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THE UNIVERSITY OF ALBERTA

SOME ASPECTS OF HETEROCYCLIC, ORGANOTHALLIUM, AND NITROSOALKANE CHEMISTRY

BY

JOHN SMITH

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF

DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING, 1973

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

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

"SOME ASPECTS OF HETEROCYCLIC, ORGANOTHALLIUM, AND NITROSOALKANE CHEMISTRY"

submitted by JOHN SMITH in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

.....John Hoog.....
Supervisor

.....Robert G. Brown.....

.....Alan Jones.....

.....Fred Stone.....

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External Examiner

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.....R. H. Wightman.....
External Examiner

Date ....April 27, 1973....

TO MOM AND DAD

All I have learned, shows me this -
How scant, how slight, my knowledge of her is.

John Masefield.

A B S T R A C T

The acid catalyzed nitrosation of 1,3-diphenylpropan-2-one was investigated in detail. It was established that the novel heterocyclic product isolated as the major component was identical to that obtained from the nitrosation of 1,3-diphenyl-1-oximidoprop-2-ene. The structure of the heterocyclics produced in these reactions was unequivocally established, by X-ray crystallographic analysis, to be of the diazacyclopentadienone oxide class.

The utility of the thallium enolates of some cycloalkanones, β-ketosulfoxides and β-dicarbonyl compounds, and some thallium nitronates in promoting C-alkylation was investigated. In all cases, alkylation provided mixtures of products. The thallium cation-counter anion combination appeared to offer no advantage over the more commonly employed alkali metal counterparts.

The deoxygenation of a number of aliphatic nitrosoalkanes was examined in the presence of triethylphosphite. Deoxygenation was found to proceed readily, with concomitant migration of a group from the α-carbon atom to nitrogen. In the majority of cases investigated, migration was not found to be selective. The reaction resulted in a mixture of imines as the primary products. Some attempt was made to probe the mechanistic nature of the reaction.

An extension of the deoxygenation reaction to in-

clude N-nitrosoalkanes was attempted. Investigations with a number of trivalent phosphorus compounds failed to produce azo compounds.

A C K N O W L E D G E M E N T S

The author wishes to thank Messrs. R. Swindlehurst and G. Bigam and their staffs for the recording of the infrared and nmr spectra, Dr. A. Hogg, Mr. A. Budd and the staff for running the mass spectra, and Mrs. D. Mahlow and Mrs. A. Dunn for determining the microanalyses. A special vote of thanks is due to Mrs. M. Waters for the typing of this manuscript.

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Many thanks are due to the members of "the group" for the hours of helpful discussion and constructive criticism, and for providing a pleasant atmosphere in which to work; and to my wife Christine whose constant patience and encouragement has added immeasurably to the outcome of this work.

Finally, the author wishes to express his sincere thanks to his research director, Dr. J. Hooz, for providing not only the basic ideas from which this work has stemmed, but also the encouragement and assistance necessary to develop them.

TABLE OF CONTENTS

Page

ABSTRACT vi

ACKNOWLEDGEMENTS viii

LIST OF TABLES xi

Studies Relating to the Preparation and Structure of the 3,4-Diazacyclopentadienone Oxides

Introduction 1

Results and Discussion 7

Experimental 15

Studies Concerning the Preparation and Alkylation of some Thallium Nitronates, and the Thallium Enolates of Certain Ketones, β-Ketosulfoxides, β-Ketoesters and β-Diketones

Introduction 25

Results and Discussion 39

Preparation and Alkylation of some Thallium Nitronates 39

Studies Related to the Alkylation of Thallium Enolates of some Cyclic Ketones. 50

Preparation and Alkylation of the Thallium Enolate of a β-Ketosulfoxide, and some β-Diketones and β-Ketoesters 61

Experimental 69

Page

Deoxygenation of Aliphatic C-Nitroso and N-Nitroso-alkanes with Trivalent Phosphorus Reagents

Introduction 95

Results and Discussion 102

Experimental 114

References 132

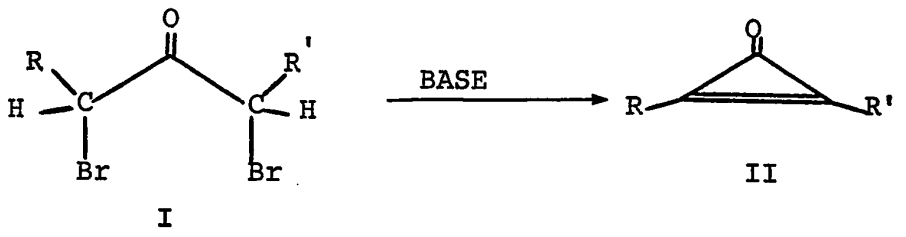
L I S T O F T A B L E S

Table		Page
I	The Reduction of Cyclohexanone with Thallous Ethoxide	56
II	Homogeneous Alkylation of the Thallium Enolates of Cyclohexanone and Cyclopentanone	59
III	Alkylation of the Thallium(I) Salt of ω-Methylsulfinylacetophenone	64
IV	The Alkylation of the Thallium(I) Salts of Acetylacetone and Ethylacetoacetate	66
V	Reaction Conditions for the Attempted Alkylation of the Thallium Salt of Nitromethane	73
VI	Deoxygenation of a Series of Aliphatic-Nitrosoalkanes with Triethylphosphite	104

STUDIES RELATING TO THE PREPARATION AND STRUCTURE OF THE 3,4-DIAZACYCLOPENTADIENONE OXIDES

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

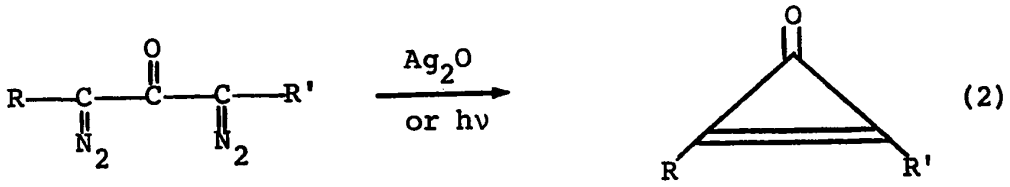
The synthesis of small, highly strained ring systems poses unique problems for the synthetic organic chemist. This fact reflects itself in the scarcity of routes available for the synthesis of one group of these compounds namely, the cyclopropenones. Indeed, at the commencement of this work, only one method was available for the synthesis of substituted cyclopropenones from acyclic precursors [1], that involving the base-catalysed cyclization



I II (1)

of α,α'-dibromoketones (eq. 1).

Conceptually, an attractive route to such ring systems involves the decomposition of 1,3-bisdiazoketones III in a manner somewhat analogous to the known method described below (eq. 2).

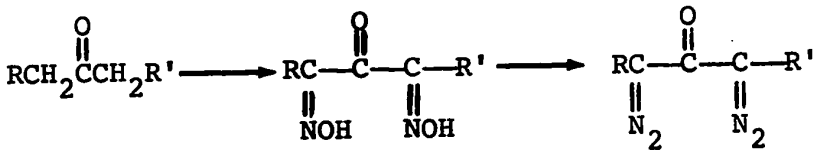


(2)

III II

The feasibility of this route has, since the completion of the work done in this thesis, been verified by Whitman and Trost [2], who have shown that the decomposition of 1,3-bisdiazo-1,3-diphenylpropan-2-one (III, R = R' = Ph) in methanolic silver oxide leads to, amongst other products, diphenylcyclopropenone (II, R = R' = Ph).

One approach to the required bisdiazoketones (III) involves either acid or base catalysed nitrosation [3] of the corresponding ketones (IV), followed by Forster reduction [4] of the 1,3-dioximes (V) thus obtained (eq. 3).



(3)

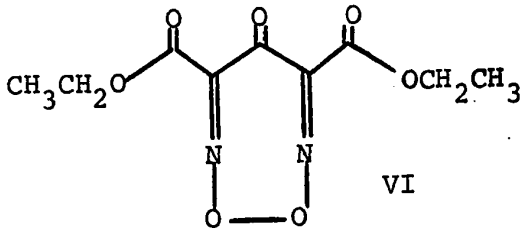
IV V III

This scheme has in fact been employed with success by Cava and co-workers [5] in the synthesis of steroidal α,α'-bis-diazoketones, and also more recently by other authors [6,7]

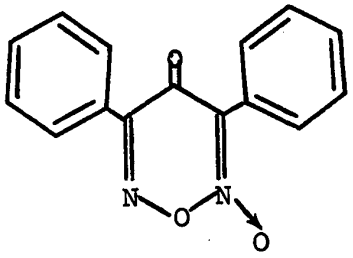
as a general route to cyclic α,α'-bisdiazoketones.

At the outset, initial attempts made by Gilani [8] to obtain the 1,3-dioxime (V, R = R' = Ph), via acid catalysed nitrosation of 1,3-diphenylpropan-2-one (IV, R = R' = Ph), resulted in the isolation of a novel heterocycle as the sole product. Henry and von Pechmann [9] had reported a similar observation concerning the oxidative nitrosation of acetone dicarboxylic ester, and had assigned the seven-membered ring structure (VI) to the isolated heterocyclic material. The stability of the compound isolated by Gilani [8] toward heat and acid was, however, inconsistent with an analogous seven-membered ring heterocycle containing such a peroxy linkage, but the spectral and analytical data were consistent with formulation of the product as either the six-membered ring oxadiazine-N-oxide (VII), or the five-membered ring diazacyclopentadienone oxide (VIII).

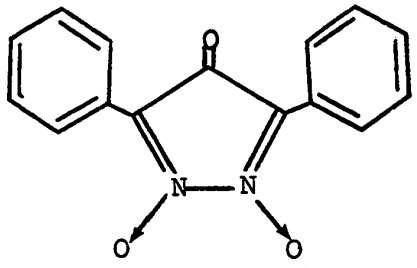
A consideration of the two possible structures, taken in conjunction with the well documented cyclization of 1,2-dioximes to furoxans [10], indicates that the product may have arisen as a result of oxidative ring closure of an intermediate 1,3-dioxime (V, R = R' = Ph). Strong support for this idea was recently provided by Freeman and co-workers [11], who have prepared the five-membered ring 2,5-diphenyl-3,4-diazacyclopentadienone oxide



VI

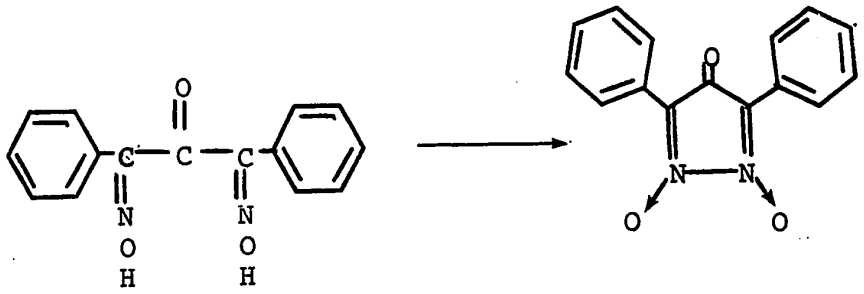


VII



VIII

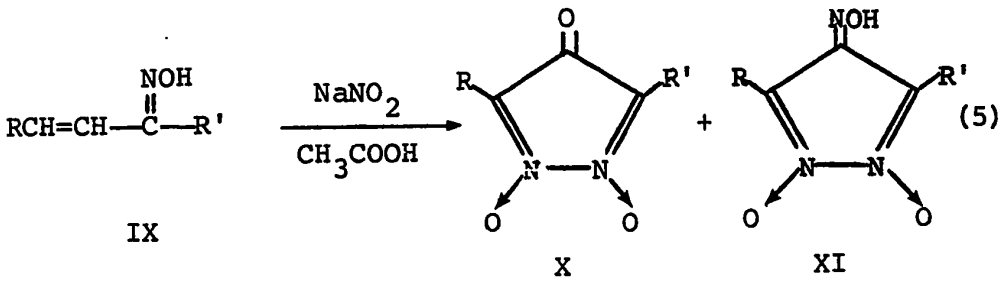
(VIII) by cyclization of the corresponding 1,3-dioximido-1,3-diphenylpropan-2-one with a suitable oxidizing agent (eq. 4).



(4)

Subsequent to the initial investigation by Gilani [8] and Klaubert [12], the question of the absolute structure of these heterocycles has become the subject of some discussion. Thus Unterhalt [13,14], and independently Freeman [15] have reported the formation of a number of five-membered ring

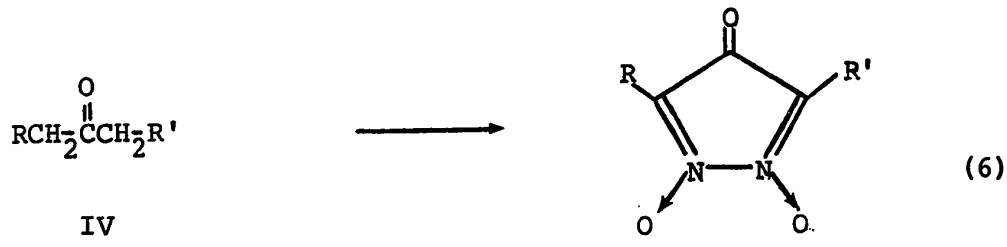
3,4-diazacyclopentadienone oxides and their oximes from the oxidative nitrosation of β-substituted α,β-unsaturated oximes (IX) (eq. 5)



IX X XI (5)

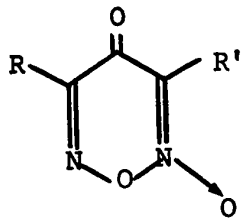
The reaction had in fact been investigated somewhat earlier by Ponzio and co-workers [16], following initial studies by Harries.[17]

It is of particular significance, that in addition to formulating the structures of the isolated products as the five-membered ring dioxides X and XI, Freeman [15] reported that the keto products X were in fact identical to the compounds isolated from the nitrosation of certain ketones (eq. 6).



IV X (6)

There exists little doubt that the compound isolated by Gilani[8] is identical with that reported by Freeman [15] and by Unterhalt [14], and the assignment of its structure as the N,N-dioxide VIII is strongly supported by physical and chemical evidence. Nuclear magnetic resonance studies [13,15] of a number of such compounds indicates the magnetic equivalence of the groups R and R', thus ruling out the six-membered unsymmetrical structure XII.



XII

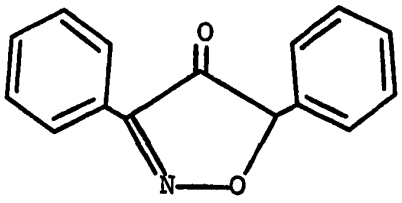
Further chemical evidence has been cited [15] which indicates a relationship between the heterocyclics in question, and five-membered ring pyrazole derivatives, observations which are also in concert with certain results obtained from early investigations by Klaubert.[12]

The purpose of this work was to investigate in more detail the nitrosation of dibenzyl ketone, and, in view of the novel structural features, to obtain unequivocal proof, by way of crystallographic analysis, of the structure of the heterocyclic product isolated in the reaction.

RESULTS AND DISCUSSION

The work of Gilani [8] concerning the nitrosation of 1,3-diphenylpropan-2-one had resulted in the isolation of a novel heterocyclic product. The low yields of recovered material reported (a maximum isolated yield of 15%) prompted a more detailed re-examination of the reaction in the hope of providing further information concerning the cyclization process.

Treatment of 1,3-diphenylpropan-2-one with butyl nitrite in the presence of an acid catalyst, as described by Klaubert [12], provided a red crystalline material (14%), showing physical and spectral properties identical to those described for the heterocyclic compound isolated previously.[8,12] Although the formation of additional products was not reported by earlier workers, treatment of the mother liquors resulting from purification of the major product, yielded a white cyrstalline material (2%), which showed (by infrared (ir) spectroscopy) a carbonyl absorption at 1790 cm^{-1}. The physical and spectral properties were consistent with formulation of the compound as 4 (5H)-3,5-diphenylisoxazolone [18] (XIII). Precedence is found in the observations of Henry and von Pechmann [9], who have reported the isolation of an analogous product from the nitrosation of acetone dicarboxylic ester. A comparison of the properties of an



XIII

authentic sample [18] of XIII with those of the minor product isolated in this present work, however, indicated that assignment of the isoxazolene structure was incorrect. Owing to the small amount of material obtained, and its tedious isolation, the exact nature of this minor product has remained undetermined.

In an attempt to isolate and identify other products, the mother liquors obtained from isolation of the major product was further treated with 2,4-dinitrophenylhydrazine reagent. This resulted in the formation of a mixture of at least six compounds (by thin layer chromatography (tlc)). Unfortunately, these components could not be successfully separated by the more commonly employed chromatographic techniques. As a result, further efforts were directed toward reducing the probability of the side reactions from which the problems presumably arise.

The reaction was repeated at a lower temperature. Significantly, the evolution of nitrous fumes, observed with earlier reactions at 25°, was not evident here, and

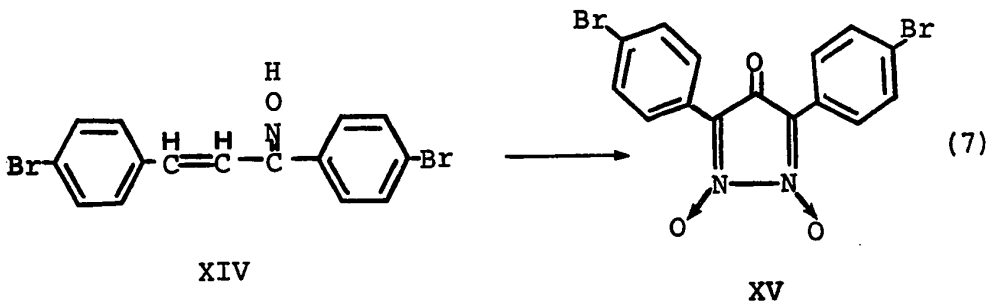
after work up, the red heterocyclic product was isolated in only very poor yield (2%). In addition, the unidentified minor product isolated from the earlier reaction was not obtained. Instead, it seemed, the monoxime, 1,3-diphenyl-1-oximidopropan-2-one was isolated, suggesting that at lower temperatures, oximation could proceed, but that cyclization to produce the red heterocyclic product was somewhat retarded.

Further attempts to isolate and identify other products proved fruitless, and as a result, further effort was not expended in this area.

At this time, it was desirable to obtain unequivocal proof (by means of X-ray crystallographic analysis) of the exact structure of the major heterocyclic product isolated from the above reaction. To aid in the practical evaluation of the structure, it was chosen to prepare the *p*,*p*'-dibromophenyl analogue XV. At the outset, confirmation was sought that the compounds X reported by Freeman and Surbey [15] (eq. 5) were in fact identical to those obtained from the nitrosation of the corresponding ketones (eq. 6). Thus, 1,3-diphenyl-1-oximidoprop-2-ene (IX; R = R' = Ph) was allowed to react with nitrous acid in the presence of oxygen, as described.[15] This afforded a product which exhibited physical and spectral properties identical to those of the heterocycle isolated

from the nitrosation of 1,3-diphenylpropan-2-one (IV, R = R' = Ph).

As a direct consequence of this result, and in light of the higher yields of heterocyclic material reported [15] from the oxime route, it was chosen to prepare the required *p,p'*-dibromophenyl compound XV via nitrosation of the corresponding α,β-unsaturated oxime XIV (eq. 7).



XIV XV (7)

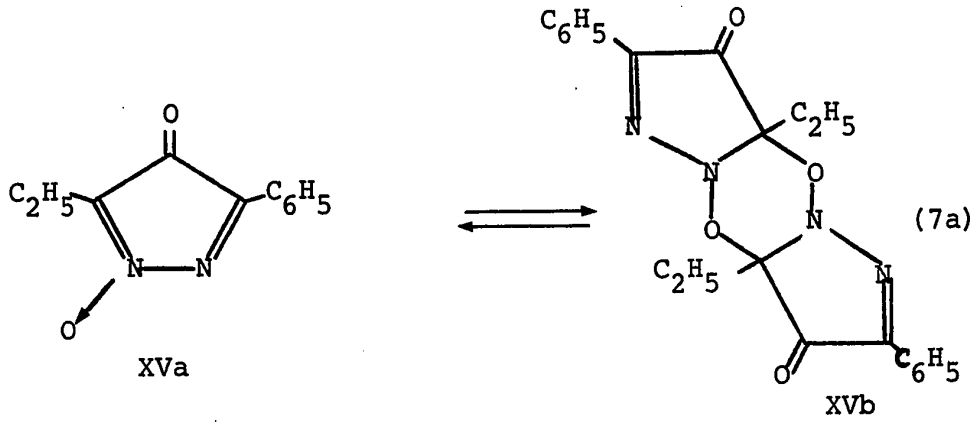
The starting enone, 1,3-di-(*p*-bromophenyl)-prop-2-en-1-one, was prepared by a modification of the method of Kohler and Chadwell.[19] Subsequent acid catalyzed oximation of the chalcone in standard fashion [19], resulted in formation of the required oxime (XIV) in good yield, although subsequent purification proved somewhat tedious (see experimental section for details).

Reaction of the oxime with excess sodium nitrite in an oxygenated acidic medium resulted in the isolation of an amorphous yellow solid (70%). It showed ir absorp-

tion for a carbonyl function at 1700 cm^{-1}, an absorption differing considerably from that expected for the required heterocyclic product (XV). Attempted purification of this material even by simple recrystallization from methylene chloride, resulted in recovery of a red crystalline product (17%), later shown to be the required 2,5-di-(*p*-bromophenyl)-3,4-diazacyclopentadienone oxide (XV). This material showed carbonyl absorption at 1638 cm^{-1}.

Isolation of the labile intermediate proved surprising, since the formation of such an intermediate from the nitrosation procedure had not been reported previously by other investigators.[13-15] The compound isolated in the present study was found to be air stable for long periods of time. However, attempts to determine its nature were frustrated, since no suitable purification technique could be found. Recrystallization, for example, resulted in the formation, and isolation of the red heterocyclic product XV.

In a recent investigation of the preparation of the 3,4-diazacyclopentadienone monoxide (XVa), Freeman and coworkers [11] reported the isolation of a labile species exhibiting similar charactersitics to those observed here. On the basis of its carbonyl absorption, and its facile conversion (upon simple dissolution) to the monomeric material (XVa), these authors have assigned the dimeric structure XVb to the labile species (eq. 7a). In the light of the



XVa

XVb

(7a)

present observations, assignment of an analogous dimeric structure to the material isolated in this work, appears to be plausible.

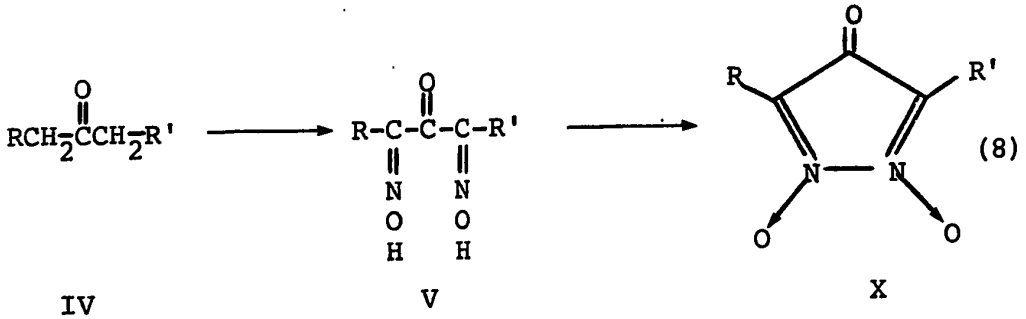
Further efforts in this area were directed toward the initial objective, that of obtaining material (XV) suitable for X-ray crystallographic analysis. Thus, the product was carefully recrystallized from methylene chloride, and submitted for diffraction studies, and high resolution nmr spectroscopy. The latter technique in fact confirmed earlier reports [13-15] that the structures of the compounds in question are symmetrical (when R = R' in X). In this case, nmr indicated both sets of aromatic protons as one simple AA'BB' quartet centred at δ 7.96.

X-ray analysis performed by Dr. N. Masaki showed that the product was indeed the symmetrical 2,5-di(*p*-bromophenyl)-3,4-diazacyclopentadienone oxide XV. The material crystallizes from methylene chloride as the monoclinic space group Cc with four molecules in the unit cell of

dimensions a = 10.59, b = 12.11, c = 12.40 Å. The intensities of 1010 reflections were visually estimated for the a and c-axes photographs. The structure was solved by the heavy atom method, and refined by full matrix least squares method to an R factor of 0.21.

The molecular structure so derived is shown in Fig. 1, where all the atoms in the molecule, excluding hydrogen are represented.

Subsequent to the work done in this thesis, Freeman and coworkers [11] have reported further studies relating to the preparation and structure of the 3,4-diazacyclopentadienone oxides, and their results again confirm the five-membered ring structure herein proven. On a mechanistic note, these authors also report the cyclization of 1,3-dioxoimido-1,3-diphenylpropan-2-one to the heterocycle X (where R = R' = Ph) in the presence of a suitable oxidizing agent, adding credence to the hypothesis that the formation of such products results from initial dinitrosation (or oximation) of the ketone (IV) followed by oxidative cyclization (eq. 8).



IV V X (8)

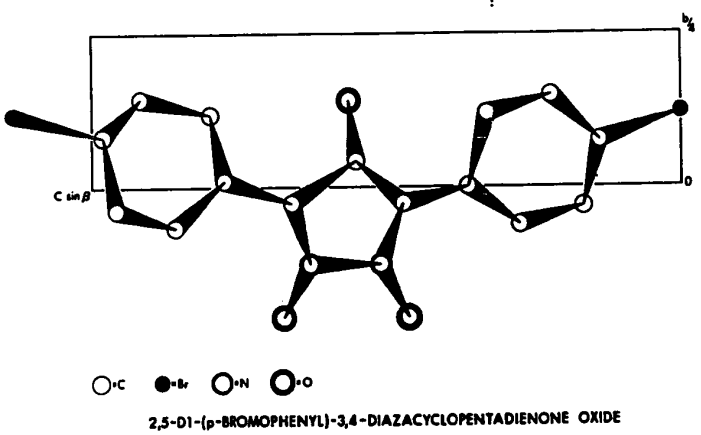


FIGURE 1. Perspective drawing of a molecule of 2,5-di-(*p*-bromophenyl)-3,4-diazacyclopentadienone oxide.

EXPERIMENTAL

General Considerations

Infrared (ir) spectra were measured using a Perkin-Elmer Model 421 high resolution grating Infrared Spectrophotometer.

Ultraviolet (uv) and visible (vis) spectra were determined using a Perkin-Elmer Ultraviolet-Visible Spectrophotometer Model 202.

Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 or HA-100 Spectrometer, and unless otherwise stated, deuterochloroform ($CDCl_3$) was employed as the solvent with tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in δ values. The following abbreviations are used in the text: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet.

Mass spectra were recorded on an AEI Model MS-2 or Model MS-9 Spectrometer. Spectra are recorded in the following manner: m/e: peak mass (relative intensity).

Elemental analyses were performed either by Galbraith Laboratories Inc., Knoxville, Tennessee, or by the Microanalytical Laboratory, University of Alberta.

Melting points were determined using a Fisher-Johns or a Reichert melting point apparatus and are uncorrected.

The X-ray crystallographic structure determination was carried out by Dr. N. Masaki, University of Alberta.

Reaction of 1,3-Diphenylpropan-2-one with *n*-Butyl Nitrite at 23°.[8,12]

To a magnetically stirred solution of 1,3-diphenylpropan-2-one (2.08 g; 10 mmole) and concentrated hydrochloric acid (16.0 ml) in methyl cellosolve (36 ml), cooled to 0°, was added dropwise *n*-butyl nitrite (6.2 g; 60 mmole). After addition was complete, the solution was stirred at 23° for 1 hr. During this time, the solution turned red with evolution of red-brown fumes. The mixture was poured onto crushed ice whereupon a dark brown oil separated. This somewhat viscous product was collected by filtration, and after washing with ice cold ethanol, yielded a reddish-brown solid (0.59 g). Four successive recrystallizations from methylene chloride-ethanol yielded 2,5-diphenyl-3,4-diazacyclopentadienone oxide as long red needle-like crystals, mp. 196-197° (lit.[14] 195-197°) in 14% yield: ir ($CHCl_3$) 1640 (C=O), 1495, 1450, 1360, 1130, 680 cm^{-1}; uv max (CH_2Cl_2) 257 (ε = 50,000), 336 mμ (ε = 5,000); vis max (CH_2Cl_2) 455 mμ (ε = 2,000); nmr: δ 8.10 - 8.50 (m, 4, Ar), 7.32 - 7.61 (m, 6, Ar); mass spectrum:m/e:(Calcd. for $C_{15}H_{10}N_2O_3$: 266.0691. Found: 266.0692): 119(33), 105(25), 104(16),

103(100), 89(15), 77(25), 76(30). Anal. Calcd. for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.76; N, 10.53. Found: C, 67.42, H, 4.05; N, 10.31.

The ethanol wash obtained from purification of the above product was concentrated to *ca.* 15 ml on a rotary evaporator and cooled to -10° for 24 hr. Filtration yielded a pale orange solid (0.16 g), which upon four successive recrystallizations from 95% ethanol yielded a white solid (2%), mp. 114°; ir ($CHCl_3$) 1790 (C=O), 1595, 1570, 1490, 1410 cm^{-1}; nmr: δ 8.05 - 8.17 (m, 2, Ar), 7.30-7.50 (m, 8, Ar), 6.06 (s, 1, CH); mass spectrum: m/e: 237 (0.2), 194(14), 193(88), 192(15), 166(8), 165(20), 119(6), 118(49), 105(19), 103(10), 91(10), 90(100), 89(50), 77(28). Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.95; H, 4.64; N, 5.91; Found: C, 75.93; H, 4.68; N, 5.72.

Reaction of 1,3-Diphenylpropan-2-one with *n*-Butyl Nitrite at 0°.

The reaction was carried out as described above, with the following changes: After addition of the *n*-butyl nitrite the reaction solution was stirred at 0° for 30 min. Although the mixture turned red in colour, there was no evolution of red-brown fumes. The mixture was poured onto crushed ice and stirred until crystals appeared.

The product was collected by filtration and washed with 95% ethanol (40 ml) to give a red brown solid (0.04 g). This material was recrystallized from methylene chloride-ethanol to give 2,5-diphenyl-3,4-diazacyclopentadienone oxide, mp. 196 - 197° (lit.[14] 195 - 197°). Spectral data were identical to that obtained above. The ethanol wash solution was concentrated to *ca.* 15 ml on a rotary evaporator, and after cooling to about -10° for 24 hr, yielded a white crystalline solid. Recrystallization from ethanol-water afforded 1,3-diphenyl-1-oximido-propan-2-one as a white crystalline solid, mp. 113 - 114° (lit.[21] 114 - 115°) in a 2% yield: ir ($CHCl_3$) 3550 (OH), 3290 (OH), 1695 (C=O), 1605 (C=N), 1500, 1360,910 cm^{-1}; nmr: δ 8.25 (s, 1, OH exchanged with D_2O), 7.02 - 7.42 (m, 10, Ar), 4.21 (s, 2, CH_2); mass spectrum:m/e:(Calcd. for $C_{15}H_{13}NO_2$: 239.0946. Found: 239.0946): 120(15), 118(37), 103(9), 92(9), 91(100), 77(23).

Preparation of 4,(5H)-3,5-Diphenylisoxazolone [18]

To a solution of hydroxylamine hydrochloride (1.2 g; 17 mmole) in water (20 ml) was added, all at once, 1,3- diphenyl-2-hydroxypropan-1,3-dione acetate [22] (3.2 g; 11 mmole) in 95% ethanol (80 ml). The resulting solution was refluxed for 2 hr, then diluted with hot water (20 ml). Upon cooling, a precipitate formed. The solid was collected by filtration, dissolved in 5% sodium hydroxide solution, and

reprecipitated by acidification with dilute hydrochloric acid. Recrystallization from ether-hexane yielded 4, (5H)-3,5-diphenylisoxazolone as a white crystalline solid (32%), mp. 121 - 122° (lit.[18] 122 - 123°): ir ($CHCl_3$) 1690 (C=O), 1595, 1580, 1490, 1450, 1315, 1285, 905 cm^{-1}; nmr: δ 7.35 - 8.05 (m). Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.95; H, 4.64; N, 5.91. Found:C, 75.66; H, 4.99; N, 5.91. A comparison of the properties with the minor component isolated above from the nitrosation of 1,3-diphenylpropan-2-one at 23° indicated that the compounds were not identical.

Preparation of 1,3-Diphenylprop-2-en-1-one Oxime [20]

Admixture of 1,3-diphenylprop-2-en-1-one (20.0 g; 100 ml) and hydroxylamine hydrochloride (13.0 g; 160 mmole) was refluxed in absolute ethanol (500 ml) for 8 hr. The ethanol was removed using a rotary evaporator, and the viscous residue shaken with water (100 ml). The mixture thus obtained was extracted with ether (2 x 50 ml), and the ethereal extracts dried over anhydrous magnesium sulfate. The dried extract was concentrated to yield a yellow-orange oil (7.0 g). This was dissolved in the minimum of boiling 95% ethanol and filtered hot. On cooling, the solution yielded pale yellow crystals which, after recrystallization from 95% ethanol (several times), afforded colour-

less crystals of 1,3-diphenyl-1-oximidoprop-2-ene (3.6 g; 16%), mp. 115 - 116° (lit.[20] 115 - 116°): ir ($CHCl_3$) 3580 (OH), 3240 (OH), 1620 (C=N), 1490, 1445, 1360 cm^{-1}; nmr: δ 9.60 (s, 1, OH, exchanged by D_2O), 7.70 (d, 1, C=CH), 7.15 - 7.60 (m, 10, Ar), 6.82 (d, 1, HC=C); uv max (EtOH) 291 (ε = 21,000), 240, 234, 227, 221, 207 mμ; mass spectrum: m/e: 223(30), 222(76), 207(34), 206(100), 205(10), 204(8), 130(9), 128(15), 105(14), 104(13), 103(18), 102(11), 77(36). Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.72; H, 5.83; N, 6.28. Found: C, 80.50; H, 5.83; N, 6.43.

Preparation of 2,5-Diphenyl-3,4-diazacyclopentadienone Oxide from 1,3-Diphenylprop-2-en-1-one Oxime [15]

To a magnetically stirred solution of 1,3-diphenyl-1-oximidoprop-2-ene (2.23 g; 10 mmole) in glacial acetic acid (50 ml), under an atmosphere of oxygen, was added, dropwise, a solution of sodium nitrite (1.87 g, 27 mmole) in water (5 ml). After addition was complete, a fine orange precipitate resulted, which gradually became deeper in colour with further stirring. After 2 hr, the red solid (4%) was collected by filtration. After recrystallization from methylene chloride-ethanol, there was obtained, 2,5-diphenyl-3,4-diazacyclopentadienone oxide, mp. 194 - 196° (lit.[14] 195 - 197°). The product thus isolated was identical in all respects to the major product isolated

from the nitrosation of 1,3-diphenylpropan-2-one.

Preparation of 1,3-Di-(*p*-bromophenyl)-prop-2-en-1-one [19]

To a solution of sodium hydroxide (3.25 g; 80 mmole) in water (30 ml) and ethanol (15 ml) cooled to *ca.* 10°, was added, with stirring, *p*-bromoacetophenone (10.7 g; 55 mmole). *p*-Bromobenzaldehyde (10.0 g; 55 mmole) was then added, and the suspension was stirred for 10 min. at 10°, and for a further 3 hr. at 25°. Cooling to 0° for 10 hr., produced a yellow solid which was collected by filtration. After trituration with warm 95% ethanol, there was obtained 1,3-di-(*p*-bromophenyl)-prop-2-en-1-one as a yellow powder (3.0 g; 75%), mp. 188 - 189°. Recrystallization from toluene yielded fine yellow crystals, mp. 187 - 188° (lit.[23] 187.5°): ir (KBr) 1660 (C=O), 1600, 1580, 1490 cm^{-1}; nmr (DMSO-d_6): δ 8.18 (d, 1, C=CH), 7.75 - 7.98 (m, 8, Ar), 7.75 (d, 1, C=CH); uv [24] max (dioxane) 244 (ε = 10,000) 317 mμ (ε = 24,000); mass spectrum m/e:368(50), 367(47), 366(100), 365(72), 364(53), 363(33), 287(83), 285(83), 211(22), 209(22), 185(27), 183(32), 178(23), 157(17), 155(19), 102(32), 89(31), 76(32), 75(27). Anal. Calcd. for $C_{15}H_{10}OBr_2$: C, 49.18; H, 2.73; Br, 43.72. Found: C, 49.15; H, 2.75; Br 43.41.

Preparation of 1,3-Di-(*p*-bromophenyl)-prop-2-en-1-one Oxime [20]

Admixture of 1,3-di-(*p*-bromophenyl)-prop-2-en-1-one (7.32 g; 20 mmole) and hydroxylamine hydrochloride (2.6 g; 32 mmole) was refluxed in absolute ethanol (100 ml) with a few drops of dilute hydrochloric acid for 12 hr. On cooling, a white solid separated which was collected by filtration. Recrystallization from ethanol yielded a yellow powder (2.4 g; 31%), mp. 161 - 171°. The product was shown to be a mixture of oxime and unreacted ketone (by tlc). Repeated recrystallization from toluene or ethanol failed to produce a pure product. Chromatography on silica gel (0.62 g of product on 20 g of adsorbent), and elution with benzene, chloroform then ethanol-chloroform resulted simply in recovery of the two component mixture (0.57 g). Trituration of the crude product (2.0 g) with benzene (2 x 40 ml), however, followed by a final recrystallization from ethanol afforded white crystals of pure 1,3-di-(*p*-bromophenyl)-1-oximido-prop-2-ene., mp. 170 - 172°: ir ($CHCl_3$) 3570 (OH), 3250 (OH), 1620 (C=N), 1600, 1580, 1480, 1400, 930 cm^{-1}; nmr (DMSO-d_6): δ 8.37 (s, 1, OH, exchanged with D_2O), 7.57 (d, 1, HC=C), 7.38 - 7.63 (m, 8, Ar), 6.70 (d, 1, C=CH); uv max (EtOH) 222 (ε = 17,000), 298 mμ (ε = 23,000); mass spectrum:m/e:383(15),

382(47), 381(36), 380(91), 379(20), 378(46), 364(17), 285(42), 283(42), 264(21), 220(100), 204(18), 189(21), 169(14), 157(10), 155(10), 131(78), 119(28), 102(38), 100(38), 76(11), 75(12). Anal. Calcd. for $C_{15}H_{11}Br_2NO$: C, 47.24; H, 2.89; N, 3.67; Br, 41.99. Found: C, 47.23; H, 2.76; N, 3.59; Br 42.19.

Preparation of 2,5-Di-(*p*-bromopheny)-3,4-diazacyclopentadienone Oxide from the Nitrosation of 1,3-Di-(*p*-bromophenyl)-prop-2-en-1-one Oxime [15]

To a magnetically stirred solution of 1,3-di-(*p*-bromophenyl)-1-oximidoprop-2-ene (2.0 g; 5.3 mmole) in glacial acetic acid (50 ml), under an atmosphere of oxygen, was added, dropwise, a solution of sodium nitrite (1.87 g; 27 mmole) in water (5 ml). During the addition, the solution became orange in colour and after 45 min. a precipitate began to form. After stirring for 2 hr, the mixture was filtered and the solid washed with water (2 x 100 ml), then cold 95% ethanol. Air drying of the product yielded an amorphous powder (1.4 g; 70%), mp. 210 - 213°. Recrystallization from methylene chloride afforded 2,5-di-(*p*-bromophenyl)-3,4-diazacyclopentadienone oxide as red needles (0.33 g; 17%), mp. 236 - 237°: ir ($CHCl_3$) 1638 (C=O), 1580, 1485, 1400, 1360, 1070, 1006 cm^{-1}; nmr (CH_2Cl_2): δ 7.96 (q, 8, Ar): uv max (CH_2Cl_2) 270

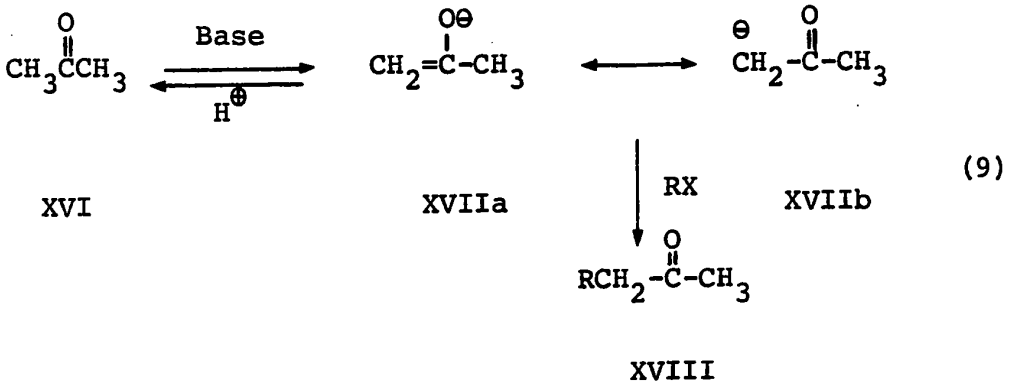
(ε = 46,000), 347 mμ (ε = 4,000); vis max (CH_2Cl_2) 460 mμ (ε = 3,000); mass spectrum: m/e: (Calcd. for $C_{15}H_8N_2O_3Br_2$: 423.8894. Found: 423.8890): 426(12), 424(24), 422(12), 200(16), 199(99), 198(18), 197(99), 195(56), 185(59), 184 (19), 183(100), 182(14), 181(100), 176(10), 169(56), 167 (56), 157(29), 155(29), 103(14), 102(98), 90(64), 88(80), 87(17), 76(49), 75(68), 74(29). Anal. Calcd. for $C_{15}H_8N_2O_3Br_2$: C, 42.45; H, 1.89; N, 6.60; Br, 37.73. Found: C, 42.55; H, 1.94; N, 6.55; Br, 37.59. The density of the compound was determined on a single crystal, the volume being determined by displacement of water. In this manner, the density was determined to be 1.525 g/cc.

STUDIES CONCERNING THE PREPARATION AND ALKYLATION OF SOME THALLIUM NITRONATES, AND THE THALLIUM ENOLATES OF CERTAIN KETONES, β-KETOSULFOXIDES, β-KETOESTERS, AND β-DIKETONES

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

The classical base catalyzed alkylation of active methylene compounds provides a general route for the homologation of a variety of species.

In general terms, the process involves removal of a proton from a carbon atom α to an activating group (for example a carbonyl, nitro, cyano, sulfur, or phenyl group), thereby forming an anion XVII which is resonance stabilized (eq. 9).



XVI XVIIa XVIIb XVIII (9)

Treatment of the anion thus obtained with an alkyl halide or other alkylating agent (RX), provides the alkylated or homologated product (XVIII).

Although the sequence as described appears conceptually simple, its practical application has proven to be

fraught with a number of serious problems [25], which result from dialkylation, Claisen-type condensations, β-dicarbonyl cleavage, oxidative coupling and O-alkylation.

The latter, that of concurrent formation of both O- and C-alkylated products is particularly prevalent in the alkylation of β-dicarbonyl compounds and relatively acidic active methylene compounds in general.[25-28] In such cases, the equilibrium concentration of enol tautomer is often relatively high (e.g. nitroalkanes, and β-dicarbonyl compounds [25]).

The possibility of a dual mode of reaction becomes clear upon examination of a typical intermediate anion (XVII for example). Covalent bond formation could conceivably occur at carbon (to give the C-alkylate), or at oxygen (to give the O-alkylate). Anions possessing this property are generally referred to as ambident [29] anions and the question of their mode of alkylation has been the subject of a great deal of investigation.[25,29-32]

The actual ratios of C- to O-alkylation of ambident anions has been shown to depend upon a number of mutually interdependent factors [25,29-32], namely: the solvent, the nature of the cation, the ambident anion, the alkylating agent and its leaving group, temperature, and the homogeneity or heterogeneity of the process.

Observations have shown [25,29-35] that, in general,

alkylation at the more electronegative atom of an ambident anion (at oxygen with enolates) is usually favoured in the presence of polar aprotic solvents,[36-40] such as hexamethylphosphoramide (HMPA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), or 1,2-dimethoxyethane (DME). A greater tendency towards carbon alkylation [33,41-45] is exhibited with polar protic, and non-polar solvents.

There would appear to be general agreement that ambident anion-counter cation combinations exist as ion pairs [46], and that the position of alkylation is determined in the main by the degree of association and aggregation of these pairs.[41,43,47-60] Thus, in non-polar solvents of low dielectric constant, the ion pairs are considered to be highly associated or to exist as ion pair aggregates.[49,50,60-64] In addition, on the basis of the electrostatic orientation of the ions, it is expected that the cation would be closest to that atom of the ambident anion which bears the highest electron and charge density.[65,66] This effective shielding of one nucleophilic centre of the ambident anion causes a greater tendency for covalent bond formation at the alternative site (carbon alkylation in preference to oxygen alkylation with enolate ions). The observed tendency toward increased oxygen to carbon alkylation ratios in polar aprotic solvents has been attributed [30,31, 41,43,57] to specific [44] solvation [36-40, 48,62,67-70]

of the cation resulting in enhanced dissociation of the ion-pair. The freer unsolvated anion is then able to alkylate at the more electronegative, and now unhindered site. The presence of unassociated ions in such systems is supported by conductance measurements.[62,71,72]

In the other extreme, the somewhat higher values of C-alkylation often observed in polar protonic solvents, where in fact some degree of dissociation may again be expected, is believed to arise through selective solvation of the anion.[41,43,62] Solvents which are able to hydrogen bond [73-76] with the more electronegative atom of the ambident anion provide some degree of steric hindrance around this centre, thus enhancing the probability of alkylation again at the alternative site.

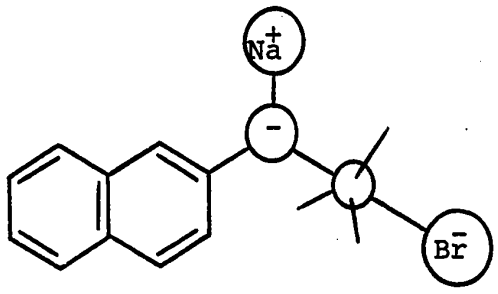
Support for the idea that enolate ions exist as ion-pairs, and that the type and degree of reactivity depends to some extent on the degree of dissociation, is found in the observations [36-40,44,48,49,54,62,67-69,77-82] that alkylations carried out in polar aprotic solvents demonstrate a very substantial increase in rate over those in alcohols or inert solvents. The increased reactivity of an anion arising from a decreased interaction with a counter-cation, or with solvent molecules with hydrogen bonding capacity, is well known.[30,36,41,62,74,75]

The general increase in O- to C-alkylation observed with increases in reaction temperature, at least in

polar aprotic media [31,35], lend further credence to the ion-pair theory. An increase in temperature would be expected to induce a greater degree of dissociation, hence higher values of O-alkylation.

Kornblum has proposed [43,53] an elegant explanation of the observed solvent effects on the basis that both the C- and the O-alkylated products, at least in the case of phenoxides, derive from associated ion-pairs and ion-pair aggregates.

Considering the transition state of XIX for oxygen alkylation, it can be seen that the charge on oxygen

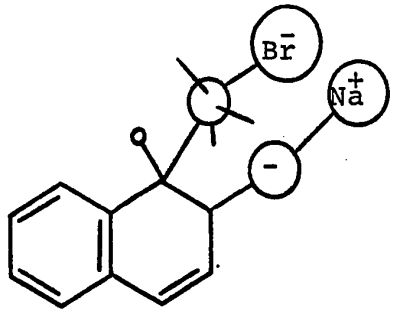


XIX

must be transferred from that atom to bromine against the attractive force of the sodium ion. In a solvent of low dielectric constant, with little ability to solvate the cation, this factor will be of greatest importance, and thus O-alkylation will be disfavoured.

However, considering the transition state of XX for carbon alkylation, it can be seen that a non-linear

arrangement exists in which the developing bromide ion is in proximity to the sodium ion.



XX

During the transfer of charge from oxygen to bromine (as C-C bond formation proceeds), little of its effect is removed from the vicinity of the sodium ion. As a result, the transition state for carbon alkylation is comparatively insensitive to solvents of low dielectric constant, and is thus favoured in these media.

Polar aprotic media of high dielectric constant have the ability to shield the departing bromide ion from the attractive force exerted by the sodium ion. In this situation, the transition state (XIX) for O-alkylation becomes energetically more favourable. In contrast, the transition state leading to C-alkylation, as before, is relatively insensitive to the dielectric constant of the medium, thus O-alkylation is favoured in polar aprotic media.

The size of the counter-cation is a particularly

important variable in the alkylation of ambident anions, and its effect is very closely related to the solvent effect described above. An increase in the size of the cation generally results in an increased tendency toward O-alkylation [31,35,43,45,47,56,58,59,83-86]. It is generally accepted [35,43,45,47,56,59,71,84,85,87] that these observations reflect the tendency for smaller cations (such as $Li^{\oplus}$) to be more tightly bound to the counter anion [46,88,89], and thereby provide some shielding of the more electronegative centre. The increase in ionization expected with increase in cation size is in fact demonstrated by the observed rates of alkylation. In general the rates are found to increase [49,51,90,91] with increase in cation size ($Li^{\oplus} < Na^{\oplus}$).

In some cases, in polar aprotic [43,57] or polar protonic solvents [43,55,92], a cation effect is not observed. This anomaly has been termed "levelling",[43] and is believed to result from the tendency of polar solvents to solvate smaller cations to a greater extent [36,40], thereby cancelling the general trend for ionization to increase with increase in cation size.

Changes in the structure of the alkyl group of an alkylating agent invariably bring about marked changes in the ratios of carbon to oxygen alkylation observed. An increase in O-alkylation usually accompanies a change from a primary to a secondary alkylating agent.[51,57,58, 62,83,92-95] In an early attempt to correlate the available

results, an apparent connection between high O-alkylation rates and a high degree of S_N1 character was emphasized.[29] This was based mainly on reports that, whereas saturated alkyl halides give C-alkylation with ethyl acetoacetate, chloromethyl ether [96] and diazomethane [97] were found to give exclusively the O-alkylated product. These latter substrates are known to undergo substitution reactions via an S_N1 process. Furthermore, in the reaction of alkali metal and silver metal nitrites with benzyl halides, more O-alkylation (as opposed to N-alkylation) is observed [29] with the latter. It was suggested [29] that the silver ion assists in increasing the amount of carbonium ion character in the transition state, thereby increasing the amount of alkylation on the more electronegative atom of the ambident nitrite ion.

In the light of more recent observations [33,57,83,98] regarding the high C-alkylation values obtained with benzylic and allylic halides compared to the corresponding saturated halides, higher values of O-alkylation would appear to correlate [31,57,83] much better with low S_N2 reactivity. In addition, strong evidence is provided by the reports that alkylations with tropylium bromide [99-101] and triphenylmethyl halides [102] provide the corresponding C-alkylate rather than the expected O-alkylate. Also, substituent effects for alkylations with a number of para-

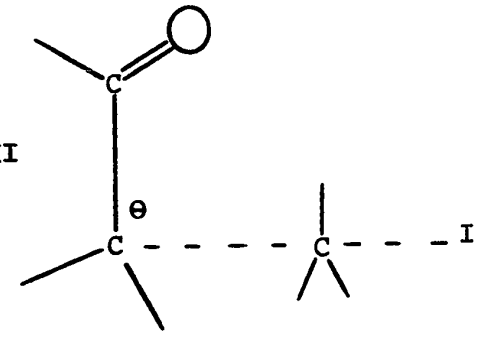
substituted benzyl halides were not found to correlate with an S_N1 mechanism.[57,103]

Support for the importance of S_N2 character is provided by the observed dependence of the C- to O-alkylation ratio [36,57,58,62,83,94,95,104], and the observed rate constants,[49,69] upon the steric demands of the alkylating agent (that is, CH_3- > CH_3CH_2- > $(CH_3)_2CH-$).

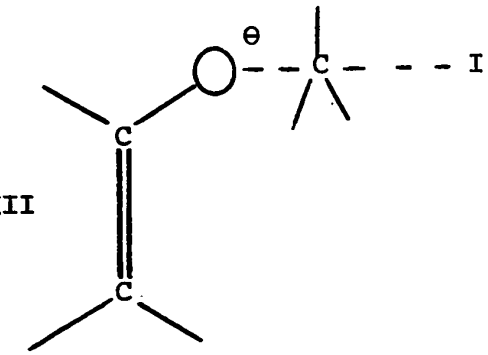
Of the factors affecting C- vs O-alkylation, the nature of the leaving group to be displaced from the alkylating agent is of particular importance. In practice variation in this factor is easily accomplished to obtain a desired result, and in general C-alkylation is promoted in the order: RI > RBr > RCl > $ROSO_2OR$ > $ROSO_2OAr$ > $R_3O^{\oplus}BF_4^{\ominus}$.[34,35,45,51,57,59,62,83,84,94,105,106]

A very successful correlation of these observations has been applied on the basis of the S_N2 reactivity [57,83] coupled with the symbiotic nature [32] of the attacking nucleophile and the leaving group. Symbiosis is the tendency of "hard" and "soft" Lewis bases to flock together at a site of displacement. Soft Lewis bases are characterized as being highly polarizable with relatively low electronegativity. The opposite is true of a hard Lewis base. Thus, the small electronegative oxygen atom of an enolate ion is harder than the larger, less electronegative carbon atom.

XXI



XXII

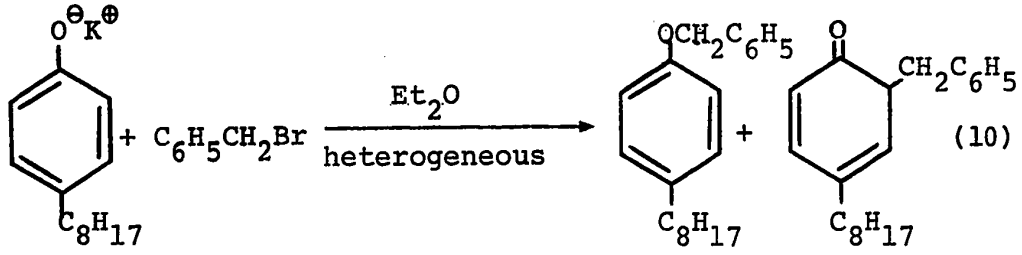


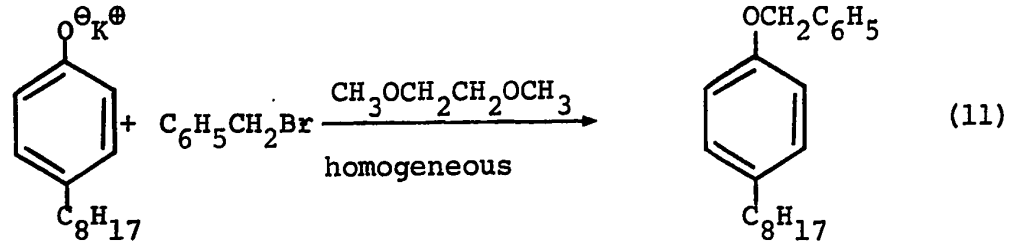
The transition state (XXI) in which the carbon centre of an enolate is displacing the soft iodide ion is of lower energy, and hence more favourable than the corresponding case (XXII) in which the hard oxygen is displacing the iodide.

The effect of the structural nature of the ambident anion itself upon the site of alkylation is particularly difficult to characterize due to the large number of variables involved.[25,30] However, one main factor emerges, that of acidity of the active methylene substrate. Increase in the acidity is generally paralleled by an increase in

O-alkylation [25,28], probably resulting from extensive delocalization of the negative charge onto atoms (in the enolate) other than carbon. The localization of the electron pair, that would be required to form a new bond at carbon, would result in the loss of a significant amount of resonance energy.

In 1959, Kornblum and Lurie [53] reported that heterogeneity of the reaction mixture was found to play a very significant role in the alkylation of ambident anions. A study of the alkylation of the potassium salt of *p*-*t*-octyl phenol with benzylic and allylic halides in diethyl ether and toluene (heterogeneous), showed that a substantial amount of C-alkylate was produced (eq. 10), whereas in ethylene glycol dimethyl ether (homogeneous), the product was that of exclusive O-alkylation (eq. 11)



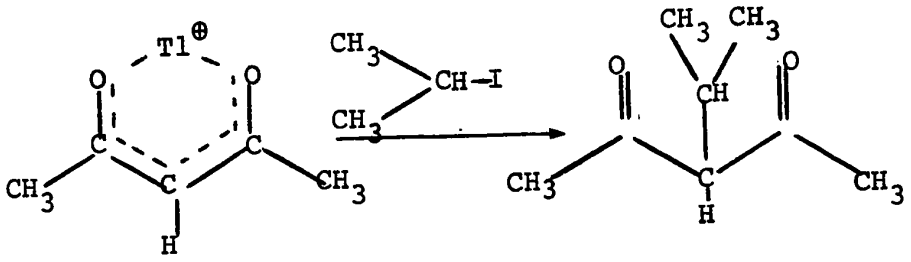


A rationalization of this somewhat striking phenomenon has been made [53] along similar lines to that proposed earlier [43] to explain observed solvent effects (vide supra). The basic assumption is made that alkylation takes place upon the phenolate ions which are part of the crystal lattice. As such, electrostatic shielding of the oxygen atom by the associated metal ion cannot be dispersed by solvation, as in solution. In the transition state for C-alkylation (c.f. XX), however, removal of cationic influence is assisted by the departing halide ion (intramolecular "solvation"). C-alkylation is thus favoured. The somewhat substantial quantities of O-alkylate produced from the "heterogeneous" process are said to result from the gradual intervention of a homogeneous reaction with time.

In a similar study, Curtin and Dybvig [60] reported that heterogeneity was not an important factor controlling alkylation in phenols. This conclusion, however, was made mainly on the basis that an increase in the amount of solid phenolate salt in the mixture did not produce an increase in the ratio of C- to O-alkylate.

Strong evidence supporting the importance of heterogeneity was recently provided by Taylor and co-workers.[107] They reported that the reaction of thallium (I) enolates of a number of β-dicarbonyl compounds with alkyl iodides

produced, in essentially quantitative yield, the products of exclusive C-alkylation, even for secondary substrates (isopropyl iodide) (eq. 12). In addition, the isolated enolates were reported [107-110] to possess a variety of attractive synthetic features. They (i) are easily



(12)

formed in virtually quantitative yield (ii) are crystalline, stable, non-hygroscopic solids and (iii) are reported to avoid all the traditionally encountered obstacles associated with β-dicarbonyl anion alkylations.

Although the preparation and alkylations of some thallium enolates had been reported earlier [86,111-113], the synthetic value of these intermediates was not recognized.

The extremely desirable properties reported by Taylor and co-workers were thought to arise as a result of their extreme insolubility. In addition, crystallographic data of the acetylacetone derivative showed the thallium cation to be closely bound to the two oxygen atoms. The thallium and oxygen atoms lie buried within the interior of the crystal, with the carbon skeleton of the enolate

being exposed at the surface. It can be seen that alkylation under heterogeneous conditions would be expected to give rise to C-alkylation.

In the light of this extremely important development, the possibility arose of applying the method to the homologation of other active methylene compounds in which the synthetic applicability of alkylation has proven to be restricted by unwanted side reactions (a more detailed discussion of the problems included with each of the substrates investigated is provided below).

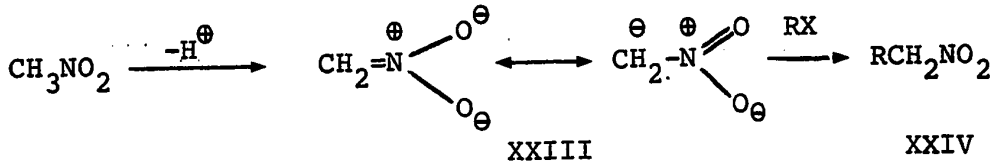
The purpose of this work was to investigate the preparation and alkylation of the thallium (I) derivatives of some nitroalkanes, β-ketosulfoxides and simple ketones, with a view to extending the scope of base catalyzed alkylation of these substrates. A reinvestigation of the β-dicarbonyl enolate alkylations was also carried out.

RESULTS AND DISCUSSION

The Preparation and Alkylation of some Thallium Nitronates

A consideration of the literature demonstrates that there are available a number of excellent methods for the preparation of nitroalkanes in moderate to good yields.[114] At the commencement of this work, however, no one general method encompassed the synthesis of the primary, secondary and tertiary classes. The purpose of this work was to develop such a method.

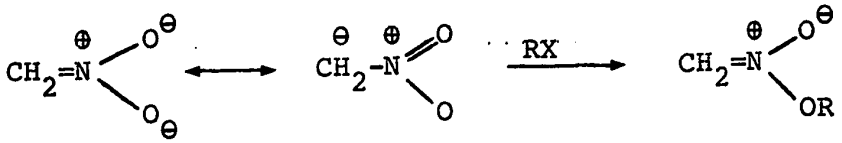
A conceptually simple approach to the problem is the base catalyzed alkylation of a nitroalkane (eq. 13).



XXIII XXIV

(13)

Removal of a proton from the nitroalkane produces, however, an ambident [29] anion (XXIII) which can undergo alkylation at carbon to produce the homologated nitroalkane (XXIV), or at oxygen to produce the nitronic ester (XXV) (eq. 14).

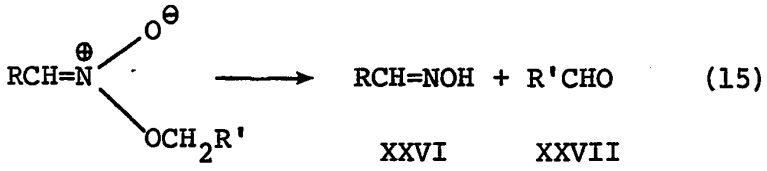


XXIII XXV

(14)

The reactions [115] of nitronate anions have been the subject of a great deal of study, and alkylations with a number of alkylating agents such as alkyl halides [116-125], alkyl sulfates [126,127], diazomethane [126,127], quaternary ammonium compounds [128], and other onium salts [129,130] have been reported. Unfortunately, the anions are generally found to undergo exclusive O-alkylation giving rise to the corresponding nitronic ester.

In a number of cases, isolation of these rather unstable nitronic esters has been reported.[117,119,124,126,130-132] Generally, however, C-alkylation of nitronates has been found to produce the corresponding decomposition products, an oxime (XXVI) and a carbonyl compound (XXVII)[99,117,118,124,125,129-135] (eq. 15).

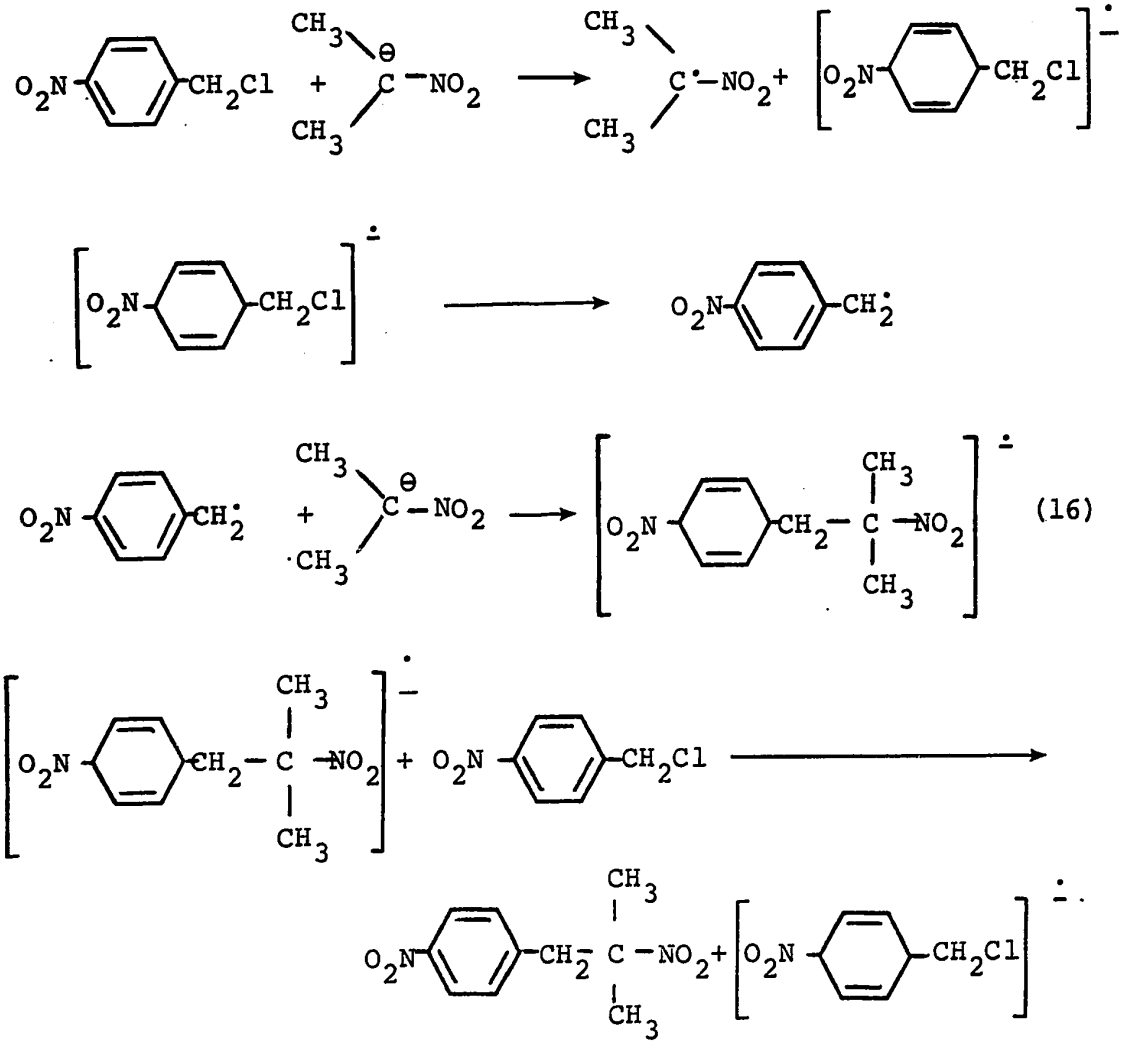


(15)

The latter observation is in fact so general, that it has led to its development as a useful synthesis of aldehydes and ketones.[117-119,125,133]

C-alkylation of nitroparaffin salts has been reported for only a few special cases in which the nitronate anion is stabilized by more than one electron withdrawing group [120-123], or in which the alkylating agent is an ortho or para-nitro substituted benzyl halide.[116-118,121,125,128,134-138]

The apparently anomalous behaviour observed with the reaction of simple nitronate salts and nitro substituted benzyl halides has been the subject of considerable interest. C-alkylation has been shown to arise from the imposition, upon the usual S_N2 displacement reaction, of a much faster electron transfer reaction. A benzyl radical is formed which unless intercepted by some trapping agent such as copper (II) chloride or para-dinitrobenzene, attacks more enolate anion to give rise to a chain reaction (eq. 16).



(16)

The elucidation of this mechanism has led to the development of a facile reaction for the displacement of leaving groups from tertiary centres [139-144] and thence to a novel olefin synthesis.[145]

The report of Taylor and McKillop [109] that thallous ethoxide would form salts with compounds of pK_a less than 20 suggested the possibility of generating thallium (I) nitronates (pK_a nitroalkanes $\approx$ 10). Their subsequent heterogeneous alkylation, giving rise to homologated nitroalkanes, appeared to be an attractive possibility.

The addition of thallous ethoxide to a solution of nitromethane in tetrahydrofuran (THF), ligroin or methylene chloride at -20° resulted in the immediate formation of ethanol, and the nitronate XXVIII as an off-white precipitate in quantitative yield (eq. 17).

$$TlOCH_2CH_3 + CH_3NO_2 \xrightarrow[-20°]{N_2} \underset{\text{XXVIII}}{[CH_2NO_2]^{\ominus}Tl^{\oplus}} + CH_3CH_2OH \qquad (17)$$

Unfortunately, attempts to isolate the crystalline material resulted in an explosive decomposition even at temperatures below -50°. The facile decomposition of nitronates of heavy metals has been noted previously by other investigators [146,147], and is believed to involve an internal redox reaction.

Further attempts to characterize and to study the reactions of the nitronate were effected under a nitrogen atmosphere and in the presence of a diluent.

Bromination with molecular bromine in methylene chloride at -15° provided an 80% yield of bromonitromethane (eq. 18). This observation served to confirm the assignment of the product XXVIII as the thallium nitronate.

$$[CH_2NO_2]^{\ominus}Tl^{\oplus} + Br_2 \xrightarrow[CH_2Cl_2,\ -15°]{N_2} BrCH_2NO_2 + TlBr \qquad (18)$$

The formation of α-bromonitroalkanes from the base-catalyzed bromination of the parent nitroalkanes is well established.[148-150]

Attention was now focussed on the possibility of alkylation. At the outset, methyl iodide was employed as the alkylating agent, and the reaction was monitored conveniently by gas-liquid chromatography (glc). Admixture of the iodide, and one equivalent of the nitronate XXVIII in THF unfortunately failed to show any noticeable reaction after long periods of time, at temperatures ranging from -40° to 30°, and resulted in quantitative (glc) recovery of the alkylating agent. The apparent lack of consumption of methyl iodide was, however,

accompanied by considerable yellowing and decomposition of the nitronate.

The instability of salts of nitromethane has been reported previously, and has been shown to give rise to the methazonate anion [151,152] XXIX (eq. 19).

$$2[CH_2\text{-}NO_2]^{\ominus}K^{\oplus} \longrightarrow K^{\oplus\ominus}\,O_2N{=}CH{-}CH{=}N\overset{\ominus}{O}\,K^{\oplus} \qquad (19)$$

XXIX

It became clear at this point that a more reactive [153] alkylating agent was required. Furthermore, it was felt that some enhancement in the reactivity of the nitronate may be observed in the absence of ethanol (produced during the formation of the anion). Ample precedence is to be found for the reduced reactivity of anions in the presence of hydrogen bonding solvents.[41,74,75]

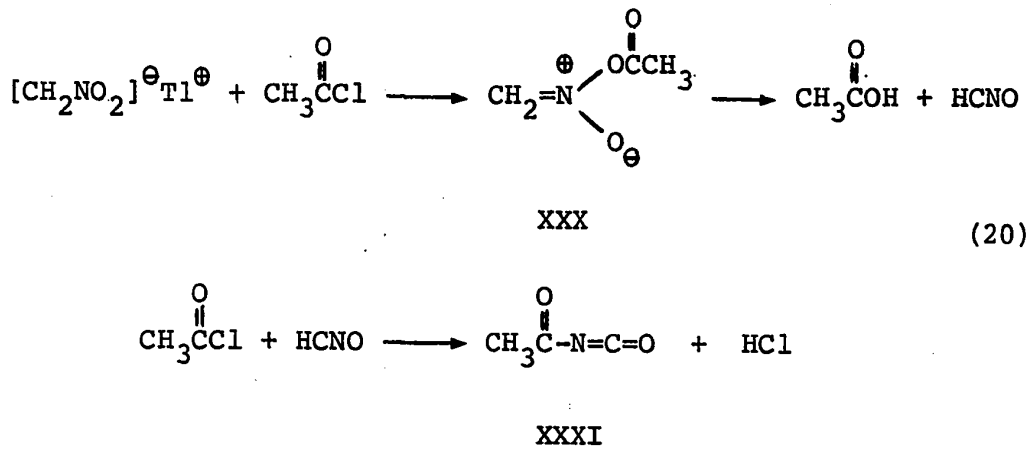
The addition of dimethyl sulfate to one equivalent of ethanol-free nitronate in THF failed to produce an observable reaction even after 17 hr. at 25°. Considerable decomposition of the nitronate was evident however. Nitroethane was not formed, nor was there any evidence of O-alkylation. A similar result was obtained with dimethyl sulfate in the absence of solvent, and with methylfluorosulfonate in methylene chloride. This

latter result proved particularly surprising in the light of the extreme reactivity generally observed with this reagent.[154-156]

The numerous reports concerning the enhancement of nucleophilicity, in the reactions of anionic species, by the addition of additives which preferentially complex with the cation [48,65-68], prompted a reinvestigation of the alkylation attempts in the presence of tetramethylethylene diamine.[68,157] The presence of this additive, however, failed to produce any noticeable enhancement in the reactivity of the thallium methylene nitronate (XXVIII), at least with dimethylsulfate in THF. Further investigations into the alkylation were therefore discontinued.

Acylation with acetyl chloride in THF was effected successfully at -78°, as shown by the appearance of infrared (ir) absorptions at 1740 and 1760 cm^{-1} coupled with a decrease in the absorption at 1805 cm^{-1} due to acetyl chloride. After warming to 25°, the reaction mixture showed only one component, corresponding to acetic acid. This was confirmed by ir spectroscopy.

Although a mechanism was not established, the formation of acetic acid under anhydrous conditions can be rationalized on the basis of initial O-acylation, giving rise to the acyl nitronate (XXX), which subsequently decomposes as shown (eq. 20).



XXX

(20)

XXXI

The presence of the acyl isocyanate XXXI was indicated by strong ir absorptions at 2250 and 1740 cm^{-1}.[158] Support for the proposed pathway is found in the observations that acylations of nitroparaffins generally give rise to an unstable acyl nitronate which can decompose in a number of ways [159-161], dependent upon its structure. Terss and McEwen [161] have in fact proposed an identical pathway to that shown above, to account for the products observed from the base-catalyzed benzoylation of nitromethane.

Nitroacetone (ie. C-acylation) was not observed. This result was not surprising, however, since C-acylation has been reported only in two other cases.[159]

In general, analogous investigations with nitroethane and 2-nitropropane proved to be somewhat more productive. Treatment of nitroethane, or 2-nitropropane with thallous

ethoxide in methylene chloride or benzene, gave the corresponding thallium nitronates (XXXII and XXXIII) as isolable, stable, off-white crystalline solids in 95% and 36% yields, respectively. The 2-nitropropane derivative XXXIII exhibited a high degree of solubility in the solvents employed, and the subsequent use of ligroin (in which it is insoluble) in its preparation resulted in an improved isolated yield of 84%.

$[CH_3CHNO_2]^{\ominus}Tl^{\oplus}$ XXXII

$[(CH_3)_2CNO_2]^{\ominus}Tl^{\oplus}$ XXXIII

The assignment of the nitronate structure XXXII to the nitroethane derivative was confirmed by hydrolysis. Treatment with acetic acid and urea, conditions developed by Kornblum and co-workers [163] for the regeneration of nitroparaffins from their salts, gave a 90% (glc) yield of nitroethane.

A slurry of the nitronate XXXII in methyl iodide, after reluxing under a dry nitrogen atmosphere for 4.5 hr., showed two volatile components corresponding (glc) to nitroethane (8%), and 2-nitropropane (17%). After a further 15 hrs, no change was observed.

In an attempt to improve the yield of the required C-alkylate (2-nitropropane), the reaction was repeated at 25°. After 15 hr, hydrolysis of the solid residue gave

only 1% nitroethane, comfirming that reaction was complete. Analysis of the reaction mixture showed (by glc) nitroethane (4%), 2-nitropropane (20%), and the corresponding O-alkylate, the methyl nitronic ester XXXIV (by ir and nuclear magnetic resonance (nmr)).

$$Tl^{\oplus}[CH_3CHNO_2]^{\ominus} + CH_3I \xrightarrow[15\ hr]{25^\circ} \underset{4\%}{CH_3CH_2NO_2} + \underset{20\%}{(CH_3)_2CHNO_2} + CH_3CH{=}\overset{\oplus}{N}(OCH_3)(O^{\ominus}) \quad (21)$$

XXXII

XXXIV

The nmr spectrum of XXXIV has been reported by Kornblum and Brown [27,130] to be observable even after 24 hr at 24°.

The formation of minor amounts of nitroethane proved to be somewhat surprising, and its origin remains unexplained. Proton exchange between the nitronate XXXII and the C-alkylate, however, remains a possibility (eq.22).

$$Tl^{\oplus}[CH_3CHNO_2]^{\ominus} + (CH_3)_2CHNO_2 \rightleftharpoons CH_3CH_2NO_2 + Tl^{\oplus}[(CH_3)_2CNO_2]^{\ominus} \quad (22)$$

Reaction of the 2-nitropropane derivative XXXIII with methyl iodide was shown to be complete after 6 hr. at 25° giving rise to 2-nitropropane plus one other volatile product. There was no evidence for the formation of the C-alkylate, 2-methyl-2-nitropropane. Distillation of the reaction mixture resulted in the isolation of acetone and some indication of the intervention of O-alkylation (by nmr).

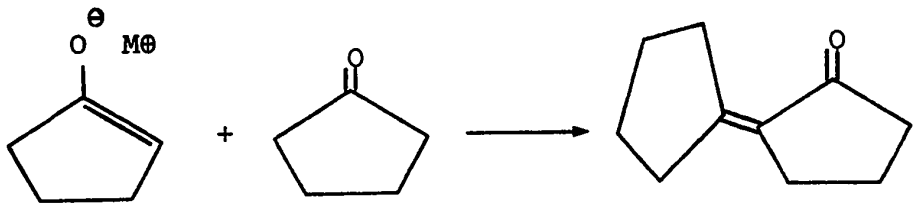
In the light of the inconclusive results obtained with methyl iodide, the alkylation was repeated using benzyl bromide, in the hope that products would be more easily detected. After 15 hr. at 25°, analysis (glc) showed the formation of 23% 2-nitropropane, 66% benzaldehyde and 22% unreacted benzyl bromide. Again, there was no evidence for C-alkylation. The results in fact parallel those reported by Hass and Bender [118] for the alkylation of the sodium salt of 2-nitropropane with benzyl chloride.

Considering the combined results obtained from the attempted alkylations of the thallium (I) derivatives of nitromethane, nitroethane, and 2-nitropropane, it would appear that the employment of this particular cation, and presumably the heterogeneity it imparts, offers no advantage over the alkali metal cations in promoting C-alkylation.

Studies Related to the Alkylation of Thallium Enolates of some Cyclic Ketones

The base-catalyzed alkylation of simple ketones is a particularly important and much studied process. A great deal of the recent interest shown in the reaction however, arises out of the observations that simple monoalkylation is generally accompanied by serious side reactions giving rise to isomer formation, polyalkylation, and aldolization.[25,153,162,164]

The problem of aldolization arises from condensation of the free ketone with its enolate ion and has been found to be particularly prevalent with cyclopentanones [153,162]

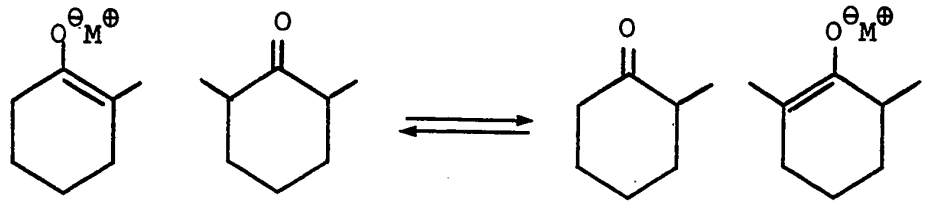


(23)

(eq. 23). Fortunately, this problem is readily overcome by the judicious use of reaction conditions and reagents. For example, the use of strong base to promote rapid and quantitative enolate formation has been found to be very effective.[165]

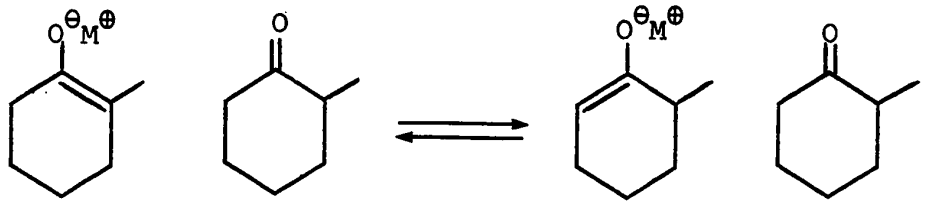
The problems of di- and polyalkylation, and isomer formation, with those ketones bearing hydrogen atoms on both α carbons, are generally much more difficult to

eliminate. These result either from the initial formation of isomeric enolates, or in the absence of excess base, from equilibration [25,162] of the starting enolate with the monoalkylation product (eq. 24), or with the starting ketone (eq. 25).



(24)

Numerous procedures have been developed in an attempt to circumvent these problems. Such developments involve



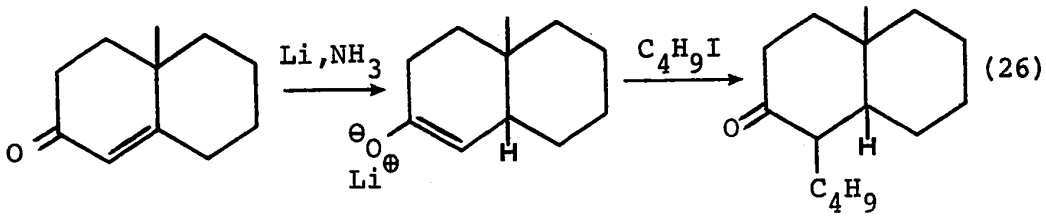
(25)

the use of blocking and activating groups [25], the alkylation of α-bromo [170,171] or α-diazoketones [166-169] with trialkyl boranes, the generation and alkylation of specific metal enolates, and the alkylation of enamines [162,172,173] and imine salts.[174,175]

Methods involving the generation of specific structural enolates have found widespread success, and arise out of the observation of House and Trost [176] that enolates generated in aprotic media, in the absence of oxygen and a proton donor (such as unionized ketone) will retain their

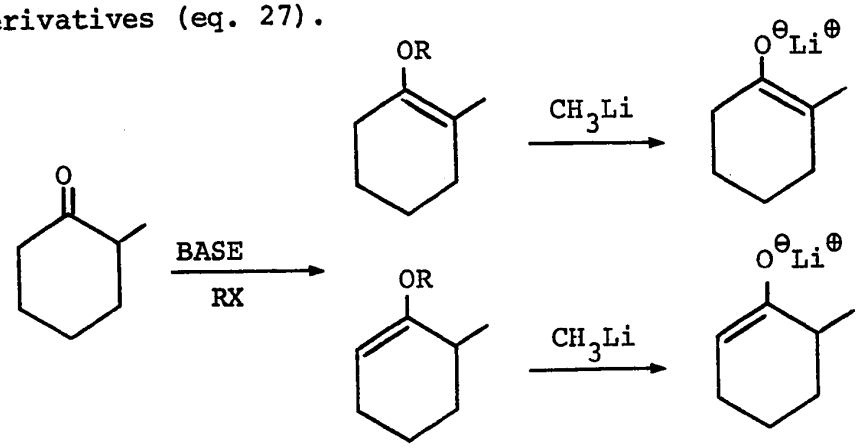
stereochemical integrity for at least several hours.

Two general routes are employed for the generation of specific enolates. Firstly, reduction of α,β-unsaturated ketones [177,178], α halo ketones or α-acyloxyketones [179-183] (eq. 26) and secondly, generation and separation of isomeric enol esters [183-185], enol silyl ethers [185-188], enol borinates [189] and other enol derivatives [190] followed by treatment with organolithium or organomagnesium



(26)

derivatives (eq. 27).



(27)

R = $-Si(CH_3)_3$, $-\overset{O}{\overset{\|}{C}}CH_3$, $-Sn(C_4H_9)_3$, $-B(C_2H_5)_2$.

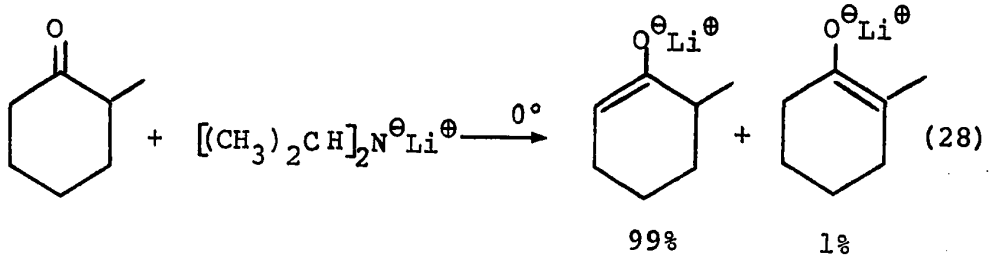
Although a high degree of regiospecificity is observed with these methods, a number of problems do emerge. The

cleavage of the enol acetates with methyllithium produces a mole of strong base which results in the formation of di- and polyalkylated products.[187] The problem can be overcome by the use of silyl enol ethers but the advantage gained is somewhat offset in this case by the difficulty in separating the enolic isomers.

The intervention of enolate equilibrium can occur (as with all enolate alkylations) once some monoalkylated product is produced. This can be overcome to a certain extent, however, by choosing a metal cation which forms more covalent bonds with the enolate ion, such as lithium [187] or trialkyl tin.[188]

In addition to the observation that each development exhibits inherent difficulties, a review of all the methods available for the promotion of monoalkylation of ketones indicates that all are indirect, and involve the initial formation of some intermediate other than the enolate itself, thereby reducing the efficiency of the process.

Some efforts leading toward the direct generation of specific enolates have, however, been reported by House and co-workers.[185,187] A strong base such as lithium diisoproplyamide has been shown to exhibit a high degree of selectivity in abstracting a proton from the less hindered position of an unsymmetrical ketone, thereby generating (under conditions of kinetic control) the less highly substituted enolate (eq. 28).



(28)

Although a high degree of alkylation at the least substituted α position of an unsymmetrical ketone can be achieved by this method, the intervention of enolate equilibration, and the rigorous control of reaction conditions required often reduces the practicality of the process.

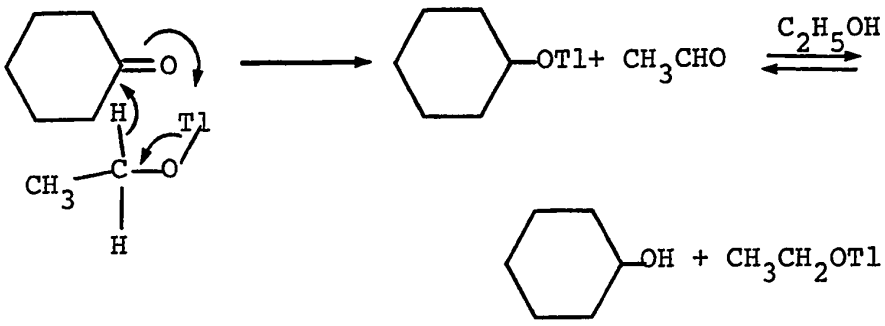
The reported [109] basicity of thallous ethoxide (vide supra) suggested the possibility of generating thallium (I) enolates of simple ketones ($pK_a \approx 20$). In the light of the observed insolubility of other thallium salts [107-110], it was felt furthermore that these may be prepared and isolated as specific isomers, under conditions of kinetic control. In addition, in the light of results obtained with other thallium induced alkylations, the possibility arose that enolate equilibration in this system may not be observed.

With these possibilities in mind, the preparation of the thallium enolate of cyclohexanone was investigated. At the outset, treatment of cyclohexanone with thallous ethoxide in benzene solution failed to produce a precipitate, or indicate any consumption of the starting ketone,

even after 15 hr. at reflux temperatures.

The use of a more polar solvent system (THF:Ethanol) in an attempt to enhance the reactivity of the base, again failed to reveal any observable enolate, but resulted in the formation of cyclohexanol in a 66% yield (glc). In the light of this unexpected result, efforts were temporarily directed towards investigation of the reduction process. The effect of solvent, reagent ratios, and time, upon the course of the reaction were determined. The results are shown in Table I.

Initially, the study indicated that the reaction exhibits characteristics similar to those of the Meerwein-Pondorff-Verley (MPV) reduction [191], and probably proceeds via an analogous route (eq. 29), although a mechanism was not rigorously established. Significantly, the product of reduction was not observed, prior to hydrolysis, in reactions carried out in the absence of alcohol. Qualitatively, the rate of reaction was found to be somewhat dependent upon the nature of the solvent, but not upon the ratio of thallous ethoxide employed.



(29)

TABLE I

The Reduction of Cyclohexanone with Thallous Ethoxide

Solvent[a]	Ratio Ethoxide:ketone	Reaction Temperature (°C)	Time (hr)	Yield of Cyclohexanol[b] (%)
THF:E	1:1.1	75	45	66[c]
B:E	1:1	70	20	10
B:E	2:1	70	20	10
B:E	2:1	70	46	30
B:E	2:1	70	72	50
T:I	1.2:1	80	22	63

(a) THF = Tetrahydrafuran, E = Ethanol, B = Benzene, T = Toluene, I = 2-Propanol.

(b) By glc analysis.

(c) Based on ethoxide employed.

The observed increase in rate in the presence of 2-propanol undoubtedly results from the formation and intervention of thallous isopropoxide in the reduction mechanism (eq. 30). Support for the hypothesis derives from the observed formation of acetone, and from the known relative reactivities of ethoxide and isopropoxide in the MPV reduction [191]

$$TlOCH_2CH_3 + (CH_3)_2CHOH \rightleftharpoons TlOCH(CH_3)_2 + CH_3CH_2OH \qquad (30)$$

A comparison of the results with those previously reported [192] for the analogous reaction with aluminum alkoxides showed that the thallous alkoxides were much less efficient reducing agents, and as such it was decided that further study in this area was not warranted.

The intial failures to obtain an isolable enolate from thallous ethoxide and cyclohexanone, it was believed, could be overcome by the use of a stronger base such as thallous *t*-butoxide.

This base was readily prepared from thallous ethoxide and *t*-butyl alcohol. Attempted reaction with cyclohexanone in ligroin or benzene solution however, failed to produce precipitation even after 15 hr. Subsequent addition of methyl iodide to the reaction mixture indicated (by glc analysis) that even after 10 hr. reflux, alkylation

(and thereby enolate formation) had not occurred.

The reported enhancement [157,193,194] in the reactivity of alkyl lithium species in metalation reactions upon the addition of tetramethylethylenediamine (TMEDA) suggested that such an additive may prove effective in increasing enolate formation with thallous alkoxide bases. Treatment of cyclohexanone with thallous *t*-butoxide in the presence of TMEDA, disappointingly, failed to yield any isolable enolate, but the subsequent addition of excess methyl iodide resulted in the precipitation of a fine yellow solid (presumably thallium iodide). After 1 hr., glc analysis showed the presence of 1-methylcyclohexanone (61%), and the corresponding dialkylated products 1,1- (10%) and 1,6-dimethylcyclohexanone (<1%). This result indicated that the thallous enolate, although not isolable, had indeed been formed under these conditions.

As a direct consequence of this observation, a detailed study of the homogeneous alkylation of the thallium enolates of cyclohexanone and cyclopentanone in the presence of an additive was undertaken. A 1:1 ratio of base to ketone was used in all cases. Effects of variations in the base, the solvent, the nature of the additive and the additive to base ratio were investigated. The results are shown in Table II.

Unfortunately, under each set of conditions employed, no indication of enolate precipitation was observed, nor

TABLE II

Homogeneous Alkylation of the Thallium Enolates of Cyclohexanone and Cyclopentanone [e]

Ketone	Base[d]	Solvent[a]	Additive[b]	Molar Ratio Additive: Base	Enolate Formation Time (hr)	Enolate Formation Temp (°C)	Alkylation Time (hr)	Alkylation Temp (°C)	Yield of Ketone Products (%)[c] Unreacted Ketone	α-Methyl	α,α-Dimethyl	α,α'-Dimethyl
		B	TMEDA	1:1	5	80	1.0	25	33	61	10	<1
		T	TMEDA	1:1	60	95	1.0	35	27	57	10	<1
		B	TMEDA	2:1	5	80	1.0	25	35	55	12	<1
		B	TMEDA	1:1	5	80	0.25	25	60	32	2	0
		B	TMEDA/HMP	1:2:2	20	80	0.25	35	31	59	11	<1
Cyclohexanone	TlO*t*Bu	B	HMPA	2:1	5	80	0.25	25	-	1-2	0	0
		B	HMPA	2:1	5	80	18.0	25	30	60	10	<1
		E	TMEDA	1:2	5	40	1.0	30	-	55	7	<1
		E	TMEDA	1:2	5	40	2.5	30	20	74	12	<1
		B	TMEDA	1:2	5	40	2.5	30	22	74	10	<1
		B	TMEDA	1:10	5	40	2.5	30	26	76	10	<1
		B	TMEDA	1:2	5	40	2.5	25	40	60	4	0
		E	TMEDA	1:2	5	40	2.5	25	44	52	5	0
Cyclohexanone	TlOEt	E	TMEDA	1:10	5	40	2.5	25	27	62	3	0
		B	TMEDA	1:2	5	80	0.25	35	34	54	8	<1
Cyclopentanone	TlO*t*Bu	B	TMEDA	1:2	5	45	0.75	30	25	35	22	11
Cyclohexanone	NaO*t*Amyl	B	None	-	5	40	0.5	30	24	64	9	2
Cyclohexanone	TMEDA	B	None	-	5	80	2.5	30	-	0	0	0

(a) B = Benzene, E = Diethyl Ether

(b) TMEDA = Tetramethylethylenediamine, HMPA = Hexamethylphosphoramide

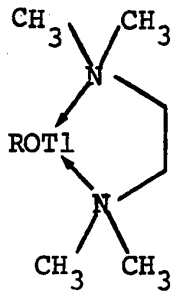
(c) By glc analysis

(d) TlO*t*Bu = Thallous *t*-butoxide, TlOEt = Thallous ethoxide, NaO*t*Amyl = Sodium *t*-amylate.

(e) Molar ratio of ketone to base = 1:1

could any significant decrease in the relative yields of dialkylated products be achieved. Although, as might be expected, small increases in temperature (over a 10° range) produced minor increases in the initial rates of alkylation, variations in the solvent, the base, or the ratios of additive to base did not produce any significant changes.

A consideration of the results indicates that both HMPA and TMEDA were effective in promoting alkylation; however, it is clear that TMEDA was particularly efficient. This may result from complexation (XXXV) of the amine with the cation, thus providing some enhancement in the basicity of the alkoxide.



XXXV

In conclusion, a direct comparison of the alkylation results with those obtained using sodium *t*-amylate as a base, clearly indicates that no advantage is to be obtained in generating thallium (I) enolates to effect alkylation of simple ketones.

The Preparation and Alkylation of the Thallium Enolate of a β-Ketosulfoxide, and some β-Diketones and β-Ketoesters

An attractive alternative to the acetoacetic ester synthesis of ketones involves the alkylation [195-197] of β-ketosulfoxides [198,199] (XXXVI) (as their sodium enolates), followed by reductive fission of the sulfoxide function [195, 196,200] (eq. 31).

$$\underset{\text{XXXVI}}{RCOCH_2SOCH_3} \longrightarrow \underset{\text{XXXVII}}{RCOCHSOCH_3\ (Na^{\oplus})} \longrightarrow \underset{\text{XXXVIII}}{RCOCH(R')SOCH_3} \longrightarrow RCOCH_2R' \qquad (31)$$

Good yields of mono- or dialkylated product can be achieved with the introduction of primary functions. However, attempts to extend the method to secondary halides have as yet been unpromising, resulting in "extremely poor yields of alkylation product".[197] The structural similarities between β-dicarbonyl compounds and β-ketosulfoxides (in that the active methylene of each is flanked by two atoms each of which is "doubly"-bonded to oxygen), coupled with the reported [107-110] advantages of using thallium β-dicarbonyl enolates in alkylation reactions (discussed in detail above), pointed to the possibility of employing

thallium β-ketosulfoxides in an effort to overcome the limitations of the ketone synthesis.

Treatment of the ketosulfoxide XXXIX, (by analogy with earlier work [195-197]) with thallous ethoxide in benzene provided, after a short period of time, the thallium salt (XL) in 80% yield (eq. 32).

$$C_6H_5COCH_2SOCH_3 \xrightarrow{TlOC_2H_5} C_6H_5\overset{\ominus}{C}OCHSOCH_3 \quad (32)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad Tl^{\oplus}$$

XXXIX XL

Subsequently, it was shown that by simple addition of ligroin to the reaction solution prior to isolation, the salt could be readily obtained in virtually quantitative yield. In addition to the similarities apparent in the preparation, the salt showed physical properties paralleling those of thallium β-dicarbonyl enolates.[107-109]

For exploratory purposes, an initial heterogeneous alkylation attempt was carried out using excess methyl iodide in THF. Admixture of the reagents resulted in a yellow precipitate (resumably thallium iodide), but after work up, the required C-alkylate XLI (R = CH_3) was obtained in only 49% yield. To assess the effect of changing the alkylation medium, a subsequent reaction was carried out in ligroin. This resulted in an 80% yield of the required

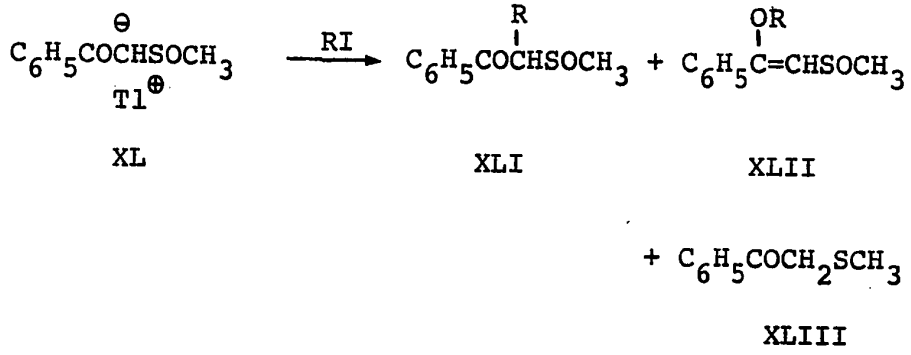
C-alkylate, and points to the advantage of ensuring maximum heterogeneity during the alkylation process. Under these conditions, isopropyl iodide failed to react even after a long period of time. However, alkylation was readily achieved with excess alkylating agent in the absence of solvent. In order to effect a comparative study, alkylation experiments with methyl, ethyl and isopropyl iodides were carried out in the absence of solvent. The results are shown in Table III.

Only methylation resulted in the exclusive formation of C-alkylate, and since the reaction of methyl iodide with the corresponding sodium enolate of XXXIX gave yields of 86% [195,196] (or 70% [197]) of XLI (R = CH_3), no advantage accrues using the thallium enolate. Disappointingly, ethylation of XL was found to be complex, and clearly inferior to ethylation of the sodium analogue in promoting efficient C-alkylation.[195-197] No C-alkylate was obtained from the reaction of XL with isopropyl iodide.

The formation of the ketosulfide XLIII is interesting, since it was not reported to be a product of the sodium enolate alkylations of ω-methylsulfinylacetophenone (XXIX). Although the mechanism for its formation has not been established, one plausible pathway involves initial O-alkylation (on sulfoxide oxygen), followed by inter- or intramolecularly promoted elimination (eq. 33). The analogous reduction of dimethylsulfoxide with alkyl halides is well documented.[201,202]

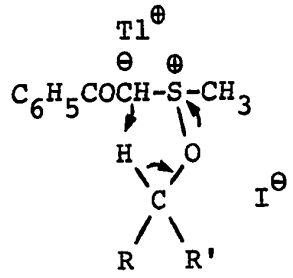
TABLE III

The Alkylation of the Thallium(I) Salt of ω-Methylsulfinyl-acetophenone



XL XLI XLII XLIII

Alkylating Agent RI	Isolated product yield % XLI	XLII	XLIII
CH_3I	81	0	0
C_2H_5I	38	17	28
i-C_3H_7I	0	42	36



$$\longrightarrow C_6H_5COCH_2SCH_3 + RR'C{=}O + TlI \qquad (33)$$

The lack of ketosulfide formation in the case of the sodium analogue is probably a reflection of the increased reactivity of the sodium enolate over that of the thallium derivative XL.

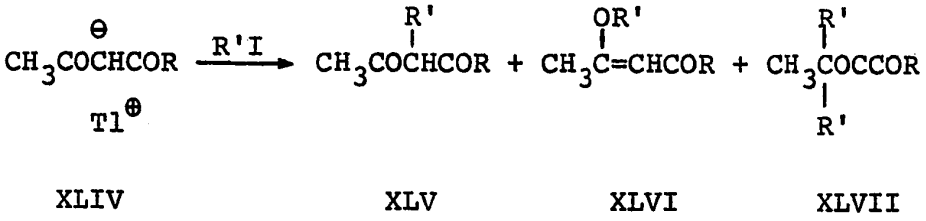
As a direct consequence of these results, a reinvestigation of the thallium β-dicarbonyl enolates was undertaken with a view to gaining some additional experience, and confirming our experimental technique.

The thallium salts of acetylacetone (XLIV(i), R = CH_3) and ethylacetoacetate (XLIV(ii), R = OC_2H_5) were prepared as described [107], and alkylations were carried out with methyl, ethyl and isopropyl iodides in the absence of solvent. The results are summarized in Table IV.

In contrast to previous reports [107], alkylation of the thallium β-dicarbonyl enolates produced, in some cases, mixtures of products. Of these, the concomitant formation of dialkylated material (XLVII), and the products of proton abstraction (XLVIII), was particulary surprising since it

TABLE IV

The Alkylation of the Thallium(I) Salts of Acetylacetone and Ethylacetoacetate



XLIV XLV XLVI XLVII

(i) R = CH_3

(ii) R = OC_2H_5

+ CH_3COCH_2COR

XLVIII

Thallium Enolate	Alkyl Iodide	Product yield %[a] XLV	XLVI	XLVII	XLVIII
XLIV (i)	CH_3I	85	0	6	5
XLIV (i)	C_2H_5I	63	13	4	3
XLIV (i)	$\underline{i}$-C_3H_7I	20	62	0	<1
XLIV (i)[b]	$\underline{i}$-C_3H_7I	20	62	0	<1
XLIV (ii)	C_2H_5I	80	2	5	2
LXIV (ii)	$\underline{i}$-C_3H_7I	67	20	0	0

(a) Yields determined by glc.

(b) Obtained from Aldrich Chemical Co. Inc., Milwaukee, Wis.

requires the intervention of an enolate equilibrium similar to that observed with homogeneous base catalyzed alkylation [25] (eq. 34).

$$CH_3COCHCOR + CH_3COCHCOR \rightleftharpoons CH_3COCCOR + CH_3COCH_2COR \quad (34)$$

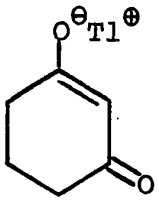
(with $\ominus$ on the enolate oxygen and $Tl^{\oplus}$ in each case)

Although the acetylacetone thallium enolate reactions appeared to be totally heterogeneous, some doubt exists as to the heterogeneity of the analogous ethylacetoacetate alkylations. Admixture of XLIV(ii) with alkyl iodide led initially to the formation of a cloudy mixture in which no solid particles were evident.

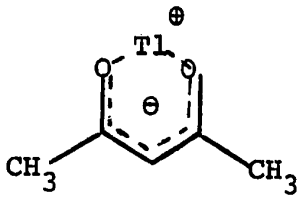
In view of the complex array of products observed, it would appear that thallium enolates of β-ketosulfoxides or β-diketones, despite their heterogeneity, and thallium enolates of β-ketoesters (despite their apparent "heterogeneity") offer no special advantages for promoting exclusive mono-C-alkylation.

Since the conclusion of this work, two groups have independently reported [203,204] that alkylation of the thallium salts of some cyclic 1,3-diketones gives rise to high degrees of O-alkylation. The results have been attributed [204] however, to the inability of the cyclic enolates XLIX to effect a chelation of the thallium cation

similar to that reported for the acyclic analogues (L).



XLIX



L

EXPERIMENTAL

General Considerations

Infrared (ir) spectra were recorded using a Perkin-Elmer 421, Perkin-Elmer 337 or Unicam S.P. 1000 Infrared Spectrophotometer.

Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 or HA-100 spectrometer. Unless otherwise stated, deuterochloroform ($CDCl_3$) was employed as the solvent with tetramethylsilane (TMS) as the internal standard, and chemical shifts are reported in δ-values. The following abbreviations are used in the text: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet.

Mass spectra were recorded at 70 eV on an AEI Model MS-2 or Model MS-9 spectrometer. Spectra are recorded in the following manner: m/e: peak mass (relative intensity).

Gas chromatographic (glc) analyses were performed using an Aerograph A90-P3 and a Varian Aerograph Series 1200 and Series 1400 chromatograph with the following columns: column A, 1/8" x 5' 10% dinonylphthalate on 60/80 Chromosorb W; column B, 1/8" x 5' 10% XF1150 on 60/80 Chromosorb W; column C, 1/4" x 10' 20% NPGSE on 60/80 Chromosorb W; column D, 1/4" x 10' 15% dinonylphthalate on 60/80 Chromosorb W; column E, 1/4" x 10' 15% XF1150 on

60/80 Chromosorb W; column F, 1/8" x 5', 10% Carbowax 6,000 on Fluoropak 80; column G, 1/8" x 5' 10% QF-1 on 60/80 Chromosorb W; column H, 1/4" x 10' 15% Apiezon L on 60/80 Chromosorb W; column I, 1/8' x 15' 15% SE-30 on 60/80 Chromosorb W; column J, 1/4" x 10' 10% SE-30 on 60/80 Chromosorb W. All products, in both the quantitative (corrected for peak response) analytical and preparative glc work, are listed in order of elution.

Column chromatography was performed using Florisil (Baker Chemical Co., Phillipsburg, N.J.) as adsorbent. Thallous ethoxide was obtained from the Aldrich Chemical Co. Inc., Milwaukee, Wis.

Analytical thin layer chromatography (tlc) was performed on silica gel plates. Pre-coated silica gel F_{254} plates, 20 x 20 x 0.2 cm (E. Merck, Darmstadt), were used for preparative tlc.

Microanalyses were performed by the Microanalytical Laboratory, University of Alberta.

Caution! Thallium compounds are insidious poisons and should be handled with great care.

The Preparation of the Thallium Salt (XXVIII) of Nitromethane

To a magnetically stirred solution of nitromethane (3.2 g; 55 mmole) in anhydrous THF (20 ml), cooled to -15° under a nitrogen atmosphere, was added dropwise a solution

of thallous ethoxide (12.5 g; 50 mmole) in anhydrous THF (20 ml). The addition resulted in the formation of a white precipitate which after stirring for 20 min. was washed with THF (3 x 20 ml) until glc analysis (column A; 60°) showed the supernatant to be ethanol free.

The preparation was found to be equally successful using ligroin or methylene chloride as solvent, and in each case the salt was prepared freshly, immediately prior to use, and stored at -20° under a nitrogen atmosphere. This procedure was found to be necessary since the dry salt was unstable above 0°.

Bromination of the Thallium Salt of Nitromethane

To the stirred thallium salt XXVIII (50 mmole), prepared as above in methylene chloride, was added dropwise a solution of bromine (10.5 g; 65 mmole) in methylene chloride (20 ml). After the addition at -15°, the mixture was stirred for a further 30 min., then hydrolysed with 15% hydrochloric acid (60 ml). The organic layer was separated, the aqueous layer extracted with methylene chloride (2 x 30 ml) and the combined organic extracts dried over anhydrous sodium sulfate. Quantitative glc analysis (column B, 130°) indicated the formation of bromonitromethane in an 80% yield.

After concentration of the reaction mixture, distil-

lation provided pure bromonitromethane (60%), bp. 139 - 142° (690 mm) (lit.[205] 146°; 715 mm): ir (liquid film) 1575, 1365 (NO_2), 1258, 750, 680 cm^{-1}; nmr: δ 5.75 (s, 2, CH_2); mass spectrum: M^+-NO_2: 95, 93.

Attempted Alkylation of the Thallium Salt of Nitromethane

Admixture of the thallium salt (XXVIII) (50 mmole) and the appropriate alkylating agent were stirred under a nitrogen atmosphere at the initial temperature indicated in Table V. When no reaction was apparent, as shown by the absence of nitroethane in the supernatant liquid (by glc analysis, column A, 70°), the temperature was progressively raised. The alkylating agent, solvent, temperatures and times employed are shown in Table V.

In all cases no evidence for the consumption of the alkylating agent, or for the formation of C-alkylate was observed, although considerable yellowing of the insoluble salt appeared to result above 0°.

Acylation of the Thallium Salt of Nitromethane

To a magnetically stirred suspension of the thallium salt (XXVIII) (47 mmole) in anhydrous THF (20 ml), cooled to -78°, was added dropwise a solution of acetyl chloride (3.3 g; 47 mmole) in THF (10 ml). The solution was then stirred at -65° for 10 min. and an aliquot was removed.

TABLE V

Reaction Conditions for the Attempted Alkylation of the Thallium Salt of Nitromethane

Solvent	Alkylating Agent (RX)	Molar Ratio Salt:RX	Temperatures (°C) Initial	Final	Time (hr)
Ligroin	CH_3I	1:1	5	25	12.5
THF	CH_3I	1:1	10	25	14.5
THF	$(CH_3)_2SO_4$	1:1	-10	25	17.5
-	$(CH_3)_2SO_4$	1:8	30	30	1.5
CH_2Cl_2	$(CH_3)_2SO_4$ [a]	1:2	-20	25	21
CH_2Cl_2	CH_3OSO_2F	1:1	-40	30	19

(a) In the presence of 1 equivalent of tetramethylethylene diamine.

An infrared of the sample showed, in addition to the carbonyl absorption at 1805 cm^{-1} (for CH_3COCl), two absorptions at 1740 and 1760 cm^{-1}.

The bulk of the reaction mixture was warmed to 25° and stirred for 10 min., whereupon infrared showed the complete absence of acetyl chloride, but strong absorptions at 1740, 1760 and 2260 cm^{-1} persisted. Qualitative glc analysis of the reaction mixture (column F, 110°, 160°) indicated only one component corresponding to acetic acid. Concentration of the reaction mixture and subsequent isolation of the product (column J, 100°) gave acetic acid: infrared spectrum identical to an authentic sample.

The Preparation of the Thallium Salt XXXII of Nitroethane

To a magnetically stirred solution of nitroethane (4.2 g; 55 mmole) in anhydrous benzene (40 ml) was added dropwise, under an atmosphere of nitrogen, a solution of thallous ethoxide (12.5 g; 50 mmole) in benzene (40 ml). After addition, the thick slurry was stirred for 5 min. and the solid thallium salt collected by vacuum filtration. This provided, after washing with methylene chloride (10 ml), an off-white crystalline solid 13.5 g (95%).

Hydrolysis of the Thallium Salt of Nitroethane

To a suspension of the thallium salt XXXII (6.95 g;

25 mmole) in diethyl ether (30 ml), cooled to 5°, was added, dropwise, a solution of urea (1.65 g; 27.5 mmole) and acetic acid (1.65 g; 27.5 mmole) in water (40 ml). Upon the addition, the insoluble salt appeared to dissolve to a yellow solution, the colour of which was discharged after 15 min. The ether layer was separated, and the volume adjusted to 50 ml. Quantitative glc analysis (column A, 60°) showed the formation of nitroethane (90%). The solution was concentrated by fractional distillation and a sample of the product was isolated by preparative glc (column D, 70°), n_D^{26} = 1.3901 (lit.[206] n_D^{25} = 1.39015); infrared spectrum identical to an authentic sample.

The Alkylation of the Thallium Salt of Nitroethane

Admixture of the thallium salt XXXII (6.6 g; 24 mmole) and methyl iodide (50 ml) was refluxed under a nitrogen atmosphere for 4.5 hr. Quantitative glc analysis (column A, 60°) showed the formation of nitroethane (8%) and 2-nitropropane (17%). After a further 15 hr. reflux glc indicated no further change. The reaction mixture was filtered and concentrated, and the products isolated by preparative glc (column D, 70°) showed the following properties: nitroethane : infrared spectrum identical to authentic material; 2-nitropropane : n_D^{26} = 1.3923 (lit.[206] n_D^{25} = 1.39206); infrared spectrum identical to an

authentic sample.

The reaction was repeated at 25°. After 15 hr. the supernatant was decanted and the residual solid washed with methylene chloride (2 x 5 ml). The organic solutions were combined and standardized to 50 ml with methylene chloride. Analysis (glc) (column A; 60°) showed nitroethane (4%) and 2-nitropropane (20%) as the only volatile products. The solid residue was suspended in diethyl ether (30 ml), and the stirred suspension cooled to 5° while a solution of urea (1.65 g; 27.5 mmole) and acetic acid (1.65 g; 27.5 mmole) in water (40 ml) was added dropwise. After 15 min. the ether layer was separated and the aqueous layer extracted with ether (3 x 10 ml). The ether layers were combined and dried with anhydrous calcium chloride. Glc analysis (column A; 60°) showed a trace of nitroethane (<1%).

Concentration of the reaction solution provided a pale yellow oil (0.7 g), the nmr spectrum of which showed in addition to nitroethane and 2-nitropropane, signals corresponding [27] to the methyl nitronic ester XXXIV: nmr: δ 6.35 (q, 1, -CH=N), 3.78 (s, 3, CH_3O), 1.90 (d, 3, CH_3).

Preparation of the Thallium Salt XXXIII of 2-nitropropane

To a magnetically stirred solution of 2-nitropropane (9.7 g; 110 mmole) in ligroin (50 ml), was added dropwise,

under a nitrogen atmosphere, a solution of thallous ethoxide (24.9 g; 100 mmole) in ligroin (50 ml). Addition resulted in the formation of a heavy cream coloured precipitate which was stirred at 25° for 1 hr. The mixture was cooled to 5° and the solid collected by vacuum filtration, washed with cold ligroin (2 x 20 ml), and air dried. The salt was obtained as a cream coloured, air stable solid.

Alkylation of the Thallium Salt of 2-Nitropropane with Methyl Iodide

Admixture of the thallium salt XXXIII (7.3 g; 25 mmole) and methyl iodide (50 ml) was magnetically stirred under a nitrogen atmosphere for 6 hr. The supernatant was decanted and the residual solid washed with methylene chloride (2 x 5 ml), and the combined organic solutions dried over anhydrous magnesium sulfate. The solid residue was hydrolyzed, as described above, and yielded only a trace of 2-nitropropane by glc analysis (column A; 60°).

The reaction solution was analyzed by glc (column A; 60°) and indicated the presence of some 2-nitropropane, but not the product of C-alkylation. The mixture was concentrated at 15 mm pressure to yield a dark brown oil which upon distillation yielded a colourless liquid bp. 50 - 55° (700 mm) which by nmr and ir spectroscopy was shown to consist of acetone: ir (liquid film) 1720 cm^{-1} (C=O);

nmr: δ 2.1 (s, $CH_3C=O$); and one other component, nmr: δ 3.43 (s, CH_3O), 1.86 (s, CH_3). Treatment of the distillate with 2,4-dinitrophenylhydrazine reagent provided the 2,4-DNP of acetone, mp. 121 - 124° (lit.[207] 126°).

Alkylation of the Thallium Salt of 2-Nitropropane with Benzyl Bromide

To a suspension of the thallium salt XXXIII (7.3 g; 25 mmole) in methylene chloride (50 ml) was added all at once benzyl bromide (4.7 g; 27.5 mmole). The suspension was stirred for 15 hr. at 25° under a nitrogen atmosphere, and filtered to produce a colourless solution whose volume was adjusted to 50 ml. Glc analysis (column B; 100°) showed the formation of 2-nitropropane (23%) and benzaldehyde (66%), and the presence of unreacted benzyl bromide (14%). The isolated products had the following properties: 2-nitropropane: n_D^{25} = 1.3921 (lit.[206] n_D^{25} = 1.39206); ir identical to an authentic sample; benzaldehyde: n_D^{25}= 1.5436 (lit.[208] $n_D^{19.5}$ = 1.54563); ir identical to an authentic sample; benzyl bromide: n_D^{25} = 1.5739 (lit.[209] n_D^{22} = 1.5742); ir identical to authentic sample.

Attempted Preparation and Isolation of the Thallium Enolate of Cyclohexanone

To a solution of freshly distilled cyclohexanone

(5.4 g; .55 mmole) in anhydrous benzene was added all at once, a solution of thallous ethoxide (12.5 g; 50 mmole) in benzene (20 ml). After stirring under a nitrogen atmosphere for 2 hr. at 25°, the reaction solution showed no signs of a precipitate forming, and glc analysis (column F; 80°) indicated no usage of cyclohexanone. The mixture was refluxed for 30 min. at 81°, but showed again, no change upon cooling. Hexamethylphosphoramide (8.9 g; 50 mmole) was added, causing some darkening of the solution, but after 15 hr. reflux, glc analysis again showed no usage of cyclohexanone.

The Reduction of Cyclohexanone with Thallous Ethoxide: General Procedure

To a magnetically stirred solution of cyclohexanone (2.45 g; 25 mmole) in ethanol or isopropanol (20 ml) was added all at once, a solution of thallous ethoxide (the relative amount is shown in Table I) in either THF, benzene or toluene (20 ml). The mixtures were stirred under a nitrogen atmosphere for the times and at the temperatures shown in Table I. The progress of the reactions was monitored by hydrolysis (with 2N hydrochloric acid) and subsequent glc analysis (column F; 100°) of aliquots. The presence of low boiling carbonyl products was detected by passing the exit nitrogen stream through a solution of

2,4-dinitrophenylhydrazine reagent.

After the requisite period of time, the mixtures were cooled and hydrolyzed with 2N hydrochloric acid (20 ml). The organic layer was separated, and the aqueous layer saturated with sodium chloride and extracted with benzene (3 x 10 ml). The combined organic layer was dried over sodium sulfate and subjected to quantitative glc analysis (column F; 100°) for the determination of cyclohexanone and cyclohexanol (the results are shown in Table I). The reaction mixture was concentrated, and the product collected by glc (column C; 155°) showed the following properties: cyclohexanol: $n_D^{24} = 1.4656$ (lit.[210] $n_D^{25} = 1.4642$) ir identical to authentic sample; mass spectrum M^+ 100. The reaction carried out in the presence of isopropanol produced a precipitate in the exit bubbler, shown to be the 2,4-DNP of acetone, mp. 123 - 125° (lit.[207] 126°).

The Preparation of Thallous *t*-Butoxide

To a magnetically stirred solution of thallous ethoxide (6.25 g; 25 mmole) in anhydrous benzene (30 ml) was added all at once, *t*-butanol (10 ml). The mixture was refluxed under nitrogen for 20 min., after which time, slow distillation of the benzene-ethanol was carried out. After about 1 hr. a white solid remained to which was added *t*-butanol (20 ml). The white solid was collected by

filtration in a nitrogen filled glove box providing thallous *t*- butoxide: nmr (benzene-d_6): δ 1.4 (s, CH_3). The base was sensitive to moist air and was thus prepared fresh immediately prior to use, and maintained under a nitrogen atmosphere.

Alkylation of the Thallium Enolate of Cyclohexanone in the Presence of TMEDA: General Procedure:

A mixture of cyclohexanone (2.5 g; 25 mmole), TMEDA (see Table II), and thallous ethoxide or thallous *t*-butoxide (25 mmole) in the appropriate solvent (see Table II) (50 ml) was stirred and heated under a nitrogen atmosphere for the times and at the temperatures shown in Table II. The mixtures were cooled to 25° to investigate the possibility of enolate precipitation which was not in evidence. Methyl iodide (36 g; 250 mmole) was added, and the mixture reheated for the times and at the temperatures shown in Table II. During reaction, a yellow-orange precipitate resulted (presumably thallium iodide). The reaction was monitored by removal, hydrolysis (with 2N HCl) and glc analysis (column A; 100°) of aliquots. After the period of time indicated, the mixture was hydrolyzed with 30% HCl (30 ml), the organic layer separated, and dried with anhydrous sodium sulfate. Quantitative glc analysis (column A; 100°) was carried out for the presence of cyclohexanone, 2-methylcyclohexanone, 2,2-dimethylcyclohexanone

and 2,6-dimethylcyclohexanone. The results are shown in Table II.

The reaction hydrolysate was concentrated and the isolated (column D; 130°) products showed the following properties: cyclohexanone: n_D^{25} = 1.4494 (lit.[211] n_D^{20} = 1.4485); ir identical to authentic sample; 2-methylcyclohexanone: nmr: δ 1.2 - 2.6 (m, 9, ring CH), 1.1 (d, 3, CH_3); ir spectrum identical to authentic sample; 2,2-dimethylcyclohexanone; n_D^{25} = 1.4482 (lit.[212] n_D^{20} = 1.4486); ir identical to an authentic sample.

Alkylation of the Thallium Enolate of Cyclopentanone in the Presence of TMEDA

A mixture of cyclopentanone (1.85 g; 22 mmole), thallous *t*-butoxide (25 mmole, prepared as above), and TMEDA (1.5 g; 12.5 mmole) in benzene (60 ml) was heated under a nitrogen atmosphere for 5 min. at 45°. On cooling to 25°, the mixture showed no enolate precipitation, thus methyl iodide (36 g; 250 mmole) was added. This resulted in the formation of a yellow precipitate (TlI). After 45 min. at 30° the mixture was hydrolyzed with 2N HCl (40 ml). The aqueous layer was saturated with sodium chloride and the organic layer was separated and dried with anhydrous sodium sulfate. Quantitative glc analysis (column A; 80°) indicated: cyclopentanone (25%); 2-methyl-

cyclopentanone (35%); 2,2-dimethylcyclopentanone (22%) and 2,5-dimethylcyclopentanone (11%). The reaction mixture was concentrated by fractional distillation and isolation of the products (glc, column D, 110°) gave cyclopentanone: n_D^{25} = 1.4355 (lit.[213] n_D^{20} = 1.4370); ir spectrum identical to authentic material; 2-methylcyclopentanone: n_D^{25} = 1.4330 (lit.[214] n_D^{20} = 1.4350); ir spectrum identical to authentic sample; 2,2-dimethylcyclopentanone: n_D^{25} = 1.4319 (lit.[184] n_D^{25} = 1.4319 (lit.[184] n_D^{25} = 1.4317); 2,5-dimethylcyclopentanone: n_D^{25} = 1.4296 (lit.[184] n_D^{25} = 1.4292); ir spectrum identical to authentic material.

Alkylation of Cyclohexanone Sodium Enolate

A mixture of *t*-amyl alcohol (2.2 g; 25 mmole) and sodium (1.15 g; 50 mmole) in benzene (50 ml) was magnetically stirred and refluxed under a nitrogen atmosphere for 5 hr. The solution was allowed to stand overnight for 17 hr. at 25° and the excess sodium removed from the gelatinous mixture. A solution of cyclohexanone (2.5 g; 25 mmole) in benzene (10 ml) was added, and the solution heated to 40° for 5 min. After cooling, methyl iodide (36 g; 250 mmole) was added and the mixture stirred at 30° for 30 min. The mixture was hydrolyzed with 2N HCl (30 ml), the organic layer separated and dried over anhydrous sodium sulfate. Quantitative glc analysis (column A; 100°) showed the following results: cyclohexanone (24%);

2-methylcyclohexanone (64%); 2,2-dimethylcyclohexanone (9%) and 2,6-dimethylcyclohexanone (2%).

Reaction of Thallous Ethoxide with ω-(Methylsulfinyl)acetophenone XXXIX to Form Salt XL

To a solution of thallous ethoxide (1.5 g; 6.0 mmole) in anhydrous THF (25 ml) magnetically stirred under a nitrogen atmosphere, was added a solution of ω-(methylsulfinyl)acetophenone (0.91 g; 5 mmole) in THF (25 ml). After stirring for about 5 min., the initially formed yellow colouration disappeared and a white precipitate resulted. The mixture was stirred (30 min.), anhydrous ligroin (40 ml) was added and stirring was continued for an additional 15 min. The product was collected by filtration, washed with ligroin, and dried to provide 1.9 g (100%) of product: mp. 139 - 141°; mass spectrum, m/e: 386, 384(2), 371(31), 369(13), 205(100), 203(37), 120(6), 105(95), 77(58). Anal. Calcd. for $C_9H_9O_2STl$: C, 28.04; H, 2.33; S, 8.32. Found: C, 28.00; H, 2.11; S, 8.31.

Alkylation of the Thallium Salt XL with Alkyl Iodides in the Presence of a Solvent: General Procedure:

To a magnetically stirred suspension of the thallium salt XL (1.9 g; 5 mmole) in the appropriate solvent (40 ml),

was added methyl iodide (5 ml), and the mixture heated to 40° for the times indicated below. The pale yellow supernatant was decanted from the orange precipitate (TlI) and passed through a short Florisil column. The column was washed with THF (2 x 40 ml), and the solutions combined and concentrated on a rotary evaporator, to a pale yellow oil.

With Methyl Iodide in THF

After a reaction time of 1 hr. and processing as above, there was obtained 0.95 g of an oil. Diethyl ether (2 ml) was added, and the mixture cooled to 0°. The crystalline product was filtered and there was obtained as a white solid 0.47 g (49%) ketosulfoxide XLI (R = CH_3): mp. 73 - 76° (lit.[197] mp. 77 - 78°); ir ($CHCl_3$) 1675 (C=O), 1050 cm^{-1} (SO)

With Methyl Iodide in Ligroin

After a reaction time of 1.5 hr. and processing as above, there was obtained 0.90 g of oil. THF (50 ml) was added and the solution made homogeneous. A sample (5 ml) was removed and concentrated. Quantitative nmr analysis indicated the presence of 80% ketosulfoxide XLI (R = CH_3).

Attempted Alkylation with Isopropyl Iodide in Ligroin

After a reaction time of 23 hr. at 60° the reaction

mixture showed little change by inspection. The orange-yellow precipitate of thallium iodide normally observed was not in evidence.

Alkylation of the Thallium Salt XL with Alkyl Iodides in the Absence of Solvent: General Procedure:

To the thallium salt XL (1.9 g; 5 mmole) was added freshly distilled alkyl iodide (40 ml) under a nitrogen atmosphere. After the magnetically stirred mixture had reacted for the times and at the temperatures indicated below, it was filtered through a short Florisil column. The column was washed with THF (2 x 40 ml), and the solutions combined and concentrated on a rotary evaporator. Products were isolated by column chromatography using Florisil as adsorbent.

With Methyl Iodide

After a reaction time of 30 min. at 25°, there was obtained 0.87 g of a colourless oil. Chromatography on Florisil (50 g) (elution with ether-acetone, 7:3 by volume) afforded 0.79 g (81%) of diastereomeric sulfoxides XLI ($R = CH_3$): ir ($CHCl_3$) 1675 (C=O), 1050 cm^{-1} (SO); nmr: δ 1.56 (d, 3, CH_3), 1.60 (d, 3, CH_3), 2.45 (s, 3, $SOCH_3$), 2.50 (s, 3, $SOCH_3$), 4.65 (q, 1, CH), 4.90 (q, 1, CH), 7.20-8.05 (m, 10, arom.). Crystallization from ether-ethylacetate

yielded white crystals, mp. 74 - 76° (lit.[197] 77 - 78°).

With Ethyl Iodide

After 1.5 hr. at 55° there was obtained 0.97 g of a pale yellow oil. Chromatography on Florisil (50 g) (elution with ether) afforded 0.24 g (28%) of XLIII, the ir and nmr spectrum of which were identical to those of a sample independently prepared from ω-(methylsulfinyl) acetophenone with sodium metabisulfite.[215]

Further elution with ether-acetone (4:1) provided 0.64 g of colourless oil, shown to be a two component mixture by analytical tlc. By preparative tlc (ethyl acetate development) there was obtained as the more mobile component, 0.39 g (38%) of diastereomeric ketosulfoxides XLI (R = C_2H_5): ir (liquid film) 1670 (C=O), 1060 cm^{-1} (SO); nmr: δ 1.05 (t, 3, CH_3), 2.40 - 1.90 (m, 2, CH_2), 2.55 (s, 3, $SOCH_3$), 4.90 - 4.55 (m, 1, CH), 7.35 - 8.25 (m, 5, arom.); mass spectrum: M^+, 210. The less mobile component XLII (R = C_2H_5) (0.175 g, 17%), was a colourless oil: ir (liquid film) 1605 (C=C), 1070 (C-O), 1040 cm^{-1} (SO); nmr δ 1.32 (t, 3, CH_3), 2.73 (s, 3, $SOCH_3$), 4.00 (q, 2, CH_2), 6.02 (s, 1, C=CH), 7.70 - 7.35 (m, 5, arom.); mass spectrum: M^+, 210.

With Isopropyl Iodide

After 6 hr. at 65° there was obtained 0.91 g of pale

yellow oil. Column chromatography on Florisil (ether elution) provided 0.325 g of pale yellow oil. Molecular distillation at 90 - 100° (bath temp.) (1 mm) yielded 0.300 g (36%) of XLIII. The ir and nmr spectra were identical to those of an authentic sample.[198]

Further elution with ether-acetone (4:1) provided 0.467 g (42%) of XLII (R = $\underline{i}$-C_3H_7): ir (liquid film) 1605 (C=C), 1060 (C-O), 1040 cm^{-1} (SO); nmr: δ 1.30 (q, 6, CH_3), 2.73 (s, 3, $SOCH_3$), 4.28 (m, 1, CH), 6.00 (s, 1, C=CH), 7.60 - 7.25 (m, 5, arom.); mass spectrum: M^+, 224. The structure was further confirmed by conversion (2N HCl, 50°, 15 min.) to the Pummerer rearrangement product $C_6H_5COCH(OH)SCH_3$ [198,199]: ir ($CHCl_3$) 1670 (C=O), 3460 cm^{-1} (OH); nmr: δ 2.00 (s, 3, SCH_3), 4.34 (s, 1, OH), 6.17 (s, 1, CH), 8.20 - 7.30 (m, 5, arom.); mass spectrum: M^+, 182.

The Preparation of the Thallium Salt XLIV(i) of 2,4-pentanedione

To a solution of 2,4-pentanedione (11.0 g; 110 mmole) in anhydrous ligroin (20 ml) was added, all at once, a solution of thallous ethoxide (25 g; 100 mmole) in anhydrous ligroin (30 ml). A heavy white precipitate formed immediately, and the mixture was magnetically stirred for *ca.* 30 min. The solid was collected (vacuum filtration)

and dried to afford 30.3 g (100%) of XLIV(i); mass spectrum: M^+, 304.

Reaction of the Thallium Salt XLIV(i) with Alkyl Iodides: General Procedure:

A heterogeneous mixture of salt XLIV(i) (15.2 g; 50 mmole) in freshly distilled alkyl iodide was magnetically stirred and refluxed for the times indicated [107] (under a nitrogen atmosphere). The mixture was then cooled to room temperature and the supernatant passed through a Florisil column. The solid residue was washed with THF (2 x 25 ml) and the washings were also passed through the column. Yields were established by quantitative glc analysis. Each component was isolated by preparative glc, and where amounts permitted, further purified by molecular distillation.

With Methyl Iodide

After a reflux period of 4 hr. and processing as described above, quantitative glc analysis (column G; 125°) gave the following results: 2,4-pentanedione (5%), XLV(i) (R' = CH_3, 85%), and XLVII(i) (R' = CH_3, 6%). The isolated (column E, 155°) materials had the following properties: 2,4-pentanedione, ir and nmr spectra identical to those of authentic material; XLV(i) (R' = CH_3), after

molecular distillation at 75 - 77° (bath) (20 mm), ir (liquid film) 3410 (enol OH), 1720, 1700 (C=O), 1610 cm^{-1} (C=C, enol); nmr: δ 1.32 (d, 3, CH_3), 2.20 (s, 6, CH_3CO), 3.67 (q, 1, CH), and in addition, signals due to approximately 25% enol content: δ 1.83 (s, 3, C=C-CH_3), 2.11 (s, 3, $CH_3C(O)=C$), 2.20 (s, 3, CH_3CO) 16.42 (OH, exch. by D_2O); mass spectrum: M^+,114: XLVII(i) (R' = CH_3), ir (liquid film) 1710 cm^{-1} (C=O); nmr: δ 1.35 (s, 6, CH_3), 2.13 (s, 6, $COCH_3$); mass spectrum: M^+, 128.

With Ethyl Iodide

After a reflux period of 16 hr. and processing as above, quantitative glc (column I, 155°) indicated: 2,4-pentanedione (3%), XLV(i) (R' = C_2H_5, 63%) XLVI(i) (R' = C_2H_5, 13%), and dialkylate XLVII(i) (R' = C_2H_5, 4%). The properties of the isolated (column J, 170°) materials were: 2,4-pentanedione, spectroscopically (ir, nmr) identical to authentic material: XLV(i) (R' = C_2H_5), (after molecular distillation at 73 - 75° (bath) (20 mm)), ir (liquid film) 3410 (OH, enol), 1725, 1700 (CO), 1600 cm^{-1} (C=C, enol); nmr: δ 0.92 (t, 3, CH_3), 1.89 (m, 2, CH_2), 2.18 (s, 6, CH_3CO), 3.56 (t, 1, CH); mass spectrum: M^+, 128: XLVI(i) (R' = C_2H_5), ir (liquid film) 1680 (CO), 1585 cm^{-1} (C=C); nmr: δ 1.35 (t, 3, CH_3), 2.13 (s, 3, $CH_3C(O)=C$), 2.27 (s, 3, CH_3CO), 3.83 (q, 2, CH_2), 5.43 (s, 1, C=CH); mass spectrum: M^+, 128: XLVII(i) (R' = C_2H_5),

ir (liquid film) 1700 cm^{-1} (CO); nmr: δ 0.72 (t, 6, CH_3), 1.94 (q, 4, CH_2), 2.08 (s, 6, CH_3CO); mass spectrum: M^+, 156.

With Isopropyl Iodide

The reaction was processed as above after being refluxed for 14 hr. The yields (quantitative glc analysis column I, 170°) were: XLV(i) (R' = $\underline{i}$-C_3H_7) 20%, and XLVI(i) (R' = $\underline{i}$-C_3H_7) 62%. Isolation (column H, 200°) provided XLV(i) (R'= $\underline{i}$-C_3H_7) which after molecular distillation at 72 - 76° (bath) (18 mm), displayed ir (liquid film) 1725, 1700 cm^{-1} (CO); nmr (100 MHz, $CDCl_3$): δ 0.90 (d, 6, CH_3), 2.17 (s, 6, CH_3CO), 2.80 - 2.20 (m, 1, CH), 3.40 (d, 1, COCH); mass spectrum: M^+, 142: and XLVI(i) (R' = $\underline{i}$-C_3H_7), ir (liquid film) 1675 (CO), 1580 cm^{-1} (C=C); nmr: δ 1.26 (d, 6, CH_3), 2.12 (s, 3, $CH_3C(O)=C$), 2.24 (s, 3, CH_3CO), 4.40 (m, 1. CH), 5.42 (s, 1, C=CH); mass spectrum: M^+, 142.

Preparation of the Thallium Salt XLIV(ii) of Ethylacetoacetate.

To a solution of ethylacetoacetate (14.3 g; 110 mmole) in a mixture of ligroin (20 ml) and toluene (20 ml) was added, all at once, a solution of thallous ethoxide (24.9 g; 100 mmole) in ligroin (30 ml). A white precipitate

formed immediately, and the mixture was magnetically stirred under nitrogen for about 30 min. After filtration and drying, there was obtained 32 g (96%) of XLIV(ii), mp. 90 - 91°; mass spectrum, M^+ 334.

Alkylation of the Thallium Salt XLIV(ii) with Alkyl Iodides: General Procedure:

A mixture of the thallium salt XLIV(ii) (16.7 g; 50 mmole) in freshly distilled alkyl iodide (40 ml) was magnetically stirred and refluxed under nitrogen for the times indicated. The mixtures were then processed as described for the alkylations of XLIV(i).

With Ethyl Iodide

Admixture of the reagents resulted in cloudiness, but no solid particles were evident. Upon refluxing, for 4 hr. the mixture turned yellow and TlI precipitated. After processing as described above, the yields (column I, 170°) were: ethylacetoacetate (2%), XLV(ii) (R' = C_2H_5, 80%), XLVI(ii) (R' = C_2H_5, 2%), and XLVII(ii) (R' = C_2H_5, 5%). Isolation (column E, 200°) provided materials with the following properties: ethyl acetoacetate, ir and nmr identical to authentic material: XLVI(ii) (R' = C_2H_5), ir (liquid film) 1710, 1625 cm^{-1}; nmr (100 MHz, $CDCl_3$): δ

1.30 (m, 6, CH_3), 2.28 (s, 3, $CH_3C(O)=C$), 3.80 (q, 2, C $C=C(O)CH_2$), 4.14 (q, 2, $COOCH_2$), 4.99 (s, 1, C=CH); mass spectrum: M^+, 158: XLV(ii) (R' = C_2H_5) (after molecular distillation at 87 - 88° (bath) (20 mm)), ir (liquid film) 1740, 1720cm^{-1}; nmr: δ 0.93 (t, 3, $CCCH_3$), 1.27 (t, 3, $OCCH_3$), 1.89 (m, 2, CCH_2C), 2.22 (s, 3, CH_3CO), 3.35 (t, 1, CH), 4.21 (q, 2, OCH_2C); mass spectrum: M^+, 158: XLVII(ii) (R' = C_2H_5), ir (liquid film) 1735, 1710 cm^{-1}; nmr: δ 0.76 (t, 6, $CCCH_3$), 1.26 (t, 3, $OCCH_3$), 1.93 (q, 4, CCH_2C), 2.12 (s, 3, CH_3CO), 4.20 (q, 2, OCH_2C); mass spectrum: M^+, 186.

With *i*-Propyl Iodide

The initial cloudy mixture turned yellow and TlI precipitated upon refluxing the mixture (19 hr.). After processing as above, the yields (column E, 165°) were: XLVI(ii) (R' = *i*-C_3H_7, 20%) and LXV(ii) (R' = *i*-C_3H_7, 67%). Separation (column E, 195°) afforded XLVI(ii) (R' = *i*-C_2H_7), which after molecular distillation at 86 - 88° (bath) (18 mm) displayed ir (liquid film) 1700 (C=O), 1615 cm^{-1} (C=C); nmr (100 MHz, $CDCl_3$) δ 1.26 (d, 6, $C(CH_3)_2$), 1.26 (t, 3, CH_3C), 2.25 (s, 3, $CH_3C(O)=C$), 4.11 (q, 2, CH_2), 4.38 (m, 1. OCH), 4.97 (s, 1, C=CH): XLV(ii) (R' = *i*-C_3H_7), after molecular distillation at 83 - 86° (bath) (20 mm) showed, ir (liquid film) 1740, 1715 cm^{-1}; nmr: δ 0.94

(q, 6, $C(CH_3)_2$), 1.25 (t, 3, $OCCH_3$), 2.19 (s, 3, CH_3CO),
2.7 - 2.2 (m, 1, CH), 3.17 (d, 1, COCH), 4.15 (q, 2, CH_2).

THE DEOXYGENATION OF ALIPHATIC C-NITROSO AND N-NITROSOALKANES WITH TRIVALENT PHOSPHORUS REAGENTS

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

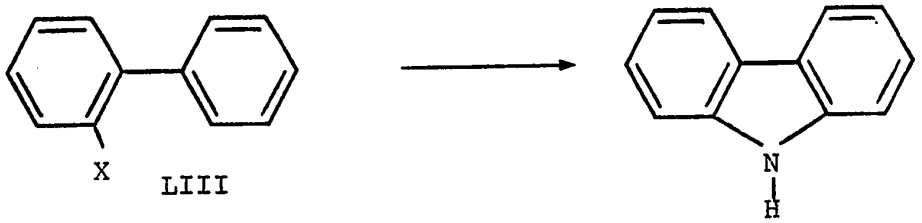
The ease with which trivalent phosphorus compounds, such as trialkyl or triaryl phosphines and trialkyl phosphites, enter into deoxygenation reactions has been recognized for some time.[216] It has been proposed [217] that the major driving force behind these reactions is the formation of a pentacovalent phosphorus derivative containing a strong phosphorus-oxygen multiple bond (eq. 35).

$$R_3P + XO \longrightarrow R_2P{=}O + X \qquad (35)$$

The versatility and scope of this general reaction was recently extended by Cadogan and co-workers who, in the wake of two earlier observations,[220,221] reported an analogous reduction of aromatic nitro [217,219] and nitroso [217,218] compounds. Reaction of nitroso aromatics with triethylphosphite (preferred reagent) was found to proceed very readily, giving rise to a mixture of the corresponding azoxybenzene LI, and the phosphorimidate LII [217,218] (eq. 36).

$$ArNO + (EtO)_3P \longrightarrow \underset{\text{LI}}{ArN{=}\overset{\overset{O}{\uparrow}}{N}Ar} + \underset{\text{LII}}{(EtO)_3P{=}NAr} + (EtO)_3PO \qquad (36)$$

Nitro aromatics required more drastic conditions, and gave rise only to tars.[219] However, later investigations [222, 223] showed that although azoxy compounds could not be detected, the phosphorimidates (LII) could be obtained as the major components among a complicated mixture of products. Extension of the method to include *o*-nitro (LIII X = NO_2) [219] and *o*-nitroso (LIII, X = NO) [218] biphenyls has been found to give excellent yields of carbazoles (LIV). In addition to its synthetic applicability, the method shows similar features to the photolytic and pyrolytic decomposition of *o*-azidobiphenyls [224] (LIII, X = N_3) (eq. 37).



LIII

X = NO, NO_2, N_3.

LIV

(37)

These initial observations of Cadogan and coworkers have prompted an expanding interest in such deoxygenation reactions. This has led ultimately to the development of a general route for the preparation of a wide variety of heterocyclic compounds including carbazoles, carbolines, indoles, indazoles, benztriazoles, anthranils, phenothiazines, azepines, benzoxazoles, and related compounds.[217,

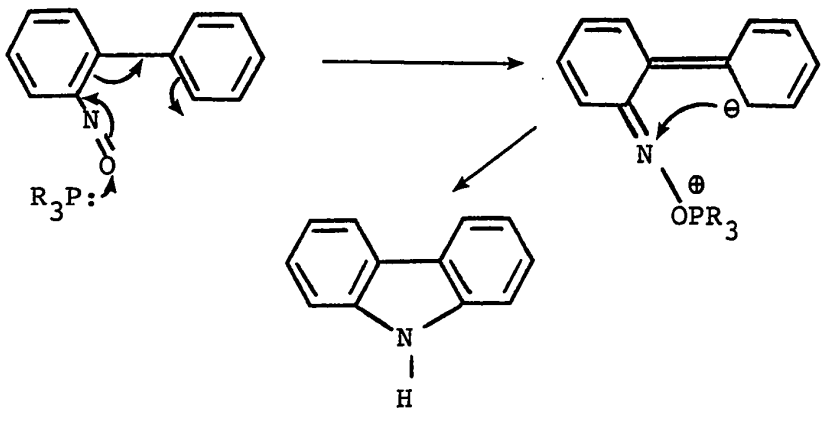
225,226

Undoubtedly, one of the major factors responsible for the recent widespread interest in nitro and nitroso deoxygenations is the early suggestion [218,219,227] that the reactions may proceed via a nitrene intermediate, formed by initial nucleophilic attack of phosphorus on oxygen, and the subsequent loss of phosphate (eq. 38).

$$ArNO + R_3P \longrightarrow ArN^{\ominus}-O-P^{\oplus}R_3 \longrightarrow ArN: + R_3PO \quad (38)$$

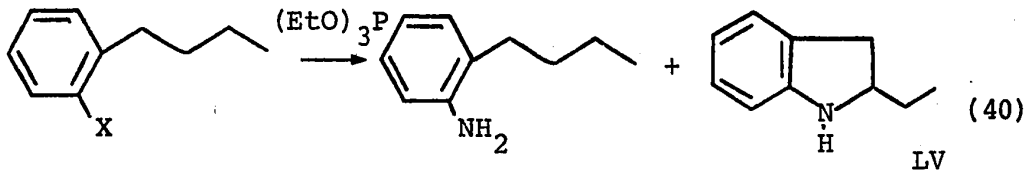
It must be stressed however, that this "nitrene" hypothesis was based solely on the fact that the deoxygenation procedure in many cases gave products analogous to those obtained from the pyrolysis of the corresponding aryl azides [224,228-230] (eq. 37). It is generally agreed [225, 231,232] that nitrenes intervene as intermediates in many aryl azide decomposition reactions.

Although other mechanisms have been suggested [219,223,281] to account for the observed products (eq. 39), strong additional evidence in support of the nitrene hypothesis



(39)

has recently been provided by the isolation of indolines (LV), and the corresponding *o*-alkyl anilines, from the deoxygenations of *o*-alkyl nitrobenzenes [222-234] and *o*-alkyl nitrosobenzenes [222] with trialkphosphite (eq. 40).



(40)

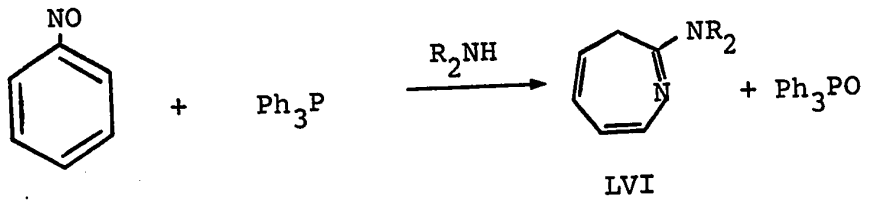
$+(EtO)_3PO$

X = NO, NO_2

The nature and ratio of the products obtained are similar to those obtained from the thermolysis of the corresponding ortho substituted aryl azides [229,235-239], and presumably arise *via* hydrogen abstraction, and insertion into a C-H bond by an initially formed nitrene intermediate. In the latter instance, such products are generally accepted [233, 240] to arise *via* the intermediacy of a monovalent nitrogen species.

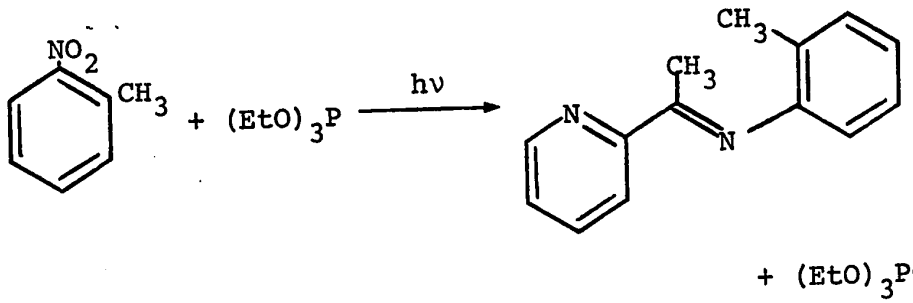
Further support for this mechanism has been provided by the recent isolation of azepines LVI (eq. 41) and additional products showing a rearranged aromatic skeleton (eq. 42), from the deoxygenation of nitro and nitroso

benzenes [222,241,242] under thermal [243] and photochemical [244, 245] conditions, using trivalent phosphorus reagents.



(41)

LVI



(42)

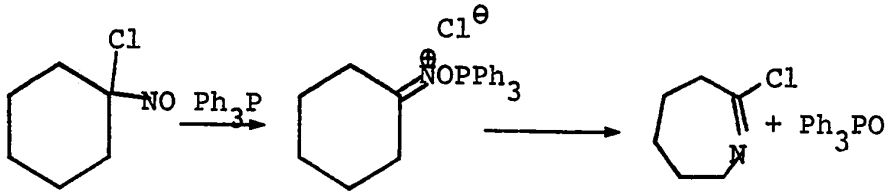
Such skeletal rearrangements are felt to be typical [240] of aryl nitrenes produced in the presence of nucleophilic species.

In spite of the reported deoxygenation of aromatic species, investigations involving aliphatic nitro and nitroso alkanes have received little attention. Of the few attempts that have been reported, little success has been

achieved from a synthetic standpoint. For example, deoxygenation of 2-phenylnitroethane was reported to provide, in low yield, benzyl cyanide, presumably by dehydration of the corresponding oxime (eq. 43).[233]

$$PhCH_2CH_2NO_2 \longrightarrow PhCH_2CH_2NO \longrightarrow PhCH_2CH{=}NOH \longrightarrow PhCH_2C{\equiv}N \qquad (43)$$

Early attempts to deoxygenate α-halonitro and α-halonitroso alkanes were shown[246,247] to produce, simply, oxime salts. However, Ohno and coworkers[248,249] later reported that treatment of the cyclic analogues with triphenyl phosphine led to deoxygenation and concomitant ring expansion.



(44)

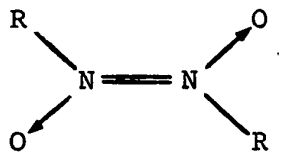
These reactions are believed to require the presence of the α chloro function in the molecule, and as such, the results may be expected to differ considerably from the deoxygenation of the simple unsubstituted analogues (cf. the Perkow

reaction [250]).

The purpose of the present study was to investigate the previously unreported deoxygenation of aliphatic nitroso compounds, with a view to the possibility of generating an alkyl nitrene. The synthetic potential of the reaction was considered, and in the light of the differing viewpoints surrounding the possible intermediacy of alkyl nitrenes [231, 232,251] in similar reactions, it was also hoped that some additional evidence could be obtained as regards the possible mechanism. During the course of the investigation, an attempt was made to extend the procedure to include N-nitroso compounds.

RESULTS AND DISCUSSION

The starting nitroso alkanes were prepared either by the hypobromite oxidation of the corresponding hydroxylamines [252], or peracetic acid oxidation of suitable imines. [252,253] The compounds were isolated and characterized [254] as the colourless crystalline *trans* dimers (LVII). [255,256]

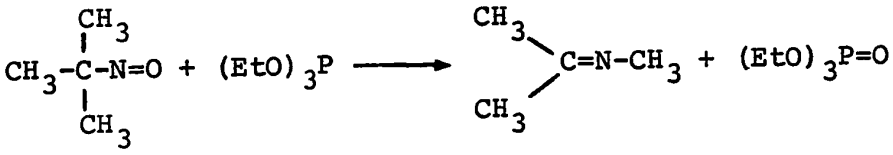


LVII

Initial attempts to obtain the tertiary nitrosoalkane dimers by direct oxidation of the corresponding primary amines, according to previous reports [257,258], failed to yield the required products.

Deoxygenation attempts of an exploratory nature were carried out using 2-methyl-2-nitrosopropane, the simplest member of the tertiary nitrosoalkanes. Dissolution of the dimeric material in methylene chloride resulted in the immediate formation of a deep blue colouration, typical of nitroso monomers. [254-256] Subsequent addition of triethylphosphite [218] led to the gradual disappearance of the blue colouration in a somewhat exothermic reaction.

After 30 min. at ambient temperatures, analysis (glc) indicated the formation of triethylphosphate (90% yield). Spectral analysis (ir, nmr) of the reaction mixture showed the presence of acetone methylimine (ir, 1665 cm^{-1}), which, after acid hydrolysis, yielded acetone (87%). This encouraging result indicated that deoxygenation had indeed occurred. The product apparently arose as a consequence of migration of a group from the α-carbon atom to nitrogen (eq. 45).



(45)

In the light of this result, the deoxygenation of a number of nitrosoalkanes (including primary and secondary classes) was undertaken, with a view to investigating the scope and nature of the reaction. Deoxygenations were effected in benzene solution, and the progress of reactions was monitored by glc analysis. In all but one case, products were analyzed as the corresponding carbonyl compounds and primary amines which result from mild acid hydrolysis of the reaction mixtures. The results thus obtained are summarized in Table VI.

It is clear from the results that the reaction is generally applicable to primary, secondary, and tertiary

TABLE VI

Deoxygenation of a Series of Aliphatic Nitrosoalkanes with Triethylphosphite [a]

	Starting Nitrosoalkane	Time (hr)	Temp (°C)	$(EtO)_3P$[d] Remaining (%)	$(EtO)_3P=O$[d] Formed (%)	Oxime[d] Formed (%)	Yield[d] of Products due to Migration of (%) H	RCH_2	CH_3	Aryl
1.	2-methyl-2-nitroso[g] propane	2.0	24-30	5	90	-	-	-	87	-
2.	2-methyl-2-nitroso[b] propane	2.0	24-30	5	90	-	-	-	90	-
3.	1-methyl-1-nitroso cyclohexane	4.0	20-30	1	93	-	-	91[e]	<3[c]	-
4.	nitrosocyclohexane	3.0	50-55	13	90	12	68	0	-	-
5.	1-nitrosoheptane[f]	3.0	50-55	35	64	33	58	0	-	-
6.	2-nitrosoheptane	3.5	50-55	trace	91	8	57	0	22	-
7.	α-methyl-α-nitroso-toluene	0.5	50-55	12	77	28	9	-	4	30
8.	α-nitroso toluene	1.0	50-55	50	45	40	27	-	-	10
9.	α-nitroso-*p*-methoxy toluene	1.0	50-55	53	45	42	27	-	-	12

(a) All reactions except entries 1 and 2 were carried out in benzene solution

(b) Cyclohexene solvent

(c) Assignment made on the basis of glc retention time using two columns

(d) Yields estimated by glc analysis

(e) Analysis effected prior to hydrolysis.

(f) Reaction carried out in the presence of water

(g) Dichloromethane solvent

nitrosoalkanes. However, a substantial difference in the reactivity of the primary and secondary as opposed to the tertiary compounds is also apparent. Initial investigation had shown that the primary and secondary dimers did not monomerize upon dissolution at 25° (blue colouration was not observed), and that the materials were recovered unchanged after long periods of time in contact with triethylphosphite. Raising the reaction temperature to *ca.* 50° overcame this problem, and resulted in the rapid formation of triethylphosphate. An independent experiment had previously established that upon heating to *ca.* 50°, a benzene solution of the α-nitrosotoluene dimer indicated the presence of the blue colouration (due to monomeric material).

These observations are in accord with the known [256, 259, 260] dissociation trends of nitrosoalkane dimers in solution†, and suggest that the first step of the deoxygenation process involves monomerization of the starting dimers. (Also, deoxygenated products bearing the basic dimer skeleton with the nitrogen-nitrogen bond unruptured were not observed).

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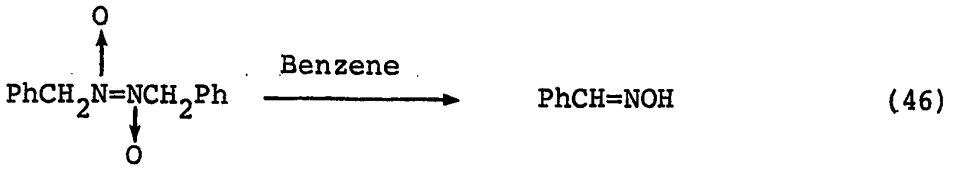
† It has recently been shown [261] that the tertiary nitroso alkane, 2-methyl-2-nitrosopropane, is *ca.* 36% dissociated in solution at 20°, whereas nitrosocyclohexane is only 0.08% dissociated at the same temperature.[259]

From a consideration of the relative yields of the products, it would appear that no rigorous conclusions concerning migration trends for all substrates can be established. However, it is clear that hydrogen migration is the preferred pathway in all but one of the cases in which that possibility arises (compare entries 4 to 9). In this respect, the overall reaction shows some similarity to the decomposition of alkyl azides.[232,251,262]

Although, in the cases of the primary and secondary compounds the spectrum of products is further complicated by the concurrent formation of the corresponding oximes, the latter reaction was shown to be independent of the deoxygenation process. Thus, in the absence of triethyl phosphite, the dimer of α-nitrosotoluene was converted (under otherwise identical conditions to those of deoxygenation) readily, although at a slow rate, to the corresponding benzaldoxime (eq. 43). The rate of oxime formation was considerably enhanced in the presence of triethyl phosphate, however. Increases in the rate of rearrangement of primary and secondary nitrosoalkanes to oximes in the presence of polar compounds is well established.[256] Further experimentation showed that oxime formation was irreversible under the reaction conditions. An equimolar mixture of benzaldoxime and phosphite was recovered unchanged after a period of 24 hr. at 50°.

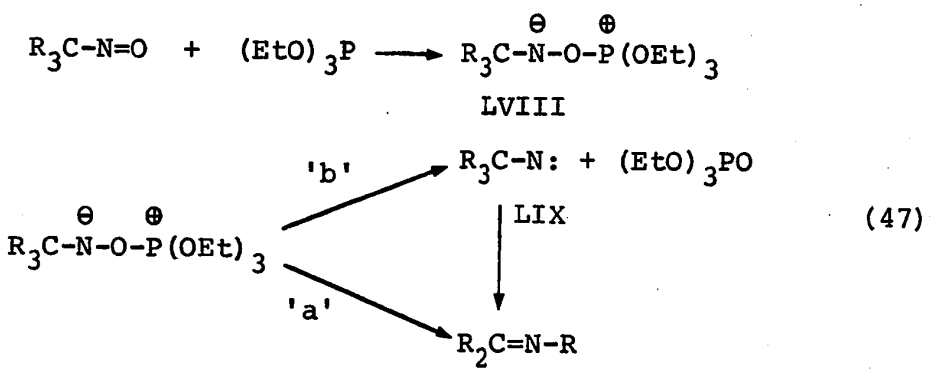


(46)

It is clear from the results that the rearrangement process exhibits some degree of selectivity. However, in the light of the low yields of material recovered in certain cases (for example, entry 7), the degree of mechanistic emphasis that can be placed on the specific values is open to question. The problem of reduced yields probably arises as a result of polymerization of the initially formed imines prior to hydrolysis. Polymerization of such unsaturated nitrogen species is well documented [263], and has been observed in similar rearrangement reactions in which imines are produced, for example, as a result of thermal or photolytic decomposition of azides.[264-266] It is significant in this regard, that initial attempts to deoxygenate 2-nitrosoheptane during this study, were found to produce only triethylphosphate as the sole volatile product even after hydrolysis. A repeat of the procedure in the presence of water (as an imine trap) afforded good yields of the expected product, hexanal.

Although a mechanism has not been rigorously established for the novel deoxygenation-rearrangement procedure reported here, an attractive possibility which encompasses

all of the observations, involves an initial nucleophilic attack of the phosphite upon the oxygen of the nitroso monomer, resulting in the formation of intermediate LVIII (eq. 47). The product-forming step could then involve either a 1,2-shift of a group from the α carbon to nitrogen with concerted loss of triethylphosphate (pathway 'a'), or initial loss of the phosphate moiety giving rise to a nitrene intermediate LIX (pathway 'b'). Rearrangement [262] of the discrete nitrene would give rise to the observed products.

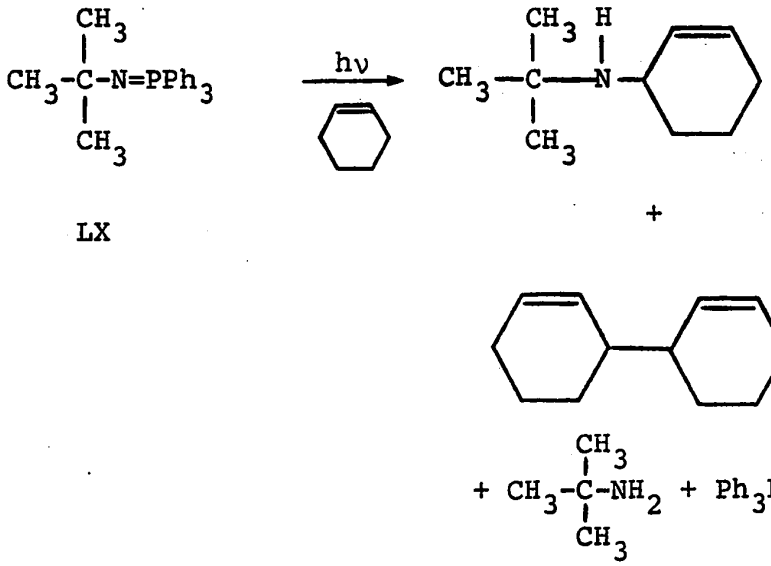


(47)

Precedence for an initial nucleophilic attack by the phosphorus is found in the observations of Cadogan and coworkers [219], who report that the rate of deoxygenation of aromatic nitroso alkanes is enhanced by the use of a more nucleophilic phosphorus reagent (that is $(EtO)_3P > PCl_3$). Since the completion of the present study, a report was published regarding the deoxygenation of aliphatic nitroso alkanes, in which identical observations to those of Cadogan

and coworkers concerning the nucleophilicity of the phosphorus reagent were described.[267]

In order to examine the possibility that a discrete nitrene intermediate may be formed during the deoxygenation process, the reaction of 2-methyl-2-nitrosopropane was repeated with cyclohexene as a solvent. This olefin is commonly employed as a trapping agent for nitrene and other similar species. Recently,[268] it has been shown to be especially efficient in capturing the *t*-butyl nitrene formed in the photolysis of the phosphine-*t*-butylimine LX (eq. 48).



LX (48)

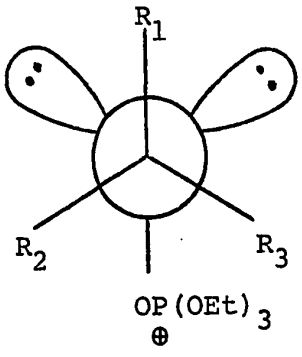
The deoxygenation was effected in cyclohexene solution, and provided essentially identical results to those obtained earlier in methylene chloride. Products attributable to a nitrene intermediate were not observed. It is

doubtful that much significance can be attached to the result, since the intermolecular trapping of alkyl nitrenes is often not observed [251], even though their presence may be strongly indicated from product studies.

In conclusion, in the light of the unmistakable degree of selectivity indicated in the rearrangement process, it would appear that a discrete nitrene is not produced, but that migration begins before the N-O bond of the intermediate LVIII is completely cleaved (pathway 'a'). There is general agreement [232,251,262,269,270] that rearrangement of alkyl nitrenes exhibit no discrimination (i.e. statistical migration aptitudes are observed).

A plausible explanation of the observed product ratios presents itself if it is first assumed that the reaction proceeds <u>via</u> pathway 'a'. Considering only the staggered conformations of the intermediate LVIII, the Newman projection LXI indicates that a "transoid" migration of group R_1 would provide one specific imine product. From the three possible conformations, the possibility of three products arises, the relative yields of which could well depend upon the populations of the corresponding conformers.

Similar conformational arguments have been employed by other authors [269,270] to explain the migration aptitudes observed in the photolysis of certain alkyl azides. More recently Skarz [267], and independently, Abramovitch [271],



LXI

have reported that the deoxygenation of aliphatic nitroso alkanes provides essentially identical results to those observed here. The latter author has suggested, on the basis of migration aptitudes, that the reaction proceeds by way of rearrangement with a concerted loss of phosphate.

As a direct consequence of the facile deoxygenation of aliphatic C-nitroso compounds reported above, the possibility arose that the analogous reaction of N-nitroso substrates may be readily effected. Such a reaction could conceivably give rise to an azo compound as the primary product, and could offer the possibility for the preparation of both the symmetrical and the unsymmetrical classes (eq. 49).

$$\begin{matrix} R \\ \diagdown \\ \quad N\text{-}NO \\ \diagup \\ R' \end{matrix} \quad + \quad (EtO)_3P \longrightarrow R\text{-}N{=}N\text{-}R' \quad + \quad (EtO)_3PO \qquad (49)$$

A literature review indicated that deoxygenation of

N-nitroso compounds had been achieved using basic solutions of sodium hydrosulfite, giving rise to products presumably derived from the corresponding dialkylaminonitrene [272] (eq. 50).

$$(PhCH(CH_3))_2NNO \xrightarrow[H_2O/OH^{\ominus}]{Na_2S_2O_4} (PhCH(CH_3))_2\ddot{N}-N: \longrightarrow PhCH(CH_3)-CH(CH_3)Ph + N_2 \qquad (50)$$

Early attempts to effect a similar transformation using triphenylphosphine, however, were found to be ineffective.[220] In view of the known reactivity of triethylphosphite in deoxygenation reactions of nitroso species [217,218], we briefly explored the possibility of oxygen removal from N-nitroso compounds with this reagent.

Thus, N-methyl-N-nitrosoaniline [273] was refluxed with triethylphosphite for a period of 6 hr. Analysis of the reaction mixture indicated that the starting materials had not reacted. The reaction was repeated using phosphorus trichloride, and subsequently, trisdimethylaminophosphine, as potential "deoxygenation" reagents. No reaction was observed for either reagent. Similar results were obtained when deoxygenation of a purely aliphatic analogue, N-nitroso-di-n-butylamine was attempted with triethylphosphite, phosphorus

trichloride or trisdimethylaminophosphine.

These results proved to be somewhat surprising, and although the reason for the lack of reactivity has not been established, the possibility arises that the electrophilicity of the oxygen is reduced due to resonance contribution from structure LXIIIb, where nucleophilic attack by phos-

LXIIIa LXIIIb

phorus species becomes less favourable.

EXPERIMENTAL

General Considerations

Infrared (ir) spectra were recorded using a Perkin-Elmer 421, Perkin-Elmer 337, or a Unicam S.P. 1000 Infrared-Spectrophotometer.

Ultraviolet (uv) spectra were determined using a Perkin-Elmer Model 202 Spectrophotometer.

Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 or HA-100 spectrometer. Unless otherwise stated, deuterochloroform ($CDCl_3$) was employed as the solvent with tetramethylsilane (TMS) as the internal standard, and chemical shifts are reported in δ-values. The following abbreviations are used in the text: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet.

Mass spectra were recorded at 70 eV on an AEI Model MS-2 or Model MS-9 Spectrometer. Spectra are recorded in the following manner :m/e: peak mass (relative intensity).

Gas chromatographic (glc) analyses were performed using an Aerograph A-90-P3 and a Varian Aerograph Series 1200 and Series 1400 chromatograph, with the following columns: column A, 1/8" x 5' 10% β,β-oxydipropionitrile on 60/80 Chromosorb W; column B, 1/8" x 10' 15% SE-30 on 60/80 Chromosorb W; column C, 1/4" x 10' 10% SE-30 on 60/80 Chromosorb W; column D, 1/4" x 5' 15% Carbowax 20 M on 60/80 Chromosorb W; column E, 1/8" x 5' 10% Carbowax 600 on

60/80 Chromosorb W; column F, 1/4" x 10' 10% XF1150 on 60/80 Chromosorb W; column G, 1/8" x 5' 20% DEGS on 60/80 Chromosorb W; column H, 1/8" x 5' 10% SE-52 on 60/80 Chromosorb W. All products, in both the quantitative (corrected for peak response) analytical, and preparative glc work are listed in order of elution.

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Refractive indices were measured on a Bausch and Lomb Abbé-3L Refractometer.

Microanalyses were performed by the Microanalytical Laboratory, University of Alberta.

Caution! Certain nitrosamines are known to be carcinogenic

Preparation of 2-Methyl-2-nitrosopropane dimer [252,253]

A solution of peracetic acid was prepared as follows: To a suspension of 90% hydrogen peroxide (15 ml; 550 mmole) in methylene chloride (50 ml) cooled to 0°, was added dropwise, with stirring, concentrated sulfuric acid (1 drop), and acetic anhydride (67.2 g; 66 mmole).

To a magnetically stirred solution of N-benzylidene-*t*-butylamine (80.5 g; 500 mmole) in methylene chloride (250 ml), cooled to 0° was added dropwise, the cooled peracetic acid solution. After addition, the reaction was allowed to warm to 25° over 24 hr. The resulting mixture was washed with ice-cold water (500 ml), cold 15% aqueous ammonia (2 x 200 ml), and finally with 10% sulfuric acid

solution (100 ml). Drying over magnesium sulfate, followed by removal of the methylene chloride solvent yielded the crude oxazirane as a pale yellow oil (85.5 g; 96%).

A magnetically stirred solution of sulfuric acid (12 ml) in methanol (200 ml) and water (20 ml) was cooled to 0°, and 2-*t*-butyl-3-phenyloxazirane (37.0 g; 200 mmole) was added dropwise. After addition, the mixture was allowed to warm to 25° and stirred for 22 hr. Water (300 ml) was added, and the solution was extracted with ether (3 x 100 ml). The aqueous layer was concentrated to about half volume, and a solution of barium chloride dihydrate (61.0 g) in water (250 ml) added. The suspension thus obtained was heated to 70° for 15 min, celite (100 g) was added, and the mixture was filtered. The filtrate was evaporated to dryness (rotary evaporator), and the remaining material dissolved in boiling ethanol (200 ml). Filtration of the ethanolic solution followed by concentration of the filtrate to about quarter volume, and the addition of ether (100 ml), resulted in the formation of a white precipitate. The precipitate was collected by vacuum filtration, and after washing with ether, yielded *t*-butylhydroxylamine hydrochloride (8.5 g; 30%), mp. 165 - 175° (lit.[274] 182 - 183°).

To a magnetically stirred solution of bromine (9.6 g; 60 mmole) and sodium hydroxide (6.0 g; 150 mmole) in water (40 ml), cooled to 0°, was added dropwise a solution of *t*-butylhydroxylamine hydrochloride (6.25 g; 50 mmole) and

sodium hydroxide (2.0 g; 50 mmole) in water (60 ml). Addition resulted in the formation of a blue suspension, which after stirring at 0° for 2 hr. yielded a pale blue solid. Filtration yielded 2-methyl-2-nitrosopropane dimer (4.0 g; 90%), mp. 80 - 82° (lit.[252] 85°): ir ($CHCl_3$) 1570 (N=O), 1270 cm^{-1} (trans dimer); nmr: δ 1.25 (s, CH_3), 1.60 (s, CH_3); mass spectrum: M^+, 174.

Preparation of 1-Methyl-1-nitrosocyclohexane Dimer [252,253]

2-(1-Methylcyclohexyl)-3-phenyloxazirane was prepared from the corresponding imine as described above for 2-*t*-butyl-3-phenyloxazirane. The crude product was obtained as a pale green oil (72.3 g; 87%).

To a magnetically stirred solution of sulfuric acid (15 ml) in methanol (250 ml) and water (25 ml), cooled to 0°, was added dropwise, the crude oxazirane (72.3 g; 330 mmole). After addition was complete (45 min), the mixture was allowed to warm to 25°, and was stirred for 24 hr. The acidic mixture thus obtained was diluted with water (350 ml) and extracted with ether (5 x 50 ml). After basification with sodium hydroxide, the aqueous layer was extracted with ether (10 x 50 ml). The ether extracts were combined, dried over potassium carbonate and concentrated to yield a pale blue oil. Cooling to -10° overnight resulted in a white crystalline solid (15.4 g) which was collected by filtration. Recrystallization from hexane

provided (1-methylcyclohexyl)hydroxylamine as a white crystalline solid (9.6 g; 21%), mp. 72 - 75° (lit.[275] 74-75°): nmr; δ 1.10 (s, 3, CH_3), 1.48 (s, 10, CH_2), 6.10 (s, 1, OH), 6.10 (s, 1, NH).

Oxidation of the hydroxylamine (6.5; 50 mmole) in a manner identical to that described above for the preparation of 2-methyl-2-nitrosopropane dimer gave upon recrystallization from ligroin at -20°, 1-methyl-1-nitrosocyclohexane dimer as colourless crystals (3.4 g; 54%), mp. 49 - 51° (lit.[258] 35 - 37°): ir ($CHCl_3$) 1550 (N=O, monomer), 1265 cm^{-1} (trans dimer); nmr: δ 0.90 (s, CH_3), 1.10 - 1.90 (m, CH_2), 1.55 (s, CH_3), 1.90 - 2.60 (m, CH_2); mass spectrum: m/e: (Calcd. for $C_{14}H_{26}N_2O_2$: 254.1994. Found: 254.1997): 224(2), 128(7), 98(6), 97(71), 81(6), 69(6), 67(5), 55(100), 43(9), 41(24), 39(10).

Preparation of Nitrosocyclohexane Dimer [252]

To a magnetically stirred solution of cyclohexylamine (19.8 g; 200 mmole) in methylene chloride (75 ml), cooled to -10°, was added, dropwise, a cold solution of peracetic acid (450 mmole, prepared as described above). After the addition period of 1 hr., the mixture was allowed to warm to 25°, and was stored for 15 hr. The resulting solution was successively washed with water (200 ml), cold 15% ammonia solution (100 ml) and 10% sulfuric acid solution

(100 ml). After drying over potassium carbonate and removal of the methylene chloride, the mixture afforded a bluish solid. Ethanol (50 ml) was added, and the suspension was cooled to -10° for 30 min. The resulting white solid (11.4 g) was collected by vacuum filtration. Recrystallization from ethanol gave nitrosocyclohexane dimer as a white crystalline solid (7.7 g; 34%), mp. 119 - 120° (lit.[252] 119 - 120°): ir ($CHCl_3$) 1450, 1390, 1330, 1210 cm^{-1} (trans dimer): nmr: δ 0.95 - 2.20 (m, 10, CH_2), 4.80 - 5.29 (m, 1, CH_3); mass spectrum: M^+,226.

General Procedure for the Preparation of α-Nitrosotoluene, α-Methyl-α-nitrosotoluene, α-Nitroso-*p*-methoxytoluene, 1-Nitrosoheptane, 2-Nitrosoheptane Dimers.

A solution of the corresponding pentylidene imine (143 mmole, prepared in a standard fashion from the amine and 3-pentanone) in methylene chloride (60 ml) was magnetically stirred and cooled to -10°, while a cold solution of peracetic acid (330 mmole, prepared as described above) was added dropwise over a period of 45 min. The mixture was stored for 16 hr. at -10°, then successivly washed with cold water (2 x 150 ml), cold saturated sodium bicarbonate solution (2 x 100 ml) and water (100 ml). Drying of the organic layer over magnesium sulfate yielded in all cases

a pale yellow oil. The addition of 95% ethanol (15 ml), followed by cooling to -15° for 16 hr., yielded white crystalline material.

α-Nitrosotoluene

From 25.0 g of imine there was obtained a white crystalline solid (13.1 g; 76%). Recrystallization from acetone afforded α-nitrosotoluene dimer (2.5 g; 14%), mp. 121 - 122° (lit.[276] 120-120.5°): ir ($CHCl_3$) 1190 cm^{-1} (trans dimer); nmr: δ 5.41 (s, 2, CH_2), 7.30 (m, 5, arom.); mass spectrum: M^+, 242.

α-Methyl-α-nitrosotoluene

From 27.0 g of imine there was obtained a white crystalline solid (2.3 g; 12%). Recrystallization from acetone gave α-methyl-α-nitrosotoluene dimer (2.0 g; 10%), mp. 103 - 104°: ir (KBr) 2990, 1490, 1445, 1360, 1215 (trans dimer), 1057, 760, 700 cm^{-1}; nmr: δ 1.55 (d, 3, CH_3), 6.25 (q, 1, CH), 7.09 - 7.51 (m, 5, arom.); uv max ($CHCl_3$) 294 mμ (ε = 9,000); mass spectrum: m/e: (Calcd. for $C_{16}H_{18}N_2O_2$: 270.1368. Found: 270.1367): 106(16), 105(100), 104(21), 103(21), 91(6), 79(35), 78(17), 77(47), 51(30), 39(15). Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.14; H, 6.71; N, 10.36. Found: C, 70.80; H, 6.87; N, 10.53.

α-Nitroso-*p*-methoxytoluene

From 29.3 g of imine was obtained an orange-white crystalline solid (8.4 g; 19%). Recrystallization from acetone yielded α-nitroso-*p*-methoxytoluene (3.2 g; 8%) mp. 112 - 113°: ir (KBr) 2960, 1610, 1585, 1510, 1382, 1240 (trans dimer) 810, 765 cm^{-1}; nmr: δ 3.76 (s, 3, OCH_3), 5.30 (s, 2, CH_2), 7.08 (q, 4, arom.); uv max ($CHCl_3$) 282 (ε = 9,700), 295 mμ (ε = 9,400); mass spectrum: m/e: 302, 151(17), 135(11), 134(13), 133(12), 121(100), 122(13), 108(15), 91(18), 90(11), 78(24), 77(25), 65(13), 64(11), 65(13), 52(13), 51(19), 50(12). Anal. Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.58; H, 5.96; N, 9.27. Found: C, 63.47; H, 5.97; N, 9.16.

1-Nitrosoheptane Dimer

From 26.1 g of imine there was obtained a white crystalline solid which upon washing with ethanol yielded 1-nitrosoheptane dimer (9.6 g; 52%), mp. 56 - 56.5°: ir (KBr), 2960, 2930, 2860, 1470 (doublet), 1390, 1330, 1285 (doublet), 1250 (trans dimer), 1210 cm^{-1}; nmr: δ 0.62 - 2.21 (m, 13, CH_2CH_3), 4.29 (t, 2, CH_2); uv max ($CHCl_3$) 290 mμ (ε = 9,700); mass spectrum: m/e: (Calcd. for $C_{14}H_{30}N_2O_2$: 258.2307. Found: 258.2311): 149(5), 110(5), 96(8), 82(29), 81(38), 69(10), 68(11), 59(20), 57(54), 55(32), 54(26), 43(100), 41(85). Anal. Calcd. for $C_{14}H_{30}N_2O_2$: C, 65.11; H, 11.69;

N, 10.85. Found: C, 64.93; H, 11.69; N, 10.73.

2-Nitrosoheptane Dimer

From 26.1 g of imine there was obtained (upon removal of the ethanol) a greenish liquid, which was dissolved in pentane (50 ml). Upon cooling to -78°, the solution yielded white crystals which were collected in a precooled funnel. The product thus obtained was dissolved in diethyl ether and the solution was dried ($MgSO_4$). Removal of the ether under vacuum yielded 2-nitrosoheptane dimer as a colourless liquid (7.1 g; 39%), n_D^{16} 1.4641: ir (liquid film) 2940, 2865, 1462, 1385, 1210 cm^{-1} (trans dimer); nmr: δ 0.62 - 2.08 (m, 14, CH_2CH_3), 5.62 - 5.11 (m, 1, CH); uv max ($CHCl_3$) 294 mμ (ε = 9,800); mass spectrum: M^+, 258. Anal. Calcd. for $C_{14}H_{30}N_2O_2$: C, 65.11; H, 11.69; N, 10.85. Found: C, 65.12; H, 11.72; N, 11.14.

Deoxygenation of 2-Methyl-2-nitrosopropane in Methylene Chloride

To a solution of 2-methyl-2-nitrosopropane dimer (0.87 g; 5 mmole) in methylene chloride (45 ml), magnetically stirred under an atmosphere of dry nitrogen was added, all at once, triethylphosphite (1.7 g; 10 mmole). The solution (which exhibited the intense blue colouration typical of a nitroso monomer), was stirred at 26° for 2 hr.

The temperature rose to 30°, and after 1 hr. the blue colouration disappeared. An aliquot analyzed by glc (column B; 180°) indicated the presence of triethylphosphate, and ir analysis showed a strong absorption at 1665 cm^{-1} (C=O). After a total reaction time of 2 hr., glc analysis indicated that the reaction was complete. Nmr analysis showed the presence of acetone methylimine: δ 1.79 (s, 3, CH_3), 1.93 (s, 3, CH_3), 3.00 (s, 3, CH_3). Water (2 drops) was added to the reaction mixture, and after hydrolysis was complete (as indicated by the disappearance of the ir absorption at 1665 cm^{-1} and the appearance of an absorption at 1710 cm^{-1} (C=O)) the solution was dried (Na_2SO_4), and the volume was brought to 50 ml. Quantitative glc analysis gave the following results: acetone, 87% (column A, 35°); triethylphosphite, 5% (column B, 170°); and triethylphosphate, 90% (column B, 185°). Distillation of the reaction mixture (spinning band) yielded acetone: ir (liquid film) 1710 cm^{-1} (C=O), 2,4-dinitrophenylhydrazone derivative (2,4-DNP), mp. 123 - 125° (lit.[207] 126°). Preparative glc (column C, 190°) yielded material with the following properties: triethylphosphite: spectroscopically (ir) identical to authentic material; triethylphosphate: ir spectrum identical to an authentic sample.

Deoxygenation of 2-Methyl-2-nitrosopropane in Cyclohexane

The reaction was carried out in an identical manner to that described above, but using cyclohexene as the solvent. Quantitative glc analysis provided the following results: acetone, 90% (column A, 35°); triethylphosphite, 5% (column B, 170°); triethylphosphate, 90% (column B, 185°).

Deoxygenation of 1-Methyl-1-nitrosocyclohexane

A solution of 1-methyl-1-nitrosocyclohexane dimer (1.27 g; 5 mmole) was prepared in benzene (45 ml) under an atmosphere of dry nitrogen. Upon dissolution, the initially colourless dimer provided a deep blue solution which was stirred at 26°, while triethylphosphite (1.7 g; 10 mmole) was added, all at once. During reaction, the temperature rose slowly to 30° with the gradual disappearance of the blue colouration. After 4 hr., glc indicated that the reaction was complete, and an ir spectrum of the colourless solution showed a strong absorption at 1665 cm^{-1} (C=N). Quantitative glc analysis (column B, 150°) after this period of time gave the following results: triethylphosphite, 1%; 7-methyl-3,4,5,6-tetrahydro-2H-azepine, 91%; triethylphosphate, 98%. Concentration of the reaction mixture and isolation of the products by preparative glc (column C, 110°) afforded: triethylphosphite: ir spectrum

identical to an authentic sample; 7-methyl-3,4,5,6-tetrahydro-2H-azepine: n_D^{20} 1.4903 (lit.[277] 1.490); ir (liquid film) 1665 (C=O), 1440 cm^{-1}; nmr: δ 1.60 (m, 6, CH_2), 2.01 (s, 3, CH_3), 2.35 (m, 2, CH_2), 3.55 (m, 2, CH_2); mass spectrum: M^+, 111; triethylphosphate, ir spectrum identical to authentic material.

General Procedure for the Deoxygenation of the Primary and Secondary Nitrosoalkanes

A solution of nitrosoalkane dimer (5 mmole) in dry benzene (45 ml) was magnetically stirred under an atmosphere of dry nitrogen while triethylphosphite (1.7 g; 10 mmole) was added all at once. The colourless solution was stirred at 50 - 55° for the times indicated in Table VI (times for complete reaction were determined by monitoring the formation of triethylphosphate by glc). The reaction mixture was cooled to 25° and the volume standardized to 50 ml. The solution was divided into two equal parts, "A" and "B". Part "A" was analyzed both quantitatively and preparatively for the presence of phosphite, phosphate and oxime. Part "B" was hydrolyzed with 2N hydrochloric acid (2 x 15 ml). The organic layer was dried and adjusted to standard volume (25 ml) to yield solution "C". The aqueous layer was basified by the addition of sodium hydroxide pellets, and extracted with benzene (2 x 10 ml). Drying over potassium carbonate and standardization of the

volume of the organic layer to 25 ml yielded solution "D".

The solutions were analyzed (glc) as described below for each individual case.

α-Methyl-α-nitrosotoluene

After a reaction time of 0.5 hr and processing as above, quantitative glc analysis yielded the following results: solution "A" showed: triethylphosphite, 12% (column B, 140°); triethylphosphate, 77% (column B, 140°); acetophenone oxime, 28% (column B, 180°): solution "C" (column B, 140°): benzaldehyde, 4%; acetophenone 9%: solution "D: (column B, 140°): aniline, 30%. Isolation of the products by glc afforded materials with the following properties: solution "A" (column C, 190°): triethylphosphite: spectroscopically (ir) identical to authentic material; triethylphosphate: ir identical to authentic sample; acetophenone oxime: mp. 58 - 59° (lit.[207] 59°); ir identical to authentic sample [207]: solution "C": benzaldehyde: 2,4-NDP, mp. 237 - 238° (lit.[207] 237°); ir identical to authentic sample: acetophenone: 2,4-DNP, mp. 247-248° (lit.[207] 249°); ir identical to authentic material: solution "D": aniline: n_D^{20} = 1.5868 (lit.[278] n_D^{20} = 1.5863); ir identical to authentic material.

α-Nitrosotoluene

After a reaction time of 1 hr. glc analysis of the reaction solutions provided the following results: solution "A": triethylphosphite, 50% (column B, 140°); triethylphosphate, 45% (column B, 140°); benzaldoxime, 40% (column B, 190°): solution "C": benzaldehyde, 27% (column B, 140°): solution "D": aniline, 10% (column B, 140°).

Isolation of the products (preparative glc) gave: solution "A" (column C, 190°): syn-benzaldoxime spectroscopically (ir, nmr) identical to an authentic sample prepared from benzaldehyde: solution "C" (column C, 180°): benzaldehyde: 2,4-DNP, mp. 237 - 238° (lit.[207] 237°); ir identical to an authentic sample: solution "D" (column C, 180°): aniline: 2,4,6-tribromo derivative, mp. 119 - 120° (lit.[207] 119°).

α-Nitroso-*p*-methoxytoluene

A reaction time of 1 hr. followed by processing as described above gave the following results: solution "A": triethylphosphite, 53% (column G, 160°); triethylphosphate, 45% (column G, 160°); *p*-methoxybenzaldoxime, 42% (column G, 190°): solution "C" (column G, 190°): *p*-methoxybenzaldehyde, 27%: solution "D" (column H, 160°): *p*-methoxyaniline, 12%.

Isolation of reaction products by preparative glc gave material with the following properties: solution "A" (column C, 200°): *p*-methoxybenzaldoxime, ir spectrum was identical to that of authentic material [207]: solution "C" (column C, 200°): *p*-methoxybenzaldehyde: spectroscopically (ir, nmr) identical to an authentic sample: solution "D" (column C, 240°): *p*-methoxyaniline: ir identical to that of an authentic sample.

Nitrosocyclohexane

Reaction time of 3 hr. provided solutions which by quantitative glc analysis showed the following results: solution "A" (column B, 140°): triethylphosphite, 13%; triethylphosphate, 90%; cyclohexanone oxime, 12%: solution "C" (column B, 140°): cyclohexanone, 68%: solution "D" indicated (column B, 100 - 200°) that no basic products were formed.

Isolation of the products formed gave the following results: solution "A" (column D, 185°): cyclohexanone oxime: mp. 88 - 89° (lit.[207] 89°); ir identical to authentic sample: solution "C" (column C, 160°): cyclohexanone: 2,4-DNP, mp. 162 - 163° (lit.[207] 162°).

1-Nitrosoheptane

The reaction was carried out in the presence of water

(10 ml), and after a reaction time of 3 hr., glc analysis showed the following results: solution "A": triethylphosphite, 35% (column G, 60°); triethylphosphate, 64% (column B, 130°); n-heptaldoxime, 33% (column B, 140°): solution "C" (column E, 70°): heptanal 58%: solution "D" indicated that no basic products other than ammonia were produced.

Isolation (preparative glc) gave products showing the following properties: solution "A" (column F, 120°): heptanonitrile (presumably from pyrolysis of n-heptaldoxime); ir identical to an authentic sample: solution "C" (column F, 120°): heptanal, 2,4-DNP, mp. 105 - 106° (lit.[207] 108°).

2-Nitrosoheptane

After a reaction time of 3.5 hr. glc analysis of the reaction solution showed the following results: solution "A": triethylphosphite, trace (column B, 140°); triethylphosphate, 91% (column B, 140°); 2-heptanone oxime, 8% (column B, 150°): solution "C" (column B, 130°): hexanal 22%, 2-heptanone, 65%: solution "D" (column B, 100 - 200°): indicated that no products were present in the acid extract.

Isolation of the materials formed by preparative glc gave the following results: solution "C" (column C, 140°):

hexanal: 2,4-DNP, mp. 101 - 103° (lit.[207] 104°): 2-heptanone: n_D^{25} = 1.4074 (lit.[279] 1.4073); ir identical to that of an authentic sample. A sample of 2-heptanone oxime isolated by preparative tlc (silica gel; elution with benzene) had an ir identical to that of an authentic sample.[207]

Preparation of N-Methyl-N-nitrosoaniline [273]

A mixture of hydrochloric acid (74 ml), N-methylaniline (54.0 g; 500 mmole) and ice (200 g) was stirred vigorously while a solution of sodium nitrite (35.0 g; 500 mmole) in water (125 ml) was added dropwise over a period of 10 min. After addition, the reaction was stirred for 1 hr. while the temperature was allowed to rise to 25°. The oily product layer was separated, and the aqueous layer extracted with benzene (2 x 50 ml). The initial oil layer and benzene layer were combined and the solvent was removed by distillation. The residue was distilled to give N-methyl-N-nitrosoaniline (60 g; 88%) bp. 107.5 - 108° (8 mm) (lit.[273] 135 - 137°; 13 mm); ir (liquid film) 1590, 1490, 1395, 1210, 1090, 955, 820, 760, 690 cm^{-1}.

Preparation of N-Nitroso-di-*n*-butylamine

The preparation was carried out in a similar manner to that described above for N-methyl-N-nitrosoaniline.

However, the addition of sodium nitrite solution was made over a period of 20 min. to an acidic solution at 70°. After stirring for 3 hr. at 70°, extraction of the product with ether (2 x 100 ml), and subsequent distillation, yielded N-nitroso-di-*n*-butylamine (71 g; 90%), bp. 92-96.5° (6 mm) (lit.[280] 234°; 760 mm); ir (liquid film) 2950, 2860, 1460, 1360, 1275, 1185, 1080, 945 cm^{-1}.

General Procedure for the Attempted Deoxygenation of Nitrosamines

To a magnetically stirred solution of nitrosamine (20 mmole) in benzene (45 ml) was added, all at once, triethylphosphite (3.65 g; 22 mmole). The mixture was stirred at 25° for 22 hr. and a sample taken at this time indicated (glc) that neither the phosphite nor the nitrosamine had been consumed. The mixture was refluxed for 6 hr. at 80°, analysis (glc) again indicated no consumption of the starting materials.

The reaction was repeated using phsophorus trichloride and subsequently trisdimethylaminophosphine. However, similar results were obtained.

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