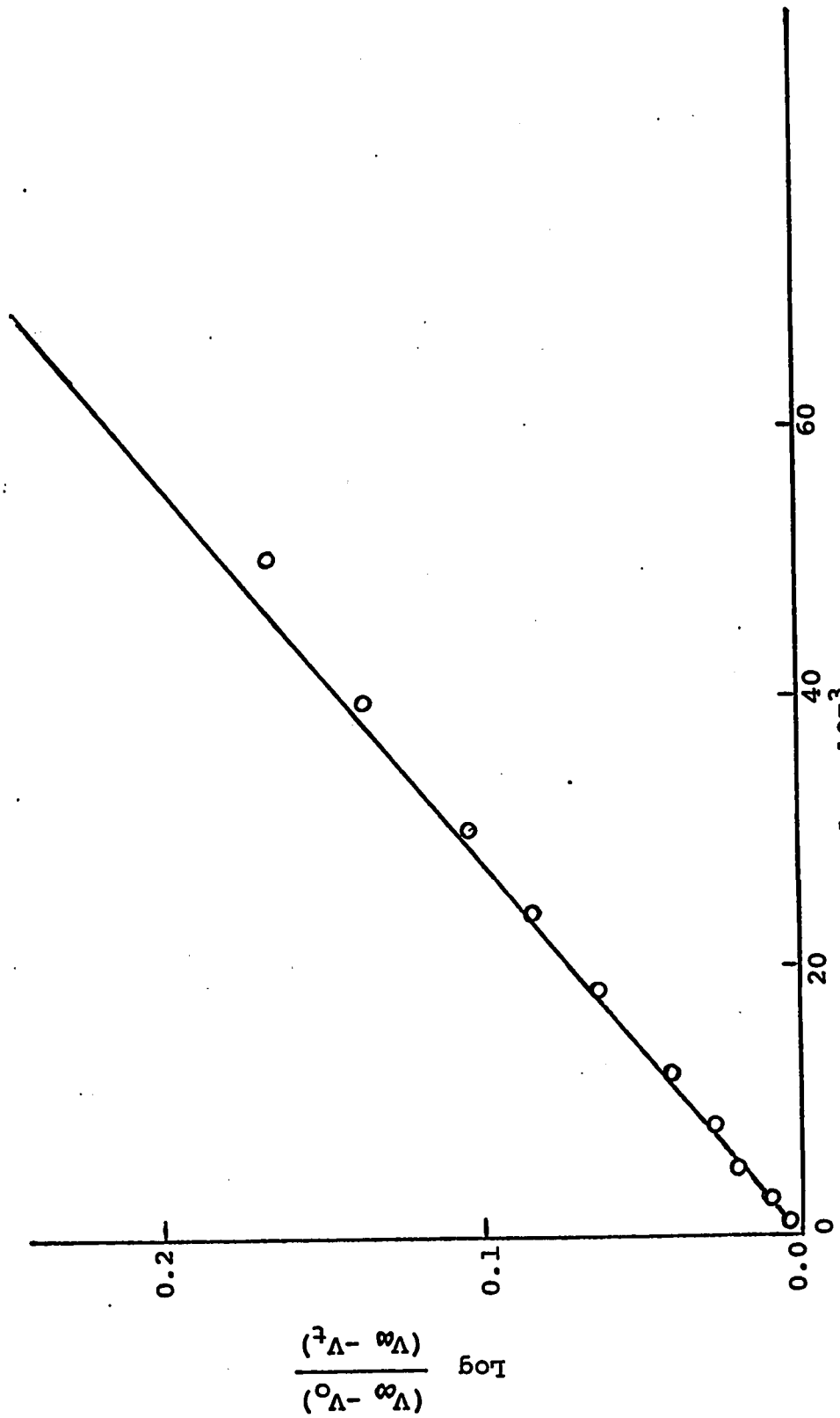


Fig. I. Decomposition of *Z*, 0.15 M, in cumene at 106.0°, k = 8.05 x 10^{-6} sec^{-1}.

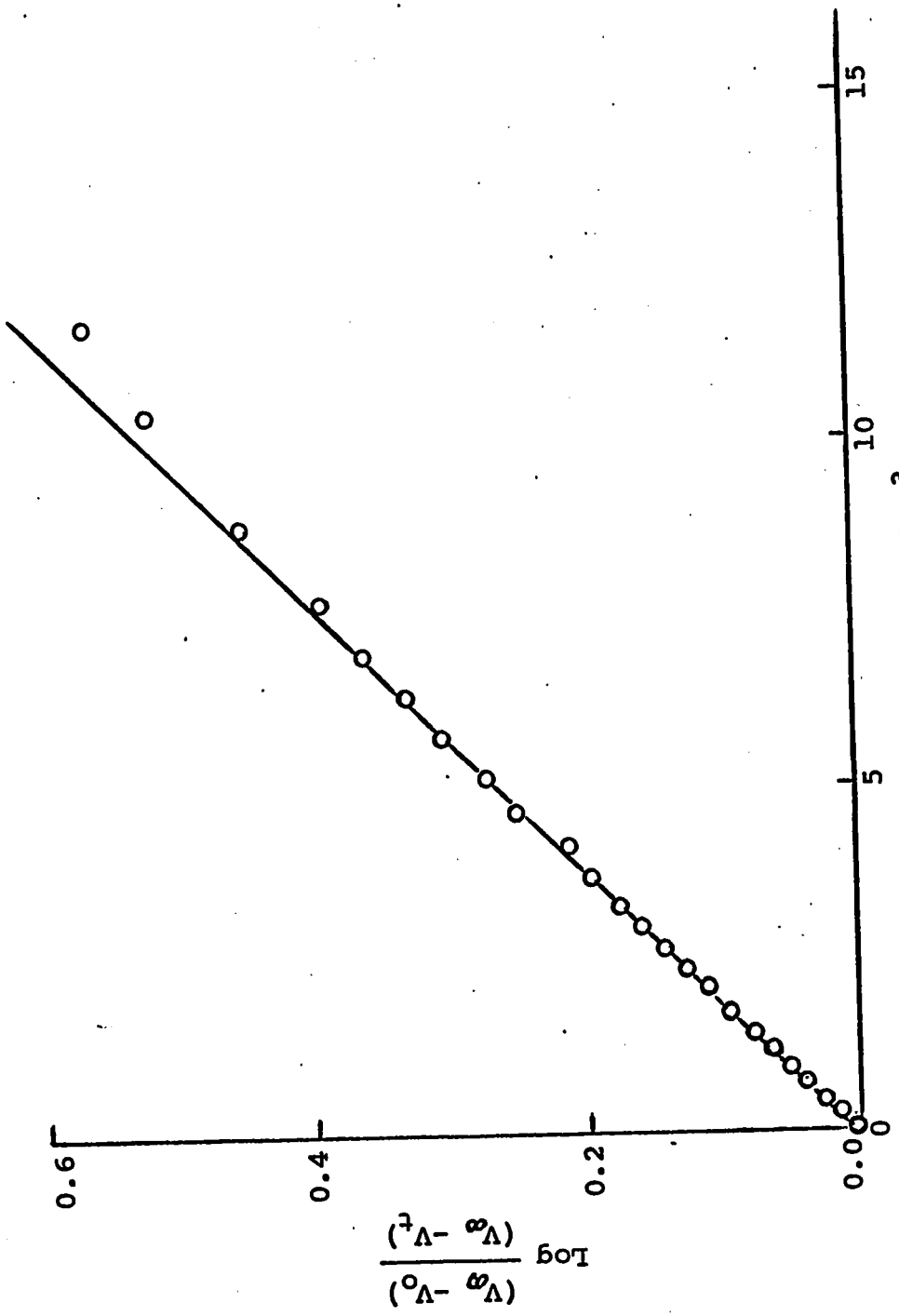


Fig. II. Decomposition of 7, 0.18 M, in cumene at 127.9°, k = 1.20 x 10^{-4} sec^{-1}.

TABLE V

Rates of Decomposition of 7 in Cumene

Temp., °C	Conc., M	Moles N_2*	k x 10^6, sec^{-1}
106.0	0.084	0.59	8.84
	0.15	0.69	8.05
	0.13	0.67	8.29
127.9	0.12	0.90	124
	0.18	0.83	120
	0.15	0.86	111

* Moles N_2 per mole of 4

At 106°C $\Delta H^{\ddagger} = 35.9 \pm 1.0$ kcal/mole,

$\Delta S^{\ddagger} = 12.5 \pm 2.2$ e.u.

PRODUCT ANALYSIS

In order to determine the products formed in the decomposition of 7, 2 g of it were heated in refluxing ethylbenzene for forty hours. After evaporation of most of the solvent, the residue was analyzed by g.l.c. (SF 96 column). Four products eluted at high retention times and these were identified as being bibenzyl, dl-2,3-diphenylpropane, 13, dl-2,3-diphenylbutane, 20, and meso-2,3-diphenylbutane, 19, by comparison with the retention times of the authentic materials.

Decomposition of a sample of 7 in benzene for a relatively short time of sixteen hours at 106°C revealed on analysis that styrene, toluene and ethylbenzene were also products of the decomposition but were present in much smaller amounts than the coupling products.

Notable quantities of two other products were observed in early runs. These had retention times intermediate between bibenzyl and styrene. These peaks "tailed" considerably on the chromatogram and were, therefore, probably polar in nature. Comparison of the retention times of these two products with those of α-phenylethanol and benzyl alcohol, indicated that these were the probable products. These peaks persisted when the samples were degassed and when 7 was decomposed in the injection port of the chromatograph. This would seem to eliminate molecular

oxygen as the source of these products. However, these samples of 7 were found to have hydrogen peroxide present as an impurity. This was known to be formed on air oxidation of hydrazobenzene (96). Its presence was noted because (a) the sample evolved a gas on addition of platinum black and (b) formed iodine on treatment with potassium iodide. When the ethereal solution of 7 was extracted with water in order to remove hydrogen peroxide, these products were minimized but not totally eliminated.

Retention times by themselves are not definitive proof of the presence of the expected products. Therefore, separation of the components of the mixture was carried out by column chromatography. Separation of the components was sufficiently good so that 20, 19 and 13 were isolated from different fractions and identified by their n.m.r. spectra. No bibenzyl was identified in this separation. However, g.l.c. analysis showed that it was present in the mixture in low concentration. A crystalline solid was obtained in a later fraction, but in too small a quantity to identify by its n.m.r. spectrum.

A quantitative study was made of the product distribution. The results can be seen in Table VI. The samples were prepared by dissolving 7 in purified benzene. This solution was then placed in tubes which were degassed to 1 μ and sealed under vacuum. These were then decomposed at

TABLE VI

Product Distribution from Decomposition

of 7 in Benzene

Temp., °C	[7]*, M	Relative yield, %					
		Toluene	Ethyl-benzene	Bibenzyl	13	19+20**	19 + 20 / bibenzyl
110	0.5	18	12	7.1	44	17.5	2.5
	0.03	-	-	12.7,12.0	65.3,70.9	22.0,17.1	1.7,1.4
	0.0063	-	-	16.9,17.1	63.3,64.0	19.8,18.9	1.2,1.1
	0.0013	-	-	17.7,19.7	65.5,63.4	16.7,17.3	0.94,0.90
132	0.13	1.9	1.9	16.7	60.0	19.4	1.16

* Not corrected for volume expansion

** Equal amounts of 19 and 20 were formed.

the desired temperature for at least six half lives and the resulting product mixture determined by g.l.c. analysis. As can be seen from Table VI, the product mixture shows a concentration dependence. This will be discussed later. Unfortunately, at lower concentrations of 7, it was not possible to estimate the relative amounts of toluene and ethylbenzene to coupling products, because the solvent peak on the chromatogram was so broad. However, at higher concentrations of 7 in benzene, the amount of these lower boiling products would seem to be 20% or less. It should be pointed out that when the reaction is run to completion, little or no styrene is observed. This is not surprising since sufficient time is available for the styrene to have undergone polymerization.

Decomposition of 7 in the presence of butanethiol

Since the main purpose of this work was to determine the stereochemistry of the coupling product, 13, which is formed in the solvent cage, it was necessary to prevent the formation of this compound outside the cage. In order to stop radical-radical reactions outside the cage, it was necessary to add a radical scavenger. Such a scavenger should be sufficiently reactive to trap all radicals which would escape from the solvent cage, but not so reactive that it would interfere with radicals in the solvent cage.

Another important property of the scavenger should be its ability to react irreversibly with the radicals.

Butanethiol seemed a good choice since it was known to react with polystyryl radicals one hundred thousand times more readily than cumene does (97). Since the rate of abstraction of a hydrogen atom from a thiol by a benzyl radical is known to be in the range 10^4 - 10^5 $\underline{M}^{-1}$ sec^{-1} (98), butanethiol can not compete with coupling in the solvent cage. The complete absence of bibenzyl, 19 and 20 from the products of the decomposition of 7 in the presence of butanethiol demonstrates that it is efficiently scavenging the radicals which escape the cage.

Butanethiol acts as a scavenger by donating hydrogen atoms to α-phenylethyl and benzyl radicals which escape from the cage, yielding ethylbenzene and toluene as products.

A comparison of the relative quantities of ethylbenzene and toluene with that of 13 formed in the decomposition of 7 in the presence of butanethiol is a measure of the cage effect. These experiments will be discussed later in greater detail.

Decompositions of (-)-7

These were carried out in various solvents and at different temperatures. Generally, these experiments were

carried out in the following manner. About 1 g of optically pure (-)-7, $[\alpha]_D^{25} = -152^\circ$, was dissolved in 50 ml of solvent. This solution was placed in a 75 ml stainless steel bomb, flushed with nitrogen and sealed. The decomposition was carried out at the desired temperature for at least six half lives. On conclusion of the decomposition the solvent was evaporated and the coupling product 13 isolated. The isolation of 13 was accomplished sometimes by column chromatography followed by preparative g.l.c. and sometimes by g.l.c. only. Occasionally, it was necessary to make a second pass of the hydrocarbon through the chromatograph in order to get the desired degree of purity. Sufficient hydrocarbon was isolated in all cases in order to obtain the rotation of 13. The isolated hydrocarbon 13 was found to be largely racemic. It did have, however, a negative optical rotation. This corresponds to net retention of configuration as shown in Scheme X. Details of the decomposition of (-)-7 are shown in Table VII.

Control Experiments

Since the hydrocarbon, 13, isolated from the decomposition of (-)-7 was almost 90% racemic, it was necessary to know if this racemization was due entirely to loss of asymmetry on the part of the α-phenylethyl radical in the solvent cage, or whether some other processes were going on

TABLE VII

Stereochemistry of (-)-13 from the Decomposition of S-(-)-7

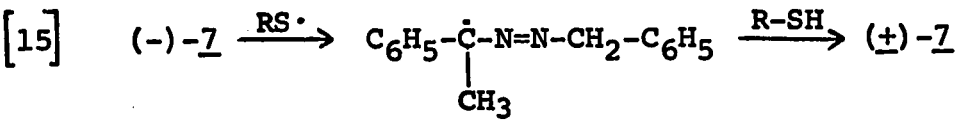
Solvent	Temp., °C	7 M *,	C_4H_9SH M *,	$[\alpha]_D^{25}$**,	Retention, %
Benzene	132	0.13	0	- 3.28	4.1
	132	0.12	1.7	- 9.29	11.5
	110	0.082	0	- 4.49	5.6
	110	0.13	1.2	- 8.27	10.3
	110	0.13	4.8	-13.5	16.7
Butanethiol	110	0.19	9.3	-13.9	17.3
	132	0.14	9.3	-11.7	14.5
Chlorobenzene	107	0.27	0	- 6.60	8.2
	107	0.33	1.1	-11.5	13.0
Cyclohexane	115	0.089	0	- 5.10	6.3
	115	0.089	1.3	- 8.8	10.9

* Not corrected for volume expansion

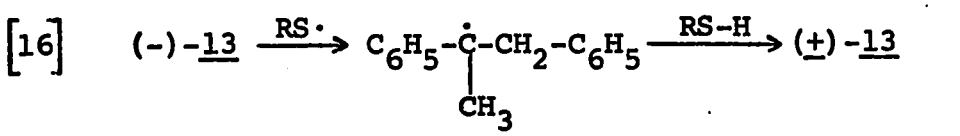
** Rotation of R-(-)-13 taken in chloroform, c 1-5

which could racemize either the starting azo compound or the product hydrocarbon.

The most probable route by which these compounds could be racemized is by abstraction of a hydrogen atom from (-)-7 or (-)-13 by a thiyl radical as shown in the equations below.



[15]



[16]

The radicals generated could react with a molecule of thiol to give racemized starting material or product.

That such a process is possible is supported by the findings of Bickel and Kooyman (99). They found that acetophenone azine is generated when 1,1'-diphenylazoethane is decomposed in the presence of octanethiol. The most probable route for the formation of this compound is successive hydrogen abstractions from the starting material. It is also supported by the finding that a yellow compound with a slightly longer retention time than the coupling product 13 is observed on the g.l.c. chromatogram when 7 is decomposed in the presence of butanethiol. This compound has not been identified. However, it is possible

that it is the mixed azine, acetophenone benzaldehyde azine.

Control experiment on (-)-13

In order to carry this experiment out, it was necessary to generate butanethiyl radicals in the presence of (-)-13 under conditions which resemble, as closely as possible, those in which (-)-13 is formed from (-)-7 in butanethiol solution. Therefore, a compound was sought which would generate radicals at about the same rate as 7. 1,1'-Diphenyl-1-methylazomethane, 22, was the closest to the ideal that could be obtained conveniently. This compound was synthesized by the method of Seltzer (55) except for the oxidation step which was carried out by the oxygenation technique already described.

Therefore, 22 was decomposed in butanethiol in which optically pure (-)-13, $[\alpha]_D^{25} = -80.5^\circ$, had been added. The α-phenylethyl radicals abstracted hydrogen atoms from the butanethiol to yield the thiyl radicals. After decomposing 22 for approximately ten half-lives, (-)-13 was isolated and its rotation taken, $[\alpha]_D^{25} = -64.1^\circ$. This represents 20% racemization of the product.

Control experiment on (-)-7

Azo compound, (-)-7, $[\alpha]_D^{25} = -152^\circ$, was heated in butanethiol for five hours at 110°C. In order to recover (-)-7 from the reaction mixture, it was reduced to (-)-6

with diimide. Diimide was chosen as the reducing agent, since it was known to reduce non-polar bonds faster than polar bonds (100). This was an advantage since reduction of the hydrazones and the azine would give racemized product. (-)-6 was extracted from the reaction mixture with dilute sulfuric acid, which was then basified and 6 extracted into ether solution. The ethereal solution was then oxygenated to yield azo compound, (-)-7, again.

An n.m.r. spectrum of the product showed it to be a mixture of 71% of (-)-7 and 29% of the hydrazone, 5. The rotation of the mixture was $[\alpha]_D^{25} = -101.4^\circ$. The rotation of azo compound was calculated on the basis of 5 being optically pure and the corrected rotation was $[\alpha]_D^{25} = -114^\circ$. This corresponds to 24% racemization of (-)-7. The hydrocarbon, (-)-13, recovered had a rotation of $[\alpha]_D^{25} = -13.93^\circ$, which was the same as the rotation obtained after 100% reaction.

The results of these control experiments indicate that while some racemization observed in the recovered hydrocarbon, (-)-13, may be due to racemization of the starting material, (-)-7, before decomposition, and of the hydrocarbon, (-)-13, after its formation, most of the racemization is due to loss of asymmetry on the part of the α-phenylethyl radical through rotation in the solvent cage.

DISCUSSION

Synthesis of azo compound 7 was straightforward and presented no difficulties. However, the chief problem was in obtaining 7 pure, as no purification process was available. It was hoped that 7 would be a solid as 1,1'-diphenylazoethane, 22, is a solid melting at 72° and 1,1'-diphenylazomethane is a solid, m.p. 30°. The more unsymmetrical 7 would be expected to have a lower melting point than 22. Attempts to obtain 7 as a solid at low temperatures failed.

There is no evidence in the literature that 22 undergoes any isomerization to acetophenone α-phenylethylhydrazone. However, 1,1'-diphenylazomethane is reported to undergo extensive isomerization (51). It would appear, therefore, that isomerization in 7 would be more likely to occur toward the benzyl group than the α-phenylethyl group.

Due to the fact that no purification process is available, great care was taken to eliminate any impurities in its synthesis. Glass-ware was neutralized and the ethereal solution of 6 was kept under an atmosphere of nitrogen until transfer to the oxygenation flask had taken place.

Since Woodward-Hoffman rules predict that 1,3 sigmatropic shifts can be effected photolytically (101), flasks

DISCUSSION

Synthesis of azo compound 7 was straightforward and presented no difficulties. However, the chief problem was in obtaining 7 pure, as no purification process was available. It was hoped that 7 would be a solid as 1,1'-diphenylazoethane, 22, is a solid melting at 72° and 1,1'-diphenylazomethane is a solid, m.p. 30°. The more unsymmetrical 7 would be expected to have a lower melting point than 22. Attempts to obtain 7 as a solid at low temperatures failed.

There is no evidence in the literature that 22 undergoes any isomerization to acetophenone α-phenylethylhydrazone. However, 1,1'-diphenylazomethane is reported to undergo extensive isomerization (51). It would appear, therefore, that isomerization in 7 would be more likely to occur toward the benzyl group than the α-phenylethyl group.

Due to the fact that no purification process is available, great care was taken to eliminate any impurities in its synthesis. Glassware was neutralized and the ethereal solution of 6 was kept under an atmosphere of nitrogen until transfer to the oxygenation flask had taken place.

Since Woodward-Hoffman rules predict that 1,3 sigmatropic shifts can be effected photolytically (101), flasks

containing 7 were wrapped in aluminum foil.

The yields of nitrogen observed in the decomposition of 7 (Table VI) show the extent to which isomerization to hydrazone was occurring. Isomerization seems to have been much more important at the lower temperature than at the higher, since yields of nitrogen at these temperatures were 65% and 85%, respectively. Examination of the graphical plots in Figures I and II shows that deviation from linearity is much less at the higher temperature and is not evident until much later in the kinetic run.

The deviation from linearity in the graphical plots of log $(V_\infty - V_t)$ versus time shows that the isomerization is not occurring solely by a first order kinetic mechanism, since with such a mechanism the data would still give a linear plot. Therefore, it would appear that the isomerization may be autocatalytic. No simple kinetic equation can be applied to the data that would make a correction for this. Therefore, value of $(V_\infty - V_o)$ was calculated in order that the rate may be calculated from the initial slope.

From Table I, it can be seen that the activation energies for the decomposition of 1,1'-diphenylazomethane and 1.1'-diphenylazoethane are 36 and 32.6 kcal/mole, respectively. If decomposition of both is a concerted process, then there is a lowering of the activation energy

of 1.7 kcal per methyl group on the α-carbons. From this the activation energy for the decomposition of 7 would be expected to be 34.3 kcal/mole.

Due to the difficulty of obtaining as good values for the rate constants as would otherwise be expected, the accuracy of the activation parameters are less certain. A value for the activation energy of 35.9 $\pm$ 1.0 kcal was obtained. This is somewhat higher than expected. However, the value of 36 kcal for the activation energy for the decomposition of 1,1'-diphenylazomethane might also be in error since extensive rearrangement also occurs in that system (51).

The enthalpy of activation is, however, sufficiently different from that obtained for the decomposition of 1,1'-diphenylazoethane to support the hypothesis of simultaneous two bond cleavage for the decomposition of azo compound 7, otherwise an enthalpy close to 32.6 kcal would have been expected.

The decomposition of α-phenylethylazoisopropane was shown by Seltzer to involve a concerted mechanism. It is reasonable to expect that 7 will also undergo a concerted decomposition since there is less difference in stability between α-phenylethyl and benzyl radicals than between α-phenylethyl radicals and isopropyl radicals.

Mechanism of product formation

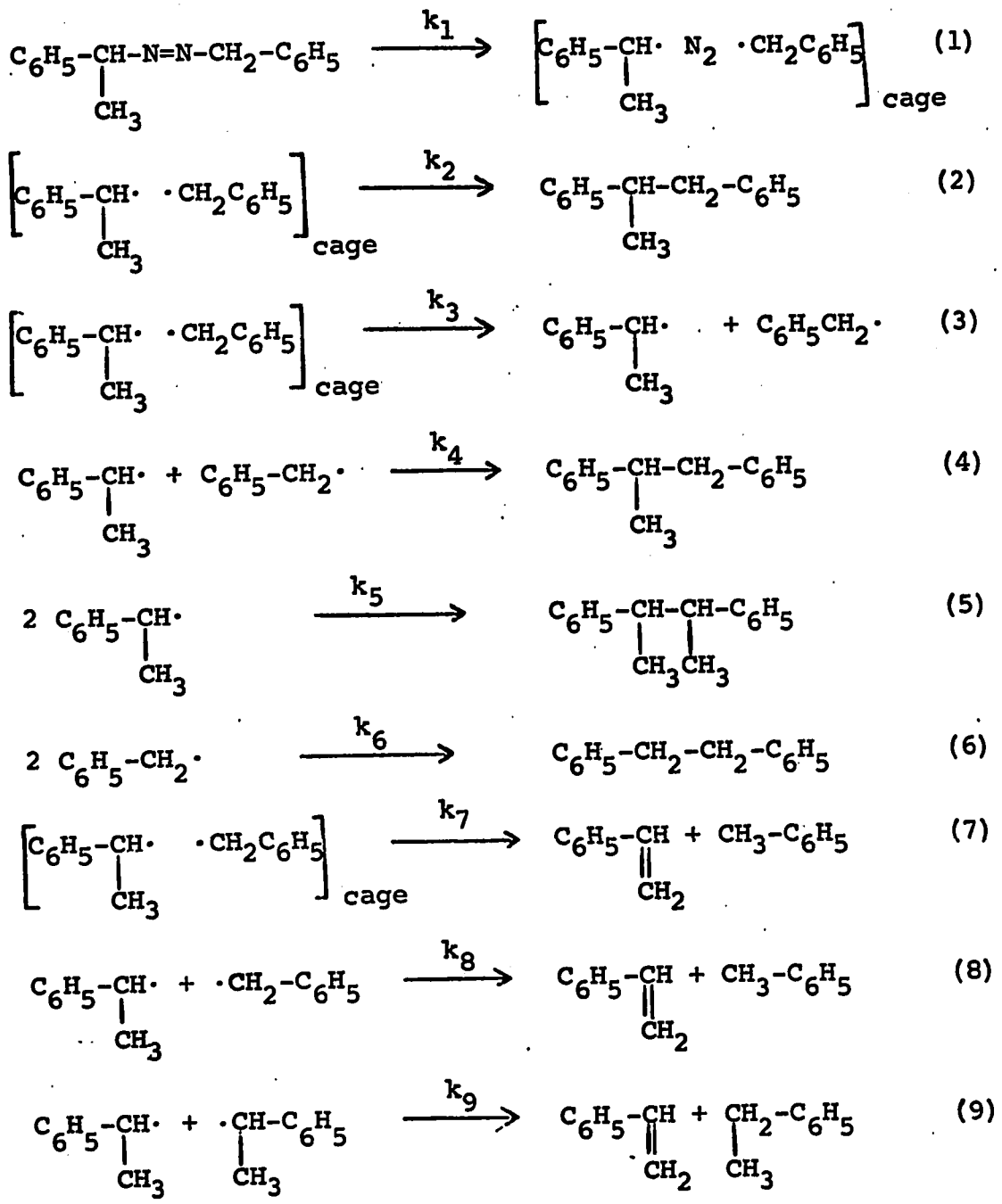
Product analysis has shown that all the expected products of the decomposition of 7 were obtained. The mechanism by which these products arise is shown in Scheme XI.

Equation (1) of this scheme shows the simultaneous generation of the radical pair in a solvent cage. No distinction is made between the cage in which the nitrogen molecule is included and one from which the nitrogen molecule has diffused, nor is any attempt made to differentiate between primary and secondary recombinations.

The two radicals in the solvent cage may either react together as shown in equations (2) and (7), or they may diffuse apart.

Radicals that have diffused from the cage may undergo random radical reactions on their diffusive excursions through the solvent. Hence an α-phenylethyl radical can couple with another α-phenylethyl radical to generate 19 and 20 or with a benzyl radical to give 13 and a benzyl radical can react with another benzyl radical to give bibenzyl. Also, an α-phenylethyl radical can react with another α-phenylethyl radical by a disproportionation process to yield ethylbenzene and styrene and an α-phenylethyl radical and a benzyl radical can disproportionate to yield toluene and styrene.

Scheme XI



The rate constants for the three coupling reactions outside the cage will, in all probability, be the same. The rate constants for radical radical coupling have been measured in only a few cases. Thus, for methyl radicals, the rate constant for coupling has been measured at 3.6×10^{10} $\underline{M}^{-1}$ sec^{-1} (102), for benzyl radicals, 3×10^{9} $\underline{M}^{-1}$ sec^{-1} (98), and for triphenylmethyl radicals, 3.6×10^{3} $\underline{M}^{-1}$ sec^{-1} (104). Bartlett has estimated the relative rate constants for the self coupling reactions of α-tetralyl, diphenylmethyl and cumyl radicals (38). He found that the rate constants for these are slower than the rate constant for methyl coupling by less than a factor of 10^2. From these results, it would appear that rate constants for radical - reactions are all extremely fast, except in cases like triphenylmethyl radicals where a large steric effect makes coupling difficult.

Since there is little difference between the rates and activation energies for a wide series of radical radical coupling reactions, it is a safe assumption that $k_4=k_5=k_6$ for the three coupling reactions in Scheme I, since the difference between the radical pairs, α-phenylethyl and α-phenylethyl, α-phenylethyl and benzyl, and benzyl and benzyl is so slight.

Since the radicals will react with each other in a random manner, they should give rise to a statistical

distribution of products. Assuming the disproportionation reactions to be negligible, ratio of bibenzyl: 13 : 19 + 20 formed outside the cage was expected to be 1 : 2 : 1.

The data in Table VI show that at high concentrations of 7 the relative amount of bibenzyl is much too small. In these cases, the benzyl radicals must be consumed by an alternate pathway. It is probable that the benzyl radicals are reacting with molecular species in the solvent. These may include 7 from which hydrogen abstraction occurs relatively easily (99). They may also include the reaction products, particularly styrene to which the benzyl radicals would add very rapidly. The faster rate of disappearance of benzyl radicals as compared with α-phenylethyl radicals must be a measure of a greater degree of reactivity and/or rate of diffusion of benzyl radicals.

Reduction of the concentration of 7 would tend to make these radical-molecule reactions less important. This has the effect of increasing the amount of bibenzyl formed, so that the ratio of 19 + 20/bibenzyl decreases from 2.5 to a limiting value of 0.9. Since the ratio is now less than one, this indicates that about 10% of α-phenylethyl radicals are disappearing by disproportionation.

It is interesting to note that at 132°C the ratio of 19 + 20/bibenzyl is close to one in spite of a fairly high concentration of 7. Since a much smaller amount of

isomerization to the hydrazones occurs at higher temperatures, it is possible that the hydrazones may have been responsible for the disappearance of the benzyl radicals in the low temperature runs.

The amounts of toluene and ethylbenzene formed could not be measured when low concentrations of 7 were decomposed, because the solvent peak in the g.l.c. chromatogram was so broad that it overlapped the peaks due to these products. At a concentration of 0.5 M at 110°C, the relative yields of toluene and ethylbenzene were 18% and 12%, respectively. This compares with yields of 2% for each at 132°C. The difference between the results at the two temperatures may be due in part to hydrogen abstraction from hydrazone which was formed in greater amounts at the lower temperature. It might also be due in part to a difference in the activation energy for the coupling and disproportionation reactions. Bartlett and Nelson (48) found that the activation energies for coupling and disproportionation in the reactions of cumyl radicals were fortuitously equal. Bartlett and McBride (37) found that the activation energy for disproportionation was greater by 2 kcal than that for coupling in the reactions of 3-methyl-2-phenyl-2-butyl radicals. It is not impossible that the activation energy for the disproportionation reactions in decomposition of 7 could be smaller than that

for coupling. In any event, it is unlikely that the ratio of disproportionation/coupling would be greater than 10%.

Cage Effects

Since coupling of radicals outside the cage is a random process, a new method is available for measurement of the cage effect without recourse to scavengers of any kind. The ratio of the products outside the cage will be bibenzyl : 13 : 19 + 20 = 1 : 2 : 1. By subtracting the sum of bibenzyl, 19 + 20 from 13, the amount of 13 formed in the cage is found. This is summarized in the following equation:

$$\% \text{ cage effect} = \frac{13 - (\text{Bibenzyl} + 19 + 20)}{13 + (\text{Bibenzyl} + 19 + 20)} \times 100$$

This has to be corrected for disproportionation products and the equation becomes:

$$\% \text{ cage effect} = \frac{(13 + A) - (\text{Bibenzyl} + 19 + 20 + B)}{(13 + A) + (\text{Bibenzyl} + 19 + 20 + B)} \times 100$$

Where A = amount of disproportionation between benzyl and α-phenylethyl radicals,

and B = amount of disproportionation between α-phenylethyl radicals.

Cage effects based on the data in Table VI, using the above equation, are to be found in Table VIII. Values of

TABLE VIII

Cage Effects Calculated from Product Distribution

Temp., °C	7 , M	Cage Effects, % *A=0% **B=0%	A=0% B=10%	A=10% B=0%	A=10% B=10%
110	0.5	28	25	33	30
	0.03	30.6	27.8	35	32.3
		41.8+	39+	46+	43.5+
	0.0063	26.6	24	31.4	29.1
		28.0	25.4	32.4	30.2
	0.0013	31.2	28.7	35.8	33.6
		26.4	24.0	31.2	28.9
132	0.13	24.8			
		22.8			

*A= fraction of benzyl and α-phenylethyl radical pairs that react by disproportionation.

**B= fraction of α-phenylethyl radical pairs that react by disproportionation.

\+ Anomalous result.

the cage effect based on different estimates for the extent of the disproportionation reactions are presented.

Since radicals outside the cage are disappearing by routes other than radical-radical reactions, an estimate of the cage effect by this method is expected to be high, particularly when the concentration of 7 is high. However, change in estimated cage effect with concentration is not as dramatic as might be expected. In fact, errors in measurement of peak areas seem to be the critical factor. This error arises because of the closeness of the four peaks on the chromatogram even under the best g.l.c. conditions. The sample size had to be kept small, otherwise an overlap in peaks occurred when large samples were used. With small peaks, the errors in the measurement of the areas are naturally increased.

Measurement of cage effects without using a scavenger has been performed by Seltzer and Hamilton (73). By decomposing a mixture of azobis-α-phenylethane-β,β,β-d_3 and its protio counterpart and analyzing for the products including the cross product by mass spectrometry, the cage effect is calculated based on the fraction of cross-product obtained. The cage effect obtained was 29% in toluene at 105°C. This compares with a value of 28% found by Greene for 1,1'-diphenylazoethane in benzene at 105°C (39).

Another method of calculating the size of the cage

effect in the present system was to use butanethiol as a scavenger. This scavenger operates by donating a hydrogen atom to radicals which escape the cage. This is shown in Scheme XII.

It becomes apparent that coupling product 13 and styrene are a measure of α-phenylethyl radicals which react inside the solvent cage and ethylbenzene is a measure of α-phenylethyl radicals which escape from the cage. Therefore, the cage effect is obtained from the following formula:

$$\% \text{ cage effect} = \frac{13 + \text{styrene}}{13 + \text{styrene} + \text{ethylbenzene}} \times 100$$

The quantity of styrene formed cannot be measured directly, but was not likely to exceed 10%. These cage effects have been calculated in Table IX assuming no disproportionation and 10% disproportionation. This makes only a small difference in the values obtained. The values obtained are reasonably close to those obtained in the absence of scavenger. The cage effect in pure butanethiol is considerably lower than those obtained for the other solvents. This is not interpreted as being due to interference with radicals in the solvent cage, but just a solvent effect. The cage effects, therefore, in pure benzene would be expected to be a little higher than those for a 1 M butanethiol solution.

Scheme XII

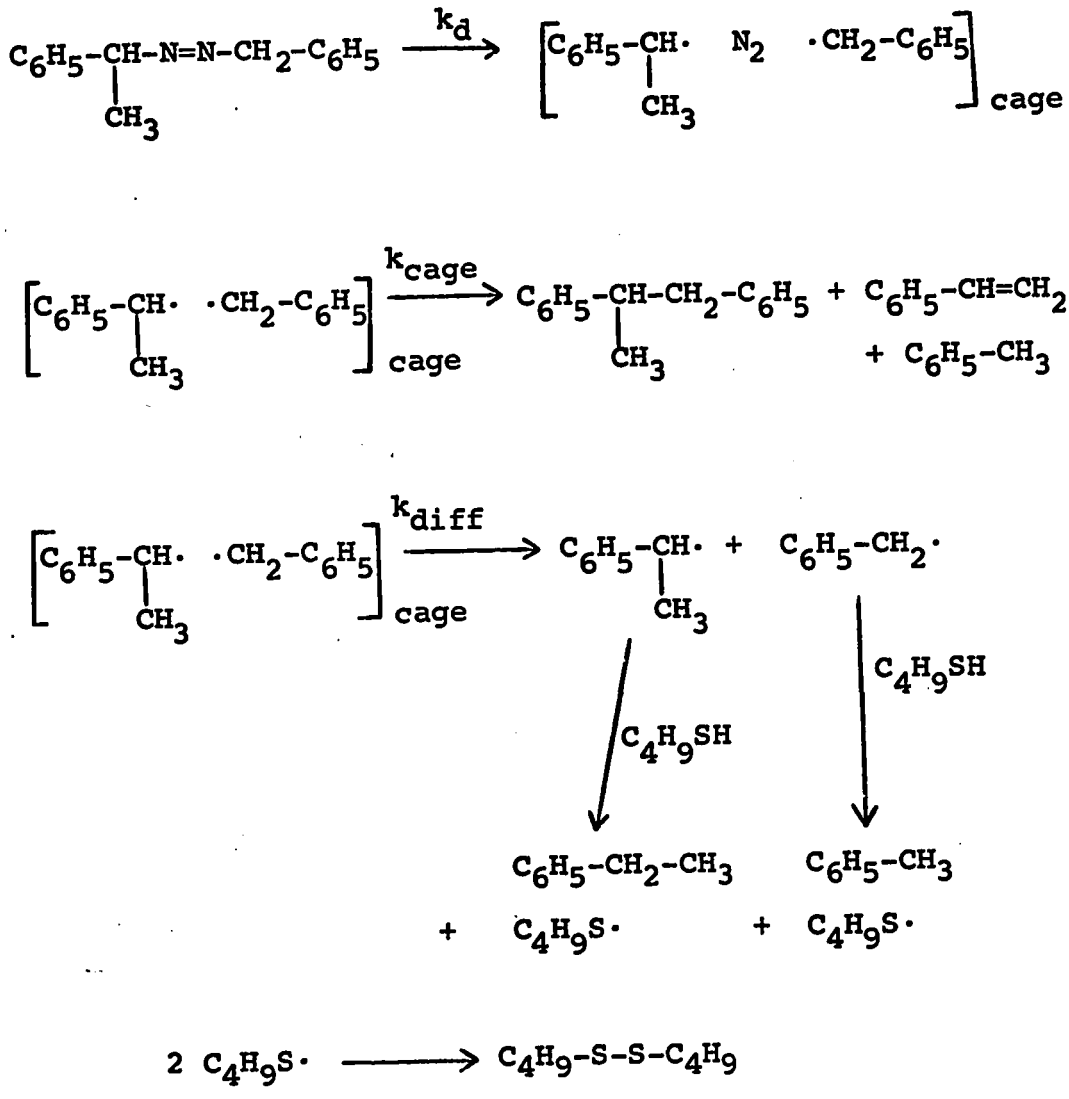


TABLE IX

Ratio of Ethylbenzene to 13 Formed on Decomposition of 7, in the Presence of Butanethiol. Calculation of Cage Effects.

Temp., °C	Solvent	$[C_4H_9SH]$, M	Ph-Et / 13	Cage Effect	*Corrected Cage Effect
110	Benzene	0.98	2.81	26.3	28.3
			2.69	27.0	29.0
			2.86	25.9	27.8
			2.86	25.9	27.8
		1.4	3.08	24.5	26.4
			3.08	24.5	26.4
			3.34	23.1	24.8
		3.1	3.38	22.8	24.6
			3.10	24.4	26.2
			3.44	22.5	24.2
			3.44	22.5	24.2
	Butanethiol	9.7	4.5	18.2	19.7
			4.75	17.8	18.8
			5.75	15.0	16.1
			5.0	16.7	18.1
115	Cyclohexane	1.3	2.4	29.4	31.5
108	Chlorobenzene	1.1	2.30	30.3	32.4
132	Benzene	1.1	3.5	22.2	22.2
			3.7	21.3	21.3

* Assuming 10% disproportionation in the cage reaction.

In fact, by going to larger concentrations of butanethiol in benzene, a range of cage effects should be observed. Since the ratio of ethylbenzene to 13 was measured for a number of concentrations of butanethiol, it was decided to test this by plotting cage effect against mole fraction of benzene. This is shown in Figure III. It would be necessary to have many more points at higher butanethiol concentrations before it could be definitely said that the relationship of mole fraction of benzene to cage effect is a linear one. The points obtained, however, deviate from the straight line by less than 1% in the cage effect. The cage effects for the other two solvents are not much different from those observed for benzene.

In using this method to calculate the cage effect, it is assumed that butanethiol will react with all radicals escaping the cage by donating a hydrogen atom to them. It is further assumed that the butanethiyl radicals produced will be sufficiently stable that they will only undergo coupling reactions with each other.

The rate constant for abstraction of hydrogen from benzyl mercaptan by benzyl radicals was calculated to be 5.1×10^4 $\underline{M}^{-1}$ sec^{-1} (98). This is very much slower than the rates of the radical coupling reactions but the differences in concentration between the radicals and butanethiol should ensure that all radicals escaping the cage are captured.

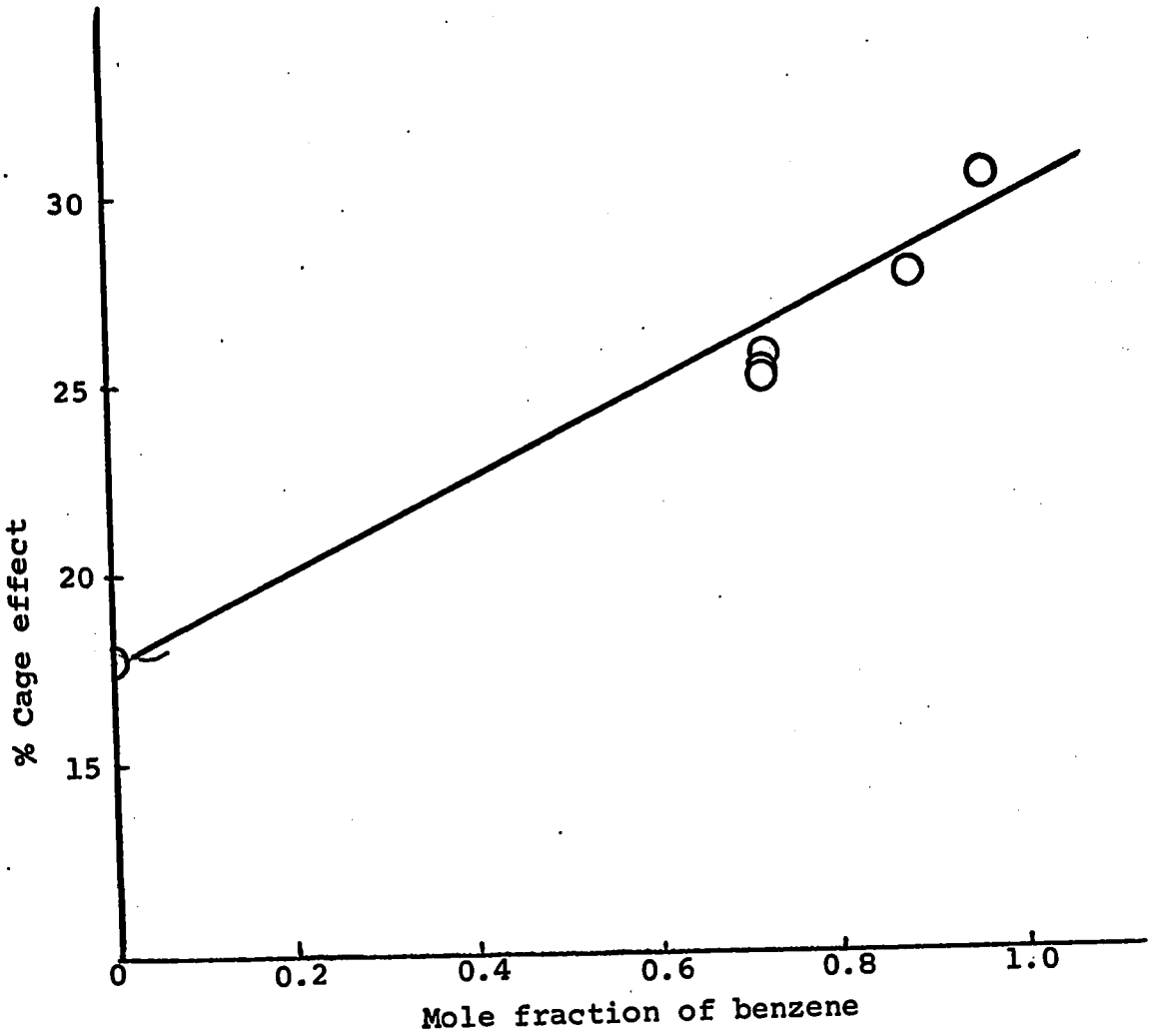


Figure III. Variation of cage effect in benzene-butanethiol solvent with change in the mole fraction of benzene.

In the case of the decomposition of 7, scavenging of the radicals by 1 M butanethiol is efficient. This is known since none of the three symmetrical coupling products that are formed exclusively outside the cage are present in the reaction mixture.

Bartlett and Nelson used this method to calculate the cage effect in the decomposition of azocumene (48). They used thiophenol as scavenger and obtained the same results with it as they got from other methods.

Hammond and coworkers (105) found butanethiol to be an efficient scavenger of radicals generated in the decomposition of AIBN, even when the butanethiol is used in stoichiometric amounts.

While it appears that butanethiol may be a good enough scavenger to consume all radicals escaping the cage it is still necessary to know whether or not the thiyl radicals are undergoing reactions other than coupling with each other. It is necessary to know this since calculation of the cage was based on product analysis. It has already been stated that thiyl radicals can abstract a hydrogen atom from the α-carbon of an azo compound (99). It is also known that butanethiyl radicals generated by photolysis will abstract a hydrogen atom from cumene (106), and less readily from ethylbenzene and toluene. It is therefore possible that butanethiyl radicals will abstract

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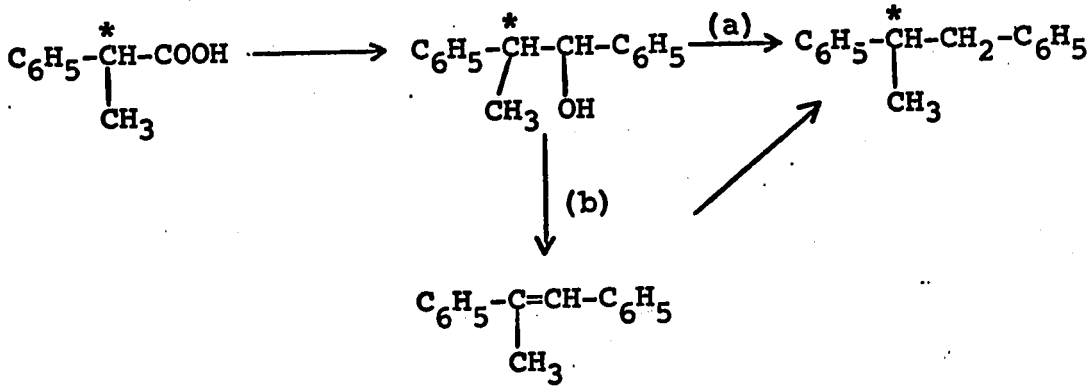
a hydrogen atom from toluene, ethylbenzene or coupling product in the decomposition of 7. In the presence of a large excess of butanethiol, it is probable that such a radical would quickly abstract a hydrogen atom from a molecule of butanethiol. However, a fraction of the radicals generated in this way could give rise to other products by coupling with, e.g., a thiyl radical. Loss of some of the product through hydrogen abstraction by thiyl radicals would be expected to be insignificant. Even if such a process was going on loss of ethylbenzene and 13 would probably be in proportion to their concentrations so that the error introduced in calculating the cage effect is negligible.

Stereochemical studies

In the presence of butanethiol, only coupling product 13 is formed. This has been found to have been formed with about 10% net retention of configuration. This figure is based on the optically pure hydrocarbon having an optical rotation of $[\alpha]_D^{25} = -80.5^\circ$ as measured in this work. Other values for the rotation of optically pure 13 have been reported as -76.7°, $+76.3^\circ$ (89) and -63.5° (88). The value of -63.5° was obtained from the hydrogenolysis of 1,2-diphenyl-1-propanol which had been synthesized from optically pure hydratropic acid as shown in Scheme XIII.

Scheme XIII



While the hydrogenolysis does not in principle affect the asymmetric centre of hydrocarbon, it is possible that the alcohol might undergo an elimination-hydrogenation sequence as shown in route (b) of Scheme XIII. This would lead to some racemization of 13. This is a plausible explanation for the lower rotation obtained if the severe conditions used, (200°C, over copper chromium oxide), and the ease of dehydration of a substrate of this kind are considered. The rotation of $[\alpha]_D^{25} = -76.3^\circ$ was also obtained by hydrogenolysis of threo-2,3-diphenyl-1-propanol. In this case the conditions used were much milder (Raney nickel, refluxing ethanol). Nevertheless, the same argument holds. The value of $[\alpha]_D^{25} = +76.3^\circ$ was obtained by hydrogenolysis at an asymmetric centre (89). No case has hitherto been reported in which hydrogenolysis has proceeded with complete retention of configuration. The

route by which (+)-13 was synthesized involved several intermediates which were used in the stereospecific syntheses of (-)-13 carried out in this work. (See Schemes VIII and IX.) The optical rotations of these intermediates were close to those reported in this work despite the use of different concentrations and solvents. They are, however, 6% and 14% lower than those obtained in this work.

The rotation of $[\alpha]_D^{25} = -80.5^o$ for optically pure (-)-13 would, therefore, seem to be the most accurate and was used to calculate the degree of retention of configuration of (-)-13 obtained from the decomposition of (-)-7.

The results of the stereochemical experiments are shown in Table VII. While the net retention of configuration in the presence of butanethiol is about 10%, it was much smaller than this in the absence of scavenger. This was because a fraction of (-)-13 had been formed outside the cage and, since this fraction resulted from freely diffusing radicals, it was completely racemic.

By comparing the rotations of (-)-13 in the presence of scavenger with the rotation obtained in the absence of scavenger, the fraction of (-)-13 formed inside the cage, F, is known. If we make the assumption made previously, that radicals outside the cage couple in a random manner, then amounts of products formed outside the cage would be:

13, (1-F); bibenzyl, (1-F)/2; 19 + 20, (1-F)/2. Therefore, total amount of product outside the cage would be: 2(1-F), and

$$\% \text{ cage effect} = \frac{F}{2(1-F) + F} \times 100$$

$$\text{where } F = \frac{[\alpha]_D^{25} \text{ without scavenger}}{[\alpha]_D^{25} \text{ with scavenger}}$$

Since some of the radicals outside the cage are consumed by processes other than radical-radical coupling, the cage effect as calculated by this method will be anomalously high. This defect has already been noted earlier for the calculation of cage effects from product distribution in the absence of scavenger. However, the defect is worse in this case, since the product distribution is based entirely on one coupling product, instead of three. Since benzyl radicals are the ones which are being consumed more rapidly, coupling products which arise from these will be more seriously effected. This means that bibenzyl and 13 will be present in smaller quantities. 19 + 20 on the other hand will be present in greater than expected yields, because some of the α-phenylethyl radicals which should have combined with benzyl radicals will give rise to 19 + 20 instead. The excess of 19 + 20 helps offset the shortage of bibenzyl and 13 in the

previous method. However, in the present method, this excess of 19 + 20 cannot be taken into consideration. The cage effects calculated by this method are presented in Table X and are as expected, higher than obtained by the other methods.

It is interesting to note that the application of this method to the data of Greene and Berwick (39) gives a value for the cage effect of 32.8% in the decomposition of 1,1'-diphenylazoethane in benzene at 105°C. This compares with 28% for the cage effect as calculated by Greene from product analysis.

Another effect which would tend to make the cage effect bigger, is racemization of (-)-7 and/or (-)-13 during the scavenged reaction. If this takes place, then the specific rotation in the presence of scavenger will be lower, e.g., 10% racemization of (-)-13 by this mechanism will cause a 4.5% drop in the cage effect in benzene at 110°C - from 37.3 to 32.8%. How much of the increase in the calculated cage effect is due to each effect is not known.

Control experiments

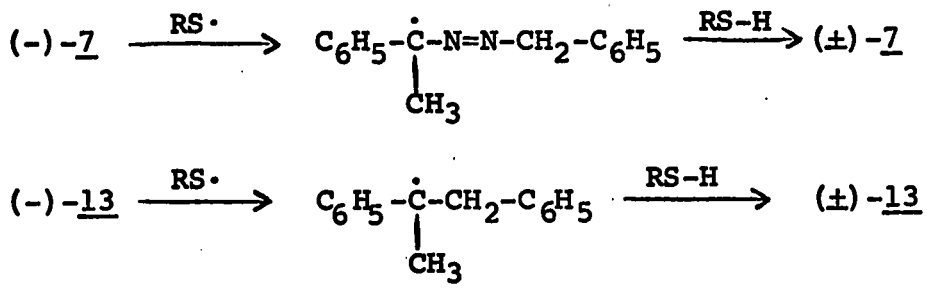
These were conducted to ascertain whether or not the high degree of racemization was due simply to loss of asymmetry on the part of the α-phenylethyl radical or

TABLE X

Cage Effects as Calculated from the Optical Rotations of (-)-13

Solvent	Temperature °C	Cage Effect, %
Benzene	132	21.7
Benzene	110	37.3
Chlorobenzene	107	40.5
Cyclohexane	115	40.7

whether it was due to any extent to reversible transfer of the hydrogen atom from the asymmetric centre of (-)-7 and/or (-)-13 to a thiyl radical. This is outlined in the following equations. In the hydrocarbon control experiment,



1,1'-diphenylazoethane was decomposed in butanethiol in the presence of (-)-13. The decomposition of this azo compound was used as a convenient method of generating thiyl radicals. The recovered (-)-13 was found to be 20% racemized. If we make the assumption that the reaction conditions in the control were the same as in the original experiment in which (-)-13 was generated from (-)-7, this means that the degree of racemization of (-)-13 as a result of reaction of (-)-13 with thiyl radicals would be 10%.

In the control experiment on (-)-7, the degree of racemization of (-)-7 was 24%. The reaction was stopped after 22% reaction as determined from the rate constant for decomposition. However, when the isomerization reaction is taken into consideration, this corresponds to about 50% reaction. The degree of racemization seemed to be high.

However, this reaction was difficult to carry out and it is possible that some of the racemized azo compound may have arisen from racemic hydrazone and/or the mixed azine which was probably formed during the reaction.

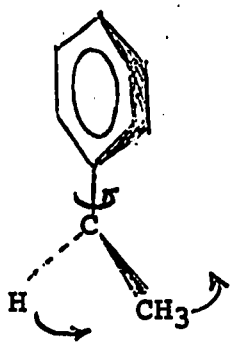
The hydrocarbon formed in this control experiment was isolated and was found to have the same degree of retention as that isolated after completion of the reaction.

If the degree of racemization had been as high as the optical rotation of recovered (-)-7 would imply, the hydrocarbon isolated from this control experiment would be expected to have a higher rotation than that of hydrocarbon isolated after decomposition of azo compound had reached completion. Since this is not the case, it would appear that racemization was somewhat less than 24%.

Interpretation of data of stereochemical experiments

It is evident that the degree of racemization of the recovered hydrocarbon, 13, is due largely to the loss of asymmetry on the part of the α-phenylethyl radical in the solvent cage. This means that in spite of the fact that the benzyl radical is ideally situated relative to the α-phenylethyl radical for coupling to occur with retention of configuration, a large fraction of the α-phenylethyl radicals can reorientate themselves so that they present the opposite face of the radical before coupling can occur.

Racemization of the product could, therefore, arise in two ways. If stabilization of the benzylic radical is negligible, racemization could occur by rotation about the carbon-phenyl bond as depicted:



However, if internal rotation of this type is prevented by partial double bond character of the bond in question, due to conjugation, then racemization can occur by rotation of the radical as a whole about an axis in the plane of the conjugated radical. No data is available on the rate of internal rotation of benzylic free radicals about the carbon-phenyl bond. However, for compounds, such as formamides in which there is partial double bond character due to conjugation, greatly reduced rates are observed compared to those which would be predicted on the basis of steric interference to rotation (107).

Since the rate of internal rotation of freely rotating compounds is not much different from the rates of molecular rotation, the latter only need to be considered.

Scheme XIV depicts the total behavior of the radical pair after generation and includes the racemization process. The ratio of (-)-13 to (+)-13 can be worked out in terms of the rate constants for the various reactions.

This involves invoking the steady state approximation for the radical pairs I and II.

$$\text{Thus } \frac{dII}{dt} = 0 = k_r[I] - (k_r + k_c + k_{diff} + k_{disp})[II]$$

$$\frac{[I]}{[II]} = \frac{k_r + k_c + k_{diff} + k_{disp}}{k_r}$$

$$\frac{(-)\text{-}13}{(+)\text{-}13} = \frac{k_c[I]}{k_c[II]} = 1 + \frac{k_c + k_{diff} + k_{disp}}{k_r}$$

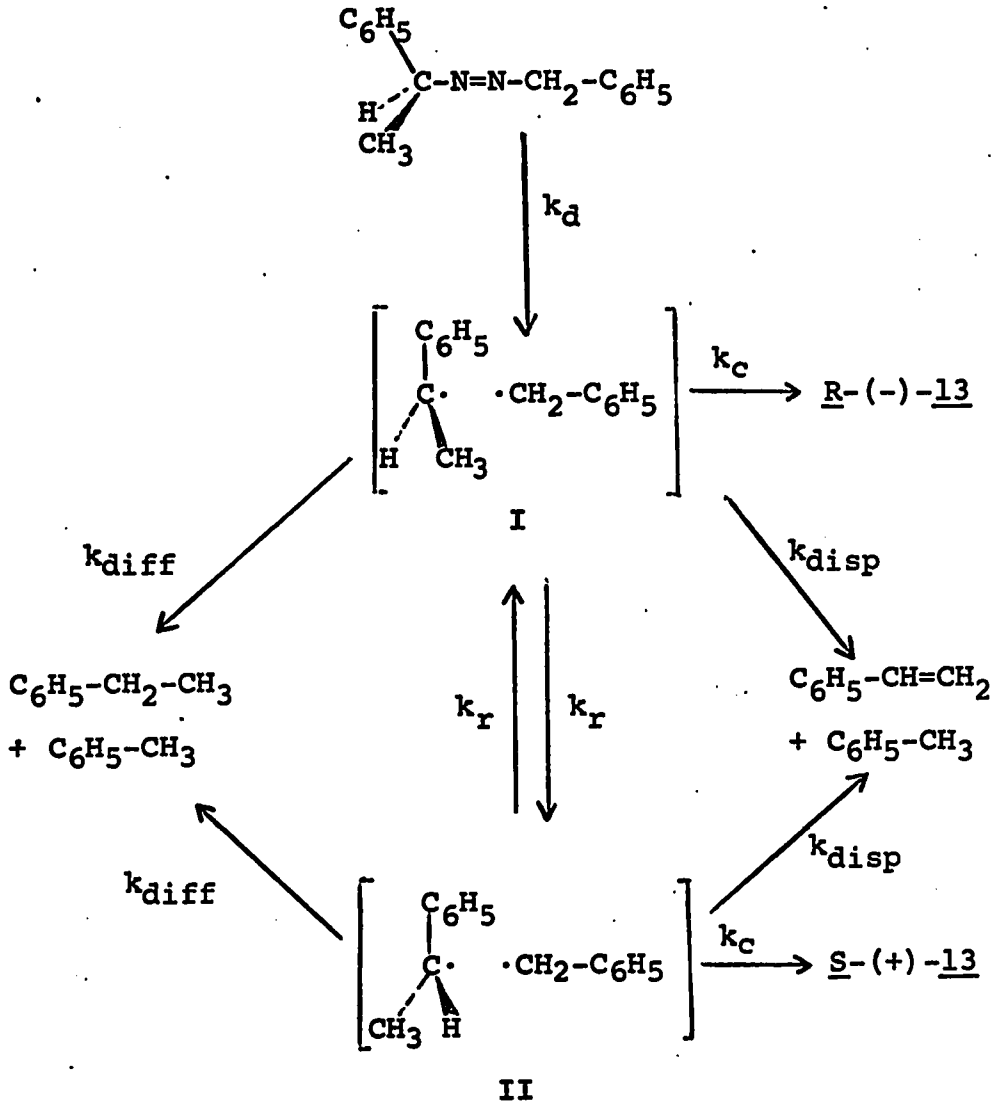
$$\frac{(-)\text{-}13}{(+)\text{-}13} - 1 = \frac{k_c + k_{diff} + k_{disp}}{k_r}$$

The rate constants, k_{diff} and k_{disp}, can now be expressed in terms of k_c, F, the cage effect, and f, the fraction of disproportionation within the cage. F and f can be expressed in terms of the rate constants thus:-

$$F = \frac{k_c + k_{disp}}{k_c + k_{disp} + k_{diff}}$$

$$\text{and} \qquad f = \frac{k_{disp}}{k_c + k_{disp}}$$

Scheme XIV


C6H5
C-N=N-CH2-C6H5
H
CH3
kd
C6H5
C·
·CH2-C6H5
H
CH3
kc
R-(-)-13
I
kdiff
kdisp
C6H5-CH2-CH3
+ C6H5-CH3
kr
kr
C6H5-CH=CH2
+ C6H5-CH3
kdisp
kdiff
C6H5
C·
·CH2-C6H5
CH3
H
kc
S-(+)-13
II

Therefore, $k_{diff} = (k_c + k_{disp})\frac{(1-F)}{F}$, and

$$\frac{(-)\text{-}\underline{13}}{(+)\text{-}\underline{13}} - 1 = \frac{k_c + k_{disp}}{k_r} \cdot \frac{1}{F}$$

Since $k_{disp} = \frac{f}{1-f} \cdot k_c$

Then $$\frac{(-)\text{-}\underline{13}}{(+)\text{-}\underline{13}} - 1 = \frac{k_c}{k_r} \cdot \frac{1}{F} \cdot \frac{1}{(1-f)}$$

Therefore, $$\frac{k_c}{k_r} = \frac{(-)\text{-}\underline{13}}{(+)\text{-}\underline{13}} - 1 \cdot F(1-f)$$

This ratio, k_c/k_r, determines the degree of retention that will be observed in any system. The results for the system studied are presented in Table XI. It can be seen that the ratio k_c/k_r varies very little on going from 0% to 10% disproportionation. These results indicate that for each time the radicals couple, the α-phenylethyl radical will rotate ten to twenty times.

Activation energy for coupling

Since we have the ratio of the rate of coupling to the rate of rotation, it is possible to calculate the activation energy for coupling relative to that of rotation.

TABLE XI

Relative Rates of Coupling and Rotation of the α-Phenylethyl Radical

Solvent	Temp, °C	Cage Effect, %	k_c/k_r*
Benzene	132	22	0.057
	110	26.3, 28.3	0.061, 0.059
Butanethiol	110	16.9, 18.2	0.071, 0.069
Chlorobenzene	107	30.4, 33.4	0.091, 0.090
Cyclohexane	115	29.7, 31.7	0.071, 0.070

* The first column assumes no disproportionation, the second 10% disproportionation in the cage reaction.

Thus the equation for activation of coupling is:

$$\log \frac{(k_c)_2}{(k_c)_1} = \frac{E_a^c}{2.3R} \cdot \frac{(T_2-T_1)}{T_2T_1}$$

and for rotation is

$$\log \frac{(k_r)_2}{(k_r)_1} = \frac{E_a^r}{2.3R} \cdot \frac{(T_2-T_1)}{T_2T_1}$$

$$\log \frac{(k_c)_2}{(k_c)_1} - \log \frac{(k_r)_2}{(k_r)_1} = \frac{E_a^c - E_a^r}{2.3R} \quad \frac{(T_2-T_1)}{T_2T_1}$$

$$\log \frac{(k_c)_2}{(k_r)_2} - \log \frac{(k_c)_1}{(k_r)_1} = \frac{\Delta E_a}{2.3R} \cdot \frac{(T_2-T_1)}{T_2T_1}$$

Since the ratio k_c/k_r is known at two temperatures, ΔE_a can be found. This was found to be in the neighborhood of 0.7 kcal. If the activation energy for the rotation process were known, one would then have an estimate of the activation for coupling. The activation enthalpy has been measured for molecular rotation for a number of compounds by Pitt and Smyth (108). They find values for ΔH^* in the region 2.0 - 2.6 kcal. If racemization is taking place by bond rotation, the activation energy for free rotation is in the region of 3.0 kcal/mole. This means that the activation energy for coupling would seem to be in the neighborhood of 2.7 - 3.3 kcal/mole.

EXPERIMENTAL

All melting points and boiling points reported are uncorrected. Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian Analytical Spectrophotometer, Model A-60, using tetramethylsilane (TMS) as internal standard. Ultraviolet spectra were recorded on a Bausch and Lomb Spectronic 600 Spectrophotometer. Optical rotations were measured with a Rudolf Polarimeter Model 80, and with a Perkin Elmer 141 Polarimeter. Optical rotatory dispersion (o.r.d.) spectra were measured on a Model ORD/UV-5 Japan Spectroscopic Company spectropolarimeter. Refractive indices were measured on a Bausch and Lomb Abbe-3L Refractometer. Gas liquid chromatographic analyses were done on an Aerograph A90-P3 fractometer using helium as the carrier gas.

Purification of Solvents

Benzene

Commercial benzene was shaken with concentrated sulfuric acid until the sulfuric acid layer was colorless. The benzene layer was then washed with water and with sodium carbonate solution. The benzene was then dried over anhydrous sodium carbonate. It was distilled from sodium metal over a 6" Vigreux column. Finally, it was redistilled over a Nester Faust teflon spinning band

column, a middle cut of the distillate being taken.

Cumene

The same procedure was adopted for the purification of commercial cumene as for commercial benzene, except that the final distillation was carried out on a four foot Podbielniak column instead of a spinning band column. A middle cut of the distillate was collected and stored in a stoppered bottle at $0^{o}C$ in the dark.

Chlorobenzene

Commercial chlorobenzene was shaken with sulfuric acid, washed and dried over anhydrous sodium carbonate as reported for benzene. This was then distilled over a 6" Vigreux column taking a middle cut of the distillate. This fraction was redistilled over a spinning band column, again taking a middle cut of the distillate.

Cyclohexane

The same procedure as used for benzene was employed.

1-Butanethiol

A small piece of sodium was added to commercial 1-butanethiol and allowed to react with it. This reaction mixture was then distilled over a 6" Vigreux column under an atmosphere of nitrogen. A middle cut of the distillate was collected and this was stored under nitrogen.

Neutralization of apparatus

All glassware employed in the oxidation of 1-benzyl-2-α-phenylethylhydrazine and in the subsequent handling of the azo compound, 7, was neutralized as follows. The glassware was dipped in concentrated sulfuric acid. It was then thoroughly washed with distilled water after which it was immersed in concentrated ammonia solution for several hours. It was left to dry for several hours in an oven at 110°C.

The stainless steel bombs used in the decomposition of (-)-7 were washed thoroughly with ether, ethanol and then distilled water. They were then immersed in concentrated ammonia solution, after which they were rinsed with distilled water and baked in an oven at 110°C.

Synthesis of acetophenone ketazine, 1

To 121 g (1 mole) of acetophenone in 100 ml of ethanol was added 30.5 g (0.5 mole) of 85% solution of hydrazine hydrate and 5 ml of glacial acetic acid. Heating the reaction mixture under reflux for a prolonged period was found to be unnecessary since the product crystallized out of the solution on standing. An almost quantative yield of the crude acetophenone azine as a yellow solid was obtained (116 g, 98% yield), m.p. 116-22° (lit (109) 122°). The product was not recrystallized but was used directly in

the next step of the synthetic sequence.

α-Phenylethylhydrazine oxalate, 3

To a solution of 23.6 g (0.1 mole) of 1 in 230 ml of ethyl acetate was added 1.0 g of 5% palladium on charcoal. Hydrogenation of the solution was carried out at an initial pressure of hydrogen of 30 p.s.i. on a Paar Hydrogenation Apparatus. After the uptake of 1 mole equivalent of hydrogen, hydrogenation was stopped. The reaction mixture was filtered. Ethyl acetate was removed on a rotary evaporator under reduced pressure. The yellow oily residue was treated with 12.7 g (0.1 mole) of oxalic acid in 50 ml of 95% ethanol and 50 ml of diethyl ether. The reaction mixture was stirred overnight. The product, α-phenylethylhydrazine oxalate, 3, slowly precipitated from solution. This was filtered off and washed with ether to remove traces of unreacted acetophenone azine. The product was a white solid, m.p. 162-70° (lit (77) 173°). The yield of the crude oxalate was 15 g (66%). Compound 3 was used directly without further purification.

α-Phenylethylhydrazine, 4

To a solution of 12.8 g (0.23 mole) of potassium hydroxide in 115 ml of water was slowly added 27 g (0.12 mole) of 3 over fifteen minutes under an atmosphere of nitrogen. The reaction mixture was stirred for a further

thirty minutes, and was then extracted with methylene chloride repeatedly. The extracts were combined and dried over anhydrous potassium carbonate. The solvent was removed and the residue distilled under reduced pressure to yield a clear liquid, b.p. 74° (1 mm) n_D^{25} 1.5435 (lit (77) b.p. 75° (1.1 mm), n_D^{25} 1.5436). The yield of 4 obtained was 11.8 g (87%). The n.m.r. spectrum (CCl_4) had the following peaks: τ2.80 (singlet, 5.0 H) due to phenyl hydrogens, τ6.4 (quartet, 1.1 H, J = 6.5 Hz) due to the methine hydrogen, τ6.95 (singlet, 3.0 H) due to the hydrogens on the nitrogens, τ8.80 (triplet, 3.0 H, J = 6.5 Hz) due to the methyl hydrogens.

Benzaldehyde α-Phenylethylhydrazone, 5

To 6.8 g (0.05 mole) of 4 in 80 ml of diethyl ether was added 6 g of anhydrous magnesium sulfate. This was stirred while 5.5 g (0.052 mole) of freshly distilled benzaldehyde in 20 ml of ether was added over thirty minutes. The reaction mixture was stirred overnight. It was then filtered, and the ether evaporated off. A light yellow oil was obtained. This was dissolved in pentane and a white solid was obtained m.p. 50-4°.

The n.m.r. spectrum (CCl_4) of the oil was identical to that obtained for the solid and showed the following peaks: τ2.5-3.1 (multiplet, 11.4 H) due to the phenyl

hydrogens and the hydrogen on the carbon nitrogen double bond, τ4.6 (broad singlet, 0.93 H) due to the hydrogen on the nitrogen, τ5.65 (quartet, 0.93 H, J = 6.5 Hz) due to the methine hydrogen and τ8.57 (doublet, 3.0 H, J = 6.5 Hz) due to the methyl hydrogens.

Alternative synthesis of benzaldehyde α-phenylethyl hydrazone, 5

To a one litre flask fitted with reflux condenser, glass stirrer and a dropping funnel was added 5.5 g of lithium metal in 100 ml of anhydrous ether and 50 g (0.3mole) of methyl iodide in 200 ml of ether was added dropwise over thirty minutes while the reaction flask was being cooled in an ice-salt bath. To the reaction mixture was added dropwise 42 g (0.19 mole) of benzalazine in 600 ml of ether. The reaction mixture was stirred for twelve hours and then neutralized by the addition of an ice-cold solution of ammonium chloride. There was rapid evolution of gas initially. The ether layer was separated and dried over magnesium sulfate. The ether was evaporated and the residue distilled under reduced pressure, b.p. 144-148^{o} (0.6-0.7 mm). The n.m.r. spectrum of 5 prepared by this method was identical to that obtained by the method above. The crude product before distillation deposited crystals of the starting material benzalazine on standing,

so the reaction was not complete. The yield obtained in the reaction was 40%.

1-Benzyl-2-α-phenylethylhydrazine oxalate, 8

Hydrazone, 5, (69 g, 0.31 mole) generated in ether solution as described in Method A was hydrogenated directly on a Paar Hydrogenation Apparatus using 1.5 g of 5% palladium on charcoal until no further uptake in hydrogen was observed. The reaction mixture was filtered under an atmosphere of nitrogen and treated with 39 g of oxalic acid in a minimum of hot ethanol (120 ml). The oxalate salt, 8, precipitated immediately, yielding 72 g of product (74%). After four recrystallizations, the melting point was 180-3°.

Anal. Calcd. for 1:1 base: acid, $C_{17}H_{20}N_2O_4$: C,64.54; H,6.40; N,8.86

Calcd. for 2:1 base: acid, $C_{32}H_{38}N_4O_4$: C,70.82; H,7.06, N,10.32

Found: C,66.30; H,6.58; N,9.63

1-Benzyl-2-α-phenylethylhydrazine, 6

To 28 g (0.5 mole) of potassium hydroxide in 125 ml of water was added slowly 60 g of recrystallized oxalate, 8, under an atmosphere of nitrogen. The aqueous layer was extracted repeatedly with methylene chloride and the combined organic layers were dried over anhydrous sodium carbonate. The methylene chloride was removed on a rotary evaporator

and the residue distilled under reduced pressure, b.p. 135° (0.5 mm) yielding 41.8 g (95%) of a viscous colorless liquid, n_D^{25} 1.5685. The n.m.r. spectrum (CCl_4) had these peaks: τ 2.83 (two overlapping singlets, 10.0 H) due to the phenyl hydrogens, τ6.16 (quartet, J = 7.0 Hz) and τ6.28 (singlet, total 3.07 H) due to the methine and methylene hydrogens, and τ6.95 (broad singlet, 2.0 H) due to the hydrogens on the nitrogen atoms and τ8.79 (doublet, 2.94 H, J = 7.0 Hz) due to the methyl hydrogens.

Resolution of 6

A solution of 108 g (0.48 mole) of 6 was added to a hot solution of 96 g (0.48 mole) of camphoric acid in 300 ml of ethyl acetate. The mixture was cooled to 5° overnight. Crystals of the camphorate precipitated. These were filtered off and washed with ether. The yield of salt was 115 g and the rotation was $[\alpha]_D^{25}$ = +11.2° (c = 3.8, methanol). The salt was recrystallized twice more and the yields of salt and the rotations obtained were 55 g, $[\alpha]_D^{25}$ = +2.73 (c = 1.7, methanol) and 30 g m.p. 95-105° $[\alpha]_D^{25}$ = -2.50 (c = 1.3, methanol). The physical properties of the salt showed no appreciable change on further recrystallization.

To 0.7 g of potassium hydroxide in 4 ml of water was added 2 g of the camphorate salt under an atmosphere of nitrogen. (-)-6 was extracted from the reaction mixture

by methylene chloride. After drying and distilling off the solvent, the residue was distilled, b.p. 110° (0.1-0.2 mm), yield 0.7 g. The rotation of (-)-6 was measured, α_D^{25} = -50.5° (neat, 1 1 dm).

1,1'-Diphenyl-1-methylazomethane, 7

All glass-ware used in this step of the synthesis was neutralized in order to minimize the risk of isomerization of the azo compound to the corresponding hydrazones.

To a 50 ml saturated solution of sodium bicarbonate was added 5 g of recrystallized 1-benzyl-2-α-phenylethyl-hydrazine oxalate, 8, under an atmosphere of nitrogen. Evolution of carbon dioxide was observed and stirring was continued until no further gas evolution took place. The reaction mixture was extracted with ether. The ether extracts were dried over anhydrous sodium carbonate. The ether solution was then placed in a flask which was stoppered with a serum cap. Oxygen was passed into the flask by means of a syringe needle and a pressure of 5 p.s.i. of oxygen was maintained in the flask. Oxygenation was carried out overnight. The ether solution was then extracted several times with distilled water, and dried over sodium carbonate. The ether was removed on a rotary evaporator at reduced pressure. Rotating was maintained for several hours. The resulting yellow oil was found to be 1,1'-diphenyl-1-methylazomethane by its n.m.r. spectrum ($CDCl_3$).

The peaks observed were: τ2.80 (multiplet, 10.6 H) due to the phenyl hydrogens, τ5.18 (singlet) and τ5.42 (quartet, J = 7.0 Hz) due to the methylene and methine hydrogens (combined area 2.9 H) and τ8.50 (doublet, 3.1 H, J = 7.0 Hz) due to the methyl hydrogens. No extraneous peaks were found in the n.m.r. spectrum. The refractive index of 7 was found to be n_D^{25} 1.5598.

U.v. analysis

A u.v. spectrum of a benzene solution of 7 was taken. This showed two maxima. The one due to azo compound occurred at 3580°A. The second absorption believed to be due to the corresponding hydrazones occurred at 2800-3000°A. The absorbance at 3580°A, at concentrations of 1.47, 0.735, 0.368, 0.184 and 0.092 x 10^{-2} M was found to be 5.88, 2.35, 1.53, 1.23 and 1.1 respectively. From these data, 7 was shown to obey Beer's Law and was found to have an extinction coefficient of 50 at 3580°A. The absorbance at 2800-3000°A was comparable to that at 3580°A at various concentrations.

Anal. Calcd. for $C_{15}H_{16}N_2$: C,80.32, H,7.19, N,12.49

Found: C,80.21, H,6.99, N,12.67

(-)-1,1'-Diphenyl-1-methylazomethane, (-)-7

This was obtained from the camphorate salt of (-)-6 in the same manner as racemic 7 is obtained from the oxalate salt. The optical rotation of (-)-7 was taken: $[\alpha]_D^{25} = -152^\circ$ (c 1.06, benzene). The o.r.d. spectrum of (-)-7 was taken in cyclohexane at a concentration of 1.79 x 10^{-2} M.

$[\Phi]_{600}$	-209°	$[\Phi]_{400}$	-1676°	$[\Phi]_{350}$	$+726^\circ$
$[\Phi]_{500}$	-377°	$[\Phi]_{380}$	-2528°	$[\Phi]_{330}$	$+2095^\circ$
$[\Phi]_{450}$	-628°	$[\Phi]_{355}$	$\pm 0^\circ$	$[\Phi]_{320}$	$+1732^\circ$

Synthesis of (-)-7 from α-phenylethylamine

Resolution of α-phenylethylamine, 10

The resolution of 10 was carried out as reported by Thielacker (86). From 250 g of dl-α-phenylethylamine was obtained 65 g of (-)-α-phenylethylamine, (-)-10, $\alpha_D^{25} = -36.6^\circ$ (neat, 1 1 dm).

(-)-α-Phenylethylhydrazine, (-)-4

This was synthesized by a modification of the method used by Gösl and Meuwsen to synthesize simple hydrazines (82). To a stirred mixture of 80 g (0.67 mole) of (-)-α-phenylethylamine $\alpha_D^{25} = -36.6^\circ$ (neat, 1 1 dm), and 500 ml of water was added 25 g (0.45 mole) of potassium

hydroxide. Freshly prepared hydroxylamine-O-sulfonic acid (110) (25 g, 0.2 mole) dissolved in a minimum of water was added dropwise. Heat was evolved and the temperature of the reaction mixture rose from 25° to 50°C over the period of addition (thirty minutes). The reaction mixture was stirred for a further two hours. It was then extracted with ether. The ether solution was dried over anhydrous sodium carbonate and the ether evaporated. The residue was distilled through a 6" Vigreux column until most of the amine had distilled over, (b.p. 80-90° (25-35 mm)). The reaction sequence was repeated twice and the residues combined. The residues were fractionally distilled. The fraction which was largely hydrazine was redistilled, b.p. 70° (1 mm), $[\alpha]_D^{25}$ = -28.95° (c 0.78, benzene), n_D^{25} 1.5436. The yield of (-)-4 was 4.8 g (8%).

(-)-1-Benzyl-2-α-phenylethylhydrazine, (-)-6

(-)-α-Phenylethylhydrazine, (-)-4, (6.8 g, 0.05 mole) synthesized as described above was dissolved in 80 ml dry ether to which 6 g of anhydrous magnesium sulfate were added. Freshly distilled benzaldehyde (5.5 g, 0.052 mole) in 20 ml of ether was added dropwise with stirring over thirty minutes. Stirring was continued overnight. After filtration and evaporation of solvent, 10.3 g of the (-)-hydrazone, (-)-5, was obtained. This was dissolved in

100 ml of 98% ethanol and hydrogenated in a Paar Hydrogenation Apparatus using 5% palladium on charcoal as catalyst. The reaction mixture was filtered, the solvent removed and the residue treated with 6.3 g of oxalic acid dihydrate in 12 ml of hot ethanol. A precipitate of the oxalate, (-)-8, was obtained in a yield of 10.5 g.

Compound (-)-8 was converted to (-)-6 by adding 5.5 g of it to 2 g of potassium hydroxide in 15 ml of water. (-)-6 was extracted as before with methylene chloride which was dried over anhydrous sodium carbonate. After removal of solvent, distillation of the residue yielded (-)-6, b.p. 116-20° (0.3 mm), $\alpha_D^{25} = -36.3°$ (neat, l 1 dm). The n.m.r. spectrum was identical with that obtained for racemic 6.

Conversion of (-)-6 into (-)-7 by oxygenation as reported for racemic 6 yielded (-)-7 together with about 7% of the hydrazones 5 and 9 as estimated by u.v. spectroscopy (assuming $\varepsilon = 15000$ for these compounds (79)). The rotation of this mixture was $[\alpha]_D^{25} = -106.7°$ (c 5.7, chloroform). Correction for the hydrazones still leaves the optical rotation of the azo compound far short of that obtained by resolution.

Method B

Since racemization of the asymmetric centre seemed probable by the method used above, the experiment was

repeated, but instead of using catalytic hydrogenation, another method of reducing the double bond was attempted.

Hydrazone, (-)-5, (2.2 g, 0.016 mole), was synthesized from (-)-10 , $\alpha_D^{25} = -36.6^\circ$ (neat, 1 1 dm), as described in Method A. The reaction mixture was filtered and 40 ml of a 25% solution of diisobutylaluminum hydride in benzene was added dropwise under an atmosphere of nitrogen. After addition was complete, the reaction mixture was stirred for two days at room temperature. It was then cooled in an ice bath and a solution of benzene-methanol (1:1) was added dropwise until no further reaction was observed. This was followed by 5 ml of water, 15 ml of 15% potassium hydroxide and then 5 ml of water. The aqueous layer was extracted with ether. The organic fractions were combined and dried over anhydrous sodium carbonate and poured into a solution of 2.6 g of oxalic acid dihydrate in 10 ml of 98% ethanol. The oxalate precipitated immediately. Recrystallization from ethanol of the 1.9 g obtained yielded 1.5 g. This was converted directly to (-)-7 as reported for racemic 7. U.v. analysis showed a negligible quantity of hydrazones present. However, the n.m.r. spectrum showed that the product contained 7.5% of (-)-4. The optical rotation of the mixture was $[\alpha]_D^{25} = -140^\circ$ (c 1.36, benzene). Correction for the fact that the starting α-phenylethylamine was 95% optically pure and for the (-)-4 present brought the rotation to $[\alpha]_D^{25} = -156^\circ$.

(+)-Benzaldehyde α-Phenylethylhydrazone, (+)-5

From 100 g of (+)-α-phenylethylamine, $\alpha_D^{25} = +35.1^\circ$ (neat, l 1 dm), hydrazine was obtained by the method of Gösl and Meuwsen (82). The hydrazone was prepared as already described. The rotation of the hydrazone was taken, $[\alpha]_D^{25} = +63.52^\circ$ (c 3.3, benzene). Since the (+)-amine was 92% optically pure, the rotation of optically pure hydrazone will be $[\alpha]_D^{25} = +69.1^\circ$.

Hydrogenolysis of (-)-7

To 1.7 g of (-)-7, $[\alpha]_D^{25} = -152^\circ$, in 40 ml of methanol was added 2 g of Raney nickel. The reaction mixture was attached to a hydrogenation apparatus and hydrogenated at atmospheric pressure. The first mole-equivalent of hydrogen was taken up quickly, but two days were required for the uptake of the second mole equivalent. The reaction mixture was filtered and the solution analyzed by g.l.c. The chromatogram showed the presence of four products. Two of these comprised over 90% of the reaction mixture. These were (-)-α-phenylethylamine, (-)-10, and benzylamine. The two minor products had the same retention times as toluene and ethylbenzene. The reaction mixture was concentrated on a rotary evaporator. (-)-10 was isolated from the reaction mixture by preparative g.l.c. Under the best g.l.c. conditions, complete separation of the two amines

could not be achieved. However, using a high flow rate of helium and an SF 96 column (6' x ¼") and a column temperature of 160°C, a sufficiently good separation was achieved so that (-)-10 was obtained pure after two passes through the fractometer. The optical rotation of (-)-10 was taken in dioxane, $[\alpha]_D^{25} = -31.4^\circ$ (c 5.4, dioxane). The specific rotation of α-phenylethylamine does not differ significantly in dioxane from the rotation of the neat liquid (111). Therefore, this corresponds to an optical purity for (-)-7 of 80%.

Synthesis of hydrocarbon coupling products

1,2-Diphenylpropene, 12

To 2.4 g (0.1 g-atom) of magnesium in 150 ml of anhydrous ether was added dropwise 15.6 g (0.11 mole) of methyl iodide in 50 ml of ether. After addition was complete, the reaction mixture was stirred for a further thirty minutes. A solution of 19.6 g (0.1 mole) of deoxybenzoin in 100 ml of ether was added slowly in order to produce a rapid rate of reflux. The reaction mixture was stirred for a further hour. It was then poured into an ice-hydrochloric acid mixture. This was extracted with ether. The combined organic fractions were dried over anhydrous sodium carbonate. The ether was evaporated and the residue distilled, b.p. 124° (1.7 mm) (lit (112) 183°

(26)). The distillate solidified and was recrystallized from ethanol, m.p. 77-80° (lit (112) m.p. 82°). The yield after recrystallization was 10.1 g (52%). The n.m.r. spectrum (CCl_4) had the following peaks: τ2.5-2.9 (multiplet, 10.3 H) due to the phenyl hydrogens, τ3.21 (doublet, 1.0 H, J = 1.5 Hz) due to vinylic hydrogen and τ7.75 (doublet, 3.0 H, J = 1.5 Hz) due to the methyl hydrogens.

dl-1,2-Diphenylpropane, 13

Compound 12 (8.5 g, 0.044 mole) was dissolved in 50 ml of 98% ethanol. This solution was then hydrogenated on a Paar apparatus using 0.5 g of 5% palladium on charcoal as catalyst. The reaction was complete in several minutes. The reaction mixture was filtered, the solvent evaporated on a rotary evaporator and the residue distilled to yield a colorless liquid, b.p. 108-9° (1.7 mm), n_D^{27} 1.5560 (lit (113) b.p. 127-30° (8 mm) and n_D^{20} 1.5585). The n.m.r. spectrum (CCl_4) of 12 had the following peaks: τ3.0-3.3 (multiplet, 10.1 H) due to the phenyl hydrogens, τ7.0-7.5 (multiplet, 2.8 H) due to methine and methylene hydrogens, and τ8.7-8.9 (multiplet approximating to a doublet, 3.1 H) due to the methyl hydrogens.

α-Phenylcinnamic acid, 14

This was synthesized by the Perkin reaction (84). A mixture of 125 g of phenylacetic acid, 150 ml of

benzaldehyde, 100 ml of triethylamine and 100 ml of acetic anhydride were heated under reflux for thirty-five minutes. The reaction mixture was cooled and 200 ml of concentrated hydrochloric acid was added with stirring. Sufficient ether was then added to dissolve the product and this was separated and washed with water. The ethereal solution was then extracted with a 3% solution of sodium hydroxide. The alkaline solution was them made acid by the addition of hydrochloric acid, and the product precipitated as a mixture of cis and trans isomers. This was filtered off and used directly in the next step of the synthetic sequence. The yield of crude acid was 180 g.

2,3-Diphenylpropionic acid, 15

α-Phenylcinnamic acid, 14, (45 g, 0.2 mole) was dissolved in 300 ml of 98% ethanol and hydrogenated in the presence of 0.5 g of 5% palladium on charcoal. The reaction was complete in two hours. The reaction mixture was filtered, the ethanol evaporated on a rotary evaporator. The yield of crude 15 was quantitative. The n.m.r. spectrum ($CDCl_3$) of 15 had the following peaks: τ2.82 and τ2.94 (two overlapping singlets, 10.0 H) due to the phenyl hydrogens, τ6.0-7.3 (multiplet, 3.03 H) due to the methine and methylene hydrogens. The downfield peak due to the carboxyl hydrogen had not been recorded.

Resolution of 2,3-diphenylpropionic acid

This was carried out as described by Pettersson (91). A solution of 65 g (0.4 mole) of ephedrine in 450 ml of acetone was added to a hot solution of 89 g (0.4 mole) of 15 in 500 ml of acetone. On standing overnight 80 g of crystals of salt formed. These were filtered and 0.5 g of the crystals were treated with dilute hydrochloric acid. (-)-15 was recovered by extracting the reaction mixture with ether. The product was recrystallized from ether-pentane and its rotation taken. The rotation of the acid, (-)-15, was found to be $[\alpha]_D^{25} = -35^\circ$. The yields of salt and optical rotation of the acid on successive recrystallizations were: 36 g, $[\alpha]_D^{25} = -81^\circ$, 22 g, -113.4°, 14 g, -123.8°, and 7 g, -132°. This was optically pure (-)-15 as determined by Pettersson (91). By evaporating the mother liquors and recrystallizing the salt obtained, a further 5 g of optically pure product were obtained.

dl-2,3-Diphenyl-1-propanol, 16

A solution of 15 (11 g, 0.049 mole) in ether was added to a slurry of 4.75 g (0.125 mole) of lithium aluminum hydride in 180 ml of ether. Rate of addition was such as to maintain gentle reflux. The reaction mixture was stirred overnight, cooled in an ice bath, and ice-water added until all excess hydride had been consumed. Then

100 ml of 6 N H_2SO_4 was added to the reaction mixture. The ether layer was separated, washed twice with 10% sodium carbonate solution and dried over anhydrous sodium carbonate. The ether was evaporated and the residue distilled, b.p. 140° (0.4 mm), n_D^{25} 1.5758 (lit. (114) b.p. 300-302°, (89) b.p. 128° (0.2 mm) n_D^{25} 1.5742).

The n.m.r. spectrum ($CDCl_3$) had the following peaks: τ2.8-3.2 (multiplet, 10.0 H) due to the phenyl hydrogens, τ6.3-6.5 (multiplet, 3.0 H) due to the methylene adjacent to the oxygen, τ6.7-7.5 (multiplet, 3.0 H) due to the methine and the benzylic methylene hydrogens, and τ8.06 (singlet 1.1 H) due to the hydroxyl hydrogen.

(-)-2,3-Diphenyl-1-propanol, (-)-16

This was carried out as described above. The refractive index of the distilled product was n_D^{25} 1.5745 (lit. (89) n_D^{25} 1.5742). The optical rotation of (-)-16 was $[\alpha]_D^{25} = -88.47°$ (c 1.08, chloroform) (lit. (89) $[\alpha]_D^{25} = +76.3°$ (c 5.3, chloroform)).

dl-2,3-Diphenyl-1-propyl p-Toluenesulfonate, 17

To an ice-cold solution of 2.15 g (0.01 mole) of 16 in 7 ml of dry pyridine was added 3.18g(0.017mole) of freshly recrystallized p-toluenesulfonyl chloride dissolved in 7 ml of ice cold, dry pyridine. The reaction mixture was left standing at room temperature for twenty-

four hours. Then, 10 ml of water was added and the reaction mixture was poured into 100 ml of ice cold 10% hydrochloric acid. This was then extracted with ether. The combined organic fractions were extracted with water and sodium bicarbonate solution and dried over anhydrous potassium carbonate. The ether was removed and the residue dissolved in ligroin-ether. The solution was left to stand, and the product crystallized out. The yield was 2.8 g (76%) and the melting point was 79.5-80.5°C.

The n.m.r. spectrum ($CDCl_3$) had the following peaks: τ2.2-3.4 (multiplet 14.0 H) due to the phenyl hydrogens, τ5.8 and τ5.92 (overlapping singlets, 1.83 H) due to the hydrogens of the methylene group adjacent to the oxygen, τ6.6-7.5 (multiplet) due to the methine and benzylic methylene hydrogens, and τ7.65 (singlet) due to the p-methyl hydrogens (combined area 6.0 H).

Anal. Calcd. for $C_{22}H_{22}O_3S$: C,72.10; H,6.05; S,8.75
Found: C,72.34; H,5.88; S,8.96

(-)-2,3-Diphenyl-1-propyl p-Toluenesulfonate, (-)-17

This was synthesized as reported above for racemic 17. It was recrystallized from ligroin-ether, m.p. 91-93.5°, $[\alpha]_D^{25} = -42.63°$ (c 0.5, chloroform) (lit. (89) m.p. 89-90° $[\alpha]_D^{25} = +40.2°$ (c 2.9, acetone)).

dl-1,2-Diphenylpropane, 13

To a 100 ml three necked flask fitted with a reflux condenser, dropping funnel and a magnetic stirrer and containing a slurry of 1.0 g of lithium aluminum hydride in 40 ml of anhydrous ether, was added a solution of 0.4 g of 17 in 15 ml of ether. The reaction mixture was stirred and heated under reflux for two days. Excess hydride was destroyed using 50% hydrochloric acid. The ether layer was separated, washed with water and dried over anhydrous sodium carbonate. The ether was evaporated and the residue analyzed by g.l.c. (SF 96 column). This showed only one peak on the chromatogram and this corresponded in retention time to that obtained for authentic 13 synthesized by the previous route. The n.m.r. spectrum and refractive index also were identical to those obtained from 13 synthesized by the previous route.

(-)-1,2-Diphenylpropane, (-)-13

Synthesis of (-)-13 was synthesized from (-)-17 according to the method described above. The crude product was purified by preparative g.l.c. The refractive index was identical to that obtained for racemic 13, n_D^{25} 1.5572 (lit. (89) n_D^{25} 1.5558). Other physical constants are: m.p. 22-23°, $[\alpha]_D^{25} = -80.51°$ (c 8.67, chloroform) (lit. (89) $[\alpha]_D^{25} = -76.3°$ (c 2.2, chloroform) (88) $[\alpha]_D^{25} = -63.5°$ (c 2.34, chloroform)).

A recheck of the rotation using another batch of tosylate gave $[\alpha]_D^{25} = -80.50^\circ$ (c 3.21, chloroform).

An o.r.d. spectrum of (-)-13 was recorded: concentration 1.503 M in cyclohexane.

$[\Phi]_{600}$	-167°	$[\Phi]_{300}$	-1666°
$[\Phi]_{450}$	-333°	$[\Phi]_{280}$	-2666°
$[\Phi]_{350}$	-833°		

meso- and dl-2,3-Diphenylbutane, 19 and 20 (93)

To 1 g (0.04 g-atom) of magnesium in 10 ml of anhydrous ether was added 11.8 g (0.084 mole) of α-phenylethyl chloride in 100 ml of ether at such a rate that the ether boiled vigorously. The reaction mixture was heated under reflux overnight. It was treated with ammonium chloride solution to destroy any Grignard still remaining. The ether layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated leaving an oily white solid as residue. The solid was recrystallized from methanol, m.p. 124° (lit. (93) m.p. 126°) This was the meso isomer. The mother liquor was concentrated and more meso isomer was obtained. When no more crystals deposited on further concentration, the solvent was removed and the residue distilled. The colorless oil

was the dl-isomer (93) n_D^{25} 1.5540.

The n.m.r. spectrum (CCl_4) of 19 had the following peaks: τ2.90 (singlet, 10.0 H) due to the phenyl hydrogens, τ 7.1-7.5 (multiplet, 2.09 H) due to the methine hydrogens and τ9.0 (multiplet approximating to a doublet, 6.1 H) due to the methyl hydrogens. Compound 19 was also pure by g.l.c. analysis. The n.m.r. spectrum (CCl_4) of 20 showed the presence of a small amount of 19. This was borne out by g.l.c. analysis.

The n.m.r. peaks were at τ2.7-3.3 (multiplet, 10.0 H) due to phenyl hydrogens, τ 6.9-7.5 (multiplet, 1.97 H) due to the methine hydrogens and τ8.77 (doublet, 6.0 H, J = 6.5 Hz) due to the methyl hydrogens.

Synthesis of 1,1'-diphenylazoethane, 22

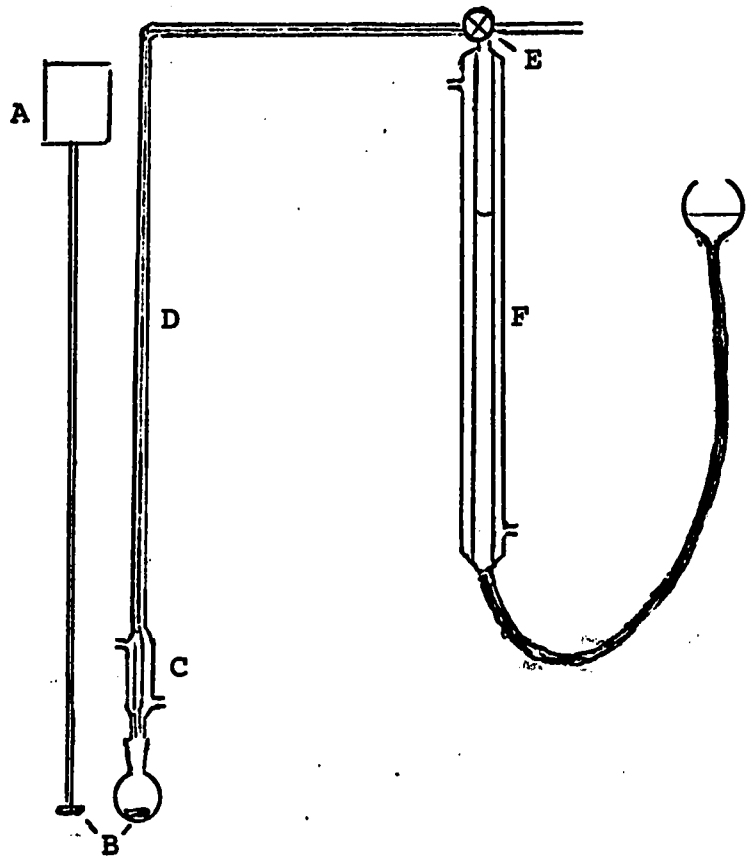
Acetophenone azine, 1, (50 g. mole) dissolved in 300 ml ethyl acetate was hydrogenated over 2 g of 5% palladium on charcoal until there was no further uptake in hydrogen. The resulting solution of 1,2-di-α-phenylethylhydrazine, 21, was filtered, the ethyl acetate evaporated and the residue taken up in ether. The solution was oxygenated as reported earlier and the resulting solution of 22 was washed several times with distilled water. The ethereal solution was dried over sodium carbonate, the solvent was removed and methanol was added to the yellow residue.

This solution was placed in the refrigerator and white crystals of 22 separated, m.p. 68-71° (lit. (52) m.p. 72.3-72.9°C). The n.m.r. spectrum ($CDCl_4$) of 22 had the following peaks: τ2.80 (singlet, 10.0 H) due to the phenyl hydrogens, τ5.32 (quartet, 1.9 H, J = 7.0 Hz) due to the methine hydrogens and τ8.45 (doublet, 6.0 H, J = 7.0 Hz) due to the methyl hydrogens.

Kinetics of decomposition of 7

The rates of decomposition of 7 were measured by observing the change in volume over the solution due to the evolution of nitrogen. The apparatus used is shown in Figure III. The decomposition was carried out in a 5 ml flask fitted with a standard taper neck. This was connected to a graduated buret by means of capillary tubing. To ensure that volatile products do not distill over a small condenser was inserted just above the reaction flask. To minimize errors in measurement of volume due to local temperature changes, the buret was surrounded by a water jacket through which thermostatted water was circulated. The reaction flask was stirred by means of a bar magnet. This magnet was operated by rotating another magnet beside the flask as shown in Figure III. Oxygen was removed from the sample to be decomposed by opening the stopcock to reaction flask only, the flask was cooled in a dry ice-acetone bath and the apparatus was evacuated to 0.05 mm.

Figure IV Apparatus Used to Measure Rates of Decomposition of 7



A. Electric motor

B. Bar magnets

C. Condenser

D. Capillary tubing

E. Three-way stopcock

F. Thermostated buret

The vacuum was released in such a way that prepurified nitrogen passed into the apparatus. Three such evacuations were performed and then the apparatus was closed by closing stopcock E.

Decompositions were commenced by lowering the flask into the bath and stirring commenced. Readings were generally commenced at 500 seconds or 1000 seconds after immersion of the reaction flask in the bath.

Since initial rates were being measured, an estimate of the time necessary to reach equilibrium temperature was required. By performing a trial run, it was reckoned to take 500 seconds at the higher temperature. Of this time, about 350 seconds were necessary for the temperature to rise over the last ten degrees, so that a correction to $(V_\infty - V_o)$ can be easily made. This correction was usually in the neighborhood of 1%. At the lower temperature, the rate is sufficiently slow that no correction of this kind was necessary. The results are presented in Tables III, IV and V.

Decomposition of 7 in ethylbenzene

A solution of 1.83 g of azo compound in ethylbenzene was heated under reflux for forty hours. The reaction mixture was then cooled and the solvent evaporated. This precluded the observation of low boiling products. The

residue was analyzed by g.l.c. to determine the higher boiling products formed in the decomposition. G.l.c. conditions were: Column, SF 96 on Chromosorb P; Injector temperature, 250°; Detector temperature, 250°; Column temperature, 180°; Flow rate (He) 80 ml/min. Four peaks were observed at retention times relative to the air peak of 10.5, 11.9, 13.8 and 15.0 minutes. Bibenzyl, 1,2-diphenyl propane, dl-2,3-diphenylbutane, meso-2,3-diphenylbutane were found to have retention times of 10.6, 12.2, 14.0 and 15.4 minutes respectively under the same g.l.c. conditions. These would, therefore, appear to be the compounds formed. To verify that these are the compounds being observed, an attempt was made to separate the constituents by column chromatography.

A column of Grade I alumina (1.5 cm x 50 cm) was made up in Skellysolve B. The residue from the decomposition of 7 was placed in the column and eluted with Skellysolve B (100 ml) and then 5% benzene - Skellysolve B. Using the latter solvent mixture, a white solid began to elute almost immediately. An n.m.r. spectrum showed this to be a mixture of 19 and 20. This mixture was recrystallized from carbon tetrachloride, m.p. 113-15°C. An n.m.r. spectrum of the recrystallized material was identical with that obtained for authentic meso-2,3-diphenylbutane, 20. The next fraction eluted had an n.m.r. spectrum which was very

complicated in the methyl region of the spectrum and was probably a mixture of 13, 19 and 20. The next fraction was identified as 1,2-diphenylpropane, 13, by its n.m.r. spectrum. No bibenzyl was isolated from the reaction mixture. Further elution of the column with 10% benzene - Skellysolve B produced trace amounts of oily solids.

Measurement of G.l.c. Response Factors.

A mixture of the following hydrocarbons was made up: 1,2-diphenylpropane (0.1207 g, 6.16×10^{-4} mole), meso-2,3-diphenylbutane (0.0226 g, 1.08×10^{-4} mole), bibenzyl (0.0202 g, 1.11×10^{-4} mole), and ethylbenzene (0.0792 g, 7.47 mole). Response factors were calculated from the equation:

$$\frac{\text{Response factor of A}}{\text{Response factor of B}} = \frac{\text{Area of A}}{\text{Area of B}} \times \frac{\text{Moles of B}}{\text{Moles of A}}$$

The results obtained are shown in Table XII. The response factors of ethylbenzene were rechecked and that for toluene calculated. This is also shown in Table XII.

The areas of the peaks were determined using the disc integrator and also by cutting out and weighing of the peaks. This method was also used since in some cases, it was necessary, when calculating the area of peaks in the chromatograms of the decomposition of azo compound.

TABLE XII

G.l.c. Response Factors

Compound	Amount Mole x 10^{-4}	Response Factors*		
Ethylbenzene	7.47	61.5	59	66
1,2-Diphenylpropane	6.16	100	100	100
Bibenzyl	1.11	81.5	84	90
meso-2,3-Diphenylbutane	1.08	93		97
Toluene	1.925	52	54.5	54.2
Ethylbenzene	1.51	56.5	60	61.5
1,2-Diphenylpropane	0.47	100	100	100

* The response factors were calculated relative to 1,2-diphenylpropane which was given the arbitrary value of 100.

Decomposition of 7 in benzene

Solutions containing various concentrations of 7 in benzene were made up. These solutions were placed in carefully neutralized glass-tubes (about 1.0 ml in each). The tubes were then sealed onto a vacuum rack, cooled in a dry-ice acetone bath and degassed to 1μ by several freeze-thaw cycles. The tubes were then sealed under vacuum and placed in an oven preheated to the required temperature. Decompositions were carried on to ten half-lives. The sealed tubes were then cooled in dry ice-acetone and opened. The mixture was analyzed by injection onto the g.l.c. column. The results are shown in Table VI.

Decompositions of 7 in the presence of butanethiol

Solutions of 7 were made up in butanethiol-benzene mixtures. The solutions were 1.0-3.1 M with respect to butanethiol in benzene and this was about ten times or more, greater than the concentration of 7. These were placed in tubes and degassed as described for benzene solutions. After decomposition, the ratio of 13 to ethylbenzene was measured by g.l.c. analysis. Toluene was not, in most cases, estimated because of partial overlap with the solvent peak. The same procedure was adopted for other solvent-butanethiol mixtures. In the case of chlorobenzene-butanethiol, the chlorobenzene peak on the g.l.c.

chromatogram overlapped the ethylbenzene peak, and so the ratio of toluene/1,2-diphenylpropane was measured.

Decompositions of (-)-7

These were carried out in stainless steel bombs. Generally, the azo compound, (-)-7, which had the maximum rotation of $[\alpha]_D^{25} = -152^\circ$, was used. Solutions were made up to 50 ml with solvent. Nitrogen was bubbled through the solution for several minutes, the bomb was sealed and decompositions carried out by placing the bomb in an oven preheated to the required temperature. Decompositions were carried out for at least six half-lives. The hydrocarbon was isolated from the reaction mixture and its rotation determined. The following runs were performed.

Run 1

Azo compound, (-)-7, (1.5 g) was dissolved in 20 ml of chlorobenzene. A stream of nitrogen was passed through the solution. Decomposition was then carried out at 108°C. Solvent and low boiling products were removed by flash distillation and the residue was chromatographed on an alumina column (1.5 x 40 cm) using hexane as eluant. The elution of coupling products was monitored by g.l.c. The size of fractions collected were 10-20 ml. By fraction 9, compounds 19 and 20 were eluting, by fraction 13, the

coupling product, (-)-13, was eluting. Fractions 24-33 contained major coupling product, (-)-13, only. These were combined and solvent removed to yield 57 mg of coupling product. The optical rotation was taken $[\alpha]_D^{25} = -6.6^o$ (c 2.84, chloroform).

Run 2

To 35 ml of chlorobenzene were added 2 g of (-)-7 and 3.3 g of butanethiol. Nitrogen was passed through solution for several minutes. The solution was then heated for thirty-six hours at 108°C. Coupling product was isolated by chromatographing the residue after evaporation of solvent on a short alumina column. It was further purified by preparative g.l.c. and the rotation was taken, $[\alpha]_D^{25} = -11.56$ (c 4.24, chloroform).

Run 3

Compound (-)-7 (1.5 g) was dissolved in 50 ml of benzene, placed in a 75 ml bomb which was then flushed with nitrogen for several minutes. The bomb was sealed and decomposition carried out at 132°C. After eleven hours the bomb was removed, solvent evaporated and the product isolated from the residue by preparative g.l.c., n_D^{25} 1.5569. The optical rotation was found to be $[\alpha]_D^{25} = -3.28^o$ (c 9.27, chloroform).

Run 4

Azo compound, (-)-7, (1.3 g) and butanethiol (7.7 g) were made up to a 50 ml solution with benzene. Decomposition was carried out at 132°C. Compound (-)-13 was isolated from the residue by column chromatography, followed by preparative g.l.c. The hydrocarbon, (-)-13, had an optical rotation of $[\alpha]_D^{25}$ = -9.29 (c 2.69, chloroform).

Run 5

Azo compound, (-)-7, (0.9 g) was dissolved in 50 ml of benzene. Decomposition was carried out at 110°C. Following removal of solvent, separation of (-)-13 was carried out by preparative g.l.c. and a second pass through the fractometer was necessary. The rotation was $[\alpha]_D^{25}$ = -4.49 (c 2.49, chloroform).

Run 6

Azo compound (1.5 g) and butanethiol (5.4 g) were made up to 50 ml with benzene. Decomposition was carried out at 110°C. After evaporation of the solvent, the residue was chromatographed on an alumina column. Further purification of (-)-13 was carried out by preparative g.l.c. The rotation of the hydrocarbon was $[\alpha]_D^{25}$ = -8.27 (c 3.4, chloroform).

Run 7

To 30 ml of butanethiol was added 0.9 g of (-)-7. Decomposition was carried out at 132°C for eleven hours.

Following evaporation of solvent, the product, (-)-13, was isolated by column chromatography and preparative g.l.c. The rotation was $[\alpha]_D^{25} = -11.74$ (c 2.36, chloroform). However, a check on the purity of (-)-13 by g.l.c. showed that it contained some dibutyl disulfide.

Run 8

To a mixture of 21 ml of benzene and 24 ml of butanethiol was added 1.4 g of (-)-7. Decomposition was carried out at 110°C. Following evaporation of solvent, isolation of (-)-13 was achieved by preparative g.l.c. Again two passes through the fractometer were necessary. The optical rotation was $[\alpha]_D^{25} = -13.54°$ (c 3.84, chloroform).

Run 9

To 25 g of butanethiol was added 1.3 g of (-)-7. Decomposition was carried out at 110°C. The solvent was removed and the hydrocarbon isolated from the residue by preparative g.l.c., (-)-13, had a rotation of $[\alpha]_D^{25} = -13.93°$ (c 0.79, chloroform).

Run 10

To 50 ml of cyclohexane was added 1.0 g of (-)-7. Decomposition was carried out at 115°C. The solvent was removed. Isolation of (-)-13 from the residue was achieved by column chromatography followed by preparative g.l.c., n_D^{25} 1.5572. Optical rotation of (-)-13 was $[\alpha]_D^{25} = -5.1°$ (c 3.2, chloroform).

Run 11

Azo compound, (-)-7, (1.0 g) and butanethiol (5.95 g) were made up in 50 ml with cyclohexane. Decomposition was carried out at 115°C. After removal of the solvent, (-)-13 was isolated from the residue by column chromatography, followed by preparative g.l.c., n_D^{25} 1.5562. The optical rotation was $[\alpha]_D^{25} = -8.85°$ (c 4.0, chloroform).

Control experiment on (-)-13

To a solution of 1.2 g of 1,1'-diphenylazoethane, m.p. 68-71°, in 30 ml of butanethiol was added 80 mg of 1,2-diphenylpropane, (-)-13, $[\alpha]_D^{25} = -80.5°$ (c 3.2, chloroform). This solution was placed in a bomb, which was then flushed with nitrogen, sealed and heated to 110°C for twelve hours. After decomposition the reaction mixture showed the presence of (-)-13, and also 19 and 20. Compound (-)-13 was isolated by preparative g.l.c. and its rotation measured, $[\alpha]_D^{25} = -64.1°$ (c 1.42, chloroform).

Control experiment on (-)-7

Azo compound (2 g), $[\alpha]_D^{25} = -152°$ (c 3.2, benzene) was dissolved in 30 ml butanethiol and placed in a bomb. After flushing the solution with nitrogen and sealing the bomb, (-)-7 was decomposed for five hours at 110°C. This corresponds to about 22% reaction for the decomposition process. The solvent was then removed on a rotary

evaporator and the residue taken up in about 50 ml of methanol. This was treated with 20 g of freshly prepared dipotassium azodicarboxylate (115) and acetic acid was dripped into the reaction mixture until evolution of nitrogen stopped. Ether was added to the reaction mixture which was then extracted with dilute sulfuric acid. The ether layer was saved, since it contained the hydrocarbon coupling product. The acid layer was then extracted with more ether. The acid solution was then made alkaline by the addition of potassium hydroxide pellets under an atmosphere of nitrogen. The alkaline solution was extracted with ether and dried over sodium carbonate. The ether solution was then oxygenated. The u.v. spectrum of the ether solution showed the presence of a substantial amount of hydrazone. After removal of the ether, an n.m.r. spectrum of the product was recorded. This showed that (-)-7 was the major product (71%) but that hydrazone, (-)-5, was also present (29%). The rotation of the mixture was taken, $[\alpha]_D^{25} = -101.4^\circ$ (c 0.91, benzene).

The hydrocarbon, (-)-13, was obtained by evaporation of the ether and (-)-13 was isolated from the residue by preparative g.l.c. Its optical rotation was measured, $[\alpha]_D^{25} = -13.9^\circ$ (c 1.2, chloroform).

C H A P T E R II

SYNTHESIS AND DECOMPOSITION OF OPTICALLY ACTIVE 1,1'-DIPHENYL-1-ETHYL-1-METHYLAZOMETHANE

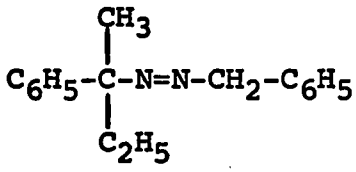
In Chapter I, azo compound (-)-7 was synthesized and decomposed to yield coupling product, (-)-13, in the solvent cage with approximately 10% retention of configuration. This corresponds to a ratio of the rate of coupling of the α-phenylethyl radical with a benzyl radical to its rate of rotation, k_c/k_r, being equal to 0.06. In other words, the α-phenylethyl radical rotates about sixteen times for each time it couples with a benzyl radical.

It would be of interest to synthesize and decompose a series of azo compounds in which the alkyl group bearing the asymmetric centre was changed in such a way as to alter the rate of rotation of the radical. If this could be done in such a way that the rate of coupling would remain unchanged, then this change in the ratio of the rate of coupling to rotation, k_c/k_r, would be reflected in a change in the degree of retention of configuration of the product. Hence the ratio, k_c/k_r, can be measured from the degree of retention, the cage effect, F, and the fraction of the radicals that disproportionate, f, as calculated from the equation derived in Chapter I.

In Chapter I, azo compound (-)-7 was decomposed to give an α-phenylethyl and a benzyl radical. It was decided to extend the study by synthesizing an azo compound which would give a tertiary benzylic radical and a primary benzylic radical on decomposition. Such a system would be expected to give different cage effects, and rates of rotation and coupling, from those obtained for (-)-7. It was anticipated that the rates of rotation and coupling would be different, also the size of the cage, which would be reflected in a change in the degree of retention.

In the decomposition of (-)-7 in the presence of thiol scavengers, racemization of both starting material and product was possible through hydrogen atom abstraction from the optically active centre. In the case of a tertiary alkyl radical, such a racemization would no longer be possible.

The system chosen for study was 1,1'-diphenyl-1-ethyl-methylazomethane.



Since this system was substituted on the α-carbons to a greater extent, decomposition will occur at lower temperatures than was the case for (-)-7.

RESULTS

Synthesis of 1,1'-diphenyl-1-ethyl-1-methylazomethane

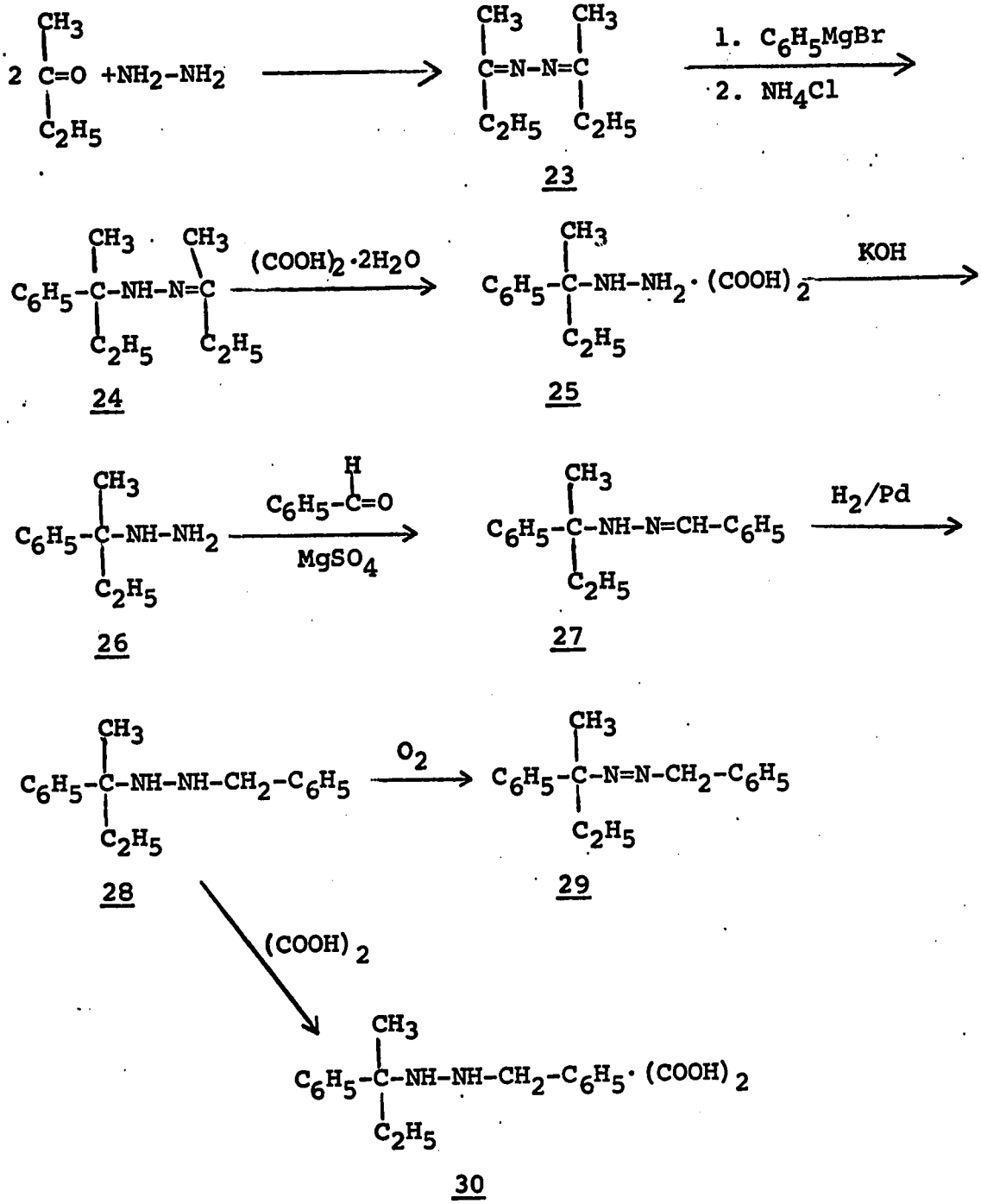
This synthesis was carried out as shown in Scheme XV. This was the method devised by Overberger and DiGiulio for the synthesis of unsymmetrical azo compounds (77).

Methyl ethyl ketone ketazine, 23, was synthesized as reported (77) and allowed to react with phenylmagnesium bromide for five days to yield methyl ethyl ketone 2-phenyl-2-butylhydrazone, 24.

Hydrazone 24 was not purified, but was hydrolyzed directly with oxalic acid dihydrate to yield 2-phenyl-2-butylhydrazine oxalate, 25. The oxalate, 25, was treated with excess potassium hydroxide solution and following extraction of the hydrazine into ether solution and evaporation of the solvent, the residue was distilled to yield 2-phenyl-2-butylhydrazine, 26. Compound 26 was identified by its n.m.r. spectrum and comparison of its refractive index with that reported (78).

Compound 26 was converted to benzaldehyde 2-phenyl-2-butylhydrazone, 27, by stirring stoichiometric amounts of 26 and freshly distilled benzaldehyde together in ether solution in the presence of anhydrous magnesium sulfate. The hydrazone was obtained as a yellow oil which was used directly in the next step of synthesis.

Scheme XV


2 C=O +NH2-NH2
CH3
C2H5
C=N-N=C
1. C6H5MgBr
2. NH4Cl
23
C6H5-C-NH-N=C
(COOH)2·2H2O
24
C6H5-C-NH-NH2·(COOH)2
KOH
25
C6H5-C-NH-NH2
C6H5-C=O
H
MgSO4
26
C6H5-C-NH-N=CH-C6H5
H2/Pd
27
C6H5-C-NH-NH-CH2-C6H5
O2
28
C6H5-C-N=N-CH2-C6H5
29
(COOH)2
C6H5-C-NH-NH-CH2-C6H5·(COOH)2
30

Hydrogenation of 27 proceeded smoothly in the presence of 5% palladium on charcoal to yield 1-(2-phenyl-2-butyl)-2-benzylhydrazine, 28. This result contrasts with that for acetone 2-phenyl-2-butylhydrazone which could not be hydrogenated to the corresponding hydrazone in the presence of various metal catalysts (81).

The structure of 28 was confirmed by its n.m.r. spectrum. Compound 28 could be converted to its oxalate salt, 30, by allowing it to react with oxalic acid in a minimum of ethanol. It could also be isolated by distillation under reduced pressure, provided the proper precautions to avoid its oxidation were taken.

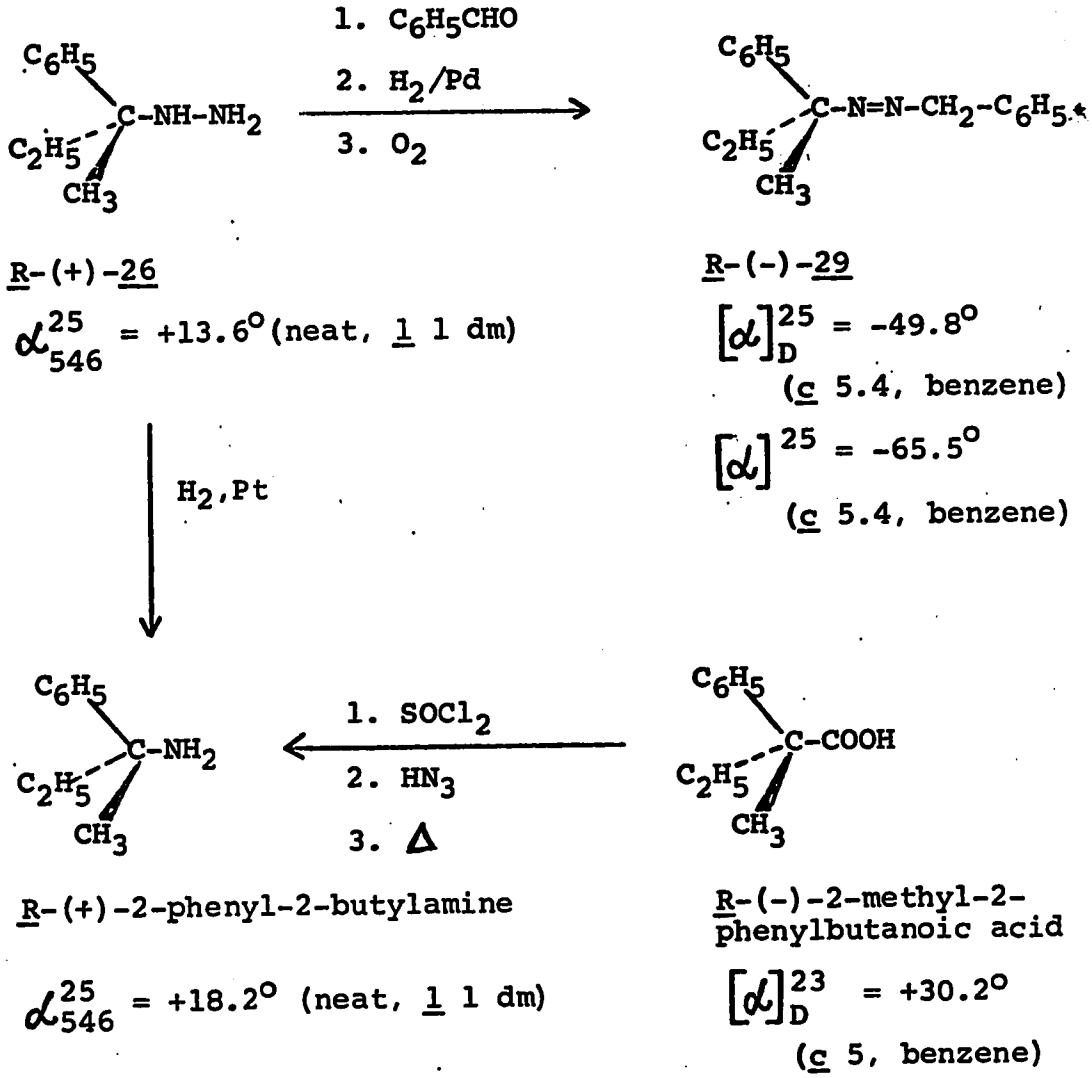
Oxidation of 28 to 1,1'-diphenyl-1-ethyl-1-methylazomethane, 29, was effected by the oxygenation technique already described. Compound 29 was obtained as a yellow oil. Its structure was confirmed by its n.m.r. spectrum. This spectrum also confirmed its purity since no extraneous peaks were in evidence. A u.v. spectrum of 29 had a weak maximum absorption at 3700^{o}A, which is in the correct region of the spectrum for azo compounds. An absorption was also observed at 2800 - 3000^{o}A. This was undoubtedly due to the presence of a minute quantity of the hydrazone, 27. However, the amount of 27 present was less than 1% (assuming ϵ = 15000 for 27). Azo compound, 29, also gave a satisfactory elemental analysis.

Synthesis of optically active 29

In principle, compound 29 can be obtained optically active either by preparing it from optically active 26, or by resolution of 28. Resolution of 26 to 80% optical purity had been achieved by Cram and Bradshaw (78) through the formation of the dibenzoyltartrate salt and fractionally crystallizing this from aqueous solution. This method of carrying out the resolution was very slow and very inefficient, so that another method of carrying out the resolution of 26 or a method of resolving 28 was sought. However, no better method was found for resolving 26 and none at all for 28 so that Cram and Bradshaw's method was used.

Compound (+)-26 was recovered from the resolution in poor yield. The optical purity of the recovered hydrazine, (+)-26, was 26%. Conversion of (+)-26 to (-)-29 was carried out as described for racemic 29. The absolute configurations and rotations of the optically pure compounds are shown in Scheme XVI. Conversion of (+)-26 to (-)-29 established that they belong to the same series i.e., the R series. The absolute configuration and the optical rotation of optically pure (+)-26 was determined by Cram and Bradshaw (78) by degrading (+)-26 to the corresponding (+)-2-phenyl-2-butylamine which in turn was synthesized from optically pure (-)-2-methyl-2-phenyl-

Scheme XVI



R-(+)-26

α_{546}^{25} = +13.6° (neat, 1 1 dm)

R-(-)-29

$[\alpha]_D^{25}$ = -49.8° (c 5.4, benzene)

$[\alpha]^{25}$ = -65.5° (c 5.4, benzene)

R-(+)-2-phenyl-2-butylamine

α_{546}^{25} = +18.2° (neat, 1 1 dm)

R-(-)-2-methyl-2-phenylbutanoic acid

$[\alpha]_D^{23}$ = +30.2° (c 5, benzene)

butanoic acid by the Curtius reaction. The absolute configuration of this acid had been established (109).

(+)-29

In the resolution of 2-phenyl-2-butylhydrazine, the mother liquor from the first recrystallization was evaporated to near dryness and the dibenzoyltartrate was broken up by the addition of potassium hydroxide. The rotation of the hydrazine, (-)-26, was taken, $\alpha^{25}_{546} = -2.04^{o}$ (neat, 1 1 dm). Therefore, it was 15% optically pure. Conversion of (-)-26 to the dihydrazine, 28, was carried out. This was not isolated but converted directly to the oxalate. A poor yield of the oxalate was obtained. This was converted to (+)-29 whose rotation was taken, $[\alpha]^{25}_{D} = +27.96^{o}$ (c 1.25, benzene). This was 56% optically pure. A further batch of the oxalate, 30, was obtained but this yielded almost inactive 29. The dihydrazine oxalate, 30, had undergone spontaneous resolution.

Hydrocarbon coupling products

Decomposition of 29 gives rise to benzyl radicals and 2-phenyl-2-butyl radicals. If random coupling takes place the products would be bibenzyl, 1,2-diphenyl-2-methylbutane, 35, and meso- and dl-3,4-dimethyl-3,4-diphenylhexane, 42 and 43. Of these coupling products, bibenzyl is available commercially and samples of the isomeric sub-

stituted hexanes were donated by a colleague (103). The major coupling product, 1,2-diphenyl-2-methylbutane, 35, was synthesized. As well as undergoing the coupling reaction, a benzyl and a 2-phenyl-2-butyl radical can disproportionate to give toluene and three isomeric 2-phenylbutenes. Also, a pair of 2-phenyl-2-butyl radicals can give these olefins and 2-phenylbutane as the products of a disproportionation reaction.

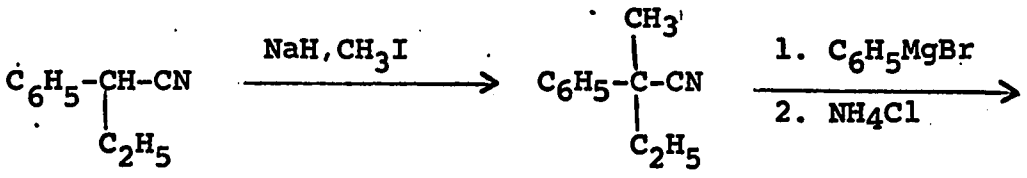
Synthesis of 1,2-diphenyl-2-methylbutane, 35

This compound had been synthesized previously by Cram and Allinger (113). A modification of the reaction pathway employed by these workers was used. An outline of synthetic sequence is shown in Scheme XVII.

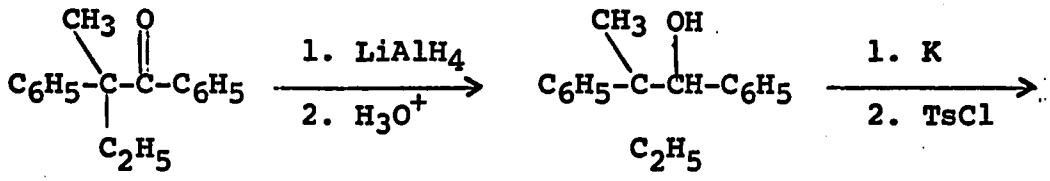
Methylation of 2-phenylbutanonitrile was carried out by using sodium hydride and methyl iodide (116). The resulting 2-methyl-2-phenylbutanonitrile, 31, was isolated and distilled. The structure of this compound was confirmed by n.m.r. analysis.

Compound 31 was converted directly to 1,2-diphenyl-2-methyl-1-butanone, 32, by treating it with phenylmagnesium bromide. The yields of 32 were not good and a substantial amount of unidentified side-product was formed. However, 32 was separated easily from this by distillation. The structure of 32 was confirmed by its n.m.r. spectrum

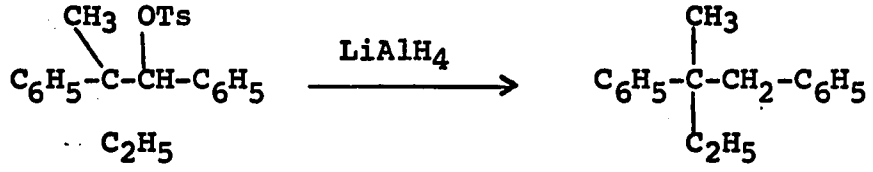
Scheme XVII



31



32 33



34 35

and comparison of its boiling point and refractive index with those previously reported (113).

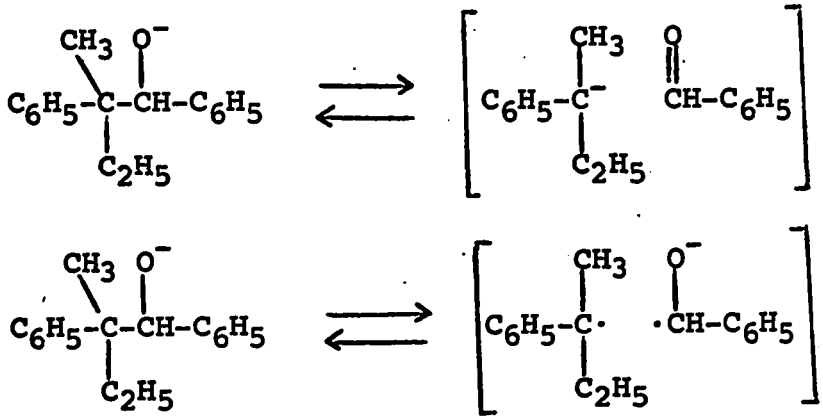
The ketone, 32, was reduced with lithium aluminum hydride to the diastereomeric mixture of alcohols, 1,2-diphenyl-2-methyl-1-butanol, 33. The n.m.r. spectrum of 33 was consistent with the structure proposed for the compounds. The distilled product was a colorless and very viscous liquid. The refractive index as reported for this mixture varies considerably and the refractive index obtained was fractionally different from that reported (113). The variation in refractive index is undoubtedly due to different ratios of the two diastereomers being obtained in the various reactions.

The alcohol, 33, was converted to the corresponding 1,2-diphenyl-2-methyl-1-butyl p-toluenesulfonate, 34, by the method of Cram and Allinger (113). This consisted in treating the alcohol with potassium metal in refluxing solvent, followed by treatment of the alkoxide with p-toluenesulfonyl chloride. The crude tosylate was isolated, but was not purified. The crude tosylate was treated directly with lithium aluminum hydride for several days. The product of the reaction was isolated and purified by preparative g.l.c. The product, 1,2-diphenyl-2-methylbutane, 35, was identified by its n.m.r. spectrum and by comparison of its refractive index with that

reported (113). The n.m.r. spectrum showed some extraneous peaks at τ 5.0-5.5 and τ 8.3-8.5, due to a small amount of impurity.

This method was used by Cram and Allinger to synthesize optically active 35. However, it was felt that the optical purity of this compound was open to some doubt.

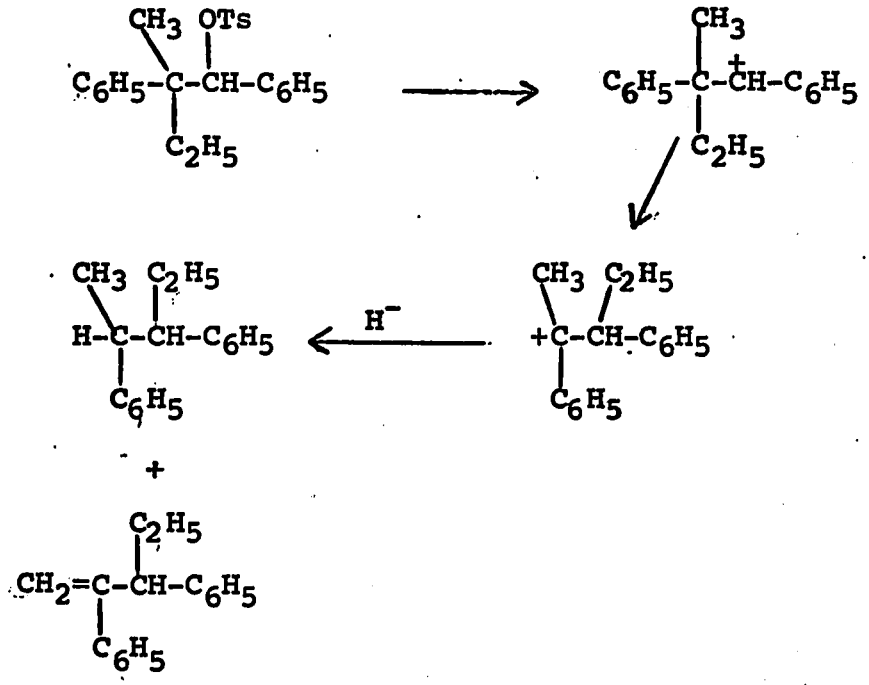
There are several possible routes by which racemization might take place. In the formation of 34, the alcohol, 33, was converted to the alkoxide by treating it with potassium in refluxing benzene. Alkoxides of this kind are known to be capable of undergoing a cleavage-recombination process (117) by a radical or an ionic pathway as shown below.



If either of these processes were going on, then some racemization would be a possibility.

The conversion of the tosylate, 34, to the hydrocarbon, 35, may also be accompanied with some rearrangement

via a carbonium ion as shown below.



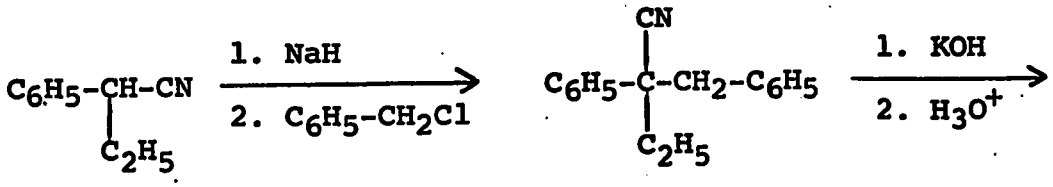
A rearranged hydrocarbon would be isomeric with 35 and may be quite difficult to separate from it.

An alternate route to hydrocarbon 35 which avoids these possibilities was sought. One such route is outlined in Scheme XVIII.

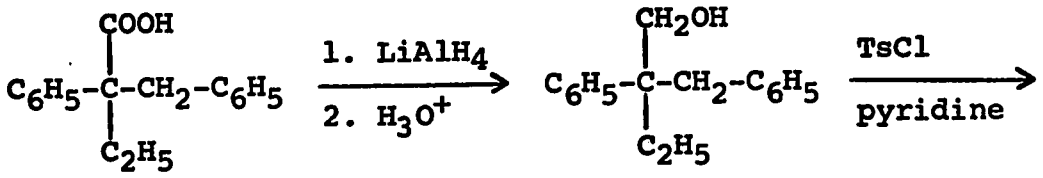
2-Phenylbutanonitrile was alkylated with benzyl chloride to yield 2-benzyl-2-phenylbutanonitrile, 36. The nitrile, 36, was then hydrolyzed to the acid, 2-benzyl-2-phenylbutanoic acid, 37. The n.m.r. spectrum of 37 was consistent with the structure proposed for the compound.

The acid, 37, was converted to the alcohol, 2-benzyl-2-phenyl-1-butanol, 38, by treating it with lithium

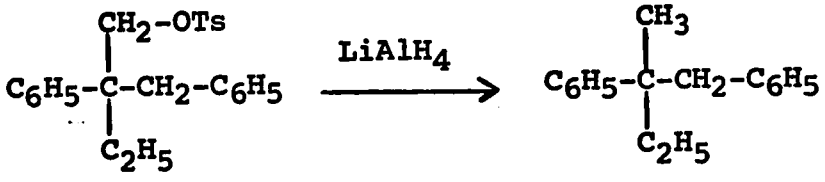
Scheme XVIII



36



37 38



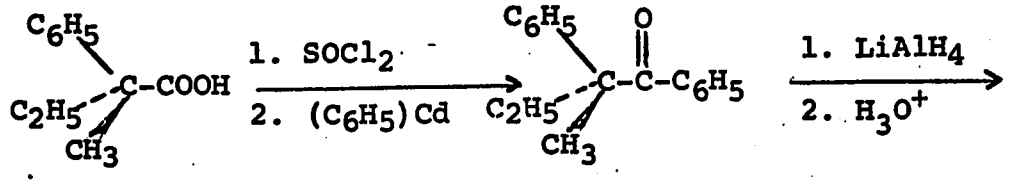
39 35

aluminum hydride. The product was a colorless, viscous liquid which was then treated with p-toluenesulfonyl chloride to yield 2-benzyl-2-phenyl-1-butyl p-toluenesulfonate, 39. Treatment of 39 with lithium aluminum hydride was expected to yield the hydrocarbon, 35. However, the product was not 35 since its g.l.c. retention time did not coincide with that of 35. The identity of the product was not pursued, but it was probably a rearrangement product via a carbonium ion. Another possibility is the oxygen-sulfur bond rather than the carbon-oxygen bond was broken in the hydrogenolysis.

A third method of synthesizing the hydrocarbon, 35, is outlined in Scheme XIX. 2-Methyl-2-phenylbutanoic acid, obtained by the hydrolysis of the corresponding nitrile, 23, was converted to the acid chloride. Treatment of the acid chloride with diphenylcadmium yielded the ketone, 32. Conversion of 32 to the alcohol, 33, was carried out as already described. Alcohol 33 was converted to its methyl ether by treating it with methyl iodide and sodium hydride while cooling the reaction flask in an ice-bath. The product, 1,2-diphenyl-1-methoxy-2-methylbutane, 40, was isolated and was identified by its n.m.r. spectrum.

Compound 40 was treated with sodium-potassium alloy. On addition of the alloy a reddish precipitate formed due to the formation of the benzylic anion. The metallated

Scheme XIX

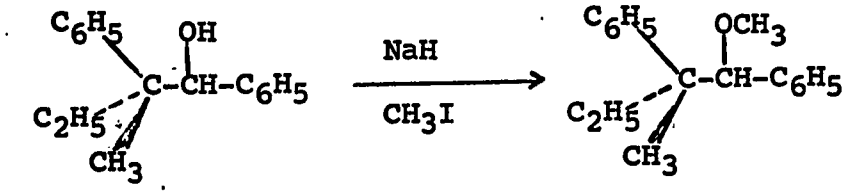


R-(-)-2-methyl-2-phenylbutanoic acid

$[\alpha]_D^{25} = -29.6^\circ$ (c 4.8, benzene)

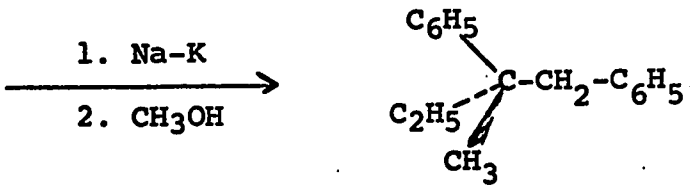
R-(-)-32

$[\alpha]_D^{25} = -61.09^\circ$ (c 6, benzene)



33

40



S-(+)-35

$[\alpha]_D^{25} = +78.33^\circ$ (c 4.7, benzene)

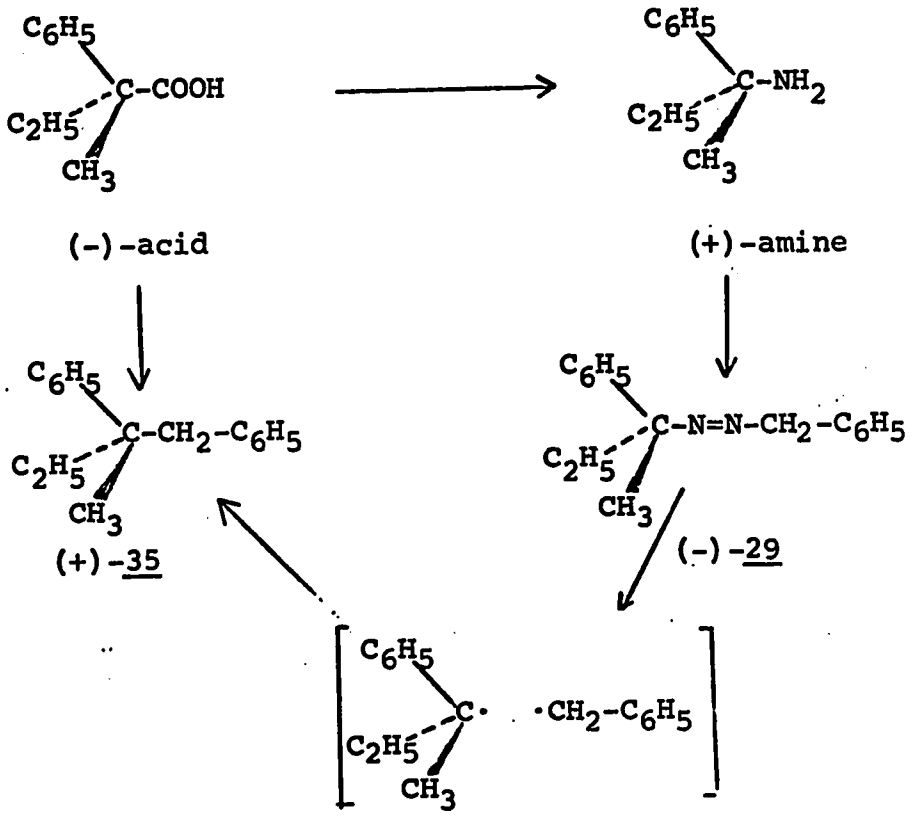
benzylic hydrocarbon was converted to 1,2-diphenyl-2-methylbutane, 35, by the addition of methanol. G.l.c. analysis of the reaction mixture revealed that the ether had been largely converted to the hydrocarbon. The hydrocarbon was purified by preparative g.l.c. (SF 96 column). The n.m.r. spectrum of this product was consistent with the structure proposed and was almost identical with that of the product obtained by the method of Cram and Allinger, except that the extraneous peaks observed in that spectrum were absent.

The stereospecific synthesis of (+)-35 was then carried out starting from 98% optically pure 2-methyl-2-phenyl butanoic acid, using this synthetic sequence. The optical rotations and absolute configurations of the compounds are shown in Scheme XIX. The rotations of 35 were measured at three wavelengths and were $[\alpha]^{25}_{D,\ 546,\ 436}$ = +78.3°, +94.7° and +178.5° (c 4.7, benzene). An o.r.d. spectrum of (+)-35 was also recorded. The optical rotation of (+)-35 obtained by Cram and Allinger was α^{25}_{D} = +67° (neat, l 1 dm). Since the conditions under which the two values were measured differed a direct comparison could not be made. However, if solvent effect is negligible, there does appear to be a significant difference between these values, since the density of 35 will be very close to 1.0.

Correlation of absolute configurations

Since the configurations of both (-)-29 and of (+)-35 have been related to (-)-2-methyl-2-phenylbutanoic acid (Schemes XVI and XIX), the stereochemical outcome of the reaction is readily found. Decomposition of (-)-29 to coupling product with overall retention of configuration would give (+)-35 as product as shown in Scheme XX.

Scheme XX



Kinetics of decomposition of 29

The rate of decomposition of 29 was followed by observing the rate of evolution of nitrogen. The equipment and technique for measuring the rate of decomposition of 29 was the same as that used in the decomposition of 7. Typical rate data are presented in Tables XIII and XIV and plots of these data are shown in Figures V and VI.

Since azo compound 29 is a more highly substituted one that azo compound 7, it was expected to decompose at a much faster rate. In fact, a tenfold increase in rate was observed at 110°C. The temperatures of decomposition used were lower than those for 7.

The deviation from linearity in the plots of $\log \frac{(V_\infty - V_o)}{(V_\infty - V_t)}$ versus time is less than that observed in the decomposition of 7. This indicates that less rearrangement is occurring during the decomposition of 29 than during the decomposition of 7. This is also evident from the yields of nitrogen obtained. Details of the decompositions are presented in Table XV. From the sparse results obtained, activation parameters were calculated. These values are tentative since little confidence can be placed in activation parameters based on so few results.

TABLE XIII

Rate Data for the Decomposition of

1,1'-Diphenyl-1-ethyl-1-methylazomethane, 29

Temperature, 104°C Solvent, Cumene

$(V_\infty - V_o)_{calculated}$ = 13.2 ml

Time (min.)	$(V_\infty - V_t)$	$\log \frac{(V_\infty - V_o)}{(V_\infty - V_t)}$	k_d, sec^{-1}
0	13.2	0.0	
3.0	12.9	0.0100	
9.0	12.35	0.0290	
18.0	11.6	0.0561	
24.0	11.15	0.0734	
45.0	9.65	0.1361	1.13×10^{-4}
54.0	9.1	0.1616	
64.0	8.55	0.1886	
74.0	8.00	0.2175	
84.0	7.55	0.2427	
114.0	6.3	0.3213	
129.0	5.8	0.3572	
144.0	5.4	0.3882	
174.0	4.65	0.4531	
210.0	4.1	0.5078	
810.0 (∞)	2.1		

TABLE XIV

Rate Data for the Decomposition of

1,1'-Diphenyl-1-ethyl-1-methylazomethane

Temperature, 86.6° Solvent, Cumene

$(V_\infty - V_o)$ calculated = 12.6 ml

Time (min.)	$(V_\infty - V_t)$	$\log \frac{(V_\infty - V_o)}{(V_\infty - V_t)}$	k_d, sec^{-1}
7	12.6	0.0	
21	12.4	0.007	
40	12.2	0.140	
60	12.0	0.0212	
130	11.35	0.0454	
180	10.90	0.0630	1.31×10^{-5}
255	10.25	0.0897	
300	9.90	0.1048	
360	9.45	0.1259	
450	8.80	0.1559	
570	8.10	0.1919	
720	7.25	0.2401	
960	6.25	0.3045	
1290	5.20	0.3844	
1470	4.75	0.4237	
1650	4.35	0.4619	
3500 (∞)	2.95		

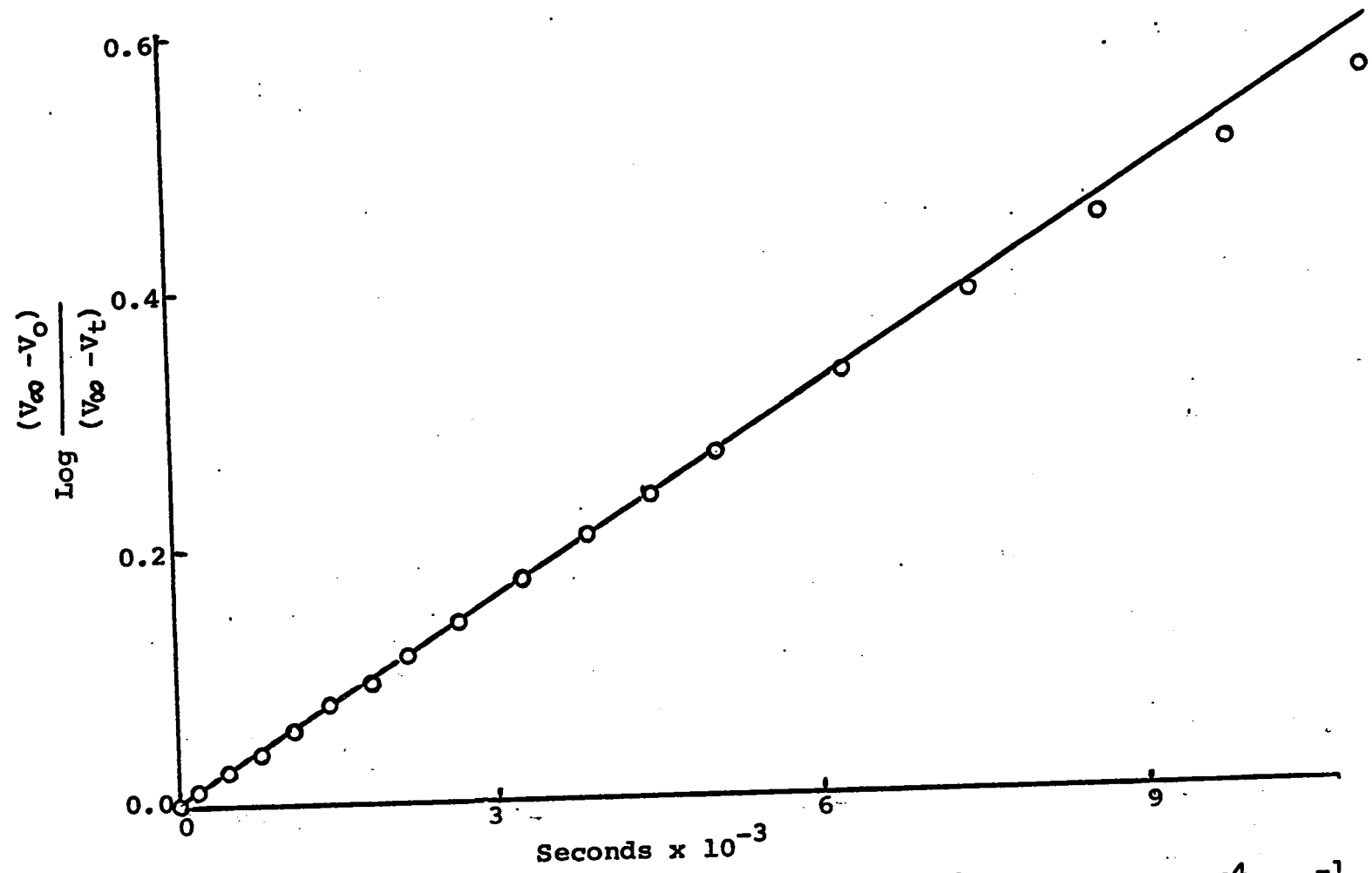


Fig. V. Decomposition of 29, 0.15 M, in cumene at 103.7°, k = 1.13 x 10^{-4} sec^{-1}.

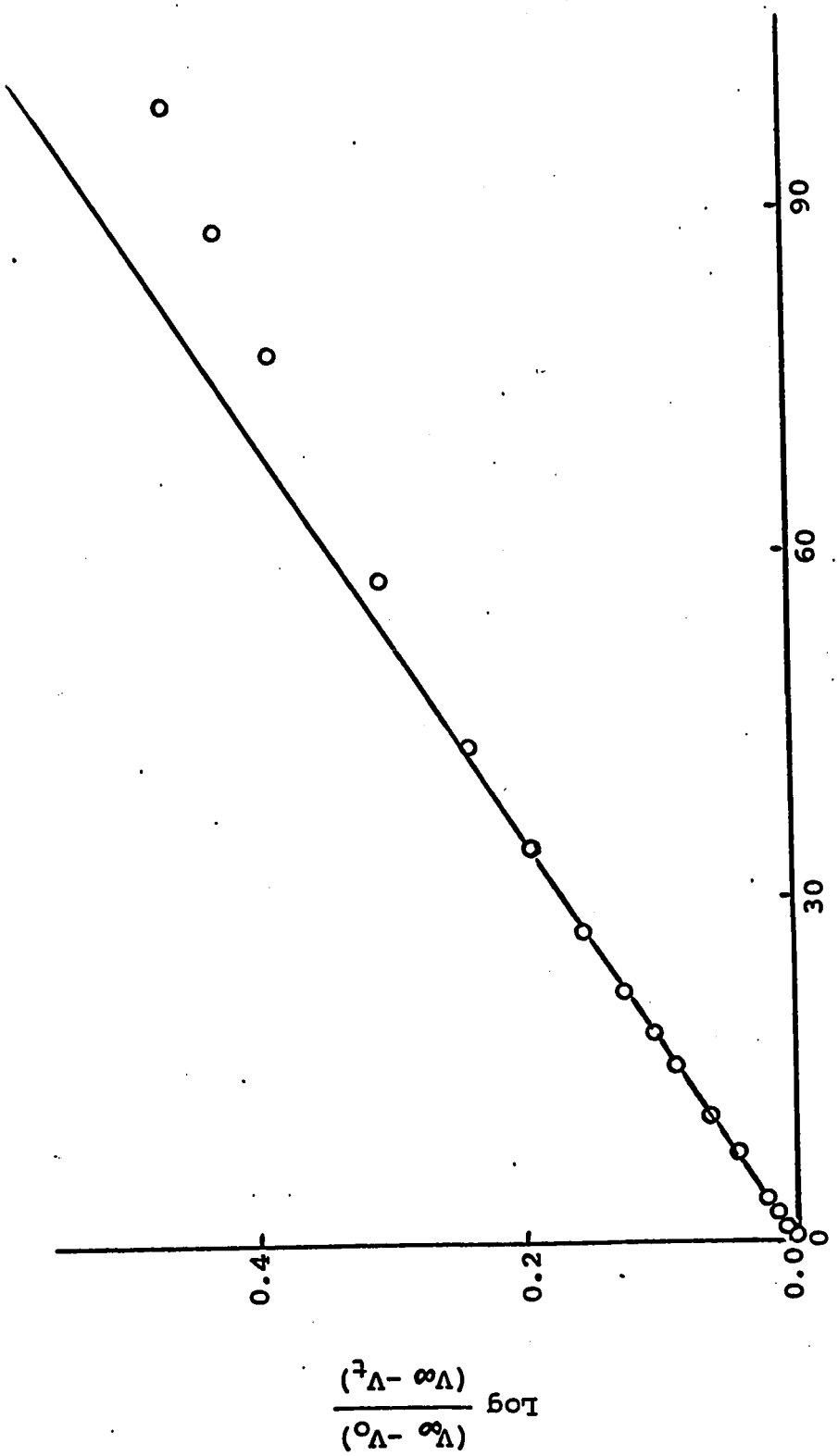


Fig. VI. Decomposition of 29, 0.16 M, in cumene at 86.6°, k = 1.31 x 10^{-5} sec^{-1}.

TABLE XV

Rate Constants for the Decomposition of

1,1'-Diphenyl-1-ethyl-1-methylazomethane, 29

Temperature °C	29 , M	Moles N_2*	k x 10^5, sec^{-1}
103.7	0.16	0.85	11.3
	0.17	0.93	12.3
86.6	0.16	0.85	1.31

At 103.7°C, ΔH = 33.1 kcal/mole, ΔS = 14.7 e.u.

* Moles of N_2 per mole of 29

Product Analysis

It was expected that the decomposition of 29 would yield as products bibenzyl, 1,2-diphenyl-2-methylbutane, 35 and meso- and dl-3,4-dimethyl-3,4-diphenylhexane, 42 and 43, as a result of random coupling of the benzyl and 2-phenyl-2-butyl radicals which are generated in the decomposition. These same radicals can also undergo disproportionation reactions to yield toluene, 2-phenylbutane and the three isomeric 2-phenylbutenes, cis- and trans-2-phenyl-2-butene, and 2-phenyl-1-butene.

In order to find out if these products were formed, azo compound 29 was decomposed and the resulting product mixture analyzed by g.l.c. Initially, analysis was carried out at a high column temperature (200°) in order to observe the coupling products at reasonable retention times. In the first instance, a benzene solution of 29 was decomposed in the injection port of the fractometer. Three peaks appeared on the chromatogram which had retention times identical to authentic samples of bibenzyl, 35 and meso-3,4-dimethyl-3,4-diphenylhexane, 42. The same retention times were also observed when decomposed solutions of 29 in cumene, benzene and pentane were injected onto the column.

The spent solutions of 29 from the kinetic runs were fractionated by g.l.c. and the product, which gave a peak of the same retention time as 35, was isolated. An

n.m.r. spectrum of this product was identical to that of 35. Temperature programmed g.l.c. analysis (100-200°) of the benzene and pentane solutions revealed the presence of toluene and a number of overlapping peaks. These peaks had the same retention times as 2-phenylbutane and the isomeric 2-phenylbutenes.

The relative quantities of the various products formed in the decomposition were calculated from g.l.c. analysis. Because the peaks due to 2-phenylbutane and the isomeric 2-phenylbutenes were so crowded it was impossible to get an estimate of the relative quantities of these materials. However, a tentative estimate of the sum of these products would be about 25% of the total. The relative quantities of the coupling products formed in the decomposition of 29 are shown in Table XVI.

It is interesting to note that the ratio of 42 + 43/ bibenzyl is equal to 1.8. This is a larger value than that obtained for the corresponding ratio in the decomposition of 7 which was equal to about 1.5 at this concentration. The quantity of toluene is not a reflection of the amount of disproportionation between benzyl and 2-phenyl-2-butyl radicals since a large amount of it probably arises through abstraction of hydrogen atoms from molecular species.

TABLE XVI

Product Distribution* from the Decomposition of 29 at 110°

Solvent	29, M x 10^{-2}	Bibenzyl	35	42 + 43	Toluene
Pentane	1.4	13.3	49.2	21.6	16.0
Benzene	1.31	14.8	57.5	27.9	
		14.2	57.4	28.3	
		14.3	60.0	25.8	
		14.8	60.2	24.8	
		13.2	52.8	22	12.0

* About 20% of total products unidentified, distribution expressed as relative yield in per cent.

Decomposition of 29 in the presence of scavengers

The scavengers which were used in these experiments were butanethiol and thiophenol. These scavengers were expected to eliminate random reactions between benzyl and 2-phenyl-2-butyl radicals outside the solvent cage, since these compounds react rapidly with radicals by donating a hydrogen atom to them.

Decomposition of 29 in the presence of butanethiol was performed and g.l.c. analysis of the product mixture showed that peaks due to the symmetrical coupling products are absent, as expected, from the chromatogram.

The analysis also revealed that toluene and 2-phenylbutane were present in considerable amount as a result of reaction of the radicals with the scavenger. Also present was the unsymmetrical coupling product, 35, which was formed in the solvent cage. Unfortunately, a large number of other products were formed. Most of these eluted between 2-phenylbutane and 35. Among these was one which had the same retention time as 35 when an SF 96 column was used. This unexpected product was isolated by g.l.c. using a Carbowax 20M column. It was a white solid and was identified by its n.m.r. spectrum which was identical with that reported for trans-stilbene (118). A discussion on the possible routes by which this and other unexpected products arise will be given later.

When thiophenol was used as a scavenger, the relative amounts of these by-products were reduced by about one half.

Stereochemical results

The procedure by which optically active 29 was decomposed and optically active 35 recovered from the product mixture was more or less the same as that reported for (-)-7 in Chapter I. However, since (+)- and (-)-29 are very difficult to obtain, the experiments were carried out on about half the quantities used in the decomposition of (-)-7. In all the experiments involving scavenger, butanethiol was used and was present in about a one molar concentration.

Since the optical purity of the starting material, 29, was low and yields of 35 were also low, it became apparent that a notable error might exist in measuring the specific rotation. Therefore, this was measured at three different wavelengths.

The results obtained from these experiments are presented in Table XVII. It can be seen from the table that (-)-29 gave (+)-35. Therefore, the decomposition proceeded with net retention of configuration. The net retention of configuration was calculated for the result at each wavelength and an average taken. The spread of results usually does not exceed 10% of the average.

TABLE XVII

Stereochemistry of 35 from Decomposition of (+)- and (-)-29

Solvent	Temp., °C	[29], M+*	[C_4H_9SH], M*	$[\alpha]_\lambda^{25}$ ++	Retention, ** %
Benzene	110	0.01	0.00	+1.37, 1.52, 2.67	6.25 ± 0.5
	110	0.04	0.85	+2.45, 3.2, 5.88	12.6 ± 0.6
	102	0.08	1.05	-4.64, 10.18	10.6 ± 0.1
	87	0.05	0.94	+2.09, 2.95, 5.11	11.3 ± 1.0
Pentane	110	0.04	0.86	+2.42, 2.83, 5.07	11.5 ± 0.5
Butanethiol	110	0.09	9.7	+2.39, 3.03, 5.54	12.0 ± 0.4

* Not corrected for volume expansion

** Average net retention calculated from the three values of the specific rotation

\+ Compound 29 used was (-)-29, $[\alpha]_D^{25} = -12.8^\circ$ (c 2.95, benzene) except for the decomposition at 102°C (+)-29, $[\alpha]_D^{25} = +27.96^\circ$ (c 1.3, benzene)

++ Specific rotations at 589, 546 and 436 mμ in columns 1,2 and 3 respectively

DISCUSSION

Kinetics of decomposition of 29

The rate constants for the decomposition of 29 were calculated in the same way as described for the decomposition of azo compound 7. Log $\frac{(V_\infty - V_o)}{(V_\infty - V_t)}$ was plotted against time, where $(V_\infty - V_o)$ was the calculated rather than the observed value. The rate constant was then found from the initial slope of the plots. Typical data are presented in Tables XIII and XIV and the plots are shown on Figures V and VI. The deviation from linearity in these is less than was observed in the plots obtained from the data on the decomposition of 7. The yields of nitrogen are also higher in these decompositions. These are presented in Table XV. The higher yields of nitrogen indicate that isomerization is less important during the decomposition of 29 than it was during the decomposition of 7.

The rate constants for the decomposition of 29 are presented in Table XV. Tentative values for the activation parameters were calculated and are included in this table.

The question now arises as to whether decomposition of 29 is a concerted process in which a pair of radicals and a nitrogen molecule are generated simultaneously, or whether it is a stepwise process in which one carbon-

nitrogen bond is broken in the rate determining step, followed by a rapid loss of a nitrogen molecule from the resulting diazoalkyl radical.

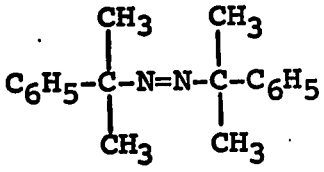
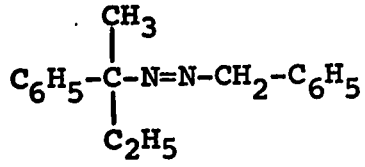
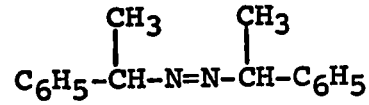
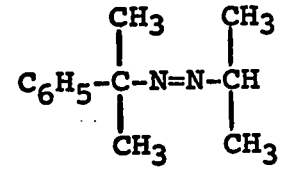
In Table XVIII are listed compounds which have certain features in common with 29, and their rates of decomposition and activation energies. For a concerted decomposition, the alkyl groups substituted on both carbon atoms alpha to the nitrogen atoms contribute to the lowering of the activation energy for decomposition. In a stepwise decomposition the alkyl groups on only one of the two α-carbons would be instrumental in lowering the activation energy.

Seltzer and coworkers (55) have pointed out that, in the case of symmetrical azo compounds, decomposition proceeds by a concerted pathway. They have also pointed out that the greater the difference in stabilities of the incipient radicals, the more probable a stepwise mechanism for decomposition becomes (56 , 57). Therefore, 2-phenyl-2,2'-azopropane is the most likely compound listed in Table XVII to decompose by a stepwise mechanism. If this compound does decompose by such a mechanism, then clearly 29 cannot, since there is a large difference in activation energy for decomposition between these two compounds. Also, the activation parameters for 29 and 1,1'-diphenylazoethane would be expected to be similar, if decomposition

TABLE XVIII

Rates and Activation Enthalpies for

Structurally Related Azo Compounds

Compound	k_d,* sec^{-1}	$\Delta H^{\ddagger}$ kcal/mole	Reference
	3.06×10^{-2}	29.0	48
	1.2×10^{-4}	33.1	This work
	8.1×10^{-5}	32.2	52
	1.5×10^{-5}	36.0	119

* Specific rate constants extrapolated to 103.7°C

of 29 is concerted, since the total of substituents on the α-carbons is the same in each case. This is indeed the case as can be seen in Table XVIII. The conclusion to be drawn from these comparisons is that decomposition of 29 is most probably a concerted process.

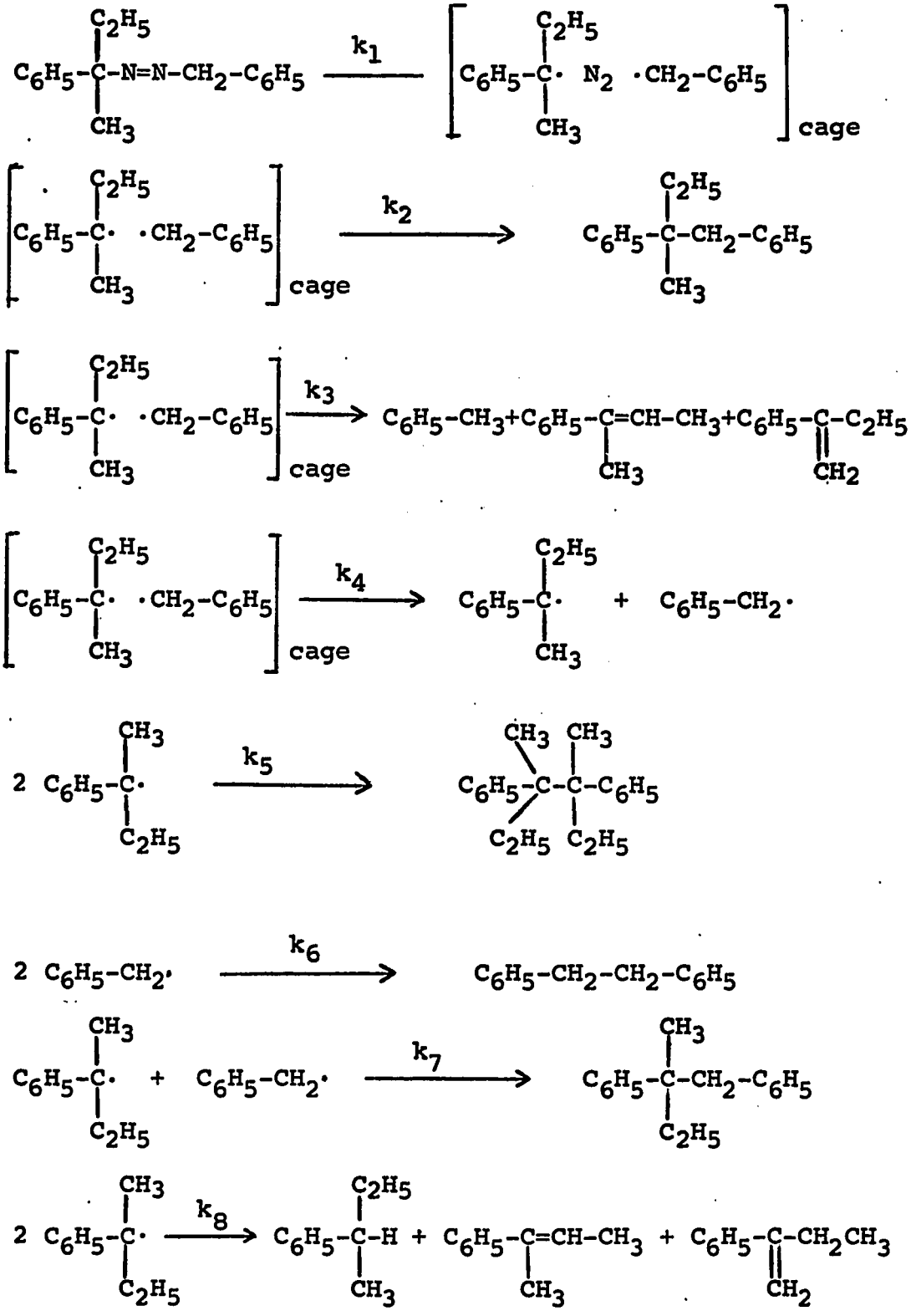
Product distribution from decomposition of 29

Compound 29 decomposed to yield all of the expected products. These arise from the various radical-radical reactions which take place as outlined in Scheme XXI.

The benzyl and 2-phenyl-2-butyl radicals generated in the decomposition may react in the solvent cage to give 1,2-diphenyl-2-methylbutane, 35, by coupling and toluene and a mixture of isomeric 2-phenylbutenes by disproportionation. They may, however, diffuse to generate two free radicals which then react in a random manner with other radicals to yield 35, bibenzyl, and meso- and dl-3,4-dimethyl-3,4-diphenylhexane, 42 and 43, by coupling reactions outside the cage. Two disproportionation reactions can also occur outside the cage yielding toluene, 2-phenylbutane and three isomeric 2-phenylbutenes. The rate constants for the coupling reactions outside the cage are not known. However, they were expected to be similar.

It might be expected that the rate of coupling of 2-phenyl-2-butyl radicals would be slower since these are

Scheme XXI



tertiary benzylic radicals and are, therefore, stabilized by resonance and hyperconjugation. There was also a possibility of steric hindrance to recombination. However, it has been reported recently (120) that the rate of coupling of cumyl radicals is faster than that of benzyl radicals so that other factors besides stability of the radicals and possible steric effects are involved in these reactions.

Completely random coupling outside the solvent cage should give a ratio of 42 + 43/bibenzyl which should be equal to one. Decomposition of 29 in benzene and pentane, however, on g.l.c. analysis revealed that this ratio was instead close to two. The data for the decomposition are presented in Table XVI. The reasons for the deviation of this ratio from the expected value are not quite clear. Presumably, the same effect as was observed in the decomposition of 7 is present here, namely, that the benzyl radicals are being consumed by reacting with molecular species in the solvent. This was not checked, however, by studying the decomposition at different concentrations.

The degree of disproportionation between benzyl and 2-phenyl-2-butyl radicals could not be determined from the product analysis, since some of the toluene observed may have arisen by abstraction of hydrogen atoms from molecules in the solvent. The degree of disproportionation between

2-phenyl-2-butyl radicals could not be determined either, since the g.l.c. peaks due to the products from this reaction were overlapped on the chromatogram.

The formula derived in Chapter I from calculating the cage effects from the product distribution is:

$$\% \text{ cage effect} = \frac{\underline{35}-(\text{bibenzyl} + \underline{42} + \underline{43})}{\underline{35}+(\text{bibenzyl} + \underline{42} + \underline{43})} \times 100$$

However, the value of calculating the cage effects from the product distribution obtained is questionable since the product distribution is seen not to be statistical in nature and the relative amounts of products from the two disproportionation reactions are not known. The values for the cage effects based on the coupling products, relative yields of bibenzyl, 35, 42 and 43, were found to be 17.3% for pentane and an average value of 18.1% for benzene at 110°C.

Cage effects calculated from the product distribution obtained from scavenged decompositions

Decomposition of 29 in the presence of a thiol yielded 35 in the solvent cage. Radicals escaping the cage were expected to react with thiol molecules by abstracting hydrogen atoms from them. This generated toluene and 2-phenylbutane.

The cage effect is calculated according to the equation derived in Chapter I:

$$\% \text{ cage effect} = \frac{35}{35 + \text{2-phenylbutane}} \times 100$$

The results obtained are presented in Table XIX. The accuracy of these results are dependent on the scavenger reacting in the manner which was predicted for it. The thiol was expected to donate a hydrogen atom to the radicals escaping the cage. The resulting thiyl radicals were then expected to couple to generate the corresponding disulfide.

In actual fact, a large number of products were formed besides those expected. These abnormal products were not identified except for one which had the same retention time as 35 when the SF 96 g.l.c. column was used to fractionate the mixture of products. This was isolated and identified as trans-stilbene by comparison of its n.m.r. spectrum with that of authentic material (118).

These additional products might have arisen through reactions of the thiyl radicals. The generation of acetophenone azine in the decomposition of 1,1'-diphenylazoethane in the presence of octanethiol has been rationalized by Bickel and Kooyman (99) as being due to successive abstractions of hydrogen atom from the azo compound by

TABLE XIX

Product Distribution* and Cage Effects from the Decomposition of 29 at 110°C

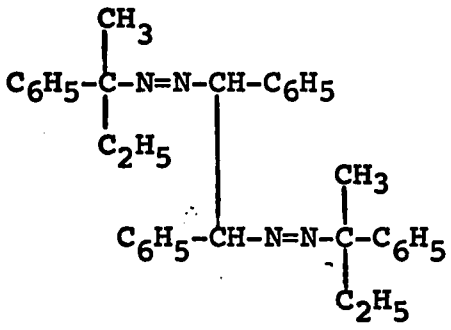
Solvent	[Thiol], M	Toluene	2-Phenyl-butane	35	Cage Effects, %
Pentane-thiophenol	1.2	36	35.5	6.5	15.5 (15.3)+
		39.5	37.5	6.2	14.2 (13.5)+
		30.2	29.2	4.4	13.2 (12.7)+
Benzene-thiophenol	0.97		14.3	4.3	23
			32.0	9.5	23
Pentane-butanethiol	0.85		20.4	4.7	18.8
			38.7	9.7	20
			21.3	4.6	17.8
			37.0	9.7	20.8
Benzene-butanethiol	0.84		12.7	6.9	35
			12.6	7.2	36.4
Butanethiol	9.7		33	9.8	23
			38.4	13.4	25.9
			34.6	12.7	26.8
			33.4	10.6	24.1

* Relative Amounts

\+ Calculated from the relative amounts of 35 and toluene

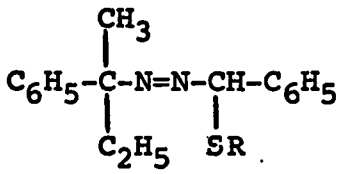
thiyl radicals. If this rationalization is correct, this would mean that the radical generated after the abstraction of the first hydrogen atom must be particularly stable otherwise it would not survive sufficiently long in the presence of octanethiol so that a second hydrogen abstraction could take place.

The radical generated in this way from 29 would also be quite stable, and furthermore, it cannot undergo a second hydrogen abstraction. Dimerization of two such radicals would give the following compound.



Decomposition of this compound could give rise to the trans-stilbene observed.

This radical might also couple with a thiyl radical to yield



Decomposition of this compound would give at least two other products.

A change of scavenger to thiophenol was undertaken to try to eliminate the abnormal products since the thiyl radical from this would be resonance stabilized and, therefore, less likely to abstract hydrogen atoms. In actual fact, a decrease of about 50% in the amounts of these products was observed. However, it is felt that in order to get precise data for the cage effects, a scavenger of a different nature is required.

In Table XIX, it can be seen that the relative yields of toluene and 2-phenylbutane are almost the same. Toluene and 2-phenylbutane are formed outside the cage as a result of the radicals abstracting hydrogen atoms from the scavenger. Toluene, however, can in principle, be formed inside the cage by a disproportionation reaction. Since the yields of toluene and 2-phenylbutane are almost equal, it follows that the disproportionation reaction is negligible.

A large difference in the cage effects using the different scavengers is observed. Since the amounts of abnormal products are less in the case of thiophenol, the results using this scavenger are probably more accurate.

This cage effect can also be calculated by a comparison of the rotation of the hydrocarbon recovered from product mixture of the decomposition of 29, in the presence and absence of scavenger.

The formula for this was derived in Chapter I and is:

$$\% \text{ cage effect} = \frac{F}{2-F} \times 100$$

$$\text{where } F = \frac{[\alpha]_\lambda \text{ no scavenger}}{[\alpha]_\lambda \text{ scavenger}}$$

For the one pair of rotations available (see Table XVII) the cage effect was calculated to be 33%. This must be considered a high estimate since no account is taken of consumption of radicals outside the cage by processes other than radical-radical reactions. The assumption is also made that the radical-radical reactions outside the cage give a statistical distribution of products.

The ratio of coupling of the 2-phenyl-2-butyl radical with a benzyl radical to its rate of rotation, k_c/k_r

This ratio can be calculated from the degree of retention of configuration observed in 35 recovered from the decomposition of optically active 29 and from the cage effects. The formula for calculating k_c/k_r derived in Chapter I is:

$$\frac{k_c}{k_r} = \left(\frac{(-)\text{-}35}{(+)\text{-}35} - 1\right) \cdot F \cdot (1-f)$$

The fraction of disproportionation in the solvent cage, f, is assumed to be zero in this calculation. The values of k_c/k_r are presented in Table XX. It can be seen that the value of the ratio depends to a large extent on the size of the cage effects. The results indicate that the 2-phenyl-2-butyl radical rotates ten to twenty-five times for each time it couples with benzyl radical under these conditions. This result is not significantly different for that obtained for the α-phenylethyl radical generated from (-)-7.

Since the studies carried out in this Chapter are preliminary in nature, any conclusions that are to be drawn from it must be tentative. Much work must be done in an effort to clean up the reactions, so that more meaningful results can be obtained. This is particularly true with respect to measurement of the cage effects, and of the degree of disproportionation in the solvent cage. However, the conclusion can be drawn that no radical difference is observed in the rate of rotation in changing from α-phenylethyl radical to 2-phenyl-2-butyl radicals.

TABLE XX

The Ratio of Coupling to Rotation (k_c/k_r) in the Generation of 35 at 110°C

Solvent	Scavenger	Cage Effect %	Retention %	k_c/k_r
Benzene	thiophenol	23	12.6*	0.067
Benzene	butanethiol	35.5	12.6	0.1
Pentane	thiophenol	14.1	11.5*	0.038
Pentane	butanethiol	19.4	11.5	0.051
Butanethiol		25.0	12.0	0.069

* It is assumed that the optical rotation of 35, which is formed in the cage, will not be affected by the change in the scavenger.

EXPERIMENTAL

Methyl ethyl ketazine, 23

This compound was synthesized by the method described previously (77). To 846 g (12 mole) of methyl ethyl ketone dissolved in 800 ml of ethanol was added slowly 368 g (6 mole) of an 85% solution of hydrazine hydrate. The reaction mixture was heated under reflux overnight. The reaction mixture was then distilled through a 6" Vigreux column. Water generated during the reaction and unreacted methyl ethyl ketone distilled over as an azeotropic mixture. When most of the water had been removed, about 100 g of methyl ethyl ketone was added and the distillation repeated. The residue was then distilled, b.p. 162-5° (700-710 mm), n_D^{25} 1.4523 (lit (78) n_D^{25} 1.4538. The n.m.r. spectrum (CCl_4) had the following peaks: τ 7.7 (quartet, 2.05 H, J = 7.5 Hz) due to methylene hydrogens, τ8.0 and τ8.2 (singlets, 3.0 H) due to the vinylic methyl hydrogens and τ8.5 (triplet, 2.9 H, J = 7.5 Hz) due to hydrogens of the methyl adjacent to the methylene group.

2-Phenyl-2-butylhydrazine oxalate, 25

This was synthesized as reported previously (78). A solution of phenylmagnesium bromide was made by adding 340 g (2.1 mole) of bromobenzene to 56 g of magnesium in 950 ml of dry ether. A solution of 140 g of 13 was slowly

added while the Grignard solution was stirred. When addition was complete (1.5 hours), the reaction was stirred under reflux for three days. The reaction mixture was cooled and added to 400 g of ammonium chloride suspended in ice. The organic layer was extracted with ether several times. Evaporation of the solvent yielded the crude 2-butanone 2-phenyl-2-butylhydrazone, 24. This was not purified but was added to a solution of 127 g of oxalic acid dihydrate in 450 ml of 95% ethanol and 450 ml of ether. The reaction mixture was stirred and 2-phenyl-2-butylhydrazine oxalate, 25, precipitated as a white solid. After ten hours the crude oxalate was filtered off and dried. The yield of crude oxalate was 142 g (56%). The crude oxalate was not purified but was used directly in the next step of the synthetic sequence.

2-Phenyl-2-butylhydrazine, 26

To a solution of 13.2 g of potassium hydroxide in 100 ml of water was added 25.4 g of 24 under an atmosphere of nitrogen. The reaction mixture was extracted with methylene chloride several times and the combined organic fractions were dried over anhydrous potassium carbonate. The solvent was evaporated and the residue distilled under reduced pressure to yield a colorless oil, b.p. 88° (1 mm), n_D^{25} 1.5358 (lit (78) b.p. 81-84° (0.4 mm), n_D^{25} 1.5354)).

The n.m.r. spectrum (CCl_4) had the following peaks: τ2.5-3.0 (multiplet, 5.0 H) due to the phenyl hydrogens, τ6.91 (broad singlet, 2.91 H) due to the hydrogens on the nitrogen atoms, τ8.4 (quartet, J = 7.5 Hz) and τ8.67 (singlet) (combined areas 5.2 H), due to methylene hydrogens and hydrogens of the methyl group on the benzylic carbon, and τ9.3 (triplet, 3.0 H, J = 7.5 Hz) due to methyl hydrogens of the ethyl group.

Optical Resolution of 26

The method of Cram and Bradshaw (78) was modified in that the solutions of the salt were concentrated during recrystallization rather than allowing them to stand for several weeks. Dibenzoyltartaric acid (79 g) was dissolved in 23 litres of boiling distilled water. To this was added 36 g of racemic 26. The solution was allowed to cool to room temperature. It was then filtered and the clear solution was left to stand at about 5°C for about a week during which crystals of the salt slowly formed. The yield of product obtained was 60 g. On concentration of the mother liquor a further 13 g of product was obtained. The two amounts were combined and recrystallized from distilled water and on gradual concentration of the solution 56 g of crystals were obtained. A further recrystallization carried out in the same way yielded 22 g of product.

Another recrystallization with concentration of solution yielded 13 g of product. This was treated with excess potassium hydroxide solution, and the reaction mixture was then extracted with ether several times. The combined ether layers were dried over anhydrous potassium carbonate, the ether evaporated and the residue distilled under reduced pressure, b.p. 86° (0.4 mm), yield 4.5 g. The optical rotation of 26 was taken and was found to be α_{546}^{25} = +3.52 ± 0.08° (neat, 1 1 dm), 26% optically pure (78). The original procedure (78), although time consuming, is better since 80% optically pure 26 is obtained.

Benzaldehyde 2-phenyl-2-butylhydrazone, 27

Compound 25 (16.4 g, 0.1 mole) was dissolved in 50 ml of ether and about 10 g of anhydrous magnesium sulfate was added. The reaction mixture was stirred and 10.6 g (0.1 mole) of freshly distilled benzaldehyde added. The reaction mixture was stirred for several hours and then filtered. The solvent was removed on a rotary evaporator and a yellow oil was obtained. No further attempts were made to purify this compound. The crude hydrazone had a refractive index of n_D^{25} 1.5530 and the n.m.r. spectrum ($CDCl_3$) had these peaks: τ2.4-3.0 (multiplet, 11.2 H) due to the phenyl hydrogens and the vinylic hydrogen, τ4.42 (broad singlet, 0.94 H) due to the hydrogen on the nitrogen atom, τ8.03 (quartet 2.3 H, J = 7.0 Hz) due to the methylene

hydrogens, τ 8.45 (singlet, 3.2 H) hydrogens of the benzylic methyl group, τ 9.25 (triplet, 2.94 H, J = 7.0 Hz) due to the methyl hydrogens of the ethyl group.

1-Benzyl-2-(2-phenyl-2-butyl) hydrazine, 28

2-Phenyl-2-butylhydrazine (2.5 g, 0.015 mole) was dissolved in 20 ml of anhydrous ether and treated with 1.6 g (0.015 mole) of freshly distilled benzaldehyde as described above. After filtration of the ethereal solution of hydrazone, 27, it was hydrogenated over 5% palladium on charcoal (0.4 g). After uptake of hydrogen was complete, the reaction mixture was carefully filtered under an atmosphere of nitrogen. The ether was removed and the residue distilled under reduced pressure to yield a colorless viscous liquid, b.p. 130-2° (0.2 mm), n_D^{25} 1.5582, yield 2.7 g (67%).

The n.m.r. spectrum (CCl_4) of the product had the following peaks: τ 2.6-2.9 (multiplet, 10.1 H) due to the phenyl hydrogens, τ 6.20 (singlet, 1.8 H) due to the benzylic methylene hydrogens, τ 6.77 (singlet, 2.0 H) due to hydrogens on the nitrogen atoms, τ 8.3 (quartet, J = 7.5 Hz) and τ 8.56 (singlet) due to the methylene hydrogens of the ethyl group and the benzylic methyl groups, respectively, (combined area 5.2 H) and τ 9.32 (triplet, 3.1 H, J = 7.5 Hz) due to the methyl hydrogens of the ethyl group.

1-Benzyl-2-(2-phenyl-2-butyl) hydrazine oxalate, 30

This was prepared simply by adding a solution of oxalic acid in a minimum of ethanol to an ether solution of 28. No oxalate formed directly, but on standing in the refrigerator for several days a white solid formed, m.p. 160-3°.

1,1'-Diphenyl-1-ethyl-1-methylazomethane, 29

The hydrazine, 28 (0.6 g), was dissolved in 50 ml of ether and placed in a neutralized flask which was then stoppered with a rubber septum through which oxygen was passed. A pressure of 5 p.s.i. of oxygen was maintained over the ethereal solution for twenty hours. The ethereal solution was washed with distilled water and dried over anhydrous potassium carbonate. The ether was then removed on a rotary evaporator leaving a yellow oil (0.45 g), n_D^{25} 1.5538. The n.m.r. spectrum ($CDCl_3$) had the following peaks: τ2.66 (singlet, 10.0 H) due to the phenyl hydrogens, τ4.97 (singlet, 2.04 H) due to the benzylic methylene hydrogens, τ7.98 (quartet, 2.1 H, J = 7.5 Hz) due to the methylene hydrogens of the ethyl group, τ8.57 (singlet, 3.1 H) due to the benzylic methyl hydrogens, τ9.30 (triplet, 3.0 H, J = 7.5 Hz) due to the methyl hydrogens of the ethyl group.

A u.v. spectrum of 29 was recorded. This showed a

maximum absorption at 3700°A which is due to the azo compound. Another maximum was observed at 2800-3000°A due to a trace of hydrazone.

Anal. Calcd. for $C_{17}H_{20}N_2$: C,80.91; H,7.99; N,11.10
Found: C,80.46; H,7.67; N,11.06
C,80.66; H,7.68

(-)-1,1'-Diphenyl-1-ethyl-1-methylazomethane, (-)-29

This was synthesized as described from (+)-26, α^{25}_{546} = +3.52° (neat, 1 1 dm), 26% optically pure. Compound 27 was not isolated but converted directly to 28 which was distilled but its rotation was not taken. Oxygenation was carried out as described above to yield (-)-29, n_D^{25} = 1.5528. Its rotation was taken: $[\alpha]^{25}_{D,\ 546,\ 436}$ = -12.88°, -16.60°, -66.88°, (c 2.95 benzene). Corrected to optical purity the rotations would be $[\alpha]^{25}_{D,\ 546,\ 436}$ = -49.23°, -65.08°, -259.92°. An o.r.d. spectrum of the azo compound, (-)-29, was taken.

$[\Phi]_{550}$	-165°	$[\Phi]_{375}$	±0°
$[\Phi]_{500}$	-230°	$[\Phi]_{350}$	+1680°
$[\Phi]_{450}$	-460°	$[\Phi]_{300}$	+755°
$[\Phi]_{400}$	-1280°		

2-Methyl-2-phenylbutanonitrile, 31

To a solution of 10 g (0.069 mole) of 2-phenylbutanonitrile in 100 ml of dry dimethoxyethane was added 10 g (0.07 mole) of methyl iodide. This reaction mixture was cooled in an ice-bath and 2 g of sodium hydride was added to the stirred solution in small amounts. Evolution of hydrogen was observed. On completion of addition, the reaction mixture was stirred for three hours. The mixture was first treated with a small quantity of ethanol and then added to water and the organic fraction extracted with ether. The combined ether fractions were extracted with water, and dried over anhydrous potassium carbonate. The ether was evaporated and the residue distilled, b.p. 62° (0.4 mm), n_D^{25} 1.5034 (lit (113) n_D^{25} 1.5036). The yield was 8.4 g (77%).

The n.m.r. spectrum (CCl_4) had the following peaks: τ2.4-2.9 (multiplet, 5.0 H) due to the phenyl hydrogens, τ8.18 (quartet, J = 7.0 Hz) due to the methylene hydrogens, τ8.46 (singlet) due to hydrogens of the benzylic methyl group, (combined areas 5.0 H) and τ9.15 (triplet, 3.1 H, J = 7.0 Hz) due to the methyl hydrogens of the ethyl group.

1,2-Diphenyl-2-methyl-1-butanone, 32

The method used to convert 31 to 32 was a modification of a method used previously (121). A solution of phenyl-

magnesium bromide was prepared by addition of 6 g (0.038 mole) of bromobenzene to 1 g (0.04 g-atom) of magnesium in 50 ml of ether. Compound 31 (5.5 g, 0.035 mole) dissolved in 20 ml of ether was added over fifteen minutes. The reaction mixture was stirred under reflux overnight. The mixture was then poured into an ice-hydrochloric mixture. This was stirred for several hours to hydrolyze the imine. The reaction mixture was then extracted several times with water and dried over anhydrous potassium carbonate. The solvent was evaporated and the residue distilled. Two fractions were obtained. The first distilled at 70-75° (0.3-0.5 mm), n_D^{22} 1.5272. This was not the desired product and its identity is not known. The second fraction distilled at 110° (0.3 mm), n_D^{22} 1.5723 (lit (113) b.p. 132° (1 mm), n_D^{25} 1.5700)). The yield of 32 was 4 g (44%). The n.m.r. spectrum (CCl_4) had the following peaks: τ 2.4-3.0 (multiplet, 10.0 H) due to the phenyl hydrogen, τ 8.0 (quartet, 2.14 H, J = 7.5 Hz) due to the methylene hydrogens, τ 8.5 (singlet, 2.9 H) due to the hydrogens of the benzylic methyl group and τ 9.25 (triplet, 3.2 H, J = 7.5 Hz) due to the methyl hydrogens of the ethyl group.

Attempted conversion of 32 to 35

A solution of 1 g of 32 in 50 ml of methanol was treated with 5 g of Raney nickel and hydrogenated. The

uptake of hydrogen appeared to be about 70% of the expected 2 mole equivalents. The reaction mixture was heated under reflux for one hour. The mixture was then tested for the presence of the hydrocarbon by g.l.c. analysis. No peaks appeared on the chromatogram at the retention time of 35. However, a peak did occur at longer retention time. This was identifed by its retention time as being due to the alcohol, 1,2-diphenyl-2-methyl-1-butanol, 33.

1,2-Diphenyl-2-methyl-1-butanol, 33

This was prepared by the method of Cram and Allinger (113). To 1.6 g of lithium aluminum hydride in 100 ml of ether was added 4.0 g (0.017 mole) of the ketone, 32. The reaction mixture was stirred under reflux overnight and was then neutralized with 1 ml of water followed by 3 ml of 15% potassium hydroxide solution and again 1 ml of water. The ether solution was decanted, dried over potassium carbonate and the solvent evaporated. The residue was distilled under reduced pressure, b.p. 125° (0.4 (0.4 mm), n_D^{22} 1.5725 (lit (113) b.p. 164° (4.5 mm), n_D^{25} 1.5719. The yield of the very viscous product was 3.1 g (75%). The n.m.r. spectrum (CCl_4) had the following peaks: τ 2.5-3.4 (multiplet, 10.2 H) due to the phenyl hydrogens, τ 5.5 (2 singlets, 0.8 H) due to the methine hydrogen, τ 7.7-9.6 (series of overlapping peaks, 8.9 H)

due to ethyl hydrogens, benzylic methyl hydrogens and hydroxyl hydrogen.

1,2-Diphenyl-2-methyl-1-butyl p-Toluenesulfonate, 34

This was synthesized as described previously (113). The alcohol, 33, (1 g) was dissolved in 20 ml of dry benzene. A piece of potassium metal (0.25 g) was added and the reaction mixture heated under reflux for four hours, during which an atmosphere of nitrogen was maintained above the reaction mixture. The mixture was then cooled in an ice-bath and p-toluenesulfonyl chloride (0.85 g) was added. The reaction mixture was stirred for about an hour. It was filtered and the solvent evaporated to yield the crude sulfonate. This was not purified but was used directly in the next step of the synthetic sequence.

1,2-Diphenyl-2-methylbutane, 35

Crude tosylate, 34, from the experiment above, was added to a slurry of 1 g of lithium aluminum hydride in 30 ml of ether. The reaction mixture was stirred for about twenty hours. Excess hydride was destroyed by addition of an ice-sodium hydroxide solution to the reaction flask. The ether layer was separated and dried over sodium carbonate. After removal of the ether, the residue was analyzed by g.l.c. and several peaks appeared on the chromatogram. The main product was isolated by

g.l.c. (50 mg) and was identified by n.m.r. analysis as being 35. The following peaks were observed in the n.m.r. spectrum (CCl_4): τ 2.5-3.5 (multiplet) due to the phenyl hydrogens, τ 7.2 (a pair of doublets, J = 13 Hz) due to the benzylic hydrogens, τ 7.7-8.6 (multiplet) due to the methylene hydrogens of the ethyl group, τ 8.8 (singlet) due to the benzylic methyl hydrogens and τ 9.3 (triplet) due to the methyl hydrogen of the ethyl group. The ratio of the areas of the phenyl hydrogens to the rest was 10.0 H : 9.2 H. There were some extraneous peaks in the n.m.r. spectrum at τ 5.0-5.6 and at τ 8.2-8.5.

2-Benzyl-2-phenylbutanonitrile, 36

A stirred solution of 29 g (0.2 mole) of phenylbutanonitrile and 26.5 g (0.21 mole) of benzyl chloride in 120 ml of dimethoxyethane was placed in an ice bath and treated with 5.4 g (0.225 mole) of sodium hydride which was added in small amounts over a two hour period. When addition was complete, the ice bath was removed and stirring was continued overnight at room temperature. It was then stirred under reflux for three hours. The reaction mixture was cooled and ethanol was added to destroy excess hydride. Water was added to the reaction mixture which was then extracted with ether. The ethereal solution was dried over anhydrous sodium carbonate. The ether was evaporated and the residue distilled, b.p. 146-9° (0.5 mm),

n_D^{25} = 1.5576, (lit (122) b.p. 201° (17 mm)). The yield was 37 g (85%). The following peaks were observed in the n.m.r. spectrum (CCl_4) of the compound: τ 2.5-3.1 (multiplet, 9.5 H) due to the phenyl hydrogens, τ 6.9 (singlet, 2.0 H) due to the benzylic methylene hydrogens, τ 7.95 (quartet, 1.9 H, J = 7.0 Hz) due to the ethyl group methylene hydrogens, and τ 9.1 (triplet, 3.3 H, J = 7.0 Hz) due to the methyl hydrogens.

2-Benzyl-2-phenylbutanoic acid, 37

To 31 g (0.8 mole) of potassium hydroxide in 120 ml of diethylene glycol was added 37 g (0.16 mole) of 2-benzyl-2-phenylbutanonitrile. The reaction mixture was heated under reflux for forty hours. It was then cooled and 600 ml of water added. The reaction mixture was then extracted with ether to remove unreacted nitrile. The aqueous layer was acidified with concentrated hydrochloric acid and 37 separated as a white solid. This was filtered off and dried yielding 36 g (90%) of 37. A small portion was recrystallized from heptane, m.p. 140.5-143° (lit (122) m.p. 140°C). The n.m.r. spectrum (CCl_4) had the following peaks: τ -2.3 (broad singlet, 1.0 H) due to the carboxylic hydrogens, τ 2.6-3.3 (multiplet, 10.3 H) due to the phenyl hydrogens, τ 6.68 (singlet, 2.06 H) due to the benzylic methylene hydrogens, τ 8.05 (quartet 2.0 H, J = 7.0 Hz) due to the methylene hydrogens of the ethyl

group and τ 9.07 (triplet, 3.06 H, J = 7.0 Hz) due to the methyl hydrogens.

2-Benzyl-2-phenyl-1-butanol, 38

To 1 g of lithium aluminum hydride in 50 ml of ether was added 2.5 g (0.01 mole) of 37. The reaction mixture was stirred overnight. The excess hydride was destroyed by addition of ice, followed by sufficient 6 N H_2SO_4 to dissolve the salts formed. The ether layer was separated, washed with water, sodium carbonate solution and dried over anhydrous sodium carbonate. After evaporation of solvent the residue was distilled, b.p. 106° (0.5 mm), n_D^{25} 1.5750, yield 38%. The n.m.r. spectrum (CCl_4) had the following peaks: τ 2.4-3.3 (multiplet 10.6 H) due to the phenyl hydrogens, τ 6.32 (singlet, 2.0 H) due to the hydrogens of the methylene group adjacent to the oxygen, τ 6.98 (doublet, 1.8 H) due to the benzylic methylene hydrogens, τ 8.1-8.6 (quartet + singlet, 3.0 H) due to the methylene hydrogens of the ethyl group and the hydroxyl hydrogen and τ 9.22 (triplet, 3.0 H, J = 6.5 Hz) due to the methyl hydrogens.

2-Benzyl-2-phenyl-1-butyl p-Toluenesulfonate, 39

An ice-cold solution of 2.4 g (0.01 mole) of 38 in 7 ml of dry pyridine was added to an ice-cold solution of 3.2 g (0.017 mole) of freshly recrystallized p-toluene-

sulfonyl chloride in 7 ml of dry pyridine. The mixture was allowed to stand at room temperature for twenty-four hours. Water was added and the mixture was poured into 10% hydrochloric acid. This was extracted with ether. The ether extracts were combined, washed with water and sodium bicarbonate solution and dried over potassium carbonate. The ether solution was concentrated and ligroin was added. This solution was placed in the refrigerator and crystals of 39 formed, yielding 3.4 g of product, m.p. 105-109° decomp. The n.m.r. spectrum ($CDCl_3$) had these peaks: τ 2.1-3.5 (multiplet, 14.0 H) due to the phenyl hydrogens, τ 5.9 (singlet, 1.9 H) due to the hydrogens of the methylene group adjacent to the oxygen atoms, τ 7.05 (singlet, 1.7 H) due to the benzylic methylene hydrogens, τ 7.6 (singlet, 2.9 H) due to the p-methyl hydrogens, τ 8.3 (quartet, 2.1 H, J = 7.5 Hz) due to the methylene hydrogens of the ethyl group and τ 9.42 (triplet, 2.7 H, J = 7.5 Hz) due to the methyl hydrogens of the ethyl group.

Attempt to synthesize 35 from 39

A solution of 1 g of 39 in 10 ml ether was added to a slurry of 1 g of lithium aluminum hydride in 20 ml of ether. The reaction mixture was stirred for two days, and then treated with crushed ice, followed by 6 N H_2SO_4.

The ether layer was separated, washed with water and dried over potassium carbonate. The solution was then analyzed by g.l.c. for 35, but no peak occurred on the chromatogram at the retention time for this product.

1,2-Diphenyl-2-methyl-1-methoxybutane, 40

1,2-Diphenyl-2-methyl-1-butanol, 33, (2.1 g, 0.009 mole) was dissolved in 30 ml of dry dimethoxyethane and a solution of 2.5 g (0.017 mole) of methyl iodide in 50 ml of dimethoxyethane added. The stirred mixture was cooled in an ice-bath and 0.3 g of sodium hydride was added slowly. Stirring was continued for four hours at room temperature, followed by three hours under reflux. The reaction was cooled and water added. It was then extracted with 100 ml of ether which was washed with water and dried over anhydrous potassium carbonate. The solvent was evaporated and the residue distilled, b.p. 94° (2.5-3 mm), n_D^{25} 1.5495, yield 1.7 g. The n.m.r. spectrum (CCl_4) of this diastereomeric mixture had the following peaks: τ 2.5-3.4 (multiplet, 9.6 H) due to the phenyl hydrogens, τ 5.94 and τ 5.97 (two singlets, 0.9 H) due to the methine hydrogens, τ 6.86 and τ 6.96 (two singlets, 3.0 H) due to the methoxy hydrogens, τ 7.6-8.6 (multiplet), due to methylene hydrogens, τ 8.77 (singlet) due to the benzylic methyl hydrogens, and τ 9.3 (quartet) due to the methyl hydrogens

of the ethyl group. Combined areas 8.2 H.

1,2-Diphenyl-2-methylbutane, 35

Compound 40 (0.8 g, 0.003 mole) was dissolved in 100 ml of anhydrous ether to which was added 2 ml of sodium potassium alloy synthesized by the method of Gilman (123). The reaction was stirred under an atmosphere of nitrogen. The reaction mixture became a reddish color and began to deposit a white precipitate. The mixture was stirred for twenty-four hours at room temperature. It was then cooled and an ice-cold ether-methanol mixture was added slowly to decompose remaining alloy. Water was then added and the ether layer was separated. The ethereal solution was dried over anhydrous potassium carbonate. G.l.c. analysis of the ethereal solution showed that the mixture was composed of 70% of 35 and 30% of 40. The hydrocarbon, 35, was isolated by preparative g.l.c. (SF 96 column), 100 mg, n_D^{25} 1.5563 (lit (113) n_D^{25} 1.5550). The n.m.r. spectrum of 35 prepared this way was closely similar to that obtained by the method of Cram and Allinger (113) except that none of the extraneous peaks observed in the n.m.r. spectrum of 35 prepared by that synthesis were present.

Stereospecific synthesis of 35

(-)-1,2-Diphenyl-2-methyl-1-butanone, (-)-32

To 1 g of (-)-2-phenyl-2-methylbutanoic acid,

$[\alpha]_D^{25} = -29.6^\circ$ (c 4.8, benzene) in 15 ml of anhydrous ether was added 3 ml of thionyl chloride. The reaction mixture was allowed to stand for four hours and then heated under reflux for a further four hours. The solvent and excess thionyl chloride were removed on a rotary evaporator and the crude acid chloride was used directly in the next step.

Diphenylcadmium was synthesized by a method previously reported (124). To a solution of diphenylcadmium, synthesized from 7 g of bromobenzene, in benzene was added a solution of 41 from the experiment above in benzene solution. The reaction mixture was stirred under reflux overnight. The reaction mixture was cooled and ice was added to it. This was followed by addition of sufficient 6 N H_2SO_4 to ensure solution of the cadmium salts. The benzene layer was separated and the aqueous layer extracted with a further portion of benzene. The combined benzene fractions were washed with water and sodium carbonate solution, and dried over anhydrous potassium carbonate. The benzene was removed on a rotary evaporator and residue distilled. Two fractions distilled over, the first of which solidified. This was readily identified as biphenyl. The second fraction was a liquid, b.p. 80-90° (0.5 mm). Owing to the small quantity, purification of this was performed by chromatographing it on 60 g of alumina using

pentane as eluant until all biphenyl had been removed. The ketone was then washed from the column with ether. The ether was removed from the ketone by rotary evaporator at reduced pressure. On removal of solvent, 160 mg of (-)-32 was obtained, $[\alpha]_D^{25} = -61.09^\circ$ (c 6, benzene) n_D^{25} 1.5705 (lit (113) α_D^{25} -63.7° (neat, l 1 dm), n_D^{25} 1.5700).

(+)-1,2-Diphenyl-2-methylbutane, (+)-35

Compound (-)-32 synthesized using the method above from 3 g of (-)-2-phenyl-2-methylbutanoic acid was converted to the alcohol 33 as reported already. One gram of this alcohol was converted to the ether, 40, as described already and this was converted to the hydrocarbon by sodium potassium alloy as described for the racemic material. The crude hydrocarbon obtained was distilled, b.p. 87°C (0.2-0.3 mm). G.l.c. analysis, however, revealed that it contained a small amount of the ether, 40. Therefore, final purification was carried out by preparative g.l.c., $n_D^{26.5}$ 1.5584. The rotation of the hydrocarbon was $[\alpha]_{D,\ 546,\ 436}^{25} = +78.3^\circ$, $+94.7^\circ$, and $+178^\circ$ (c 4.7, benzene), (lit (113) $\alpha_D^{25} = +67^\circ$, (neat, l 1 dm)).

An o.r.d. spectrum of the hydrocarbon, (+)-35, was

recorded, solvent, benzene; concentration, 0.21 M.

$[\Phi]_{600}$	+118°	$[\Phi]_{400}$	+500°
$[\Phi]_{550}$	+167°	$[\Phi]_{350}$	+880°
$[\Phi]_{500}$	+224°	$[\Phi]_{300}$	+1835°
$[\Phi]_{450}$	+326°		

Kinetics of decomposition of 29

These were carried out in exactly the same manner as for the decomposition of 7 in Chapter I. By carrying out the reactions at lower temperatures, the rates of evolution were about the same as for 7. The data and plots for the decompositions are shown in Tables XIII and XIV.

Products of decompositions

The products of decomposition of 29 were identified in the following manner. A few microlitres of 29 dissolved in benzene were injected directly into the injection port of the g.l.c. fractometer. The fractometer conditions were: Injector temp, 270°; Detector temperature, 250°; Column (SF 96) temperature 200°; Helium flow rate 85 ml/min. Due to the high column temperature, low boiling products came off the column at the same time as solvent.

However, three peaks at retention times of 4.2, 8.2 and 19.1 minutes were observed. By comparison of these with the retention times of authentic samples, these were found to be bibenzyl, 35 and 42 and 43, respectively. Spent solutions of 29 in cumene from the kinetic runs were also analyzed and were found to have these peaks. The compound giving rise to the peak at a retention time of 8.2 minutes was collected as it eluted from the column and an n.m.r. spectrum was taken of this material. The spectrum was identical in all respects with that of 35 obtained by synthesis from 2-phenylbutanonitrile.

Determination of product distribution

Benzene Solution

Azo compound, 29, (0.363 g) was dissolved in 110 ml of redistilled benzene. This was placed in a steel bomb which was then flushed with nitrogen for several minutes. The bomb was sealed and decomposition was carried out at 110° for twenty hours. A sample of this solution was then analyzed for product distribution. Results are shown in Table XVI.

Pentane Solution

Azo compound, 29, (0.068 g) was dissolved in 20 ml of pentane, placed in a bomb which was then flushed with nitrogen for several minutes, sealed and the decomposition

carried out at 110° for twenty hours. The solution from this decomposition was analyzed directly by g.l.c. The results are shown in Table XVI.

Decomposition of optically active 29 in the presence of scavengers

Optically active azo compound 29 of both positive and negative rotations were decomposed. The solvent was removed by flash distillation and the product, 35, was isolated in each case by preparative g.l.c. using a 10% Carbowax 20M on 60/80 Chromosorb W Column (6' x ¼"). Run 1 was performed on (+)-29. Runs 2-6 were performed on (-)-29 of rotation $[\alpha]_D^{25} = -12.88°$, 26% optically pure.

Run 1

Azo compound (+)-29 (0.97 g), $[\alpha]_D^{25} = +27.96°$ (c (c 1.25, benzene), 56% optically pure, and butanethiol (4.7 g) were dissolved in 50 ml of benzene. This was placed in a bomb which was then flushed with nitrogen and sealed. The bomb was heated at 102°C for about thirty hours. The bomb was then cooled and opened. The solvent was evaporated and the residue fractionated by g.l.c. on an SF 96 column. Material that had the retention time of 35 was collected. This was found to consist of a mixture of a white solid and a liquid. In order to separate these a new column was required. A satisfactory one was Carbo-

wax 20M operated under the following conditions: He flow rate, 80 ml/min; column temperature, 200°C; Injector temperature, 250°C; Detector temperature, 250°C. Under these conditions the liquid, 35, had a retention time of four minutes and the solid had a retention time of seven minutes. The solid was collected and its n.m.r. spectrum taken. This was equivalent to that reported for trans-stilbene. Compound (-)-35 was collected and its rotation measured, $[\alpha]^{25}_{D,\ 436} = -4.64\ ,\ -10.1^{\circ}$ (c 1.8, benzene).

Run 2

Azo compound (-)-29 (0.46 g), $[\alpha]^{25}_{D} = -12.88^{\circ}$ (c (c 2.95, benzene), $n^{25}_{D} = 1.5527$, and butanethiol (3.48 g) were dissolved in 50 ml of benzene and placed in a bomb. This was flushed with nitrogen and sealed. Decomposition was carried out at 110°C for fifteen hours. The bomb was cooled and opened. A sample of the solution was saved for analysis and the remainder was taken and solvent evaporated off. The coupling product, (+)-35, was isolated from the residue by preparative g.l.c. using Carbowax 20M at a temperature of 200° and a helium flow rate of 85 ml/min. Under these conditions, the retention time of the coupling product was about five minutes. Forty milligrams of (+)-35 was isolated. This was dissolved in 1 ml of benzene and rotations taken at three wavelengths, $[\alpha]^{25}_{D,\ 546,\ 346} = +2.45^{\circ}, +3.2^{\circ}$ and $+5.8^{\circ}$ (c 4.0, benzene).

Run 3

Azo compound (-)-29 (0.45 g), and butanethiol (3.9 g) were made up to 50 ml with pentane. This was placed in a bomb which was flushed with nitrogen before sealing. The decomposition was carried out at 110°C. After decomposition was complete and the solvent removed, (+)-35 was isolated by preparative g.l.c. (+)-35 had rotations of $[\alpha]^{25}_{D,\ 546,\ 436} = +2.42^{\circ}, +2.83^{\circ}, +5.07^{\circ}$ (c 2.3, benzene).

Run 4

Azo compound, (-)-29 (1.17 g), dissolved in 40 ml of butanethiol was decomposed at 110°C for twenty hours. The solvent was evaporated and (+)-35 isolated from the residue by preparative g.l.c. as described for the earlier runs. The isolated hydrocarbon had a refractive index of n_D^{25} 1.5565. Its n.m.r. spectrum was taken and was found identical with those obtained for synthesized material. The optical rotations were measured, $[\alpha]^{25}_{D,\ 546,\ 346} = +2.23^{\circ}, +2.87^{\circ}, +5.16^{\circ}$ (c 6.38, benzene). A second pass through the fractometer was then performed and the rotation of collected material was $[\alpha]^{25}_{D,\ 546,\ 436} = +2.39^{\circ}, +3.03^{\circ}$ and $+5.54^{\circ}$ (c 4.2, benzene).

Run 5

Azo compound, (-)-29 (0.36 g), was dissolved in 110 ml of redistilled benzene and placed in a bomb which was

flushed with nitrogen and sealed. The bomb was then heated for twenty hours at 110°C. The reaction mixture was then concentrated and the hydrocarbon product, (+)-35, isolated by preparative g.l.c. The optical rotations were measured $[\alpha]_{D,\ 546,\ 436} = +1.37^{\circ}, +1.52^{\circ}, +2.67^{\circ}$ (c 3.9, benzene).

Run 6

Azo compound, (-)-29 (0.6 g), and butanethiol (4.2 g) were dissolved in 45 ml of benzene and heated for three and one half days at 86°C. The coupling product, (+)-35, was isolated from the reaction mixture by preparative g.l.c. The rotations were $[\alpha]_{D,\ 546,\ 436} = +2.09^{\circ}, +2.95^{\circ}, +5.11^{\circ}$ (c 4.2, benzene).

Product distribution in scavenged runs

In runs 2, 3 and 4, samples of the decomposition mixture before evaporation of solvent were saved in order to determine by g.l.c. analysis (Carbowax 20M column) the relative quantities of 2-phenylbutane and coupling product, 35. This was done by temperature programmed analysis. The initial column temperature was 100° rising to 200° over thirty minutes. The results of these experiments are shown in Table XIX.

Decomposition in presence of thiophenol

Azo compound 29 (0.28 g) and thiophenol (2.65 g) were dissolved in 25 ml of benzene. The bomb was flushed with nitrogen and sealed. The solution was heated for twenty hours. Analysis of the reaction mixture was by temperature programmed g.l.c. (Carbowax 20M column). A similar procedure was adopted for thiophenol-pentane solvent. The results are shown in Table XIX.

CONCLUSION

These investigations into stereochemistry of the cage recombination in the decomposition of azo compounds show that cage products were 85-90% racemic. A similar study by Greene and Berwick (39) on the decomposition of optically active 1,1'-diphenylazoethane confirmed these findings.

These results contrast with those obtained for the decomposition of optically active diacyl peroxides by Greene (22), Kharasch and coworkers (23) and deTar and coworkers (24). They found 15-30% racemization in the alcohol moiety of the esters produced.

A mechanism proposed for ester formation in the decomposition of diacyl peroxide involves cleavage to two acyl radicals followed by loss of carbon dioxide from one to form an alkyl radical. This alkyl radical then combines with the other acyl radical in the solvent cage.

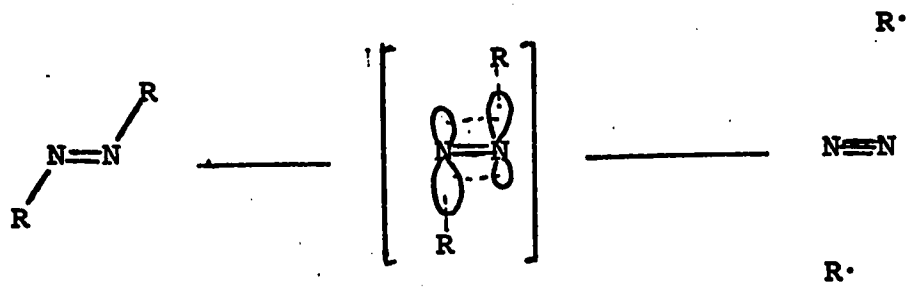
Since the results indicate a high degree of retention of configuration, this implies that the alkyl radical formed had retained its asymmetry. For this to occur, the coupling of the alkyl radical with the acyl radical must be very fast relative to its rate of rotation and it must have been generated in close proximity to the acyl radical. This implies that loss of carbon dioxide from the acyl radicals must be very fast. If this is the case, then it

is surprising that more hydrocarbon coupling product is not formed in these reactions. Rapid loss of carbon dioxide does not seem probable in view of Martin and Taylor's finding that there is a high degree of recombination of acyl radicals to regenerate the starting material in the decomposition of acetyl peroxide (125). It would seem, therefore, that the high degree of retention observed might be due to an alternate mechanism for the formation of ester product formed in these decompositions.

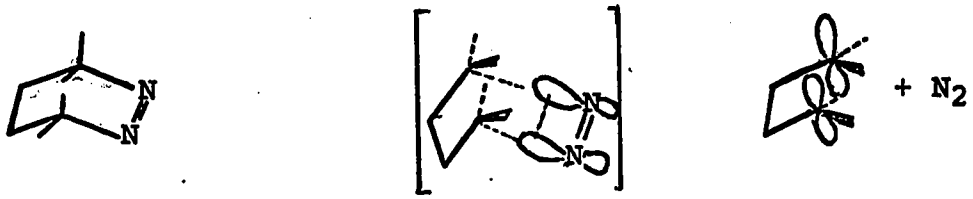
Decomposition of meso- and dl-3,6-diethyl-3,6-dimethyl-3,4,5,6-tetrahydropyridazine yielded the corresponding cyclobutanes with 98% retention of configuration (38). The difference between these azo compounds and cyclic azoalkanes is in the geometry of the nitrogen-nitrogen double bond. In acylic azoalkanes, the two alkyl groups are in a trans conformation. Therefore, as they decompose, the carbon nitrogen bonds stretch and alkyl groups move so as to permit overlap of the nitrogen orbitals. The result of this is the two alkyl radicals when formed are an estimated 7 ^{o}A apart and are separated by a molecule of nitrogen (37).

On the other hand, the substituted tetrahydropyridazines have cis geometry about the nitrogen-nitrogen double bond. Decomposition should bring the two α-carbons closer together. This may explain the much higher degree

of retention of configuration. However, it would be expected that orbitals of the trigonal carbon atoms would be parallel to each other immediately following decomposition so that it would appear that inversion and retention of configuration are equally probable.



transition state



transition state

A stereochemical study of this kind could be used to investigate the nature of the cage effect since product arising from primary recombinations would be expected to yield product of higher retention of configurations than that arising from secondary recombinations. However, the scavenger, butanethiol, used in this study, was of low reactivity so that interference with secondary recombi-

nation was neither anticipated nor observed. The results indicate, however, that some diffusion in the solvent cage is possible. Since the lifetime of a collision (126) (10^{-11} seconds) is of the same order of magnitude as the relaxation time for rotation and since the rate of coupling to rotation, k_c/k_r, indicates that the radicals can rotate ten to twenty times faster than they couple, some diffusion by radicals, which contribute to the cage effect, may occur.

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