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THE JOURNAL OF Organic Chemistry

Published biweekly by the American Chemical Society at 20th and Northampton Streets, Easton, Pennsylvania

Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Washington, D. C., and at additional mailing offices.

Production Staff: Manager, Editorial Production, CHARLES R. BERTSCH; Production Editor, EILEEN SEGAL; Assistant Editor, FERN S. JACKSON; Editorial Assistants, ANDREW J. D'AMELIO and DEBORAH K. MILLER.

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THE JOURNAL OF Organic Chemistry®

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NOTES

COMMUNICATIONS

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THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 16

AUGUST 11, 1972

The Chemistry of 9β,19-Cyclo Steroid Derivatives[1,2]

S. MORRIS KUPCHAN,*[3] JOHN W. A. FINDLAY, PETER HACKETT, AND ROBERT M. KENNEDY

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Received December 20, 1971

The 9β,19-cyclo-11-keto steroid system has been found to show a marked difference in reactivity from the corresponding triterpenoid derivatives. 11-Hydroxy-9,19-cyclo-5α,9β-pregnane-3,20-dione bis(ethylene ketals) **10** and **11** underwent ring opening in acid medium to give alcohol **15** and diene **17**, in contrast to the *Buxus* alkaloid **8**, which gave the conjugated diene **9**. No product of the conjugated diene type was detected under a variety of reaction conditions using the model cyclopropyl carbinol **11**. Hydride reduction of a series of steroidal 11-ketoamines also proceeded to a different extent from that of the triterpenoid alkaloids. These results are rationalized on the basis of significant differences in molecular conformations between the steroid and triterpenoid series.

In 1962, we reported the elucidation of the structure[4] and configuration[5] of cyclobuxine D (**1**), an alkaloid isolated from *Buxus sempervirens* L.[6] Cyclobuxine D was shown to be the prototype of a new class of steroidal alkaloids which contain the 9,19-cyclo-5α,9β-pregnane system **2** and has a substitution pattern at C-4 and C-14 which is intermediate in the biogenetic scheme between lanosterol- and cholesterol-type steroids. Subsequent studies have characterized many structurally related alkaloids.[7] In 1964, the isolation and characterization of buxenine G[8a] ("norbuxamine"[8b]) was reported, and this alkaloid was later proven to possess the novel structure and configuration **3**.[9] Several additional alkaloids possessing the unusual 9(10→19)*abeo*-5α-pregnane system (**4**) have been found.[8b,10-12]

In part XIII[1] of this series we reported that Huang-Minlon reduction of 9,19-cyclo-5α,9β-pregnane-3,11,20-trione 3,20-bis(ethylene ketal) (**5**)[13] proceeded in an unusual direction, to give a mixture of 9(10→19)-*abeo*-$\Delta^{9(11)}$-5α,10β-pregnene 3,20-bis(ethylene ketal) (**6**) and its C-10 isomer **7**, rather than the initially expected 11-deoxy compound. This provided a synthetic entry to the 9(10→19)*abeo*-5α-pregnane system (**4**) in the steroid series.

In a continuation of these studies on potential routes to B-homo steroid analogs of buxenine-G type alkaloids, we have examined the chemistry of some derivatives of the 9β,19-cyclo-11-keto steroid system **5**, including the synthesis of some amino steroids which are direct analogs of some of the *Buxus* alkaloids. In this paper we report the results of this work, which indicate a marked difference in reactivity between the 11-keto cyclopropyl system in the steroid model compounds and the triterpenoid alkaloids.

Goutarel has reported[14] the conversion of the cyclopropyl carbinol **8** (derived from cycloxobuxidine F by $LiAlH_4$ reduction, and of unspecified configuration at C-11) to the 9(10→19)*abeo*-$\Delta^{9(11),10(19)}$-pregnadiene (**9**) by mild treatment with sulfuric acid. When the nonaminated steroidal cyclopropyl carbinols **10** and **11**, derived from **5** by metal hydride reduction, were treated with acid, quite different products were isolated.

Lithium aluminum hydride reduction of **5** gave a mixture which was homogeneous by tlc on silica layers, but which could be separated by chromatography on

(1) *Buxus* Alkaloids. XIV. For part XIII see S. M. Kupchan, E. Abushanab, K. T. Shamasundar, and A. W. By, *J. Amer. Chem. Soc.*, **89**, 6327 (1967).

(2) This work was supported by a grant from the National Heart Institute (HE 12957), National Institutes of Health.

(3) Author to whom inquiries should be directed: Department of Chemistry, University of Virginia.

(4) K. S. Brown, Jr., and S. M. Kupchan, *J. Amer. Chem. Soc.*, **84**, 4590 (1962); **86**, 4414 (1964).

(5) K. S. Brown, Jr., and S. M. Kupchan, *ibid.*, **84**, 4592 (1962); **86**, 4424 (1964).

(6) K. Heusler and E. Schlittler, *Helv. Chim. Acta*, **32**, 2226 (1949).

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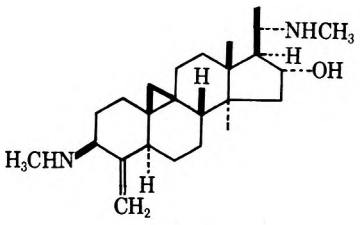

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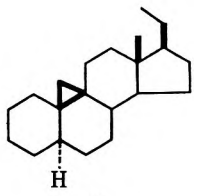

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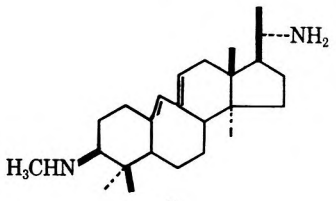

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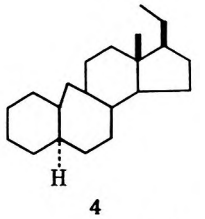

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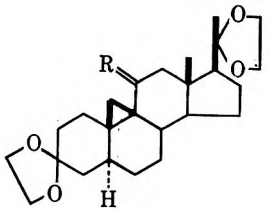
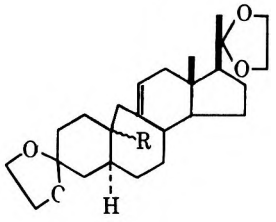
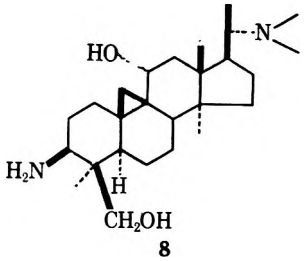


5, R = O
10, R = β-OH, α-H
11, R = α-OH, β-H
12, R = β-OAc, α-H
13, R = α-OAc, β-H



6, R = β-H
7, R = α-H



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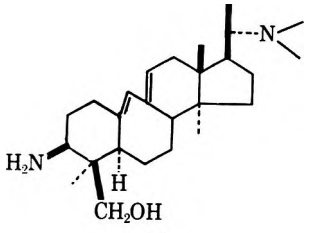

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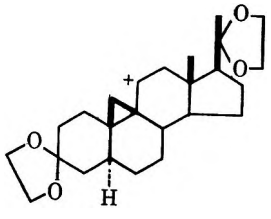

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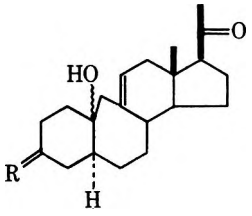
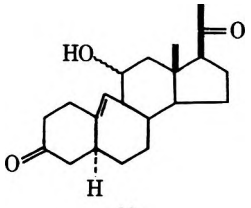


15, R = O
19, R = β-NEt2, α-H



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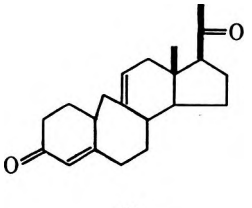

17

alumina to give 11β-hydroxy-9,19-cyclo-5α,9β-pregnane-3,20-dione bis(ethylene ketal) (**10**, 11%) and the corresponding 11α-hydroxy isomer (**11**, 65%). Inspection of Drieding models of ketone **5** has revealed that the 11-carbonyl group is appreciably less hindered than in the normal steroid nucleus.[1] Consequently, the major product of hydride reduction is the equatorial (11α) alcohol,[15] a result which has been found recently with a similar cyclopropyl ketone.[16] Zurcher's rules[17] predict that the hydroxyl groups in **10** and **11** should cause the C-18 methyl protons in **10** to resonate at approximately τ 0.2 lower field than that in **11**, all other ring C and D substituents being equal. In **10**, this resonance is at τ 8.95, while in **11** it occurs at τ 9.10, a difference of τ 0.15. The assignment was confirmed by examination of the nmr spectra of the respective C-11 acetates **12** and **13**, in which the C-18 methyl in the β-acetate should resonate at approximately τ 0.06 lower field than the α, under the conditions stated above.[17] Here the C-18 methyl in **12** resonated at τ 9.06, while in **13** the signal was at τ 9.10, a difference of τ 0.04. Reduction of ketone **5** did not proceed with sodium borohydride at room temperature, but in boiling isopropyl alcohol an increased amount of the 11β alcohol was formed, isolated yields being 21% of **10** and 31% of **11**. The increased steric accessibility of the 11 position in these compounds was emphasized by the ease of formation of the 11β-acetate compared to the analogous situation in normal steroids.[18]

On treatment with 30% v/v or 30% w/w sulfuric acid at room temperature for reaction times of 2–15 hr, both alcohols **10** and **11** gave very similar product mixtures, indicating that the dehydration reaction proceeds in both cases *via* a common intermediate, such as the carbonium ion **14**. In view of this, most of the subsequent work was done on the major alcohol (*i.e.*, **11**). Crystallization of the crude product from acid treatment gave the major product as a colorless solid in 70–82% yield, the amount of by-products increasing with longer reaction times. The major product has been assigned the homoallylic alcohol structure **15** on the basis of the following physical and chemical evidence. Elemental analysis supported assignment of an empirical molecular formula of $C_{21}H_{30}O_3$, and the mass spectrum confirmed the molecular weight as 330. A prominent peak in the mass spectrum at *m/e* 312, corresponding to loss of H_2O, indicated the presence of a hydroxyl group, while the absence of peaks at *m/e* 99 and 87 indicated that loss of the ketal groups had occurred at both C-3 and C-20. The ir spectrum showed bands at 5.85 and 5.90 (carbonyl) and 2.90 μ (hydroxyl), while the nmr spectrum indicated loss of the cyclopropyl ring (no signal at approximately τ 9.5). The absence of any new methyl resonance suggested that the cyclopropyl ring had opened to give a B-homo steroid. The presence of a new double bond was revealed by a broad singlet ($W_{1/2}$ = 9 Hz) at τ 4.57. No ketal resonance was present, and a three-proton singlet at τ 7.85 was attributed to the C-21 methyl group, while the C-18 methyl group resonated as a singlet at τ 9.32. The absence of a strongly absorbent chromophore in the uv spectrum showed that the double bond was not conjugated with a ketone nor with another double bond, as in the initially expected

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9(11),10(19)-diene (*cf.* ref 14). These data supported structures **15** or possibly **16** as likely. Structure **15** was preferred, since no signal corresponding to the C-11 methine proton of **16** could be found in the nmr spectrum, and no acetate ester was formed from the ring-opened product under normal conditions of acetylation of steroidal secondary alcohols. Treatment of the acetate **13** with sulfuric acid under similar conditions also gave the alcohol **15**. The minor product from the acid treatment of **11** was isolated as a gum (6% after 2 hr), and was also formed as the major product on further acid treatment of **15**. The uv spectrum [λ_{max} 237 nm (ϵ 22,410)] of this material indicated a conjugated π system other than the 9(10→19)*abeo*-$\Delta^{9(11),10(19)}$-pregnadiene system.[14] Mass spectral measurements showed the compound to be a dehydration product of **15** (M^+ at *m/e* 312), while the nmr spectrum showed a singlet at τ 4.20 for one additional olefinic proton, three-proton singlets at τ 7.86 (C-21 Me) and 9.38 (C-18 Me), and a broad signal at τ 4.57 (C-11 H). The ir spectrum now had a band at 6.03 μ (α,β-unsaturated carbonyl) and no OH band. This evidence supported the structure **17** for the new diene dione. The formation of **17** from **15** can be readily rationalized mechanistically as dehydration to the 5(10)-olefin **18** (not isolated), followed by acid-catalyzed migration of the double bond into conjugation with the C-3 ketone. The latter reaction type is well documented.[19]

In an attempt to alter the direction of dehydration of **15** away from formation of conjugated ketone **17** and possibly toward a 9(11),10(19)-diene system, a C-3β-amino function was introduced by a Leuckart reduction.[20] Treatment of ketone **15** with formic acid and diethylamine in refluxing toluene gave 3β-diethylamino-9(10→19)*abeo*-$\Delta^{9(11)}$-5α-pregnan-10ε-ol-20-one (**19**) in good yield. Confirmation of the presence of the C-3 diethylamino group was obtained from the nmr spectrum (triplet at τ 8.97, J = 7 Hz, $>NCH_2CH_3$, quartet at τ 7.44, J = 7 Hz, $>NCH_2CH_3$) and from the mass spectral fragment ions at *m/e* 138 and 112, highly characteristic of a 3β-diethylamino-5α-pregnane.[21] However, the amine **19** was inert to dehydration under all but the most forcing conditions. The inertness of compound **19** to dehydration was also evident from its mass spectrum, in which the molecular ion (*m/e* 387) was of enhanced intensity relative to that of **15**, and the M − 18 peak was much weaker than in the spectrum of **15**.

When alcohols **10** or **11** were treated with acid under more vigorous conditions (50% sulfuric acid with heating on steam bath for 10 min), a complex mixture of products was produced. The major component (44%), isolated as a gum by preparative tlc, was shown to be dione **17**. Two other products of higher R_f value were also isolated, but these were less stable than compound **17**, and only partial spectral characterization was possible. The higher R_f compound had signals in the nmr spectrum at τ 9.42 (3 H, C-18 Me), 7.86 (3 H, C-21 Me), 4.59 and 4.48 (both 1 H, >C=CH), and bands in the ir spectrum at 5.87, 6.19, and 6.24 μ. No α,β-unsaturated ketone could be detected by ir or uv measurement. On the basis of this evidence, the high R_f compound is tentatively formulated as the diene **20**, which also could be formed by dehydration of **15**. The third material crystallized on standing, and appeared to be homogeneous in several tlc systems. However, nmr examination showed two closely overlapping peaks at τ 9.34 and 9.36 for the C-18 methyl resonance, suggesting that the apparently homogeneous material was a mixture of two very similar compounds. Signals also occurred at τ 7.83 (C-21 Me), 4.49 (broad s, >C=C< H), 4.06 (d, J = 10 Hz, >C=CH), and 3.17 (t, J_1 = 10 Hz, J_2 = 12.5 Hz, >C=CH). The ir spectrum showed a band for an α,β-unsaturated carbonyl group at 6.02 μ, different from that of **17**. From these data it is suggested that one compound present in this mixture is the diene **21**. Mass spectral examination revealed a peak at *m/e* 330 in addition to a stronger *m/e* 312 peak, indicating that the other component may be an alcohol corresponding to $C_{21}H_{30}O_3$.

Tosylation of alcohol **11** followed by elimination was next considered as a possible route to the 9(11),10(19)-diene. No tosylate could be isolated from treatment of **11** with *p*-toluenesulfonyl chloride in pyridine, elimination having occurred spontaneously to give a mixture (nmr spectrum) of olefins which was homogeneous by tlc. The uv spectrum of this mixture, when examined soon after isolation, exhibited absorbance at 248 nm, with shoulders at 238 and 255 nm, typical of the 9(10→19)*abeo*-$\Delta^{9(11),10(19)}$-pregnadiene system, but the extinction coefficient at 248 nm suggested a maximum of 9–14% diene content. The olefin mixture proved quite unstable, but the main component was isolated by partition chromatography as a crystalline solid, and was shown to have the olefinic structure **22**. In the nmr spectrum of **22**, the C-11 proton resonated as a doublet (J = 10.5 Hz) at τ 3.67, while the C-12 proton was a doublet (J = 10.5 Hz) at τ 4.81. No other stable component of the olefin mixture was fully characterized, and no 9(11),10(19)-diene was isolated. Olefin **22** could not be converted to such a diene on treatment with acid. Alcohol **11** behaved in a similar way upon attempted mesylation.

In addition to the sulfuric acid mediated ring opening reactions described above, a wide variety of standard dehydration reagents, including $POCl_3$, PCl_5, and alumina/pyridine, were allowed to react with alcohols **10** and **11**. The alcohols were also subjected to glc treatment. In all cases complex and intractable mixtures of olefins resulted, having no uv absorption characteristic of the 9(10→19)*abeo*-$\Delta^{9(11),10(19)}$-pregnadiene system.

Although the vagaries of the chemistry of "bicyclobutonium" ions have been alluded to previously,[22] these are insufficient to explain the difference of our results from those of Goutarel.[14] At no stage was any of the 9(11),10(19)-diene isolated, and only in the product from attempted tosylation of **11** was it apparently detected. In general, the crude reaction mixtures in this work were found to decompose on standing (particularly the tosylation product), and it is conceivable that the desired steroidal diene, although

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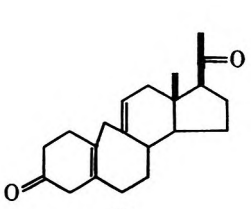
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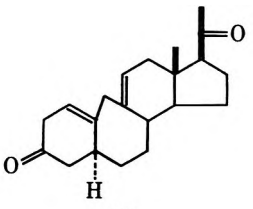
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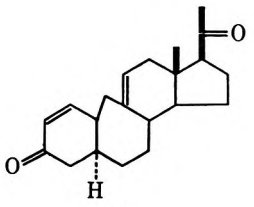
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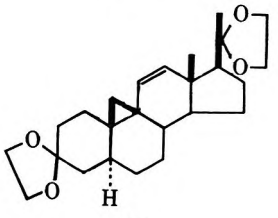
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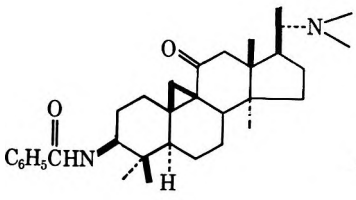
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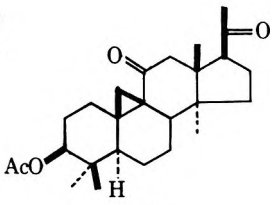
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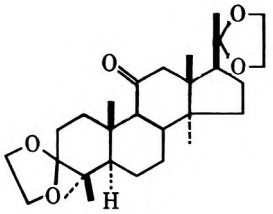
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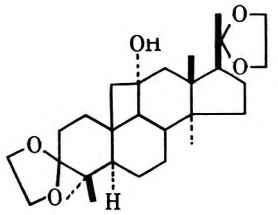
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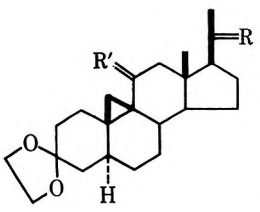

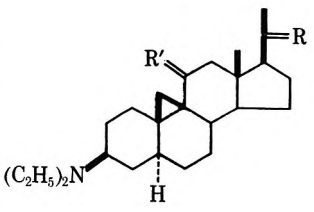

27, R = R′ = O
28, R = NOH; R′ = O
29, R = α-NH_2, β-H; R′ = O
30, R = β-NH_2, α-H; R′ = O
31, R = α-NH_2, β-H; R′ = α-OH, β-H
32, R = β-NH_2, α-H; R′ = α-OH, β-H
33, R = R′ = O
34, R = $(OCH_2)_2$; R′ = O
35, R = NOH; R′ = O
36, R = α-NMe_2, β-H; R′ = O
37, R = β-NMe_2, α-H; R′ = O

formed initially, was too unstable to isolate. The difference in reactivity of Goutarel's cyclopropyl alcohol **8** and the steroidal alcohols **10** and **11** may be due to the hydroxymethyl group at C-4 in **8** acting as a neighboring group in a directed ring-opening reaction. Hydrogen bonding between the OH group and one of the cyclopropyl protons would render such a proton more acidic and thus more easily removable in a directed process leading to the 9(11),10(19)-diene. However, a brief survey of some of the relevant literature, combined with our own results, indicates that the difference is more probably due to a fundamental difference in conformation of the triterpenoid *Buxus* alkaloid molecule and the unsubstituted steroid, which causes the 9β,19-cyclo-11-keto steroid to have different reactivity (or to give products of different stability). Thus we have shown recently[12] that *N*-benzoylcycloxobuxine-F (**23**) can be reduced to the 11-deoxy compound by vigorous reduction with $LiAlH_4$ in dioxane. The ketone **5** was only reduced to the corresponding alcohols **10** and **11** under these conditions. Nakano, *et al.*, have recently reported[16] that the triterpenoid cyclopropyl ketone **24** can be reduced, under similar conditions, to a 2:1 mixture of the 11-alcohol and 11-deoxy compound. A further anomaly between 11-ketones of the triterpene and steroid series is in their behavior upon irradiation. When photolyzed in ethanol, the diketal **25** gives none of the expected cyclobutanol[16] **26**, the triterpene analog of the main product of similar irradiation of 5α-pregnane-3,11,20-trione 3,20-bis(ethylene ketal).[13] Supporting evidence for a difference in molecular conformation of ketones **5** and **23** was obtained from the ORD curves of the two molecules. Both curves were positive, but widely different in amplitude, indicating a significant difference in conformation of the respective molecules.[12]

The possible effect of amino functions at C-3 and C-20 (*e.g.*, by intramolecular basic catalysis or as complexation agents) on the extent of reduction at C-11 was evaluated by the synthesis of 9β,19-cyclo 11-ketones possessing these groups. By brief treatment with warm aqueous acetic acid–methanol, diketal **5** was selectively hydrolyzed in high yield to the 3-monoketal **27**, which in turn was transformed to the oxime **28** by reaction with hydroxylamine hydrochloride in pyridine. Hydrogenation of this oxime at room temperature and atmospheric pressure in acetic acid over Adams catalyst afforded a mixture of isomeric 20-amino steroids, which was separated by partition chromatography[23] to give 20α-amino-9,19-cyclo-5α,9β-pregnane-3,11-dione 3-ethylene ketal (**29**, 37%) and 20β-amino-9,19-cyclo-5α,9β-pregnane-3,11-dione 3-ethylene ketal (**30**, 24%). The isomers could be distinguished by nmr spectroscopy. As well as the anticipated paramagnetic shift of the C-18 tertiary methyl protons in β isomer **30** (3.5 Hz) due to the deshielding effect of the neighboring C-20 nitrogen function,[17a,24] the C-21 methyl protons in **30** resonated at higher field (doublet, J = 6 Hz, at τ 8.97) than in **29** (doublet, J = 6 Hz, at τ 8.88). The C-12 methylene signal occurred at higher field in **29** (doublets, J = 14 Hz, at τ 7.22 and 7.90) than in **30** (doublets, J = 15 Hz, at τ 7.02 and 7.82). The preponderance of α isomer **29** over β isomer **30** is in accord with previous experimental findings on the hydrogenation of 20-oximino steroids.[25-28] Treatment of amino ketones **29** and **30** with $LiAlH_4$ in refluxing dioxane for 48 hr gave the corresponding 11-hydroxy compounds **31** and **32** as the predominant reaction products. The crystalline alcohols were assigned the 11α configuration by analogy with the hydride reductions of 9,19-cyclo-11-keto steroids discussed earlier. A minor product, having spectral data in agreement with the 11β-hydroxy epimer, was isolated as an oil from reduction of the 20α-amino steroid. The lack of formation of any 11-deoxy com-

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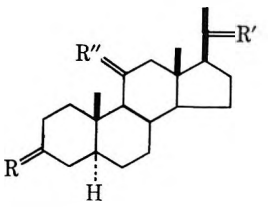
(26) M.-M. Janot, F. Lainé, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 111 (1962).
(27) L. Nedelec, *ibid.*, 557 (1963).
(28) F. Ramirez and S. Stafiej, *J. Amer. Chem. Soc.*, **77**, 134 (1955).

pounds in these reductions indicates that a C-20 amino function has no effect on the extent of reduction of a C-11 ketone in these 9β,19-cyclo steroids, and that no intramolecular basic catalysis was operating. In separate experiments, it was also shown that the ketone **5** gave a very similar mixture of products when treated with $LiAlH_4$ as above in the presence of an externally added amine, *N*-methylbenzylamine, as when this base was absent. Thus, in the cyclopropyl steroid series of C-20 monoamines, no supporting evidence has been found for inter- or intramolecular basic catalysis as an explanation for the further reduction of the *Buxus* alkaloid **23** to the corresponding 11-deoxy compound.

Ketone **5** was completely deketalized by heating with methanol–acetic acid at 70–80° for 3 hr, and was then subjected to Leuckart reduction with formic acid and diethylamine to give, after partition chromatography, 3β-diethylamino-9,19-cyclo-5α,9β-pregnane-11,20-dione (**33**). The presence of the cyclopropyl ring reduced the intensity of the peaks at *m/e* 138 and 112 in the mass spectrum and gave rise to a new peak at *m/e* 99.[21] Attempted ketalization of **33** with a catalytic amount of *p*-toluenesulfonic acid in ethylene glycol–benzene gave only traces of the 20-ketal **34**. Use of 1.1 equiv of the acid for the same reaction time gave a main product as a gum which had M^+ at *m/e* 473 in the mass spectrum, indicating it to be an 11,20-diketal. This was confirmed by ir spectroscopy (no carbonyl band). The absence of any signal in the olefinic region of the nmr spectrum indicated that the compound possessed either a 9β,19-cyclo-11,20-bis(ethylene ketal) or a $\Delta^{5(10)}$-9(10→19)*abeo*-pregnene-11,20-bis(ethylene ketal) structure. This compound was not characterized further, and, to obtain a C-20-functionalized 3-amino 11-ketone, the synthesis of a 3,20-diamino-9β,19-cyclo-11-keto steroid was pursued.

The amine **33** was allowed to react with hydroxylamine hydrochloride in boiling ethanol–pyridine to yield the 20-oxime **35**. Hydrogenation of **35** in acetic acid with Adams catalyst gave a crude mixture of the 20-amines, which, upon N-methylation, gave the corresponding *N*,*N*-dimethylamines. By direct crystallization of the crude product a crystalline solid was isolated which appeared to be homogeneous by tlc, but which showed two singlets at τ 7.79 and 7.86 for $-NMe_2$ groups in the nmr spectrum. Although two such signals have been reported for a C-3-dimethylamino steroid,[29] later work with the 10-methyldiamines **45** and **46** suggested that the above product consisted of a mixture of 20α- and 20β-dimethylamines **36** and **37**. In view of the small amount of the mixture in hand, no attempt was made to separate the isomers, and the mixture *per se* was treated with excess $LiAlH_4$ in refluxing dioxane for 48 hr. Work-up gave a gum which again appeared homogeneous by tlc, but which probably represents a mixture of C-20 isomeric amines and 11α- and 11β-alcohols, with a predominance of the 11α isomer. Mass spectral analysis confirmed the addition of 2 H (M^+ at *m/e* 416), while the ir spectrum showed loss of cyclopropyl ketone and presence of hydroxyl. The latter was also confirmed by the presence of a multiplet at τ 5.74 (nmr spectrum) for the C-11 methine proton.

A final comparison of conformation *vs.* reactivity at the 11 position involved the reduction of the corresponding 3β,20α-diamine in the 10-methyl steroid series. 3β-Diethylamino-20α-dimethylamino-5α-pregnan-11-one (**45**) was chosen as a model diamine, possessing no 9β,19-cyclopropyl ring and no alkyl substituents likely to cause alterations in the known conformation[9] of the 11-keto-5α-pregnane skeleton. Leuckart reduction[20] of 5α-pregnane-3,11,20-trione (**38**) with diethylamine as the base gave the 3β-diethylamino-11,20-dione **39**, characterized as the hydrochloride **40**. Treatment of this amine with 1 equiv of hydroxylamine hydrochloride in refluxing dry pyridine–absolute ethanol for 30 min gave 3β-diethylamino-5α-pregnane-11,20-dione 20-oxime (**41**) as the sole product upon crystallization of the crude product from methanol. Reaction times of 3–4 hr and the use of excess hydroxylamine hydrochloride led to mixtures of **41** and the 11,20-dioxime **42**. Refluxing with a large excess of hydroxylamine hydrochloride for 18 hr gave dioxime **42** as the sole product. The 20-oxime **41** was hydrogenated over Adams catalyst at room temperature and atmospheric pressure to give a mixture of the C-20 epimeric primary amines. The major constituent (20α) was characterized as the dihydrochloride **43** and the acetamide **44**. N-methylation of the crude hydrogenation product with formic acid–formalin gave a mixture of the corresponding 20α- and 20β-dimethylamino compounds **45** and **46**. Although these isomers could not be distinguished by tlc, a combination of partition chromatography and careful fractional crystallization resulted in the isolation of the individual 20β- and 20α-dimethylamines (mp 203–205° and 147–148°, respectively) in yields of 18 and 33%, respectively. No appreciable paramagnetic shift of the C-18 methyl group in the nmr spectrum of the β isomer **46** relative to **45** was observed in this case. The isomers were most readily distinguished by the observed shift to lower field (τ 0.07) of the dimethylamino group and the C-21 methyl group in the 20α isomer relative to the 20β isomer.



38, R = R′ = R″ = O
39, R = β-NEt_2, α-H; R′ = R″ = O
40, R = β-NEt_2·HCl, α-H; R′ = R″ = O
41, R = β-NEt_2, α-H; R′ = NOH; R″ = O
42, R = β-NEt_2, α-H; R′ = R″ = NOH
43, R = β-NEt_2·HCl, α-H; R′ = α-NH_2·HCl, β-H; R″ = O
44, R = β-NEt_2, α-H; R′ = α-$NHCOCH_3$, β-H; R″ = O
45, R = β-NEt_2, α-H; R′ = α-NMe_2, β-H; R″ = O
46, R = β-NEt_2, α-H; R′ = β-NMe_2, α-H; R″ = O
47, R = β-NEt_2, α-H; R′ = α-NMe_2, β-H; R″ = β-OH, α-H
48, R = β-NEt_2, α-H; R′ = α-NMe_2, β-H; R″ = α-OH, β-H

Reduction of diamine **45** with $LiAlH_4$ in refluxing dioxane for 48 hr gave 3β-diethylamino-20α-dimethylamino-5α-pregnan-11β-ol (**47**) as the major product (58% yield). A second crystalline product, isolated in 13% yield, is probably the 11α-hydroxy isomer **48**, and a third band from the partition chromatographic purification yielded a colorless oil (13%), which was not investigated further. No evidence for the formation of any 11-deoxydiamine was found in the series.

(29) T. Nakano and Z. Votický, *J. Chem. Soc. C*, 590 (1970).

This result, when considered with those from similar reductions of the 9β,19-cyclopropyldiamines **36** and **37**, and the cyclopropyl monoamines **30** and **31** indicate that the presence of amino functions at C-3 and C-20 does not affect the degree of reactivity of the 11-ketone toward $LiAlH_4$ reduction, either in the presence of a conjugated cyclopropyl ring system or a normal 10-methyl steroid system.

The results of these hydride reductions enhance the proposals made above to account for the differences in reactivity of cyclopropyl carbinols **8** and **11** towards acid media. Only in the case of alkyl-substituted *Buxus* alkaloids was any 11-deoxy compound isolated from $LiAlH_4$ reduction of the 11-ketones. In all other cases, C-11 alcohols were formed as the predominant products, thus providing strong support for the proposal that there is a significant difference in molecular conformation between the 9β,19-cyclotriterpenes and 9β,19-cyclo and 10-methyl steroids.[30]

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus or on a Mettler FP2 apparatus. Infrared spectra were determined as KBr pellets or chloroform solutions on a Beckman IR-5A or Perkin-Elmer 257 recording spectrophotometer. Ultraviolet absorption spectra were measured in ethanol on a Beckman DK-2A ratio recording spectrophotometer. Optical rotations were measured, in chloroform solutions unless otherwise stated, on a Zeiss-Winkel polarimeter or a Perkin-Elmer 141 polarimeter, and are approximated to the nearest degree. Nuclear magnetic resonance spectra were determined on a Varian Associates A-60A or a Hitachi Perkin-Elmer R20 recording spectrometer at 60 MHz unless otherwise stated. Chemical shifts have been recorded in τ values. Low-resolution mass spectra were determined on a Hitachi Perkin-Elmer RMU-6E spectrometer. High-resolution mass spectra were determined on an AEI MS-902 spectrometer. Thin layer chromatography employed silica gel GF254 unless otherwise stated. Spots were located by spraying with $Ce(SO_4)_2$ (3%) in H_2SO_4 (3 *N*) followed by heating until colored spots appeared. The solvent system (A) used for partition chromatography was a mixture of Skellysolve B, ethylene dichloride, methanol, and water (10:1:2:0.16), unless otherwise indicated. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Solvent evaporations were carried out under reduced pressure below 40°. All solutions were dried over anhydrous magnesium sulfate, unless otherwise stated.

Lithium Aluminum Hydride Reduction of Ketone 5.[12]—A solution of **5** (100 mg) in anhydrous ether (35 ml) was treated with lithium aluminum hydride (35 mg). After 1 hr at room temperature, the excess hydride was destroyed by careful addition of methanol. Water (30 ml) was added, and the organic layer was separated. The aqueous layer was extracted with ether (2 × 30 ml), and the combined ethereal layers were washed with water and dried. Removal of solvent left a colorless solid (98 mg) which was homogeneous by tlc on silica gel, but showed two well-separated spots on alumina tlc (Merck type T) using chloroform as eluent. The product was chromatographed on neutral Woelm grade IV alumina (50 g). Elution with benzene–chloroform (6:4, 55 ml) gave 11β-hydroxy-9,19-cyclo-5α,9β-pregnane-3,20-dione bis(ethylene ketal) (**10**) as a colorless gum (11 mg): ir λ_{max} 2.85, 6.96, 7.25, 8.10, 8.65, 9.22, and 10.40 μ; nmr τ 6.04 (8 H, C-3, C-20 ketal H), 6.30 (1 H, m, C-11 H), 8.71 (3 H, s, C-21 CH_3), 8.95 (3 H, s, C-18 CH_3), and 9.79 (1 H, d, J = 5 Hz, C-19 H).

Anal. Calcd for $C_{25}H_{39}O_5$: mol wt, 418.2770. Found (high resolution mass spectrum): mol wt, 418.2720.

Further elution with the same solvents (20 ml) gave a mixture of **10** and **11** (9 mg). Continued elution with this solvent mixture (30 ml) followed by chloroform (100 ml) gave pure 11α-hydroxy-9,19-cyclo-5α,9β-pregnane-3,20-dione bis(ethylene ketal) (65 mg). Recrystallization from methanol–Skellysolve B gave colorless needles of alcohol **11**: mp 179–180°; $[\alpha]^{26}D$ +15° (*c* 1.10); ir λ_{max} 2.91, 6.82, 6.93, 7.17, 7.30, 8.18, 8.68, 8.92, 9.33, and 10.57 μ; nmr τ 6.01 (8 H, C-3, C-20 ketal H), 6.41 (1 H, m, C-11 H), 8.68 (3 H, s, C-21 CH_3), 9.10 (3 H, s, C-18 CH_3), and 9.47 (2 H, C-19 H); mass spectrum *m/e* 418 (M^+), 403, 400, 385, 373, 356, 338, 99, 91, and 87. This material was identical (melting point, mixture melting point, and tlc) to a previously isolated sample of unassigned configuration.[12]

Sodium Borohydride Reduction of Ketone 5.—A solution of **5** (100 mg) in isopropyl alcohol (40 ml) was heated under reflux with sodium borohydride (250 mg) for 17 hr. After removal of solvent, the residue was partitioned between chloroform (50 ml) and water (50 ml). The aqueous phase was extracted with chloroform (2 × 30 ml). After drying, the combined chloroform layers gave a colorless gum (98 mg). Chromatography on neutral Woelm grade IV alumina gave four fractions. The first fraction, eluted with benzene (40 ml), gave a mixture of ketone **5** and alcohol **10** (11 mg); the second fraction, eluted with chloroform–benzene (1:9, 21 ml) gave alcohol **10** (21 mg); the third fraction, eluted with chloroform–benzene (1:9, 24 ml) gave a mixture of **10** and **11** (32 mg); the fourth fraction, eluted with chloroform–benzene (1:9, 24 ml) and chloroform–benzene (1:1, 52 ml), gave alcohol **11** (31 mg).

11β-Acetoxy-9,19-cyclo-5α,9β-pregnane-3,20-dione Bis(ethylene ketal) (12).—A solution of alcohol **10** (12 mg) in pyridine (0.3 ml) and acetic anhydride (0.3 ml) was allowed to stand at room temperature overnight. The solution was then diluted with saturated sodium bicarbonate and extracted with chloroform. After drying the solution, removal of solvent left a residue which was taken up in chloroform and filtered through silica gel (1 g) to yield **12** as a colorless gum (12 mg): ir λ_{max} 5.84, 6.95, 7.30, 7.94, 8.83, 9.30, 9.51, 9.63, 9.76, 10.39, and 10.57 μ; nmr τ 5.05 (1 H, m, C-11 H), 6.01 (8 H, C-3, C-20 ketal H), 7.92 (3 H, s, C-11 $COCH_3$), 8.69 (3 H, s, C-21 CH_3), and 9.73 (1 H, d, J = 5 Hz, C-19 H); mass spectrum *m/e* 400 ($M^+ - CH_3CO_2H$), 356, 279, 149, 99, 87, 71, 69, 57 and 55.

11α-Acetoxy-9,19-cyclo-5α,9β-pregnane-3,20-dione Bis(ethylene ketal) (13).—Acetylation of **11** was carried out as for **10**. Crystallization of the product from Skellysolve B gave colorless prisms of the acetate **13**: mp 178–180°; $[\alpha]^{25}D$ +10° (*c* 1.10); ir λ_{max} 5.83, 6.93, 7.30, 7.72, 7.94, 8.68, 9.10, 9.28, 9.86, 10.57, 11.60, and 12.40 μ; nmr τ 5.38 (1 H, m, C-11 H), 6.03 (8 H, C-3, C-20 ketal H), 8.00 (3 H, s, C-11 $COCH_3$), 8.72 (3 H, s, C-21 CH_3), 9.10 (3 H, s, C-18 CH_3), and 9.48 (2 H, C-19 H); mass spectrum *m/e* 460 (M^+), 400.2600 ($M - CH_3CO_2H$) (calcd for $C_{25}H_{36}O_4$: 400.2613), 356, 99, 91, and 87.

Mild Acid Treatment of Alcohol 11.—A solution of alcohol **11** (48 mg) in dry dioxane (3.5 ml) was stirred with 30% (v/v) sulfuric acid (1 ml) for 20 hr at room temperature. The reaction mixture was then poured into saturated sodium chloride solution (50 ml) and extracted with ethyl acetate (3 × 25 ml). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution and water, and then dried. Removal of solvent left a dull white solid, which, on crystallization from benzene–ether, gave colorless needles of alcohol **15** (27 mg); mp 186–188°; $[\alpha]^{25}D$ +32° (c 0.34); ir λ_{max} 2.90, 5.85, 6.90, 7.05, 7.21, 7.34, 8.59, 8.80, 9.25, and 10.40 μ; nmr τ 4.57 (1 H, broad s, $W_{1/2}$ = 9 Hz, C-11 H), 7.85 (3 H, s, C-21 CH_3), and 9.32 (3 H, s, C-18 CH_3); mass spectrum *m/e* 330 (M^+), 312, 269, 105, 91, 86, 81, 79, 55, and 43.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.36; H, 9.09. Found: C, 76.29; H, 8.93.

Chromatography of the crystallization mother liquors on neutral Woelm grade IV alumina (2.5 g) gave, on elution with benzene (30 ml), dione **17** (4.3 mg), identical (ir, uv, tlc) with the main product of vigorous acid treatment of ketone **5**.

3β,Diethylamino-10ε-hydroxy-9(10→19)*abeo*-Δ$^{9(11)}$-5α-pregnen-20-one (19).—A solution of dione **15** (27 mg) in dry toluene (3 ml) was added to a mixture of diethylamine (90 mg) and formic acid (97% solution, 19 mg). The mixture was refluxed in a preheated oil bath for 2 hr, then diluted with ether (30 ml) and extracted with 2 *N* hydrochloric acid (2 × 30 ml). The combined acidic extracts were basified with aqueous sodium hydroxide solution (2 *N*) and extracted with $CHCl_3$ (2 × 50 ml). The chloroform layer was washed with water (20 ml), dried, and evaporated to leave a crystalline residue (28 mg), mp 155–158°. Recrystallization from benzene–Skellysolve B gave pure amine

(30) F. Khuong-Huu, D. Herlem, and J. J. H. Simes [*Bull. Soc. Chim. Fr.*, 258 (1969)] have reported that the course of Wolff–Kishner reduction of the 9β,19-cyclo-11-keto steroid system in triterpenoid *Buxus* alkaloids differs from that of reduction of **5** (*cf.* part XIII[1]).

19 (16.5 mg): mp 161–162°; $[\alpha]^{25}D$ +11° (c 0.21); ir λ_{max} 3.00, 5.91, 6.82, 6.93, 7.25, 7.38, 7.74, 8.15, 8.40, 8.65, 9.30, 9.98, 10.27, and 10.87 μ; nmr τ 4.65 (1 H, broad s, C-11 H), 7.43 (4 H, q, J = 12 Hz, C-3 NCH_2CH_3), 7.77 (3 H, s, C-18 CH_3), 8.97 (6 H, t, J = 12 Hz, C-3 NCH_2CH_3), and 9.34 (3 H, s, C-18 CH_3); mass spectrum m/e 387 (M^+), 372, 369, 359, 330, 138, 112, 99.

Anal. Calcd for $C_{25}H_{41}NO_2$: M, 387.3137. Found (high resolution mass spectrum): M, 387.3128.

Mild Acid Treatment of Acetate 13.—A solution of acetate **13** (8 mg) in dioxane (1.5 ml) was treated with 30% v/v sulfuric acid (12 drops) overnight at room temperature. The solution was diluted with water, and extracted with chloroform (3 × 30 ml). The combined chloroform layers were extracted with saturated sodium bicarbonate (15 ml) and water (15 ml), and dried. Removal of solvent left a semicrystalline residue (6 mg) which was identical (ir, nmr, and tlc) with the alcohol **15**.

Vigorous Acid Treatment of Alcohol 11.—A solution of alcohol **11** (425 mg) in dioxane (40 ml) was heated with 50% v/v sulfuric acid (12 ml) on the steam bath for 15 min. The solution was diluted with water and extracted with chloroform (3 × 50 ml). The organic layers were extracted with saturated sodium bicarbonate solution and water, and then dried. Removal of solvent left a yellow-brown gum (340 mg) which exhibited no conjugated diene absorption in the uv spectrum.[14] This product was separated into three bands, by preparative tlc, using chloroform as developing solvent. Elution of band 1 (most polar) gave ketone **17** as a colorless gum (140 mg): $[\alpha]^{25}D$ +39° (c 0.54); uv λ_{max}^{EtOH} 237 nm (ε 22,410); ir λ_{max} 5.90, 6.03, 6.20, 6.92, 7.06, 7.37, 7.95, 8.20, 8.59, 8.85, 10.18, 11.01, 11.15, and 11.64 μ; nmr τ 4.20 (1 H, s, C-4 H), 4.51 (1 H, broad s, C-11 H), 7.86 (3 H, s, C-21 CH_3), and 9.38 (3 H, s, C-18 CH_3); mass spectrum m/e 312 (M^+), 269, 242, 227, 157, 91, 85, 83, 69, 43, and 41.

Anal. Calcd for $C_{21}H_{28}O_2$: M, 312.2089. Found (high resolution mass spectrum): M, 312.2094.

Band 2 gave a colorless gum (58 mg): ir λ_{max} 5.90, 5.98, 6.20, 6.93, 7.06, 7.22, 7.37, 7.60, 7.90, 8.12, 8.60, 8.80, 9.13, and 11.10 μ; nmr τ 3.19 (1 H, broad t, J = 10, J′ = 12.5 Hz, C-1 H), 4.06 (1 H, d, J = 10 Hz, C-2 H), 4.49 (1 H, broad s, C-11 H), 7.83 (3 H, s, C-21 CH_3), 9.34 (3 H, s, C-18 CH_3), and 9.36 (3 H, s, C-18 CH_3). One of the components of this band is suggested to be the Δ^1-3-ketone **21**.

Band 3 gave a colorless gum (42 mg): ir λ_{max} 5.88, 6.19, 6.25, 6.92, 7.05, 7.25, 7.37, 7.90, 8.14, 8.54, and 9.98 μ; nmr τ 4.37–4.75 (2 H, m, C-11 H, and C-1 H), 7.86 (3 H, s, C-21 CH_3), and 9.42 (3 H, s, C-18 CH_3). The $\Delta^{1(10),9(11)}$-3-keto-*B*-homodiene structure **20** is suggested as a possible structure for this compound.

Conversion of Alcohol 15 to Diene 17.—A solution of alcohol **15** (5 mg) in dioxane (1 ml) was heated under reflux with 30% w/w sulfuric acid (1 ml) for 6 hr. The mixture was worked up as previously described to give a colorless gum (4.5 mg), which was separated by tlc in the system benzene–ethyl acetate (2:1) to give diene **17** (2.2 mg) and a trace of higher R_f material.

Attempted Tosylation of Alcohol 11.—Alcohol **11** (220 mg) in pyridine (40 ml) was heated with *p*-toluenesulfonyl chloride (1 g) on the steam bath for 2 hr. The solvent was removed, and the residue was filtered through a short column of silica gel (Merck, 0.05–0.2 mm, 20 g) eluting with chloroform. Removal of solvent left a yellow gum (201 mg), which contained no starting material (tlc), but showed uv absorption as follows: λ_{max}^{EtOH} 246 (238 sh, 255 sh) nm (ε 1700–2550 in successive experiments). Assuming a value of ε of 21,900 for the $\Delta^{9(11),10(19)}$-diene,[14] this indicates that the crude product contained approximately 9–14% of the desired conjugated diene. A partition chromatography column was set up by impregnating Celite 545 (350 g) with 170 ml of the lower phase of the solvent system, cyclohexane–dimethylformamide–ethyl acetate–water (10:4:2.5:0.3). This was dry-packed in several increments into a column of suitable size (column volume 650 ml), and the upper phase of the solvent system was allowed to pass through the column for 20 hr. A portion of the crude product (125 mg) was applied to the column in 3 ml of the upper phase, and elution continued with the upper phase. The first 620 ml eluted no material; the next 30 ml gave crystals (44 mg) of olefin **22**. Recrystallization from methanol gave colorless needles: mp 94–95°; $[\alpha]^{25}D$ +54° (c 0.53); ir λ_{max} 6.18, 6.95, 7.31, 7.73, 8.12, 8.54, 8.67, 8.78, 8.92, 9.32, 9.65, and 10.53 μ; nmr τ 3.65 (1 H, d, J = 10 Hz, C-12 H), 4.81 (1 H, d, J = 10 Hz, C-11 H), 6.03 (8 H, C-3, C-20 ketal H), 8.63 (3 H, s, C-21 CH_3), 9.09 (3 H, s, C-18 CH_3), and 9.65 (1 H, d, J = 4.5 Hz, C-19 H); mass spectrum m/e 400 (M^+), 356, 313, 311, 294, 286, 257, 99, and 87.

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.26; H, 9.04.

Further elution gave several fractions which were shown (by nmr) to be mixtures.

9,19-Cyclo-5α,9β-pregnane-3,11,20-trione 3-Ethylene Ketal (27).—A mixture of diketal **5** (200 mg), glacial acetic acid (1 ml), methanol (4 ml), and water (4 ml) was heated at 55° for 10 min to dissolve the steroid. Heating at this temperature was continued for a further 10 min, then ice water was added to the cooled solution, followed by solid sodium bicarbonate until the mixture was alkaline. The aqueous mixture was extracted with methylene chloride, the organic extracts were dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. An ethereal solution of the residue was filtered through alumina (Woelm, basic, grade III, 8 g) to yield a colorless oil (190 mg) which crystallized from Skellysolve B to give the monoketal **27** (149 mg): mp 126–128°; $[\alpha]^{28}D$ +141° (c 0.46); ir λ_{max} 5.86, 5.98, 7.35, and 10.55 μ; nmr τ 6.05 (4 H, s, C-3 ketal H), 7.12 (1 H, d, part of AB d, J = 14 Hz, C-12 H), 7.87 (3 H, s, C-21 CH_3), 9.18 (1 H, d, part of AB d, J = 4 Hz, C-19 H), and 9.32 (3 H, s, C-18 CH_3); mass spectrum m/e 372 (M^+), 357, 344, 328, 310, 286, and 99.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.00; H, 8.50.

9,19-Cyclo-5α,9β-pregnane-3,11,20-trione 3-Ethylene Ketal 20-Oxime (28).—Hydroxylamine hydrochloride (34 mg) was added to a solution of the monoketal **27** (136 mg) in pyridine (4 ml), and the resulting solution was allowed to stand at room temperature for 18 hr. The solution was poured into water and extracted with ether. The combined ether extracts were washed several times with water, dried over anhydrous Na_2SO_4, and concentrated. Tlc of the residue revealed one major and two minor components. Separation of the major band by thick layer chromatography gave a white foam which crystallized from ether–Skellysolve A to afford the oxime **28** (118 mg): mp 177–178°; $[\alpha]^{28}D$ +82° (c 0.56); ir λ_{max} 2.79, 3.05, 6.00, and 10.55 μ; nmr τ 1.77 (1 H, m, =NOH), 6.05 (4 H, C-3 ketal H), 7.23 and 7.79 (2 H, AB d, J = 14.5 Hz, C-12 H), 8.12 (3 H, s, C-21 CH_3), 9.19 (1 H, d, part of AB d, J = 4 Hz, C-19 H), and 9.31 (3 H, s, C-18 CH_3); mass spectrum m/e 387 (M^+), 371, 356, 342, 325, 308, 301, 99, 87, and 57.

Anal. Calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.61. Found: C, 71.20; H, 8.70; N, 3.71.

Catalytic Hydrogenation of Oxime 28.—A solution of oxime **28** (1.55 g) in glacial acetic acid (40 ml) was added to prereduced Adams catayst (500 mg) in glacial acetic acid (20 ml). Hydrogenation was carried out at atmospheric pressure and room temperature. After 10 hr, the hydrogenation was stopped. The reaction mixture was filtered, basified by addition of ammonium hydroxide, and extracted with ether. The combined ether extracts were washed with water, dried, and concentrated to yield a colorless oil (1.560 g). Partition chromatography[23] of the oil gave two large red bands on the column. Fractions collected before either band was eluted gave, on evaporation, the starting oxime (191.5 mg). The first red band (band 1) was eluted, and the solvent was removed to give a mixture of starting oxime and the 20β-amine **30** (352.4 mg) as shown by tlc. Chromatography of this mixture on alumina (Woelm, neutral, grade IV, 20 g) gave, on elution with benzene (25 ml), the starting oxime **28** (64.2 mg) with traces of the amine **30**. Further elution with benzene (50 ml) afforded isomer **30** (276.4 mg) which crystallized from ether–Skelly B to give 20β-amino-9,19-cyclo-5α,9β-pregnane-3,11-dione 3-ethylene ketal **30** (248.5 mg): mp 123–124°; $[\alpha]^{29}D$ +82° (c 1.02); ir λ_{max} 2.82, 2.90, 6.00, 6.31, 7.01, and 10.55 μ; nmr τ 6.02 (4 H, C-3 ketal H), 7.02, and 7.82 (2 H, AB d, J = 15 Hz, C-12 H), 8.97 (3 H, d, J = 6 Hz, C-21 CH_3), and 9.22 (3 H, s, C-18 CH_3); mass spectrum m/e 373 (M^+), 356, 330, 314, 311, 287, 233, 99, and 44.

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.74. Found: C, 73.76; H, 9.32; N, 3.63.

The second red band from the partition column gave a mixture of the starting oxime **28** and the 20α-amine **29** (703 mg). Chromatography of this mixture on alumina (Woelm, neutral, grade III, 50 g), on elution with benzene (775 ml) and benzene–ether (9:1, 400 ml) gave oxime **28** (219 mg). Elution with ether (100 ml) gave a mixture of the oxime and the 20α-amine (32.5 mg). Elution with ether (100 ml), 2% methanol in ether (400 ml), and finally methanol (500 ml) gave pure isomer **29** (399

mg). Crystallization from ether–Skellysolve B gave 20α-amino-9,19-cyclo-5α,9β-pregnane-3,11-dione 3-ethylene ketal (384.4 mg): mp 121–123°; $[\alpha]^{29}D$ +85° (c 0.91); ir λ_{max} 2.86, 2.96, 6.00, 6.32, 7.02, and 10.55 μ; nmr τ 6.05 (4 H, C-3 ketal H), 7.22, and 7.90 (2 H, AB d, J = 14 Hz, C-12 H), 8.88 (3 H, d, J = 6 Hz, C-21 CH_3), and 9.27 (3 H, s, C-18 CH_3); mass spectrum m/e 373 (M^+), 356, 330, 311, 205, 99, 85, and 83.

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.74. Found: C, 73.98; H, 9.35; N, 3.74.

20α-Amino-11α-hydroxy-9,19-cyclo-5α,9β-pregnan-3-one Ethylene Ketal (31).—A solution of the amine **29** (100 mg) in dry dioxane (15 ml) was added to a suspension of lithium aluminum hydride (215 mg) in dry dioxane (5 ml). The reaction mixture was heated under reflux for 48 hr and cooled, and the excess hydride was destroyed by careful addition of ether saturated with water. After filtration, the inorganic precipitates were thoroughly washed with methylene chloride, and the filtrate was dried. Removal of solvent left an oil (96 mg). Partition chromatography gave four clearly separated red bands which were collected separately. Bands 1 and 2 gave noncrystalline materials (16 and 4 mg, respectively) which were shown to be mixtures (tlc).

Band 3 gave an oil which did not crystallize, but appeared to be homogeneous by tlc (16 mg); ir λ_{max} 2.72, 2.79, 3.00, 5.90, 6.30, and 10.55 μ; nmr τ 6.01 (4 H, C-3 ketal H), 6.42 (1 H, m, C-11 H), 8.93 (3 H, d, J = 6 Hz, C-21 CH_3), 9.15 (3 H, s, C-18 CH_3), and 9.48 (2 H, C-19 H).

Band 4 gave a solid (59 mg), homogeneous by tlc. Crystallization from ether–Skellysolve B gave the alcohol **31**: mp 140–142°; $[\alpha]^{28}D$ +3° (c 0.82); ir λ_{max} 2.72, 2.78, 3.00, 6.30, and 10.55 μ; nmr τ 6.02 (4 H, C-3 ketal H), 6.42 (1 H, m, C-11 H), 8.95 (3 H, d, J = 6 Hz, C-21 CH_3), 9.22 (3 H, C-18 CH_3), and 9.50 (2 H, C-19 H); mass spectrum m/e 375 (M^+), 357, 340, 332, 314, 299, 252, 99, 69, and 44.

Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.38; H, 10.04; N, 3.69.

20β-Amino-11α-hydroxy-9,19-cyclo-5α,9β-pregnan-3-one Ethylene Ketal (32).—The ketone **30** (100 mg) was treated with lithium aluminum hydride (215 mg) in dioxane (20 ml) as described above for ketone **29**. The crude product (101 mg of an oil) was chromatographed on a partition column as above, giving three bands. Band 1 gave an oil (21 mg) which appeared to be homogeneous by tlc, but apparently was still a mixture by examination of its nmr spectrum.

Band 2 yielded an oil (8 mg) which was a mixture of two compounds (tlc).

Band 3 gave a crystalline material (68 mg), mp 141–143°, which appeared to be homogeneous (tlc). Crystallization from ether–Skellysolve B afforded the alcohol **32**: mp 145°; $[\alpha]^{28}D$ −4° (c 0.61); ir λ_{max} 2.78, 2.96, 6.31, and 10.55 μ; nmr τ 6.03 (4 H, C-3 ketal H), 6.37 (1 H, m, C-11 H), 7.18 (1 H, diffuse m, C-20 H), 8.97 (3 H, d, J = 6 Hz, C-21 CH_3), 9.16 (3 H, s, C-18 CH_3), and 9.49 (1 H, C-19 H); mass spectrum m/e 375 (M^+), 357, 340, 332, 314, 299, 99, 83, 57, and 44.

Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.52; H, 10.04; N, 3.68.

3β-Diethylamino-9,19-cyclo-5α,9β-pregnane-11,20-dione (33).—A solution of 9,19-cyclo-5α,9β-pregnane-3,11,20-trione (650 mg) in dry toluene (42 ml) was heated under reflux with diethylamine (940 mg) and 97% formic acid (195 mg) for 3.5 hr. The reaction mixture was cooled, diluted with ether (80 ml), and extracted with 2 *N* hydrochloric acid (3 × 30 ml). The organic layer was washed with water and dried. Removal of solvent left unreacted trione (110 mg). This material was recycled in the amination reaction. The combined acid extracts were basified with aqueous sodium hydroxide solution, and extracted with methylene chloride (4 × 40 ml). The organic layer was washed with water and dried. Removal of solvent left the crude product as a transparent oil (610 mg). Partition chromatography[23] of a portion (250 mg) of this product on Celite 545 using solvent system A gave one major and two minor bands. The first and third bands gave mixtures (tlc). The second, major band gave amine **33** as a colorless gum (208 mg): ir λ_{max}^{film} 5.86, 5.97, 6.90, 7.01, 7.23, 7.36, 7.86, 8.08, 8.62, 9.03, 10.82, and 11.85 μ; nmr (100 MHz[31]) τ 7.28 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.81 (3 H, s, C-21 CH_3), 8.85 (6 H, t, J = 7 Hz, NCH_2CH_3), and 9.24 (3 H, s, C-18 CH_3); mass spectrum m/e 385 (M^+), 370, 356, 342, 328, 312, 138, 112, 99, and 86. For analytical characterization, this compound was converted to the C-20 oxime (*vide infra*).

Attempted Formation of C-20 Ketal 34 from Amine 33. A. Using a Catalytic Amount of *p*-Toluenesulfonic Acid.—A solution of amine **33** (400 mg) in dry benzene (10 ml) was heated under reflux with ethylene glycol (2.5 ml) for 2 hr. *p*-Toluenesulfonic acid (40 mg) was added, and the mixture was heated under reflux for a further 24 hr. After cooling, solid sodium bicarbonate (0.1 g) was added to the mixture, followed by water (5 ml) and ammonium hydroxide (5 ml). Extraction with chloroform, followed by washing and drying of the organic extract, gave a pale yellow gum (370 mg). Tlc indicated a small amount of material of slightly higher R_f than the starting amine. Partition chromatography gave three bands, only partly separated. Band 1 gave an oil (41 mg), which was shown to be a mixture by tlc; the mass spectrum showed that one of the components of the mixture was probably the desired monoketal (peak at m/e 429).

Band 2 also gave an oil (40 mg) which was shown to be a mixture by tlc. Band 3 gave the starting amine as a gum (281 mg).

B. Using 1.16 Equiv of *p*-Toluenesulfonic Acid.—The reaction was carried out as described above, using **33** (270 mg) and *p*-toluenesulfonic acid (147.5 mg). The usual work-up gave the product as a pale yellow gum (285 mg), which was chromatographed on alumina (Woelm, basic, grade II, 20 g). Elution with benzene (120 ml) gave nonpolar oily impurities (15 mg). Further elution with the same solvent (265 ml) and benzene–chloroform (4:1; 125 ml) gave the diketal fraction as a colorless gum (110.4 mg), homogeneous by tlc (R_f higher than that of **33**): ir λ_{max} 6.94, 7.30, 8.23, 9.17, 9.55, 10.55, and 13.25 μ; nmr (100 MHz) τ 6.09 (8 H, C-11, C-20 ketal H), 7.36 (4 H, q, J = 7 Hz, C-3 NCH_2CH_3), 8.68 (3 H, s, C-21 CH_3), 8.85 (6 H, t, J = 7 Hz, C-3 NCH_2CH_3), and 9.03 (3 H, s, C-18 CH_3); mass spectrum m/e 473 (M^+), 458, 445, 428, 400, 386, 372, 359, 112, 99, 87, 85, and 83.

Further elution with benzene–chloroform (4:1, 110 ml), benzene–chloroform (6:4, 175 ml), and benzene–chloroform (4:6; 85 ml) gave a mixture of the diketal and starting amine (119 mg).

Elution with benzene–chloroform (1:4, 100 ml) and chloroform (200 ml) gave starting amine (9.8 mg).

3β-Diethylamino-9,19-cyclo-5α,9β-pregnane-11,20-dione 20-Oxime (35).—A solution of amine **33** (100 mg) and hydroxylamine hydrochloride (30 mg) in absolute ethanol (2 ml) and dry pyridine (2 ml) was heated under reflux for 3 hr. The solution was cooled and treated with saturated aqueous sodium bicarbonate solution followed by excess ammonium hydroxide. The mixture was extracted with chloroform (3 × 30 ml), and the combined organic layers were washed with water and dried. Removal of solvent gave the oxime **35** as a colorless gum (94 mg) which crystallized on standing. Two recrystallizations from benzene–Skellysolve B gave colorless crystals: mp 199–201°; $[\alpha]^{26}D$ +63° (c 0.59); ir λ_{max} 5.99, 6.82, 6.91, 7.24, 7.93, 8.08, 8.43, 8.56, 9.01, 9.13, 10.39, and 11.30 μ; mass spectrum m/e 400 (M^+), 385, 371, 369, 138, 112, 99, and 86.

Anal. Calcd for $C_{23}H_{40}N_2O_2$: C, 74.96; H, 10.06; N, 6.99. Found: C, 74.82; H, 9.99; N, 6.89.

3β-Diethylamino-20α-dimethylamino-9,19-cyclo-5α,9β-pregnan-11-one (36) and 3β-Diethylamino-20β-dimethylamino-9,19-cyclo-5α,9β-pregnan-11-one (37).—A solution of oxime **35** (100 mg) in glacial acetic acid (10 ml) was hydrogenated at room temperature and atmospheric pressure over platinum oxide (10 mg). After stirring overnight, uptake of hydrogen had stopped, with consumption of 13.8 ml (2.5 equiv). Removal of solvent left a mixture of 20-aminosteroids as a colorless gum (102 mg). This was not purified, but treated immediately with formic acid (3 ml) and 40% formaldehyde solution (3 ml) on the steam bath under a nitrogen atmosphere for 6 hr. The mixture was cooled, diluted with aqueous ammonium hydroxide, and stored in the refrigerator overnight. Filtration gave a pale brown solid (84 mg), which crystallized from aqueous ethanol to give a mixture of diamines **36** and **37** as colorless prisms (27 mg): mp 101–103°; $[\alpha]^{26}D$ +26° (c 1.30); ir λ_{max} 5.96, 6.88, 7.24, 7.90, 8.36, 8.68, 9.00, 9.15, 9.90, and 10.83 μ; nmr (100 MHz) τ 6.87 (1 H, d, J = 14 Hz, C-12 H), 7.42 (4 H, q, J = 7 Hz, C-3 NCH_2CH_3), 7.79 and 7.86 [6 H, 2 s, $N(CH_3)_2$], 8.91 (6 H, t, J = 7 Hz, C-3 NCH_2CH_3), 9.08 (3 H, d, J = 7 Hz, C-21 CH_3), and 9.22 (3 H, s, C-18 CH_3); mass spectrum m/e 414 (M^+), 399, 385, 112, 99, 86, and 72.

(31) 100-MHz spectra were recorded on a Varian HA-100 recording spectrometer.

Anal. Calcd for $C_{27}H_{46}N_2O$: M, 414.3609. Found (high resolution mass spectrum): M, 414.3597.

Further crops of material obtained from the liquors of the crystallization were shown to be mixtures by tlc.

Lithium Aluminum Hydride Reduction of Ketones 36 and 37.—A mixture of ketones **36** and **37** (23 mg) in dioxane (0.75 ml) was added to a suspension of $LiAlH_4$ in dioxane (0.75 ml), and the mixture was heated under reflux for 48 hr. After the usual work-up, the organic product was isolated as a colorless gum (21 mg). Two consecutive purifications by tlc, each developed twice in the top phase of the solvent system *n*-butyl alcohol–acetic acid–water (4:1:5), gave only one major band as a colorless gum (9 mg): ir λ_{max} 2.94, 6.85, 7.28, 7.94, 8.74, 9.08, and 9.90 μ; nmr (100 MHz) τ 5.74 (1 H, broad s, C-11 H), 6.25 (1 H, m, C-20 H), 7.17 (1 H, d, J = 7 Hz, C-12 H), 7.41 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.83 and 7.87 [6 H, 2 s, $N(CH_3)_2$], 8.93 (6 H, t, J = 7 Hz, NCH_2CH_3), 8.96 (3 H, s, C-18 CH_3), and 9.12 (3 H, d, J = 6.5 Hz, C-21 CH_3); mass spectrum m/e 416 (M^+), 401, 399, 114, 113, 112, 99, 83, 72, 69, 57, 55, 45, 43, and 41. This material decomposed on standing, with production of base line tlc material.

3β-Diethylamino-5α,pregnane-11,20-dione (39).—A solution of 5α-pregnane-3,11,20-trione (1.6 g), 97% formic acid (0.49 g), and diethylamine (2.32 g) in dry toluene (105 ml) was heated under reflux for 4 hr. After cooling, the solution was diluted with ether (200 ml) and extracted with 2 *N* hydrochloric acid (5 × 150 ml). The organic layer was washed with water and dried, and the solvent was removed to leave unreacted starting material as a colorless solid (0.314 g). This material was recycled in the reductive amination, to leave less than 0.05 g of brown gum in the neutral layer. The combined acid layers were basified with aqueous sodium hydroxide solution and extracted with methylene chloride (5 × 150 ml). The organic layers were washed with water, dried, and evaporated *in vacuo* to yield amine **39** as a transparent gum (1.65 g) which partially crystallized on standing. Purification *via* hydrochloride **40** gave, after regeneration by basification and crystallization from aqueous ethanol, a colorless solid: mp 89–92°; $[\alpha]^{24}D$ +70° (c 0.92); ir λ_{max} 5.88, 6.95, 7.35, 7.40, 7.89, 8.31, 8.50, 8.68, and 9.50 μ; nmr τ 7.42 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.88 (3 H, s, C-21 CH_3), 8.97 (6 H, t, J = 7 Hz, NCH_2CH_3), 9.00 (3 H, s, C-19 CH_3), and 9.43 (3 H, s, C-18 CH_3); mass spectrum m/e 387 (M^+), 372, 358, 344, 330, 223, 215, 139, 138, 113, 112, 105, 99, 84, 57, 56, 55, 43, and 41. For final characterization the amine was converted to the hydrochloride **40**, which crystallized as colorless needles from methanol: mp 278° dec; $[\alpha]^{25}D$ +53° (c 1.02, MeOH); ir λ_{max} 2.77, 2.93, 3.79, 4.02, 5.98, 6.92, 7.25, 7.38, 7.88, 8.22, 8.46, 8.63, and 9.72 μ; mass spectrum m/e 387 (M^+ − HCl), 372, 358, 344, 330, 139, 138, 113, 112, 99, 84, 71, 69, 57, 56, 55, 43, and 41.

Anal. Calcd for $C_{25}H_{42}ClNO_2$: C, 70.81; H, 9.98; Cl, 8.34; N, 3.30. Found: C, 70.66; H, 9.87; Cl, 8.42; N, 3.26.

3β-Diethylamino-5α-pregnane-11,20-dione 20-Oxime (41).—A solution of amine **39** (1.5 g, crude) and hydroxylamine hydrochloride (272 mg) in absolute ethanol (30 ml) and dry pyridine (30 ml) was heated under reflux for 25 min. The solvents were removed *in vacuo* and saturated aqueous sodium bicarbonate solution was added to the residue, followed by concentrated ammonium hydroxide. The mixture was stored in the refrigerator overnight, and the precipitate was then filtered, washed thoroughly with water, and dried in a vacuum desiccator over KOH overnight. Crystallization from methanol gave **41** as colorless needles (875 mg): mp 196–197.5°; two recrystallizations from the same solvent raised the melting point to 198–199°: $[\alpha]^{24}D$ +50° (c 1.16); ir λ_{max} 3.17 and 3.27 (broad), 5.88, 6.87, 7.25, 7.35, 8.20, 8.65, 10.33, 11.02, 13.32, and 14.28 μ; nmr τ 7.45 (4 H, q, J = 7.5 Hz, NCH_2CH_3), 8.23 (3H, s, C-21 CH_3), 8.97 (6 H, t, J = 7.5 Hz, NCH_2CH_3), 9.02 (3 H, s, C-19 CH_3), and 9.44 (3 H, s, C-18 CH_3); mass spectrum m/e 402 (M^+), 387, 371, 345, 331, 330, 329, 315, 138, and 112.

Anal. Calcd for $C_{25}H_{42}N_2O_2$: C, 74.58; H, 10.51; N, 6.96. Found: C, 74.66; H, 10.66; N, 6.94.

3β-Diethylamino-5α-pregnane-11,20-dione Dioxime (42).—A solution of dione **39** (40 mg) in dry pyridine (4 ml) and absolute ethanol (4 ml) was heated under reflux with hydroxylamine hydrochloride (40 mg) for 18 hr. Work-up as described above gave a colorless precipitate which crystallized from methanol to give **42** as colorless needles (34 mg): mp 265–269°, raised after two recrystallizations from methanol to 271–273°; $[\alpha]^{24}D$ +64°[32] (c 0.25, MeOH); ir λ_{max} 3.08 and 3.17 (broad), 6.14, 6.93, 7.32, 9.66, 10.35, 11.30, 12.80, and 14.18 μ; mass spectrum m/e 417 (M^+), 402, 401, 400, 385, 384, 370, 368, 138, 112, 84, 57, 56, and 41.

Anal. Calcd for $C_{25}H_{43}N_3O_2$: C, 71.90; H, 10.38; N, 10.06. Found: C, 71.81; H, 10.53; N, 9.98.

Hydrogenation of Oxime 41.—A solution of **41** (1.1 g) was hydrogenated at room temperature and atmospheric pressure in the presence of pre-reduced Adams catalyst (130 mg). The hydrogenation was stopped when the oxime **41** was consumed (tlc). This required approximately 25 hr. The mixture was filtered and the filtrate was basified with ammonium hydroxide and extracted with chloroform. The organic extract was washed with water, dried, and evaporated to leave a mixture of the epimeric C-20 primary amino steroids as a clear oil (1.15 g). The dihydrochloride **43** crystallized from methanol–acetone as colorless prisms: mp 297° dec; three recrystallizations from the same solvents raised the melting point to 328° dec; $[\alpha]^{23}D$ +19° (c 1.17, MeOH); ir λ_{max} 2.91, 3.77, 4.01, 5.88, 6.23, 6.88, 7.20, 7.88, 8.30, 9.65, and 9.93 μ; mass spectrum m/e 389, 388 (M^+ − 2 HCl), 374, 373, 357, 331, 139, 138, 113, 112, 99, 84, 71, 56, 44, and 41.

Anal. Calcd for $C_{25}H_{46}Cl_2N_2O$: Cl, 15.36; N, 6.07. Found: Cl, 15.18; N, 5.97.

20α-Acetamido-3β-diethylamino-5α-pregnan-11-one (44).—A solution of the crude product (150 mg) from the above hydrogenation in dry pyridine (3 ml) and acetic anhydride (0.3 ml) was allowed to stand at room temperature overnight. The solution was diluted with water (230 ml) and ammonia (23 ml) and extracted with chloroform. The organic extract was washed with 2 *N* sodium hydroxide and water and dried. Removal of solvent left a colorless oil (152 mg). Trituration with Skellysolve B gave **44** as a colorless solid: mp 198–205°, raised by two recrystallizations from Skellysolve B–benzene to 221–223° dec; $[\alpha]^{23}D$ +41° (c 1.22); ir λ_{max} 2.98, 3.23, 5.85, 6.08, 6.45, 6.90, 7.26, 7.79, 8.28, 8.80, 9.45, and 10.25 μ; nmr τ 4.17 (1 H, m, NH-$COCH_3$), 6.01 (1 H, m, C-20 H), 7.33 (4 H, q, J = 7.5 Hz, NCH_2CH_3), 8.04 (3 H, s, $COCH_3$), 8.91 (6 H, t, J = 7.5 Hz, NCH_2CH_3), and 9.32 (3 H, s, C-18 CH_3); mass spectrum m/e 430 (M^+), 415, 138, 112, 57, 56, and 41.

Anal. Calcd for $C_{27}H_{46}N_2O_2$: C, 75.30; H, 10.77; N, 6.50. Found: C, 75.21; H, 10.73; N, 6.43.

3β-Diethylamino-20α-dimethylamino-5α-pregnan-11-one (45) and 3β-Diethylamino-20β-dimethylamino-5α-pregnan-11-one (46).—A solution of the crude diamine mixture (1.15 g), obtained by hydrogenation of oxime **41**, in 37% formaldehyde solution (24 ml) and 97% formic acid (24 ml) was heated on the steam bath for 7 hr, then allowed to stand overnight at room temperature. Ice water was added, followed by ammonium hydroxide, and the precipitated material was extracted with chloroform. The organic extract was washed (water), dried, and evaporated *in vacuo* to afford a colorless, crystalline solid (1.51 g). On addition of a small volume of the top phase of solvent system A to the residue, some solid (*ca.* 330 mg) remained insoluble.[33] Partition chromatography[23] of the filtrate after removal of this material gave rise to only one, rather diffuse, red band. This band was collected in nine fractions.

Fractions 1 and 2 were combined and evaporated to give 158 mg of a colorless, crystalline solid. Recrystallization from methanol gave the 20β-amine **46** as plates (98 mg): mp 197–199°, raised to 202–204° after two further recrystallizations from methanol; $[\alpha]^{24}D$ +39° (c 0.82); ir λ_{max} 5.91, 6.93, 7.28, 7.93, 8.30, 8.62, 9.29, and 10.80 μ; nmr (100 MHz) 6.38 (1 H, m, C-20 H), 7.25 (1 H, d, J = 12 Hz, C-12 H), 7.51 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.97 [6 H, s, $N(CH_3)_2$], 9.00 (6 H, t, J = 7 Hz, NCH_2CH_3), 9.03 (3 H, s, C-19 CH_3), 9.27 (3 H, d, J = 6.5 Hz, C-21 CH_3), and 9.40 (3 H, s, C-18 CH_3); mass spectrum m/e 416 (M^+), 415, 402, 401, 359, 139, 138, 112, 99, 84, 72, 56, and 41.

Anal. Calcd. for $C_{27}H_{48}N_2O$: C, 77.83; H, 11.61; N, 6.72. Found: C, 77.90; H, 11.64; N, 6.75.

Fractions 3–7 gave a colorless, crystalline solid (695 mg), which was separated by repeated fractional recrystallization from methanol into the 20β-amine **46** (113 mg) and the 20α-amine **45**

(32) Owing to the insolubility of **42**, this value is approximate.

(33) On recrystallization from methanol or acetone, this compound formed small, shiny prisms, subliming at 282°. Combustion and mass spectral analysis supported a $C_7H_{12}N_4$ formula; the compound was not investigated further.

(379 mg): mp 147–148°; $[\alpha]^{23}D$ +48° (c 0.95); ir λ_{max} 5.88, 6.85, 6.94, 7.24, 7.29, 7.91, 8.30, 8.38, 8.67, 9.40, and 10.80 μ; nmr (100 MHz) τ 6.36 (1 H, m, C-20 H), 7.50 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.90 [6 H, s, $N(CH_3)_2$], 9.01 (6 H, t, J = 7 Hz, NCH_2CH_3), 9.03 (3 H, s, C-19 CH_3), 9.20 (3 H, d, J = 7 Hz, C-21 CH_3), and 9.40 (3 H, s, C-18 CH_3); mass spectrum m/e 416 (M^+), 402, 401, 139, 138, 113, 112, 99, 84, 73, 72, 71, 58, and 56.

Anal. Calcd for $C_{27}H_{48}N_2O$: C, 77.83; H, 11.61; N, 6.72. Found: C, 77.62; H, 11.58; N, 6.70.

Fractions 8 and 9 gave colorless gums (22 and 2 mg, respectively) which did not crystallize.

Lithium Aluminum Hydride Reduction of Diamine 45.—A solution of **45** (180 mg) in dioxane (20 ml) was added to a suspension of $LiAlH_4$ (275 mg) in dioxane (15 ml). The mixture was heated under reflux for 48 hr, cooled, and treated with ether saturated with water. The suspension was filtered, and the inorganic precipitate was washed with boiling dichloromethane (2 × 30 ml). The combined filtrates were dried and concentrated to leave a colorless, crystalline solid (164 mg). Partition chromatography separated this residue into three bands.

Band 1 (highest R_f) gave a colorless solid (44 mg), mp 130–133°, which was shown by nmr to be a mixture of two compounds. Repeated partition chromatography of this material gave two red bands. Removal of solvent from the first band gave a colorless oil (24 mg) which crystallized from methanol to give 11α-hydroxydiamine **48** as colorless plates: mp 165–167°; $[\alpha]^{24}D$ +21° (c 0.50); ir λ_{max} 2.93, 6.88, 6.94, 7.29, 7.36, 8.39, 8.66, 9.15, 9.31 9.51, and 10.80 μ; nmr (100 MHz) τ 5.83 (1 H, m, C-11 H), 6.46 (1 H, m, C-20 H), 7.50 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.94 [6 H, s, $N(CH_3)_2$], 9.00 (6 H, t, J = 7 Hz, NCH_2CH_3, and 3 H, s, C-19 CH_3), 9.13 (3 H, s, C-18 CH_3), and 9.28 (3 H, d, J = 6 Hz, C-21 CH_3); mass spectrum m/e 418 (M^+), 417, 403, 347, 138, 113, 112, 99, 98, 86, 84, 81, 73, 72, 71, 69, 57, 56, 55, 43, and 41.

Anal. Calcd for $C_{27}H_{50}N_2O$: C, 77.45; H, 12.04; N, 6.69. Found: C, 77.32; H, 11.88; N, 6.59.

The second band gave **47** as a colorless solid (11 mg), identical with the product obtained from band 2 of the first chromatography.

Band 2 gave 3β-diethylamino-20α-dimethylamino-5α-pregnan-11β-ol (**47**) as a colorless solid (94 mg) which crystallized from methanol as colorless plates: mp 178–179°; $[\alpha]^{24}D$ +30° (c 0.69); ir λ_{max} 2.94, 6.92, 7.36, 8.38, 8.68, 9.43, 9.53, and 10.85 μ; nmr (100 MHz) τ 5.80 (1 H, m, C-11 H), 6.38 (1 H, m, C-20 H), 7.49 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.89 [6 H, s, $N(CH_3)_2$], 9.00 (6 H, t, J = 7 Hz, NCH_2CH_3, and 3 H, s, C-19 CH_3), 9.15 (3 H, s, C-18 CH_3), and 9.16 (3 H, d, J = 6 Hz, C-21 CH_3); mass spectrum m/e 418 (M^+), 417, 403, 348, 347, 138, 113, 112, 84, 73, 72, 57, 56, 55, and 41.

Anal. Calcd for $C_{27}H_{50}N_2O$: C, 77.45; H, 12.04; N, 6.69. Found: C, 77.25; H, 12.04; N, 6.66.

Band 3 gave a colorless oil (24 mg) which was shown to be a mixture of at least two compounds (tlc). It showed bands at 5.77, 6.88, 7.26, and 7.94 μ in the ir spectrum.

Registry No.—**10**, 34599-35-4; **11**, 34564-99-3; **12**, 34565-00-9; **13**, 34608-93-0; **15**, 34565-01-0; **17**, 34599-36-5; **19**, 34565-02-1; **21**, 34565-03-2; **22**, 34599-37-6; **27**, 34599-38-7; **28**, 34565-04-3; **29**, 34565-05-4; **30**, 34565-06-5; **31**, 34565-07-6; **32**, 34565-08-7; **33**, 34565-09-8; **35**, 34565-10-1; **36**, 34565-11-2; **37**, 34565-12-3; **39**, 34599-39-8; **40**, 34565-13-4; **41**, 34565-14-5; **42**, 34565-15-6; **43**, 34565-16-7; **44**, 34565-17-8; **45**, 34565-18-9; **46**, 34599-40-1; **47**, 34565-19-0; **48**, 34565-20-3.

Berlandin and Subacaulin, Two New Guaianolides from *Berlandiera Subacaulis*[1]

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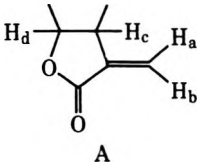
Received February 18, 1972

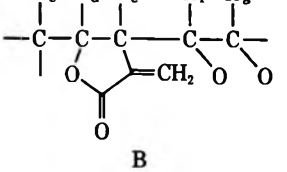
Two new guaianolides, berlandin and subacaulin, have been isolated from *Berlandiera subacaulis* (Nutt.) Nutt. Structure **2a** has been deduced for subacaulin. Berlandin is either **1a** or differs from acetylsubacaulin (**2b**) in configuration of the epoxide ring.

In the course of our investigations of subtribe Melampodiinae, tribe Heliantheae, family Compositae,[2] we are studying constituents of the North American genus *Berlandiera*.[3] The isolation and structure determination from *Berlandiera subacaulis* (Nutt.) Nutt. of two new guaianolides, which we have named berlandin and subacaulin, is reported herewith.

Berlandin (**1**), $C_{22}H_{26}O_7$ (high-resolution mass spectrum), mp 183–185°, $[\alpha]D$ +110.9°, was a conjugated γ lactone (ir bands at 1780 and 1670 cm^{-1}, very strong uv end absorption). The nmr spectrum (Table I) exhibited the characteristic doublets of H_a and H_b in partial structure A at 6.13 and 5.43 ppm. These signals were replaced by a new methyl doublet in the nmr spectrum of the tetrahydro derivative **3**. Irradiation at the frequencies of H_a and H_b established the location of H_c at 3.33 ppm in the usual fashion,[4] but the location of H_d, one of three protons in the region 3.6–5.8 ppm, could not be established unambiguously at this stage. Irradiation at the frequency of H_c did not affect a broad doublet at 5.59 ppm, but collapsed a triplet at 5.21 ppm to a doublet. The appearance of the broad doublet and the triplet suggested that the protons responsible for them were coupled to each other. Since the chemical shift of the signal at 5.21 ppm was too low for a proton under a lactone ether oxygen and since the nmr spectrum contained a doublet of doublets at 3.71 ppm,[5] it appeared very likely that A should be expanded



A



B

to B where H_d, H_f, and H_g are represented by the signals at 3.71, 5.21, and 5.59 ppm, respectively.

The ir spectrum of berlandin showed the presence of two additional carbonyl groups (bands at 1744 and 1722 cm^{-1}) which were attributed to ester functions,

(1) Supported in part by grants from the U. S. Public Health Service (GM-05814-13 and CA-13121-14) and Hoffmann-La Roche, Inc.

(2) The original impetus for these studies is given by W. Herz, S. V. Bhat, and A. L. Hall, *J. Org. Chem.*, **35**, 1110 (1970).

(3) D. J. Pinkava, *Brittonia*, **19**, 285 (1967).

(4) W. Herz, S. Rajappa, M. V. Lakshmikantham, and J. J. Schmid, *Tetrahedron*, **22**, 693 (1966).

(5) This partially overlapped the H_c resonance and could therefore not be decoupled satisfactorily.

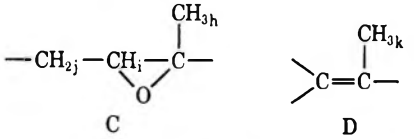
TABLE I

NMR SPECTRA OF BERLANDIN, SUBACAULIN, AND DERIVATIVES[a]

Compd	H-2	H-3	H-5	H-6	H-7	H-8	H-9	H-13	H-14[b]	H-15[b]	Ac[b]	H-3′	2-Me[b]	3′-Me[b]
1	2.89 d br[c] (18) 2.41 d br[c] (18)	3.42 br	3.32 d br[d] (10.7)	3.71 dd (10.7, 10)	3.33 m[d]	5.21 t[e] (10)	5.59 d br[c] (10)	6.13 d (3.1) 5.43 d (2.8)	1.64 br	1.68	1.99	6.25 dq	2.02 dq	1.87 m
2a	2.76 d br[c] (18) 2.45 d br[c] (18)	3.39 br	3.17 d br[d] (10)	3.64 t[e] (10)	3.03 m[d]	3.75 td[e,g] (9.8, 4.8)	5.42 d (9.8)	6.18 d[f,h]	1.59 br	1.65		6.10 m[f]	~2.0 m	1.95 m
2b	2.80 d br[c] (17) 2.49 d br[c] (17)	3.42 br	3.22 d br[d] (10)	3.69 t (10)	3.27 m[d]	5.14 t[e] (10)	5.62 d br[c] (10)	6.14 d[f] (3.0) 5.42 d (2.8)	1.63 br	1.68	2.04	6.19 m[f]	2.01 dq	1.87 m
3	2.77 d br[c] (18) 2.47 d br[c] (18)	3.40 br	3.07 d br (10.5)	3.65 dd (10.5, 9.5)	*i*	4.95 t[e] (10)	5.44 d br[c] (10)	1.19[b,i] (7)	1.60 br	1.69	2.06	*i*	1.30 d (7)[j]	0.93 t (7)
4a	*i*	3.40 br	3.04 t (10)	3.66 t[d] (10)	*i*	3.54 t[d] (10)	5.27 d br (10)	1.18 d[b,i] (7)	1.59 br	1.64		*i*	1.42 d[j] (7)	0.94 t (7)
4b	2.77 d br[c] (18) 2.47 d br[c] (18)	3.40 br	3.10 d br (10.5)	3.66 dd (10.9, 9.5)	*i*	4.95 t (10)	5.50 d br (10)	1.19 d[b,i] (7)	1.64 br	1.69	2.06	*i*	1.31 d[j] (7)	0.95 t (7)
5	2.47 d br[d] (16) *i*	3.46 br	2.50 d[d] (11)	3.88 dd (11, 10.6)	3.22 m	5.41 t[e] (10.6)	4.82 d (10.6)	6.20 d[f] (3.2) 5.53 d[e] (3.0)	1.36	1.72	2.01	6.3 m[f]	2.04 m	1.87 m
6	*i*	4.30 t[d] (10)	*i*	4.20 t[d] (10)	3.15 m	5.35 t[e] (8.5)	5.55 d br[c] (8.5)	6.27 d[e] (3.4) 5.66 d (3.0)	1.65 br	1.39	2.02[f]	6.27 m[e]	2.0 m[f]	1.88 m
7	*i*	4.18 d br (4.5)	3.07 d br[d] (10)	4.55 t (10)	3.24 m[d]	5.37 t[e] (8.5)	5.50 d br[c]	6.24 d[e] (3.4) 5.60 d (3.0)	1.73 br	1.89[f]	2.02[f]	6.3 m[e]	2.02 m[f]	1.89[f]

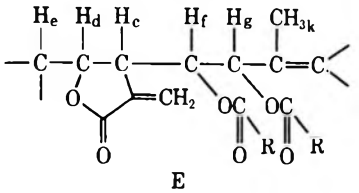
[a] Run at 90 MHz on a Bruker nmr spectrometer in $CDCl_3$ using TMS as internal standard. Chemical shifts are in parts per million. Signals are denoted in the usual way: d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened singlet. Unmarked signals are singlets. Figures in parentheses are line separations or coupling constants in hertz. [b] Three-proton signal. [c] AB part of more complex system. [d–f] Overlapping signals. [g] Collapses to triplet on D_2O exchange. [h] Two-proton signal. [i] Obscured. [j] Arbitrary assignment.

one conjugated, the other unconjugated, since the CD curve lacked the n,π^* transition of a ketone. Confirmation was provided by the nmr spectrum, which displayed the typical signals of an angeloyl group (one-proton multiplet at 6.25, vinyl methyl multiplets at 2.02 and 1.87 ppm).[6] These disappeared on reduction to **3** and were replaced by a new methyl doublet and a methyl triplet (Table I). The unconjuated ester was an acetate (molecular formula and nmr singlet at 1.99 ppm). The presence of the angeloyl and acetyl function was further shown by the high-resolution mass spectrum, which had peaks corresponding to M − C_2H_2O, M − $C_2H_4O_2$, M − C_5H_7O, and M − $C_5H_8O_2$ and a base peak at 83 corresponding to C_5H_7O. The seventh and last oxygen atom was ascribed to the presence of partial formula C (three-proton singlet of



C

D

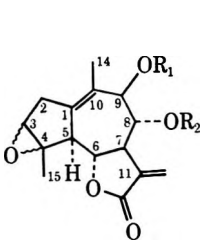


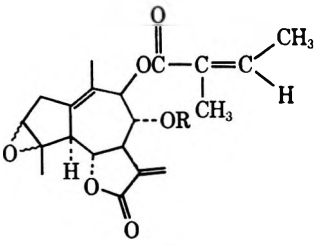
E

H_h at 1.68 ppm). Although H_i of C was a broad singlet at 3.42 ppm, its environment was clarified by treatment of berlandin with HCl–dioxane. This resulted in opening of the epoxide ring and formation of two isomeric chlorohydrins, **6** and **7**. In the nmr spectra of these compounds, H_i appeared as a sharp triplet or a broadened doublet, thus establishing the presence of a neighboring $-CH_2-$ group (H_j).[7]

The presence of partial structure D was indicated by a somewhat broadened three-proton signal (H_k) at 1.64 ppm which sharpened and moved upfield on epoxidation of berlandin to **5**. Since the number of low-field protons remained unaffected by this transformation, the double bond of D was tetrasubstituted. The only other significant alteration in the nmr spectrum of **5** was a sharpening and pronounced diamagnetic shift to 4.82 of the broad H_g doublet formerly at 5.59 ppm. It was reasonable to associate this change with the effect produced on an allylic proton by epoxidation of D; consequently, and in view of the presence of two ester functions, B and D were combined to give E.

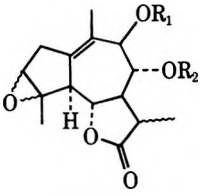
Irradiation of **5** at the frequency of H_e established the correctness of E by collapsing a triplet at 5.41, now logically assigned to H_f, and a doublet of doublets at 3.88 ppm, now logically assigned to H_d,[8] to doublets. Irradiation at 5.41 collapsed the doublet at 4.82 (H_g) and irradiation at 3.88 collapsed a doublet at 2.50 ppm (H_e). Combination of C and E then leads to the carbon skeleton of **1** because of the multiplicity of the



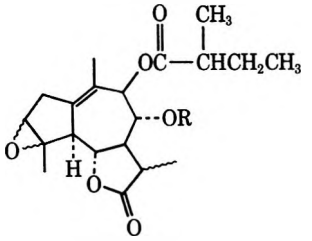


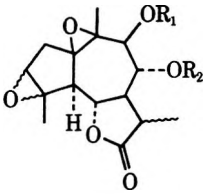
1a, R^1 = Angeloyl; R_2 = Ac
b, R^1 = Ac; R^2 = Angeloyl

2a, R = H
b, R = Ac



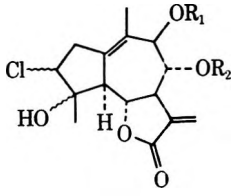
3a, R_1 = 2-methylbutyryl; R_2 = Ac
b, R_1 = Ac, R_2 = 2-methylbutyryl

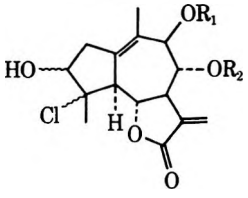




4a, R = H
b, R = Ac

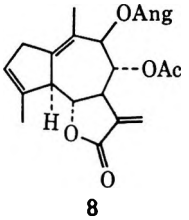
5a, R_1 = Ang; R_2 = Ac
b, R_1 = Ac; R_2 = Ang





6a, R_1 = Ang; R_2 = Ac
b, R_1 = Ac, R_2 = Ang

7a, R_1 = Ang, R_2 = Ac
b, R_1 = Ac; R_2 = Ang



8

H_e and H_j signals. Moreover, the upfield shift of these protons on conversion of **1** to **5** indicates that they, like H_g, are allylic as required by the formula.

This was confirmed by examining the nmr spectrum of **3**. In this spectrum the signal at 5.44 (H_g = H-9) and not the signals at 4.95 (H_f = H-8) and 3.65 ppm (H_d = H-6) was shown by double irradiation to be partially responsible for broadening of the C-10 methyl singlet. The existence of long-range coupling between H-14 (H_k) and H-5 (H_e), between H-14, H-2a, and H-2b and between H-9 and H-2b was also demonstrated and was consonant with the derived structure.

We defer consideration of the remaining problem of how to distribute the acetoxy and angeloxy residues over C-8 and C-9 until we have dealt with the structure of subacaulin (**2a**). This substance, $C_{20}H_{24}O_6$ (high-resolution mass spectrum), mp 160–162° dec, $[\alpha]_D$ +129.9°, polymerized at room temperature and dif-

(6) W. Herz and M. V. Lakshmikantham, *Tetrahedron*, **21**, 1711 (1965).

(7) In the nmr spectrum of **1**, H_i, H_{j1}, and H_{j2} appeared as an ABX system with H_i as a broad singlet at 3.42, and H_{j1} and H_{j2} as broadened doublets ($|J|$ = 18 Hz) at 2.89 and 2.41 ppm. The assignment was confirmed by spin decoupling.

(8) Nmr spectra of a large number of sesquiterpene lactones containing ester functions at C-6 or C-8 and at C-9 are now on record. Invariably, the resonance of the ester protons is found at lower field than the signal of the lactone proton.

fered from berlandin in having a free secondary hydroxyl group instead of an acetate function. This was evidenced by the empirical formula and the mass spectrum, which had peaks at M − C_5H_7O and M − $C_5H_8O_2$ and the base peak at 83. The nmr spectrum was similar to that of berlandin but lacked the sharp acetate singlet and had a triplet (after D_2O exchange) characteristic of HCOH at 3.75 instead of at 5.21 ppm (Table I). Double irradiation showed that this triplet was coupled to H-7 and H-9. Hence the free hydroxyl group was located at H-8[9] and subacaulin possesses formula **2a**.

Acetylation of subacaulin furnished a monoacetate **2b**, mp 154–156°, whose tlc behavior, rotation, and ir spectrum were practically identical with those of berlandin but whose nmr spectrum differed reproducibly in minor, but significant detail from that of **1** (Table I). Again, the optical and spectral properties of acetyltetrahydrosubacaulin (**4b**) and tetrahydroberlandin (**3**) were exceedingly similar, but the compounds were not identical. On this basis the conclusion lay near that berlandin probably differed from **2b** in having the acetoxyl and angeloxyl groups interchanged as in **1b**.

Attempts to settle this question by partial hydrolysis of berlandin were generally frustrated, although one run employing sodium carbonate–methanol treatment of berlandin resulted in isolation of a fraction containing an inseparable mixture of desacetyl derivatives (ir and nmr spectrum). In the nmr spectrum of the mixture, the signal apparently corresponding to H-8 had moved upfield to *ca.* 3.7 ppm while, more significantly, the signals of H-13a and H-13b had coalesced. This definitely suggested[11] that the free hydroxyl group of the hydrolysate was at C-8 and that the acetate function of berlandin had originally been attached to C-8 as in **1a**. On this basis berlandin and acetylsubacaulin would have to be epimers. On the other hand the possibility of an acyl migration from C-8 to C-9 or a relactonization from C-6 to C-8[13] during the K_2CO_3 treatment of berlandin, which would also account for the nmr spectrum of the hydrolysate, could not be excluded.

In the following we briefly consider the stereochemistry of **1** and **2a**. If the assumption be made that the C-7 side chain of berlandin is equatorial and β as in all guaianolides of established absolute configuration, the lactone ring fusion is trans and H-6 is β because of the magnitude of $J_{6,7}$ (10 Hz). The magnitude of $J_{7,8}$ (10 Hz) requires that H-7 and H-8 be cis if the seven-membered ring is a boat, and trans if the seven-membered ring is a chair. Dreiding models indicate that H-6 and H-9 interact strongly in the former and H-6 and H-8 in the latter case. Experimentally the existence of a strong (18%) nuclear Overhauser effect between H-6 and H-8 shows[15] that H-8 is β.

The values of $J_{5,6}$ (10.7 Hz) and $J_{8,9}$ (10.0 Hz) require a trans relationship of H-5 and H-6 on the one hand and H-8 and H-9 on the other; hence H-5 and H-9 are both α. Inspection of the model indicates that this forces H-5, H-7, and H-9 into close proximity and indeed an appreciable NOE between H-5 and H-9 (18%) was found.[16] The epoxide ring is constrained to be cis, by virtue of its attachment to a five-membered ring. However, the absolute stereochemistry at C-3 and C-4 remains in doubt because the observed coupling constants between H-2 and H-3 (Table I) are satisfied in both the α and β orientation of the epoxide ring (model).

Since the nmr spectra of berlandin and acetylsubacaulin exhibit almost identical coupling constants and chemical shifts, we conclude that the configurations of these compounds at C-5, C-6, C-7, C-8, and C-9 are identical. If berlandin possesses formula **1a**, the difference between berlandin and acetylsubacaulin must lie in the configuration at C-3 and C-4. Although this should not affect the coupling constants appreciably, one might expect somewhat greater differences in the chemical shifts of certain signals than are actually observed (model). In that case deoxygenation of berlandin and acetylsubacaulin should produce the same guaianolide **8**; however, an attempt to carry out this transformation by treatment with zinc–copper couple[17] failed.[18] If berlandin possesses formula **1b**, the close coincidence in the nmr spectra suggests that configurations of **1b** and **2b** at C-3 and C-4 are the same. A solution to the dilemma will be sought when more berlandin becomes available.

Experimental Section[19]

Isolation of Berlandin and Subacaulin.—Above ground parts of *Berlandiera subacaulis* (Nutt.) Nutt., wt 15.2 kg, collected by Mr. Robert Lazor on July 19, 1969, 6 miles west of Steinhatchee, Taylor County, Florida (Lazor voucher #3736 on deposit in herbarium of Florida State University), was extracted with chloroform and worked up in the usual manner.[20]

The crude gum, wt 45 g, was chromatographed over 1 kg of silicic acid (Mallinckrodt 100 mesh), 1-l. fractions being collected in the following order: 1–15 (benzene), 16–30 (benzene–chloroform, 3:1), 31–45 (benzene–chloroform, 1:1), 46–60 (benzene–chloroform, 1:3), 61–80 (chloroform), 81–95 (chloroform–methanol, 97:3), 96–110 (chloroform–methanol, 19:1), 111–125 (chloroform–methanol, 9:1). Fractions 32–41, which showed a major spot on tlc, were combined and recrystallized from ethyl acetate–hexane to give 1.4 g of pure berlandin. Fractions 47–55 on recrystallization from ethyl acetate–hexane gave 4.3 g of subacaulin. All other fractions were gums showing several spots.

Pure berlandin (**1**) had mp 183–185°; $[\alpha]^{20}D$ +110.9° (*c* 2.8); ir bands at 1780, 1748, 1722, 1670, and 1742 cm^{-1}; uv end ab-

(9) Table I contains an additional item which provides conspicuous evidence for the location of the hydroxyl group at C-8 and for its α orientation (*vide infra*). Comparison of the spectra of **2a** and **2b** reveals that acetylation is accompanied by a large diamagnetic shift of H-13a Such a shift is characteristic of an 8α-oriented hydroxyl group in eudesmanolides and guaianolides[10,11] and, to a somewhat lesser degree, in pseudoguaianolides.[11,12]

(10) See, for example, M. A. Irwin and T. A. Geissman, *Phytochemistry*, **10**, 637 (1971); **8**, 305 (1969).

(11) H. Yoshioka, T. J. Mabry, M. A. Irwin, T. A. Geissman, and Z. Samek, *Tetrahedron*, **27**, 3317 (1971).

(12) N. F. Fischer and T. J. Mabry, *ibid.*, **23**, 2529 (1967).

(13) Germacranolides containing α-oriented lactonizable groups at C-6 and C-8 preferentially lactonize toward C-8.[14] Lactone ring orientation in the guaianolide series under basic conditions is well-known but the factors determining the preferential direction of ring closure are not defined.

(14) H. Yoshioka, W. Renold, and T. J. Mabry, *Chem. Commun.*, 148 (1970).

(15) Tetrahydroberlandin was used for the NOE experiments because the signals of H-5, H-6, H-8, and H-9 were well separated and since inspection of the models showed that the relative orientation of these protons and of H-7 did not differ significantly in berlandin and tetrahydroberlandin.

(16) Since the H-7 resonance was obscured in **1** and superimposed on the signal of H-5 in **5**, the NOE'S involving H-7 could not be investigated experimentally.

(17) S. M. Kupchan and M. Maruyama, *J. Org. Chem.*, **36**, 1187 (1971).

(18) Prolonged exposure (1 week) to the reagent in ethanol solution resulted not in deoxygenation but in partial opening of the epoxide ring.

(19) Experimental conditions specified by W. Herz, S. V. Bhat, and A. L. Hall, *J. Org. Chem.*, **35**, 110 (1970), apply. High-resolution mass spectra were run at 70 meV on a MS-902 high resolution mass spectrometer.

(20) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).

sorption at 207 nm (ε 25,800); CD curve λ_{max} 246 nm (θ +1377, c 1.02). The high resolution mass spectrum exhibited a very weak M^+ peak.

Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51; O, 27.83; mol wt, 402.1678. Found: C, 65.80; H, 6.58; O, 27.79; mol wt, 402.1682.

Subacaulin (2a) had mp 160–162°; $[\alpha]^{20}D$ +129.9° (*c* 2.1); ir bands at 3582, 3520, 1770, 1720, 1670, and 1644 cm^{-1}; CD curve λ_{max} 249 nm (θ +2226, *c* 0.56); it polymerized on standing. The high resolution mass spectrum exhibited a weak M^+ peak (0.4%).

Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71; O, 26.64; mol wt, 360.1571. Found: C, 67.04; H, 6.85; O, 26.16; mol wt, 360.1558.

Acetylsubacaulin (2b).—Acetylation of 0.2 g of 2a with 1 ml of acetic anhydride and 2 ml of pyridine overnight at room temperature followed by the usual work-up gave a gum which showed one major and two minor spots on tlc. Repeated preparative tlc resulted in homogeneous, crystalline material which had mp 154–156°; ir bands (KBr) at 1775, 1748, 1715 (split), 1662, and 1630 cm^{-1}; $[\alpha]^{26}D$ +110.6° (*c* 1.85).

Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51; O, 27.83; mol wt, 402.1679. Found: C, 65.25; H, 6.62; O, 27.61; mol wt, 402.1686.

Tetrahydroberlandin (3).—A solution of 78 mg of berlandin in 20 ml of ethyl acetate was reduced catalytically with 58 mg of 5% Pd–C in an atmosphere of hydrogen for 5 hr. The filtered solution was evaporated *in vacuo*, and the residue was purified by preparative tlc and recrystallized from ethyl acetate–hexane: yield 48 mg; mp 130–132°; ir bands at 1778, 1745, 1735, and 1645 cm^{-1}.

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44; O, 27.55; mol wt, 406.1991. Found: C, 65.33; H, 7.40; O, 27.21; mol wt, 406.1991.

Tetrahydroacetylsubacaulin (4b).—Hydrogenation of 60 mg of 2b in the manner described for berlandin and purification by preparative tlc gave 58 mg of a gum, ir bands at 1778, 1740, 1735, and 1650 cm^{-1}. The gum did not give a satisfactory elemental analysis, but its mass spectrum exhibited a relatively weak (1.2%) molecular ion of the correct composition. Other significant peaks in the high-mass region corresponded to the loss of C_2H_4 (1.4%), C_2H_2O (1%), C_2H_3O (1.5%), C_2H_4O (1.4%), and $C_2H_4O_2$ (14.0%); base peak $C_5H_9O^+$.

Anal. Calcd for $C_{22}H_{30}O_7$: mol wt, 406.1990. Found: mol wt, 406.1979.

Tetrahydrosubacaulin (4a).—Hydrogenation of 102 mg of 2a, purification by preparative tlc, and recrystallization from ethyl acetate–hexane afforded 80 mg of 4b, mp 165–168°, ir bands at 3500, 1770, 1735, and 1640 cm^{-1}. The mass spectrum exhibited a weak molecular ion (0.7%); the next three peaks were also weak and corresponded to M − H_2O (0.2%), M − C_5H_8O (0.6%), and M − C_5H_9O (1.0%).

Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74; O, 26.34; mol wt, 364.1884. Found: C, 65.54; H, 7.72; O, 26.23; mol wt, 364.1886.

Berlandin Epoxide (5).—A solution of 0.1 g of 1 and 75 mg of *m*-chloroperbenzoic acid in 3 ml of chloroform was left overnight and worked up in the usual manner. Purification of the product by preparative tlc and recrystallization of the major fraction from ethyl acetate–hexane afforded 46 mg of 5, mp 228–232° dec, ir bands at 1775, 1750, 1720, 1665, and 1640 cm^{-1}.

Anal. Calcd for $C_{22}H_{28}O_8$: C, 63.15; H, 6.28; O, 30.59. Found: C, 63.46; H, 6.28; O, 29.90.

Reaction of Berlandin with HCl.—A mixture of 102 mg of 1, 5 ml of dioxane, and 0.2 ml of concentrated HCl was stirred at room temperature for 2 days and concentrated at reduced pressure. The residue was purified by preparative tlc. The less polar fraction (6) was recrystallized from ethyl acetate–hexane: yield 80 mg; mp 144–145°; ir bands at 3662, 3580, 1775, 1740, 1720, 1662, and 1642 cm^{-1}. Since the material was recovered unchanged after attempted acetylation with acetic anhydride–pyridine at room temperature, the hydroxyl group was assumed to be tertiary.

Anal. Calcd for $C_{22}H_{27}O_7Cl$: C, 60.10; H, 6.10; Cl, 8.20. Found: C, 60.58; H, 6.27; Cl, 7.96.

The more polar fraction (7) was recrystallized from ethyl acetate–hexane: yield 10 mg; mp 200–202°; ir bands at 3670, 3590, 3450, 1770, 1745, 1720, 1662, and 1645 cm^{-1}.

Anal. Calcd for $C_{22}H_{27}O_7Cl$: C, 60.10; H, 6.10; Cl, 8.20. Found: C, 59.97; H, 6.24; Cl, 7.93.

Registry No.—1, 34829-00-0; 2a, 34837-46-2; 2b, 34837-47-3; 3, 34829-01-1; 4a, 34837-48-4; 4b, 34837-49-5; 5, 34829-02-2; 6, 34829-03-3; 7, 34829-04-4.

Neighboring Group Participation in Carbohydrate Chemistry. III.[1] Neighboring Group Participation of the 6-Hydroxyl Group in a Nucleophilic Displacement of a 5-*p*-Toluenesulfonate[2a]

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Received September 20, 1971

The neighboring group participation of a 6-hydroxyl group in the nucleophilic displacement of a 5-*p*-tolylsulfonyl group by acetate in a model compound, 1,2-*O*-isopropylidene-3,5-di-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (3), was investigated. The conversion of 3 into 6-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose (5) by refluxing a solution of 3 in *N*,*N*-dimethylformamide containing anhydrous potassium acetate was assumed to proceed *via* a transition state or an intermediate involving the protonated 5,6-anhydro derivative 12. The solvent dependence of the reaction was studied. Solvolysis of 3 in *N*,*N*-dimethylformamide, in the presence and absence of $CaCO_3$, yielded 6-*O*-formyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose (13). A mechanism for this reaction, which probably involves the neighboring group participation of the hydroxyl group, is proposed.

The hydroxyl group in its un-ionized form has generally been considered to have a low driving force for neighboring group participation,[3,4] and there are only a few examples reported in the carbohydrate literature where such participation could be assumed.[5,6] However, the alkoxide anion is known[7] as a good par-

(1) Part II: M. Miljković, D. Miljković, A. Jokić, V. Andrejević, and E. A. Davidson, *J. Org. Chem.*, **36**, 3218 (1971).

(2) (a) This work was supported by Grant AM12074 from the National Institute of Arthritis and Metabolic Diseases, National Institute of Health, U. S. Public Health Service. (b) To whom all correspondence should be addressed. (c) Department of Chemistry, Faculty for Natural and Mathematical Sciences, Novi Sad, Yugoslavia.

(3) S. Winstein and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 828 (1948).

(4) L. Goodman, *Advan. Carbohyd. Chem.*, **22**, 112 (1967).

(5) B. Capon and D. Thacker, *J. Amer. Chem. Soc.*, **87**, 4200 (1965).

(6) J. W. Green and E. Pascu, *ibid.*, **59**, 1205 (1937).

(7) S. Winstein and H. J. Lucas, *ibid.*, **61**, 1576 (1939); A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, p 291.

ticipating group. During our studies on the neighboring group participation of various functional groups at the C-6 carbon atom in nucleophilic displacements of a 5-*p*-toluenesulfonate,[1,8] some interesting observations regarding the participation of the C-6 hydroxyl group have been made; the results obtained are described in this manuscript.

Results

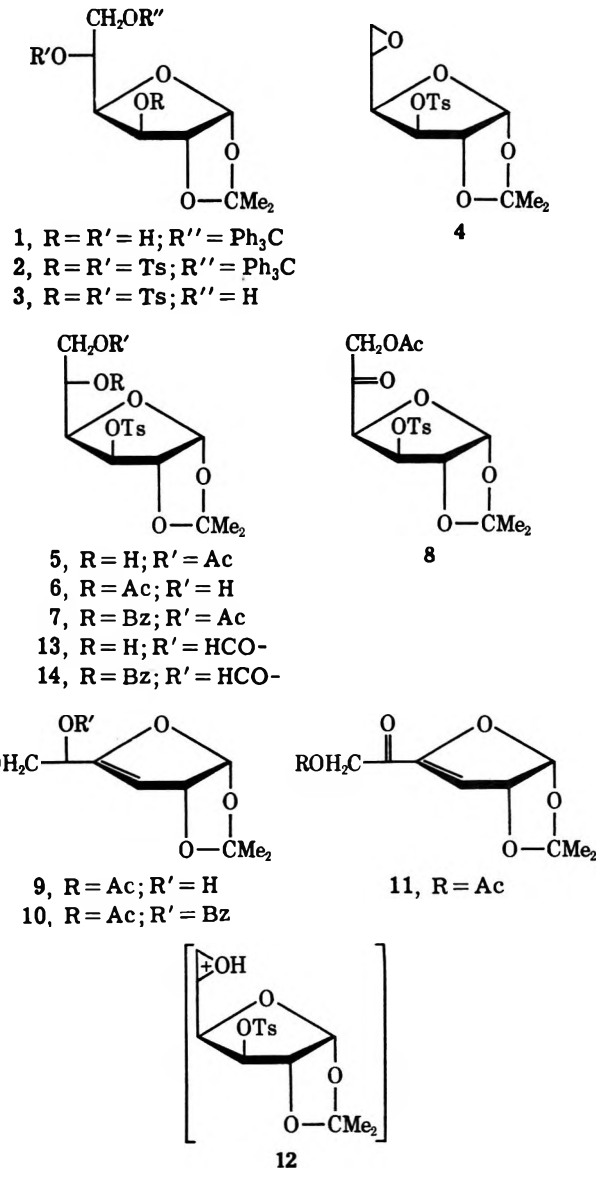
As a model compound for our studies, 1,2-*O*-isopropylidene-3,5-di-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (**3**) was synthesized according to the following scheme. Tosylation of 1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-glucofuranose (**1**)[9] with *p*-tolylsulfonyl chloride in pyridine afforded the corresponding 3,5-di-*O*-*p*-tolylsulfonyl derivative **2** (96%), which was smoothly detritylated with hydrobromic acid in glacial acetic acid at 0° to give compound **3** (73%).

Refluxing of an acetonitrile solution of **3** with anhydrous potassium acetate for 10 days afforded three products, in addition to a small amount of starting material.

The first product (**4**), isolated in 53% yield, was identified as 5,6-anhydro-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose,[10] by comparison (ir and nmr spectra) with an authentic sample synthesized according to the procedure of Meyer and Reichstein.[10]

The second product (**5**) (32%) showed (ir and nmr spectra) in addition to the 1,2-*O*-isopropylidene group (two three-proton singlets at δ 1.48 and 1.30), the presence of a hydroxyl group (broad peak at 3590 cm^{-1}), one acetoxy group (1735 and 1245 cm^{-1}, C=O and CO stretch vibrations; a three-proton singlet at δ 2.05), and one *p*-tolylsulfonyl group (1192 and 1180 cm^{-1}, SO_2-symmetrical stretch vibration; three-proton singlet at δ 2.45). Since it was known from previous studies[8a,11] that the 3-*O*-*p*-tolylsulfonyl group is unreactive toward nucleophilic displacements in 1,2-*O*-isopropylidine-α-D-glucofuranose derivatives, the C-3 carbon atom was considered to be an unlikely location for the acetoxy group which was introduced during the course of the reaction. In order to determine whether the acetoxy group was on C-6 (most likely) or C-5, compound **5** was oxidized with RuO_4. The ir spectrum of the oxidation product **8** indicated the presence of two chemically nonequivalent carbonyl groups (1742 and 1732 cm^{-1}), and lacked an absorption in the region expected for a hydroxyl group. The peak at 1742 cm^{-1} was apparently the C=O stretch absorption of the acetoxy carbonyl group, whereas the peak at 1732 cm^{-1} was typical for a carbonyl group having an electron-withdrawing substituent in the α position, in this case, presumably due to an oxygen atom.[12] The nmr spectrum of compound **8** showed the absence of an aldehydic proton, thus excluding the carbonyl group from the terminal C-6 position. The significant downfield shift of resonance signals for H-4, H-6, and H′-6 in **8** (0.5–1.0 ppm), as compared to the chemical shifts of the same protons in **5** (an unresolved multiplet at δ 3.9–4.4), the absence of the resonance signal for the H-5 proton, and the presence of an acetoxy group in the nmr spectrum of **8**, could be explained only if the structure of the oxidation product **8** were 6-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-xylohexofuran-5-ulose.[8a] This suggests that the acetyl group of the parent monoacetyl derivative **5** is attached to the C-6 carbon atom and that the correct structure for **5** is 6-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose.[8a] The above conclusions, derived from the spectroscopic data, were confirmed chemically as follows. Compound **5** could also be obtained by treatment of the 5,6-anhydro derivative **4** with anhydrous potassium acetate in refluxing *N*,*N*-dimethylformamide, and, in addition, the benzoylation of **5** with benzoyl chloride in pyridine gave the known 6-*O*-acetyl-5-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose.[8,13]

The structure of the third product (**9**) (3%) was deduced from the following observations. It was evident from the ir and nmr spectra that **9** had lost



(8) (a) M. Miljković, A. Jokić and E. A. Davidson, *Carbohyd. Res.*, **17**, 155 (1971); (b) M. A. Miljković and E. A. Davidson, *ibid.*, **13**, 444 (1970).

(9) C. T. Bishop, *Can. J. Chem.*, **35**, 61 (1957).

(10) A. S. Meyer and T. Reichstein, *Helv. Chim. Acta*, **29**, 152 (1946).

(11) M. L. Wolfrom, J. Bernsmann, and D. Horton, *J. Org. Chem.*, **27**, 4505 (1962).

(12) N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., and London, 1964, pp 241–242, and literature cited therein.

(13) R. C. Chalk, D. H. Ball, M. A. Lintner, and L. Long, Jr., *Chem. Commun.*, 245 (1970); R. C. Chalk, D. H. Ball, and L. Long, Jr., *Carbohyd. Res.*, **20**, 151 (1971).

both *p*-tolylsulfonyl groups, and that a hydrogen-bonded hydroxyl group (3580 and 3450 cm^{-1}) was present; one acetoxy group (1732 and 1250 cm^{-1}; three-proton singlet at δ 2.03) and a trisubstituted double bond (1664 and 823 cm^{-1}; one-proton singlet at δ 5.21) were also identified. The significant downfield shift of the H-2 resonance signal in **9** (0.4–0.6 ppm), as compared to the chemical shift for H-2 in **5** (δ 4.73) could be accounted for if one assumes that the double bond, present in **9**, is located between carbon atoms **3** and **4**, since in that case H-2 would be in an allylic position and should absorb at lower magnetic field strength. Furthermore, the formation of an endocyclic (C-3–C-4) double bond would also be in accordance with our previous findings[8a] that 6-*O*-benzoyl-1,2-*O*-isopropylidene-3,5-di-*O*-*p*-tolylsulfonyl-α-D-glucofuranose eliminates the 3-*O*-*p*-tolylsulfonyl group relatively easily to give the C-3–C-4 double bond. The oxidation of **9** with MnO_2 in carbon tetrachloride at room temperature afforded **11**, the ir spectrum of which showed an acetoxy group (1742 cm^{-1}), a carbonyl group (1720 cm^{-1}), and a trisubstituted double bond (1630 and 825 cm^{-1}). The uv spectrum of **11** exhibited an absorption maximum at 266 nm (ϵ 1300), indicating conjugation of the carbonyl group with a trisubstituted double bond. A structure which would be compatible with the above spectroscopic data would be 6-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidenehex-3-enefuran-5-ulose.[14] This suggests that the structure of the parent olefinic sugar **9** is 6-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-β-L-*threo*-hex-3-enofuranose,[8a] a conclusion which was subsequently proven chemically since benzoylation of **9** yielded the known 6-*O*-acetyl-5-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-β-L-*threo*-hex-3-enofuranose (**10**).[8a]

Treatment of compound **3** with anhydrous potassium acetate in refluxing *N*,*N*-dimethylformamide for 50 min gave the same three products, in addition to a small amount of starting material (3%). The yield of the 5,6-anhydro derivative **4** was slightly decreased (49%) and the yield of the monohydroxy derivative **5** was unaffected (32%), whereas the yield of the olefinic sugar **9** was increased twofold (6%).

Refluxing compound **3** in pure *N*,*N*-dimethylformamide,[17] or in the presence of anhydrous $CaCO_3$, for 50 min gave, in addition to large amounts of starting material (72 and 59%, respectively), two products. The less polar fraction, isolated in very small yield (3 and 8%, respectively) was identified (ir and nmr spectra) as the 5,6-anhydro derivative **4**, whereas the more polar fraction (7 and 8%, respectively) was a new product, **13**, not previously observed. The ir spectrum of **13** showed the presence of a hydroxyl group (3600 cm^{-1}), a carbonyl (an ester group) (1720 cm^{-1}), and a *p*-tolylsulfonyl group (1191 and 1179 cm^{-1}). The nmr spectrum clearly showed the presence of only one *p*-tolylsulfonyl group (three-proton singlet at δ 2.50, Me from Ts). Except for the lack of the resonance signal for the acetate methyl group at δ 2.05, the general appearance of the nmr spectrum of **13** resembled very much that of **5**, suggesting that compound **13** may also be a 1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose derivative. This was supported by the fact that hydrolysis of **13** afforded the known 1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose[8a] (identical ir and nmr spectra with an authentic sample). Since there was a one-proton singlet at δ 8.03 in the nmr spectrum of **13**, which is typical for formate esters,[18] it was assumed that **13** might be 6-*O*-formyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose. In order to substantiate this an *N*,*N*-dimethylformamide solution of the 5,6-anhydro derivative **4** was refluxed with anhydrous sodium formate in the presence of catalytic amounts of formic acid. A product identical with **13** (ir and nmr spectra) was obtained (11%). Since it is known[8a] that the acetate anion opens the 5,6-oxirane ring in **4**, under similar experimental conditions, by attacking the less substituted 6 carbon atom, it was concluded that compound **13** must be 6-*O*-formyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose. Benzoylation of **13** with benzoyl chloride in pyridine afforded the 5-*O*-benzoyl-6-*O*-formyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose (**14**) (86%).

The 6-*O*-formyl derivative **13** had to be characterized as the 5-*O*-benzoyl derivative **14**, since, unlike the other C-6 acylated derivatives (6-*O*-acetyl and 6-*O*-benzoyl) of 1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose, it hydrolyzes very easily.

Discussion

The formation of 5,6-anhydro derivative **4** and 6-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose (**5**) on refluxing a *N*,*N*-dimethylformamide or acetonitrile solution of 1,2-*O*-isopropylidene-3,5-di-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (**3**) with anhydrous potassium acetate suggests that the nucleophilic displacement of the 5-tosylate with acetate in **3** proceeds *via* the neighboring group participation of the 6-hydroxyl group. Whether this participation occurs with the 6-hydroxyl group in its un-ionized form, or in the form of an alkoxide anion, cannot be determined on the basis of the available experimental results.

The reaction of the 5,6-anhydro derivative **4** with anhydrous potassium acetate in refluxing *N*,*N*-dimethylformamide affords **5** in 12% yield, whereas refluxing an *N*,*N*-dimethylformamide solution of **4** with anhydrous potassium acetate in the presence of acetic acid affords **5** in 38% yield. Since heating of an *N*,*N*-dimethylformamide solution of **3** with anhydrous potassium acetate under reflux gives **5** in 32% yield, it is apparent that the conversion of **4** to **5** requires protonation of **4** with acetic acid either in transition state, or with the formation of **12** as an intermediate, prior to the nucleophilic opening of the 5,6-oxirane ring.

(14) The calculated absorption maxima for the above compound would be 262 nm,[15,16] which is in fair agreement with the experimentally determined value; the estimated molar extinction coefficient, ϵ 1300, is, however, lower than expected, possibly due to impurities present in the sample.

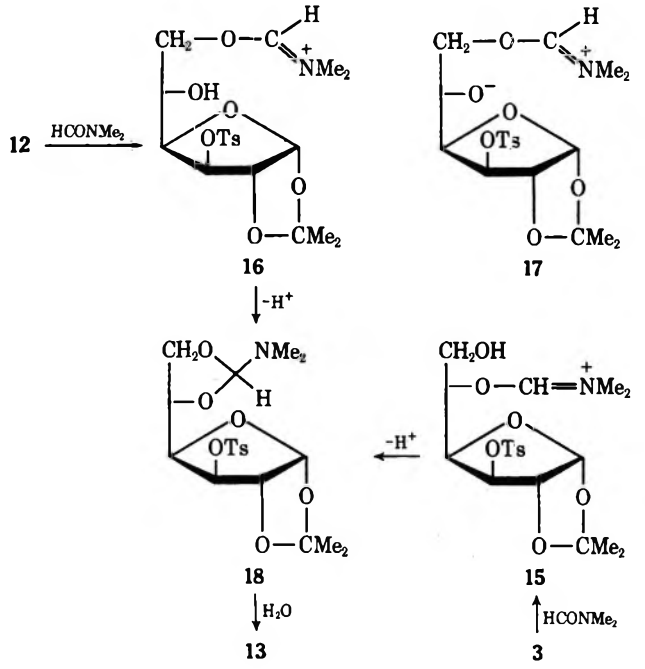
(15) R. B. Woodward, *J. Amer. Chem. Soc.*, **63**, 1123 (1941); **64**, 72, 76 (1942).

(16) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 19.

(17) *N*,*N*-Dimethylformamide used for our studies was analyzed by mass spectrometry for formic acid content. It was found that the formic acid content must be less than 0.16%, and may be zero.

(18) "High Resolution NMR Spectra Catalog," compiled by N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 9; N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 77.

The formation of 6-*O*-formyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose (**13**) on refluxing of **3** in pure *N*,*N*-dimethylformamide, or in the presence of $CaCO_3$, can be formulated as follows. Since it is known that *N*,*N*-dimethylformamide has considerable nucleophilic character with a partial negative charge located at the oxygen atom,[19] it is plausible to assume that *N*,*N*-dimethylformamide could either directly displace the 5-*O*-*p*-tolylsulfonyl group in **3** to give **15**,



or it could open the oxirane ring in **4** and/or the protonated oxirane ring in **12** by attacking the C-6 carbon atom to give **16** and/or **17**. All three charged intermediates (**15**, **16**, and **17**) thus obtained could be easily stabilized by cyclizing into the *N*,*N*-dimethylaminoorthoformate intermediate **18**, which on hydrolysis (on silica gel, or in the presence of water) would lose dimethylamine and give **13** as the sole product. The nucleophilic opening of the oxirane ring in **4** by *N*,*N*-dimethylformamide can be, however, excluded since it was found that the 5,6-anhydro derivative **4** does not react when refluxed in *N*,*N*-dimethylformamide with or without $CaCO_3$.

Experimental Section

General.—The silica gel used for all column chromatographies was E. Merck (Damstadt, Germany) silica gel, grain size <0.08 mm. The melting points are uncorrected. Optical rotations were determined with a Cary 60 spectropolarimeter in a 1.0-cm cell. The ir spectra were recorded with a Perkin-Elmer infrared spectrophotometer model 337, and nmr spectra with a Varian T-60 spectrometer with tetramethylsilane as the internal standard. Chemical shifts (δ) are expressed in parts per million.

1,2-*O*-Isopropylidene-3,5-di-*O*-*p*-tolylsulfonyl-6-*O*-triphenylmethyl-α-D-glucofuranose (2).—A chloroform solution (100 ml) containing *p*-toluenesulfonyl chloride (16.0 g, 84 mmol) was added to a pyridine solution (100 ml) of 1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-glucofuranose (**1**) (8.0 g, 17 mmol), and the reaction was allowed to proceed for 5 days at 37°. The reaction mixture was then poured into 2 l. of ice–water and extracted with chloroform. The chloroform extract was evaporated *in vacuo* and the crude material (14.60 g) was chromatographed on silica gel (300 g). Elution with 95:5 benzene–2-propanol gave pure **2** (13.94 g, 96%): mp 82–85°; $[\alpha]^{27}D$ +193° (*c* 0.1, $CHCl_3$); ir ($CHCl_3$) 3010 (aromatic CH), 1600 (aromatic C=C), 1190 and 1180 cm^{-1} (Ts, sym SO_2 stretch); nmr ($CDCl_3$) δ 7.9–7.0 (m, 23, one trityl and two Ts groups), 5.71 (d, $J_{1,2}$ = 3.6 Hz, 1, H-1), 4.96 (d, $J_{3,4}$ = 2.8 Hz, 1, H-3), 4.81 (d, $J_{1,2}$ = 3.6 Hz, 1, H-2), *ca.* 4.81 (d, 1, H-4), *ca.* 4.58 (m, 1, H-5), 3.31 (d, $J_{5,6}$ = 4.8 Hz, 2, H-6 and H′-6), 2.45 and 2.40 (two s, 6, Me of Ts), 1.40 and 1.25 (two s, 6, Me of Ip).

Anal. Calcd for $C_{42}H_{42}O_{10}S_2$: C, 65.44; H, 5.49; S, 8.32. Found: C, 65.20; H, 5.29; S, 8.45.

1,2-*O*-Isopropylidene-3,5-di-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (3).—Compound **2** (12.83 g, 16 mmol) was dissolved in glacial acetic acid (55 ml) and the resulting solution was treated with freshly prepared 40% HBr in acetic acid (5.48 g) for 45 sec. The precipitate (triphenylmethyl bromide) was removed by filtration and the filtrate was poured into 1 l. of ice–water. The emulsion was extracted with chloroform and the chloroform extract was dried over anhydrous $MgSO_4$. The crude product obtained after removal of chloroform *in vacuo* (8.80 g) was chromatographed on silica gel (300 g). Elution with 95:5 benzene–2-propanol afforded pure **3** (6.36 g, 72%) as an oil: $[\alpha]^{27}D$ −15.2° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 3575 (broad peak, hydrogen bonded OH), 3010 (aromatic CH), 1600 (aromatic C=C), 1195 and 1183 cm^{-1} (Ts, sym SO_2 stretch); nmr ($CDCl_3$) δ 8.0–7.2 (m, 8, two Ts), 5.83 (d, $J_{1,2}$ = 3.6 Hz, 1, H-1), 5.00 (d, $J_{3,4}$ = 3.0 Hz, 1, H-3), 4.76 (d, $J_{1,2}$ = 3.6 Hz, 1, H-2), 4.8–4.6 (m, 1, H-5), 4.40 (m, $J_{3,4}$ = 3.0 and $J_{4,5}$ = 6.0 Hz, 1, H-4), *ca.* 3.8 (m, 2, H-6 and H′-6), 2.46 (s, 6, Me from Ts), 1.43 and 1.26 (two s, 6, Me from Ip).

Anal. Calcd for $C_{23}H_{28}O_{10}S_2$: C, 52.26; H, 5.34; S, 12.13. Found: C, 52.00; H, 5.33; S, 11.89.

Treatment of 1,2-*O*-isopropylidene-3,5-di-*O*-*p*-tolylsulfonyl-α-D-glucofuranose with Potassium Acetate in Acetonitrile under Reflux.—An acetonitrile solution (75 ml) containing **3** (1.80 g, 3 mmol) was treated with anhydrous potassium acetate (930 mg, 9 mmol) under reflux for 10 days. At the end of the third and sixth day, additional amounts (930 mg) of anhydrous potassium acetate were added. When the reaction was terminated, the suspension was filtered, and the filtrate was evaporated *in vacuo* to dryness. The crude product (1.50 g) was chromatographed on silica gel (100 g). Elution with 95:5 benzene–2-propanol gave as the first fraction the 5,6-anhydro derivative **4** (652 mg, 53%) as an oil: $[\alpha]^{27}D$ +81° (*c* 0.1, $CHCl_3$); ir ($CHCl_3$) 3015 (aromatic CH), 1595 (aromatic C=C), 1192 and 1180 (sym SO_2 stretch, Ts), 870 cm^{-1} (sym C–O–C stretch, monosubstituted oxirane ring); nmr ($CDCl_3$) δ 7.9–7.2 (m, 4, Ts), 5.95 (d, $J_{1,2}$ = 3.8 Hz, 1, H-1), 4.88 (d, $J_{3,4}$ = 3.0 Hz, 1, H-3), 4.62 (d, $J_{1,2}$ = 3.8 Hz, 1, H-2), 3.87 (m, $J_{3,4}$ = 3.0 and $J_{4,5}$ = 5.7 Hz, 1, H-4), 3.2–2.9 (m, 1, H-5), 2.7–2.3 (m, 2, H-6 and H′-6), 2.46 (s, 3, Me from Ts), 1.43 and 1.27 (two s, 6, Me from Ip).

Anal. Calcd for $C_{16}H_{20}O_7S$: C, 53.93; H, 5.66; S, 9.00. Found: C, 53.74; H, 5.47; S, 9.18.

The second fraction obtained was 6-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-iodofuranose (**5**) (452 mg, 32%) as an oil: $[\alpha]^{27}D$ −24.7° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 3600 (broad peak, hydrogen bonded OH), 3010 (aromatic CH), 1735 (acetate C=O), 1600 (aromatic C=C), 1230 (acetate C–O), 1190 and 1180 cm^{-1} (sym SO_2 stretch, Ts); nmr ($CDCl_3$) δ 7.9–7.2 (m, 4, Ts), 5.95 (d, $J_{1,2}$ = 3.8 Hz, 1, H-1), 4.92 (d, $J_{3,4}$ = 3.0 Hz, 1, H-3), 4.73 (d, $J_{1,2}$ = 3.8 Hz, 1, H-2), 4.4–3.8 (m, 4, H-4, H-5, H-6 and H′-6), 2.45 (s, 3, Me from Ts) 2.05 (s, 3, Me from Ac), 1.48 and 1.30 (two s, 6, Me from Ip).

Anal. Calcd for $C_{18}H_{24}O_9S$: C, 51.92; H, 5.81; S, 7.70. Found: C, 51.86; H, 5.69; S, 7.89.

The third product (**9**) was isolated in very small amounts (28 mg, 3%). It was an oil: $[\alpha]^{27}D$ −17.5° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 3580 (OH), 3010 (aromatic CH), 1740 (acetate C=O), 1665 (olefinic C=C stretch), 1250 (acetate C–O), 823 cm^{-1} (trisubstituted olefin, CH wag); nmr ($CDCl_3$) δ 6.01 (d, $J_{1,2}$ = 4.5 Hz, 1, H-1), 5.3–5.1 (m, 2, H-2 and H-3), 4.6–4.1 (m, 3, H-5, H-6, and H′-6), 2.02 (s, 3, Me from Ac), 1.42 (s, 6, Me from Ip).

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.06; H, 6.54.

Treatment of 3 with Anhydrous Potassium Acetate in Refluxing *N*,*N*-Dimethylformamide.—An *N*,*N*-dimethylformamide solution (60 ml) of **3** (3.63 g, 6.8 mmol) was treated with anhydrous potassium acetate (3.63 g, 37 mmol) under reflux for 50 min.

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After the solution was cooled to room temperature, water (60 ml) was added and the reaction mixture was extracted with three 200-ml portions of ether. The ethereal extract was successively washed with saturated aqueous sodium bicarbonate solution and water, and dried over anhydrous magnesium sulfate. The removal of ether *in vacuo* gave a crude product (2.540 g) which was chromatographed on silica gel. Elution with 95:5 benzene–2-propanol gave (1) 5,6-anhydro derivative **4** (1.193 g, 49%); (2) monohydroxy sugar **5** (916 mg, 32%); (3) starting material **3** (127 mg, 3%); and (4) unsaturated sugar **9** (102 mg, 6%).

6-*O*-Acetyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose (5).—An *N*,*N*-dimethylformamide solution (10 ml) containing 5,6-anhydro compound **4** (500 mg, 1.4 mmol) and anhydrous potassium acetate (500 mg, 5.1 mmol) was heated at reflux for 50 min. The mixture was cooled to room temperature, water was added (10 ml), and the solution obtained was extracted with three 100-ml portions of ether. The combined ether extracts were washed with saturated aqueous sodium bicarbonate solution and water, and then dried over anhydrous $MgSO_4$. The crude product (525 mg), obtained after removal of ether *in vacuo*, was chromatographed on silica gel (50 g). Elution with 95:5 benzene–2-propanol gave starting material **3** (320 mg, 64%), monoacetate **5** (72 mg, 12%), and unsaturated sugar **9** (6 mg, 2%).

6-*O*-Acetyl-5-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose (7).—Benzoyl chloride (0.3 ml) was added to a pyridine solution (1.0 ml) containing 6-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose (**5**) (100 mg, 0.24 mmol) and the reaction was allowed to proceed for 1 hr at room temperature. The reaction mixture was cooled to 0° and methanol was added. The solvents were evaporated *in vacuo* and the residue was recrystallized from ethanol. The white, crystalline product (50 mg, 40%), mp 125–126°, was identical (mixture melting point and ir spectra) with the known 6-*O*-acetyl-5-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-L-β-idofuranose (**7**).[8,13]

6-*O*-Acetyl-5-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-β-L-*threo*-hex-3-enofuranose (10).—Benzoyl chloride (0.1 ml) was added to a pyridine solution (1.0 ml) of compound **9** (50 mg, 0.2 mmol). After standing at room temperature for 20 min, the reaction mixture was cooled to 0° and methanol was added. The pyridine and excess of methanol were evaporated *in vacuo*, the residue was dissolved in chloroform, and the chloroform solution was washed successively with saturated aqueous sodium bicarbonate solution and water. The chloroform extract was then dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The crude product (75 mg) was chromatographed on silica gel (8 g). Elution with 3:1 hexane–acetone gave 46 mg (64%) of pure **10**, which was identical (ir and nmr spectra) with an authentic sample.[8a]

Treatment of 5,6-Anhydro Derivative 4 with Anhydrous KOAc/AcOH in Refluxing *N*,*N*-Dimethylformamide.—An *N*,*N*-dimethylformamide solution (10 ml) containing 5,6-anhydro derivative **4** (300 mg, 0.84 mmol) was treated with glacial acetic acid (60 mg, 1 mmol) and anhydrous potassium acetate (300 mg, 3 mmol). The reaction mixture was heated under reflux for 50 min and cooled to room temperature, and water (10 ml) was added. The resulting solution was extracted with three 100-ml portions of ether and the combined ethereal extract was dried over anhydrous $MgSO_4$. Ether was removed *in vacuo* and the residue (281 mg) was chromatographed on silica gel (30 g). Elution with 95:5 benzene–2-propanol afforded starting material (27 mg, 9%), 6-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose (**5**) (139 mg, 38%), and unsaturated sugar **9** (79 mg, 37%).

Oxidation of Unsaturated Sugar 9 with MnO_2.—The carbon tetrachloride solution (2.5 ml) of olefinic sugar **9** (50 mg, 0.2 mmol) was treated with freshly prepared MnO_2 for 24 hr at room temperature. After removal of MnO_2 by filtration, the solvent was evaporated *in vacuo* and the residue (18 mg) was chromatographed on silica gel (8 g). Elution with 95:5 benzene–2-propanol gave compound **9** (10 mg, 20%) which was homogenous by tlc (solvent systems: 95:5 benzene–2-propanol and 3:1 hexane–acetone): $[\alpha]^{27}D$ −59° (c 0.2, ethanol); ir ($CHCl_3$) 1750 (acetate C=O stretch), 1720 (carbonyl C=O stretch), 1635 (olefinic C=C stretch), 1240 (acetate C—O stretch), 825 cm^{-1} (trisubstituted double bond, CH wag); uv max (95% EtOH) 266 nm (ε 1300).

6-*O*-Acetyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-xylo-hexofuran-5-ulose (8).—The oxidation of compound **5** with RuO_4 was previously described.[8a] The specific rotation, not reported earlier,[8a] is $[\alpha]^{27}D$ −90° (*c* 0.6, $CHCl_3$).

Solvolysis of 1,2-*O*-Isopropylidene-3,5-di-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (3) in Refluxing *N*,*N*-Dimethylformamide. A. Without $CaCO_3$.—An *N*,*N*-dimethylformamide solution (15 ml) of compound **3** (200 mg) was heated under reflux for 50 min. The reaction mixture was cooled, the solvent was removed by distillation *in vacuo*, and the crude material was chromatographed on silica gel. Elution with 95:5 benzene–2-propanol afforded, in addition to the starting material (144 mg, 72%), the 5,6-anhydro derivative **4** (4 mg, 3%) and 6-*O*-formyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose (**13**) (10 mg, 6%) as an oil: ir ($CHCl_3$) 3600 (OH), 1720 (formate C=O), 1585 (aromatic C=C), 1210 (formate C–O), 1190 and 1180 cm^{-1} (sym SO_2 stretch, Ts); nmr ($CDCl_3$) δ 8.03 (s, 1, HCOO–), 7.9–7.2 (m, 4, Ts), 5.97 (d, $J_{1,2}$ = 3.8 Hz, 1, H-1), 4.93 (d, $J_{3,4}$ = 2.4 Hz, 1, H-3), 4.73 (d, $J_{1,2}$ = 3.8 Hz, 1, H-2), 4.3–4.0 (m, 4, H-4, H-5, H-6 and H′-6), 2.47 (s, 3, Me from Ts), 1.50 and 1.30 (two s, 6, Me from Ip).

B. In the Presence of $CaCO_3$.—An *N*,*N*-dimethylformamide solution (15 ml) of **3** (200 mg) was refluxed in the presence of $CaCO_3$ (200 mg) for 50 min. The reaction mixture was cooled down, $CaCO_3$ was filtered off, the filtrate was evaporated *in vacuo*, and the crude product (220 mg) was chromatographed on silica gel (15 g). Elution with 95:5 benzene–2-propanol afforded (1) the 5,6-anhydro derivative **4** (10 mg, 7%), (2) starting material (118 mg, 59%), and (3) the 6-*O*-formyl derivative **13** (12 mg, 8%).

C. In the Presence of $CaCO_3$ for 5.5 Hr.—An *N*,*N*-dimethylformamide solution (15 ml) containing compound **3** (200 mg) and $CaCO_3$ (200 mg) was refluxed for 5.5 hr. After removal of $CaCO_3$ by filtration, evaporation of the solvent *in vacuo*, and chromatography of the crude product on silica gel, compound **13** was isolated in considerably higher yield (46 mg, 30%).

Refluxing of the 5,6-Anhydro Derivative 4 in *N*,*N*-Dimethylformamide.—An *N*,*N*-dimethylformamide solution (15 ml) containing the 5,6-anhydro derivative **4** (130 mg) was heated under reflux for 5 hr, and the reaction mixture was examined by tlc. There were no detectable amounts of **13** or any other reaction product present in the mixture.

5-*O*-Benzoyl-6-*O*-formyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose (14).—To a pyridine solution (2 ml) of **13** (59 mg), benzoyl chloride (0.15 ml) was added. The reaction mixture was allowed to stand at room temperature for 1 hr, and then diluted with water. The aqueous solution was extracted with ether, and the etheral extracts were dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The oily residue (167 mg) was chromatographed on silica gel. Elution with 4:1 benzene–acetone afforded pure **14** (64 mg, 86%) as an oil: $[\alpha]^{27}D$ −11.8° (*c* 0.79, $CHCl_3$); ir ($CHCl_3$) 1725 and 1715 (formate and benzoate C=O), 1270 (benzoate C–O), 1190 and 1178 cm^{-1} (sym SO_2 stretch, Ts); nmr ($CDCl_3$) δ 8.1–7.2 (m, 10, Ph, Ts, and HCOO), 6.00 (d, $J_{1,2}$ = 4.0 Hz, 1, H-1), 5.8–5.4 (m, 1, H-5), 5.07 (d, $J_{3,4}$ = 3.2 Hz, 1, H-3), 4.80 (d, $J_{1,2}$ = 4.0 Hz, 1, H-2), 4.57 (m, $J_{3,4}$ = 3.2 and $J_{4,5}$ = 8.0 Hz, 1, H-4), 4.4–4.2 (m, 2, H-6 and H′-6), 2.47 (s, 3, Me from Ts), 1.53 and 1.30 (two s, 6, Me from Ip).

Anal. Calcd for $C_{24}H_{26}O_{10}S$: C, 56.91; H, 5.17; S, 6.33. Found: C, 57.13; H, 5.09; S, 6.49.

Registry No.—**2**, 34885-58-0; **3**, 34885-59-1; **4**, 34885-60-4; **5**, 28642-59-3; **7**, 28642-56-0; **8**, 32785-86-7; **9**, 34885-84-2; **13**, 34885-64-8; **14**, 34885-65-9.

Nucleophilic Reactivity of the Carbon–Carbon Double Bond. VI. Products from 5-Hexenyl, Cyclopentylmethyl, and Cyclohexyl Cations with Different Leaving Groups

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Received June 22, 1971

The products of acetolysis of 5-hexenyl, cyclopentylmethyl, and cyclohexyl *p*-nitrobenzenesulfonates are compared with those formed in similar media from carbonium ions with uncharged leaving groups. Cyclohexylmercuric acetate produced cyclohexene and cyclohexyl acetate in a ratio identical with that from the sulfonate, but cyclopentylmethylmercuric acetate failed to react at a comparable rate or to produce analogous products. Cyclopentylmethylamine and cyclohexylamine diazotization with isoamyl nitrite in acetic acid produced cyclohexene and cyclohexyl acetate and other products. No cyclization occurred with 5-hexenylamine.

Related carbonium ion intermediates formed from precursors differing either in structure or in leaving group have sometimes been observed to give products differing in relative amounts.[1,2] It has been suggested that nucleophilicity of the leaving group, especially in solvents of low nucleophilicity, affects the ratio of products formed by elimination to those formed by substitution.[2] Alternatively, partial internal return of the leaving group from the ion pair after rearrangement of the cation may be responsible for product differences.[3-5] When the carbonium ion is formed by paths as different as the π route and the σ route,[6] the position of the anion may be significant. For bicyclic cations, it may be difficult to assess the relative importance of anion proximity and cation conformation.[7]

If the effect of the leaving group is steric rather than electrostatic, a neutral leaving group would cause product differences of the same kind as a charged leaving group.[8]

We have conducted experiments utilizing two methods of generating carbonium ions with neutral leaving groups, solvolysis of alkylmercuric acetates and diazotization of alkylamines. These were done under conditions directly comparable with the acetolyses of 5-hexenyl, cyclopentylmethyl, and cyclohexyl tosylates,[5] in order to determine the effect of leaving groups on the product ratios.

Results

The product analysis for acetolysis of 5-hexenyl, cyclopentylmethyl, and cyclohexyl *p*-nitrobenzenesulfonates and corresponding alkylmercuric acetates and for deamination of the appropriate alkylamines are compared in Table I.

The reactions occurred in homogeneous solutions in all cases, at closely comparable concentrations, and at temperatures near 80°. Product stability under the reaction conditions was shown to depend upon the absence of acids stronger than acetic acid in the medium; so the solutions were "buffered" by the addition of anhydrous sodium acetate in sufficient amount to react with the *p*-nitrobenzenesulfonic acid formed during the reaction of the sulfonate esters and in low concentration in other cases simply to assure the absence of strong acid. The product ratios are known to be affected slightly by added salts, but not substantially by concentrations of less than 0.03 *M*.[5]

A careful inspection of the 5-hexenyl *p*-nitrobenzenesulfonate product evinced no trace of cyclopentylmethyl acetate. A measurable quantity of five-membered ring closure could have provided a second parameter in addition to the cyclohexene/cyclohexyl acetate ratio for the detection of differences in the reaction intermediates. Under conditions capable of detecting 0.1%, no cyclopentylmethyl acetate could be seen in the chromatogram.

Acetolysis of cyclohexylmercuric acetate proceeded cleanly as reported by Jensen.[9] A longer reaction period was required when the solution contained sodium acetate to prevent secondary product interconversion. The product ratio was identical with that from the classical cyclohexyl cation derived from the *p*-nitrobenzenesulfonate. Cyclopentylmethylmercuric acetate reacted slowly, as shown by the formation of some sludge containing mercury, but no analogous organic products were found.

The results of some typical diazotization experiments are given in Table II. When isoamyl nitrite was used to diazotize cyclohexylamine, the product ratio was almost invariant with changes in the mole ratio or with added base. Consequently, product studies were made with equimolar amounts of amine and isoamyl nitrite and with a low concentration of sodium acetate present to assure product stability.

Diazotization of cyclohexylamine produced 64% cyclohexylacetate, 33% cyclohexene, and 3% bicyclo[3.1.0]hexane. The latter was observed in the aqueous diazotization of cyclohexylamine to the extent of 2%, but is reportedly formed in more substantial amount in "aprotic" diazotization.[10]

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TABLE I

PRODUCTS OF ACETOLYSIS OF *p*-NITROBENZENESULFONATES AND ALKYLMERCURY ACETATES COMPARED WITH ALKYLAMINE DEAMINATION PRODUCTS, MOLE PER CENT[a]

Substrate (Registry no.)	Reaction time, hr	Yield, %	1-Methylcyclopentene	Cyclohexene (A)	5-Hexenyl acetate	Cyclopentanemethyl acetate	Cyclohexyl acetate (B)	Other products	A/B
p-Nitrobenzenesulfonate Acetolysis[b]									
5-Hexenyl (788-97-6)	86	94	0	4.7	83.7	0	11.6	0	0.40
Cyclopentylmethyl (788-96-5)	52.3	83	15.1	61.9	0	0	18.0	0	3.4
Cyclohexyl (788-92-1)	0.7	82	0	87.0	0	0	13.0	0	6.7
Alkylmercury Acetate Acetolysis[c]									
Cyclopentylmethyl (34825-68-8)	691	0	0	0	0	0	0	0	
Cyclohexyl (10341-90-9)	135	49	0	87.0	0	0	13.0	0	6.7
Alkylamine Deamination[d]									
5-Hexenyl[e] (34825-70-2)	1.0	60	0	0	55	0	0	1,5-Hexadiene, 22 1-Hexen-5-yl acetate, 20 Unknown, 3	
Cyclopentylmethyl[f] (6053-81-2)	1.0	57	7	25	0	9	49	1-Methylcyclopentyl acetate, 7 Unknown, 3	0.51
Cyclohexyl (108-91-8)	1.0	66	0	33	0	0	64	Bicyclo[3.1.0]hexane, 3	0.52

[a] By gas chromatography of pentane extracts, using an internal standard. Product yields normalized to add to 100%. [b] Initial concentration 0.17 *M*, sodium acetate 0.27 *M*, 80.8°. [c] Initial concentration 0.22 *M*. Cyclopentylmethylmercuric acetate gave 14% yield of free mercury in the form of brown sludge after 691 hr, but no organic product could be found by the usual extraction and analysis procedure. 5-Hexenylmercuric acetate acetolysis was not tried. [d] Initial concentration 0.18 *M*, reacted with isoamyl nitrite, initially 0.20 *M*, sodium acetate 0.011 *M*, 79.7°. [e] Phenylthiourea derivative, 34825-65-5. [f] Phenylthiourea derivative, 34825-67-7.

TABLE II

DIAZOTIZATION OF CYCLOHEXYLAMINE[a]

Reagent	Mole ratio[b]	Medium	Yield, %	C_6H_{10}[c]/Cyclohexyl acetate
IAN[d]	1.02	HOAc	55	0.52
$NaNO_2$	1.0	HOAc	30	0.44
IAN	1.02	0.011 *M* NaOAc/HOAc	66	0.54
IAN	1.02	0.27 *M* NaOAc/HOAc	60	0.54
IAN	1.02	0.011 *M* NaOAc/HOAc	60	0.56
IAN	1.12	0.011 *M* NaOAc/HOAc	66	0.57
IAN	1.20	0.011 *M* NaOAc/HOAc	62	0.54
IAN	1.29	0.011 *M* NaOAc/HOAc	58	0.50

[a] The reactions occurred at 70.68° for 1 hr in anhydrous acetic acid with an amine concentration of about 0.175 *M*. [b] Diazotization reagent/cyclohexylamine. [c] C_6H_{10} consists of cyclohexene and a minor amount of bicyclo[3.1.0]hexane, which were not resolved in these gas chromatograms. [d] Isoamyl nitrite. Unreacted isoamyl nitrite was detected in glc analyses as well as a 15% yield of isoamyl acetate and less than 1% of pentenes apparently derived from isoamyl nitrite. A certain amount of isoamyl acetate was formed by acetolysis of isoamyl nitrite but control samples indicated that the initial rate was only $^1/_{220}$th the diazotization rate at the concentrations used.

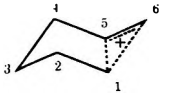
Diazotization of cyclopentylmethylamine produced, in addition to products from cyclohexyl cation, 7% of 1-methylcyclopentyl acetate. Cyclohexene and cyclohexyl acetate were produced in the ratio of 0.51.

5-Hexenylamine upon diazotization produced 1,5-hexadiene and 1-hexen-5-yl acetate, which were not found in detectable amount from acetolysis of 5-hexenyl *p*-nitrobenzenesulfonate. Neither cyclohexene nor cyclohexyl acetate could be detected in the product extract under conditions at which 1% of either would have been distinct.

All of the diazotization reactions were of 1 hr duration and the results probably do not represent the maximum yield attainable.

Discussion

The acetolysis of 5-hexenyl *p*-nitrobenzenesulfonate occurs with kinetic enhancement compared to *n*-hexyl *p*-nitrobenzenesulfonate and results in cyclic products, 4.7% cyclohexene and 11.6% cyclohexyl acetate.[5] This implies that the π electrons of the double bond are involved in supporting the positive charge in the transition state leading to cyclic products. Charge distribution is open to question, although a preference for symmetrical transition states in carbonium ions formed by the π route was demonstrated by Bartlett and Sargent.[11] Though the cyclization of 5-hexenyl *p*-nitrobenzenesulfonate does not itself result in the formation of products having five-membered rings, derivatives substituted at C-6 do close with the formation of both five- and six-membered rings.[12] Therefore, it is reasonable to postulate a nonclassical carbonium ion such as I for the reaction intermediate which leads to cyclic products. The π and σ route intermediates, in



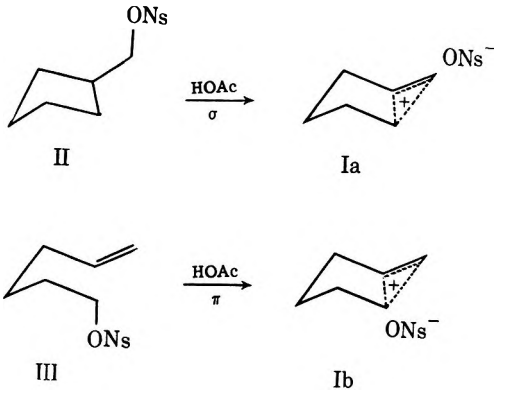
I

approaching the geometry of I, still retain the leaving group in the neighborhood of the carbon atom to which it was attached. Kinetic rate enhancement shows that electron mobilization in both cases accompanies the departure of the leaving group.

In acetolysis of alkylmercuric acetates, rapid ionization equilibrium with the alkylmercuric cation is established, followed by rate-controlling loss of free mer-

(11) P. D. Bartlett and G. D. Sargent, *J. Amer. Chem. Soc.*, **87**, 1297 (1965).

(12) E. M. Nicholson, Thesis, Harvard University, 1965; W. S. Johnson, D. M. Bailey, R. Owyang, R. A. Bell, B. Jaques, and J. K. Crandall, *J. Amer. Chem. Soc.*, **86**, 1959 (1964).



cury.[9] The utilization of the reaction for the comparison of σ and π route cations would lead to the suppression of counterion differences according to the internal return and electrostatic mechanisms, whereas steric effects might remain. That is, the mercury atom is unlikely to undergo internal return with rearrangement.

$$RHgOAc \underset{\text{fast}}{\rightleftharpoons} RHg^+ + OAc^- \xrightarrow[\text{slow}]{}$$
$$R^+ + Hg + OAc^- \xrightarrow[\text{fast}]{} \text{products}$$

An electrostatic effect on elimination is also unlikely. However, the process failed to provide the necessary σ and π route cations because mercury is poor as a leaving group with primary carbonium ions. The reaction occurred so slowly that general deterioration of the samples was apparent.

In the one comparison obtained, acetolysis of cyclohexylmercuric acetate gave the same cyclohexene/cyclohexyl acetate ratio as cyclohexyl *p*-nitrobenzenesulfonate, both under kinetic control. Electrostatic assistance to elimination therefore seems to be absent in this process. Both processes apparently involve a classical cyclohexyl cation.

The reaction of alkylamines with nitrous acid or with alkyl nitrites is considered to be analogous to diazotization of aromatic amines except that the diazonium ion is unstable and suffers immediate loss of nitrogen with the formation of the carbonium ion.[13] The nitrogen molecule constitutes the neutral leaving group in this case.

$$RNH_2 + HONO + H^+ \longrightarrow 2H_2O + RN_2^+ \longrightarrow$$
$$N_2 + R^+ \longrightarrow \text{products}$$

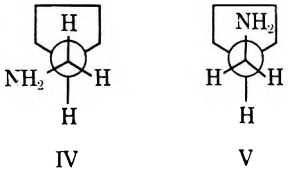
Since the products from 5-hexenyl, cyclopentylmethyl, and cyclohexyl *p*-nitrobenzenesulfonates were extremely subject to alterations of the medium,[5] it was important to run the diazotization–decomposition reactions of the amines under strictly comparable conditions. The use of nitrite esters as the diazotization reagent facilitated reaction in homogeneous solution with a comparable reaction rate at 80°.[14]

The cyclohexene/cyclohexyl acetate ratio realized from cyclohexylamine and isoamyl nitrite was 0.52, whereas sodium nitrite yielded a ratio of 0.44 for total C_6H_{10}/cyclohexyl acetate (Table II). It seems possible that the considerable evolution of gas from the latter sample may be responsible for some loss of the more volatile product.

Addition of sodium acetate to the medium had little effect on the product ratio. In the comparable ester solvolyses, even lithium perchlorate led to marked alteration of the elimination–substitution ratio, in the direction of more elimination.[5] This insensitivity of the product ratio argues for an indiscriminate cation, an indication of a very exothermic product-forming step.[15]

The products formed by the reaction of isoamyl nitrite and cyclopentylmethylamine indicate that two kinds of rearrangement processes are occurring. Hydride migration leads to the formation of 1-methylcyclopentene and 1-methylcyclopentyl acetate, together about 14% of the total product. Ring expansion leads to the production of cyclohexene and cyclohexyl acetate, 25 and 49%, respectively.

The prevalence of ring expansion over hydrogen migration is explicable on the basis of a preferred conformation of the ground state, IV. Migration in diazotization of 3-phenyl-2-butylamine and [1-^{14}C]-2,2-diphenyl-2-*o*-tolylethylamine is faster than the establishment of rotational equilibrium.[2a,16] The population of conformer IV and its enantiomer should be more than twice that of V.



IV V

The fact that cyclopentylmethylamine and cyclohexylamine gave the same ratio of cyclohexene to cyclohexyl acetate permits the assumption that the carbonium ion intermediates in the two cases are identical. This lack of memory of original structure may be due to poor charge solvation. That is, the charge is either localized or distributed over several carbon atoms of the cation, but in any case the solvent molecules in the neighborhood are not oriented to stabilize the charge. This is possible because of the different energy contour of diazotization is compared to solvolysis. According to the Hammond postulate, the structure of the transition state for diazotization, by virtue of the exothermic nature of the reaction, is similar to that of the starting material. Huisgen and Rüchardt have elaborated this to the extent of suggesting that, in the transition state for diazotization, the carbon attached to nitrogen is still essentially sp^3 hybridized.[17] It seems clear that in the passage from the respective transition states to the carbonium ion intermediate solvation from the rear is not necessary and the front side is shielded by the forming nitrogen molecule. This observation of leveling of the product ratio when a neutral molecule is the leaving group indicates that the mechanism of memory effects in this cation system is electrostatic. This same result

(13) H. Zollinger, "Azo and Diazo Chemistry," Interscience, New York, N. Y., 1961, Chapters 1, 2, 3, 6.

(14) G. Seidl and R. Huisgen, *Chem. Ber.*, **97**, 249 (1964); D. Y. Curtin, J. A. Kampmeier, and M. L. Farmer, *J. Amer. Chem. Soc.*, **87**, 874 (1965); L. Friedman and A. T. Jurewicz, *ibid.*, **91**, 1808 (1969), and preceding work in this series.

(15) J. D. Roberts, C. C. Lee, and W. H. Saunders, *J. Amer. Chem. Soc.*, **76**, 4501 (1954); D. J. Cram and J. E. McCarty, *ibid.*, **79**, 2866 (1957); D. Y. Curtin and M. C. Crew, *ibid.*, **76**, 3719 (1954).

(16) V. F. Raaen and C. J. Collins, *ibid.*, **80**, 1409 (1958).

(17) R. Huisgen and C. Rüchardt, *Justus Liebigs Ann. Chem.*, **601**, 1, 21 (1956); see also P. D. Bartlett and E. S. Lewis, *J. Amer. Chem. Soc.*, **72**, 1005 (1950). Moss has recently summarized suggestions that in primary diazonium ions the carbon–nitrogen bond is broken only upon attack by a nucleophile at carbon: R. A. Moss, *Chem. Eng. News*, **49** (47), 28 (1971).

TABLE III
ALKYLMERCURIC BROMIDES, RHgBr

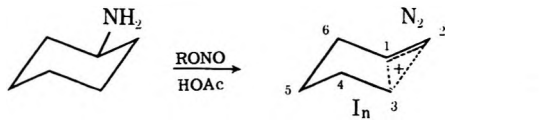
Registry no.	R	Mp, °C	Analysis, % Carbon Calcd	Carbon Found	Hydrogen Calcd	Hydrogen Found	Mercury Calcd	Mercury Found	Bromine Calcd	Bromine Found
10192-55-9	Cyclohexyl[a]	153.5–154.0	19.82	19.76	3.05	3.46	55.16	54.78	21.97	21.61
33631-67-3	Cyclopentylmethyl	61.0–62.5	19.82	19.77	3.05	3.43	55.16	54.81	21.97	21.80
27936-01-2	5-Hexenyl	102.5–104.0	19.82	19.87	3.05	3.32	55.16	54.60	21.97	21.80

[a] Cyclohexylmercuric bromide, mp 153°: G. Grüttner, *Chem. Ber.*, **47**, 1651 (1914).

might occur in solvolysis intermediates *if* the rearrangement led to charge development at a point sufficiently remote from the leaving group to avoid its electrostatic effect and if the activation energy for rearrangement were low enough to permit migration without concurrent solvent reorientation.[18]

Reaction of 5-hexenylamine with isoamyl nitrite gave no detectable amounts of cyclic products; so this prospective route to cyclohexyl cation failed.

Bicyclo[3.1.0]hexane was found in 3% yield from cyclohexylamine diazotization, along with 33% cyclohexene. Presumably these come from a common intermediate I_n by the competitive loss of H from two positions, C_3 (to form bicyclo[3.1.0]hexane) and C_2 (to form cyclohexene). The argument that a bicyclic intermediate is necessary to explain a bicyclic product is not compelling, but it is more convenient than a classical cyclohexyl cation. We consider the diazotization to produce a cation without benefit of solvation. Delocalization of the σ bonds follows in the sense of internal "solvation" of the charge, producing I_n. The stability of bicyclo[3.1.0]hexane under the reaction conditions, work-up, and analysis was carefully checked; so the proposal that it is an intermediate which forms other products is not correct in this case.[18a]



Experimental Section

Melting points were obtained on a Monoscop V block melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 137 Infracord spectrophotometer in carbon tetrachloride or chloroform solution and calibrated with respect to polystyrene film. Nmr spectra were obtained in carbon tetrachloride or deuteriochloroform solutions on a Varian A-60 spectrometer and chemical shifts in Hertz were measured from internal tetramethylsilane. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory.

p-Nitrobenzenesulfonates.—The preparation and properties of cyclohexyl, cyclopentylmethyl, and 5-hexenyl *p*-nitrobenzenesulfonates have been described.[5]

Amines.—Cyclohexylamine was used as received (Eastman 2496). 5-Hexenylamine was prepared from 4-pentenyl *p*-nitrobenzenesulfonate.[5] In dimethyl sulfoxide solution 12.5 g of sodium cyanide and 29.3 g of 4-pentenyl *p*-nitrobenzenesulfonate reacted in 4.5 hr at room temperature to form 5-hexenenitrile: 6.7 g; bp 82° (51 mm); n^{25}D 1.4243 [lit.[19] bp 54–59° (16 mm); n^{25}D 1.4268]; nmr 90–150 (area 6.0), 280–320 (1.8), 320–370 Hz (0.9); ir 3.24 (m), 3.39 (s), 4.44 (m), 6.07 (s), and 6.97 μ (s). The product contained 0.4% of a lower boiling impurity (glc, LAC 446). 5-Hexenenitrile, 6.7 g, with 2.7 g of lithium aluminum hydride in ether for 1 hr gave 5-hexenylamine: 1.9 g; bp 58° (55 mm) (lit.[20] bp 125–126°); n^{25}D 1.4349; nmr 70–100 (area 6.0), 110–130 (2.0), 150–170 (2.0), 280–310 (1.9), and 320–370 Hz (0.9); ir 2.94 (s), 3.24 (m), 3.42 (s), 6.08 (s), and 6.96 μ (s). The nmr spectrum in deuteriochloroform had a sharp spike at 87 Hz which was assigned to $-NH_2$ because of ready deuterium exchange. The best 5-hexenylamine obtained had 3% of a higher boiling impurity (glc, UCON 550x/Diatoport W). The phenylthiourea derivative, recrystallized from ethyl acetate–ligroin and from ethyl alcohol, had mp 57°; ir 2.92, 3.44, 6.12, 6.28, 6.54, 6.69, and 10.9 μ. *Anal.* Calcd for $C_{13}H_{18}N_2S$: C, 66.60; H, 7.74; N, 11.95; S, 13.68. Found: C, 66.81; H, 7.74; N, 11.74; S, 13.96.

Cyclopentanecarboxylic acid was converted to cyclopentanecarboxamide by treatment with thionyl chloride and then ammonium hydroxide, mp 179–180° (subliming) (lit.[21] mp 179°). The amide, 10.4 g, with 3.5 g of lithium aluminum hydride in tetrahydrofuran was refluxed for 14 hr. The solution gave 3.4 g of cyclopentylmethylamine, bp 138–140° (768 mm), n^{25}D 1.4538 (lit.[22] bp 140°), containing trace amounts (less than 1%) of ether, tetrahydrofuran, and a third volatile impurity (glc, UCON 550x/Haloport F). The ir spectrum had bands at 3.02, 3.48, 3.56, 6.20, 6.89, and 9.3 μ. The phenylthiourea derivative was obtained as square plates from alcohol or from ethyl acetate–ligroin: slightly yellow; mp 132.5–133.0°; ir 2.97, 3.44, 3.55, 6.30, 6.54, and 6.68 μ. *Anal.* Calcd for $C_{13}H_{18}N_2S$: H, 7.74; N, 11.95; S, 13.68. Found: H, 7.61; N, 11.62; S, 13.34.

Alkylmercuric Acetates.—Cyclohexyl-, cyclopentylmethyl-, and 5-hexenylmercuric acetates were prepared *via* Grignard reagents.[23] Cyclohexyl bromide (Eastman) was redistilled before use. Cyclopentylmethanol was converted to the bromide by phosphorus tribromide.[24] 5-Hexen-1-ol obtained from PCR, Inc., contained about 10% impurities (glc, UCON) even after redistillation. It was converted to the bromide in the same way, but the bromide after distillation contained about 5% of a contaminant (glc, UCON). The Grignard reagents, free from magnesium metal, reacted exothermically with mercuric bromide to form alkylmercuric bromides (Table III). Equivalent amounts of the alkylmercuric bromide and silver acetate slurried in methanol for 4 hr at room temperature gave the alkylmercuric acetates (Table IV). Ir and nmr spectra were in agreement with the expected structures.

Products.—1,5-Hexadiene and cyclohexene were obtained commercially. Bicyclo[3.1.0]hexane was prepared in 71% yield.[25] The preparation and properties of cyclopentylmethyl, 5-hexenyl, and 1-methylcyclopentyl acetates have been described.[5]

1-Hexen-5-ol and its acetate were obtained following a procedure of Kharasch.[26] Allyl Grignard reagent with propylene oxide (Eastman) gave the products listed in Table V. Identification of the components is by nmr spectra of certain distillation fractions.

1-Hexen-5-ol was obtained 98.6% pure (glc, UCON): bp 87° (98 mm); n^{25}D 1.4293 (lit.[27] bp 138–139°; n^{24}D 1.4286); ir 3.00, 3.31, and 6.11 μ; nmr 67 (doublet, area 3), 78–110 (2),

(18) The idea that a rearranged carbonium ion would have "open" or unsolvated character was clearly expounded by Silver, while Renk and Roberts took the opposite position: (a) M. S. Silver, *J. Amer. Chem. Soc.*, **83**, 3482 (1961); M. S. Silver, *J. Org. Chem.*, **28**, 1686 (1963); (b) E. Renk and J. D. Roberts, *J. Amer. Chem. Soc.*, **83**, 878 (1961).

(19) F. B. LaForge, N. Green, and W. A. Gersdorff, *ibid.*, **70**, 3707 (1948).

(20) CIBA, Ltd., Belgian Patent 626,292 (June 19, 1963); *Chem. Abstr.*, **60**, P 9158C (1964).

(21) N. Zelinsky, *Chem. Ber.*, **41**, 2627 (1908).

(22) K. Jewers and J. McKenna, *J. Chem. Soc.*, 2209 (1958).

(23) J. H. Robson and G. F. Wright, *Can. J. Chem.*, **38**, 21 (1960).

(24) L. H. Smith, *Org. Syn.*, **23**, 88 (1943).

(25) H. E. Simmons and R. D. Smith, *ibid.*, **41**, 72 (1961); *J. Amer. Chem. Soc.*, **81**, 4256 (1959).

(26) M. S. Kharasch, L. Biritz, W. Nudenberg, A. Bhattacharya, and N. C. Yang, *ibid.*, **83**, 3229 (1961).

(27) J. Colonge and A. Lagier, *Bull. Soc. Chim. Fr.*, 15 (1949).

TABLE IV

ALKYLMERCURIC ACETATES, $RHgOCOCH_3$

R (Registry no.)	Mp, °C	Analysis, % Carbon Calcd	Carbon Found	Hydrogen Calcd	Hydrogen Found	Mercury Calcd	Mercury Found
Cyclohexyl	88.0–88.5	28.03	28.38	4.12	4.20	58.52	58.58
Cyclopentylmethyl	88.5–90.0	28.03	28.20	4.12	4.19	58.52	58.85
5-Hexenyl (34825-75-7)	39.0–40.5	28.03	28.01	4.12	4.36	58.52	58.34

TABLE V

PRODUCTS OF REACTION OF ALLYL GRIGNARD REAGENT WITH PROPYLENE OXIDE

Compd	% (g.c area)
2-Methyl-4-penten-2-ol	1
Propylene chlorohydrin	10
1-Hexen-5-ol	67
2-Methyl-4-penten-1-ol	8
Yield	86

110–144 (2), 185 (1), 200–240 (1), 280–320 (2), and 320–360 Hz (1). The acetate was obtained in 80% yield, bp 86° (74 mm), $n^{25}D$ 1.4150 [lit.[28] bp 152° (750 mm), $n^{18}D$ 1.4211].

Acetolysis Procedure.—Acetolysis and extractive work-up of the *p*-nitrobenzenesulfonates in ampoules has been described.[5] The alkylmercuric acetates were treated in the same way, except that in the absence of rate data the time period required for complete reaction was estimated from observation of the amount of mercury precipitated. The weight of free mercury served as a measure of the extent of reaction of samples, or, if brown sludge resulted, it was dissolved in dilute nitric acid and assayed by standard methods.[29] The glc analysis of the organic products usually gave a yield in agreement.

Addition of a catalytic amount of perchloric acid in the acetolyses of alkylmercuric acetates resulted in an increase in the reaction rates but the product studies were useless because secondary interconversion of the products occurred. Cyclohexylmercuric acetate in 0.01 *M* perchloric acid in acetic acid reacted completely in 2 hr at room temperature, forming 99% of theoretical mercury. Analysis of the product extract showed 90% cyclohexene and 10% cyclohexyl acetate in 75% yield. Cyclohexylmercuric acetate in 0.01 *M* sodium acetate in acetic acid required 135 hr at 80.8° to attain 61% reaction based on the weight of recovered mercury. Glc gave 87% cyclohexene and 13% cyclohexyl acetate in the product extract, with 49% yield.

Acetolysis of cyclopentylmethylmercuric acetate was much slower. In 0.01 *M* perchloric acid in acetic acid, 0.15 *M* solution failed to react at room temperature. However, treatment at 79.7° for 2 hr led to deposition of black sludge containing 51% of theoretical mercury. The organic product, 19% yield, was less than 5% cyclohexene, the rest being cyclohexyl acetate. In 0.01 *M* sodium acetate in acetic acid, a solution of 0.25 *M* cyclopentylmethylmercuric acetate at 80.8° for 691 hr precipitated only 14% of the free mercury expected, along with a substantial amount of brown sludge. The pentane extract of the solution contained no detectable amount of either cyclohexene or cyclohexyl acetate.

Diazotization of the amines was done in a flask with an efficient cold-finger condenser and magnetically stirred in the constant-temperature bath. Sodium nitrite was added in small portions, but reaction was violent with considerable foaming and gas evolution, including nitrous anhydride. The reaction was smoother when isoamyl nitrite was employed as the nitrosating agent introduced *via* syringe through a septum. Gas evolution was moderate throughout and only slightly reddish in color. The reaction mixture was homogeneous, in contrast to the situation with sodium nitrite, which required several minutes to dissolve.

Product Studies.—Product analyses were by glc with area response calibration and using internal standards for the calculation of the absolute yields of individual products. F & M Model 609 and 5750 and Varian Aerograph Model 1520 gas chromatographs with flame ionization detectors were used for the quantitative work. Identification of products was based on ir of fractions condensed from preparative gas chromatography or for minor components by comparison of retention times with authentic samples, verified on two different columns. These were usually silver nitrate in diethylene glycol on Chromosorb P for resolution of the olefins and diisodecyl phthalate on Chromosorb P for acetates. Quantitative work was generally on UCON 550x.

There were indications that methylenecyclopentane was a primary product from cyclopentylmethyl *p*-nitrobenzenesulfonate and was converted to 1-methylcyclopentene. Control samples showed this conversion to occur. However, direct injection of the acetolysis medium produced chromatograms showing somewhat variable amounts of methylenecyclopentane ranging from 2 to 4%. This led to rapid deterioration of the silver nitrate–diethylene glycol columns used for the resolution of methylenecyclopentane and 1-methylcyclopentene, probably due to precipitation of silver acetate.

The resolution of bicyclo[3.1.0]hexane and cyclohexene was best accomplished on a 10 ft × 0.25 in. 10% oxydipropionitrile on Chromosorb P column.

1,5-Hexadiene was chromatographed on a short silver nitrate column because of long retention caused by the very large complexation constant of this olefin.[30]

The stability of cyclohexene, 5-hexenyl acetate, cyclohexyl acetate, and cyclopentylmethyl acetate to the acetolysis conditions was demonstrated with control samples on which gas chromatography showed good recovery and no trace of alteration of the product. This demonstration of kinetic control of the products was reinforced by examination of the products after 2 and 4 half-lives as well as after 10. The product ratios were the same in all cases. When sodium acetate was omitted from the acetolysis medium, changes in the product ratios due to acid-catalyzed rearrangement and addition of acetic acid to unsaturated products were observed. Cyclohexene and cyclohexyl acetate samples in 0.2 *M* perchloric acid in acetic acid at 80° for 2 hr virtually reached equilibrium. The cyclohexene was 96.2% converted to cyclohexyl acetate and 3.4% of cyclohexene was found in the cyclohexyl acetate control. Both samples contained small amounts of extraneous products as well.

5-Hexenyl acetate treated with anhydrous acetic acid containing 0.01 *M* perchloric acid gave products of rearrangement and addition believed to be 4-hexenyl acetate and two isomeric diacetates because of glc characteristics.

The amount of unreacted isoamyl nitrite remaining in the diazotization product extracts was measurable. This was best done on an Apiezon N column, on which the separation from cyclohexene was still just barely adequate. A control sample containing only isoamyl nitrite in 0.011 *M* sodium acetate–acetic acid solution at 79.68° reacted slowly to form isoamyl acetate.

Acknowledgments.—This paper is based chiefly on the doctoral thesis of the author at Harvard University, 1965. The work was initiated under the direction of Professor P. D. Bartlett and was supported by the National Science Foundation and the National Institutes of Health through grants to P. D. Bartlett and by a grant from the Robert A. Welch Foundation (Y-232) to T. J. Cogdell.

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(30) M. A. Muhs and F. T. Weiss, *J. Amer. Chem. Soc.*, **84**, 4697 (1962).

Cyclopropylcarbinyl–Allylcarbinyl Radical Rearrangements in the Benzobicyclo[4.1.0]heptene System

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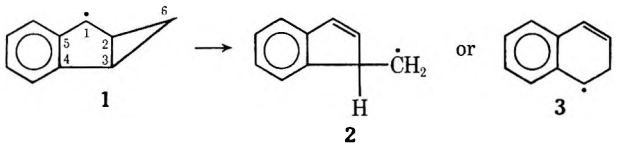
Received November 30, 1971

Preparation of benzobicyclo[4.1.0]hept-3-ene, and a study of its light-initiated free-radical bromination using *N*-bromosuccinimide in carbon tetrachloride, is reported. Also, an investigation of the free-radical tri-*n*-butyltin hydride reduction of 2-bromomethyl-1,2-dihydronaphthalene was carried out. In both the bromination and tin hydride reduction studies in the benzobicyclo[4.1.0]heptenyl system, examination of the product compositions revealed that the benzobicyclo[4.1.0]hepten-2-yl radical undergoes cyclopropylcarbinyl–allylcarbinyl rearrangement *via* 1,7 bond cleavage to the primary allylcarbinyl radical species in preference to rearrangement *via* 1,6 bond cleavage to the corresponding secondary allylcarbinyl radical species. This is explained as resulting mainly from orbital overlap control of the directionality of rearrangement.

In our earlier work on the azobisisobutyronitrile-initiated free-radical α bromination of cycloprop[2,3]-indene with *N*-bromosuccinimide (NBS) at 77° in carbon tetrachloride,[1,2] which proceeds *via* initial formation of the cyclopropylcarbinyl radical **1**, we found that the rearranged homoallylic bromide product derived from the primary homoallyl radical **2** was obtained in five times as great a yield as that obtained from the secondary benzylic homoallyl radical **3**. Also,



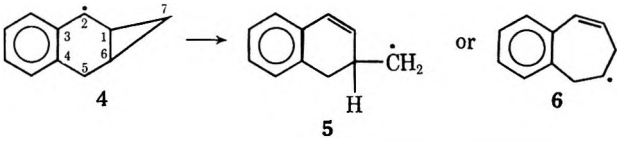
1 2 3

we later observed[2] that the organotin hydride reductions of 1-bromocycloprop[2,3]indene at low temperature gave 10–20% as much of the product resulting, after free-radical cyclopropylcarbinyl–allylcarbinyl rearrangement, from the primary radical **2** as from the benzylic radical **3**. Thus, it appears from both the bromination and organotin hydride reduction studies that on cyclopropylcarbinyl–allylcarbinyl radical rearrangement the cycloprop[2,3]inden-1-yl radical (**1**) prefers to undergo 2,6 bond cleavage to give a primary radical product rather than undergo 2,3 bond cleavage to give a benzylic radical product.

This result was somewhat unexpected. It is well known from other studies of free-radical reactions that, for electronic reasons, benzylic radicals are considerably more stable than primary radicals.[3] Thus, if these factors are reflected in the energies of the activated complexes for rearrangement of **1** to **2** or **3**, one might have expected to find much more rearrangement to the benzylic radical product **3**.

A possible explanation for the observation that rearrangement proceeds preferentially to the primary radical **2** may be that the phenyl group at the 3 position of the partially formed cycloprop[2,3]inden-1-yl radical (**1**) at the transition state for cyclopropylcarbinyl–allylcarbinyl radical rearrangement exhibits an electron-withdrawing inductive effect rather than an electron-releasing resonance effect. Thus, the 3 position would be destabilized to formation of the benzylic radical **3**, occurring *via* ring scission between carbons 2 and 3. An alternative explanation, however, could be that conformational control of the directionality of bond cleavage by more favorable orbital overlap between the p orbital at carbon 1 and the C_2–C_6 bond, as proposed by Dauben[4] to explain the direction of cyclopropylcarbinyl–allylcarbinyl rearrangement of the 2-hydroxybicyclo[3.1.0]hex-2-yl radical, is more important than electronic control and thus determines the course of the rearrangement.

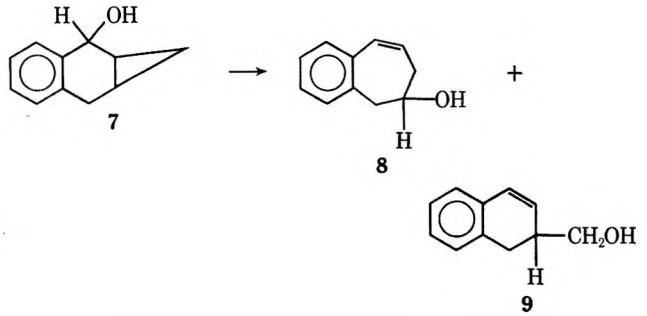
One way to test the first explanation is to study cyclopropylcarbinyl–allylcarbinyl radical rearrangements in the structurally similar benzocyclo[4.1.0]hepten-2-yl[5] radical system **4**. In this system the 6 position of the



4 5 6

cyclopropane ring is insulated from the phenyl ring by a methylene group, and thus an inductive effect of the phenyl group should have little or no effect on 1,6 bond breaking to give the secondary benzocycloheptadienyl radical (**6**) *vs.* the primary radical **5**.

In connection with the above, it should be noted that, in work carried out by Julia and coworkers[6] on cationic cyclopropylcarbinyl reactions in the benzobicyclo-[4.1.0]heptene-2-yl system **7**, the product resulting formally from the cation related to **6** was preferred under conditions of kinetic control. Thus reaction of benzobicyclo[4.1.0]hepten-2-ol (**7**) under mild conditions with aqueous sulfuric acid and ether at room temperature gave a mixture consisting of 40% 6-hydroxy-6,7-dihydro-5*H*-benzocycloheptene (**8**) and only 12%



7 8 9

(1) E. C. Friedrich, *J. Org. Chem.*, **34**, 528 (1969).
(2) E. C. Friedrich and R. L. Holmstead, *ibid.*, **36**, 971 (1971).
(3) A. F. Trotman-Dickenson, *Advan. Free-Radical Chem.*, **1**, 1 (1965).
(4) W. G. Dauben, L Schutte, R. E. Wolf, and E. J. Deving, *J. Org. Chem.*, **34**, 2512 (1969).
(5) Radical **4** and its derivatives will be named and numbered for simplicity as derivatives of the bicyclo[4.1.0]heptenyl system rather than using the 1,1a,7,7a-tetrahydro-2*H*-cyclopropa[*b*]naphthalene nomenclature.
(6) S. Julia, M. Julia, and C. Hugnh, *Bull. Soc. Chim. Fr.*, 84 (1960).

2-hydroxymethyl-1,2-dihydronaphthalene (**9**). However, reaction of **7** under thermodynamic controlled conditions with acetic acid and concentrated sulfuric acid on a steam bath gave, after saponification of the acetate product, a 45% yield of 2-hydroxymethyl-1,2-dihydronaphthalene (**9**). Thus, since electronic factors which stabilize cations also stabilize the corresponding radicals, one might expect the cyclopropylcarbinyl–allylcarbinyl radical rearrangements in the benzobicyclo[4.1.1]heptene system to proceed preferentially with formation of the benzocycloheptadienyl radical (**6**).

As an entry into the benzobicyclo[4.1.0]hepten-2-yl radical system, we chose to use the same initial approach as we did with the cycloprop[2,3]indene system reported earlier,[2] *i.e.*, *via* free-radical α bromination of benzobicyclo[4.1.0]heptene (**10**). Besides studying the benzobicyclo[4.1.0]hepten-2-yl radical *via* free-radical α bromination procedures, it was also anticipated that free-radical organotin hydride reduction studies could be done on the cyclopropylcarbinyl and homoallyl bromides which we hoped to obtain as products from the bromination studies.

Results and Discussion

Bromination of Benzobicyclo[4.1.0]heptene (10).—A pure sample of benzobicyclo[4.1.0]heptene was prepared by Simmons–Smith[7] methylenation of 1,4-dihydronaphthalene. The free-radical NBS α bromination of **10**, using light as the initiator and a 1:1 mole ratio of **10** to NBS, proceeded smoothly at 26°. However, this procedure proved to be unsatisfactory for our purposes due to the formation of a considerable amount of the 2,5 dibromination product **11**. Although this compound could not be isolated and its structure proved directly, its formation was evidenced by its transformation into 2-(bromomethyl)naphthalene (**12**) upon standing or heating. This rearrangement presumably occurs *via* an ion-pair mechanism and its justification may be seen by consideration of the results of Julia and coworkers.[6] They observed that, when benzobicyclo[4.1.0]heptene-2,5-diol was treated with a 45% sulfuric acid solution in ether at room temperature for 6 hr, 2-(hydroxymethyl)naphthalene was obtained in a 62% yield after recrystallization. 1-Hydroxy-2-hydroxymethyl-1,2-dihydronaphthalene was proposed by Julia and coworkers as an intermediate, although it was not isolated.

(7) (a) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959); (b) E. P. Blanchard and H. E. Simmons, *ibid.*, **86**, 1337 (1964); (c) H. E. Simmons, E. P. Blanchard, and R. D. Smith, *ibid.*, **86**, 1347 (1964).

Because of the problem encountered using a 1:1 mole ratio of **10** to NBS, a 2:1 mole ratio was used in further studies. Also, the reactions were not carried to completion, but were stopped before all of the NBS had reacted. The results of the bromination reactions are given in Table I. The free-radical mechanism for the formation of the products of bromination of **10** should be analogous to that given earlier[1] for the bromination of cycloprop[2,3]indene.

TABLE I

NBS BROMINATION OF BENZOBICYCLO[4.1.0]HEPTENE (10) USING LIGHT INITIATION[a]

Starting material, mmol		Convn[b] of 10,	Temp,	Yield of products,[c] %				
10	NBS	%	°C	13	14	15	11	Unknown
1	1	95[d]	26	14	66	0	15	5
2	1	42	26	73	16	0	4	7
2	1	42	5	90	6	0	2	2

[a] All reactions were complete in 1.25 hr. [b] Based on starting 10. [c] Based on reacted 10; the results of duplicate runs. [d] The reaction mixture was allowed to stand for a period of 4 hr at room temperature after completion of the bromination.

Controls were carried out which showed that the initially formed cyclopropylcarbinyl bromide **13**, which was identified by its characteristic nmr absorption peaks, was not stable under the reaction conditions. It rearranged on standing, presumably *via* an ion-pair type mechanism, to the more thermodynamically stable bromide **14**. The rearrangement was followed by nmr and shown to have a half life of *ca.* 2 hours at room temperature in the dark. Under the reaction conditions, *i.e.*, 26° and irradiating with light, the rearrangement of **13** to **14** was complete in less than 1 hr. Therefore, the amounts of compound **14** shown in Table I probably result mainly from the ion-pair rearrangement of the cyclopropylcarbinyl bromide **13** rather than from **14** being a direct product of the radical reaction. No evidence for compound **15** was found; and, if it is formed in the reaction, its yield is either less than or equal to the amount of unknown reported in Table I.

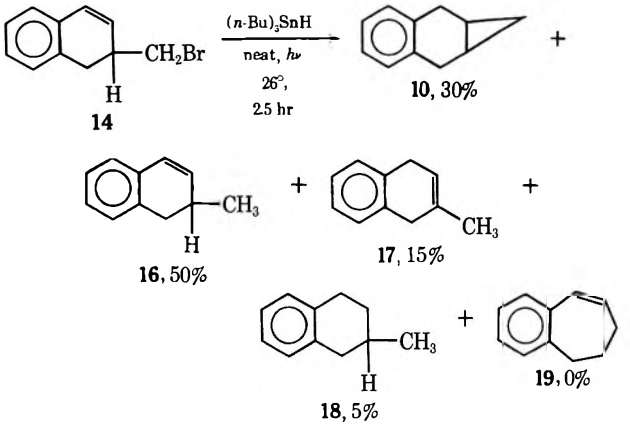
It is interesting to note that the nmr spectrum of 2-bromobenzobicyclo[4.1.0]heptene (**13**) in the reaction mixture showed only a single clean doublet at δ 5.7 (J = 2.5 Hz) for hydrogen attached to the carbon bearing the bromine atom rather than a pair of doublets due to exo and endo hydrogens, as was the case with the 1-bromocycloprop[2,3]indenes.[1] If both the exo and endo isomers are formed, either one predominates greatly or their absorptions occur at the same place with identical coupling.

Thus, in the NBS bromination of benzobicyclo[4.1.0]heptene (**10**) little can be said concerning the free-radical rearrangements of the initially formed cyclopropylcarbinyl radical **4**. If any rearrangement of the radical **4** does occur, it is probably to the primary homoallyl radical **5**, since no evidence for rearrangement to the secondary radical **6** was observed. However, one can say that bromination of **10** is very selective, giving primarily the cyclopropylcarbinyl bromide **13**. In fact it appears to be even more selective than the bromination of cycloprop[2,3]indene described earlier.[1,2]

With the hope of obtaining more information regarding free-radical rearrangements in the benzobicyclo[4.1.0]heptenyl system, we decided next to carry out organotin hydride reductions on the bromination products obtained.

Organotin Hydride Reductions.—Due to the problems of stability encountered with cyclopropylcarbinyl bromide **13**, reductions of this material could not be carried out. We were, however, able to obtain a pure sample of 2-(bromomethyl)-1,2-dihydronaphthalene (**14**) by the procedure reported in the Experimental Section. Thus, free-radical reductions were carried out on this material with tri-*n*-butyltin hydride.

The reductions were carried out using equimolar amounts of **14** and tri-*n*-butyltin hydride for 2.5 hr with photoinitiation and gave a 100% yield of hydrocarbon products based on reacted bromide **14**. The results, which are shown below, are the average values from experiments carried out in triplicate. The per cent yields shown are reproducible to *ca.* ±1%. The products were identified in the case of **10** and **16** by nmr analysis as described in the Experimental Section. As



is seen, a significant yield (30%) of benzobicyclo[4.1.0]-heptene (**10**) is formed. This can be compared to the 13% yield of cycloprop[2,3]indene formed when 1-bromomethylindene is reduced under the same conditions.[2]

Along with the normal reduction products, at least two other hydrocarbon products were obtained. On the basis of its mass spectrum one of the unknown compounds, obtained in 5% yield, was postulated to be 2-methyl-1,2,3,4-tetrahydronaphthalene (**18**). The mechanism for its formation is not readily apparent, however. The other product, obtained in 15% yield, is postulated to be 2-methyl-1,4-dihydronaphthalene (**17**) on the basis of its mass spectrum. The mechanism for the formation of **17** should be analogous to that postulated earlier for the formation of 3-methylindene[2] in the organotin hydride reductions of 1-bromomethylindene.

Finally, it is seen that benzosuberene (**19**), if formed at all, is present only in extremely small quantities. This result indicates that in this system, as well as in the cycloprop[2,3]indene system, cyclopropylcarbinyl–allylcarbinyl ring opening favors formation of the primary homoallyl radical over the secondary radical. The results also indicate that the postulated[1,2] electron-withdrawing inductive effect of the phenyl substituent in the cycloprop[2,3]indene system most likely has very little, if anything, to do with the direction of ring opening. Thus, the direction of ring opening probably depends mainly upon overlap between the orbital containing the odd electron and the adjacent orbitals of the cyclopropane ring leading to the primary radical being most favorable, as proposed by Dauben[4] for the 2-hydroxybicyclo[*n*.1.0]alk-2-yl radicals. In order to investigate this phenomenon in more detail, cyclopropylcarbinyl radical rearrangement studies in the simple bicyclo[3.1.0]hexyl and bicyclo[4.1.0]heptyl systems were carried out as are described in the following paper. In these two systems there are no electronic or steric complications caused by a phenyl or other substituent which might affect the direction of ring opening.

Experimental Section

Boiling points are uncorrected. Mass spectra were run on a CEC Model 21-104 single-focusing instrument by Mr. J. Voth. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

Nuclear Magnetic Resonance Spectra.—All nmr data were obtained using procedures similar to those described earlier[1,2] for the free-radical studies in the cycloprop[2,3]indene system.

Glpc Analyses.—Gas–liquid phase chromatographic (glpc) analyses were carried out using an Aerograph A90-P3 instrument equipped with a Pyrex injector insert. Separation of the bromination products was carried out on a 5 ft × 0.25 in. stainless steel column with a 20% SE-30 on 60/80 mesh Chromosorb W packing. The temperature of the column was maintained at 150° while the helium flow rate was at 60 ml/min. The retention times in minutes of the various compounds encountered were, benzobicyclo[4.1.0]heptene, 6; 2-bromomethyl-1,2-dihydronaphthalene, 20; and 2-bromomethylnaphthalene, 30. Analysis of the hydrocarbon products was carried out on three different columns: (1) a 2 m × 0.25 in. copper column with a 20% di-*n*-decylphthalate on 80/100 mesh Chromosorb W packing, with column temperature maintained at 120° and a helium flow rate of 86 ml/min—retention times in minutes of the various hydrocarbons encountered were, 2-methyl-1,2-dihydronaphthalene, 2-methyl-1,2,3,4-tetrahydronaphthalene, and 2-methyl-1,4-dihydronaphthalene, 24; benzobicyclo[4.1.0]heptane, 30; and benzosuberene, 56; (2) a 2 m × 0.25 in. copper column with 20% 3-nitro-3-methylpimelonitrile (NMPN) on 80/100 mesh Chromosorb W packing, with the temperature maintained at 100° and a helium flow rate of 47 ml/min—retention times in minutes on this column were, 2-methyl-1,2,3,4-tetrahydronaphthalene, 20; 2-methyl-1,2-dihydronaphthalene, 24; 2-methyl-1,4-dihydronaphthalene, 27; and benzobicyclo[4.1.0]-heptene, 29; (3) a 4 ft × 0.125 in. column with a 20% Carbowax 20M on 80/100 mesh Chromosorb W packing; temperature was maintained at 150° and helium flow rate at 30 ml/min—the retention times in minutes of the various hydrocarbon products were 2-methyl-1,2,3,4-tetrahydronaphthalene, 11; 2-methyl-1,2-dihydronaphthalene, 13; 2-methyl-1,4-dihydronaphthalene, 14; and benzobicyclo[4.1.0]heptene, 15.5.

Photolysis Equipment.—The light-initiated experiments were carried out using a 275-W G. E. sun lamp placed approximately 10 cm from the object being irradiated. All glassware used was Pyrex.

Preparation of 1,4-Dihydronaphthalene.—This material was prepared by the method of Ivanoff and Markov.[8] The reaction

(8) C. Ivanoff and P. Markov, *Naturwissenschaften*, **50**, 688 (1963).

of 19 g (0.78 mol) of powdered magnesium and 75 g (0.58 mol) of naphthalene in 1 l. of liquid ammonia gave, after work-up and distillation, 59 g of a mixture consisting of *ca.* 88% of 1,4-dihydronaphthalene (81.5% theory) and *ca.* 12% of naphthalene. Removal of the naphthalene was accomplished by the procedure of Sand and Gensler[9] using 30 g of the above mixture and 74 g (0.286 mol) of mercuric acetate. Distillation, after work-up, gave 12.2 g (46% recovery) of pure 1,4-dihydronaphthalene: bp 80–82° (*ca.* 8.5 mm); n^{24}D 1.5587 [lit.[10] bp 84° (9.5 mm); n^{33}D 1.5549]; nmr (CCl_4) δ 2.7 (s, 4 H), 5.35 (s, 2 H, vinyl), and 6.4–6.7 ppm (multiplet, 4 H, aromatic).

Preparation of Benzobicyclo[4.1.0]heptene (10).—Compound **10** was prepared using the LeGoff[11] modification of the Simons–Smith procedure. The zinc–copper couple was prepared using 0.8 g of cupric acetate monohydrate, 90 ml of glacial acetic acid, and 50 g (0.76 mol) of 30-mesh zinc granules. The couple was added to a 1-l. three-necked flask fitted with a dropping funnel and containing 200 ml of anhydrous ether. The mixture was stirred mechanically and heated to reflux. To the refluxing solution was added 60 g (0.34 mol) of dibromomethane and this mixture was allowed to reflux for 5–10 min. Then a solution containing 62 g (0.35 mol) of dibromomethane and 59 g of a mixture of 1,4-dihydronaphthalene (*ca.* 88%) and naphthalene was added dropwise to the flask over a period of 2 hr. This mixture was refluxed for 46 hr, after which time the solution became very pink and viscous. Normal work-up procedures were then carried out yielding a solution which, upon distillation through a 60-cm spinning band column, gave 15 g (26% isolated yield) of pure benzobicyclo[4.1.0]heptene: bp 93° (11 mm); nmr (CCl_4) δ 0.3 (m, 2 H, cyclopropyl, J = 5 Hz), 1.3 (m, 2 H, cyclopropyl), 3.0 (s, 4 H, benzylic), and 6.8 ppm (m, 4 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 144 (48), 129 (100), 128 (43), 116 (37), 115 (26).

Anal. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.38. Found: C, 91.84; H, 8.42.

Bromination of Benzobicyclo[4.1.0]heptene Using NBS.—Into a 15 × 150 mm Pyrex test tube was weighed 0.432 g (3.0 mmol) of benzobicyclo[4.1.0]heptene, 0.267 g (1.5 mmol) of NBS, and 2 ml of CCl_4. A thermometer was inserted into the solution and the tube was irradiated while being stirred magnetically. Cooling was carried out by running tap water over the outside of the tube, or in the lower temperature reactions, by a cold brine solution. After 1.25 hr irradiation was stopped. The succinimide was filtered off, and an nmr spectrum of the solution was taken immediately. 2-Bromobenzobicyclo[4.1.0]-heptene (**13**) was readily identified by its characteristic absorptions in the nmr spectrum: nmr (CCl_4, reaction mixture) δ 0.6 (m, 2 H, cyclopropyl), 1.8 (m, 2 H, cyclopropyl), 3.4 (d, 2 H, benzylic, J = 4 Hz), 5.7 (d, 1 H, –CHBr–, J = 2.5 Hz), and 7.3 ppm (m, 4 H, aromatic).

Product Analyses in the Bromination Reactions.—In the bromination of benzobicyclo[4.1.0]heptene, the per cent yields of the bromide products were determined by nmr using the aromatic region (4 H) as the internal standard. Yields of the various products were calculated in the following manner. 2-Bromobenzobicyclo[4.1.0]heptene (**13**) was identified by the characteristic doublet of the –CHBr group at δ 5.7 (J = 2.5 Hz). The amount of 2-bromomethyl-1,2-dihydronaphthalene (**14**) was determined by observing the change in the vinylic proton region (δ 6.0 and 6.6) when the reaction mixture was heated at 80° for 30 min. The difference between the amount of vinylic absorption before and after rearrangement of the cyclopropylcarbinyl bromide **13** gave the amount of bromide **14** formed initially. The amount of dibromide **11** was calculated from the nmr absorption of the methylene protons (δ 4.7, 2 H) of 2-(bromomethyl)naphthalene (**12**), which was formed from the dibromide upon heating at 80° for 30 min. No evidence for compound **15** was observed.

2-(Bromomethyl)naphthalene (12).—A sample of this material was isolated by preparative glpc techniques from the bromination product mixture. After recrystalization from ethanol, it had a melting point of 54–55° (lit.[12] mp 54°). Its nmr and ir spectra were identical with those of an authentic sample of **12** prepared by the method of Chapman and Williams[12] from NBS bromination of 2-methylnaphthalene in CCl_4 solution at reflux in the presence of benzoyl peroxide initiator: nmr (CCl_4) δ 4.7 (s, 2 H, CH_2Br) and 7.9 ppm (m, 7 H, aromatic).

Preparation and Isolation of 2-Bromomethyl-1,2-dihydronaphthalene (14).—Bromination, as previously described, was carried out on benzobicyclo[4.1.0]heptene (**10**). Removal of the CCl_4 solvent by distillation was carried out on the final reaction mixture. The remaining yellow mixture was then separated into its various components by preparative glpc. 2-Bromomethyl-1,2-dihydronaphthalene was collected from the 1-m SE-30 column previously described. The slightly yellow liquid (n^{24}D 1.6055) was identified by nmr: nmr (CCl_4) δ 2.6 (m, 1 H), 2.8 (s, 2 H, benzylic), 3.2 (d, 2 H, $-CH_2Br$, J = 7 Hz), 6.0 (q, 1 H, vinyl, J = 10, 4 Hz), 6.6 (d, 1 H, vinyl, J = 10 Hz), and 7.1 ppm (m, 4 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 224 (11), 222 (11), 143 (43), 142 (24), 141 (30), 129 (100), 128 (40), 115 (27).

Anal. Calcd for $C_{11}H_{11}Br$: C, 59.21; H, 4.96; Br, 35.81. Found: C, 59.51; H, 5.10; Br, 35.53.

Organotin Hydride Reductions of 2-Bromomethyl-1,2-dihydronaphthalene (14).—Into a polished glass nmr tube was weighed 0.223 g (1 mmol) of bromide **14** and 0.290 g (1 mmol) of tri-*n*-butyltin hydride. The mixture was then irradiated at 26°. Cooling was accomplished by running tap water over the tube. When the reaction was complete, and after spectra were taken, the mixture was distilled under vacuum through a micro apparatus to separate the hydrocarbon products. The hydrocarbon fraction was collected to a pot temperature of 120° (5 mm). The pot residue remaining consisted of tri-*n*-butyltin bromide. The hydrocarbons were then analyzed by nmr, glpc, and mass spectral techniques.

Product Analysis in the Organotin Hydride Reductions of 2-Bromomethyl-1,2-dihydronaphthalene (14).—In the tri-*n*-butyltin hydride reductions of **14**, the per cent yields of hydrocarbons were obtained by nmr examination using the aromatic region (4 H) as an internal standard as follows. The yield of benzobicyclo[4.1.0]heptene was determined by using the integration of its singlet at δ 3.0 (4 H). The relative yields of benzobicyclo[4.1.0]heptene, 2-methyl-1,2-dihydronaphthalene (**16**), 2-methyl-1,2,3,4-tetrahydronaphthalene (**18**), and 2-methyl-1,4-dihydronaphthalene (**17**) were then determined by glpc analysis as described below. The actual yields of **16**, **17**, and **18** were then calculated using the previously calculated yield for benzobicyclo[4.1.0]heptene obtained by nmr analysis.

The hydrocarbon mixture was first injected into the didecylphthalate glpc column. Two peaks emerged and the corresponding hydrocarbons were collected. One was found to be benzobicyclo[4.1.0]heptene by comparison of its spectral properties with those of an authentic sample. The other peak collected was found to be a mixture of hydrocarbons. This mixture was injected into the NMPN column previously described yielding three peaks which were collected. The major component was found to be 2-methyl-1,2-dihydronaphthalene (**16**): nmr (neat) δ 0.8 (d, 3 H, $-CH_3$, $-CH_3$, J = 7 Hz), 2.4 (m, 3 H, CH_2-CH–), 5.4 (d, 1 H, vinyl, J = 9 Hz), 6.05 (d, 1 H, vinyl, J = 9 Hz), and 6.7 ppm (s, 4 H, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 144 (35.5), 129 (100), 128 (35), 115 (11).

Anal. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.38. Found: C, 91.73; H, 8.28.

Another component was determined to be 2-methyl-1,2,3,4-tetrahydronaphthalene (**18**) by nmr analysis and comparison of its mass spectrum to the literature:[13] mass spectrum (70 eV) *m/e* (rel intensity) 146 (49), 131 (23), 117 (11.2), 104 (100), 91 (36).

The last component was postulated to be 2-methyl-1,4-dihydronaphthalene (**97**). The mass spectrum gave a parent ion of *m/e* 144: mass spectrum (70 eV) *m/e* (rel intensity) 144 (34.57), 130 (10.7), 129 (100), 128 (34.5), 115 (10.37).

Preparation of Benzosuberene (19).—The procedure used essentially follows that of Huisgen, *et al.*[14] Using 1 g (6.25 mmol) of benzosuberone, 0.95 g of the corresponding alcohol was prepared by reduction with lithium aluminum hydride. Dehydra-

(9) I. Sand and O. Gensler, *Ber.*, **36**, 3705 (1903).
(10) K. Von Anwers, *ibid.*, **46**, 2988 (1913).
(11) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).
(12) N. B. Chapman and F. A. Williams, *J. Chem. Soc.*, 5044 (1952).
(13) "Mass Spectral Data Tables," American Petroleum Institute, Project 44, Serial No. 1211.
(14) R. Huisgen, E. Rauenbusch, G. Seidle, and I. Wimmer, *Justus Liebigs Ann. Chem.*, **671**, 41 (1964).

tion was accomplished using polyphosphoric acid yielding, after distillation, 0.5 g (55% yield) of pure benzosuberene: bp 100° (10 mm); n^{24}D 1.5863 [lit.[14] bp 100–102° (10 mm); n^{25}D 1.5867]; nmr (CCl_4) δ 2.0 (m, 2 H), 2.35 (m, 2 H), 2.85 (m, 2 H), 5.8 (sextet, 1 H, J = 12.5 and 1.5 Hz, vinyl), 6.4 (sextet, 1 H, J = 12.5 and 1.5 Hz, vinyl), and 7.0 ppm (s, 4 H, aromatic); mass spectrum (70 eV) m/e (rel intensity) 144 (45), 129 (100), 128 (35), 116 (20), 115 (27).

Registry No.—**10**, 6571-72-8; **13**, 34825-86-0; **14**, 34825-87-1; **16**, 21564-79-4.

Acknowledgment.—The authors wish to thank the Academic Senate Committee on Research of the University of California, Davis, for partial support of this research.

Cyclopropylcarbinyl–Allylcarbinyl Radical Rearrangements in the Simple Bicyclo[3.1.0]hexyl and -[4.1.0]heptyl Systems

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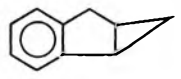
Received November 30, 1971

A study of the low-temperature photoinitiated free-radical tri-*n*-butyltin hydride reductions of the 2-bicyclo[3.1.0]hexyl and -[4.1.0]heptyl chlorides is reported. Cyclopropylcarbinyl–allylcarbinyl radical rearrangements in these systems were observed to be very selective, yielding almost entirely the primary allylcarbinyl radical products *via* external cyclopropane bond fission. Studies of the reversibility of the cyclopropylcarbinyl–allylcarbinyl radical rearrangements in the bicyclo[3.1.0]hexyl and -[4.1.0]heptyl systems, by means of tri-*n*-butyltin hydride reductions of the corresponding allylcarbinyl halides, were also carried out. Reversibility was observed, under the reduction conditions employed, only with the 3-cyclopentenylmethyl and 4-cycloheptenyl radicals.

In previous papers[1,2] we reported our studies, by means of both free-radical bromination and tin hydride reduction procedures, of cyclopropylcarbinyl–allylcarbinyl free-radical rearrangements in the cycloprop[2,3]indene (**1**) benzobicyclo[4.1.0]heptene (**2**) systems. It



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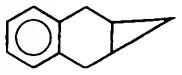
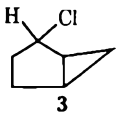


2

was noted that with both systems rearrangement of cyclopropylcarbinyl radicals to primary allylcarbinyl radicals proceeds in preference to rearrangement to secondary benzylic or simple secondary allylcarbinyl radicals, respectively. Based on the stabilities expected for the rearranged radical products,[3] the opposite behavior might have been predicted. However, a reasonable explanation is that the directionality of the rearrangements is controlled by overlap between the orbital containing the odd electron and the adjacent orbitals of the cyclopropane ring, leading to the primary radical being most favorable, and of more importance than the stabilities of the radical products as reflected in the energies of the respective activated complexes for rearrangement. This is similar to the stereoelectronic, conformational control argument proposed by Dauben[4] to explain the preferred direction of cyclopropylcarbinyl–allylcarbinyl rearrangements of the 2-hydroxybicyclo[3.1.0]hex-2-yl and -[4.1.0]hept-2-yl radicals.[5]

In order to examine in greater detail the apparent preference of cyclopropylcarbinyl radicals in bicyclo[*n*.1.0]alkyl systems to undergo external cyclopropane bond fission during rearrangement to give primary allylcarbinyl radicals rather than undergo internal bond fission to give secondary allylcarbinyl radicals, a study of cyclopropylcarbinyl radical rearrangements in the simple bicyclo[3.1.0]hexyl and -[4.1.0]heptyl systems was undertaken. To do this, the chlorides **3** and **4** were



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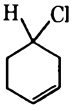

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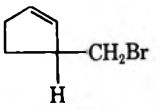

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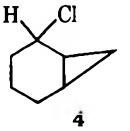

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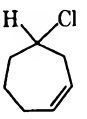

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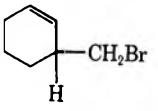


8

reduced under free-radical conditions[6] using tri-*n*-butyltin hydride. In these systems any effects, either steric, electronic, or conformational, due to the phenyl substituents present in the analogous cycloprop[2,3]indene (**1**)[1] or benzobicyclo[4.1.0]heptene (**2**)[2] systems or to the α-hydroxy groups in Dauben's[4] compounds, are not present. To be able to better understand the results obtained with the cyclopropylcarbinyl systems, we also carried out tri-*n*-butyltin hydride reductions on the halides **5**–**8**, related to the allylcarbinyl radicals which might be produced by cyclopropylcarbinyl–allylcarbinyl rearrangements of the initial radicals produced from **3** and **4**. It was necessary to use the bromides rather than the chlorides in the primary systems **7** and **8** because of the low reactivities of the chlorides under our low-temperature tin hydride reduction conditions.

(1) E. C. Friedrich and R. L. Holmstead, *J. Org. Chem.*, **36**, 971 (1971).

(2) E. C. Friedrich and R. L. Holmstead, *ibid.*, **37**, 2546 (1972).

(3) (a) S. J. Cristol and R. V. Barbour, *J. Amer. Chem. Soc.*, **90**, 2832 (1968); (b) D. C. Neckers, A. P. Schaap, and J. Hardy, *ibid.*, **88**, 1265 (1966); (c) D. C. Neckers and A. P. Schaap, *J. Org. Chem.*, **32**, 22 (1967).

(4) W. G. Dauben, L. Schutte, R. E. Wolf, and E. J. Deving, *ibid.*, **34**, 2512 (1969).

(5) After the present work was already completed, a communication by A. L. J. Beckwith and G. Phillipou, *Chem. Commun.*, 658 (1971), appeared describing an elegant, clear-cut example in which highly selective stereoelectronic control of radical fragmentation in the 3β,5-cyclocholestan-6-yl radical takes place. Also, P. K. Freeman, M. F. Grostic, and F. A. Raymond, *J. Org. Chem.*, **36**, 905 (1971), reported that free-radical addition of methanethiol to bicyclo[3.1.0]hex-2-ene gives, selectively, besides the bicyclic product resulting from simple addition to the double bond, *cis*- and *trans*-3-methyl-5-thiomethylcyclopentene. No evidence for cyclopropane ring opening to form a secondary radical was observed.

(6) (a) H. G. Kuivila, *Accounts Chem. Res.*, **1**, 229 (1968); (b) W. P. Neumann, "The Organic Chemistry of Tin," Wiley, New York, N. Y., 1970.

Results and Discussion

Synthesis of Starting Halides.—2-Chlorobicyclo[3.1.0]hexane (**3**) (89% endo, 11% exo) was prepared in 80% yield, as described by Freeman and coworkers,[7] by the reaction of thionyl chloride with *endo*-2-bicyclo[3.1.0]hexanol. 2-Chlorobicyclo[4.1.0]heptane (**4**) (82% endo, 18% exo) in 90% yield and 4-chlorocyclohexene(**5**) in 90% yield were prepared by similar procedures starting with *endo*-2-bicyclo[4.1.0]heptanol and 4-hydroxycyclohexene, respectively.

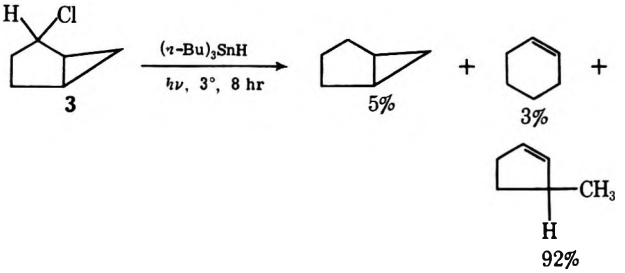
Attempts to prepare a pure sample of 4-chlorocycloheptene (**6**) by reaction of 4-hydroxycycloheptene with thionyl chloride and tri-*n*-butylamine in ether under reflux, or by reaction of *endo*-2-bicyclo[4.1.0]heptanol with 37% hydrochloric acid at room temperature, were unsuccessful. In the first case a 43% yield of a 70:30 mixture, and in the second case a 90% yield of a 82:18 mixture, of 6 and 3-(chloromethyl)cyclohexene was obtained. Attempts to separate the isomeric chlorides by preparative glpc were not successful. However, a technique was devised for carrying out the organotin hydride reductions directly on the mixture so that separation of the isomeric chlorides was not absolutely necessary.

In the preparation of 3-(bromomethyl)cyclopentene (**7**), the procedure of Hanack and Schneider[8] was employed with only slight modifications for the synthesis of methyl cyclopentene-3-carboxylate. The methyl ester was then reduced to 3-(hydroxymethyl)cyclopentene in 81% yield using the selective Vitride reagent.[9] Reaction of the alcohol with triphenylphosphine and carbon tetrabromide in dichloromethane[10] gave, after work-up and distillation, a mixture consisting of 40% bromoform and 60% **7** (55% yield). The bromide **7** was purified by preparative scale glpc.

For the preparation of 3-(bromomethyl)cyclohexene (**8**) advantage was taken of a side reaction reported by Staley and Wiseman[11] in their studies of the reaction of 5,5-dimethylcyclohexen-3-ol with methylene iodide and a zinc–copper couple. Thus, 3-hydroxycyclohexene upon reaction with methylene iodide and a zinc–copper couple under reflux in ether for 12 hr gave a 23% yield, after work-up and distillation, of pure 3-(iodomethyl)-cyclohexene.[12] This was then treated with tetraethylammonium bromide in DMF to give an 85% yield of **8**, based on starting iodide.

Tri-*n*-butyltin Hydride Reductions in the 2-Bicyclo[3.1.0]hexyl and Related Allylcarbinyl Systems.—All reductions described below were carried out at least in duplicate, and the product compositions reported are reproducible to ±2%. The tri-*n*-butyltin hydride to halide mole ratio was 1:1, and the yield of hydrocarbon products was greater than 97% in all cases. Also, controls showed that all reactants and products were stable toward rearrangement or further reaction, respectively, under the reduction conditions.

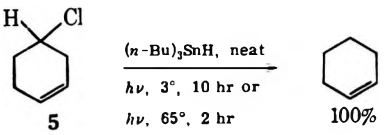
The 11% *exo*-, 89% *endo*-2-chlorobicyclo[3.1.0]-hexane mixture (**3**) was reduced in the absence of a solvent with tri-*n*-butyltin hydride at 3° using light initiation. The results of the reductions are shown below.



3-Methylcyclopentene, the product obtained from rearrangement of the initially formed cyclopropylcarbinyl radical to give the primary allylcarbinyl radical, is formed in considerably higher yield than is cyclohexene. Thus, the direction of cyclopropylcarbinyl–allylcarbinyl radical rearrangement observed here is very similar to that observed in the cycloprop[2,3]-indene system.[2]

The high selectivity of the ring fission in the reduction of **3** can be accounted for on the basis of better orbital overlap between the outer cyclopropane bond and the adjacent radical center, as Dauben[4] has suggested. From examination of molecular models it appears that maximum orbital overlap for opening of the outside cyclopropane bond requires a chair form conformation of the bicyclo[3.1.0]hexane ring. However, nmr studies[13] indicate that the preferred conformation of this system is a boat form. If this is the case, models suggest that orbital overlap control only slightly prefers fission of the outside over the inside bond of the cyclopropane ring. However, a planar five-membered ring also shows clear preference for opening of the outer bond.

It should be noted that selective formation of 3-methylcyclopentene could also result if the primary radical precursor of 3-methylcyclopentene is much more reactive toward hydrogen atom abstraction from the tin hydride than is the secondary radical precursor of cyclohexene, and if the secondary radical formation is rapidly reversible. To evaluate this possibility we carried out a tri-*n*-butyltin hydride reduction on 4-chlorocyclohexene (**5**) to find out whether any bicyclo[3.1.0]hexane or 3-methylcyclopentene, formed *via* ring closure to the cyclopropylcarbinyl radical, is obtained. The results are shown below. Cyclohexene was the



sole product formed, either at 3° or at 65°, thus eliminating the possibility of rapid reversibility of the formation of the 4-cyclohexenyl radical. This result is similar to that of Slaugh,[14] who observed that the thermal decomposition of *tert*-butyl cyclohexene-4-percarboxylate at 140° in the presence of *p*-cymene gives cyclohexene as the only monomeric product. Thus, the orbital overlap explanation for selective

(7) P. K. Freeman, F. A. Raymond, J. C. Sutton, and W. R. Kindley, *J. Org. Chem.*, **32**, 24 (1967).

(8) M. Hanack and H. J. Schneider, *Tetrahedron*, **20**, 1363 (1964).

(9) Hanack and Schneider[8] reported obtaining only a very small yield of the desired alcohol by reduction with lithium aluminum hydride.

(10) R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, **36**, 403 (1971).

(11) S. W. Staley and F. L. Wiseman, Jr., *ibid.*, **35**, 3868 (1970).

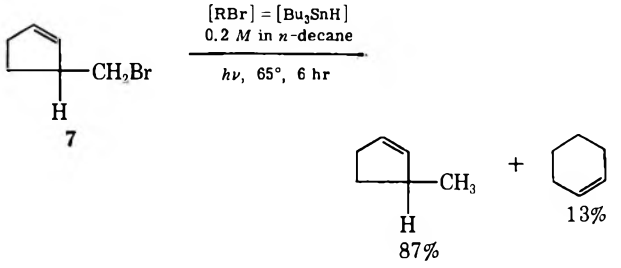
(12) Note that reaction of 3-hydroxycyclopentene with CH_2I_2 and a Zn–Cu couple under reflux in ether for 24 hr gave only a 28% yield of *endo*-2-bicyclo[3.1.0]hexanol and no observable 3-(iodomethyl)cyclopentene.

(13) S. Winstein, E. C. Friedrich, R. Baker, and Yang-I Lin, *Tetrahedron, Suppl. 8, Part II*, 621 (1966).

(14) L. H. Slaugh, *J. Amer. Chem. Soc.*, **87**, 1522 (1965).

fission of the outer bond of the cyclopropane ring in the bicyclo[3.1.0]hexane system seems to best explain the results obtained.

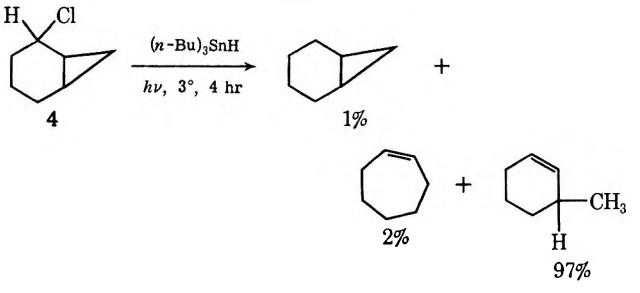
As a final experiment in our studies of cyclopropylcarbinyl–allylcarbinyl radical rearrangements and their reversibility in the bicyclo[3.1.0]hexane system, we carried out the tri-*n*-butyltin hydride reduction of 3-(bromomethyl)cyclopentene (**7**). Using a 1:1 mole ratio of **7** to tin hydride at 3° with light initiation in the absence of a solvent, only 3-methylcyclopentene was obtained. In an attempt to give the initially formed 3-cyclopentenylmethyl radical more time to undergo possible ring closure before capture by hydride occurred, we also carried out a reduction of **7** in *n*-decane solvent and at higher temperature. The results are shown below. The presence of cyclohexene in the



product mixture indicates that ring closure to the cyclopropylcarbinyl radical, although slow, does actually occur. These results also agree with those of Slaugh,[14] who observed that the thermal decomposition of *tert*-butyl cyclopenten-3-yl-peracetate at 140° in the presence of *p*-cymene gives both 3-methylcyclopentene (12%) and cyclohexene (47%).

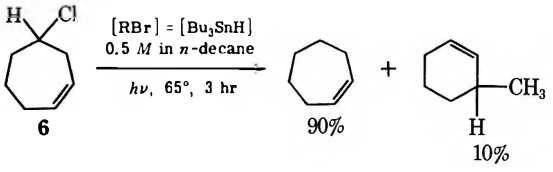
Tri-*n*-butyltin Hydride Reductions in the 2-Bicyclo[4.1.0]heptyl and Related Allylcarbinyl Systems.—All reductions described in this section were also carried out at least in duplicate, and the product compositions reported are reproducible to ±2%. The yields of hydrocarbon products were greater than 97% in all cases. Controls showed that all reactants and products were stable toward rearrangement or further reaction, respectively, under the reduction conditions employed. All reductions were done using a 1:1 mole ratio of tri-*n*-butyltin hydride to halide.

The 18% *exo*-, 82% *endo*-2-chlorobicyclo[4.1.0]-heptane mixture (**4**) was reduced at 3° using light initiation with tri-*n*-butyltin hydride in the absence of a solvent. The results shown below indicate that cyclo-

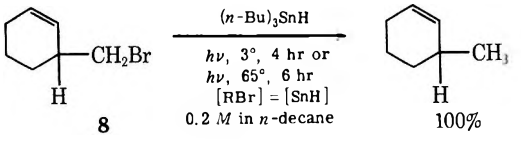


propylcarbinyl–allylcarbinyl radical rearrangement occurs here, as in the 2-bicyclo[3.1.0]hexyl system, with high selectivity to give a primary allylcarbinyl radical in preference to a secondary allylcarbinyl radical. Consideration of molecular models of the bicyclo[4.1.0]-heptane system indicate that only when the cyclohexane ring is in the boat form is inside cyclopropane bond fission preferred. All other conformations would lead to better overlap of the p orbital containing the radical electron with the outside bond of the cyclopropane ring. Since a boat form bicyclo[4.1.0]heptane conformation is clearly unfavorable,[4] a similar orbital overlap argument to that advanced for the bicyclo-[3.1.0]hexane system can be given to explain the very selective β scission of the outer cyclopropane bond in the present case.

To examine the possibility of rapid reversibility of the 2-bicyclo[4.1.0]hexyl–cyclohepten-4-yl radical rearrangement, tri-*n*-butyltin hydride reduction of 4-chlorocycloheptene (**6**) was carried out. Unfortunately, as mentioned earlier, we were unable to obtain a pure sample of **6**, but only an isomeric mixture of **6** and 3-(chloromethyl)cyclohexene. However, the tin hydride reduction could still be carried out on this mixture, since control experiments showed a pure sample of 3-(chloromethyl)cyclohexene to be unreactive toward tri-*n*-butyltin hydride both at 3° and at 65° under the reaction conditions employed. Thus, the reduction of **6** with tri-*n*-butyltin hydride at 3° in the absence of a solvent gave cycloheptene as the only product. However, when the reduction was carried out at 65° and the reactants were diluted with *n*-decane, 3-methylcyclohexene was also formed. Thus, the cyclopropylcarbinyl–allylcarbinyl radical rearrangement in question is clearly reversible, although slow.



The last compound of the series to be studied was 3-(bromomethyl)cyclohexene (**8**). The reduction of **8** with tri-*n*-butyltin hydride both at 3° in the absence of a solvent, or at 65° in the presence of solvent *n*-decane, gave only 3-methylcyclohexene. Thus, reversibility of



the 2-bicyclo[4.1.0]hexyl–cyclohexene-3-methyl radical rearrangement does not occur with either the low-temperature neat or high-temperature dilution conditions.

As a final point, brief comment should be made on the reasons for the observed reversibility or irreversibility of the cyclopropylcarbinyl–allylcarbinyl radical rearrangements studied in the present work. For example, allylcarbinyl–cyclopropylcarbinyl radical ring closure was observed indirectly with the 3-cyclopentenylmethyl and 4-cycloheptenyl radical systems, but was not observed at all with the 3-cyclohexenylmethyl and 4-cyclohexenyl radical systems under the reaction conditions employed. However, note that ring closure was clearly observed with both of the related indene-1-methyl[1] and 1,2-dihydronaphthalene-2-methyl[2] radical systems.

The simplest explanation for the occurrence or non-occurrence of ring closure by an allylcarbinyl radical system is one based on orbital overlap considerations. For ring closure to be favorable the p orbital containing the odd electron and the orbitals of the double bond must be close enough together and of proper orientation for good overlap to take place. From inspection of simple molecular models it appears that the above conditions are better satisfied in the systems where ring closure was observed than in those systems where no ring closure took place, although the situation is not clear cut. The reason for the occurrence of ring closure with the 1,2-dihydronaphthalene-2-methyl radical[2] but not with the closely related simple 3-cyclohexenylmethyl radical is probably due mainly to flattening of the six-membered ring by the phenyl substituent in the former system, thus orienting the double-bond orbitals better for overlap with the radical center.

Experimental Section

Boiling points, nmr and mass spectra, and microanalyses were obtained as previously reported.[2]

Glpc Analyses.—These were done using a Varian Aerograph Series 1400 flame ionization instrument. Separation of the hydrocarbon products was carried out on a 3 m × 0.125 in. copper column with a 20% 1,2,3-tris(2-cyanoethoxy)propane (TCEP) on 60/80 mesh firebrick packing. The column temperature was maintained at 65° while the helium flow rate was 10–15 ml/min. The retention times in minutes of the various compounds encountered were, 3-methylcyclopentene, 2.2; bicyclo[3.1.0]hexane, 3.2; cyclohexene, 3.5; 3-methylcyclohexene, 5.8; bicyclo[4.1.0]heptane, 8.5; and cycloheptene, 8.7.

2-Chlorobicyclo[3.1.0]hexane (3).—The procedure used for the preparation of this material followed that of Freeman and coworkers.[7] 2-Chlorobicyclo[3.1.0]hexane was obtained in an 80% yield based on reacted *endo*-2-bicyclo[3.1.0]hexanol:[15] bp 50–70° (11 mm) (pot); n^{24}D 1.4912 (literature, no physical constants reported); nmr (neat) δ 0.5 (m, 2 H), 1.65 (b m, 6 H), and 4.5 ppm (m, 1 H, CHCl); mass spectrum (70 eV) *m/e* (rel intensity) 118 (3.08), 116 (9.67), 81 (44), 80 (100), 79 (48). The ratio of endo to exo chloride (89:11) formed was similar to that reported by Freeman.[7]

4-Chlorocyclohexene (5).—4-Hydroxycyclohexene, the precursor to 5, was prepared by the method of Zelinski and Zitova.[16] Using the procedure of Zweifel, *et al.*,[17] for conversion of alcohols to the corresponding chlorides, 4-chlorocyclohexene was obtained from 4-hydroxycyclohexene in 90% yield: bp 35° (14 mm); n^{24}D 1.4813 (no literature[7] physical constants, only nmr spectrum reported); nmr (neat) δ 1.8 (b m, 6 H), 3.8 (m, 1 H, CHCl), and 5.3 ppm (b s, 2 H, vinyl); mass spectrum (70 eV) *m/e* (rel intensity) 118 (3.08) 116 (9.67), 80 (100), 79 (48), 54 (42).

3-(Hydroxymethyl)cyclopentene.—Methyl cyclopentene-3-carboxylate, the precursor to 3-(hydroxymethyl)cyclopentene, was prepared *via* the method of Hanack and Schneider.[8] For the reduction of the methyl ester to the corresponding alcohol, the following procedure was used. To a 50-ml three-necked microware flask fitted with a calcium chloride drying tube, dropping funnel, and a low-temperature alcohol thermometer was added 3.0 g (24 mmol) of methyl cyclopentene-3-carboxylate and 30 ml of anhydrous ether. The magnetically stirred solution was then cooled to −40°, and 7.25 ml (7.5 g, 26 mmol of hydride) of Vitride reducing agent, diluted with 5 ml of anhydrous ether, was added dropwise over a period of 20 min. The resulting light yellow solution was stirred at −40° for 15 min longer, after which time the solution was allowed to warm up to 0°. At this point several drops of 20% sulfuric acid were added to destroy excess hydride. The resulting mixture was extracted twice with 20% sulfuric acid, water, and saturated sodium chloride solution and then dried over anhydrous magnesium sulfate. Removal of the ether yielded a light yellow liquid which upon distillation through a short-path apparatus gave 1.9 g (81% yield) of 3-(hydroxymethyl)cyclopentene: bp 52° (12 mm); n^{24}D 1.4745 [lit.[8] bp 51–53° (12 mm)]; nmr (CCl_4) δ 1.3–2.6 (b m, 4 H), 2.75 (m, 1 H, $CHCH_2OH$), 3.4 (d, 2 H, CH_2OH, J = 6.5 Hz), 4.85 (s, 1 H, OH), and 5.7 ppm (m, 2 H, vinyl); mass spectrum (70 eV) *m/e* (rel intensity) 98 (1.31), 80 (18.8), 67 (100), 66 (14.5), 41 (28), 39 (23), 27 (10).

3-(Bromomethyl)cyclopentene (7).—The alcohol–bromide conversion procedure of Weiss and Snyder[10] was employed for the conversion of 3-(hydroxymethyl)cyclopentene to 7. Bromoform, a side product of the reaction, was removed from the distilled reaction mixture by preparative glpc using a 2 m × 0.375 in. column packed with 10% silicone SF-96, 0.25% Carbowax 20M on 60/80 mesh Chromosorb G. Pure 3-(bromomethyl)cyclopentene was obtained in a 55% yield based on reacted 3-(hydroxymethyl)cyclopentene: bp *ca.* 53° (12 mm); n^{24}D 1.5066; nmr (CCl_4) δ 1.4–2.4 (b m, 2 H), 2.2–2.6 (m, 2 H), 3.0–3.5 (m, 1 H, $CHCH_2Br$), 3.3 (m, 2 H, CH_2Br), and 5.6–6.0 ppm (m, 2 H, vinyl); mass spectrum (70 ev) *m/e* (rel intensity) 162 (4), 160 (4.1), 81 (31), 79 (12), 67 (100), 53 (10), 41 (16), 39 (17), 27 (14).

Anal. Calcd for C_6H_9Br: C, 44.75; H, 5.63; Br, 49.62. Found: C, 44.61; H, 5.70; Br, 49.44.

2-Chlorobicyclo[4.1.0]heptane (4).—The procedure used was similar to that employed for the preparation of 2-chlorobicyclo[3.1.0]hexane.[7] 2-Chlorobicyclo[4.1.0]heptane was obtained in a 90% yield based on reacted *endo*-2-bicyclo[4.1.0]heptanol:[15] bp (pot) 50–70° (10 mm); n^{24}D 1.4921; nmr (neat) δ 0.05–0.34 (q, 0.36, exo CH_2 cyclopropyl, J = 5 Hz), 0.37–1.1 (complex multiplet, 1.64 H, endo CH_2 cyclopropyl), 1.6 (b m, 8 H), and 4.65 ppm (b m, 1 H, CHCl); mass spectrum (70 eV) *m/e* (rel intensity) 132 (3.27), 130 (9.97), 95 (71.9), 94 (31.7), 81 (57), 79 (100), 77 (25), 67 (49.5), 53 (37), 41 (51), 39 (79), 27 (56).

Anal. Calcd for $C_7H_{11}Cl$: C, 64.36; H, 8.48; Cl, 27.14. Found: C, 64.75; H, 8.61; Cl, 27.18.

The ratio of endo to exo bicyclic chlorides was determined to be approximately 82:18, as calculated by comparison of the nmr absorption values of the cyclopropylmethylene protons in *endo*- and *exo*-2-bicyclo[4.1.0]heptanol[18] to the values obtained for the bicyclic chloride mixture. The amount of exo chloride was thus determined from the quartet at 0.05–0.34 ppm, while the amount of endo chloride was determined from the multiplet at 0.37–1.1 ppm.

4-Hydroxycycloheptene.—The procedure used for preparation of this material was that of Friedrich and Winstein.[19] *endo*-2-Bicyclo[4.1.0]heptanol[15] (4.0 g, 35.7 mmol) was treated with 40 ml of a 0.5% by weight solution of 70% perchloric acid in glacial acetic acid at 50° for 45 min. The work-up consisted of extracting the resulting yellow solution with pentane, washing the pentane with three 25-ml portions of water, 20 ml of saturated $NaHCO_3$, and two 20 ml portions of saturated NaCl and drying the pentane extract over anhydrous $MgSO_4$. After removal of the pentane by distillation, the remaining liquid was added dropwise to a mixture of 1.35 g (35.7 mmol) of lithium aluminum hydride in 150 ml of anhydrous ether. This mixture was stirred at room temperature for 2 hr. The mixture was worked up in the usual manner, and after removal of the ether the resulting yellow liquid was distilled in a one-piece micro apparatus to give 3.4 g (85% yield) of pure 4-hydroxycycloheptene: bp (pot temperature) 80° (10 mm); n^{25}D 1.4869 [lit.[19] bp (pot temperature) 90° (20 mm); n^{25}D 1.4870]; nmr (CCl_4) δ 1.0–2.5 (b m, 8 H), 3.4 (m, 1 H, CHOH), 3.8 (s, 1 H, OH), and 5.6 ppm (m, 2 H, vinyl).

Attempted Preparation of Pure 4-Chlorocycloheptene (6).—Two procedures were tried. The first was similar to that reported earlier in the conversion of 4-hydroxycyclohexene to 4-chlorocyclohexene, but using 4-hydroxycycloheptene (3.0 g, 26.8 mmol). After the usual work-up procedure a dark liquid resulted which, upon distillation, yielded 1.5 g (43%) of a colorless liquid, bp *ca.* 65° (25 mm). Analysis of this liquid by nmr showed it to be a mixture of 4-chlorocycloheptene and 3-(chloromethyl)cyclohexene in a ratio of 70:30. Since 3-(chloromethyl)-cyclohexene had already been prepared by an alternative route, described in a later section, its nmr spectrum was available. The nmr spectrum of 4-chlorocycloheptene was thus able to be determined by difference and is as follows: nmr (neat) δ 1.0–2.5 (b m, 6 H), 2.6 (t, 2 H, J = 6 Hz), 3.85 (m, 1 H, CHCl), and

(15) W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **85**, 468 (1963).

(16) D. Zelinski and A. N. Zitova, *Ber.*, **64**, 1399 (1931).

(17) G. Zweifel, A. Horng, and J. T. Snow, *J. Amer. Chem. Soc.*, **92**, 1427 (1970).

(18) K. E. Rubenstein, Ph D. Thesis, University of Wisconsin, 1967, pp 90, 94.

(19) E. C. Friedrich and S. Winstein, unpublished work.

5.7 ppm (m, 2 H, vinyl, J = 5.5 Hz). Quantitative values were determined using the vinyl region as an internal standard, the multiplet at 3.85 ppm of 4-chlorocycloheptene, and the sharp doublet at 3.38 ppm of 3-(chloromethyl)cyclohexene. Attempts to separate the isomeric mixture by preparative glpc using columns containing TCEP, NMPN, SE-30, and Carbowax 20M were not successful. Elemental analysis was thus carried out directly on the isomeric mixture.

Anal. Calcd for $C_7H_{11}Cl$: C, 64.36; H, 8.48; Cl, 27.14. Found: C, 64.61; H, 8.54; Cl, 26.94.

The other method attempted for the preparation of **6** was a modification of the procedure used by Staley and Wiseman[11] for the preparation of 4-bromo-6,6-dimethylcycloheptene. Into a small flask was placed 1 g (8.93 mmol) of *endo*-2-bicyclo[4.1.0]-heptanol[15] and 6 ml of 37% hydrochloric acid. This mixture was stirred at room temperature for 3 hr, after which time the solution was extracted with pentane. The pentane extract was washed with water, saturated sodium bicarbonate, and saturated sodium chloride, and dried over anhydrous sodium sulfate. Removal of the pentane yielded a light yellow liquid which upon distillation gave 1.05 g (90%) of an isomeric mixture of 4-chlorocycloheptene and 3-(chloromethyl)cyclohexene in a ratio of 82:18, respectively.

3-(Iodomethyl)cyclohexene.—The procedure used was a modification of that employed by Staley and Wiseman[11] for the preparation of 5,5-dimethyl-3-(iodomethyl)cyclohexene. The reaction of 30 g (0.31 mol) of 3-hydroxycyclohexene, 38 g (0.57 mol) of 30 mesh zinc–copper couple, and 110 g (0.41 mol) of methylene iodide in ether was carried out under reflux for 12 hr. At this point, the flask was cooled in an ice bath and then *ca.* 100 ml of saturated NH_4Cl was added slowly dropwise to the pink viscous mixture. Work-up was carried out in the usual manner. After removal of the ether by distillation, the remaining brownish liquid was distilled quickly through a small distillation apparatus to remove any starting material. The resulting distillate was then redistilled through a 60-cm spinning-band column to give 15.2 g (22.5%) of pure 3-(iodomethyl)cyclohexene: bp 85° (10 mm); $n^{24}D$ 1.5610; nmr (CCl_4) δ 1.7 (b m, 6 H), 2.35 (m, 1 H, $CHCH_2I$), 3.1 (d, 2 H, CH_2I, J = 7 Hz), and 5.7 ppm (m, 2 H, vinyl); mass spectrum (70 eV) m/e (rel intensity) 222 (0.44), 127 (8.44), 95 (100), 79 (9.9), 67 (22.5), 55 (15), 41 (26), 39 (21).

Anal. Calcd for $C_7H_{11}I$: C, 37.86; H, 4.99; I, 57.14. Found: C, 38.04; H, 5.05; I, 56.90.

3-(Chloromethyl)cyclohexene.—This material was prepared from 3-(iodomethyl)cyclohexene using a procedure similar to that employed by Weaver and Hutchinson[20] for the conversion of *n*-butyl iodide to *n*-butyl chloride. 3-(Iodomethyl)cyclohexene (3.0 g, 13.5 mmol) was added to a magnetically stirred solution of 1 g (23.5 mmol) of dry lithium chloride in 11 ml of anhydrous dimethylformamide (DMF). The reaction mixture was then heated at 50° for 48 hr. Work-up consisted of pouring the mixture into 20 g of ice and extracting the aqueous layer with three 20-ml portions of ether. The combined ether layers were washed several times with saturated NaCl and then dried over anhydrous $MgSO_4$. Removal of the ether gave a yellowish liquid which, when distilled, gave 1.5 g (85%) of 3-(chloromethyl)-cyclohexene: bp *ca.* 45° (10 mm); $n^{24}D$ 1.4832; nmr (CCl_4) δ 1.8 (b m, 6 H), 2.45 (m, 1 H, $CHCH_2Cl$), 3.38 (d, 2 H, CH_2Cl, J = 6.5 Hz), and 5.7 ppm (m, 2 H, vinyl); mass spectrum (70 eV) m/e (rel intensity) 132 (2.62), 130 (8.12), 95 (5.88), 81 (100), 53 (14.8), 41 (16.9), 27 (16.8).

Anal. Calcd for $C_7H_{11}Cl$: C, 64.36; H, 8.48; Cl, 27.14. Found: C, 64.53; H, 8.60; Cl, 27.27.

3-(Bromomethyl)cyclohexene (8).—Into a 50-ml erlenmeyer flask was placed 25 ml of anhydrous DMF, 4.78 g (20 mmol) of tetraethylammonium bromide, and 3.0 g (13.5 mmol) of 3-(iodomethyl)cyclohexene. The flask was then heated at 40° for 22 hr. The mixture was worked up in the same manner as described for the preparation of 3-(chloromethyl)cyclohexene. Distillation afforded 2.0 g (85%) of 3-(bromomethyl)cyclohexene: bp *ca.* 65° (10 mm); $n^{24}D$ 1.5128; nmr (CCl_4) δ 1.7 (b m, 6 H), 2.45 (m, 1 H, $CHCH_2Br$), 3.28 (d, 2 H, CH_2Br, J = 7 Hz), and 5.7 ppm (m, 2 H, vinyl); mass spectrum (70 eV) m/e (rel intensity) 176 (1.18), 174 (1.22), 95 (100), 81 (33.3), 67 (19.4), 53 (14.8), 41 (21.5), 39 (23.3).

Anal. Calcd for $C_7H_{11}Br$: C, 48.02; H, 6.33; Br, 45.54. Found: C, 48.33; H, 6.48; Br, 45.34.

Tri-*n*-Butyltin Hydride Reductions.—The free-radical tri-*n*-butyltin hydride reductions of the halides **3**–**8** were carried out following procedures similar to those described earlier.[1,2] Controls for reactant and product stabilities were in each case carried out under the reduction conditions in the presence of tri-*n*-butyltin halide. Hydrocarbon product characterization was accomplished by comparison of their nmr spectra and glpc retention times with those of known samples which were available in our laboratories. Qualitative results for yields of the hydrocarbon products were obtained by analytical glpc techniques, using conditions as described at the beginning of this Experimental Section.

Registry No.—**3**, 34825-89-3; **4**, 34825-90-6; **5**, 930-65-4; **6**, 32446-16-5; **7**, 17645-61-3; **8**, 34825-93-9; 3-(iodomethyl)cyclohexene, 34825-94-0; 3-(chloromethyl)cyclohexene, 19509-49-0.

Acknowledgment.—The authors wish to thank the Academic Senate Committee on Research of the University of California, Davis, for partial support of this research.

(20) W. M. Weaver and J. D. Hutchison, *J. Amer. Chem. Soc.*, **86**, 261 (1964).

Rearrangement Accompanying the Addition of Acetic Acid to Two Bicyclo[n.1.0]alkanes[1]

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Received January 18, 1972

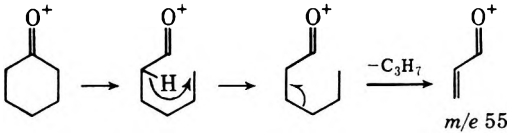
Addition of acetic acid-*O*-*d* to bicyclo[2.1.0]pentane and subsequent cleavage of the resulting acetate by $LiAlH_4$ gave cyclopentanol-d_1. The alcohol was oxidized and the resulting cyclopentanone was treated with base to effect α-deuterium exchange. Mass spectral isotopic distributions were determined for cyclopentanol-d_1 and cyclopentanone-d_1 before and after exchange. No label was lost on oxidation but 33–36% of the label was lost in exchange. Similar experiments were carried out with bicyclo[3.1.0]hexane. Again no oxidation loss was observed. Exchange losses were less than in the bicyclopentane system. That hydride migration occurs chiefly from C_6 was demonstrated from the degree of shift of m/e 55, the base peak in the mass spectrum of the labeled cyclohexanone. Neither oxidative nor exchange losses were observed for methylcyclopentyl acetates, produced along with cyclohexyl acetates, in the addition of acetic acid to bicyclo[2.1.0]hexane.

Halogen addition to bicyclo[2.1.0]pentane has been observed to proceed with rearrangement giving principally 1,2-dihalocyclopentanes rather than the 1,3-dihalocyclopentanes,[2] products of direct addition. These results, as well as other demonstrations of rearrangements accompanying ionic addition to simple cyclopropanes,[3] prompted us to examine for rearrangement the acid-promoted acetolysis of two bicyclo[*n*.1.0]alkanes. Bicyclo[2.1.0]pentane (**1**) and bicyclo[3.1.0]hexane (**2**) were chosen for the study because the principal position of bond rupture and addition is different in the two bicycloalkanes. Earlier work in our laboratory[4] showed that bicyclo[2.1.0]pentane gave only the acetate resulting from rupture of the internal $0^{1,4}$ bond. In contrast, bicyclo[3.1.0]hexane gave an acetate–olefin mixture consisting largely of those products formed by rupture of an external $1^{1,6}$ bond. Nevertheless, the latter bicycloalkane also gave 17% cyclohexyl acetate, an acetate resulting from rupture of the $0^{1,6}$ bond.

The two bicycloalkanes were treated with acetic acid-*O*-*d*, 0.08 *N* in deuteriosulfuric acid, for 46–48 hr at 25°. The crude mixtures of cycloalkyl acetates thus obtained were converted by lithium aluminium hydride to the cycloalkanols, which were oxidized with chromic acid in acetone to the corresponding ketones. The ketones in turn were treated with sodium methoxide–methanol at 25° for 8 days to exchange deuterium at the α positions. Isotopic distributions were determined for the cyclopentanols, methylcyclopentanols, and all the ketones, and are summarized in Table I. Also given in Table I are the corresponding percentage losses of deuterium by oxidation and exchange. Reliable isotopic distributions could not be obtained for the cyclohexanols because of the interference of an $M^+ - 1$ peak which was large relative to M^+. Therefore, the isotopic distributions of the cyclohexanol were assumed to be the same as that of the *trans*-2-methylcyclopentanol produced in the same ring-opening experiment.

To ascertain the extent of β deuterium loss in the oxidation of alcohols, the efficiency of deuterium exchange, and the limits of error of the mass spectral analyses of cycloalkanols and cycloalkanones, cyclohexanol-*2*-d_1 and cyclopentanol-*2*-d_1 were prepared by treating the appropriate cycloalkene oxide with lithium aluminum deuteride. These labeled cycloalkanols were oxidized and samples of the resulting cyclohexanones were treated under various conditions to establish that methanol–sodium methoxide at 25° for 8 days was sufficient to exchange all of the deuterium in the labeled ketones. These ancillary experiments also showed that no β deuterium was lost in the standard oxidation of cyclopentanol-*2*-d_1 to cyclopentanone-*2*-d_1. For reasons already given, the oxidative loss of label from cyclohexanol-*2*-d_1 could not be determined. Isotopic distributions and limits of error for this series of experiments are given in the Experimental Section.

Information about label location was also gained in one case from the shift of mass spectral fragmentation peaks. In this manner, we learned that addition of DOAc to bicyclo[3.1.0]hexane produced no cyclohexyl acetate labeled at C_4. This result was obtained by determining the percentage shift of the base peak of the exchanged cyclohexanone. Earlier mass spectral studies[5] of deuterium-labeled cyclohexanones have demonstrated that the base peak at m/e 55 is generated through the fragmentation depicted below.



According to this fragmentation mechanism, 50% of m/e 55 will be shifted to m/e 56 if all the label is located at C_3 and all the label has been exchanged from C_2. Any deuterium located at C_4 would necessarily be lost. Therefore, if no label is located at C_4, the percentage m/e 55 → 56 shift should be one-half the d_1 content of the ketone after exchange. For both exchanged cyclohexanone samples the determined percentage shifts[6]

(1) (a) Paper XI in a series dealing with carbon–carbon bond fission in cyclopropanes. (b) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society and the National Science Foundation, for support of this work. Acknowledgment is also made to the National Science Foundation for support in obtaining the mass spectrometer used in this study.

(2) R. T. LaLonde, *J. Amer. Chem. Soc.*, **87**, 4217 (1965).

(3) (a) A. Aboderin and R. L. Baird, *ibid.*, **86**, 2300 (1964); (b) N. C. Deno, D. LaVietes, J. Mockus, and P. C. Scholl, *ibid.*, **90**, 6457 (1968); (c) N. Deno and D. N. Lincoln, *ibid.*, **88**, 5357 (1966); (d) H. Hart and R. H. Schlosberg, *ibid.*, **90**, 5189 (1968).

(4) R. T. LaLonde and L. S. Forney, *ibid.*, **85**, 3767 (1963).

(5) For references see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 143, 144.

(6) The method of calculating peak shift is that given by J. Karliner and C. Djerassi, *J. Org. Chem.*, **31**, 1945 (1966).

Table I

Percentage Isotopic Composition of Cycloalkanols and Cycloalkanones Originating from the Addition of Acetic Acid and Acetic Acid-*O*-*d* to Bicyclo[*n*.1.0]alkanes, 1 and 2

			Isotopic composition, %			Percentage deuterium loss[a]	
				Cycloalkanone			
Bicycloalkane	Cycloalkyl acetate	Expt no.	Cycloalkanol	Before exchange	After exchange	Oxidation[b]	Exchange[c]
1 [2.1.0]	Pentyl	1	d_0, 24	35	*d*		
			d_1, 73	69			
			d_2, 3	6			
2		2	21	18	47		
			79	80	52		
			0	2	1	0	36
3		3	27	27	49		
			70	70	51		
			3	3	0	0	33
[3.1.0]	Hexyl	1	d_0	19	28		
			d_1	75	68		
			d_2	6	4		10
[3.1.0]	*trans*-	2	22 ± 1[e]	20 ± 1	20 ± 2		
	2-Me		74 ± 1	75 ± 1	75 ± 2		
	Pentyl		4 ± 1	5 ± 1	5 ± 2	0	0
	Hexyl	2	22 ± 1[f]	21 ± 1	30 ± 1		
			74 ± 1	76 ± 1	66 ± 1		
			4 ± 1	3 ± 1	4 ± 3	0	13

[a] Calculated as the percentage loss relative to the total deuterium content of alcohol and the percentage loss relative to the total deuterium content of the ketone prior to exchange. [b] Calculated as $100\% \times (\Sigma\%d_i \times i$, alcohol $- \Sigma\%d_i \times i$, ketone$)/\Sigma\%d_i \times i$, alcohol. [c] Calculated as $100\% \times (\Sigma\%d_i \times i$, ketone $- \Sigma\%d_i \times i$, ketone after exchange$)/\Sigma\%d_i \times i$, ketone. [d] Insufficient material remained for an exchange experiment. [e] Isotopic distributions are the averages of three mass spectra and limits represent the maximum deviation from the average. [f] The isotopic distribution of the deuterated cyclohexanol is assumed to be the same as that of 1-methylcyclopentanol.

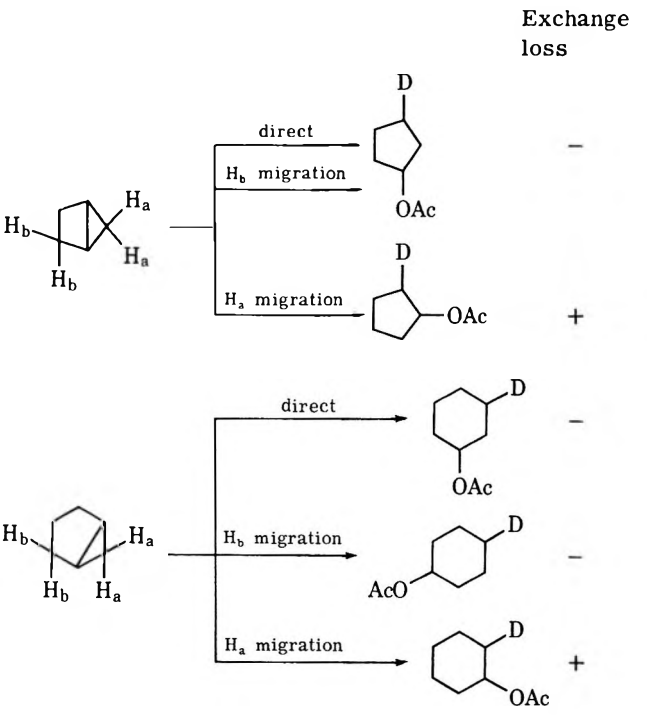
m/e 55 → 56 were 34%. One-half of the observed d_1 content in the cyclohexanone samples after exchange is 34 and 33% (Table I, rows 4 and 6). Since the determined percentage shifts agree well with the calculated values, it is concluded that no deuterium is located at C_4.

Discussion

There are three outstanding aspects of the results pointing to three principal features of the process through which deuterium is introduced. First, the amount of d_2 species in ketones originating from DOAc addition to bicyclo[*n*.1.0]alkanes in no case is greater than 6%. This result indicates that neither deuteron–proton exchange preceding bond fission nor acetate formation through addition to olefins are important competing processes. Second, DOAc addition to an internal bond of unlabeled bicycloalkanes ultimately leads to ketones which lose label on exchange. This result indicates that addition of acetic acid across the bond connecting bridgehead carbons is not a simple 1,3 addition but must involve rearrangement, at least in part. Third, the lack of oxidative and exchange loss from methylcyclopentanol and methylcyclopentanone, coupled with the formation of less than 2% of 1-methylcyclopentyl acetate,[4] indicates a near absence in external addition of the type of rearrangement which accompanies internal addition.

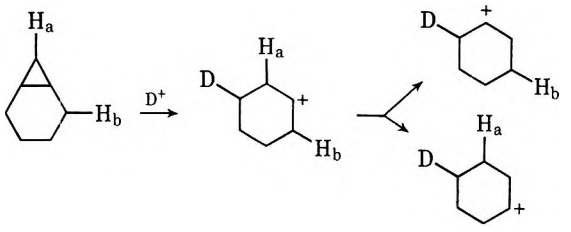
The second of the above three characteristics is interpreted within the framework of Scheme I. The scheme allows for addition across the internal bond of the bicyclo[*n*.1.0]alkanes to proceed by three routes: direct addition, hydride migration from the one-carbon bridge (H_a), and hydride migration from the *n*-carbon bridge (H_b). Acetates formed by direct addition and H_b-migration routes are indistinguishable by exchange loss of label.

Scheme I



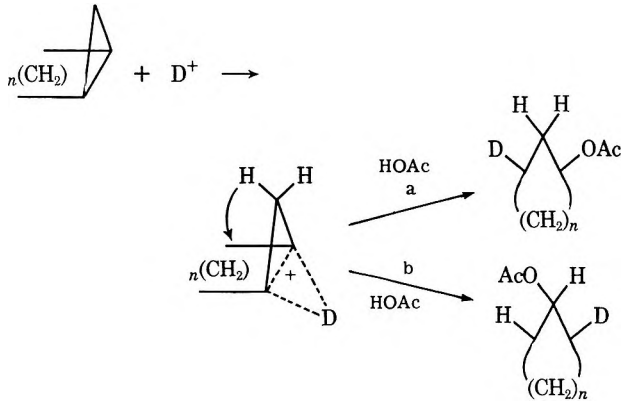
However, in the case of cyclohexyl-*d* acetate, no label could be detected at C_4 in the mass spectral shift value study. On this basis, the total amount of rearrangement is occurring by H_a migration only. In the case of bicyclo[2.1.0]pentane, the results based on exchange experiments indicate only the extent of rearrangement which takes place by H_a migration. Interestingly, H_a migration taking place in the addition to the more highly strained bicyclopentane is occurring more than twice as often as it does in the addition to the bicyclohexane.

Exclusion of H_b migration in the addition to the bicyclohexane means that free carbonium ions, as depicted below, can be eliminated as the major route in rearrangement, since there is no reason why H_a should migrate and H_b should not. The major involvement of a carbonium ion intermediate in the acid-promoted



acetolysis of bicyclo[n.1.0]alkanes has been rejected previously[7] on the basis of stereochemical results. That rearrangement by way of H_a and H_b migration occurs with unequal facility is not unreasonable if the rearrangement should take place through a transition state closely resembling the starting bicycloalkane. In this case H_b is virtually a cyclopentyl proton while H_a is much like a cyclopropyl proton, a proton type already known to display migrating tendencies in the course of addition reactions.[3] However, various corner- and edge-protonated cyclopropane intermediates in equilibrium—the type proposed previously by other workers to explain rearrangement in halogenation, acylation, and acid-promoted solvolysis of simple cyclopropanes[3]—are inappropriate for the acid-promoted acetolysis of the two bicycloalkanes. Such intermediates in equilibrium should lead to labeled acetates which would undergo oxidative loss of label. No oxidative loss was detected in studies of either bicycloalkane.

The simplest possible mechanism consistent with the results of H_a migration consists of deuteration of the internal bridge followed by (a) solvent attack to give the product of direct addition and (b) migration of a hydrogen from the one-carbon bridge and solvent attack at the same carbon center to give rearranged product.



Finally, it is noteworthy that addition of DOAc to the internal bond of *endo*-6-methylbicyclo[3.1.0]hexane was found earlier to give labeled *cis*-2-methylcyclohexyl acetate, which on sequential hydrolysis, oxidation, and exchange lost no deuterium.[7] The reason for the lack of hydride migration remains to be established.

(7) (a) R. T. LaLonde and M. A. Tobias, *J. Amer. Chem. Soc.*, **86**, 4068 (1964); (b) R. T. LaLonde and A. D. Debboli, Jr., *J. Org. Chem.*, **35**, 2657 (1970).

Experimental Section

Spectra were obtained as follows: nmr, in CCl_4, 2% TMS (10 τ) using a Varian A-60A spectrometer; ir, in CCl_4 using a Perkin-Elmer 621 spectrometer, absorption maxima at 2115 and 2169 cm^{-1} of carbon monoxide were used as calibration standards for measuring C–D stretching frequencies; mass, 20 eV, chamber temperature 165° using a Hitachi Perkin-Elmer RMU-6 spectrometer with an all-glass heated indirect inlet at 25°. Isotopic distributions were calculated by the method of Biemann.[8] Glpc was performed on a Varian Aerograph Model 200 using columns 5 ft × 0.25 in. containing the liquid phase on Chromosorb W.

Materials.—Sulfuric acid-d_2, D_2O, and $LiAlD_4$ were purchased from Merck Sharp and Dohme of Canada Limited, Montreal. Acetic acid-*O*-*d* was prepared from excess acetic anhydride and D_2O and contained 25% HOAc according to nmr analysis. Bicyclo[2.1.0]pentane was prepared according to the procedure of Criegee[9] and bicyclo[3.1.0]hexane was prepared by the method of Smith and Simmons.[10] The preparations of cyclopentanol-2-d_1 and cyclohexanol-2-d_1 are described elsewhere in this section under separate headings.

General Procedure for $LiAlH_4$ Hydrogenolysis of Acetates.—The crude acetate obtained from ring opening was dissolved in a small amount of ether and the solution was added dropwise to $LiAlH_4$ in anhydrous ether. The resulting mixture was heated to reflux for 1 hr and then stirred overnight. The excess $LiAlH_4$ was decomposed by careful addition of water and the salts were dissolved by addition of cold, dilute H_2SO_4. The ether layer was dried ($MgSO_4$). Removal of the ether by distillation through a 12-in. Vigreux column gave a residue from which the desired alcohol was separated by glpc. All hydrogenolyses were carried out by the method described above unless otherwise indicated. When only a small sample of the crude mixture of alcohols was available, a portion of the mixture was separated by glpc for purposes of identification and mass spectral analysis and the oxidation step was carried out on the remaining portion of the crude mixture.

General Procedure for the Oxidation of Alcohols to Ketones.—A cooled acetone solution of the alcohol was treated with Jones reagent[11] added in a dropwise manner until a faint yellow color persisted. The mixture was poured into 25–50 ml of water and the resulting mixture was extracted continuously with ether for 48 hr. The ether extract was separated, washed twice with saturated $NaHCO_3$ solution, and dried ($MgSO_4$). Ether was removed by careful distillation to give a residue from which the desired ketone was separated by glpc.

General Procedure for Deuterium–Hydrogen Exchange.—A solution of NaOMe in MeOH, prepared by adding about 30 mg of sodium to 1 ml of MeOH, was added to the ketone in 2 ml of methanol. The resulting solution was stored at room temperature in a sealed glass tube for 8 days. Thereafter, the solution was poured into 50 ml of water and the resulting mixture was extracted continuously with ether for 3 days. The ether layer was separated and dried ($MgSO_4$). Removal of the ether by careful distillation gave a residue from which the exchanged ketone was isolated by glpc. All exchange experiments were carried out by the method described above.

Addition of DOAc to Bicyclo[2.1.0]pentane.—A sealed glass tube containing 2.55 g of bicyclo[2.1.0]pentane, 400 mg of sulfuric acid-d_2, and 100 ml of acetic acid-*O*-*d* was maintained at 25° for 48 hr. Thereafter, the contents of the tube were added to 200 ml of saturated brine and the resulting mixture was extracted continuously with 400 ml of ether for 2 days. The ether extract was neutralized cautiously with solid Na_2CO_3 and dried ($MgSO_4$). Careful distillation of ether left 4.5 g of light yellow oil. Glpc (5 ft, 15% 20M Carbowax, 90°) showed peaks corresponding to cyclopentanol (<3%, 7.5 min), cyclopentyl acetate (6.3 min), and some residual ether. The procedure described here is typical of the three ring-opening experiments carried out with bicyclo[2.1.0]pentane.

A. $LiAlH_4$ Hydrogenolysis.—The crude acetate, 4.5 g, afforded 520 mg of cyclopentanol-d_1 purified by preparative glpc.

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(9) R. Criegee and R. Rimmelin, *Chem. Ber.*, **90**, 414 (1957).

(10) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959).

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

The mass spectrum showed M^+, m/e 87, and the isotopic composition given under the appropriate heading of Table I, row 3. Isotopic compositions of cyclopentanol-d_1 obtained in experiments 1 and 2 are given in rows 1 and 2, respectively.

B. Oxidation.—The 520-mg sample of cyclopentanol-d_1 was oxidized to 350 mg of cyclopentanone-d_1 purified by preparative glpc (5 ft, 15% Carbowax 20M, 100°). The mass spectrum showed M^+, m/e 85, and the isotopic composition given under the appropriate heading of Table I, row 3. Isotopic compositions of cyclopentanone-d_1 obtained in runs 1 and 2 are given in rows 1 and 2, respectively.

C. Exchange.—Cyclopentanone-d_1, 350 mg, gave after purification by glpc 40 mg of cyclopentanone, whose isotopic distribution is given in row 3.

Addition of DOAc to Bicyclo[3.1.0]hexane.—In the first experiment, a sealed glass tube containing 3.52 g of bicyclohexane, 400 mg of sulfuric acid-d_2, and 100 ml of acetic acid-*O*-*d* was maintained at 25° for 47 hr. Thereafter the contents of the tube were poured into 800 ml of water and the resulting mixture was extracted continuously with ether for 8 days. The extract was washed with saturated $NaHCO_3$, dried ($MgSO_4$), and reduced in volume to 50 ml by careful distillation of the ether. The concentrated extract was treated immediately with $LiAlH_4$. In the second experiment, 3.32 g of bicyclo[3.1.0]hexane was treated with 400 mg of D_2SO_4 and 100 ml of acetic acid-*O*-*d*; processing as described for the first sample gave 4.14 g of yellow oil after removal of most of the ether by distillation.

A. $LiAlH_4$ Hydrogenolysis.—The ethereal solution of acetates from the first experiment afforded, after purification by glpc (5 ft, 15% Carbowax 20 M, 125°), 250 mg of cyclohexanol-d_1: mass spectrum m/e (rel intensity) 101 (10), 100 (20), 99 (10), 98 (9), 84 (62), 83 (84), 82 (35), 67 (48), 66 (43), 59 (36), 58 (100), 57 (70). In the second experiment, the sample of crude acetates gave a mixture of alcohols from which was isolated by glpc 530 mg of *trans*-2-methylcyclopentanol-d_1, mass spectrum m/e (rel intensity) 101 (20), 100 (3), 83 (38), 82 (12), 68 (20), 67 (26), 58 (23), 57 (100); nmr τ 6.32 (m, 1 H, CHOH), 9.03 (br d, J = 6.5 Hz, 2.3 H, $CHCH_3$), and cyclohexanol-d_1, mass spectrum identical with that of the first sample. The isotopic composition of the cyclohexanol (row 6) was taken to be the same as that of the methylcyclopentanol-d_1 which is given in Table I, row 5.

B. Oxidation.—A sample of the cyclohexanol-d_1 (250 mg) obtained from the first experiment gave after purification by glpc (5 ft, 15% Carbowax 20 M, 100°) 99 mg of cyclohexanone-d_1: mass spectrum m/e (rel intensity) 99 (80), 70 (47), 69 (50), 57 (28), 56 (78). The isotopic composition is given in Table I, row 4. A 100-mg sample of the cyclohexanol-d_1 from the second experiment was oxidized and gave, after purification by glpc, 55 mg of cyclohexanone-d_1 whose isotopic composition is given in Table I, row 6. A 327-mg sample of *trans*-2-methylcyclopentanol-d_1 on oxidation gave, after purification by glpc, 110 mg of 2-methylcyclopentanone-d_1, mass spectrum m/e 99 (M^+), whose isotopic composition is given in Table I, nmr τ 8.96 (d, $CH_3/CH_2 + CH = 0.32$).

C. Exchange.—Samples of cyclohexanone-d_1 originating from first and second experiments, and 2-methylcyclopentanone-d_1, afforded samples of the corresponding exchanged ketones whose isotopic compositions are given in Table I, rows 4, 6, and 5, respectively.

Cyclopentanone-2-d_1 from Cyclopentene Oxide.—Cyclopentene oxide, 4.693 g, was treated with $LiAlD_4$ in ether solution and gave 4.5 g of cyclopentanol-2-d_1 after distillation. A sample was purified further by glpc for mass spectral analysis. The isotopic distribution was d_0, 16 ± 1%; d_1, 80 ± 1%; d_2, 5 ± 2%. Jones oxidation and processing in the usual manner gave 2.7 g of cyclopentanone-2-d_1 whose isotopic distribution was d_0, 18 ± 1%; d_1, 77 ± 1%; d_2, 5 ± 1%. A 1.07-g sample which had been treated with NaOMe–MeOH (~5 *M*) for 8 days at 25° and processed in the usual manner had the following isotopic distribution: d_0, 99 ± 1%; d_1, 2 ± 1%; d_2, 2 ± 1%.

Cyclohexanone-2-d_1 from Cyclohexene Oxide.—Following the procedure used in the preparation of cyclopentanone-2-d_1, cyclohexene oxide (6.34 g) was treated with $LiAlD_4$ and a 986-mg portion of the resulting alcohol (3.03 g) was oxidized by the Jones procedure to give 460 mg of cyclohexanone-2-d_1 whose isotopic distribution was d_0, 20 ± 2%; d_1, 79 ± 2%; d_2, 1 ± 1%. A sample treated with NaOMe–HOMe (~5 *M*) for 8 days at 25° gave cyclohexanone: d_0, 98 ± 2%; d_1, 2 ± 1%; d_2, 0.

Registry No.—**1**, 185-94-4; **2**, 285-58-5; acetic acid, 64-19-7; *trans*-2-methylcyclopentanol, 25144-04-1.

Intramolecular Cyclizations Leading to N-Bridgehead Bicyclics. 5,5-Diphenylhydantoin Derivatives

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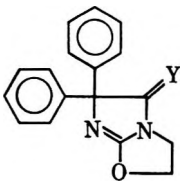
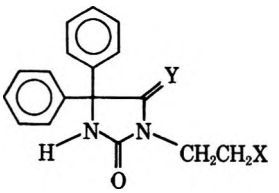
Received January 27, 1972

The synthesis and study of the intramolecular cyclizations of 3-(2-hydroxyethyl)-5,5-diphenylhydantoin mesylate (**2a**) and 1-(2-hydroxyethyl)-4,4-diphenyl-2-imidazolidinone mesylate (**2b**) are described. Although both N- and O-alkylation reactions are possible, only the products resulting from intramolecular O-alkylations were obtained.

The reported high concentrations of 5,5-diphenylhydantoin (DPH) in brain tissue and its preferred localization in primary brain tumors[1,2] suggested the synthesis of highly reactive DPH analogs as potential brain antitumor agents.[3] The nitrogen bridgehead bicyclic compounds **1a** and **1b** are part of the results of this work, and, in addition to their behavior as powerful alkylating agents, these compounds have clarified the course of intramolecular cyclization in the 3-substituted hydantoin and the 1-substituted imidazolidinone ring systems.



1a, Y = O
b, Y = H_2



2a, Y = O; X = OSO_2CH_3
b, Y = H_2; X = OSO_2CH_3
c, Y = O; X = OH

The synthesis of **2a** and **2b** and the determination of the structures of their cyclized products helped to resolve the question of whether intramolecular N-

(1) H. Firemark, C. G. Barlow, and L. J. Roth, *Int. J. Neuropharmacol.*, **2**, 25 (1963).

(2) I. Rosenblum and A. A. Stein, *Biochem. Pharmacol.*, **12**, 1453 (1963).

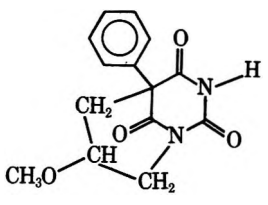
(3) V. E. Marquez, L.-M. Twanmoh, H. B. Wood, Jr., and J. S. Driscoll, Abstracts of Papers, 162nd National Meeting of the American Chemical Society, Washington, D.C., Sept 1971, Division of Medicinal Chemistry, paper no. 36.

alkylation or O-alkylation would take place in the aforementioned ring systems.

In **2a** the more acidic imide nitrogen (N-3) is substituted and in **2b**, where both nitrogens are amidic, only one is substituted. Both systems, therefore, possess an amide nitrogen as a potential site for alkylation. On the other hand, in their tautomeric forms, intramolecular alkylation can be envisaged to take place at the oxygen atom.

Intermolecular amide nitrogen (N-1) alkylations are well known in 3-substituted hydantoins but they occur under more severe conditions than the simple N-3 imide alkylations usually encountered with unsubstituted hydantoins. In the intramolecular reactions studied here, however, the presence of the alkylating group in the same molecule at the 3 position presents a somewhat different problem because the intramolecular process will be controlled by the thermodynamic stabilities of the two possible bicyclic products resulting from N- or O-alkylation.

Smissman, *et al.*, suggest that the use of NaH and DMF generally favors intramolecular N-alkylation. This group succeeded in preparing the N-alkylated bicyclic derivative of 5-phenyl-5-(2-methoxy-3-bromopropyl)barbituric acid[4] (**3**) and, under similar conditions, they obtained two N-1 alkylated bicyclohydantoins when the alkylating group was located in the 5 position (**4a**,**b**).[5]



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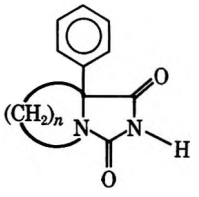
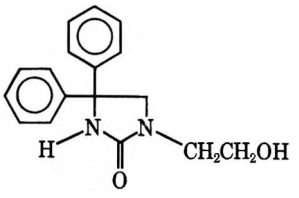


4a, $n = 3$
b, $n = 4$

O-Alkylation in hydantoins bearing the alkylating group on the side chain at the 5 position does not seem to be favored. On the other hand, O-alkylation occurs with ease in the 5-haloalkylbarbituric acids.[6] In our 3-substituted hydantoin system, bicyclic products resulting from both N- or O-alkylation seemed possible.

A common starting material for both 3-(2-hydroxyethyl)-5,5-diphenylhydantoin mesylate (**2a**) and 1-(2-hydroxyethyl)-4,4-diphenyl-2-imidazolidinone mesylate (**2b**) was the known 3-(2-hydroxyethyl)-5,5-diphenylhydantoin (**2c**).[7] The conversion of **2c** to **2a** was easily accomplished by treatment with methanesulfonyl chloride in dry pyridine at room temperature. The sequence leading to **2b** was planned based on the previously reported reductions of hydantoins with $LiAlH_4$. This reaction selectively reduces the amide carbonyl.[8] The reduction of **2c** to **5** with $LiAlH_4$ in refluxing THF, however, failed to proceed to completion. Even with a large excess of $LiAlH_4$ and prolonged reaction times a mixture of **5** and another partially reduced component, **6**, was always obtained. When **2c** was allowed to react with $LiAlH_4$ at room temperature in THF, practically no **5** was formed. Instead, the hydroxy imidazolidinone **6** was obtained. The infrared spectrum of this compound showed absorptions at 3250, 3150, and 1680 cm^{-1}, which indicated that partial reduction of one carbonyl group had taken place. The nmr gave a two-proton set of two doublets (OH,CH coupling) centered at δ 5.80 which collapsed into a one-proton singlet after D_2O exchange. The mass spectrum of **6** presented a molecular ion peak at m/e 298.



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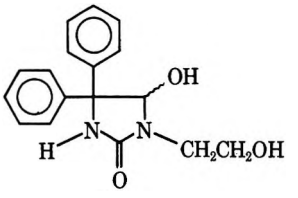
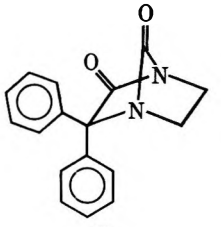


6

When excess Red-Al was used in refluxing THF, **2c** was reduced to the desired product, **5**. A characteristic ir band at 1690 cm^{-1}, important nmr signals at δ 4.04 (singlet for the ring methylene hydrogens), 3.30 (A_2B_2X system of the side chain), 4.70 (triplet, hydroxyl proton), and 7.92 (singlet, amide hydrogen), plus a molecular ion at m/e 282, confirmed the structure. Treatment of **2c** with methanesulfonyl chloride afforded **2b** in good yields.

When the mesylate **2a** was caused to react with NaH in refluxing benzene only the O-alkylated hydantoin, 2,3-dihydro-6,6-diphenylimidazo[2,1-*b*]oxazole-5(6*H*)-one (**1a**) plus some polymeric material was observed. The bridged bicyclic compound **7** was not detected in the reaction mixture.



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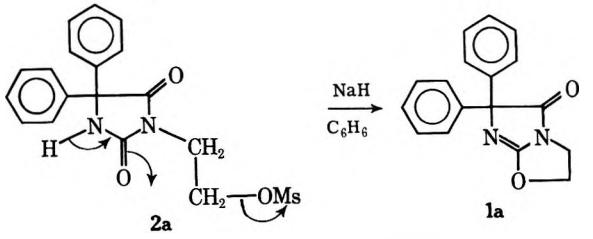


2a **1a**

In the nmr spectrum of **1a**, two distinct triplets were observed at δ 3.80 and 4.88 corresponding, respectively, to the methylene hydrogens adjacent to the nitrogen and oxygen. If the N-alkylated bicyclic compound **7** had been obtained, the methylene signals should have been nearly equivalent. When **1a** was dissolved in detuerioacetone with added traces of D_2O and CF_3COOH and its nmr spectrum was observed over a period of time, both triplets gradually collapsed to a

(4) E. E. Smissman, R. A. Robinson, J. B. Carr, and A. J. B. Matuszak, *J. Org. Chem.*, **35**, 3821 (1970).

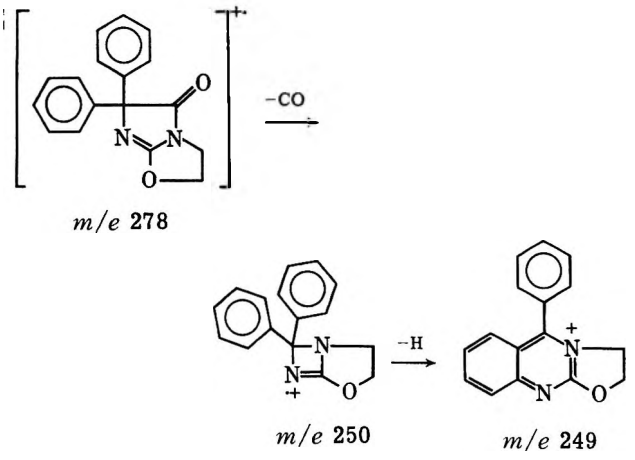
(5) E. E. Smissman, P. L. Chien, and R. A. Robinson, *ibid.*, **35**, 3818 (1970).

(6) E. E. Smissman, R. A. Robinson, and A. J. R. Matuszak, *ibid.*, **35**, 3823 (1970).

(7) K. Schlögl, F. Wessely, O. Kraupp, and H. Stormann, *J. Med. Pharm. Chem.*, **4**, 231 (1961).

(8) F. J. Marshall, *J. Amer. Chem. Soc.*, **78**, 3697 (1956).

singlet which was characteristic of the spectrum of **2c** in deuterioacetone after D_2O exchange. Therefore, **1a** was hydrolyzed to **2c** in the same manner as the O-alkylated barbiturates hydrolyzed in acid to the corresponding alcohols.[9] In addition to a molecular ion peak at *m/e* 278, the mass spectrum of **1a** showed important peaks at *m/e* 250 and 249 corresponding, respectively, to the loss of CO and further rearrangement to produce a stable ion *via* loss of a hydrogen radical.[10]



m/e 278 *m/e* 250 *m/e* 249

The infrared spectrum of **1a** exhibited strong absorptions at 1745 and 1700 cm^{-1}. The higher wavenumber absorption band was assigned to the carbonyl group, and the 1700-cm^{-1} band, although somewhat high, was attributed to the C=N stretching frequency. The lack of planarity induced by the strained rings in **1a** is responsible for the abnormally high frequency of the C=N bond. This assignment was also confirmed by comparison with **1b**.

Under the same conditions used to cyclize **2a**, the mesylate **2b** afforded 2,3,5,6-tetrahydro-6,6-diphenylimidazo[2,1-*b*]oxazole (**1b**) in good yield. Nmr signals were present at δ 3.80 (singlet, isolated ring methylene hydrogens) and 3.22 and 4.62 (triplets, corresponding to methylenes adjacent to nitrogen and oxygen). In addition to the molecular ion peak at *m/e* 264, important peaks were found at *m/e* 208, 187, 165, and 160. The strong ir band observed at 1680 cm^{-1} was assigned to the C=N bond of this puckered bicyclic compound.

The unsubstituted parent ring system of **1a** and **1b** has been mentioned in the literature, but no spectral data were reported.[11,12] The compound, named as Δ^7-1-oxa-4,7-diazabicyclo[3.3.0]octene, was the reaction product of 1-(2-chloroethyl)-2-imidazolidone with methanolic KOH.

The reaction of both **1a** and **1b** with *p*-nitrobenzylpyridine (see Experimental Section) gave an intense blue color[13] indicating the strong electrophilic character of these compounds. The study of this reactive bridgehead nitrogen ring system is being continued, since its lactim ether functionality is related to certain new types of antitumor agents.[14]

(9) E. E. Smissman and R. A. Robinson, *J. Org. Chem.*, **35**, 3532 (1970).
(10) R. A. Corral, O. O. Orazi, A. M. Duffield, and C. Djerassi, *Org. Mass. Spectrom.*, **5**, 551 (1971).
(11) A. F. McKay, G. Y. Paris, and M. E. Kreling, *J. Amer. Chem. Soc.*, **79**, 5276 (1957).
(12) A. F. McKay and M. E. Kreling, *Can. J. Chem.*, **37**, 427 (1959).
(13) T. J. Bardos, N. Datta-Gupta, P. Hebborn, and D. J. Triggle, *J. Med. Chem.*, **8**, 167 (1965).

Experimental Section[15]

3-(2-Hydroxyethyl)-5,5-diphenylhydantoin Methanesulfonate Ester (2a).—Methanesulfonyl chloride (1.46 ml, 0.018 mol) was added in one portion to a solution of **2c** (5.14 g, 0.017 mol) in 40 ml of dry pyridine and the reaction mixture was stirred overnight with the exclusion of moisture. The solution was added to 40 ml of chilled, concentrated HCl, and the solid formed was vigorously stirred, filtered, washed with water, and dried. Recrystallization from MeOH afforded 4.75 g (73%) of **2a**: mp 174–176°; ir 3200, 1760, 1700, 1170, 910, and 810 cm^{-1}; nmr δ 3.05 (s, 3), 3.82 (t, 2), 4.40 (t, 2), 7.35 (s, 10), and 9.63 (s, 1).

Anal. Calcd for $C_{18}H_{18}N_2O_5S$: C, 57.74; H, 4.84; N, 7.48; S, 8.56. Found: C, 57.79; H, 4.71; N, 7.22; S, 8.26.

2,3-Dihydro-6,6-diphenylimidazo[2,1-*b*]oxazole-5(6*H*)-one (1a).—Compound **2a** (3.85 g, 0.0103 mol) was dissolved in 500 ml of hot benzene. To the cooled solution, 0.435 g of NaH (57% oil suspension) was added in one portion and the mixture was refluxed for 5 hr. Tlc analysis [silica gel, AcOEt–$CHCl_3$ (1:1)] showed complete disappearance of the spot corresponding to starting material (R_f 0.39). One spot (R_f 0.32), which corresponded to product, was observed. The reaction mixture was filtered hot, and a small amount of a polymeric substance was discarded. The filtrate was reduced to dryness, triturated with ether, and filtered. Recrystallization from toluene afforded 2.60 g (91%) of **1a**: mp 188–190°; ir 1750, 1690, 1710, 1270, 1030, 975, 850, 770, 760, 730, 710, and 705 cm^{-1}; nmr δ 3.80 (t, 2), 4.88 (t, 2), 7.25 and 7.54 (multiplets, 10); mass spectrum *m/e* (rel intensity) 278 (37) (parent), 250 (25), 249 (100), 149 (35), 91 (32), and 40 (40).

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.50; H, 5.24; N, 10.03.

(±)-5-Hydroxy-1-(2-hydroxyethyl)-4,4-diphenyl-2-imidazolidinone (6).—A solution of **2c** (1.5 g, 5.08 mmol) in 25 ml of THF was added dropwise to a slurry of $LiAlH_4$ (0.590 g, 15.2 mmol) in 15 ml of THF. The reaction was stirred for 5 hr at room temperature and the excess of hydride was stirred for 5 hr at room temperature and the excess of hydride was destroyed by the careful addition of CH_3OH and a saturated solution of Na_2SO_4 in water. After the solid was discarded, the organic layer of the filtrate was separated. Following the addition of an equal volume of $CHCl_3$ to the organic layer, it was washed with water and saturated NaCl solution and dried (Na_2SO_4). After removal of the solvents, the oily residue obtained was triturated with ether to give 0.950 g (63%) of **6** as a pure substance, mp 151–152°. The compound was recrystallized from acetone: mp 153–154°; ir 3250, 3150, 1680, 1080 (broad), 865, 768, 750, and 700 cm^{-1}; nmr δ 3.23 (m, 2), 3.42 (m, 2), 4.70 (t, 1), 5.62 (d, 1, J = 7 Hz, resolved into a singlet after D_2O exchange), 5.92 (d, 1, J = 7 Hz, disappeared after D_2O exchange), 7.24 (m, aromatic), and 7.91 (s, 1, amide NH); mass spectrum *m/e* (rel intensity) 298 (8) (parent), 280 (98), 262 (13), 249 (47), 236 (66), 221 (25), 209 (27), 208 (58), 182 (98), 165 (100), 104 (99), 77 (99), and 72 (99).

Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.43; H, 6.08; N, 9.39. Found: C, 68.44; H, 6.08; N, 9.41.

1-(2-Hydroxyethyl)-4,4-diphenyl-2-imidazolidinone (5).—A solution of **2c** (1.86 g, 6.3 mmol) in 40 ml of THF was added dropwise to a mixture of Red-Al[16] (12.5 ml, 45 mmol of H_2) and

(14) A. Hoshi, F. Kanzawa, K. Kuretani, M. Saneyoshi, and Y. Arai, *Gann*, **62**, 145 (1971).
(15) Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were measured with Perkin-Elmer 621 and 137 spectrometers as Nujol mulls unless otherwise specified. Nmr spectra were recorded on a Varian HA-100D spectrometer and chemical shifts are given in parts per million from tetramethylsilane. Nmr spectra were determined as approximately 5% solutions in DMSO-d_6 unless otherwise stated. Elemental analyses were carried out by Dr. W. C. Alford, NIAMD, NIH. Electron bombardment mass spectra were determined by Mr. W. R. Landis, NIAMD, NIH, on a Hitachi Perkin-Elmer RMU-7 instrument at 80 eV. Developed tlc plates were visualized by spraying with a 4% solution of *p*-nitrobenzylpyridine in 4:1 methanol–water. The plates were heated at 120° for 10 min and then sprayed with a 0.1 *N* KOH in 4:1 methanol–water solution. Blue spots indicate compounds with alkylating properties.
(16) 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene.

THF (20 ml). The mixture was refluxed for 5 hr. The excess of hydride was destroyed by the addition of an aqueous concentrated solution of Na_2SO_4 and the purification procedure followed was identical with that described for compound **6**. The yield of product after ether trituration was 0.9 g (51%), mp 159–160°. The compound recrystallized from acetone as white prisms: mp 161–162°; ir 3450, 3200, 1680, 1675 (shoulder), 1300, 1070, 1030, 860, 850, 790, 765, 745, and 710 cm^{-1}; nmr δ 3.48 (t, 2), 3.53 (q, 2), 4.04 (s, 2), 4.70 (t, 1), 7.32 (m, 10), and 7.92 (s, 1); mass spectrum *m/e* (rel intensity) 282 (33) (parent), 252 (34), 251 (76), 209 (15), 208 (69), 205 (24), 178 (34), 108 (40), 105 (56), 91 (55), 77 (45), 74 (54), 72 (42), 58 (64), and 43 (100).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.31; H, 6.42; N, 9.92. Found: C, 72.17; H, 6.60; N, 9.87.

1-(2-Hydroxyethyl)-4,4-diphenyl-2-imidazolidinone Methanesulfonate Ester (2b).—Following the procedure for the preparation of **2a**, compound **5** (0.58 g, 2.07 mmol) was treated with methanesulfonyl chloride (0.19 ml, 2.17 mmol) in 5 ml of pyridine. After the addition of concentrated HCl, the solution was extracted with $CHCl_3$. The chloroform layer was washed with water and dried (Na_2SO_4). The oil recovered after removal of the solvent was triturated with ether and the solid formed was recrystallized from benzene to yield 0.40 g (54%) of **2b**: mp 124–125°; ir 3200, 1680, 1370, 1340, 1180, 1000, 990, 900, 805, 750, 715, and 705 cm^{-1}; nmr δ 3.02 (s, 3), 3.42 (t, 2), 4.00 (s, 2), 4.27 (t, 2), 7.28 (m, 10), and 8.10 (s, 1).

Anal. Calcd for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77; S, 8.89. Found: C, 59.83; H, 5.71; N, 7.65; S, 8.92.

2,3,5,6-Tetrahydro-6,6-diphenylimidazo[2,1-*b*]oxazole (1b).—Following a similar procedure for the synthesis of **1a**, compound **2b** (0.40 g, 1.15 mmol) was treated with 0.2 g of NaH (57% oil suspension) in toluene. The reaction was completed in 1.5 hr according to tlc analysis [one spot, R_f 0.33, silica gel, $CHCl_3$–EtOAc (1:1)]. The starting material in the same system had an R_f value of 0.18. After work-up, 0.25 g (85%) of **1b** was obtained. One recrystallization from toluene afforded an analytical sample: mp 197–198°; ir 1670, 1260, 1210, 980, 780, 755, 732, 710, and 700 cm^{-1}; nmr δ 3.22 (t, 2), 3.80 (s, 2), 4.64 (t, 2), and 7.26 (m, 10); mass spectrum *m/e* (rel intensity) 264 (100) (parent), 208 (96), 187 (60), 180 (30), 165 (38), 160 (100), 132 (22), 105 (31), 91 (33), and 77 (83).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.24; H, 6.10; N, 10.60. Found: C, 77.40; H, 6.15; N, 10.70.

Registry No.—**1a**, 34806-22-9; **1b**, 34792-37-5; **2a**, 34806-23-0; **2b**, 34792-38-6; **5**, 34806-24-1; **6**, 34806-21-8.

^1H and ^{13}C Nuclear Magnetic Resonance Spectra of Cyclopentadienylmagnesium Compounds in Tetrahydrofuran

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Received February 11, 1972

Low-temperature pmr spectra of mixtures of magnesium cyclopentadienide and magnesium chloride and of magnesium cyclopentadienide and magnesium bromide, 0.05–0.56 *M* in tetrahydrofuran, indicate that the cyclopentadienylmagnesium halides consist of Schlenk equilibrium mixtures, $(C_5H_5)_2Mg + MgX_2 \rightleftarrows 2C_5H_5MgX$, in which the C_5H_5MgX predominates. A rapid exchange between cyclopentadienylmagnesium chlorides and cyclopentadienyl impurities (presumedly alkoxides) has been detected. ^{13}C nmr chemical shifts of cyclopentadienyl-, methylcyclopentadienyl-, 1,3-dimethylcyclopentadienyl-, and trimethylsilylcyclopentadienylmagnesium chlorides are reported and discussed in terms of the charge distributions in substituted cyclopentadienides.

The observation that benzyne adds to cyclopentadienylmagnesium bromide ("C_5H_5MgBr")[2] to give benzonorbornadien-9-ylmagnesium bromide[3] has stimulated investigation of the structure of cyclopentadienylmagnesium compounds. Ir and uv spectra of "C_5H_5MgBr" and "C_5H_5MgCl" and magnesium cyclopentadienide [$(C_5H_5)_2Mg$] in tetrahydrofuran (THF) indicated that the principal components of these compounds in solution all have magnesium atoms located on or near the C_5 axes of the cyclopentadienide ions.[4] They do not have carbon–magnesium σ bonds. X-Ray analysis proved that a solvated C_5H_5MgBr crystal had a similar structure,[5] and the crystallographic unit cell parameters of $(C_5H_5)_2Mg$ suggested that it was isostructural with ferrocene.[6] This spectroscopic and X-ray data, however, provide no clue as to the nature of aggregation of cyclopentadienylmagnesium compounds in solution.

In 1929 Schlenk[7] suggested that Grignard reagents were equilibrium mixtures as shown in eq 1, because

$$R_2Mg + MgX_2 \rightleftarrows 2RMgX \quad (1)$$

addition of dioxane to "RMgX" precipitated MgX_2. In spite of numerous attempts to detect Schlenk equilibria,[8] only recently has direct identification of RMgX and R_2Mg in solution by nmr established positions of equilibrium quantitatively.[9,10] Evans and Fazakerley[9] reported ^{19}F and ^1H spectra of RMgX and R_2Mg for over 20 different Grignard reagents and found the position of equilibrium to be highly dependent on the alkyl or aryl group and the solvent. Temperatures of −68° and below were needed to observe slow exchange pmr spectra of CH_3MgBr and $(CH_3)_2Mg$ in THF. A similar study of "C_5H_5MgCl" and "C_5H_5MgBr" in THF is reported here.

In an extension of our cycloaddition research benzyne was generated in solutions of several substituted "cyclo-

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(2) In this paper "C_5H_5MgBr" denotes cyclopentadienyl Grignard reagent without specification of its composition, and C_5H_5MgBr denotes cyclopentadienylmagnesium bromide, a specific component of the Schlenk equilibrium mixture.

(3) (a) G. Wittig and E. Knauss, *Chem. Ber.*, **91**, 895 (1958); (b) W. T. Ford, R. Radue, and J. A. Walker, *Chem. Commun.*, 966 (1970).

(4) W. T. Ford, *J. Organometal. Chem.*, **33**, 27 (1971).

(5) G. D. Stucky, personal communication.

(6) E. Weiss and E. O. Fischer, *Z. Anorg. Allg. Chem.*, **278**, 219 (1955).

(7) W. Schlenk and W. Schlenk, *Ber.*, **62**, 920 (1929).

(8) For a review of earlier literature on Schlenk equilibria see E. C. Ashby, *Quart. Rev., Chem. Soc.*, **21**, 259 (1967).

(9) D. F. Evans and G. V. Fazakerley, *J. Chem. Soc. A*, 184 (1971).

(10) (a) G. E. Farris and E. C. Ashby, *J. Amer. Chem. Soc.*, **93**, 1206 (1971); (b) J. A. Magnuson and J. D. Roberts, *J. Org. Chem.*, **37**, 133 (1972).

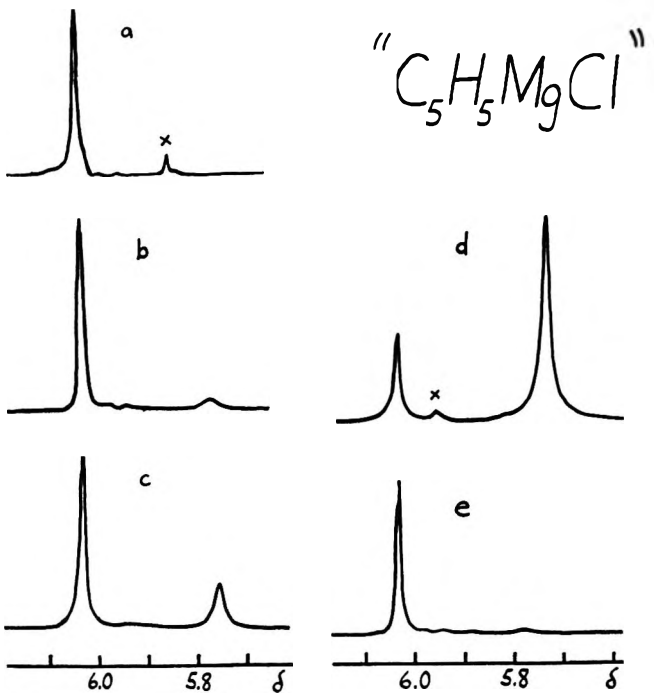

Figure 1.—Low-temperature pmr spectra of "C_5H_5MgCl" in THF: (a) 0.185 M "C_5H_5MgCl", 0°; (b) 0.093 M "C_5H_5MgCl", −60°; (c) 0.093 M "C_5H_5MgCl", −85°; (d) 0.267 M $C_5H_5^-$, 0.175 M Mg^{2+}, 0.084 M Cl^-, −95°; (e) 0.077 M $C_5H_5^-$, 0.144 M Mg^{2+}, 0.211 M Cl^-, −75°. Peaks marked × are spinning side bands.

pentadienylmagnesium chlorides."[11] The resulting isomeric substituted benzonorbornadienes were formed neither randomly nor highly selectively. In order to determine whether charge distributions in the substituted cyclopentadienylmagnesium compounds affected their courses of addition to benzyne, ^{13}C chemical shifts of their ring carbons were measured.

Experimental Section

Preparations of substituted cyclopentadienes, cyclopentadienylmagnesium chlorides, and $(C_5H_5)_2Mg$ were described earlier.[4,11] Magnesium methylcyclopentadienide [$(CH_3C_5H_4)_2Mg$] was prepared by a procedure identical with that for $(C_5H_5)_2Mg$.[4] Tetrahydrofuran was freshly distilled from potassium fluorenide.

Anhydrous magnesium chloride was prepared from mercuric chloride and magnesium turnings in THF.[12] Analyses[13] of white powder after drying for 3 hr at 120° *in vacuo* follow. *Anal.* Calcd for $MgCl_2$: Mg, 25.53; Cl, 74.47. Found: Mg, 11.79; Cl, 33.81. This corresponds to an atom ratio Cl/Mg of 1.966. A pmr spectrum in THF revealed no water peak. A pmr spectrum in D_2O revealed a large amount of THF in the sample. We suspect that the literature preparation[12] of anhydrous $MgCl_2$ also contained THF, although the authors did not report it. Since all our spectra were recorded in THF, the solvent in the solid sample did not matter as long as the composition of the solid was known.

Anhydrous magnesium bromide was prepared from 1,2-dibromoethane and magnesium turnings in THF. Analyses[13] of the white powder which remained after evaporation of solvent and drying 12 hr at 130° *in vacuo* follow. *Anal.* Calcd for $MgBr_2 \cdot C_4H_8O$: Mg, 9.48; Br, 62.37. Found: Mg, 9.67; Br, 61.52. This corresponds to an atom ratio Br/Mg of 1.941. A pmr spectrum of the sample in D_2O revealed THF signals.

Preparation of Cyclopentadienide Solutions.—All of the ^{13}C chemical shifts and some preliminary low-temperature pmr spectra were obtained with solutions prepared as described earlier[4,11] from Alfa 3.0 M ethylmagnesium chloride in THF and Alfa 2.95 M methylmagnesium bromide in diethyl ether. When low-temperature pmr showed an extraneous cyclopentadienide peak in solutions prepared from these commercial Grignard reagents, their use was discontinued and all subsequent solutions for pmr study were prepared from $(C_5H_5)_2Mg$ and anhydrous magnesium halides. (See Results and Discussion for explanation.) All ^{13}C samples were 1.0 M in cyclopentadienide, magnesium, and chloride. Pmr samples of "C_5H_5MgCl" were prepared from analyzed[13] stock solutions of 0.40 M $MgCl_2$ in THF and 1.01 M $(C_5H_5)_2Mg$ in THF. Pmr samples of "C_5H_5MgBr" were prepared from weighed amounts of $MgBr_2 \cdot C_4H_8O$ and the stock solution of 1.01 M $(C_5H_5)_2Mg$ in THF. All nmr samples were prepared in an argon-filled drybox. The capped tubes were sealed immediately after removal from the drybox. No changes were observed when selected spectra were repeated after periods of 60 days or more.

Spectra.—Proton spectra were obtained with a Varian HA-100 instrument. Proton chemical shifts were measured relative to the β-CH_2 of THF (1.767 ppm) with a Varian V-4315 frequency counter. Temperatures were determined to ±1° with a calibrated methanol sample.

Carbon spectra were obtained at 25.2 MHz with a Varian XL-100 spectrometer. Deuterioacetone, contained in a concentric tube, provided the lock signal. Proton noise or off-resonance decoupling techniques were used in all cases. Carbon chemical shifts were determined relative to internal tetrahydrofuran and are reported relative to TMS. Tetrahydrofuran shifts C_α = 65.8, C_β = 22.7 were determined relative to internal benzene and converted to TMS scale using the relationship $\delta_{TMS} = \delta_{benzene} + 128.5$. The addition of $MgCl_2$ to THF did not change the shifts by more than 1 Hz. Temperatures were measured with a 5-mm Wilmad long-stem thermometer placed in a 12-mm tube containing methanol. We have noted that simple replacement of the 12-mm sample tube by the 5-mm thermometer leads to errors as large as 20°. This discrepancy can be traced to the change in gas flow in the probe with change in tube size.

Results and Discussion

At probe temperature (28°) the pmr spectra of "C_5H_5MgBr" and "C_5H_5MgCl" in THF were sharp singlets. Upon cooling either Grignard reagent the signal broadened and at about −60° a second signal appeared at higher field. Further cooling to −90° sharpened the higher field signal and increased its relative area. Sample spectra of "C_5H_5MgCl" are shown in Figure 1. A sample of "C_5H_5MgCl" prepared with excess $(C_5H_5)_2Mg$ showed the same two peaks at $< -60°$, but the relative area of the higher field peak was markedly increased (Figure 1d). A sample of "C_5H_5MgCl" prepared with excess $MgCl_2$ showed the lower field peak at $\leq -60°$ but only a trace of the higher field peak (Figure 1e). Similar experiments with C_5H_5MgBr, $(C_5H_6)_2Mg$, and $MgBr_2$ gave similar results. The relative areas of the two signals in low temperature pmr spectra of "C_5H_5MgCl" were independent of concentration over a 0.056–0.56 M range. The relative peak areas in low temperature spectra of "C_5H_5MgBr" also were independent of concentration over a 0.050–0.40 M range.

This spectral behavior is the same as that observed with other Grignard reagents[9,10] and is consistent with the Schlenk equilibrium (eq 1) in which the lower and higher field pmr signals are due to C_5H_5MgX and $(C_5H_5)_2Mg$, respectively. Moreover, the chemical shifts of the two signals are the same as those of separate solutions of "C_5H_5MgX" and $(C_5H_5)_2Mg$ at 27°.[4] Actually these and the previous[9,10] nmr results are also consistent with a host of other equilibria similar to eq 1 but involving higher states of aggregation.

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(12) E. C. Ashby and R. C. Arnott, *J. Organometal. Chem.*, **14**, 1 (1968).
(13) Analyses for magnesium by EDTA titration and for halides by mercuric thiocyanate titration were performed by J. Nemeth.

The independence of position of equilibrium on Grignard reagent concentration rules out equilibria involving different states of aggregation, such as 2 monomer $\rightleftarrows$ dimer. We presume, however, that "C_5H_5MgX" and "C_5H_5MgBr" are monomeric in THF because several other Grignard reagents have been found previously to be monomeric in THF by ebulliometry.[14]

In a preliminary investigation of low-temperature pmr spectra of "C_5H_5MgCl" and "C_5H_5MgBr" prepared from commercial Grignard reagents not two, but three well-resolved peaks appeared. The third peak was located between those assigned to C_5H_5MgX and $(C_5H_5)_2Mg$. Since the third peak did not appear in samples prepared from $(C_5H_5)_2Mg$ and anhydrous magnesium halides, it apparently was an impurity derived from the commercial Grignard reagents. We suspect the impurity was a cyclopentadienylmagnesium alkoxide because low-temperature spectra of a "C_5H_5MgBr" sample to which a drop of methanol was added also contained a third peak at approximately the same position.

The Schlenk equilibrium constants for "C_5H_5MgBr" and "C_5H_5MgCl" were temperature dependent (see Table I). Extrapolation of the -65 to $-90°$ data

TABLE I

EQUILIBRIUM CONSTANTS IN THF FOR

$$(C_5H_5)_2Mg + MgX_2 \underset{}{\overset{K}{\rightleftarrows}} 2C_5H_5MgX$$

Temp, °C[b]	K[a] X = Br[c]	K[a] X = Cl[d]
−65	233	106
−70	114	75
−75	74	54
−80	46	39
−85	26	29
−90	13.6	19.0
$\Delta H°$, kcal mol^{-1} [e]	7.3 ± 1.3	5.1 ± 1.8
$\Delta S°$, cal deg^{-1} mol^{-1} (−75°)[e]	45 ± 7	34 ± 9

[a] At most temperatures only one measurement was made. Values at −75° were reproducible to ±5% in duplicate experiments. [b] ±1°. [c] 0.20 *M* "C_5H_5MgBr." [d] 0.093 *M* "C_5H_5MgCl." [e] Errors estimated from maximum deviations of points from lines in log K *vs.* $1/T$ plots.

indicates that "C_5H_5MgBr" contains 0.5 mol % $(C_5H_5)_2Mg$ and "C_5H_5MgCl" contains 1.3 mol % $(C_5H_5)_2Mg$ at 25°.

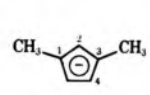
Although the relative areas of peaks in low-temperature "C_5H_5MgBr" and "C_5H_5MgCl" pmr spectra were independent of concentration, the linewidths of the C_5H_5MgX peaks at −60 and −75° increased as the concentration of "C_5H_5MgX" increased. This implies that exchange of C_5H_5MgX is of kinetic order greater than one in C_5H_5MgX, or that impurities are catalyzing the exchange process. Second-order kinetics for inversion of primary alkyl groups and exchanges of alkyl groups in Grignard reagents have been noted before.[15] No attempt was made to obtain better kinetic data because the Grignard solutions in this investigation were prepared from common "Grignard" grade magnesium turnings and may contain impurities which catalyze alkyl group exchange.[16] Although minor impurities may affect greatly the kinetic processes in Grignard reagents, they should not affect the position of the Schlenk equilibrium much.

The proton chemical shifts of substituted "cyclopentadienylmagnesium chlorides" provided little indication of charge distribution in the cyclopentadienide ions.[11] However, ^{13}C chemical shifts are more closely related and more sensitive to charge density than are proton chemical shifts. There is theoretical justification for an approximately linear ^{13}C chemical shift *vs.* charge density relationship in cyclic aromatic systems.[17]

Carbon chemical shifts of the "cyclopentadienylmagnesium chlorides" appear in Table II. Assignments were made from proton-coupled and off-resonance-decoupled spectra when possible. The tentative C_2 and C_3 assignments of methylcyclopentadienide were made by analogy to 1,3-dimethylcyclopentadienide.

TABLE II

^{13}C CHEMICAL SHIFTS[a] OF "CYCLOPENTADIENYLMAGNESIUM CHLORIDES"[b]

			
C 103.8	C_1 116.1 C_2 104.1 C_3 101.6 CH_3 11.1	C_1 114.4 C_2 105.2 C_4 101.4 CH_3 11.2	C_1 112.6 C_2, C_3 112.5, 105.7 CH_3 −3.8

[a] In parts per million downfield from TMS; values are accurate to ±0.3 ppm (see footnote 24). [b] 1.0 *M* in THF at 35°.

Methyl substitution for hydrogen in cyclopentadienide shifts the ^{13}C signal of the methyl-bound ring carbon downfield 12.3 and 10.6 ppm, respectively, in the methyl and 1,3-dimethyl compounds, but has little effect on the unsubstituted ring carbons. Comparisons of ^{13}C chemical shifts of methylbenzenes to benzene give very similar results,[18] although the changes of chemical shifts in the cyclopentadienides are slightly greater than in the benzenes, as expected for nonalternant systems.[19] If we take toluene as a model for methyl group effects on ring carbon chemical shifts, then all other structural factors influencing chemical shifts change the methyl- and 1,3-dimethylcyclopentadienide ring carbons by $\leq$3.2 ppm compared to unsubstituted cyclopentadienide.[20] A linear correlation between ^{13}C chemical shift and charge density has been established for a series of ionic and neutral monocyclic aromatic systems with a slope of 167.8 ppm per unit

(14) F. W. Walker and E. C. Ashby, *J. Amer. Chem. Soc.*, **91**, 3845 (1969), and references therein.

(15) (a) G. M. Whitesides and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 4878 (1965); (b) G. Fraenkel and D. T. Dix, *ibid.*, **88**, 979 (1966); (c) H. O. House, R. A. Latham, and G. M. Whitesides, *J. Org. Chem.*, **32**, 2481 (1967); (d) G. Fraenkel, C. E. Cottrell, and D. T. Dix, *J. Amer. Chem. Soc.*, **93**, 1704 (1971).

(16) For a discussion of the nature of impurities in common magnesium turnings which attributes line broadening to the presence of Mn(II) see ref 15c, p 2483. The $(C_5H_5)_2Mg$ stock solution in this work was pink, also suggestive of Mn(II) impurities.

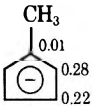
(17) (a) M. Karplus and J. A. Pople, *J. Chem. Phys.*, **38**, 2803 (1963); (b) T. Tokuhiro and G. Fraenkel, *J. Amer. Chem. Soc.*, **91**, 5005 (1969).

(18) (a) P. C. Lauterbur, *ibid.*, **83**, 1838 (1961); (b) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961).

(19) A. J. Jones, T. D. Alger, D. M. Grant, and W. M. Litchman, *J. Amer. Chem. Soc.*, **92**, 2386 (1970).

(20) [$\Delta\delta$ for CCH_3 in $CH_3C_5H_4^-$ (−12.3 ppm)] − [$\Delta\delta$ for CCH_3 in $CH_3C_6H_5$ (−9.1 ppm)[18b]] = −3.2 ppm.

charge.[21] Thus we conclude that methyl substitution has left the charge distribution in the cyclopentadienide ring almost unchanged. This conclusion contrasts with the charge densities predicted by simple HMO theory shown below.[22] We believe that the ^{13}C chemical shifts provide a more reliable guide.



The sum of downfield chemical shifts of ring carbons in cyclopentadienide due to trimethylsilyl substitution is −30.0 ppm (see Table I) compared to −18.9 ppm for trimethylsilyl substitution on benzene.[23] This is evidence for withdrawal of electron density from cyclopentadienide by silicon.

Qualitative low-temperature ^{13}C nmr spectra of "C_5H_5MgCl" and "$CH_3C_5H_4MgCl$" were similar to each other and to the pmr spectra of "C_5H_5MgCl." At −67° a proton-decoupled spectrum of C_5H_5MgCl prepared from commercial Grignard reagent showed two peaks separated by 21 Hz with relative areas of 4:1. These peaks must be "C_5H_5MgCl" and an impurity (probably a cyclopentadienylmagnesium alkoxide), because the proton spectra indicate that $(C_5H_5)_2Mg$ should not be detectable at the sensitivity limits available in the ^{13}C experiment. Spectra of "$CH_3C_5H_4MgCl$" prepared from commercial Grignard reagent showed sharp proton-decoupled peaks at 50°. The peaks due to C_2 and C_3 were examined as a function of temperature. On cooling each peak broadened and then separated into two sharp peaks at −38°. The intensity ratio of each pair of peaks was 4:1 and this ratio remained unchanged down to −65°. Peak separations were 10 and 33 Hz for C_2 and C_3, respectively. Only sharp singlets could be seen in a spectrum of "$CH_3C_5H_4MgCl$" prepared from $(CH_3C_5H_4)_2Mg$ and anhydrous $MgCl_2$ even at −67°. All of the Grignard solutions prepared from commercial Grignards showed similar exchange phenomena in their ^{13}C spectra. These observations show that cyclopentadienylmagnesium chlorides are in rapid equilibria with the impurities (presumably alkoxides) in commercial Grignard solutions.[24] Precautions should be taken to prevent this complication in kinetic studies. The high solute concentrations required without the aid of Fourier transform spectroscopy prevented observation of the Schlenk equilibrium by carbon magnetic resonance.

Registry No.—$MgCl_2$, 7786-30-3; $MgBr_2$, 7789-48-2; $(C_5H_5)_2Mg$, 1284-72-6; cyclopentadienylmagnesium chloride, 11112-17-7; methylcyclopentadienylmagnesium chloride, 11112-18-8; 1,3-dimethylcyclopentadienyl chloride, 11112-19-9; trimethylsilylcyclopentadienylmagnesium chloride, 11112-20-2.

Acknowledgments.—We thank R. L. Thrift and S. Silber for running the low-temperature pmr spectra and R. E. Santini and R. L. Spaeth for assistance with the ^{13}C spectra. W. T. F. thanks the Merck Company Foundation and E. I. du Pont de Nemours and Company and J. B. G. thanks Eli Lilly and Company for financial support.

(21) (a) H. Spiesecke and W. G. Schneider, *Tetrahedron Lett.*, 468 (1961); (b) E. A. LaLancette and R. E. Benson, *J. Amer. Chem. Soc.*, **87**, 1941 (1965).

(22) S. McLean and P. Haynes, *Tetrahedron*, **21**, 2313 (1965).

(23) G. E. Maciel and J. J. Natterstad, *J. Chem. Phys.*, **42**, 2427 (1965).

(24) The impurities affect only slightly the chemical shifts in Table II. For example, in the contaminated sample of "$CH_3C_5H_4MgCl$" the 33-Hz separation between the two C_3 peaks at −38° corresponds to a chemical shift difference of only 0.26 ppm between $CH_3C_5H_5MgCl$ and the weighted average of $CH_3C_5H_5MgCl$ and impurity. Since all other peak separations in all the compounds in Table II at low temperature were smaller than 33 Hz, the errors in chemical shifts due to impurities are <0.3 ppm.

Oxidation by Metal Salts

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Received December 14, 1971

Oxidation of *p*-cymene with cobalt(III) acetate gives *p*-isopropylbenzyl acetate and *p*-isopropylbenzaldehyde as predominant products. With manganese(III) acetate, however, a mixture of cymene dimers is formed predominantly. In the presence of oxygen, with the cobalt salt, *p*-isopropylbenzoic acid is formed, and with the manganese salt, a mixture of *p*-toluic acid and *p*-methylacetophenone. The different nature of the products suggests two mechanisms, electron transfer with cobalt and a free-radical pathway with manganese.

The catalytic effect of transition metal ions in the autooxidation of hydrocarbons is well established. Metal ions take part in the initiation step by decomposing hydroperoxides into radicals which propagate the chain mechanism.[1-3] Recently, direct interactions of metal ions with hydrocarbons have been stressed. Such interactions appear to be important when rather large, as opposed to catalytic, concentrations of metal ions are used. Two of the ions, Co(III)[4-10] and Mn(III),[11-13] have been studied in detail. Initially, both were thought to operate in an analogous manner. Now, it is believed that Co(III) functions primarily

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TABLE I
REACTION OF *p*-CYMENE WITH OXYGEN

Catalyst[a]	$C_{10}H_{14}$,[b] *M*	Conditions	$C_{10}H_{14}$, % Conversion	Products (% molar selectivity)
0.2 *M* $Co(OAc)_2 \cdot 4H_2O$/HOAc	1.0	100°, 22 atm O_2,[c] 1.5 hr	100	*p*-Isopropylbenzoic acid (90) *p*-Acetobenzoic acid (10)
0.2 *M* $Mn(OAc)_2 \cdot 4H_2O$/HOAc	1.2	100°, 22 atm O_2,[c] 2.0 hr	~29	*p*-Toluic acid (68) *p*-Methylacetophenone (16) *p*-Isopropylbenzoic acid (16)

[a] Each experiment was initiated with MEK. [b] *Ca.* 2 mol of *n*-butane was added for promotion. [c] Total pressure, partial pressures of C_4H_{10} and O_2.

TABLE II
REACTION OF *p*-CYMENE WITH Co(III) AND Mn(III) ACETATES

Catalyst	$C_{10}H_{14}$	Conditions	Products (mmol, % molar selectivity)
98 mmol of Co(III)	100 mmol, and 40 mmol of NaOAc/100 cc of HOAc	65°, 1.5 days	*p*-Isopropylbenzyl acetate (35.4, 81.2) *p*-Isopropylbenzaldehyde (6.6, 15.1) *p*-Isopropylbenzaldehyde diacetate (1.0, 2.3) Dimers (0.6, 1.4) *p*-Methylacetophenone (trace, 0.1)
Cymene converted: 32%			
167 mmol of Mn(III)	245 mmol/540 cc of HOAc[a]	95°, 4 days	Dimers (*m/e* 266, 280)[b] (6.4, 80.0) Methyl isopropyl benzyl acetates (*m/e* 206) (0.7, 8.7) *p*-Methylacetophenone (0.4, 5.0) Assorted products (?, ~7.0)
Cymene converted: ~7%			

[a] With added NaOAc, oxidation of intermediate radicals is rapid (120°, 2 hr) so that $-CH_2OAc$ and $-CH_2COOH$ adducts are formed predominantly. [b] Analysis showed ~38% of bicymyls, $C_{20}H_{26}$, and ~62% of $C_{21}H_{28}$. The latter can be formed by a series of radical reactions involving (a) cross-coupling of cymyl and carboxymethyl radicals[11] to give *p*-$MePhC(Me)_2CH_2COOH$, (b) reaction of this acid with $Mn(OAc)_3$ followed by thermolysis to give $C_{11}H_{15}\cdot$, and (c) coupling of $C_{11}H_{15}\cdot$ with another cymyl radical. This reaction is therefore dominated by the coupling of cymyl radicals. The precise structure of dimers at this time is not known.

via electron transfer, while Mn(III) is effective by both electron transfer and a free-radical pathway, depending on experimental conditions and the reactivity of the substrate. Mechanisms were proposed mostly on the basis of kinetic evidence, trapping of intermediates, and spectroscopic data. We noticed, however, that these studies, with or without oxygen, were mostly limited to toluene. Compounds such as ethyltoluenes and cymenes, in which competition between alkyl groups is possible, were not examined, probably because of the ease with which they are oxidized by a free-radical mechanism, and due to the complexity of the products formed. Russell, *et al.*,[14] reported difficulty in oxidizing alkoxycumenes in acetic acid because of apparent decomposition of the hydroperoxide into phenolic materials. In the only reference available,[5] *p*-cymene was oxidized in acetic acid with cobaltic acetate to determine its reactivity, but products of this reaction have not been cited. We have reported results on the Co(III) ion catalyzed oxidation of *p*-cymene with oxygen to form *p*-isopropylbenzoic acid.[15,16] Now, we comment on the Mn(III) ion catalyzed oxidation of *p*-cymene with oxygen, as well as the reaction of cymene with Co(III) and Mn(III) acetates.

(14) G. A. Russell and R. C. Williamson, Jr., *J. Amer. Chem. Soc.*, **86**, 2357 (1964).
(15) A. Onopchenko, J. G. D. Schulz, and R. Seekircher, *Chem. Commun.*, 939 (1971).
(16) A. Onopchenko, J. G. D. Schulz, and R. Seekircher, *J. Org. Chem.*, **37**, 1414 (1972).

Results and Discussion

Experiments with oxygen are summarized in Table I. Under comparable conditions, oxidation of *p*-cymene with oxygen proceeds more readily with the cobalt than with the manganese catalyst. This may be attributed, in part, to the difference in the redox potentials of the two systems. More striking, however, is the different nature of the products formed. Whereas *p*-isopropylbenzoic acid is the major product in the cobalt system, *p*-toluic acid and its precursor *p*-methylacetophenone are predominant when mangenese is used. These results suggest that different mechanisms are operative. Selectivities with manganese-catalyzed oxidations are analogous to those from noncatalytic air oxidation of *p*-cymene reported by Serif, *et al.*[17]

Results of cymene oxidation by Co(III) and Mn(III) acetates are summarized in Table II. Major products with Co(III) salt are *p*-isopropylbenzyl acetate and *p*-isopropylbenzaldehyde. Both were isolated and characterized by vpc, nmr, ir, and derivatives. Identification of minor products was based primarily on vpc behavior. It is surprising that essentially no attack on the isopropyl group occurred. This suggests that the 10% of *p*-acetobenzoic acid formed in the presence of oxygen may have come by a competitive free-radical pathway.

(17) G. S. Serif, C. F. Hunt, and A. N. Bourns, *Can. J. Chem.*, **31**, 1229 (1953).

Oxidation of cymene with Mn(III) salt was carried out in the absence of sodium acetate and without removal of water, conditions favoring an electron transfer mechanism.[11] Even under such conditions, coupling of cymene radicals was the dominant course of the reaction. Some dimers could also be formed by gradual addition of diacetyl peroxide to boiling cymene.[18] Minor products consisted of 15 components (vpc), mostly esters and some acids. Only a trace or *p*-isopropylbenzaldehyde, its diacetate, and *p*-isopropylbenzyl acetate was detected. Analysis of the total product by nmr after removal of unreacted cymene by column chromatography showed that virtually all of the isopropyl groups had reacted.

Conclusion

Products formed in the oxidation of *p*-cymene using cobaltic or manganic salts alone or in conjunction with oxygen indicate operation of different mechanisms in the two cases studied. Electron transfer with cobalt and a free-radical path with manganese are in accord with our results as well as published data.

(18) H. C. McBay and P. T. Groves, *J. Org. Chem.*, **21**, 691 (1956).

Experimental Section

Reactions with oxygen at elevated pressure were carried out as previously reported.[16] Experiments with metal salts alone were done in sealed tubes under nitrogen atmosphere. Concentrations of metal ions were determined by iodometric titration. After termination of the reaction, the mixture was taken up in ether and repeatedly extracted with cold water. The organic layer was dried ($MgSO_4$) and filtered, and the ether was removed. After addition of methyl palmitate as internal standard, the residue was analyzed by vpc (6 ft × 0.25 in., OV-1 column, programmed from 50 to 275° at 10°/min). Unreacted cymene was removed from the product by column chromatography over silica gel. Standard analytical procedures were then used for the characterization of the residual product mixture. Cobaltic acetate and manganic acetate were prepared by published procedures.[10,13]

Registry No.—*p*-Cymene, 99-87-6; Co(III) acetate, 917-69-1; Mn(III) acetate, 993-02-2.

The Formation of 1,4 Diketones, Monoketones, and β-Epoxy Ketones by Reaction of Iron Pentacarbonyl with α-Halo Ketones. A Possible Mechanism for Iron Pentacarbonyl–Halide Reactions

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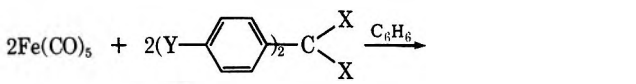
Received January 11, 1972

Iron pentacarbonyl reacts with a variety of primary, secondary, and tertiary aryl and alkyl α-halo ketones in refluxing 1,2-dimethoxyethane, followed by treatment with water, to generally give the coupled 1,4 diketones and the reduced monoketones. Use of deuterium oxide instead of water results in α-deuterio ketone formation. β-Epoxy ketones were produced in several instances. The reaction apparently occurs *via* organoiron tetracarbonyl halide and organoiron halide complexes. Some support is presented for the intermediacy of such complexes. The reactions of $Fe(CO)_5$ with sulfonyl chlorides and *gem*-dihalides likely proceed *via* similar intermediates.

A number of papers have appeared in the literature concerning the reaction of iron pentacarbonyl with halides. A simple preparation of tetraarylethylenes (2) was reported by Coffey,[2a] in 1961, by treatment of



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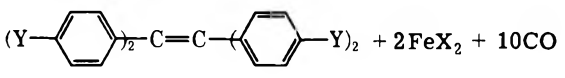

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X = Cl; Y = H, CH_3, $C(CH_3)_3$, CH_3, Cl
X = Br; Y = NO_2

certain *gem*-dihalides (1) with $Fe(CO)_5$ in refluxing benzene. Activating groups such as aryl, halo, cyano, and carbalkoxy must be attached to the halogen-bearing carbon in order for this thermal reaction to occur, but substituted ethylenes are not produced in all instances; *e.g.*, (i) although bisfluorenylidene was obtained by reaction of 9,9-dibromofluorene with the metal carbonyl in hot benzene, the alkene and 9,9′-dibromobisfluorenyl are formed by using dioxane as the solvent; (ii) diethyl dibromomalonate and dibromomalonitrile react with $Fe(CO)_5$ in benzene giving iron-containing materials of no apparent synthetic utility; (iii) some hexachloroethane, along with substantial amounts of tar, resulted when carbon tetrachloride was the starting halide.[2] Some *gem*-dihalides with other activating groups failed to react with the metal carbonyl (*e.g.*, dichloromethyl phenyl sulfone).[3] Vicinal dihalides are dehalogenated by $Fe(CO)_5$.[1,3]

Coffey observed no reaction between $Fe(CO)_5$ and any monohalide. Recently, Pankowski and Bigorgne reported that no reaction occurred when methyl iodide and $Fe(CO)_5$ were mixed at room temperature.[4] However, Bruce[5] showed that decafluorobenzhydryl bromide (3) reacts with $Fe(CO)_5$ in hot petroleum ether (bp 100–120°) to give the expected coupling product 4, in 37% yield, and small amounts of bis(pentafluorophenyl)methane (5), the formation of the latter attrib-

(1) Taken in part from the B.A. (Honors) thesis of E. C. H. Keung, May 1972; presented in part at the Third Northeast Regional Meeting of the American Chemical Society, Buffalo, N. Y., Oct 1971, Abstract 172.

(2) (a) C. E. Coffey, *J. Amer. Chem. Soc.*, **83**, 1623 (1961); (b) A. Mittasch, *Angew. Chem.*, **41**, 827 (1928).

(3) H. Alper and E. C. H. Keung, unpublished results.

(4) M. Pankowski and M. Bigorgne, *J. Organometal. Chem.*, **30**, 227 (1971).

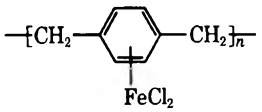
(5) M. I. Bruce, *ibid.*, **10**, 495 (1967).

$$(C_6F_5)_2CHBr + Fe(CO)_5 \longrightarrow \underset{3}{}$$

$$(C_6F_5)_2CHCH(C_6F_5)_2 - (C_6F_5)_2CH_2$$
4 5

uted to the presence of traces of moisture in the solvent or the metal carbonyl. Perfluoroalkyliron tetracarbonyl iodides have been obtained from reaction of perfluoroalkyl iodides with $Fe(CO)_5$.[6,7]

Thermal reaction of $Fe(CO)_5$ and some halides not having strongly electron-attracting groups results in the formation of polymeric materials. Reaction of benzyl chloride and the metal carbonyl in tetrahydrofuran at 30° gives $(C_6H_4CH_2)_n$ where $n \sim 62$.[8] α,α-Dichloro-*p*-xylene and 1,4-dichloro-2-butene (of unspecified stereochemistry) react with $Fe(CO)_5$ in xylene at 100–110° to give, it is claimed, **6** and **7**,



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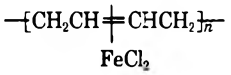

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respectively.[9] Other allyl halides usually form allyl halide–iron tetracarbonyl complexes[10] or π-allyliron-tricarbonyl halides.[11,12] Aryl halides show low thermal reactivity toward $Fe(CO)_5$. Iodobenzene, for example, fails to react with the metal carbonyl at temperatures of 30–60°.[8]

Koerner von Gustorf and coworkers[13–15] have investigated the irradiation of $Fe(CO)_5$ with a number of simple saturated halides. Coupling or photoelimination products were obtained from these reactions, subject to the nature of the organic reactant. An iron tetracarbonyl complex has been isolated from photolysis of $Fe(CO)_5$ in dibromodifluoromethane.[16] Ferraindene–iron carbonyl complexes have been obtained by a novel 1,4-dehydrobromination of *o*-bromostyrene, on irradiation of the latter with $Fe(CO)_5$.[17] Vinyl halides react with $Fe(CO)_5$ on irradiation to form iron tetracarbonyl complexes.[15,18,19]

Fluorinated nitrogen compounds such as tetrafluorohydrazine, perfluoroethylenediamine, and *N*,*N*-dichlorotrifluoromethylamine undergo dehalogenation upon reaction with $Fe(CO)_5$ in a sealed tube.[20–23] Treatment of sulfonyl halides with a 1:1 mixture of $Fe(CO)_5$ and boron trifluoride etherate in preferably dipolar aprotic solvents provides a convenient preparation of thiosulfonate esters.[24] Disulfides have been obtained from the coupling reaction of some sulfenyl halides and $Fe(CO)_5$ in tetrahydrofuran in the cold.[25] In some instances (perchloro- or perfluoroalkanesulfenyl chlorides) partial dehalogenation of the coupled product occurs. The tin halide, tri-*n*-butyltin chloride, reacts with the metal carbonyl to form di-*n*-butyl ketone in low yield (among other products).[26] Finally, acid halides form a variety of products (coupling,[27] solvent incorporation[28]) upon reaction with $Fe(CO)_5$, the nature of the products depending on the reaction conditions and the type of acid halide.

Recently, Noyori and coworkers[29] reported a new route to troponoid compounds by reaction of α,α′-dibromo ketones with diiron enneacarbonyl at 60° in the presence of 1,3-dienes. The authors briefly noted that $Fe(CO)_5$ was not as useful for effecting this cyclization reaction. Their communication prompts us to present our results on the reaction of α-halo ketones and $Fe(CO)_5$. The purpose of this investigation was to attempt to answer the following: (a) what products are formed in these reactions (coupling, dehalogenation, other)?; (b) what are some of the possible mechanisms for the reactions?; (c) if coupling products are obtained as in several other halide–$Fe(CO)_5$ reactions, is the reaction pathway unique to a given type of halide or perhaps common to all?

Results and Discussion

Reaction of $Fe(CO)_5$ with α-halo ketones [**8**, 2:1.14 ratio of **8**:$Fe(CO)_5$] in refluxing anhydrous 1,2-dimethoxyethane [DME] for 5–19 hr, followed by treatment with water, gave 1,4 diketones (**9**), monoketones (**10**), and/or β-epoxy ketones (**11**). The reaction time, yields, melting points of new compounds, and pertinent nmr data for the reaction products are listed in Table I.

In general, 2-bromoacetophenone and its *p*-phenyl- and *p*-methoxy-substituted derivatives gave the 1,4 diketone as the major product with the methyl ketone formed as the by-product. The presence of strongly electron-attracting para substituents (Br, F) on the benzene ring results in the formation of β-epoxy ketones (**11**) and **10**, but little, if any, 1,4 diketone. Rather surprisingly, the secondary and tertiary halides, **8**, R = C_6H_5, R′ = CH_3, R″ = H, and **8**, R = C_6H_5, R′ = R″ = CH_3, respectively, gave **9** in moderate

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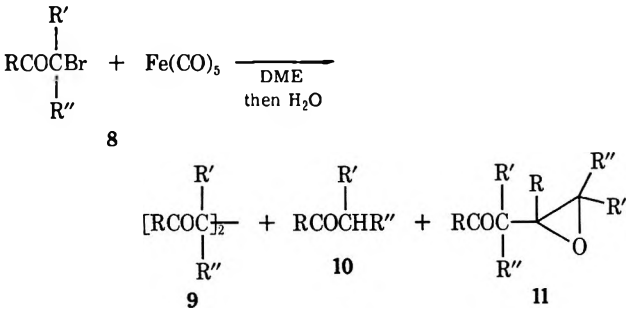
TABLE I

PRODUCTS OBTAINED FROM REACTION OF $Fe(CO)_5$ WITH α-HALO KETONES IN DME[a]

α-Halo ketone (8)	Registry no.	Reaction time, hr	Products[b]	Registry no.	New compd[c] mp, °C	Yield, %	Pertinent nmr data,[d] ppm
2-Bromoacetophenone	70-11-1	5	**9**, R = C_6H_5; R′ = R″ = H			35	3.45 (s, CH_2, DMSO-d_6)
			10, R = C_6H_5; R′ = R″ = H			25	2.59 (s, CH_3, $CDCl_3$)
2-Bromo-4′-phenylacetophenone	135-73-9	5	**9**, R = p-$C_6H_5C_6H_4$; R′ = R″ = H	34733-52-3	200–202	63	3.31 (s, CH_2, DMSO-d_6)
			10, R = p-$C_6H_5C_6H_4$; R′ = R″ = H			30	2.59 (s, CH_3, DMSO-d_6)
2,4′-Dibromoacetophenone	99-73-0	5	**9**, R = p-BrC_6H_4; R′ = R″ = H			5.3	3.29 (s, CH_2, DMSO-d_6)
			10, R = p-BrC_6H_4; R′ = R″ = H			17	2.47 (s, CH_3, CCl_4)
			11, R = p-BrC_6H_4; R′ = R″ = H	34733-53-4	92 dec	20	3.06 (m, CH_2 chain, $CDCl_3$)
							2.58 (m, CH_2 ring, $CDCl_3$)
2-Bromo-4′-fluoroacetophenone	403-29-2	5	**9**, R = p-FC_6H_4; R′ = R″ = H			Trace	3.28 (s, CH_2, $CDCl_3$)
			10, R = p-FC_6H_4; R′ = R″ = H			34	2.46 (s, CH_3, CCl_4)
			11, R = p-FC_6H_4; R′ = R″ = H	34733-54-5	93–94	21	3.41 (m, CH_2 chain, $CDCl_3$)
							2.55 (m, CH_2 ring, $CDCl_3$)
2-Bromo-4′-methoxyacetophenone	2632-13-5	12	**9**, R = p-$CH_3OC_6H_4$; R′ = R″ = H			51	3.37 (s, CH_2, $CDCl_3$)
			10, R = p-$CH_3OC_6H_4$; R′ = R″ = H			25	2.47 (s, CH_3CO, CCl_4)
α Bromopropiophenone	2114-00-3	5.5	**9**, R = C_6H_5; R′ = CH_3; R″ = H	34733-55-6	85–86	46	1.23 (d, CH_3, $CDCl_3$)
							3.92 (m, CH, $CDCl_3$)
			10, R = C_6H_5; R′ = CH_3; R″ = H			31	1.16 (t, CH_3, CCl_4)
							2.85 (q, CH_2, CCl_4)
α-Bromoisobutyrophenone	10409-54-8	5	**9**, R = C_6H_5; R′ = R″ = CH_3	34733-56-7	113–115	47	1.38 (s, CH_3, $CDCl_3$)
			10, R = C_6H_5; R′ = R″ = CH_3			14	1.20 (d, CH_3, $CDCl_3$)
							3.51 (se, CH, $CDCl_3$)
α-Bromo-2′-acetonaphthone	613-54-7	19	**9**, R = 2-$C_{10}H_7$; R′ = R″ = H	34733-57-8	213–215	6.0	*e*
			10, R = 2-$C_{10}H_7$; R′ = R″ = H			24	2.57 (s, CH_3, $CDCl_3$)
α-Bromo-9′-aceto-1,2,3,4,5,6,7,8-octahydroanthrone	34733-51-2	5.5	**9**, R = 9-Anthryl; R′ = R″ = H	34733-58-9	235–237	15	3.49 (s, CH_2, DMSO-d_6)
			10, R = 9-Anthryl; R′ = R″ = H			13	2.42 (s, CH_3, $CDCl_3$)
1-Adamantyl bromomethyl ketone	5122-82-7	14	**9**, R = 1-Adamantyl; R′ = R″ = H	34733-59-0	220–222	4.6	*e*
			10, R = 1-Adamantyl; R′ = R″ = H			25	2.08 (s, CH_3, $CDCl_3$)

[a] 2:1.14 mole ratio of 8:$Fe(CO)_5$. [b] Satisfactory analytical data were obtained for C and H. [c] The melting point or boiling point and spectral data for known products were in good agreement with data reported in the literature. [d] s = singlet, d = doublet, t = triplet, q = quartet, se = septet, m = multiplet. [e] Insufficiently soluble for nmr purposes.



yields along with smaller amounts of **10** (no elimination products were observed). 1-Adamantyl bromomethyl ketone and *d*-3-bromocamphor (to be considered in detail in a forthcoming publication) gave low yields of **9** and **10** when treated with $Fe(CO)_5$.

Variations of the reaction conditions were studied using 2-bromo-4′-phenylacetophenone as the reactant α-halo ketone. 2-Deuterio-4′-phenylacetophenone was obtained when the reaction mixture (in DME) was poured into deuterium oxide rather than water, indicating that this reaction may provide for a simple synthesis of α-deuterio ketones. If the reaction mixture was not poured into water, then no methyl ketone formation occurred, clearly showing that the hydrogen for **10** arises from water and not from DME. The presence of water inhibited reaction, since only starting material was recovered when the α-halo ketone and $Fe(CO)_5$ were refluxed in DME–water (9:1). The reaction is not catalytic in $Fe(CO)_5$ and is not affected by the addition of azobisisobutyronitrile, a radical initiator.[30] Dipolar aprotic solvents such as *N*,*N*-dimethylacetamide and tetramethylurea could be used but yields were lower than when DME was the reaction solvent.

It should be pointed out that only in the case of the 2-bromo-4′-phenylacetophenone–$Fe(CO)_5$ reaction was experimentation carried out toward determining the optimum reaction conditions (93% total product yield). Hence, it is likely that the total yields for some of the other reactions could be improved using more suitable reaction conditions. Many of the 1,4 diketones,[31] produced in this simple reaction, are new compounds (see Table I) and may be precursors to as yet unknown, but potentially useful, five-membered ring heterocycles *via* the well-known Paal–Knorr[32a–c] synthesis and to cyclopentenones *via* treatment with base.[32d]

A possible mechanism (Scheme I) for the α-halo ketone–$Fe(CO)_5$ reaction involves initial oxidative addition to give **12**. The latter can lose carbon monoxide to form **13**, which can then be converted to **10** by cleavage of the iron–carbon bond (addition of water or deuterium oxide), and to **9** and/or **11** by reaction with more **8**. It is also possible that **12** can react directly with additional **8** to give the coupled products or with H_2O or D_2O to form **10**.

An alternative mechanism (Scheme II) proposes radical generation *via* reaction of **12** with **8**. The radical could then give **9** by dimerization, **10** by hydrogen abstraction from solvent, and **11** by attack on **8** followed by cylization. However, some evidence against a radical process was noted earlier (the failure of a radical initiator to affect the reaction).

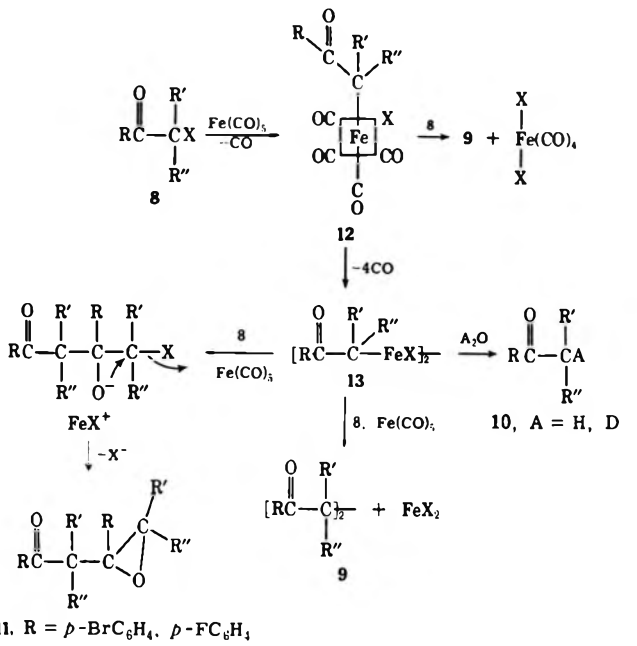
In order to determine the validity of the mechanism outlined in Scheme I as a possible rationale for the α-halo ketone reaction, we treated 2-bromo-4′-phenylacetophenone with the more reactive diiron ennea-

(30) C. Walling and E. S. Huyser, *Org. React.*, **13**, 115 (1963).

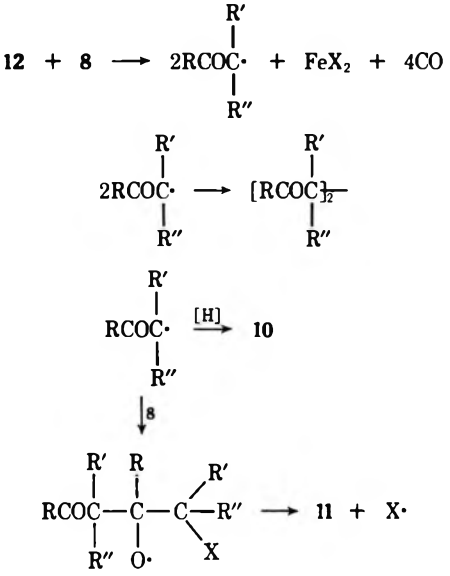
(31) For a review of synthetic approaches to 1,4-diketones see E. Ritchie and W. C. Taylor, *Aust. J. Chem.*, **24**, 2137 (1971).

(32) (a) C. Paal, *Chem. Ber.*, **17**, 2757 (1884); (b) L. Knorr, *ibid.*, **17**, 2863 (1884); (c) E. E. Campaigne and W. O. Foye, *J. Org. Chem.*, **17**, 1405 (1952); (d) *e.g.*, J. E. McMurry and J. Melton, *J. Amer. Chem. Soc.*, **93**, 5309 (1971). A study of the cyclization reactions of some of the 1,4 diketones prepared in this study is currently in progress.

Scheme I

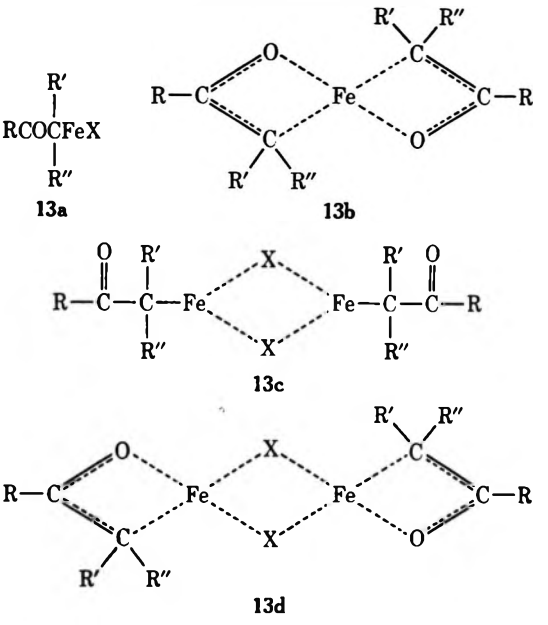


Scheme II

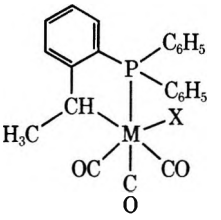


carbonyl at room temperature. In this manner, we succeeded in isolating **12** (R = *p*-$C_6H_5C_3H_4$; R′ = R″ = H; X = Br), identified by elemental analysis and mass spectral data (parent peak at *m/e* 443; important fragments at *m/e* 415, 387, 359, 331). Complex **12** has the cis configuration, since the ir spectrum shows three bands in the terminal metal carbonyl stretching region at 2104, 2041, and 1982 cm^{-1} (KBr, four bands in methylene chloride). The trans isomer would have given only one band in this region.[33] Cis oxidative addition has also been observed in the addition of halogen to the trigonal bipyramidal *trans*-$Os(CO)_3[P(C_6H_5)_3]_2$.[34]

Complex **12** (R = *p*-$C_6H_5C_6H_4$; R′ = R″ = H; X = Br) was only moderately stable under nitrogen and slowly decarbonylated to **13** by standing at room temperature, or rapidly when heated in DME. We had hoped to prepare a more stable analog of **12** by reaction of **8** (R = *p*-$C_6H_5C_6H_4$; R′ = R″ = H) with triphenylphosphineiron tetracarbonyl, but only starting material] were recovered when the reactants were refluxed in DME.[35] A number of structures (**13a–d**)



could be assigned to **13**. Structures **13a** and **13b** were eliminated since the molecular weight of the compound was 644 as determined by vapor phase osmometry. The molecular weight (662) of **13c** or **13d** (R = *p*-$C_6H_5C_6H_4$; R′ = R″ = H) was in reasonable accord with the osmometrically determined value. We favor **13d** rather than **13c** as the structure for the organoiron halide, since the carbonyl stretching frequency was shifted from 1687 (for **8**) to 1577 cm^{-1} (for **13**), thereby indicating coordination of the keto group to the metal in some manner. Bennett and coworkers[36] have recently suggested that decomposition (loss of carbon monoxide) of octahedral Fe(II) and Ru(II) carbon σ-bonded chelate complexes (**14**) may result in the formation of halogen-bridged dimers.



14
M = Fe, Ru
X = Cl, Br

Complex **13** could be converted to **10** by treatment with water, the latter cleaving the Fe–C σ bond. When **13** was heated with **8** (R = *p*-$C_6H_5C_6H_4$; R′ = R″ = H) under conditions described for the $Fe(CO)_5$ reaction [*i.e.*, refluxing DME for 5 hr], only traces of the

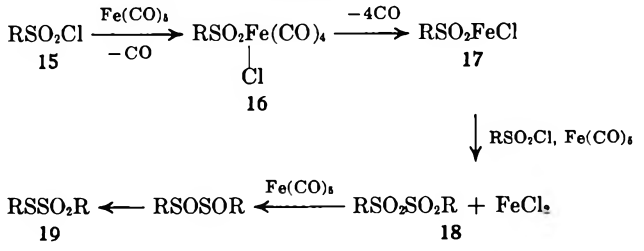
(33) F. A. Cotton and C. S. Kraihanzel, *J. Amer. Chem. Soc.*, **84**, 4432 (1962).

(34) J. P. Collman and W. R. Roper, *ibid.*, **88**, 3504 (1966).

(35) C. H. Bamford and W. R. Maltman, *Trans. Faraday Soc.*, **62**, 2823 (1966), found that triphenylphosphineiron tetracarbonyl is more active than $Fe(CO)_5$ in producing the trichloromethyl radical from treatment with carbon tetrachloride and methyl methacrylate. These results are opposite to those observed with **8**.

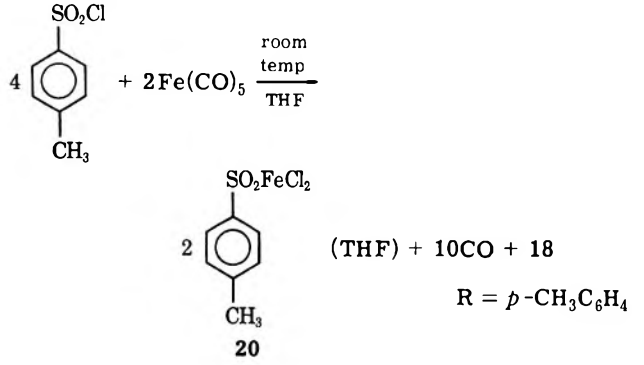
(36) M. A. Bennett, G. B. Robertson, I. B. Tomkins, and P. O. Whimp, *J. Organometal. Chem.*, **32**, C19 (1971).

SCHEME III



1,4 diketone were produced. However, if the metal carbonyl was present in catalytic amounts, **9** (R = *p*-$C_6H_5C_6H_4$; R′ = R″ = H) was obtained in good yield. An unsymmetrical 1,4 diketone resulted when **13** (R = *p*-$C_6H_5C_6H_4$; R′ = R″ = H) was treated with **8** (R = C_6H_5; R′ = R″ = H) in the presence of $Fe(CO)_5$. The formation of β-epoxy ketone **11** depends on R being an effective electron-attracting group, thereby making the carbonyl carbon of **8** more positive and hence more susceptible, than the halogen-bearing carbon, to attack by **13** (treating this step as a displacement).

Now that the reaction pathway as outlined in Scheme I had been established, we next considered whether coupling products obtained from several other $Fe(CO)_5$–halide reactions were formed *via* the same or a similar process. The postulated mechanism for the formation of thiolsulfonate esters, from treatment of sulfonyl chlorides **15** with $Fe(CO)_5$ in various solvents, invoked initial iron incorporation into the sulfur–chlorine bond (**16**).[24] The resulting organometallic could then react with additional sulfonyl chloride to give an α disulfone and $Fe(CO)_4Cl_2$. The α disulfone, as shown independently,[24] could be deoxygenated by more $Fe(CO)_5$ to the thiolsulfonate ester. This proposed mechanism, with minor modifications (Scheme III, decarbonylation of **16** prior to reaction with more **15**), is supported by the following results. (a) Treatment of **15** (R = CF_3) with $Fe(CO)_5$ in *n*-heptane at temperatures below −20° gave **16** (R = CF_3) in 80% yield.[37] If allowed to warm to room temperature, **16** was decarbonylated to **17** (R = CF_3). Treating **15** (R = CF_3) with $Fe(CO)_5$ in tetrahydrofuran (THF) at −20° gave solvated **17** (R = CF_3) directly. (b) *p*-Toluenesulfonyl chloride is substantially less reactive toward $Fe(CO)_5$ than **15** (R = CF_3 or CCl_3),[24,37] and gives the iron halide **20** as well as the α disulfone (in unspecified yield) when treated in THF at room temperature for 4 days.[37,38]



(c) Reaction of **20** with **15** (R = *p*-BrC_6H_4) in *N*,*N*-dimethylacetamide under conditions employed for the $Fe(CO)_5$ reaction gave no α disulfone or thiolsulfonate. However, as observed before with α-halo ketones, the presence of $Fe(CO)_5$ resulted in rapid formation of the unsymmetrical thiolsulfonates, *p*-$BrC_6H_4SSO_2C_6H_4CH_3$-*p* and *p*-$CH_3C_6H_4SSO_2C_6H_4Br$-*p*. The vigorous reaction was so rapid that we could isolate but traces of the expected α disulfone. Ferric chloride was also formed in the reaction.

Coffey[1] proposed that the *gem*-dihalide–$Fe(CO)_5$ reaction giving substituted ethylenes proceeds *via* a carbene intermediate. We believe, on the basis of preliminary experiments, that a mechanism similar to that outlined in Schemes I and III is operative here (Scheme IV). Our support for this mechanism is based on the following results. (a) As previously noted, treatment of 9,9-dibromofluorene with $Fe(CO)_5$ in refluxing dioxane gave both the alkene and 9,9′-dibromobisfluorenyl, corresponding to **23**. (b) Reaction of **1** (X = Cl; Y = H) and $Fe(CO)_5$ in benzene at 5° for 4 days gave **2** (X = Cl; Y = H) and a purple-red complex, probably the halogen-bridged dimer of **22** (X = Cl; Y = H). In addition, the unstable *cis*-dichlorotetracarbonyliron was formed in the reaction and identified by comparison of its physical properties with those reported in the literature.[39] That the source of *cis*-$Fe(CO)_4Cl_2$ was the dehalogenation of **23** was demonstrated by its formation, along with tetraphenylethylene, when **23** (X = Cl; Y = H) was treated with $Fe(CO)_5$ in benzene at 5°. The formation of both **22** and CO in the reaction of **1** (X = Cl; Y = H) with $Fe(CO)_5$ indicated that **21** was produced but that it was probably too unstable to permit isolation.

In summary, this paper has described a simple, and useful, synthesis of 1,4 diketones, monoketones, and α-deuterio ketones, subject to reaction conditions. We have shown that the mechanisms for the reactions of $Fe(CO)_5$ with α-halo ketones, sulfonyl chlorides, and probably *gem*-dihalides are similar and we believe that some of the other halide reactions, *e.g.*, sulfenyl halides,[25] proceed by an analogous pathway. An important step of this mechanism, the reaction of the organoiron halide intermediate with additional reactant halide, requires the presence of $Fe(CO)_5$. It should be noted that involvement of radicals at some stage(s) of the reaction pathway outlined in Schemes I, III, and IV has not, as yet, been ruled out.

Studies in progress with optically pure α-halo ketones [*d*-3-bromocamphor, enantiomers of desyl chloride] are directed toward determining the stereochemical consequences of the α-halo ketone reaction, insofar as the halogen-bearing carbon is concerned.

Experimental Section

General.—Melting points were determined on a Fisher-Johns or Gallenkamp apparatus and are uncorrected. Elemental analysis (Table II) were carried out by A. Bernhardt, West Germany, and PCR, Inc., Gainesville, Fla. Infrared spectra were obtained on Perkin-Elmer 457 and 521 spectrophotometers; the wavelength readings were calibrated with a polystyrene film. Nmr spectra were obtained on a Varian A-60 spectrometer, employing tetramethylsilane as the internal standard. Mass spectra were recorded using an Atlas CH-5 spectrometer.

(37) E. Lindner, H. Weber, and G. Vitzthum, *J. Organometal. Chem.*, **13**, 431 (1968).

(38) We recovered starting materials, along with small amounts of polymer, when triphenylphosphineiron tetracarbonyl and **15**, R = *p*-BrC_6H_4–, were allows to react in *N*,*N*-dimethylacetamide at 80°.

(39) R. C. Taylor and W. D. Horrocks, Jr., *Inorg. Chem.*, **3**, 584 (1964).

Scheme IV

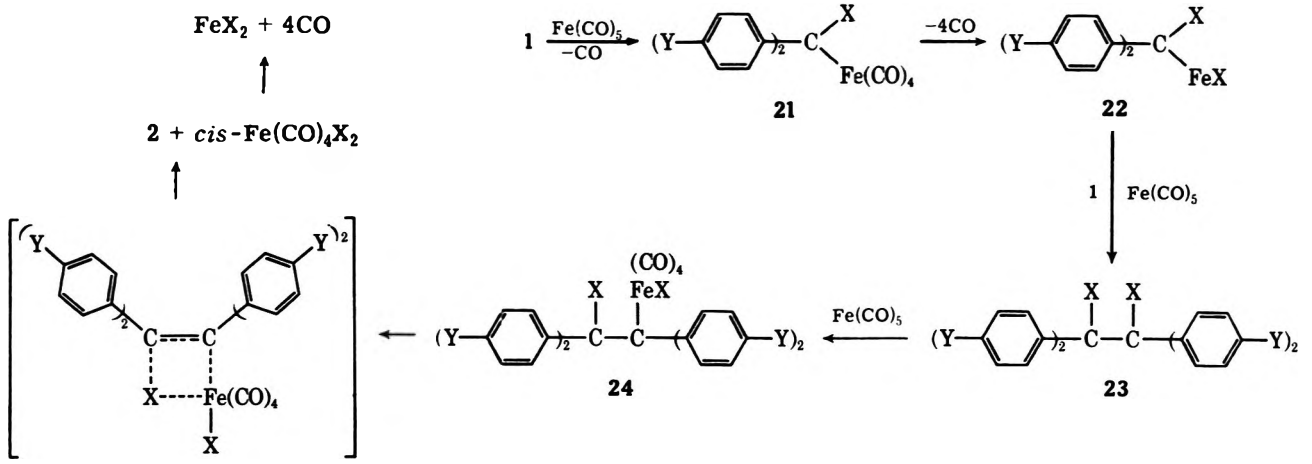


Table II

Analytical Data

Compd	Formula	Calcd, % C	Calcd, % H	Calcd, % Fe	Found, % C	Found, % H	Found, % Fe
9, R = *p*-$C_6H_5C_6H_4$; R′ = R″ = H	$C_{28}H_{22}O_2$	86.12	5.68		86.30	5.53	
11, R = *p*-BrC_6H_4; R′ = R″ = H	$C_{16}H_{12}Br_2O_2$	48.52	3.05		48.87	3.00	
11, R = *p*-FC_6H_4; R′ = R″ = H	$C_{16}H_{12}F_2O_2$	70.07	4.41		70.03	4.51	
9, R = C_6H_5; R′ = CH_3; R″ = H	$C_{18}H_{16}O_2$	81.17	6.87		80.94	6.67	
9, R = C_6H_5; R′ = R″ = CH_3	$C_{20}H_{22}O_2$	81.60	7.53		81.26	7.26	
9, R = 2-$C_{10}H_7$; R′ = R″ = H	$C_{24}H_{18}O_2$	85.18	5.36		85.11	4.98	
9, R = 1,2,3,4,5,6,7,8-octahydroanthryl; R′ = R″ = H	$C_{22}H_{28}O_2$	84.54	8.42		84.61	8.47	
9, R = 1-Adamantyl; R′ = R″ = H	$C_{24}H_{34}O_2$	81.31	9.67		81.57	9.32	
12, R = *p*-$C_6H_5C_6H_4$; R′ = R″ = H; X = Br	$C_{18}H_{11}BrFeO_5$			12.60			12.69
13, R = *p*-$C_6H_5C_6H_4$; R′ = R″ = H; X = Br	$C_{28}H_{22}Br_2Fe_2O_2$	50.80	3.35	16.87	51.12	3.53	16.38
1-Phenyl-4-*p*-phenylphenyl-1,4-butanedione	$C_{22}H_{18}O_2$	84.05	5.77		83.75	5.96	

Iron pentacarbonyl and diiron enneacarbonyl (Pressure Chemical Co.) were used as received. The α-halo ketones were commercial products and were recrystallized or distilled prior to use. Solvents were dried and purified by standard methods. All reactions were run under a dry nitrogen atmosphere.

Reaction of $Fe(CO)_5$ with α-Halo Ketones.—A mixture of the α-halo ketone (11.6 mmol) and $Fe(CO)_5$ (6.61 mmol) in anhydrous DME (15–30 ml) was refluxed (95–100° oil bath temperature) with stirring. At the end of the reflux time (see Table I), the reaction mixture was heated to an oil bath temperature of 140° for 5 min, cooled, and then poured into 250–350 ml of cold water. The resulting precipitate was filtered and dried. Work-up was effected in the following manner for the various reactions.

A. 8 (R = C_6H_5; R′ = R″ = H).—The red-brown solid was treated with chloroform (30 ml) and filtered through Celite, and the filtrate was evaporated *in vacuo* to give a dark red oil. Crystallization from pentane afforded 9 (R = C_6H_5; R′ = R″ = H), which was recrystallized from 70% aqueous ethanol.

The aqueous filtrate was extracted six times with ether (100 ml), and the ether extract was dried and distilled to give 10 (R = C_6H_5; R′ = R″ = H).

B. 8 (R = *p*-$C_6H_5C_6H_4$; R′ = R″ = H).—The solid was continuously extracted (Soxhlet) with pentane. Evaporation of pentane extract gave 10 (R = *p*-$C_6H_5C_6H_4$; R′ = R″ = H). The residue in the thimble was treated with hot acetone. Gradual evaporation of the solvent deposited crude 1,4 diketone, which was filtered. The filtrate was evaporated to dryness, pentane was added, and additional precipitated 1,4 diketone was filtered. The two fractions of 9 (R = *p*-$C_6H_5C_6H_4$; R′ = R″ = H) were combined and recrystallized from benzene.

C. 8 (R = *p*-BrC_6H_4; R′ = R″ = H).—The yellow-brown solid was continuously extracted (Soxhlet) with pentane. Removal of pentane gave 10 (R = *p*-BrC_6H_4; R′ = R″ = H). The nonextractable material was now continuously extracted with tetrahydrofuran. Removal of solvent gave an oil which was treated with hot benzene and filtered through Celite, and the filtrate was gradually reduced to give crystalline 9 (R = *p*-BrC_6H_4; R′ = R″ = H). The β-epoxy ketone 11 (R = *p*-BrC_6H_4; R′ = R″ = H) was obtained by evaporation of the mother liquor.

D. 8 (R = *p*-FC_6H_4; R′ = R″ = H).—The pale brown solid was treated repeatedly with ether and filtered. The residue from evaporation of the filtrate was chromatographed on Florisil using carbon tetrachloride as eluent. The methyl ketone 10 (R = *p*-FC_6H_4; R′ = R″ = H) was eluted first, followed by recovered starting material and then 11 (R = *p*-FC_6H_4; R′ = R″ = H). Elution with chloroform gave traces of 1,4 diketone. Purification of the methyl ketone was effected by vacuum distillation, while the β-epoxy ketone was recrystallized from hexane.

E. 8 (R = *p*-$CH_3OC_6H_4$; R′ = R″ = H).—The aqueous filtrate was extracted with ether, and the ether extract was dried and evaporated to an oil. Crystallization from pentane gave 10 (R = *p*-$CH_3OC_6H_4$; R′ = R″ = H).

The water-insoluble solid was continuously extracted with pentane–benzene (1:1) to give additional methyl ketone. Extraction of the residual solid with ether–methylene chloride (1:2) gave 9 (R = *p*-$CH_3OC_6H_4$; R′ = R″ = H).

F. 8 (R = C_6H_5; R′ = CH_3; R″ = H).—In this case, a yellow oil resulted when the reaction mixture was poured into water. It was extracted six times with ether (100-ml portions), and the ether extract was dried and evaporated. Pentane was added to the resulting oil and white crystals of 9 (R = C_6H_5; R′ = CH_3; R″ = H) crystallized out when the solution was chilled in an ice bath. The 1,4 diketone was filtered, and the filtrate was distilled to give 10 (R = C_6H_5; R′ = CH_3; R″ = H).

G. 8 (R = C_6H_5; R′ = R″ = CH_3).—A gummy substance was obtained when the reaction mixture was poured into water. The aqueous solution was decanted and pentane was added to the gum to give, on cooling, 9 (R = C_6H_5; R′ = R″ = CH_3), which was recrystallized from benzene.

The ketone 10 (R = C_6H_5; R′ = R″ = CH_3) was obtained by extracting the aqueous solution with ether, combining the ether and pentane extracts, and fractionally distilling the mixture.

H. 8 (R = 2-$C_{10}H_7$; R′ = R″ = H).—The solid was treated with hot chloroform and filtered, and the filtrate was evaporated *in vacuo*. Sublimation of the resulting solid gave 10 (R =

2-$C_{10}H_7$; R′ = R″ = H). Recrystallization of the sublimation residue gave the 1,4 diketone.

I. 8 (R = 1,2,3,4,5,6,7,8-Octahydroanthryl; R′ = R″ = H).—The gray-green paste was continuously extracted with pentane. Removal of the solvent gave a brown paste which nmr indicated to be a mixture of methyl ketone and starting material. The paste was treated with hot methanol (200 ml), the solution was decanted, and the volume of methanol was reduced until crystals of starting material began to appear. The methanol-insoluble solid was recrystallized from hexane to give pure methyl ketone.

Further extraction of the gray-green paste with methylene chloride gave the 1,4 diketone, which was purified by recrystallization from hexane–benzene (7:3).

J. 8 (R = 1-Adamantyl; R′ = R″ = H).—The semisolid was treated with chloroform and methanol was added slowly. A white precipitate of 9 (R = 1-adamantyl; R′ = R″ = H) was isolated by filtration. Starting material and the methyl ketone were obtained by evaporation of the filtrate *in vacuo*.

Reaction of 8 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H) under Different Conditions. A. Adding the Reaction Mixture to Deuterium Oxide.—By pouring the reaction mixture into deuterium oxide (99.8%) rather than water, 2-deuterio-4′-phenylacetophenone was obtained using the work-up conditions described above. Mass spectral analysis indicated >95% monodeuteration.

B. Anhydrous Reaction Conditions.—After refluxing for 5 hr, the reaction mixture was cooled and the solvent was removed *in vacuo*. Work-up according to part B of the previous section gave 1,4 diketone but no methyl ketone.

C. Using DME–Water as Solvent.—The α-halo ketone and $Fe(CO)_5$ were refluxed in a mixture of DME (27 ml) and water (3 ml). Work-up as above gave recovered starting materials along with a small amount of triiron dodecacarbonyl.

D. Using Catalytic Quantities of $Fe(CO)_5$.—The reaction is not catalytic, as treatment of 8 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H) with $Fe(CO)_5$ in a 20:1 ratio gave almost complete recovery of α-halo ketone accompanied by small amounts of 9 and 10.

E. Presence of Azobisisobutyronitrile.—The procedure described for 2-bromo-4′-phenylacetophenone was repeated in the presence of azobisisobutyronitrile (1.0 mmol). The product yields were not altered and neither did the reaction appear to proceed any faster.

F. Solvent Variation.—Using dry *N*,*N*-dimethylacetamide or tetramethylurea as solvents gave the 1,4 diketone and 4-phenylacetophenone in 10–15% lower yields than obtained when DME was the reaction solvent.

Reaction of 8 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H) with Diiron Enneacarbonyl.—A mixture of 8 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H) (3.19 g, 11.6 mmol) and diiron enneacarbonyl (4.22 g, 11.6 mmol) in anhydrous benzene (55 ml) was stirred at room temperature for 6 hr. The solution was filtered to give 2.94 g of 12 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H). The ir and mass spectral data for this complex are given in the text. Evaporation of the filtrate *in vacuo* gave 13 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H).

Complex 13 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H).—The decarbonylated product was obtained in quantitative yield by heating 12 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H) in DME at reflux temperature for 3 hr. Reaction of the α-halo ketone with diiron enneacarbonyl in benzene for 4 days at room temperature gave 13 as the sole product.

Reaction of Triphenylphosphineiron Tetracarbonyl with 8 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H).—Triphenylphosphineiron tetracarbonyl[40] [4.30 g, 10.0 mmol] and 2-bromo-4′-phenylacetophenone (4.81 g, 17.5 mmol) were refluxed in DME (35 ml) for 5 hr. The solution was evaporated *in vacuo* and continuous ether extraction of the resulting solid gave the two starting materials.

Conversion of 13 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H) to Organic Products. A.—To DME [15 ml] was added 5.0 mmol of 13 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H) followed by water (100 ml) and the mixture was stirred for 4 hr. Work-up as described above gave 10 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H).

B.—A mixture of 13 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H) and 2-bromo-4′-phenylacetophenone in DME (15 ml) was refluxed for 5 hr and then poured into ice–water (150 ml). Only trace amounts of 1,4 diketone (*p*-phenylacetophenone was the principal product) were isolated using the work-up conditions described in part B. However, repeating the reaction in the presence of $Fe(CO)_5$ gave the 1,4 diketone in 80% yield with the monoketone 10 formed as a by-product. Ferrous chloride was also obtained.

C.—When 13 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H) was treated with 2 equiv of 8 (R = C_6H_5; R′ = R″ = H) in the presence of 1–2 drops of $Fe(CO)_5$, under the same conditions as above, 1-phenyl-4-*p*-phenylphenyl-1,4-butanedione, mp 183–185°, was isolated in 74% yield.

Reaction of 20 with *p*-Bromobenzenesulfonyl Chloride.—A mixture of complex 20 (1.24 g, 3.50 mmol) and 15 (R = p-Br-C_6H_4) (0.894 g, 3.50 mmol) in *N*,*N*-dimethylacetamide (14 ml) was heated with stirring at 60° for 8 hr. The solution remained dark red-brown in color. Work-up gave starting materials. When the reaction was repeated with dropwise addition of $Fe(CO)_5$ at 60°, the solution immediately turned from dark red-brown to pale yellow. The solution was cooled and poured into water [350 ml], and the resulting solid was filtered to give 0.946 g (79%) of a mixture of thiosulfonate esters, recrystallized from *n*-heptane or isopropyl ether. Trace quantities of α disulfone were insoluble in hot *n*-heptane. Chromatography of the mixture on silica gel using benzene–hexane as eluent gave pure *p*-bromophenyl *p*-toluenethiolsulfonate, mp 92.0–94.0° (lit.[41] mp 93.5–94.5°), and *p*-tolyl *p*-bromophenylthiolsulfonate, mp 124–125° (lit.[41] mp 122–123°). The aqueous solution contained ferric chloride.

Reaction of Dichlorodiphenylmethane (1, X = Cl; Y = H) with $Fe(CO)_5$ at Room Temperature.—To a 5° solution of dichlorodiphenylmethane (7.11 g, 30.0 mmol) in dry benzene (20 ml) was added $Fe(CO)_5$ (2.03 ml, 15.0 mmol) and the reaction mixture was stirred for 4 days. During this time, a yellow solid precipitated out of solution. The yellow compound was filtered under nitrogen. It proved to be extremely air sensitive and gradually decomposed to ferrous chloride and carbon monoxide even when kept in the refrigerator under N_2. The ir spectrum ($CHCl_3$) shows terminal metal carbonyl stretching bands at 2173 (w), 2132 (vs), and 2087 cm^{-1} (s) in reasonable agreement with the values reported by Taylor and Horrocks[39] for *cis*-$Fe(CO)_4Cl_2$ [$\nu_{C=O}$ at 2166.9 (w), 2125.8 (vs), and 2081.7 (s), solvent not stated].

The deep purple filtrate was evaporated *in vacuo*, the residue was treated repeatedly with 50-ml portions of petroleum ether (bp 38–51°) and filtered, and this filtrate was evaporated to a white solid and a liquid. The liquid was decanted from the solid and identified as unreacted dichlorodiphenylmethane. The petroleum ether insoluble solid was then treated with carbon tetrachloride and filtered, and the filtrate was evaporated *in vacuo* to give 0.93 g of tetraphenylethylene, mp 226–227° (lit.[1] mp 224–226°). The carbon tetrachloride insoluble solid was red-purple in color and displayed modest air stability. The ir spectrum lacked any bands due to terminal metal carbonyl stretching but did show the typical benzene ring absorptions. The molecular weight was 535 (vapor phase osmometry) compared to a calculated value of 586 for dimeric 22.

Tetraphenylethylene and *cis*-$Fe(CO)_4Cl_2$ were obtained when a mixture of 1,2-dichloro-1,1,2,2-tetraphenylethane and $Fe(CO)_5$ was allowed to react at 5° as described for 1 (X = Cl; Y = H).

Registry No.—$Fe(CO_5)$, 13463-40-6; 12 (R = p-$C_6H_5C_6H_4$; R′ = R″ = H; X = Br), 34728-92-2; 13d (R = p-$C_6H_5C_6H_4$; R′ = R″ = H; X = Br), 34728-93-3; 1-phenyl-4-*p*-phenylphenyl-1,4-butanedione, 34733-60-3.

Acknowledgments.—Acknowledgment is made to the Petroleum Research Fund, administered by the American Chemical Society.

(40) We thank Mr. R. A. Partis for providing us with generous quantities of this compound.

(41) J. Weidner and S. S. Block, *J. Med. Chem.*, **10**, 1167 (1967).

Products from Cyanoethylation of 2-Octanone[1]

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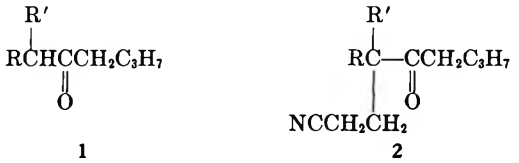
Received February 22, 1972

2-Octanone has been cyanoethylated with solid KOH as catalyst, in dimethoxyethane (DME) as reaction solvent, and with KOH solution in *tert*-butyl alcohol; both mono- and dicyanoethylated products have been examined. No product of cyanoethylatian in the terminal position (on methyl) could be detected. In DME as solvent, there were obtained 3-(β-cyanoethyl)-2-octanone (**3**) and a small amount of 3,3-bis(β-cyanoethyl)-2-octanone (**4**), but the principal product was **5** resulting from cyclization of **4**. In *tert*-butyl alcohol as solvent, under a variety of conditions, none of **4** could be isolated, only **3** and **5**. Mass spectrometry was of significance in establishing the structure of **5**, and interesting fragmentation patterns were observed. Acid-catalyzed hydrolysis of cyclic product **5** yielded none of the expected diketone, only an acidic product which proved to be the keto diacid which would result from hydrolysis of the open-chain keto dinitrile **4**. Acid-catalyzed methanolysis of **5** yielded an initial product whose structure was established as the hemiketal (**9**) of the keto nitrile which would result from hydrolysis of the imino group in **5**. This structure exhibits two hydroxyl absorptions and two carbonyl absorptions in the ir, one set of which is ascribed to the chelated structure possible when carbonyl and hydroxyl are cis to each other. Methanolysis of the intermediate hemiketal **9** to keto diester **8** proceeded much more rapidly with HCl catalysis than with H_2SO_4 catalysis. Among additional compounds reported in the literature which have two β-cyanoethyl groups on a single carbon, 1,1,1-tris(β-cyanoethyl)acetone has been examined by mass spectrometry and found to exist in a cyclic structure (**11**).

In an earlier investigation[2] in this laboratory, monocyanoethylation of unsymmetrical ketones of the general formula **1** was examined. That investigation



1 **2**

was limited to a single solvent and catalyst system, a solution of potassium hydroxide in commercial *tert*-butyl alcohol. Dicyanoethylation products were not examined; indeed, the analytical devices then available were taxed to the limit in separation and identification of the isomeric monocyanoethylation products. Nevertheless, under the conditions employed, the evidence was convincing that cyanoethylation favors the more substituted isomer **2**, unless steric hindrance becomes sufficient to interfere with the substitution giving a quaternary carbon in the product. Extremes examined were 2-methyl-3-heptanone (**1**, R = R′ = CH_3), which gave 87% of the monocyanoethylation product as structure **2**, and 6-ethyl-5-decanone (R = C_4H_9, R′ = C_2H_5), which gave only 25% of structure **2**. Preference for substitution at the tertiary carbon was attributed to the greater acidity of the hydrogen at that position; however, under the equilibrium conditions used for the reactions in that investigation, preference for the more substituted position could result from lower energy of the more branched structure. If this latter explanation be correct, steric interference would still cause a shift to the less substituted side of the carbonyl group. In the careful investigations of House and coworkers,[3] the more substituted hydrogen has proved to be the more acidic as presumed by us;[2] however, the ratio of ions reported by these investigators[4] for open-chain structures was much less favorable to the more substituted hydrogen than observed by us[2] for cyanoethylation of 2-methyl-3-heptanone.

In follow-up of work begun[5,6] nearly twenty years ago, Jolly has recently[7] pointed out that the enormous basicity of potassium hydroxide can be realized, without loss of activity due to solvation of the hydroxide ion, by use of a suspension of solid potassium hydroxide in a nonhydroxylic solvent (rather than a solution of the base in a hydroxylic solvent). This increase may amount to considerably more than ten powers of ten; for example, in dimethyl sulfoxide as solvent, solid potassium hydroxide converts more than 90% of triphenylmethane to its anion. In view of our success in improvement of KOH-catalyzed cyanoethylations[8] by replacement of the long-used aqueous or alcoholic solvents[9] with solid KOH in DME, we have undertaken an investigation of the cyanoethylation of unsymmetrical ketones in DME as solvent and in *tert*-butyl alcohol as solvent. Large differences in results obtained in the two solvents have been observed for *n*-alkyl *sec*-alkyl ketones; however, other unexpected complications have caused us to confine the present report to cyanoethylation of a methyl *n*-alkyl ketone, 2-octanone.

In cyanoethylations of methyl *n*-alkyl ketones reported by Bruson and Riener,[9] a large preference for substitution at the secondary position was reported; however, the principal analytical device applied was isolation of a product obtained in dominant amount. More recently, House and Trost[4] examined the actual distribution of anions between the methyl and methylene positions in 2-heptanone, using potassium tri-

(1) Grateful acknowledgment is made for support of this investigation by a grant from the Research Corporation. The high-resolution mass spectra were determined on a CEC 21-110B instrument provided by a departmental grant from the National Science Foundation.

(2) J. Cason and M. P. Chang, *J. Org. Chem.*, **21**, 449 (1956).

(3) H. O. House, *Rec. Chem. Progr.*, **28**, 98 (1967).

(4) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).

(5) W. L. Jolly, *J. Phys. Chem.*, **58**, 250 (1954).

(6) Early work by Cram and coworkers was directed toward the great increase in base strength of alkoxides in dimethyl sulfoxide as solvent; *e.g.*, D. J. Cram, C. A. Kingsbury, and B. Rickborn, *J. Amer. Chem. Soc.*, **83**, 3688 (1961).

(7) W. L. Jolly, *Inorg. Chem.*, **6**, 1435 (1967); *J. Chem. Educ.*, **44**, 304 (1967).

(8) After some 25 years of futile efforts to discover the cause of erratic results in cyanoethylations (low yields, no reaction at all, etc.), we followed the recommendations of Professor Jolly and have obtained consistent, high-yield results by complete elimination of hydroxylated solvents. For cyanoethylation of 2-ethylhexanal, *cf.* J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry", 3rd ed, Prentice-Hall, Englewood Cliffs, N. J., 1970, pp 351, 355.

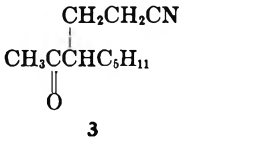
(9) Most procedures have derived from those reported by H. A. Bruson and T. W. Riener, *J. Amer. Chem. Soc.*, **64**, 2850 (1942).

phenylmethide in DME. Under equilibrium conditions, as normally assumed to occur in Michael condensations, they reported that about 42% of the anion is terminal, *i.e.*, results from removal of hydrogen from methyl. In view of this ion distribution, we were surprised to discover that no evidence could be secured, in our investigations of 2-octanone, for any cyanoethylation on methyl, under a variety of experimental conditions. Both mono- and dicyanoethylation products were examined by gas chromatography. The components responsible for all peaks in the gc tracing amounting to more than about 1% of the total were collected and examined by mass spectrometry. In a Michael condensation with cyclic ketones, House and coworkers[10] also found a higher ratio of substitution in the more substituted position than expected from their studies of anion distribution. In this instance, however, the discrepancy was not large, and it seems reasonable to explain it, as they did,[10] by the more rapid loss in a second cyanoethylation of the product substituted at the secondary position. Only monocyanoethylation products were examined. In our work with 2-octanone, however, both mono- and dicyanoethylation products were examined, and there was no detectable amount of substitution on methyl in any product.

A plausible explanation of the large difference in substitution pattern between our cyanoethylations and the ion distributions reported[4] involves the large steric requirements of the bases used by House and coworkers, as well as the higher rate of reaction of the more substituted anion.[11] The base used by us, hydroxide, which is perhaps the smallest available, would give a very rapid removal of the more hindered but more acidic secondary hydrogen, much more rapid than would be observed in determination of kinetic acidity with the large base.[4] Rapid reaction of the anion with acrylonitrile would then give the observed preference for the methylene position, in the initial forward reaction. Our investigations of reversibility of the cyanoethylations, using *n*-alkyl *sec*-alkyl ketones, indicated essentially no reversal in *tert*-butyl alcohol, very slow reversal in DME. Evidence of the influence of the steric factor is also found in acid-catalyzed formation of enol acetates, as reported most recently by House and coworkers.[11] Whereas formation of enol acetates of 2-heptanone *via* the anions produced under equilibrating conditions with a large base gave about 58% internal acetates, acid-catalyzed formation of the enol acetates from the ketone and isopropenyl acetate yielded[11] about 84% internal enol acetates.

Even with severe discrimination in favor of the internal anion on account of use of a very small base, exclusive reaction of acrylonitrile at the internal position must also depend on a substantially higher rate of reaction of the more substituted anion. This higher rate of reaction at the more hindered position has been ascribed[11] to a decrease in state of aggregation of the enolates caused by the steric interference of additional branching. The decision that the obviously present hindrance would interfere with one reaction more than the other seems to us difficult to reach. On the other hand, especially in reaction with the minimally hindered acrylonitrile, hindrance at the secondary position rather than the primary one should not tend to greatly increase the energy at the transition state. The more branched *product* is of substantially lower energy, however, and, if the transition state is well along the reaction coordinate toward the product, then the substitution at the internal position should, indeed, have the lower-energy transition state, and this product would be formed at a higher rate. This explanation seems especially plausible in conjugate addition to a small linear, highly reactive molecule such as acrylonitrile.

When cyanoethylation was carried out with KOH catalysis in dry DME, only one monocyanoethylation product, **3**, was observed in gc and only one dicyanoethylation product, **4**. The largest peak in the gc tracing occurred at longer retention time than the peak from **4**, at the point where the alternate dicyanoethylation product was expected; however, the mass spectrum of the product responsible for this peak revealed that this is not the second dicyanoethylation product. As discussed subsequently, this principal product of the reaction proved to be cyclization product, **5**. Since **5** is formed by reaction of an anion of **4** (formula **6**), it might be presumed that use of *tert*-butyl alcohol as solvent, greatly decreasing the basicity of KOH, would lead to a larger yield of **4**, less further reaction to **5**. Experiment revealed that *none* of **4** could be detected with *tert*-butyl alcohol as solvent, whether after a few minutes of reaction time, a few hours, or overnight. Addition of increments of water to the *tert*-butyl alcohol also failed to yield any of product **4**. The principal effect of water addition was slowing of the rate of reaction, as would be expected on account of the decrease in basicity of hydroxide which results from solvation by water.



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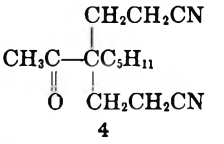

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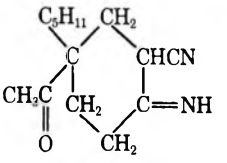

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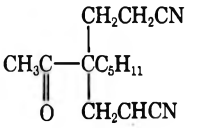


6

Actually, the rate of formation of ion **6** from dinitrile **4** is probably not directly involved in conversion of **4** to the cyclic product **5**, because ion **6** is the initial product of reaction of acrylonitrile with the anion of 3-(β-cyanoethyl)-2-octanone (**3**). Furthermore, less than 0.1 molar equiv of KOH was used for the reactions. It follows that appearance of **4** as a product of the reaction must depend on competitive reactions of anion **6** with some acidic species (such as 2-octanone) and intramolecular reaction to give an anion of the cyclic product **5**. Although use of the acidic *tert*-butyl alcohol as solvent increases the concentration of a possible reactant with ion **6**, it would also greatly reduce the basicity of this ion by solvation, an effect known to be quite large in the case of hydroxide ion.[7] This could increase the lifetime of anion **6** and thus increase the probability of its reaching the proper conformation for cyclization.

(10) H. O. House, W. L. Roelofs, and B. M. Trost, *J. Org. Chem.*, **31**, 646 (1966).

(11) H. O. House, M. Gall, and H. D. Olmstead, *ibid.*, **36**, 2361 (1971).

Given the proper conformation, reaction to give the six-membered ring should occur rapidly even with the solvated anion **6**. Alternate explanations may be evolved which depend on the fact that in DME an amount of the anion of **5** equivalent to the KOH consumed will be present at the conclusion of the reaction, whereas at least part of this anion would react with *tert*-butyl alcohol if it is present as solvent. Such explanations are discounted by the observation that increase of KOH to a full equivalent in *tert*-butyl alcohol solvent results in no appearance of dinitrile **4** in the reaction product. Excess of acrylonitrile also yields none of **4**.

The mass spectrum of the cyclic product, **5**, provided conspicuous evidence that this is not the alternate dicyanoethylation product, for the most abundant ion in the spectrum is *m/e* 43, and mass measurement showed it to be acetyl, CH_3CO. Of course cyanoethylation at methyl would obviate the possibility of acetyl as a cleavage product. The fragmentation pattern presented by this mass spectrum (*cf.* Table I) is unlikely

TABLE I
PARTIAL MASS SPECTRUM OF CYCLIZATION PRODUCT 5

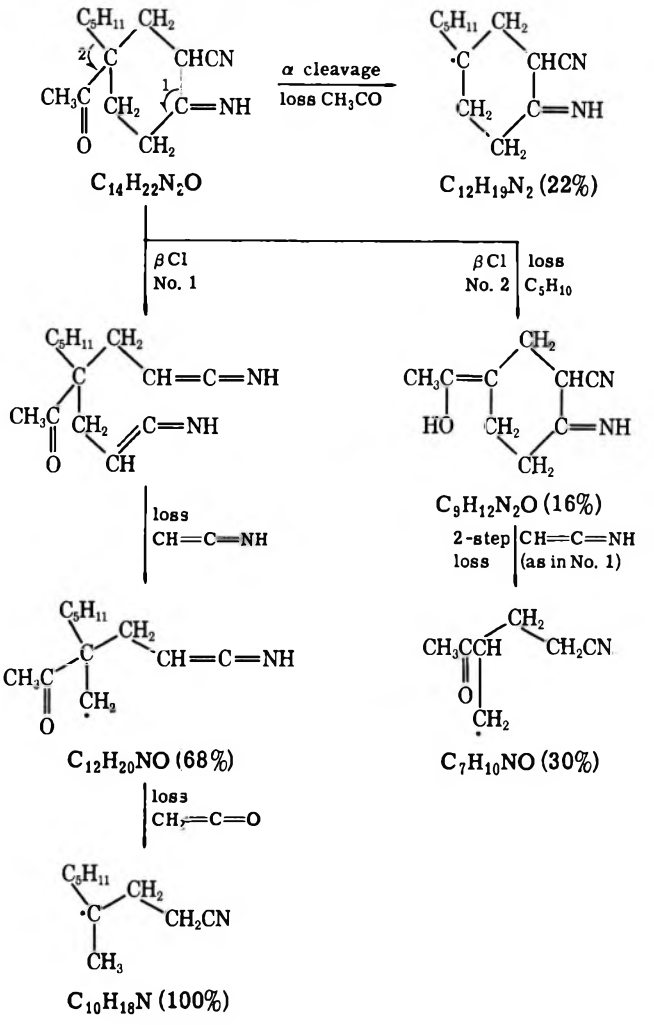
Ion formula	Mass[a]	Per cent
CH_3CO	43	>100[b]
C_5H_9	69	20
C_5H_{11}	71	7
$C_6H_{10}N$	96	26
$C_7H_{13}O$	113	11
$C_7H_{10}NO$	124	30
$C_8H_{11}N_2$	135	14
$C_8H_{12}N_2$	136	11
$C_9H_{16}N$	138	4
$C_9H_{17}O$	141	5
$C_9H_{12}N_2$	148	13
$C_{10}H_{18}N$	152	100
$C_9H_{12}N_2O$	164	17
$C_9H_{12}N_2$	191	22
$C_{12}H_{20}NO$	194	68
$C_{14}H_{22}N_2O$ (M)	234	28

[a] All ions in this table were mass measured at high resolution by one of us (C. W. K.) on a CEC 21-110B instrument; *cf.* ref 1. [b] More meaningful comparisons with the fragmentation patterns from other structures, or spectra acquired on other instruments, become possible when the inordinately abundant ion of *m/e* 43 is not used as the base peak.

to initially suggest the true structure; however, it bears no resemblance to an open-chain dicyanoethylation product such as **4**, in which the only ions in abundances greater than 17% are *m/e* 43 (100%), C_5H_{11} (71, 63%), and $C_9H_{12}N_2O$ from β cleavage (164, 54%). The very abundant ion at *m/e* 152 ($C_{10}H_{18}N$) would hardly be predicted, and it was especially surprising when the study of metastable ions revealed that the route to this highly abundant ion (152) is *via* initial loss of C_2H_2N (40), followed by loss of C_2H_2O (42). Nevertheless, analysis of the data reveals that the observed ions result from logical fragmentation pathways presented in part in Chart I.

It may be noted that the three initial cleavage reactions shown in Chart I involve one classical α cleavage (separation of the acetyl group) and two β cleavages which yield the most abundant ions. It is apparent that there are possible two additional β cleavages involving the carbonyl group, and these can lead (by

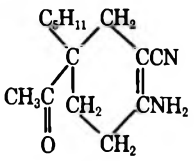
CHART I



fragmentations similar to those in β cleavages no. 1 and no. 2) to ions $C_9H_{17}O$ (*m/e* 141) and $C_9H_{16}N$ (*m/e* 138). The minor abundance of these ions is consonant with fragmentations consistently observed by us in cyanoethylation products from ketones. If the γ hydrogen which must rearrange in a β cleavage is also α to a cyano group, that β cleavage is quite minor or not observable at all (<1% in **4**). The loss of C_2H_2N in both prominent pathways initiated by a β cleavage is rather surprising, in that this might be presumed to be CH_2–CN, a logical fragment for loss from the open-chain product, **4**. In reality, this cleavage is absent or negligible in **4**: M − 40 (*m/e* 191) is only 2%, and M − 43 − 40 (*m/e* 151) is <1%. The loss of C_2H_2N from structure **5** becomes possible after a hydrogen is transferred by β cleavage at cyano. Subsequent bond rupture to lose CH=C=NH may be regarded as an extended α cleavage.

The minimal occurrence of a β cleavage involving rearrangement of hydrogen α to the imino structure depicted in **5** suggests that the imino structure is present, rather than the isomeric vinyl amine structure, **7**. This is contrary to observations reported[12] for the imine derived from an open-chain β-keto ester; however, spectral data also support structure **5**. Whereas

(12) B. Witkop, *J. Amer. Chem. Soc.*, **78**, 2873 (1956). In neutral solution the characteristic spectrum was observed for the vinyl amine structure, whereas in dry acid solution the spectrum became that of the β-imino ester cation (broad absorption at 4.97 μ, trivial absorption at 6–6.2 μ).



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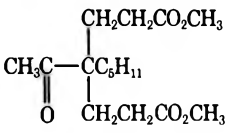

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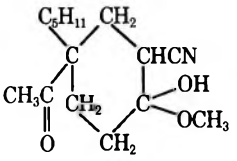
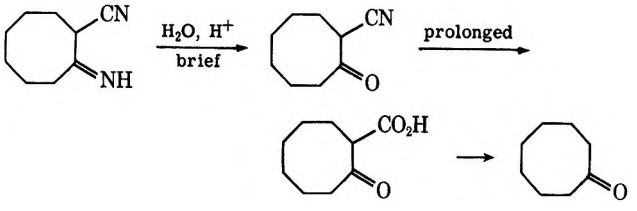


9

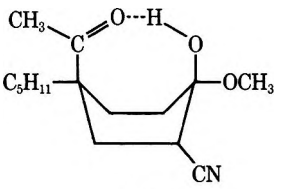
the β-amino ester[12] exhibited in the ir strong absorption at 6.16 μ, characteristic of the carbon–carbon double bond, and a doublet at 2.85 and 2.99 μ for the two NH absorptions, our cyclic product was entirely clear of absorption in the 6.0–6.7-μ region and there was a single absorption at 2.91 μ. Also observed for **5** was the expected absorption at 4.44 (nitrile) and 5.87 μ (carbonyl). Absence of the carbon–carbon double bond in the cyclic product was also demonstrated by the uv spectrum—no absorption above 200 nm with an extinction coefficient as great as 50. The nmr spectrum is consistent with structure **5**, but less definitive than the uv and ir absorption, for the resonance line for the single hydrogen α to cyano in **5** is blended into the downfield edge of the unsplit peak (δ 2.1) for the three hydrogens α to carbonyl. However, the downfield side of the methyl spike is spread and triplet splitting is just visible. This location for hydrogen α to cyano is established by the nmr spectrum of the monocyanoethylation product, **3**, in which the triplet for the two hydrogens α to cyano (centered at δ 2.18) is just resolved from the methyl spike and the tracing stands out above that representing the single hydrogen α to carbonyl.

When the solvolytic behavior of cyclic product **5** was examined, interesting anomalies were observed in comparison with the observations of Ziegler and coworkers[13] on similar compounds without ring substituents. These investigators utilized the products from cyclization of dinitriles as an entry to cyclic ketones of ring sizes difficult to secure in other ways. For cyclooctanone, the hydrolytic sequence was as follows.



On account of facile hydrolysis of the imino structure and slow hydrolysis of cyano, the intermediate keto nitrile could be readily isolated, but more prolonged acid-catalyzed hydrolysis gave a good yield of cyclic ketone. In the case of structure **5**, acid-catalyzed hydrolysis yielded only acidic products, and esterification of this acid yielded the open-chain diester **8**, which would result from methanolysis of the dicyanoethylation product, **4**.

In order to give products more readily examined by gc and mass spectrometry, **5** was methanolized with acid catalysis. There proved to be rather slow formation of an intermediate, which was converted to diester **8** sufficiently rapidly to maintain a relatively low concentration of the intermediate. The intermediate was difficult to separate from both starting material **5** and **8** by gc; however, after a few hours of reaction time it was possible to separate samples of the intermediate containing only small amounts of **8**. The molecular ion of the intermediate (*m/e* 267) was in very low abundance, always less prominent than the ion of *m/e* 269, assigned to the fragment resulting from loss of methoxy (31) from impurities of diester **8**, whose molecular weight is 300. It proved possible to mass measure the molecular ion of the intermediate, in spite of its low abundance, and the formula assigned was $C_{15}H_{25}NO_3$. The most abundant ion in this mass spectrum was *m/e* 225 (M − 75), which results from loss of acetyl (43) and methanol (31); thus the methanolysis has introduced a methoxy group. This is supported by the prominent ion (31%) of *m/e* 236 (M − 31). Further, the second most abundant ion (45%) was *m/e* 185 (M − 82), resulting from loss of the same fragments which yield the base peak for cyclic product **5**; hence, retention of the ring system and cyano group of **5** is strongly indicated. The ir spectrum also showed that the nitrile had persisted (4.45 μ), and the 6–6.5-μ region remained clear, but there were observed *two* strong carbonyl absorptions (5.75, 5.86 μ) and *two* weak hydroxyl absorptions (2.92, 3.17 μ). There was no significant absorption in the uv above 200 nm, as in **5**, and the nmr spectrum also was similar to that of **5** except that there appeared a spike representing three hydrogens at the position observed (δ 3.3) when methyl is attached to oxygen, as in methyl esters. Since the nitrile group remains present, a methyl ester cannot be present to account for the methoxy revealed by both mass spectrum and nmr spectrum. This combination of spectral characteristics and molecular formula restricts the structure to two geometric isomers of the hemiketal **9**. The isomer with acetyl and hydroxyl cis to each other, in the flexible form shown in structure **9f**, is subject to



9f

rather strong chelation, hence the second hydroxyl absorption at longer wavelength and the second carbonyl absorption at shorter wavelength.

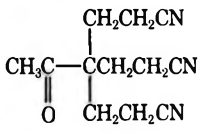
Isolation of the hemiketal **9** by work-up of the reaction mixture using water, followed by gc at about 200°, seems surprising; however, this structure differs from the hemiketal form of a keto sugar only in that the ether oxygen is not in the ring. Stability of this structure, accompanied by severe hindrance to hydrolysis of the nitrile group, is probably responsible for the occurrence of ring opening at a much more rapid rate than solvolysis of the nitrile. Further, the sharp contrast in chemical behavior between the unsub-

(13) K. Ziegler, H. Eberle, and H. Ohlinger, *Justus Liebigs Ann. Chem.*, **504**, 94 (1933).

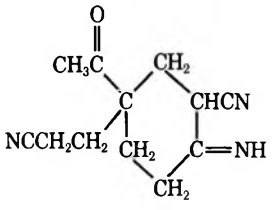
stituted imino nitriles of Ziegler and coworkers[13] and our structure **5** must be ascribed to presence of the quaternary carbon in **5** and the effect thereof on the geometry of the ring.

Although we have been unable to discover conditions which yield a significant amount of dicyanoethylation product **4**, it is practical to convert the cyclic product **5** to the open-chain keto diester **8**. Methanolysis with dry hydrogen chloride as catalyst yields the diester uncontaminated with starting material or the intermediate hemiketal. On the other hand, if sulfuric acid is used as catalyst, large amounts of the intermediate hemiketal **9** remain after 96 hr of heating under reflux. With dry methanol as solvent, gc analysis indicates about equal amounts of intermediate and diester. Addition of 2% of water to the methanol solvent almost doubled the ratio of diester; however, the intermediate was eliminated only by shift to hydrogen chloride catalysis.

Since we were able to obtain none of dicyanoethylation product **4** from the Michael reaction in wet or dry *tert*-butyl alcohol., and a minor amount of it in dry DME, it seems probable that other products reported in the literature with two cyanoethyl groups on one carbon actually have a cyclic structure analogous to **5**. Bruson and Riener[9] reported several products of the requisite structure, of which one was the tricyanoethylation product of acetone, described as structure **10**.



10



11

The cyclized structure would be **11**. The mass spectrum of a sample of this compound, prepared in *tert*-butyl alcohol solvent according to Bruson and Riener, proved definitive in establishing the actual structure as that in **11**, not the open-chain structure **10**. An analysis of the data is presented in Table II, wherein are considered the

TABLE II

MASS SPECTROMETRIC ANALYSIS OF STRUCTURE OF THE TRICYANOETHYLATION PRODUCT OF ACETONE

Ion (*m/e*)	Analogous ion in Table I, Chart I	Predicted ion abundance,[a] % 10	11	Obsd ion abundance,[a] %
M − 82 (135)	$C_{10}H_{18}N$ (152)	6	23	29
M − 43 (174)	$C_{12}H_{19}N_2$ (191)	13	6.5	1
M − 40 (177)	$C_{12}H_{20}NO$ (194)	2	13	16

[a] As per cent of base peak, *m/e* 43 (CH_3CO), in each instance.

two prominent ions in the fragmentation termed β cleavage No. 1 (Chart I), and the fragments from the dominant α cleavage shown in Chart I. It is apparent that the least abundant ion in the observed spectrum, of the four reported in Table II, is that predicted as least abundant for structure **11**, but most abundant in structure **10**. Also observed in the spectrum is an abundance for the ion of *m/e* 135 about twice that for the ion of *m/e* 177, in excellent agreement with the prediction for structure **11**.

Experimental Section[14]

Cyanoethylation of 2-Octanone. A. Preparative Procedures.—To a solution of 0.5 g of KOH pellets in 48 ml of *tert*-butyl alcohol (dried by distillation from sodium), stirred in an atmosphere of nitrogen, 24.5 g of 2-octanone was added in one portion. After this stirred solution had been warmed to 55°, 12.1 g (1.2 molar equiv) of acrylonitrile[15] was added as rapidly as consistent with keeping the temperature in the range 55–60° by cooling; time of addition is not important. After completion of addition, the reaction mixture was stirred for 2 hr as the temperature was maintained at 55–60° by warming. After the cooled reaction mixture had been acidified with 6 *N* HCl, it was diluted with 200 ml of water, and the products were extracted with benzene. The washed and dried benzene solution was either diluted to a measured volume for analysis by gc, or distilled to leave a residue which was distilled from a small Claisen flask at reduced pressure.

In a typical run, analysis by gc (10-ft column, 10% SE-30, 198°, 30-psi He pressure) showed yields of 9.7 g of recovered 2-octanone, 8.2 g (24%) of **3-(β-cyanoethyl)-2-octanone** (**3**), and 6.0 g (13%) of cyclic product **5**. With the ratio of acrylonitrile used, 2-octanone is not the limiting reagent for formation of **5**, but was used for comparison purposes in per cent yield calculation. Retention times for 2-octanone, **3**, and **5** were 15 sec, 68 sec, and 13 min. The 2-octanone peak was so narrow that accurate area measurement was not possible. Distillation gave ready separation of 2-octanone, bp ~56° (10 mm), **3**, bp ~160° (10 mm), and **5**, bp in the range of 200–220° (3 mm). The cyclic product must be distilled in lots no greater than 15 g, with rapid elevation of the bath to 280° and warming of the side neck of the Claisen flask to promote rapid distillation. Slower distillation causes extensive decomposition. Purification and characterization of the cyclic product is given below. For determination of the mass spectrum of **3**, a sample was collected from gc: *m/e* (rel intensity) α cleavage 43 (100), 138 (5); β cleavage (minus C_5H_{10}) 111 (55); molecular ion, 181 (3).

Anal. Calcd for $C_{11}H_{19}NO$: mol wt, 181.1467. Found: mol wt, 181.1468.

In a preparation carried out as above, but favoring cyclic product **5** by use of 2.4 equiv of acrylonitrile, yields determined as before by gc were 5 g (21%) of recovered 2-octanone, 2.6 g (7%) of **3**, and 13.3 g (30%) of **5**. Use of still larger ratios of acrylonitrile did not improve the yield significantly or consume all of the 2-octanone.

3,3-Bis(β-cyanoethyl)-2-octanone (**4**) could be obtained only in DME as solvent, and in small amount isolable by gc. In the process which is probably best applicable to securing this product, procedure was as described for use of *tert*-butyl alcohol solvent, with the following quantities: 7.7 g of 2-octanone, 4.1 g (1.3 equiv) of acrylonitrile, 19.2 ml of DME (dried over molecular seives), and 0.19 g of KOH (pellets rapidly crushed and added to reaction mixture). The best time interval for obtaining **4** was determined by withdrawing 3-ml aliquots at appropriate times, working up as described for runs using *tert*-butyl alcohol as solvent, analyzing by gc, and using collected samples for establishment of response factors. Representative data follow (Table III).

TABLE III

Time, hr	Products in 3-ml aliquot, g: 3	4	5
0.25	0.8	0.02	0.01
0.5	1.3	0.03	0.04
1	1.3	0.02	0.2
4	1.3	0.02	0.2

(14) Microanalyses and low-resolution mass spectra were determined by the Analytical Laboratory, University of California, Berkeley. The mass spectra were recorded on a CEC Model 21-103C instrument, with inlet heated to about 180° and ionizing voltage at 70 eV. The instrument had been equipped with narrower slits and an ion multiplier and otherwise modified to give unit resolution to about 600. High-resolution mass spectra were determined as described in Table I, footnote *a*. Ir spectra were recorded on a Perkin-Elmer instrument, Model 137, and the uv spectra on a Perkin-Elmer Model 202 instrument. Gas chromatography was on an Aerograph Model A-90P.

(15) There appears to be considerable loss of acrylonitrile by polymerization during the Michael condensation, and this loss is increased if old, partly polymerized samples of acrylonitrile are used. Material used for the procedures reported in these investigations was distilled and then stored in the presence of a few crystals of hydroquinone.

Thus, a short reaction time is probably a small advantage; after 30 min the entire reaction mixture contained about 250 mg of product 4.

A sample of 4 for mass spectrum was collected by gas chromatography (10 ft × 0.375 in. column, 10% SE-30, 200°, He flow rate 200 cc/min): retention times 14 min for 4, 22 min for 5; mass spectrum *m/e* (rel intensity) α cleavage 43 (100), 191 (13); β cleavage (minus C_5H_{10}) 164 (54); C_5H_{11} 71 (63); β cleavage involving γ hydrogen which is β to cyano, <1%; molecular ion, M, 234 (3).

Anal. Calcd for $C_{14}H_{22}N_2O$: mol wt, 234.1732. Found: mol wt, 234.1739. Calcd for $C_{13}{}^{13}CH_{22}N_2O$: mol wt, 235.1766. Found: mol wt, 235.1780.

When the same procedure was used for reaction in DME solvent to which 4% of water had been added, *none* of 4 was detectable by gc.

B. Analytical Runs.—Small runs were carried out to determine effect of time and of addition of water in *tert*-butyl alcohol as solvent. The procedure was the same as that described for the preparative run using 1.2 equiv of acrylonitrile except that 4.1 g of 2-octanone was used and aliquots were withdrawn at appropriate times. Since comparative data only were desired, the ratio of areas of the respective peaks in gc was divided by the ratio of response factors, in order to determine ratio of amounts at each time. As before, data for 2-octanone are only approximate, on account of the very short retention time. The trend of the data is indicated in a run in dry *tert*-butyl alcohol (Table IV).

TABLE IV

	Product ratios		
Time, hr	2-Octanone	3	5
0.5	1.3	1.2	3.8
1	1.1	1.1	4.7
2	1	1.2	5.3
4	1	1.3	5.0
8	1	1.5	4.3
24	1	1.5	4.2

A similar trend was observed when 4, 10, or 20% of water was added to the butanol solvent; however the reaction is slowed markedly by addition of water, and the ratio of octanone surviving increases because more acrylonitrile is lost by polymerization or reaction with solvent. With addition of 20% of water to the solvent, after 4 hr the ratio of the three components in the order shown in the tabulation was 1:0.23:0.15. Use of a larger ratio of KOH fails to increase the ratio of 2-octanone reacting with acrylonitrile. It may be noted that excessive reaction time appears to destroy the cyclic product 5.

In addition to peaks representing the compounds included in the tabulation, there were also three small peaks, of which only one was as large as 1% of the total peak area. This latter peak was absent when dry *tert*-butyl alcohol was solvent, and became about 1.5% of the peak area with 4–10% water present and about 5% of the peak area with 20% water present. Mass spectrometry of the sample collected from this peak showed it to be not a reaction product from 2-octanone, probably a product from reaction of acrylonitrile with solvent.

Characterization of Cyclic Product 5.—Crude, distilled cyclic product 5 was a syrup which crystallized on storage overnight in the refrigerator. After two crystallizations from 95% ethanol, 5.57 g of distillate yielded 2.71 g of fine white crystals, mp 43–44.5°, and a second crop of 1 g, mp 41–43°. Further crystallization gave a maximum melting point of 44.0–44.5°.

Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.8; H, 9.4; N, 12.0; mol wt, 234.1732. Found: C, 72.1; H, 8.8; N, 12.1; mol wt, 234.1739.

The more significant features of the mass spectrum of 5 are assembled in Table I.

Solvolysis of Cyclic Product 5. A. Isolation of Intermediate Hemiketal 9.—A solution of 0.835 g of pure 5, mp 44.0–44.5°, in 5.76 ml of methanol (dried with Mg) and 0.23 ml of concentrated H_2SO_4 was heated under reflux in an oil bath at about 110° for 6 hr. The cooled reaction mixture was worked up by dilution with water and extraction with benzene. The extract was washed with water and 1 *N* NaOH, solvent was evaporated, and the residue was dissolved in 5 ml of benzene for gc on a 0.25 in. × 10 ft column, 10% SE-30, temperature 210°. The gc tracing showed three extensively overlapping peaks with retention times of 4.2, 5, and 6.3 min. About three-fourths of the area (as extrapolated) was in the third peak, while the second peak was barely detectable as a hump in the valley between the two major peaks. Attempted separation on other partitioning agents was less satisfactory.

The third peak in the gc tracing was shown by coinjection to be that for starting material, 5, while the first peak was shown by collection and examination to be that of 9; the collected sample was contaminated by diester 8 (the center minor peak), as well as 5. For analytical examination, the first two-thirds of the first peak was collected, then reinjected and collected again to separate small amounts of the other two compounds, using a 0.375 in. × 20 ft column, SF-96.

Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.4; H, 9.4; N, 5.2; mol wt, 267.1834. Found: C, 67.15; H, 9.5; N, 5.1; mol wt, 267.1832.

Significant features, especially for analytical purposes, of the mass spectra of 5, 8, and 9 are assembled in Table V and designation of fragments lost to give the ions is found in the footnotes to the table. The ions of *m/e* 257 and 269, although of small abundance in the spectrum for 9, suggest that our best sample of hemiketal is contaminated with significant amounts of the diester 8; however, the elementary analysis does not reveal this.

TABLE V

COMPARATIVE MASS SPECTRAL DATA

	Ion	Relative abundance, %		
m/e	formula	5	9	8
152	$C_{10}H_{18}N$	*100[a]	19	5
153		14	25[b]	20
164	$C_9H_{12}N_2O$	*17[c]	32[d]	2.5
185			45[a]	37[e]
192	$C_{12}H_{18}NO$	5	*100[f]	2
193			21[g]	38
194	$C_{12}H_{20}NO$	*68[h]	33[i]	8
197	$C_{10}H_{15}NO_3$		*18[c]	20
225	$C_{13}H_{21}O_3$		46	*100[f]
234	$C_{14}H_{22}N_2O$	*28 (M)	1	
236	$C_{14}H_{22}NO_2$		*31[j]	1
257	$C_{14}H_{25}O_4$		7	*26[k]
267	$C_{15}H_{25}NO_3$		*2 (M)	
269	$C_{16}H_{26}O_4$		3	*7[j]
300	$C_{16}H_{28}O_5$			*1 (M)

[a] Formulas given for those ions which have been mass measured, as indicated in each instance by the asterisk. M − 40 (CH_2CN) − 42 (CH_2CO). [b] M − 32 (CH_3OH) − 40 (CH_2CN) − 42 (CH_2CO). [c] M − 70 (C_5H_{10}), β cleavage. [d] M − 32 (CH_3OH) − 71 (C_5H_{11}). [e] M − 73 ($CH_2CO_2CH_3$) − 42 (CH_2CO). [f] M − 32 (CH_3OH) − 43 (CH_3CO). [g] M − 31 (CH_3O) − 43 (CH_3CO). [h] M − 40 (CH_2CN). [i] M − 31 (CH_3O) − 42 (CH_2CO). [j] M − 31 (CH_3O). [k] M − 43 (CH_3CO).

B. Formation of Keto Diester 8.—Dry HCl from a cylinder was passed into 5.76 ml of dried methanol until 10% by weight had been absorbed, then 0.835 g of 5 was added. The reaction mixture, protected by a drying tube, was heated under reflux for 4 days, then worked up as described in A above. Gc on the 10-ft SE-30 column at 219° revealed a single band (except for a small band in edge of solvent) with a retention time of 4.2 min. An analytical sample was collected from the gc. The fragmentation pattern for this product was quite different from that of the cyclic products (Table V).

Anal. Calcd for $C_{16}H_{28}O_5$: mol wt, 300.1937. Found: mol wt, 300.1936.

Near absence of the ion of *m/e* 192 in the mass spectrum of 8 (Table V) demonstrates that this hydrolytic procedure eliminates the intermediate hemiketal 9.

When the same solvolytic procedure (dried methanol, heating time 4 days) was used except that catalysis was by 0.23 ml of concentrated H_2SO_4, gc in the same column at 217° gave two overlapping peaks of equal height, with retention times of 5 and 5.7 min. Mass spectra of samples collected from each peak demonstrated that the first peak contains 8 and the second peak 9, the *opposite order of emergence* than that observed when the

charge for gc consisted to about 75% of the starting material 5 (*cf.* A above). This obnoxious behavior was observed in five runs as here described, and in gc of several samples from two runs as in A.

When the solvolytic procedure differed from that just described by addition of 2% of water to the solvent, rate of conversion of the intermediate was accelerated; the first peak in gc (identified as 8 by mass spectrum) was of approximately twice the height of the second.

Two samples of diester 8 were hydrolyzed to acid, which was reesterified to give the original ester, as an additional confirmation that 8 is not the hemiketal of the cyclic β-keto ester. For this purpose, 50 mg of 8 collected from gc was heated under reflux for 18 hr with 2 ml of a solution prepared from 4.3 ml of concentrated H_2SO_4, 7.3 ml of glacial acetic acid, and 7.6 ml of water. The reaction product, which was acidic, was esterified as in A except that reaction time was 4 hr. Gc of the product on the column used for the above analyses, at 198°, gave three peaks in the tracing, not overlapping significantly, with retention times of 6.3, 10, and 12.5 min, with areas (in the same order) in the approximate ratio of 4:3.5:1. The first peak proved to be the diester 8 (mass spectrum), while the compounds giving longer retention times were not encountered in other phases of this work, and have not been investigated.

One sample of cyclic product 5 was hydrolyzed in aqueous acid as described for hydrolysis of the diester 8, above. The product of hydrolysis, which was entirely acidic material, was esterified as described just above. Gc showed two peaks of short retention time and a major peak of retention time expected for 8; mass spectrum of the collected product verified this identity.

Cyanoethylation Product from Acetone (11).—Application of cyanoethylation to acetone in DME solvent, with solid KOH as catalyst, yielded a red, waxy material, from which no homogeneous product could be isolated. The procedure previously described[9], using a solution of KOH in *tert*-butyl alcohol, yielded the product described by Bruson and Riener, but in about one-fourth the yield. Our recrystallized sample consisted of colorless crystals, mp 149–154° (lit.[9] mp 154°).

Registry No.—**3**, 34917-90-3; **4**, 34886-35-6; **5**, 34886-36-7; **8**, 34886-37-8; **9**, 34886-38-9; **11**, 34886-39-0; 2-octanone, 111-13-7.

The Synthesis and Properties of 2-(2-Cyanoethylidene)-1,3-dithiane and Its Isomeric Ketene Thioacetal[1a]

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Received February 15, 1972

The preparation of 2-formyl-1,3-dithiane from 2-lithio-1,3-dithiane and dimethylformamide is reported. Wittig reaction of this versatile aldehyde gave, under different conditions, both "normal" coupling (1) and the rearranged ketene thioacetal 6. Base-catalyzed treatment of 1 gave exclusively 6, indicating the thermodynamic preference for the ketene thioacetal structure. Alkylation of 1 or 6 *via* its lithio salt gave only products derived from the carbanion α to the cyano group (11); yet at equilibrium the conjugation of the double bond favored the ketene thioacetal structure. These results suggest that there is considerable relief of ring strain when the 2 position is sp^2 hybridized. A further effect to account for these results may lie in enhanced overlap by 3p orbitals with the 2p orbitals of carbon when two adjacent sulfur atoms are present.

The synthetic utility of 1,3-dithianes as nucleophilic acylating agents is now well documented[2] by a variety of transformations leading to aldehydes and ketones. As part of another study, it was necessary to prepare 2-(2-cyanoethylidene)-1,3-dithiane (1) as a highly functionalized intermediate for further synthesis. The most direct approach seemed to involve the Wittig coupling of cyanomethylphosphorane (2) with 2-formyl-1,3-dithiane (**3**, R = H). Although 2-methyl-2-formyl-1,3-dithiane (**3**, R = Me) has been reported[2] from 2-lithio-2-methyl-1,3-dithiane (**4**, R = Me) and dimethylformamide, there was no mention of the preparation of **3** (R = H). The latter synthesis proved to be less than straightforward. When the lithio salt of 1,3-dithiane **4** (R = H) was treated with dimethylformamide, a complex mixture was obtained. However, when the previously prepared lithio dithiane was added to excess dimethylformamide at −10°, a viscous oil was isolated which exhibited both hydroxyl and formyl bands in the infrared. Distillation of this material afforded 2-formyl-1,3-dithiane in 81% yield. Thus, the viscous crude product is considered to be the dimer **5** arising from an aldol-type process which underwent thermal reversal to the desired product. The formyl dithiane slowly dimerized at room temperature although it is quite stable at −20° for several days.

When the formyl dithiane was added to a THF solutaining 1.1 equiv of cyanomethylphosphorane 2,[3] the product was not the desired olefin **1** but instead the isomeric ketene thioacetal **6** (Figure 1, top). This product is undoubtedly the result of an isomerization by excess base (phosphorane or butyllithum from which it was prepared) present in the reaction medium. Base-catalyzed or thermal (~200°) equilibration attempts did not lead to any detectable quantities of the cyanovinyl dithiane **1**. The Wittig reaction was repeated using 0.9 equiv of the phosphorane so that no excessive base would be present. Indeed, this resulted in a 63% yield of the cyanovinyl dithiane **1** completely devoid of any isomeric material. To confirm the base-catalyzed lability of **1**, it was treated with 0.2 equiv of sodium ethoxide in ethanol at −20° and allowed to stand overnight at this temperature. Recovery after neutralization provided pure **6**. The isomerization was carried out at low temperature due to the instability of dithiane anions at ambient temperatures,[2] resulting in extensive decomposition of **1**. These results may be interpreted by assuming that the presence of *two* adjacent sulfur atoms causes sufficient 3p–2p π overlap in **6** to outweigh the 2p–2p π overlap in **1**. The importance of

(1) (a) This study was supported by the National Institutes of Health (NIGMS-17941-02). (b) Address correspondence to this author at the Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521.

(2) For an excellent review on this subject, see D. Seebach, *Synthesis*, **1**, 17 (1969).

(3) G. Schiemenz and E. Engelhard, *Ber.*, **94**, 578 (1961).

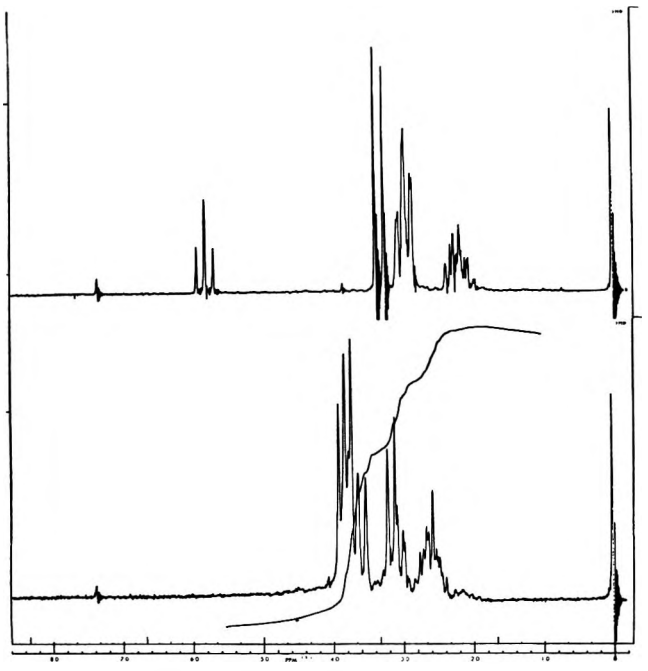
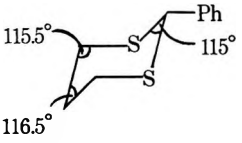


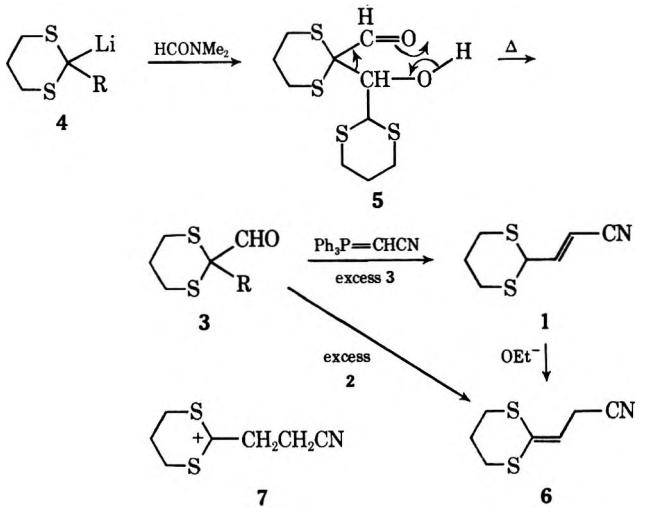
Figure 1.—(Top) 60-MHz spectrum of 6 in deuteriochloroform. (Bottom) 60-MHz spectrum of 6 in deuteriochloroform 5 min after addition of 20 equiv of trifluoroacetic acid.

3p–2p π overlap in vinyl sulfides has been questioned[4] and rightly so due to the unfavorable alignment of 3p and 2p orbitals on adjacent atoms. An alternative explanation for this phenomenon is based upon the large bond angles found for 1,3-dithianes from X-ray studies[5] on 2-phenyl-1,3-dithiane.



If the 2 position were allowed to rehybridize from an sp^3 to an sp^2 carbon, this would widen the S–C–S angle to approximately 120° and shorten the S–C bond distance, resulting in a decrease in the already strained C–C–C (116.5°) and C–C–S (115.5°) angles. There would also be considerable alteration in the dihedral angles between adjacent protons. Thus, it is concluded that the isomerization of **1** to **6**, which appears to be 99+% in favor of the latter (based upon nmr) and amounts to a $\Delta F°$ of 2.7–3.0 kcal/mol, could be the result of angle strain relief and added to this the 3p-2p π overlap by the two adjacent sulfur atoms. An X-ray study on **6** would shed some light on the relative importance of the angle strain theory.

The cyanovinyl dithiane **1** was also found to slowly isomerize to the ketene thioacetal **6** on standing or distillation, although this could be due to traces of base present. Fortunately, the crystalline cyanovinyl dithiane could be purified by passing through a silica gel column. Of further interest was the observation that the cyanovinyl dithiane **1** was perfectly stable to acidic conditions with no evidence of isomerization to **6**. This was convincingly demonstrated by addition of excess trifluoroacetic acid to a solution of **1** in deuteriochloroform. After 18 hr, there was no change in its nmr spectrum.



On the other hand, the ketene thioacetal **6** reacted within 5 min with excess trifluoroacetic acid, as evidenced by the disappearance of the vinyl signal to give the stable cation **7** (Figure 1, bottom). This behavior has recently been noted for a series of related ketene thioacetals derived from 1,3-dithianes.[6] The rapid reaction of **6** with acid to give a stable cation must be reckoned with when considering the importance of 3p–2p π overlap in sulfur systems.

Due to the facile base-catalyzed isomerization of **1** to **6** an investigation into the site of alkylation of the carbanions was prompted.[7] One may anticipate a highly delocalized anion **8** upon proton removal from either **1** or **6** possessing three potential sites for alkylation (A, B, C). Alkylation at A would give rise to **9**, alkylation at C would give **10**, and alkylation at B would produce **11**. Precedent for alkylation at A has been described by Seebach,[2] whereas ketenimine formation from alkylation of α carbanions of nitriles has been reported by Newman.[8] Since protonation of **8** has already shown to proceed exclusively at B to give **6**, it was not surprising to learn that alkylation afforded exclusively **11**. The anion **8** was generated at −78° and treated at this temperature with ethyl iodide, producing a crude mixture of **11a** and **11b** containing >95% **11a** (R = Et) (Figure 2, top). The yield of ethylated material was 74%. In addition, there was obtained a small quantity of geminal diethylated material (6–8%) due presumably to the slight inequity in the amount of butyllithium employed. Since the isolation of alkylated material did not involve any aqueous work-up, but simply solvent evaporation, only neutral material was recovered and there was little opportunity for equilibration of the products. This kinetically controlled mixture was equilibrated with a catalytic amount of sodium in ethanol at −20°. It was surprising to learn that the equilibrium mixture did in fact contain approximately 25% of the cyano-

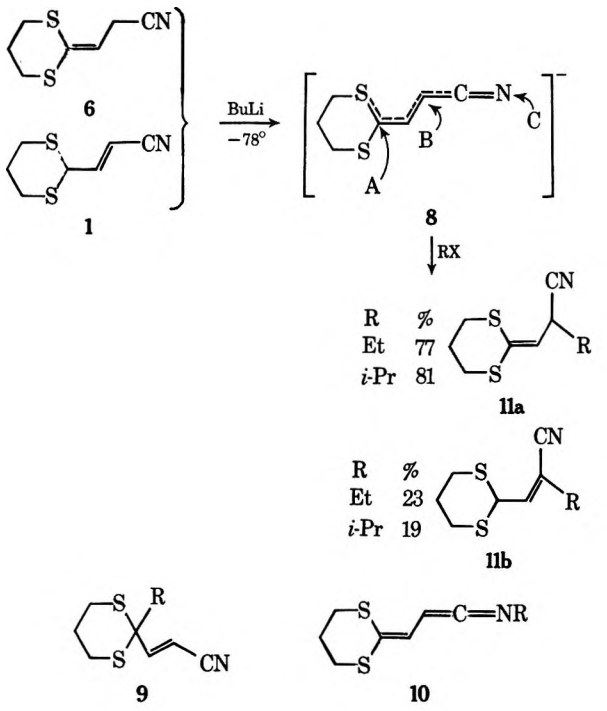
(4) For discussions relating to the importance of 3p–2p π bonding in sulfur compounds, see M. C. Caserio, R. E. Pratt, and R. J. Holland, *J. Amer. Chem. Soc.*, **88**, 5747 (1966); R. L. Autrey and P. W. Scullard, *ibid.*, **90**, 4924 (1968), and earlier references cited in these reports.

(5) H. T. Kalff and C. Romers, *Acta Crystallogr.*, **20**, 490 (1966).

(6) F. A. Carey and J. R. Neergard, *J. Org. Chem.*, **36**, 2731 (1971).

(7) A recent study on the resonance-stabilized anion of 2-styryl-1,3-dithianes [D. L. Coffen, T. E. McEnter, and D. R. Williams, *Chem. Commun.*, 913 (1970)] described alkylation at *two sites* in the molecule, contrary to what was found in this study for **1** and **6**.

(8) M. S. Newman, T. Fukunaga, and T. Miwa, *J. Amer. Chem. Soc.*, **82**, 873 (1960).



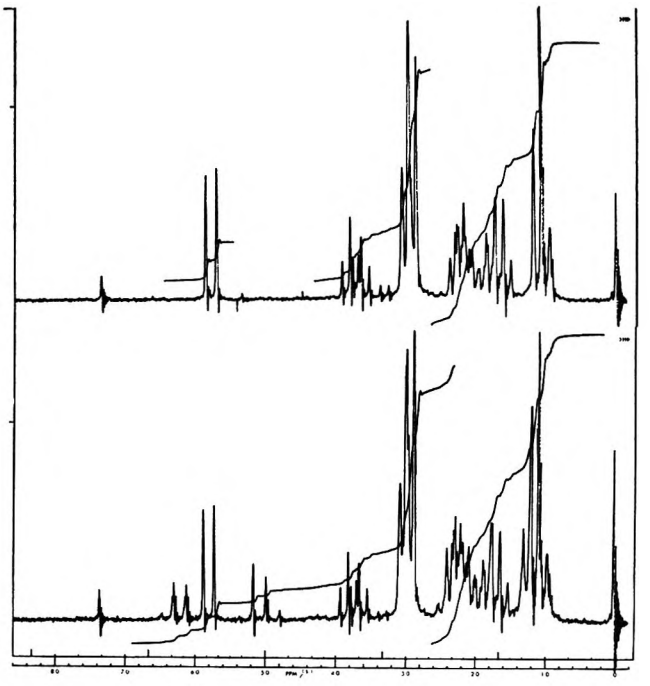


Figure 2.—(Top) 60-MHz spectrum of **11a** before equilibration with sodium ethoxide. (Bottom) 60-MHz spectrum showing **11a** and **11b** after equilibration.

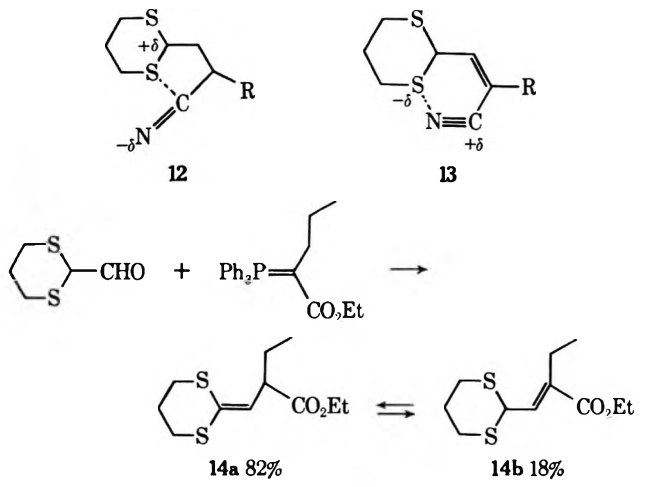
vinyl dithiane, **11b** (R = Et). From Figure 2 (bottom), the doublets at 5.1 (J = 11 cps) and 6.2 ppm (J = 11 cps) arising from the protons α to sulfur and at the vinyl carbon, respectively, in **11b** are clearly visible. The gas chromatogram of **11a**, which showed only a single peak, exhibited two discernible peaks in the ratio 77:23 after equilibration, indicating that the composition of the mixture was thermally unaffected. Repeated alkylations of **1** and **6**, using varying amounts of base, afforded prior to equilibration 75–95% of **11a** and 5–25% of **11b** (by nmr assessment) with similar ratios observed on vpc examination. This further supports the assumption that the kinetic product compositions are thermally inert. Treatment of these various mixtures with sodium ethoxide–ethanol at −20° as mentioned above converted them to the equilibrium value (77:23). Thus, the presence of the ethyl group has lowered the energy difference between the isomeric dithianes. The reason for this fact is not clearly visible. One factor could be that the steric bulk of the ethyl group in **11** is responsible since it is absent in **6** and **1**. The introduction of a larger alkyl group should then increase the proportion of **11b** over **11a**. With this in mind, the anion **8** was similarly alkylated with isopropyl bromide and resulted in a 31% yield of **11a** and **11b** (R = *i*-Pr). The ratio of **11a** to **11b** both in the crude and equilibrated material was found to be 81:19. This is not significantly different from the ratios observed for the ethylated derivatives and one must therefore conclude that the size of the alkyl groups plays little or no role in the equilibrium composition.

The minor components in the equilibrated system, **11b**, were assigned structures with the alkyl group and the dithiane ring trans to each other. Although, *a priori*, this would be a reasonable assignment in view of the fact that the two largest groups would be at maximum distance, the nmr spectrum of **11** (**a** and **b**) support this configuration. The vinyl protons in **11b** (R = Et, *i*-Pr) appear as a doublet (J = 11 cps) at 6.2–6.3 ppm, whereas the β-vinyl proton in **1** appears at 6.9 ppm as a pair of doublets. The J value for the α- and β-vinyl protons in **1** is 16 cps, indicative of the trans configuration; the β-vinyl proton is therefore cis to the cyano group. Since the vinyl protons in **11b** are at considerably higher field than that found in **1**, it is reasonable to assume that they are trans to the cyano group and out of its deshielding region.

The possibility of sulfur interaction with the cyano group in **11b** to account for its increased stability and presence in the equilibrium mixture was considered. Either 3p–2p bonding as in **12** or 3d–2p bonding as in **13** could conceivably enhance the stability of this system since, as mentioned above, the cyano group is cis to the dithiane moiety. These effects were precluded when 2-formyl-1,3-dithiane (**3**) was treated with the phosphorane derived from ethyl α-bromobutyrate, producing, after equilibrium, an 82:18 mixture containing proportions of the ketene thioacetal **14a** and vinyl dithiane **14b** in close agreement with that obtained from the nitrile. It should be noted that the initially isolated esters obtained from this reaction indicated by the nmr spectrum a high proportion of **14b** (~90% kinetic product). Distillation in order to purify the material then produced the 82:18 mixture mentioned earlier (thermodynamic product). The similar isomer distribution in **11** and **14** would tend to dispute any unusual interaction of the cyano group in the alkylated vinyl dithianes, since the carboethoxy group, presumably trans to the dithiane, could not engage in such behavior.

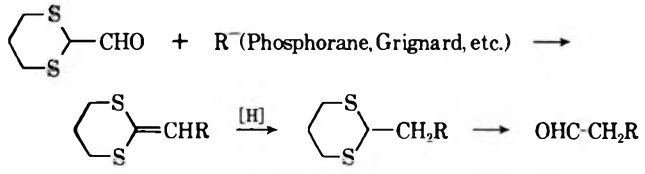
It, therefore, seems likely that the effect of alkyl substitution on the cyano- or carboethoxyvinyl dithiane (**11** and **14**, respectively) with regard to their double bond positions rests mainly on the accepted fact that increasing the alkyl substitution on carbon–carbon double bonds increases their thermodynamic stability.

The results of this study invite further investigation into its potential synthetic utility. For example, the readily available 1-formyl-1,3-dithiane would allow



coupling with a variety of Wittig-type reagents or other nucleophilic species (RLi, RMgX, etc.) to afford directly the ketene thioacetals, which may be reduced and cleaved[2] to the aldehydes (Scheme I).

SCHEME I



The scheme, if successfully implemented, would in effect provide a versatile and useful two-carbon homologation of alkyl and aryl halides to aldehydes, which has not been available through the dithiane route.[9,9a]

Experimental Section

Nmr spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane as internal standard. Chemical shifts are reported in parts per million (δ). Infrared spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer and peaks are reported in wavenumbers (cm^{-1}). The gas chromatography was performed on Hewlett-Packard 5750 instruments using 0.25 in. × 8 ft columns. Collection of samples was made with a small U-shaped pyrex collecting tube. 1,3-Dithiane was either prepared by the method of Corey[10] or purchased from Aldrich Chemical Co. Mass spectra were obtained using an AEI MS-9 at 70 eV. Microanalysis were performed by Midwest Microlab, Indianapolis, Ind.

2-Formyl-1,3-dithiane (3, R = H).—A solution containing 24.0 g (0.20 mol) of 1,3-dithiane in 400 ml of anhydrous tetrahydrofuran was cooled with stirring under nitrogen to −30° (Dry Ice–isopropyl alcohol) and treated dropwise with 59.2 g (0.20 mol) of 26 wt % *n*-butyllithium in hexane. After 1 hr of additional stirring the solution was transferred by syringe and added dropwise to a flask containing previously cooled (−10°) dimethylformamide (60 ml). The mixture was allowed to stir for 2 hr at −10° and then stored overnight at 0°. The resulting suspension was poured into ice water (400 ml) and the mixture was extracted several times with pentane. The aqueous layer was neutralized with dilute (1 *N*) hydrochloric acid and then extracted several times with ether. The ethereal extracts were dried ($MgSO_4$) and concentrated to give a viscous, cloudy oil which was distilled: bp 83–85° (0.45 mm); yield 24.0 g (81%) of colorless liquid; infrared (neat) 2675 (CHO), 1715 (C=O), 912 cm^{-1} (dithiane); nmr ($CDCl_3$) δ 9.6 (d, 1, *J* = 2 Hz, -CHO), 4.2 (s, 1, >CHCHO), 2.4–3.4 (m, 4, $-CH_2S-$), 1.8–2.3 (m, 2, $-CH_2-$). The product was stored at −20° to prevent dimerization, which occurs slowly at room temperature.

Anal. Calcd for $C_5H_8OS_2$: C, 40.51; H, 5.44; O, 10.79. Found: C, 40.60; H, 5.48; O, 10.49.

2-(2-Cyanovinyl)-1,3-dithiane (1).—Triphenylcyanomethylphosphonium chloride was prepared in 80% yield by heating chloroacetonitrile and triphenylphosphine (50% excess) in benzene overnight, collecting the phosphonium salt, washing with benzene, and drying *in vacuo*. Butyllithium (2.59 g, 8.5 mmol) as a 21 wt % solution in hexane was added at 0° to a suspension of the phosphonium salt (3.38 g, 10.0 mmol) in 40 ml of anhydrous tetrahydrofuran under a nitrogen atmosphere. The yellow suspension was stirred for 1 hr at room temperature and then cooled to −30° (Dry Ice–acetone). To this was rapidly added 1-formyl-1,3-dithiane (**3**, R = H, 1.48 g, 10.0 mmol) in 5 ml of tetrahydrofuran. The mixture was allowed to warm slowly to room temperature with stirring. After 2 hr, the solvents were removed by rotatory evaporation and the residue was triturated several times with warm ether or pentane. The ethereal (or pentane) solution was concentrated, affording an orange oil which solidified on standing. Elution of this material through neutral silica gel with ether–hexane (1:1) gave a colorless, crystalline product: yield 0.90 g (63%); mp 63–65°; infrared (KBr) 3040 (=CH), 2215 (C≡N), 1618 (C=C), 960 cm^{-1} (*trans*-CH=CH); nmr ($CDCl_3$) δ 6.9 [d (*J* = 16 Hz) of d (*J* = 6 Hz), 1, CH=CHCN], 5.7 [d (*J* = 16 Hz) of d (*J* = 2 Hz), 1, -CH=CHCN], 4.6 [d (*J* = 6 Hz) of d (*J* = 2 Hz), 1, <CHCH=CHCN], 2.6–3.1 (m, 4, CH_2S), 1.7–2.2 (m, 2, $-CH_2-$).

Anal. Calcd for $C_7H_9NS_2$: C, 49.08; H, 5.30; N, 8.17. Found: C, 49.08; H, 5.12; N, 8.23.

The crude product was also purified by recrystallization from ether–pentane but gave a slightly lower melting product, mp 61–63°. The latter is presumably contaminated with the isomeric dithiane, **6**, although not detectable in the nmr spectrum.

2-(2-Cyanomethylvinylidene)-1,3-dithiane (6).—Butyllithium (7.78 g, 25.5 mmol) as a 21 wt % hexane solution was added to a suspension of triphenylcyanomethylphosphonium chloride (9.26 g, 27.4 mmol) in 60 ml of dry tetrahydrofuran at 0–3°. After the yellow suspension was stirred for 1 hr at room temperature, 1-formyl-1,3-dithiane (3.44 g, 23.2 mmol) in 10 ml of tetrahydrofuran was added dropwise and the mixture was stirred for 2 hr. The solvents were removed by rotatory evaporation and the oily residue was distilled, producing 2.5 g (63%) of a colorless oil: bp 108–110° (0.1 mm); infrared (neat) 3020 (=CH), 2245 (C≡N), 1579 ($-S_2C=C$); nmr ($CDCl_3$) δ 5.81 (t, 1, *J* = 7 Hz, C=CH), 3.33 (d, 2, *J* = 7 Hz, $-CH_2CN$), 2.8–3.1 (m, 4, CH_2S), 1.9–2.4 (m, 2, $-CH_2-$). The product was stored at −20° since it tends to darken on standing at 0–25° after several days.

Anal. Calcd for $C_7H_9NS_2$: C, 49.08; H, 5.30; N, 8.17. Found: C, 49.03; H, 5.22; N, 8.19.

Equilibration of 2-(2-Cyanovinyl)-1,3-dithiane (1) to 2-(2-Cyanomethylvinylidine)-1,3-dithiane (6).—A solution containing 206 mg (1.20 mmol) of **1** in 10 ml of absolute ethanol was cooled to −30° and treated with 2 ml of ethanolic sodium ethoxide in which 10 mg of sodium was dissolved. The pale yellow solution was stored for 30 hr at −20°, after which it had turned orange in color. The cold solution was neutralized with dilute acetic acid, at which point the orange color had returned to pale yellow. The solvents were evaporated *in vacuo* and the residue was taken up in chloroform, the latter solution washed with dilute bicarbonate and then with water, dried ($MgSO_4$), and concentrated. An oily residue remained (178 mg, 86%) whose ir and nmr spectra were identical with those of **6**. When the equilibration was attempted at room temperature, the solution took on a deep brown color and several products were formed suggesting decomposition of **1** or **6** under these conditions.

Alkylation of 1 or 6 with Ethyl Iodide.—In a typical experiment, *n*-butyllithium (534 mg, 1.75 mmol, 21 wt %) was added to **1** or **6** (300 mg, 1.75 mmol) in 6 ml of anhydrous tetrahydrofuran at −78°. The solution immediately became yellow and a suspension formed. After the solution was stirred at this temperature for 30 min under nitrogen, ethyl iodide (546 mg, 3.50 mmol) in 1 ml of tetrahydrofuran was added. The mixture was stirred for 1 hr at −78° and then allowed to warm to room temperature. The solvents were removed by rotary evaporation and the residual material was triturated several times with hot hexane. Con-

(9) Two-carbon homologations of alkyl halides to aldehydes are available from other systems; *cf.* A. I. Meyers, G. R. Malone, and H. W. Adickes, *Tetrahedron Lett.*, **No. 42**, 3715 (1970), and earlier references cited therein.

(9a) NOTE ADDED IN PROOF.—The preparation of ketene thioacetals from 2-lithio-2-trimethylsilyldithianes has recently been reported by Professor D. Seebach (University of Giessen) in *Angew. Chem., Int. Ed. Engl.*, in press, and Professor F. A. Carey, *J. Org. Chem.*, **37**, 1923 (1972).

(10) D. Seebach, E. J. Corey, and N. R. Jones, *J. Org. Chem.*, **33**, 300 (1968).

centration of this solution left an orange-colored oil, 258 mg (74%), a portion of which was injected into the gas chromatograph (240°, UCW-98 column). The ratio of **11a** to **11b** varied among several such alkylations from 75–95% **11a** to 5–25% **11b** depending upon the amount of butyllithium and the care exercised in the work-up to exclude moisture. Since the products were very sensitive to base, equilibration conditions were difficult to circumvent. The highest proportion (<95%) of **11a** (Figure 2) was accomplished in the above described experiment: nmr ($CDCl_3$) δ 5.80 (1, d, J = 10 Hz, =CH), 3.75 [1, d (J = 10 Hz) of t (J = 7 Hz), CHCN], 2.8–3.1 (m, 4, CH_2S), 2.1–2.4 (m, 2, $-CH_2CH_2S$), 1.75 (2, p, J = 7 Hz, CH_2CH_3), 1.1 (3, t, J = 7 Hz, CH_3); infrared (neat) 2239 cm^{-1} (unconjugated C≡N); m/e 199 (calcd 199). The gas chromatogram indicated a small amount of a second component poorly resolved from the main peak of **11a**.

Equilibration of **11a** in sodium ethoxide–ethanol at −20° for 30 hr gave after recovery (as described for equilibration of **1** to **6**) a product which exhibited two distinct peaks in the gas chromatogram (UCW-98 column, 240°) integrating at 23:77. The nmr ($CDCl_3$) for this equilibrated product is shown in Figure 2 (bottom). The infrared (neat) shows two clearly separated bands at 2240 (unconjugated C≡N) and 2219 cm^{-1} (conjugated C≡N).

Alkylation of 1 or 6 with Isopropyl Bromide.—To 150 mg (0.88 mmol) of **6** or **1** in 2 ml of anhydrous tetrahydrofuran cooled to −78° under nitrogen was added 267 mg (0.88 mmol) of 21 wt % n-butyllithium in hexane. After 30 min 221 mg (1.8 mmol) of isopropyl bromide in 1 ml of tetrahydrofuran was added and the reaction was allowed to warm to room temperature. The solvents were evaporated and the residue was triturated several times with 15-ml portions of hot hexane. Filtration of the hexane solution followed by concentration left a yellow oil, 58 mg (31%). Vpc examination (UCW-98, 250°) revealed two distinct peaks (19 and 81%). Collection from the vpc gave m/e 213 (calcd 213), **11a** and **11b** (R = i-Pr): infrared (neat) 2240, 2220 cm^{-1} (unconjugated and conjugated CN); nmr ($CDCl_3$) δ 6.2 [d, J = 11 Hz, 0.2 H, $CH{=}C(CN)C_3H_7$], 5.85 (d, J = 9 Hz, 0.8 H, $-S_2C{=}CH$), 5.1 (d, J = 11 Hz, 0.2 H, $-S_2CH-$), 3.7 [d (J = 9 Hz) of d (J = 9 Hz), 0.8 H, −CHCN], 2.9–3.1 (m, 4, CH_2S), 1.6–2.6 [m, 3, CH_2CH_2S, $CH(CH_3)_2$], 0.9–1.4 [m, 6, $(CH_3)_2C$].

Equilibration of this mixture with sodium ethoxide–ethanol at −20° for 30 hr gave no significant changes in the vpc, ir, and nmr analyses.

Wittig Coupling of 2-Formyl-1,3-dithiane with the Phosphorane of Ethyl α-Bromobutyrate (14a and 14b). A. ***N*-Propyltriphenylphosphonium Bromide.**—A solution of triphenylphosphine (48 g) and 1-bromopropane (22.4 g) in dry xylene was heated under reflux for 20 hr. Upon cooling, the solid was removed by filtration, washed with dry ether, and dried: yield 63 g (90%); nmr ($CDCl_3$) δ 7.6–8.2 (m, 15), 3.5–4.0 (m, 2, $-CH_2P^+Ph_3$), 1.1–2.1 (m, 5, CH_3CH_2).

B. **1-Carboethoxy-*n*-propyltriphenylphosphonium Chloride.**[11]—n-Propyltriphenylphosphonium bromide (28.4 g, 73.6 mmol) as a suspension in dry benzene (50 ml) at 0° under nitrogen was treated with n-butyllithium (38 ml, 61 mmol) as a 15 wt % solution in hexane. The mixture was stirred for 1 hr, a solution of ethyl chloroformate (3.33 g, 30.5 mmol) in 5 ml of benzene was added, and stirring was continued for an additional 1 hr at room temperature. The phosphorane thus formed *in situ* was then treated with a benzene solution (5 ml) of 2-formyl-1,3-dithiane (5.0 g, 33 mmol). The mixture was stirred at room temperature for 16 hr and then poured into ice water. The benzene layer was separated and the aqueous solution was extracted with ether. Combination of the organic extracts, drying ($MgSO_4$), and concentration produced a residue, 6.4 g, which was distilled, bp 110–114°, (0.1 mm). The gas chromatogram (UCW-98, 240°) showed that two components in the ratio 82:18 were present: nmr ($CDCl_3$) δ 6.65 (d, J = 10 Hz, 0.18 H, CH=C in **14b**), 5.82 (d, J = 10 Hz, 0.82 H, $-S_2C{=}CH$ in **14a**), 4.82 (d, J = 11 Hz, 0.18 H, $-S_2CH$ in **14b**), 4.15 (two overlapping quartets for $-OCH_2-CH_3$ in **14a**, **14b**), 3.40 [d (J = 7 Hz) of t (J = 10 Hz), 0.82 H, $-CH(C_2H_3)CO_2Et$ in **14a**], 2.8–3.1 (m, 4, SCH_2), 2.0–2.5 (m, 2, CH_2CH_2S), 0.85–1.9 (m, 8); m/e 246 (calcd 246).

Registry No.—**1**, 34906-11-1; **3** (R = H), 34906-12-2; **6**, 34906-13-3; **11a**, 34906-14-4; **11b**, 34906-15-5; **14a**, 34906-16-6; **14b**, 34906-17-7.

Acknowledgment.—The authors are grateful to the Lithium Corporation of America for their continuing interest and contribution of generous quantities of organolithium reagents. Certain technical assistance by Dr. Eric W. Collington and Mr. G. Ray Malone is also gratefully acknowledged.

(11) H. J. Bestmann and H. Schulz, *Angew. Chem.*, **72**, 27 (1961), has described the *in situ* preparation of α-alkylcarboethoxy phosphoranes.

The Structure of Aroyl Isocyanide Trimers[1]

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Received February 23, 1972

The structure of the trimer of benzoyl isocyanide prepared by the action of silver cyanide on benzoyl bromide is shown to be 7-benzoylimino-2,5-diphenyloxazolo[5,4-*d*]pyrimidin-7-one (**2**) on the basis of chemical and spectroscopic evidence. The scope and limitation of the trimerization reaction is discussed.

The trimer of benzoyl isocyanide was first reported in 1895 by Nef[2] who prepared it by treating benzoyl bromide with silver cyanide. Diels and Stein[3] repeated this work in 1907 and on the basis of chemical evidence proposed the azetine structure **1**. In a review of trimethylenimines,[4] Moore noted that structure **1** was quite unlikely for the trimer. The benzoyl isocyanide trimer is also formed[5] as a minor product (2%) in the thermolysis of 2-azido-5-phenyl-1,3,4-oxadiazole along with benzoyl cyanide (35%).

Results

The benzoyl isocyanide trimer has been shown to be 7-benzoylimino-2,5-diphenyloxazolo[5,4-*d*][1,3]oxazine (**2**) on the basis of spectral and chemical evidence. The mass spectrum of the trimer afforded a molecular ion at m/e 393 consistent with $(PhCONC)_3$. The nmr spectrum indicated the presence of aromatic hydrogens only. The ir spectrum was devoid of triple-bond absorption and exhibited maxima at 1718 (sh), 1700, 1660, and 1640 cm^{-1}. Considered in conjunction with the chemical evidence presented below only structures **2** and **3** are consistent with the data. Structure **2**, a primary adduct, is favored over Dimroth rearrangement

(1) Presented in part at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 12–17, 1971.

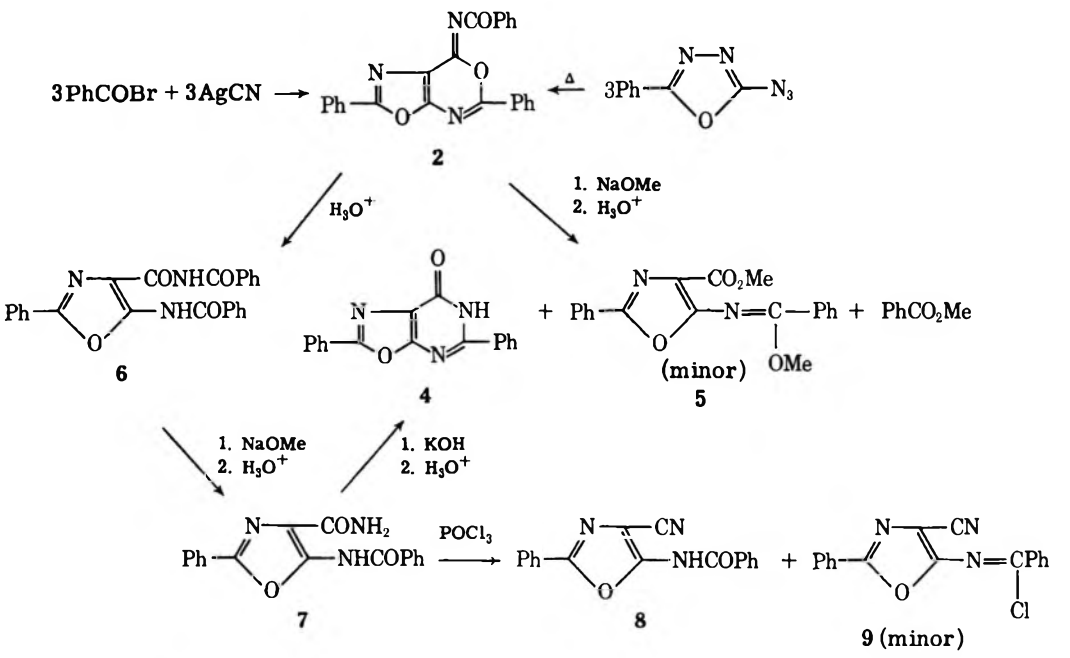
(2) J. U. Nef, *Ann.*, **287**, 303 (1895).

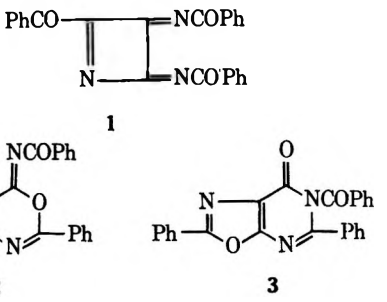
(3) O. Diels and H. Stein, *Ber.*, **40**, 1655 (1907).

(4) J. A. Moore in "Heterocyclic Compounds with Three and Four Membered Rings," Part II, R. Weissberger, Ed., Interscience, New York, N. Y., 1964, p 916.

(5) P. A. S. Smith in "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y. 1970, p 149; H. Dounchis, Ph.D. Thesis, The University of Michigan, Ann Arbor, Mich, 1967.

SCHEME I





1

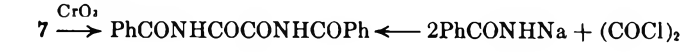
2 3

product **3** on the basis of the carbonyl frequency. Compound **3**, being an imide, would be expected[6] to display absorption above that observed.

The chemical evidence which supports structure **2** is as follows. Treatment of the trimer with sodium methoxide[3] yielded a sodium salt and methyl benzoate. Protonation of this salt gave rise to a high melting solid which was shown to be 2,5-diphenyloxazolo[5,4-*d*]-pyrimidin-7-one (**4**) by comparison with authentic material which was independently synthesized. Traces of the imidate ester **5** were also isolated. The depicted sequence of transformations (Scheme I) supports the structural assignment.

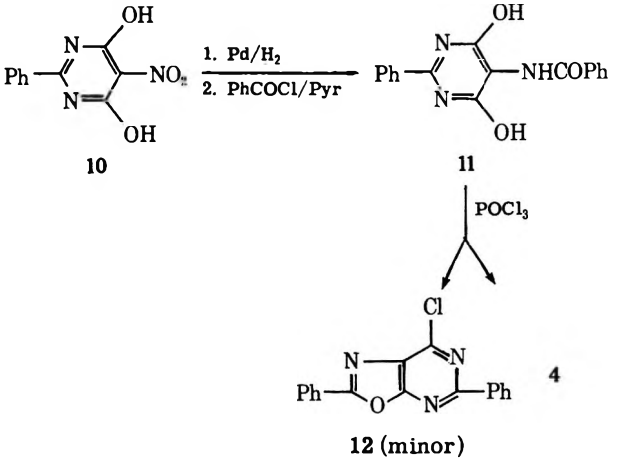
The trimer underwent facile hydration in aqueous acetic acid to afford **6** which exhibited characteristic imide absorption at 1720 cm^{-1} ($CHCl_3$). Sodium methylate smoothly debenzoylated **6** to give carboxamide **7**. Compound **7** was cyclized to **4** with hot aqueous potassium hydroxide. Dehydration of **7** to nitrile **8** was accomplished with phosphorus oxychloride. A small amount of imidoyl chloride **9** was also isolated. Compounds **4**, **6**, and **7** were characterized by Diels and Stein but were not assigned correct structures.

Structure **7** is also consistent with the chromic acid oxidation of this derivative which Diels and Stein reported gave dibenzoyloxamide.



2,5-Diphenyloxazolo[5,4-*d*]pyrimidin-7-one (**4**) was independently prepared by the synthetic sequence shown in Scheme II. Nitropyrimidine **10**[7] was catalytically reduced to the corresponding amine which was acylated with benzoyl chloride in pyridine to give 5-benzamido-4,6-dihydroxy-2-phenylpyrimidine (**11**). Benzamide **11** was cyclized to oxazolopyrimidine **4** with phosphorus oxychloride. A small amount of 7-chloro-2,5-diphenyloxazolo[5,4-*d*]pyrimidine (**12**) was also formed.

SCHEME II



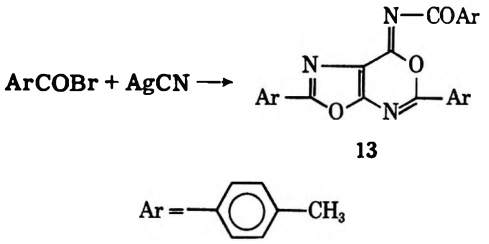
10 11 12 (minor)

Compound **4** prepared in the above sequence was identical with the product obtained from the debenzoylation of the benzoyl isocyanide trimer **2**.

Treatment of *p*-toluoyl bromide with silver cyanide afforded the oxazolo[5,4-*d*]oxazine **13** in 81% yield. Compound **13** reacted with sodium methoxide and with aqueous acetic acid to give analogs of **4** and **6**, respectively. Complex mixtures resulted when acetyl bro-

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1962, p 221.

(7) J. A. Hendry and R. F. Homer, *J. Chem. Soc.*, 328 (1951).



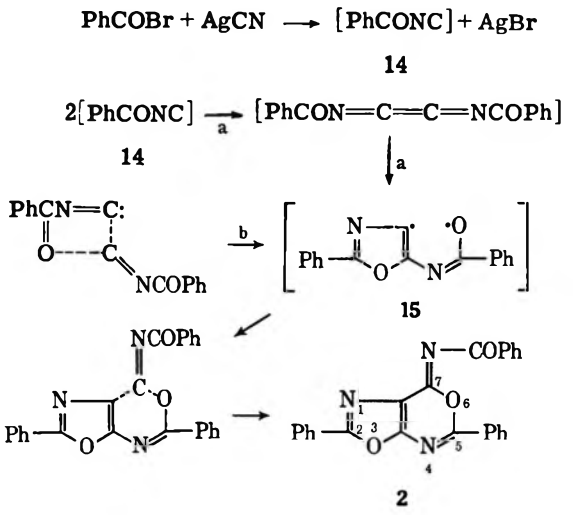
13

mide and *n*-butyl bromide were treated with silver cyanide.

Discussion

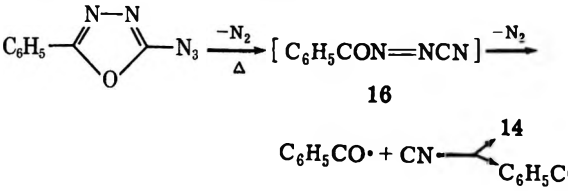
A detailed mechanism for the formation of trimer **2** must await further study. The formation of **2** can, however, be rationalized in general terms by the sequence shown in Scheme III.

SCHEME III



14 can be rationalized by a head to head dimerization of two isocyanide molecules followed by isomerization to a diradical or carbenoid oxazole **15** (path a) or *via* a 1:1 cyclization to **15** (path b) followed by a novel[9] 1:5 cyclization with a third molecule of isocyanide Analogy to the 1:4 cyclization depicted in path b can be seen in the ring closure of acyl isocyanates and isocyanides to oxazole derivatives.[10] It is of interest to note that no evidence for the formation of the oxazolooxazole which would form by ring closure of **15** has been obtained.

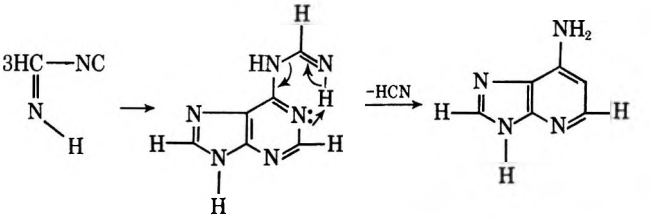
A mechanism for the formation of **2** from isocyanide **14** *via* a complex with silver appears attractive, *a priori*, on several counts. Silver is known[11] to form stable complexes with isocyanides and such a complex might be expected to be a suitable intermediate for the highly specific trimerization observed. The fact that **2** is also formed in the thermolysis of 2-azido-5-phenyl-1,3,4-oxadiazole, in which case there is no transition metal present, argues against such a mechanism although it does not rule it out. It is likely that **14** is an intermediate in the azide thermolysis. Its formation can be explained by decomposition of the azide to benzoyl azocyanide **16** which undergoes loss of nitrogen to afford



benzoyl radicals and ambident cyano radicals which couple to give either benzoyl cyanide or **14** which trimerizes.

Oxazolo[5,4-*d*]oxazine **2** undergoes facile addition of nucleophiles (*i.e.*, amines, CH acids) to give high yields of 1:1 adducts which arise predominately from O_6–C_7 bond cleavage although some O_6–C_5 cleavage is observed for nucleophiles with low steric requirements. These reactions will be discussed in a subsequent paper.

The formation of **2** may have implication for the biogenetic synthesis of adenine *via* the trimerization of dimeric hydrogen cyanide in the isonitrile form followed by loss of hydrogen cyanide.



Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The nuclear magnetic resonance spectra were determined on a Varian Associates spectrophotometer, Model A-60A. Ir spectra were obtained with a Perkin-Elmer Model 421 ir spectrophotometer. Mass spectra were recorded on a Consolidated Electrodynamics Corporation Type 21-103C mass spectrometer. Elemental analyses were performed by the staff of the Analytical Laboratory of the Central Research Group, FMC Corporation.

7-Benzoylimino-2,5-diphenyloxazolo[5,4-*d*][1,3]-oxazine (2).[2,3] —This compound was prepared by a slight modification of the procedure of Diels and Stein. A solution of benzoyl bromide, 100 g, in 600 ml of anhydrous ether in which was suspended 100 g of silver cyanide, was vigorously stirred and refluxed for 21 hr. The solids were collected and washed with cold ether. Hot chloroform separated the yellow product from the silver salts. Concentration of the chloroform solution followed by recrystallization of the residue from benzene afforded 56.2 g

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(9) B. Zeeh *Syn.*, **2**, 65 (1969).
(10) R. Neidlein, *Ber.*, **97**, 3476 (1964).
(11) L. Malatesta and F. Bonati, "Isocyanide Complexes of Metals," Wiley, New York, N. Y., 1969, Chapter 3.

(79.6%) of a yellow solid, mp 190–193° (lit.[3] mp 191°). Subsequent recrystallization gave a product of mp 192–193°: uv max (EtOH) 282 nm (ε 19,000), 235 (23,800) and 205 (34,500); ir ($CHCl_3$) 1718 (sh), 1700, 1660, and 1640 cm^{-1}; nmr ($CDCl_3$) τ 2.80–2.60 (m, 9 H), 2.20–1.90 (m, 6 H); mass spectrum (70 eV) *m/e* (rel intensity) 393 (2.5), 137 (3), 129 (4), 125 (3), 123 (4), 112 (3), 111 (7).

Anal. Calcd for $C_{24}H_{15}N_3O_3$: C, 73.27; H, 3.82; N, 10.68. Found: C, 73.02; H, 4.10; N, 10.63.

2,5-Diphenyloxazolo[5,4-d]pyrimidin-7-one[3] (4) and Methyl *N*-(4-Carbomethoxy-2-phenyloxazol-5-yl)benzimidate (5).—Trimer **2**, 7.20 g, was stirred at ambient temperature for 16 hr in 70 ml of anhydrous methanol containing 2.0 g of sodium methoxide. The presence of methyl benzoate in the reaction mixture was shown by vpc analysis. The mixture was filtered and 4.28 g (75%) of the sodium salt of **4** was obtained after washing with methanol and drying. The sodium salt was converted to **4**, mp 376–379° (lit.[3] mp 365°), in quantitative yield by stirring in 50% aqueous acetic acid: **4** was too insoluble to obtain an nmr spectrum; ir (KBr) 3240, 3200 (NH) and 1685 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 289 (100), 187 (10), 186 (81), 115 (91), 105 (54), 104 (15).

Anal. Calcd for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53. Found: C, 70.72; H, 3.89; N, 14.39.

The initial filtrate deposited 0.70 g (14.7%) of **5** as yellow crystals, mp 110–113°, upon standing, which were pure by tlc. Recrystallization from cyclohexane afforded an analytical sample: mp 113–114°; ir ($CHCl_3$) 1730 and 1650 cm^{-1}; nmr ($CDCl_3$) τ 6.30 (s, 3 H), 5.82 (s, 3 H), 2.70–2.50 (m, 8 H), and 2.10–1.85 (m, 2 H); mass spectrum *m/e* (rel intensity) 336 (100), 207 (15), 202 (8), 174 (2), 162 (6), 146 (3), 105 (21).

Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.84; H, 4.80; N, 8.33. Found: C, 68.16; H, 4.54; N, 8.29.

***N*-(4-*N*-Benzoylcarboxamido-2-phenyloxazol-5-yl)benzamide (6).**—This compound was prepared according to the procedure[3] of Diels and Stein. Thus, 20 g of **2** was heated 15 min at 80–90° in 300 ml of 50% aqueous acetic acid to afford a quantitative yield of pure **6** after collecting and drying: mp 186–188° (lit.[3] 187–188°); uv max (EtOH) 283 nm (ε 20,700), 238 (30,000), 206 (33,000); ir ($CHCl_3$) 3390, 3320, 1720, 1690, 1685, and 1660 cm^{-1}; nmr ($CDCl_3$) τ 2.70–2.30 (m, 9 H), 2.10–1.80 (m, 6 H), 0.00 (s, 1 H), and −0.04 (s, 1 H) (the latter two absorptions collapsed with D_2O); mass spectrum *m/e* (rel intensity) 411 (6.3), 292 (3.5), 291 (2.7), 290 (9.7), 188 (2.5), 121 (9.8), 115 (3.0), 105 (100), 104 (5).

***N*-(4-Carboxamido-2-phenyloxazol-5-yl)benzamide (7).**—Compound **6**, 18.0 g, was refluxed for 3 hr in a solution of methanolic sodium methoxide prepared from 2.80 g of sodium in 50 ml of methanol. The mixture was concentrated, acidified with 50% aqueous acetic acid, warmed to 80° for 5 min, and cooled to room temperature, and the resulting product was collected and recrystallized from ethanol affording 5.16 g (86.2%) of **7**: mp 210–211° (lit.[2] mp 208–210°); uv max (MeOH) 283 nm (ε 20,000) and 207 (26,300); ir (KBr) 3460, 3420, 3325, 3260, 1695, 1670 cm^{-1}; nmr (DMSO-d_6) τ 2.5–2.0 (m, 8 H), 2.0–1.8 (m, 4 H), and −1.0 (s, 1 H) (two H at 2.5–2.0 and that at −1.0 are exchangeable with D_2O); mass spectrum *m/e* (rel intensity) 307 (100), 105 (100), 89 (4), 77 (36).

Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26. Found: C, 66.64; H, 4.45.

5-Benzamido-4-cyano-2-phenyloxazole (8) and *N*-(4-Cyano-2-phenyloxazol-5-yl)benzimidoyl Chloride (9).—Carboxamide **7**, 6.51 g, was suspended in 50 ml of stirred phosphorus oxychloride and heated for 50 min at 48–53°. The mixture was cooled to room temperature affording 1.25 g (19.2%) of starting material **7**. Concentration of the filtrate gave 4.1 g (67%) of **8** after washing with water and drying: mp 215–216°; uv max (EtOH) 293 nm (ε 28,200) and 208 (27,600); ir ($CHCl_3$) 3420, 2240, and 1700 cm^{-1}; nmr (DMSO-d_6) τ 2.45–2.20 (m, 6 H), 2.10–1.80 (m, 4 H), and −1.8 to 2.2 (m, 1 H); mass spectrum *m/e* (rel intensity) 289 (10), 105 (100), and 77 (6).

Anal. Calcd for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53. Found: C, 70.33; H, 3.78; N, 14.33.

Chromatography of the above filtrate on silica gel yielded ~0.50 g of **9**, mp 140–140.5°, upon elution with 9:1 chloroform–ethyl acetate, extraction with ether, and recrystallization from heptane: ir ($CHCl_3$) 2270 and 1640 cm^{-1}; mass spectrum *m/e* (rel intensity) 309 (34), 308 (20), 307 (100), 228 (31), 227 (15), 226 (95), 192 (18), 169 (52), 141 (36).

Anal. Calcd for $C_{17}H_{10}N_3OCl$: C, 66.30; H, 3.25; N, 13.65. Found: C, 66.58; H, 3.71; N, 13.33.

5-Benzamido-4,6-dihydroxy-2-phenylpyrimidine (11).—4,6-Dihydroxy-5-nitro-2-phenylpyrimidine,[7] 2.80 g, was suspended in 50 ml of acetic acid containing 300 mg of 10% palladium on charcoal and hydrogenated at 35 psi for 2 hr at ambient temperature. The mixture was treated with 75 ml of DMF to dissolve the white precipitate and filtered through Celite and the filtrate was concentrated at reduced pressure. The resulting solid was washed with ethanol and dried to give 1.1 g of a red-tinged solid. The product was dissolved in 25 ml of concentrated HCl and a small amount of insoluble solid was filtered off. The filtrate was diluted with 150 ml of water and carefully neutralized to pH 6.5 with sodium hydroxide at which point the off-white crystalline product precipitated. The product was collected, washed with water, and dried under vacuum over P_2O_5 at 80° for 1 hr. The amine weighed 0.65 g (37.2%) and melted at 245–248° dec. The amine became colored upon standing in the light at room temperature [ir (Nujol) 3450, 3325, 3225, 3100–2600, 1660 cm^{-1}].

The amine, 200 mg, was dissolved in 2 ml of pyridine and treated with 180 mg (20% excess) of benzoyl chloride. A voluminous precipitate formed after 2 min at ambient temperature. The mixture was poured into 25 ml of water after 20 min and collected. The solid was washed with water and then methanol and dried under vacuum over P_2O_5 giving 200 mg (66%) of **11**, mp 328–330° dec. An analytical sample, mp 329–330° dec, was prepared by recrystallization from aqueous DMF: ir (Nujol) 3350, 1645, and 1620 cm^{-1}; mass spectrum *m/e* (rel intensity) 307 (61), 289 (28), 203 (12), 188 (19), 122 (17), 105 (100), and 77 (21).

Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.68. Found: C, 66.50; H, 4.43; N, 13.40.

2,5-Diphenyloxazolo(5,4-*d*)pyrimidin-7-one (4) by Cyclization of 5-Benzamido-4,6-dihydroxy-2-phenylpyrimidine (11).—Benzamide **11**, 100 mg, was suspended in 5 ml of phosphorus oxychloride and heated at reflux for 1.5 hr. The reaction mixture was cooled and a white solid precipitated. It was collected and washed with ethanol and dried at 95° under vacuum giving 28 mg of pure **4**, mp 376–378° dec. Concentration of the filtrate gave a clear oil which yielded an additional 35 mg of **4** (combined crude yield 67%) which was contaminated by a trace of 7-chloro-2,5-diphenyloxazolo[5,4-*d*]pyrimidine (**12**) as indicated by tlc. Compound **4** thus obtained was identical (ir, mass spectrum, R_f on tlc, and mixture melting point) with **4** obtained from treatment of **2** with sodium methoxide followed by acidification.

Anal. Calcd for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53. Found: C, 70.55; H, 4.02; N, 14.58.

7-Chloro-2,5-diphenyloxazolo[5,4-*d*]pyrimidine (12).—2,5-Diphenyloxazolo[5,4-*d*]pyrimidin-7-one (**4**), 13.2 g, *N*,*N*-diethylaniline, 6.80 g, and phosphorus oxychloride, 50 ml, were refluxed for 16 hr. The phosphorus oxychloride was removed by distillation at reduced pressure and the residue was taken up in methylene chloride. The resulting solution was washed with 5% hydrochloric acid, water, 5% aqueous sodium bicarbonate, and water and dried (Na_2SO_4). Filtration and removal of the solvent gave an oil which solidified upon trituration with petroleum ether affording 14.90 g of crude **12**, mp 195–197°. Successive recrystallizations from cyclohexane and ethyl acetate yielded 8.60 g (61.5%) of pure **12**: mp 209–211°; uv max (EtOH) 399 nm (ε 14.000), 326 (22,000), 256 (5,400), and 209 (14,800); ir (Nujol) 1620, 1600 cm^{-1}; nmr ($CDCl_3$) τ 2.5–2.3 (m, 6 H), 1.7–1.5 (m, 4 H); mass spectrum, *m/e* (rel intensity) 309 (34), 307 (100), 168 (15), 141 (25), 105 (17), 103 (39), and 89 (48).

Anal. Calcd for $C_{17}H_{10}N_3OCl$: C, 66.40; H, 3.25; N, 13.65. Found: C, 66.29; H, 3.00; N, 13.34.

7-*p*-Toluoylimino-2,5-di-*p*-tolyloxazolo[5,4-*d*][1,3]oxazine (13).—According to the procedure for compound **2**, from *p*-toluoyl bromide (39.0 g), silver cyanide (41.0 g), and ether (400 ml) there was obtained 22.9 g (81%) of **13**: mp 216–216.5°: ir (Nujol) 1730, 1680, 1625 cm^{-1}; nmr ($CDCl_3$) τ 7.58 (s, 9 H), 2.90–2.60 (m, 6 H), 2.10–1.80 (m, 6 H); mass spectrum *m/e* (rel intensity) 435 (100), 310 (8), 129 (7), 119 (53).

Anal. Calcd for $C_{27}H_{21}N_3O_3$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.07; H, 4.61; N, 9.64.

***N*-(4-*N*-*p*-Toluoylcarboxamido-2-*p*-tolyloxazol-5-yl)-*p*-toluamide (17).**—By the procedure used to prepare compound **6**, there

was obtained, from 6 g of **13**, 5.82 g (93.5%) of **16**: mp 207–208°; ir (Nujol) 3500, 3450, 3300, 1740, 1695 cm^{-1}; nmr ($CDCl_3$) τ 7.55 (split s, 9 H), 2.80–2.50 (m, 6 H), 2.20–1.90 (m, 6 H), 0.16 (s, 1 H, exchanges very slowly with D_2O), −0.05 (S, 1 H, exchanges rapidly with D_2O); mass spectrum exhibits highest peak at m/e 334 ($p^+ - CH_3C_6H_4CO$).

Anal. Calcd for $C_{27}H_{23}N_3O_4$: C, 71.51; H, 5.11; N, 9.27. Found: C, 71.40; H, 4.88; N, 9.19.

2,5-Di-*p*-Tolyloxazolo[5,4-*d*]pyrimidin-7-one (18).—From 9.0 g of **13** was obtained, according to the procedure for compound **4**, 4.0 g (58%) of **17**: mp >320°: ir (Nujol) 3200, 1720, 1620 cm^{-1}; nmr (CF_3CO_2H) τ 7.43 (s), 7.37 (s), 2.60–2.30 (m), 1.96–1.68 (m) (the solution was too dilute for meaningful integration); mass spectrum m/e (rel intensty) 317 (47), 200 (52), 158.5 (7, p^{2+}), 119 (100).

Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.63; H, 4.52; N, 12.95.

Registry No.—**2**, 34905-95-8; **4**, 34905-96-9; **5**, 34905-97-0; **6**, 34905-98-1; **7**, 34905-99-2; **8**, 34906-00-8; **9**, 34906-01-9; **11**, 34906-02-0; **12**, 34906-03-1; **13**, 34906-04-2; **16**, 34906-05-3; **17**, 34906-06-4; **18**, 34906-07-5; 5-amino-4,6-dihydroxy-2-phenylpyridine, 34906-08-6.

Reaction between Tetrasulfur Tetranitride and Some Hydrocarbons[1]

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Received February 4, 1972

9,10-Dihydrophenanthrene reacts with S_4N_4, by heating or uv radiation, to give a mixture of phenanthrene and phenanthro[9,10-*c*]-1,2,5-thiadiazole (**1**) in the ratio 7.6:1. Under analogous conditions, the tetrahydronaphthalene reacts to give a mixture of 3,4-dihydronaphtho[1,2-*c*]-1,2,5-thiadiazole (**2**), naphtho[1,2-*c*]-1,2,5-thiadiazole (**3**), and naphtho[1,2-*c*:3,4-*c'*]bis-1,2,5-thiadiazole (**4**) in the ratio 20:5:1. Compound **2** also reacts with S_4N_4 to give **3** and **4** in the ratio 5:1. Compound **1**, by reaction with Grignard reagents followed by hydrolysis, is transformed into 9,10-phenanthrenedione. Analogies between the reactions of S_4N_4 with hydrocarbons and autoxidation reactions have been pointed out and a free-radical initiation mechanism has been proposed for the former.

In a previous paper[2] we have shown that sulfur nitride, S_4N_4, reacts easily with unsaturated hydrocarbons such as acetylene and ethylene, displaying strong dehydrogenating power. Moreover, ethane is practically unreactive,[2] although its reactivity is substantially improved by the presence of aryl substituents; ethylbenzene, 2-ethylnaphthalene, and 1,2-diphenylethane all react with S_4N_4 in refluxing xylene to give the corresponding 1,2,5-thiadiazole derivatives, together with elemental sulfur and ammonia.[3]

In order to obtain some preliminary information on the mechanism of the reaction between S_4N_4 and paraffins we have focused on the effects of the aryl substituents and examined the reactivity of S_4N_4 toward 9,10-dihydrophenanthrene and tetrahydronaphthalene. These reactions afforded complex mixtures of products, always containing ammonia and elemental sulfur.

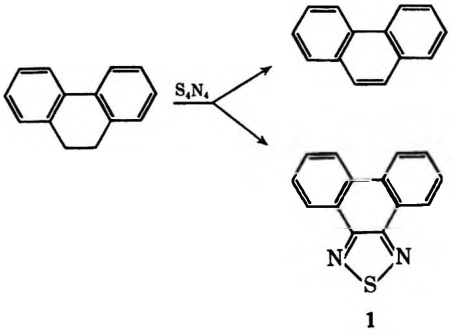
The reaction of S_4N_4 with 9,10-dihydrophenanthrene, carried out in boiling xylene, gave a mixture of phenanthrene and phenanthro[9,10-*c*]-1,2,5-thiadiazole[4,5] (**1**) in the ratio 7.6:1 (Scheme I).

The reaction between S_4N_4 and tetrahydronaphthalene at about 140°, both with and without xylene, yielded a mixture of 3,4-dihydronaphtho[1,2-*c*]-1,2,5-thiadiazole (**2**), naphtho[1,2-*c*]-1,2,5-thiadiazole (**3**), and naphtho[1,2-*c*:3,4-*c'*]bis-1,2,5-thiadiazole (**4**) in the ratio 20:5:1 (Scheme II). Dehydrogenation derivatives of tetrahydronaphthalene were not found.

Compound **3** was obtained in good yields carrying out the aromatization of **2** by heating with sulfur. It was also synthesized, for the sake of comparison, by reaction of 1,2-diaminonaphthalene with thionyl chloride according to Michaelis, *et al.*[6]

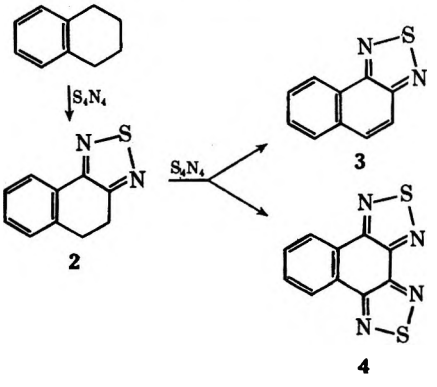
Compound **1**, on reaction with Grignard reagent followed by hydrolysis, was transformed into 9,10-phenanthrenedione in good yield. This reaction shows that the sulfur atom of **1**, analogous to the behavior of

SCHEME I



1

SCHEME II



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(2) V. Bertini and A. De Munno, *Gazz. Chim. Ital.*, **97**, 1614 (1967).

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(4) G. Tuchtenhagen and K. Rühlmann, *Justus Liebigs Ann. Chem.*, **711**, 174 (1968).

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other 1,2,5-thiadiazole derivatives,[7,8] easily undergoes attack by strong nucleophiles, consistent with the structure of the product. The assigned structures are also in full accord with the analytical, cryoscopic, and spectroscopic data (see Experimental Section).

The formation of phenanthrene in the reaction with 9,10-dihydrophenanthrene confirms the dehydrogenating character of S_4N_4, which was noted earlier in the reactions with acetylene and ethylene. However, S_4N_4 has no dehydrogenating effect on tetrahydronaphthalene, which could eliminate four hydrogen atoms to give an aromatic system. Instead the reaction between S_4N_4 and tetrahydronaphthalene involves the formation of compound **2**, which, upon further reaction with S_4N_4, is dehydrogenated to **3** or transformed into **4**. To confirm this, the reaction between S_4N_4 and compound **2** was carried out in boiling xylene; it gave a mixture of **3** and **4** in about the same ratio as the product originating from tetrahydronaphthalene.

Several observations, such as the multiplicity of products, changes of color, and the competition between the dehydrogenation and formation of 1,2,5-thiadiazole rings, are reminiscent of other reactions of the 9,10-dihydrophenanthrene and tetrahydronaphthalene which are of free-radical nature and resemble in this respect oxidation reactions.[9] Moreover, if the initiation of reaction between S_4N_4 and hydrocarbons originated with a free radical, the activating effect of aryl substituents on the ethane system could be understood on the basis of the high reactivity of the benzylic positions. This is also suggested by the observation that S_4N_4 easily gives under a variety of conditions several free-radical species which have been identified by their esr spectra.[10,11]

On this assumption the reaction of S_4N_4 with 9,10-dihydrophenanthrene and tetrahydronaphthalene was undertaken at room temperature in the presence of uv light as the source of the radical initiators. Both of these reactions took place readily and yielded a mixture of products whose composition in each case was similar to that obtained from the same reagents in the corresponding thermal reaction. These results support the suggestion that the initiator abstracts one hydrogen atom from a benzylic position, thus bringing about a sequence of reactions culminating in aromatization or cyclization.

Experimental Section

Melting points were determined with a Kofler apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 225 spectrophotometer. Ultraviolet spectra were determined with a Hilger-Watts "Uvispek" H-700 apparatus. Nmr spectra were run on a DA-60 IL Varian instrument.

Reaction of S_4N_4 with 9,10-Dihydrophenanthrene. A. Thermal.—A mixture of 6.00 g (32.56 mmol) of S_4N_4, 30 ml of xylene (mixture of the isomers), and 5.85 g (32.45 mmol) of 9,10-dihydrophenanthrene was refluxed under nitrogen with stirring. The heating was continued to the end of ammonia evolution (5–6 hr), the solvent was distilled and the residue was extracted with petroleum ether (bp 40–60°), and the extracts were chromatographed on a column of alumina (Merck Al_2O_3 according to Brockmann, 80 g; column diameter 21.5 mm, height 245 mm; eluent petroleum ether, bp 40–60°). This yielded 4.38 g (24.57 mmol) of phenanthrene and a sample of **1**, which after treatment with decolorizing carbon in benzene solution and crystallization from ligroin weighed 0.763 g (3.23 mmol): colorless needles; mp 169–170° (lit.[4] mp 167–168.5°); nmr ($CDCl_3$) δ 8.67 (m, 2, 4- and 5-H), 8.43 (m, 2, 1- and 8-H), 7.60 (m, 2, 2- and 7-H), 7.50 (m, 2, 3- and 6-H).

B. Uv Irradiation.—A homogeneous solution of 2.00 g (10.85 mmol) of S_4N_4, 250 ml of benzene, and 2.95 g (16.37 mmol) of 9,10-dihydrophenanthrene in a reactor equipped with a low-pressure mercury vapor immersion lamp was irradiated for 54 hr at room temperature under a slow stream of nitrogen. After removal of the solvent by evaporation at room temperature and reduced pressure, the residue was extracted with petroleum ether and the extracts were chromatographed on a column of alumina. After the unreacted 9,10-dihydrophenanthrene was collected, 0.124 g (0.70 mmol) of phenanthrene and 0.027 g (0.11 mmol) of **1** were isolated.

Reaction between 1 and Ethylmagnesium Bromide.—A solution of 0.113 g (0.48 mmol) of **1** in 10 ml of benzene was added dropwise to 3.5 ml (5 mmol) of a solution of ethylmagnesium bromide, prepared from 1.216 g of magnesium and 5.45 g of ethyl bromide in ether (final volume 35 ml). The mixture was refluxed for about 3 hr, hydrolyzed with iced water, acidified with HCl, and extracted with ether. The residue after removal of the solvent, as determined by tlc analysis on Merck GF_{254} silica gel (eluent benzene–acetone, 98:2), appeared to be free from compound **1**. Purification of the residue by preparative layer chromatography yielded orange crystals (0.088 g, 0.42 mmol), mp 207–208°, ir spectrum superimposable on that of an authentic sample of 9,10-phenanthrenedione.

Reaction of S_4N_4 with Tetrahydronaphthalene. A. Thermal (Molar Ratio 1:7.6).—A 6.00-g (32.56 mmol) sample of S_4N_4 in 32.55 g (246 mmol) of tetrahydronaphthalene was heated to 140–145° under a nitrogen atmosphere with continuous stirring. Copious evolution of ammonia was observed while the color of the solution changed from red to green-brown. When the evolution of ammonia ceased (11–12 hr) the excess tetrahydronaphthalene was distilled at about 20 Torr and the residue was extracted with petroleum ether. The solution, after separation of the elemental sulfur, was chromatographed on a column of alumina (Merck Al_2O_3 according to Brockmann, 85 g; column diameter 21.5 mm, height 260 mm; eluent petroleum ether, bp 40–60°). The fractions collected yielded a mixture of **3** and **2** and 0.186 g (0.76 mmol) of **4**. The compound **4**, after treatment with decolorizing carbon in benzene solution, crystallization from petroleum ether (bp 60–80°), and sublimation at 150° (0.005 Torr), yielded white needles: mp 208–209°; molecular weight by cryoscopy in benzene 246; uv max (isooctane) 239 nm (log ϵ 4.83), 264 (4.41), 290 (4.43), 295 (4.46), 300 (4.47), 308 (4.46), 315 (4.54), 322 (4.45), 330 (4.69), fine structure in the region 230–260 nm; ir (KBr) 1406, 777, 523 cm^{-1}; nmr ($CDCl_3$) δ 8.59 (dd, 2, J = 6 and 3.2 Hz, 5- and 8-H), 7.73 (dd, 2, J = 6 and 3.2 Hz, 6- and 7-H).

Anal. Calcd for $C_{10}H_4N_4S_2$: C, 49.17; H, 1.65; N, 22.93; S, 26.25. Found: C, 49.10; H, 1.89; N, 22.79; S, 26.44.

The mixture of **2** and **3** was separated by preparative layer chromatography on Merck PF_{254} silica gel (thickness 1.5 mm; eluent 35:65 benzene–petroleum ether, bp 40–60°), yielding 0.704 g (3.78 mmol) of **3** and 2.810 g (14.93 mmol) of **2**. The ir spectrum of **3** (mp after crystallization from methanol 80–81°) appeared to duplicate that of an authentic sample.[6,12] Compound **2**, on crystallization from methanol and sublimation at room temperature (0.1 Torr), gave white crystals: mp 29–30°; molecular weight by cryoscopy in benzene 185; uv max 226 nm (log ϵ 3.94), 287 (4.11), 304 (4.26); ir (liquid film) 1409, 787, 533 cm^{-1}; nmr (CCl_4) δ 7.91 (m, 1, 8-ArH), 7.16 (m, 3, 5-, 6-, and 7-ArH), 3.07 (s, 4, two CH_2).

Anal. Calcd for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; N, 14.88; S, 17.03. Found: C, 63.66; H, 4.47; N, 15.10; S, 16.87.

B. Thermal (Molar Ratio 1:1).—A mixture consisting of 6.00 g (32.56 mmol) of S_4N_4, 24 ml of xylene (mixture of the isomers), and 4.36 g (32.98 mmol) of tetrahydronaphthalene was refluxed under a nitrogen atmosphere with continuous stirring until the end of ammonia evolution. The solvent was then

(7) V. Bertini, A. De Munno, and P. Pino, *Chim. Ind. (Milan)*, **49**, 1384 (1967).

(8) V. Bertini, X Congresso Nazionale della Società Chimica Italiana, XIII-58, Padova, June 1968.

(9) C. E. Frank, *Chem. Rev.*, **46**, 155 (1950).

(10) D. Chapman and A. G. Massey, *Trans. Faraday Soc.*, **58**, 1291 (1962).

(11) D. A. C. McNeil, M. Murray, and M. C. R. Symons, *J. Chem. Soc. A*, 1019 (1967).

(12) H. Beecken, *Chem. Ber.*, **100**, 2164 (1967).

distilled and the residue was chromatographed as described for the preparation above, yielding 0.110 g (0.45 mmol) of **4**, 0.417 g (2.24 mmol) of **3**, and 1.796 g (9.54 mmol) of **2**.

C. Uv Irradiation.—A homogeneous solution of 1.35 g (7.33 mmol) of S_4N_4, 200 ml of benzene, and 4.15 g (31.39 mmol) of tetrahydronaphthalene was irradiated for 206 hr at room temperature. After removal of the solvent under vacuum at room temperature, the residue was chromatographed. In addition to the unreacted tetrahydronaphthalene, 0.256 g (1.36 mmol) of **2** and 0.067 g (0.36 mmol) of **3** were obtained. Compound **4** was recovered in traces and identified by tlc analysis.

Reaction of S_4N_4 with 2.—A 0.748-g (3.97 mmol) sample of **2** in 20 ml of xylene was treated with 1.10 g (5.97 mmol) of S_4N_4 and the mixture was refluxed for about 8 hr under nitrogen atmosphere with stirring. After removal of the solvent by distillation at 20 Torr, the residue was chromatographed, yielding 0.059 g (0.24 mmol) of **4**, 0.229 g (1.23 mmol) of **3**, and 0.469 g (2.49 mmol) of **2**.

Reaction of 2 with Sulfur.—A mixture of 0.109 g (0.58 mmol) of **2** and 0.022 g (0.69 mmol) of sulfur was heated at 250–270° for 2.5 hr. After cooling the residue gave after crystallization from methanol 0.078 g (0.42 mmol) of **3**.

Registry No.—**1**, 1143-73-3; **2**, 34910-55-9; **3**, 233-68-1; **4**, 34910-56-0; **5**, 28950-34-7; 9,10-dihydrophenanthrene, 776-35-2; tetrahydronaphthalene, 119-64-2.

Acknowledgment.—This work was supported by C. N. R., Roma, Italy.

New Precursors for Arylcarbenes. Photocycloelimination Reactions of Cyclic Sulfites[1,2]

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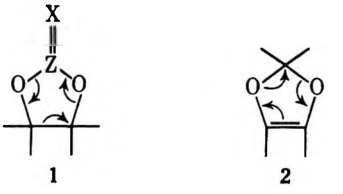
Received June 28, 1971

Cyclic arylpinacol sulfites are found to undergo [5 → 2 + 2 + 1] photocycloeliminations to give arylcarbenes in addition to other products. The sulfites studied include benzopinacol sulfite, fluorenopinacol sulfite, *meso*- and *dl*-hydrobenzoin sulfites, and methyl-substituted hydrobenzoin sulfites. With the exception of fluorenopinacol sulfite all fragment to give carbenes and have synthetic utility. Arylcarbenes formed by photolysis of these substrates when generated in methanol give methyl ethers and the transient obtained by photolysis of *meso*- and *dl*-hydrobenzoin sulfites is shown to be virtually identical in properties with that obtained from conventional precursors such as *trans*-2,3-diphenyloxirane and phenyldiazomethane; *i.e.*, the secondary to primary insertion selectivity in pentane and the high stereoselectivity of addition to *cis*-2-butene are the same for phenylcarbene generated from the hydrobenzoin sulfites, 2,3-diphenyloxirane and phenyldiazomethane. The observed lack of dependence of chemical behavior on precursor structure suggests that free phenylcarbene is involved in each case. [5 → 3 + 2] cycloelimination to sulfur trioxide and substituted stilbenes appears to be a competitive process. Under the reaction conditions the stilbenes undergo a secondary reaction, namely cyclization to phenanthrenes. In addition, 1,2-aryl migrations, preceded or accompanied by loss of sulfur dioxide, also compete with cycloelimination. The rearrangements are shown to occur with retention of the substitution patterns on the aryl groups. Thermal reactions of the cyclic sulfites have also been studied and a comparison of the sulfite photo- and thermochemistry made. Possible mechanisms are discussed.

An increasing number of photocycloelimination reactions leading to carbenes have appeared in the literature and these reactions have been surveyed recently.[4] Their thermal counterparts are also the subject of a recent review.[5] In continuing efforts to broaden the scope and synthetic utility of photocycloelimination reactions for the preparation of arylcarbenes, several precursors of the type shown in the general structures **1** and **2** have been investigated.[2,6,7] Substrates of the type **1** were selected for evaluation in cycloelimination studies because of their ready accessibility from the corresponding diols, which themselves may be prepared under reductive conditions. Consequently, such reagents would complement the existing oxirane



1 **2**

carbene precursors which in general are formed oxidatively.[8]

In previous investigations we have established that many vicinal diaryl-substituted heterocyclic systems undergo photocycloelimination to give arylcarbenes.[6,7,8] *A priori*, one might expect that systems such as **1** and **2** undergo cycloelimination reactions in the [5 → 2 + 2 + 1] and [5 → 4 + 1] modes, respectively, and indeed members of these classes behave as anticipated.[9]

For example, *trans*-4,5-diphenyl-4,5-dicyano-1,3,2-dioxa-P^V-phospholane (**3**), a system structurally related to **1**, undergoes [5 → 2 + 2 + 1] cycloelimination as

(1) We gratefully acknowledge financial support of this research from the National Science Foundation (Grants GP 9434 and GP 28171) and The Petroleum Research Fund (Grant PRF 5471).

(2) For preliminary communications on this and related work see (a) R. L. Smith, A. Manmade, and G. W. Griffin, *J. Heterocycl. Chem.*, **6**, 443 (1969); (b) R. L. Smith, A. Manmade, and G. W. Griffin, *Tetrahedron Lett.*, 663 (1970).

(3) Abstracted in part from the Ph.D. Dissertation of A. Manmade, Louisiana State University in New Orleans, 1971.

(4) G. W. Griffin, *Angew. Chem.*, **83**, 604 (1971); *Angew. Chem., Int. Ed. Engl.*, **10**, 537 (1971).

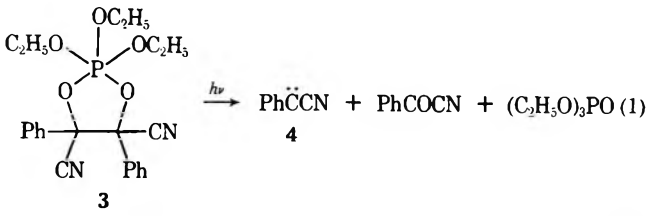
(5) R. W. Hoffmann, *Angew. Chem.*, **83**, 595 (1971); *Angew. Chem., Int. Ed. Engl.*, **10**, 529 (1971).

(6) P. Petrellis and G. W. Griffin, *Chem. Commun.*, 1099 (1968).

(7) R. M. G. Nair, E. Meyer, and G. W. Griffin, *Angew. Chem.*, **80**, 442 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 462 (1968).

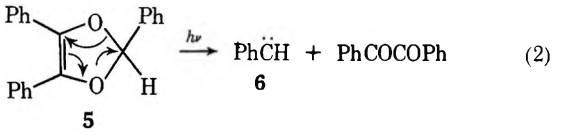
(8) For the latest papers in the oxirane series see (a) R. S. Becker, R. O. Bost, J. Kolc, N. R. Bertoniere, R. L. Smith, and G. W. Griffin, *J. Amer. Chem. Soc.*, **92**, 1302 (1970); (b) N. R. Bertoniere, S. P. Rowland, and G. W. Griffin, *J. Org. Chem.*, **36**, 2956 (1971).

(9) We shall employ the convention suggested by R. Huisgen [*Angew. Chem.*, **80**, 329 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 321 (1968)] in which cycloadditions and cycloeliminations are classified on the basis of the size of the ring formed or destroyed and the number of ring members contributed to each fragment.

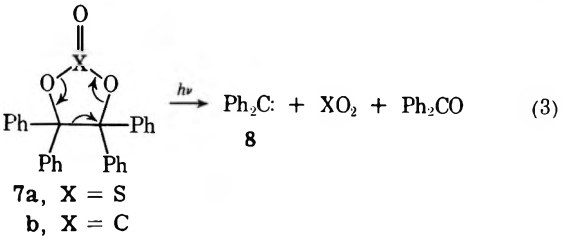


indicated in eq 1 to give phenylcyanocarbene (**4**), benzoyl cyanide, and triethyl phosphate.[6]

In the case of substrates such as **2** the carbene is extruded with formation of a diketone, as exemplified by the photoconversion of 2,4,5-triphenyl-1,3-dioxole (**5**) to phenylcarbene (**6**) and benzil (eq 2).[7] For convenience the cycloelimination reactions are formulated mechanistically in a concerted fashion, although intermediates have not been excluded and in fact may be involved in several cases.[4,8]



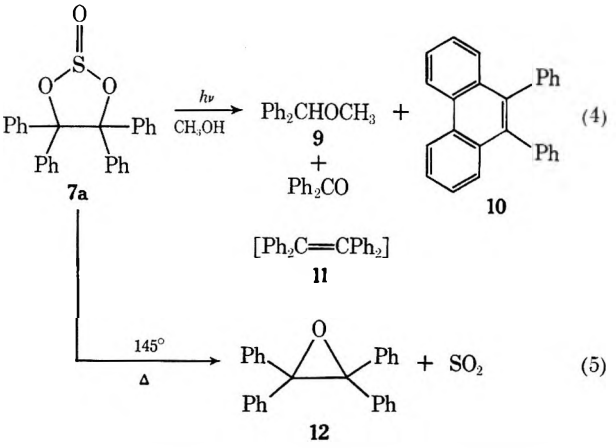
On the basis of the reactions cited above and related examples,[7,10] it was felt that suitably substituted cyclic sulfites such as **7a** or carbonates **7b** also should undergo [5 → 2 + 2 + 1] photocycloeliminations to give arylcarbenes such as **8** as depicted in eq 3. While this paper is restricted to a discussion of the photochemistry of sulfites related to **7a**, the photolytic behavior of carbonates such as **7b** also has been investigated extensively[2] and will be the subject of a future full communication.



Results and Discussion

Benzopinacol sulfite (**7a**), a cyclic sulfite incorporating the desired structural prerequisites, was selected as a substrate for our preliminary photocycloelimination studies in this area since the anticipated carbene, diphenylcarbene (**8**), has been studied extensively both chemically[11] and spectroscopically.[12,13a] Kirmse, Hörner, and coworkers[11] have established that diphenylcarbene obtained photolytically from diphenyldiazomethane is nucleophilic in character and is readily protonated in alcohols to give the benzhydryl carbonium ion, which subsequently solvolyzes to give benzhydryl ethers. Consequently, for this as in previous studies,[2,6,7] methanol was selected as a solvent trapping agent in initial screening studies of potential carbene precursors.

Benzopinacol sulfite (**7a**) is conveniently synthesized by a modification of the procedure employed for hydrobenzoin sulfites described by Thompson and coworkers[14] consisting of addition of thionyl chloride in methylene chloride to a solution of benzopinacol and pyridine in methylene chloride. Upon irradiation (254 nm) in methanol, benzopinacol sulfite (**7a**) does undergo photocycloelimination to produce diphenylcarbene (**8**), as evidenced by the formation of benzhydrylmethyl ether (**9**) (40%). Other compounds identifiable among the reaction products after separation by thick layer chromatography included benzophenone (15%) and 9,10-diphenylphenanthrene (**10**) (10%) (eq 4).



Tetraphenylethylene (**11**) is known to undergo dehydrophotocyclization to 9,10-diphenylphenanthrene (**10**), a result which suggests that the phenanthrene **10** may in fact be a secondary photoproduct arising from **11**.[15] The formation of **11** from **7a** requires [5 → 3 + 2] cycloelimination with extrusion of sulfur trioxide, since dimerization of diphenylcarbene (**8**) to **11** is a process not generally observed in solution at ambient temperatures.[16] That sulfur dioxide is formed upon photolysis of **7a** was confirmed by infrared and mass spectroscopic examination of an aliquot of the effluent gas. It is noteworthy that tetraphenyloxirane (**12**) could not be detected by thin layer chromatography among the photoproducts of **7a** even at low conversions. Consequently, prior oxirane formation and subsequent fragmentation appears an unlikely primary source of **8**, at least at ambient temperature, since the relative extinction coefficients for **7a** and **12** are such that a steady state concentration of **12** sufficient for detection would be required for competitive cycloelimination.

In contrast to the photochemical behavior, benzopinacol sulfite (**7a**) does give tetraphenyloxirane (**12**) upon thermolysis at 145° in essentially quantitative yield (eq 5), and no rearrangement products which might have been anticipated on the basis of the photochemistry of related sulfite substrates (*vide infra*) were detected. The theoretical implications of these contrasting photo- and thermochemical results are presently under study.

Fluorenopinacol sulfite (**13**), which is structurally re-

(10) C. Bischoff and H. Brandtstaedter, *Monatsber. Deut. Akad. Wiss. Berlin*, **8**, 888 (1966); *Chem. Abstr.*, **68**, 68222*h* (1968).

(11) W. Kirmse, L. Hörner, and H. Hoffmann, *Justus Liebigs Ann. Chem.*, **614**, 19 (1958); W. Kirmse, *ibid.*, **666**, 9 (1963).

(12) R. S. Becker, J. Kole, R. O. Bost, H. Dietrich, P. Petrellis, and G. W. Griffin, *J. Amer. Chem. Soc.*, **90**, 3292 (1968).

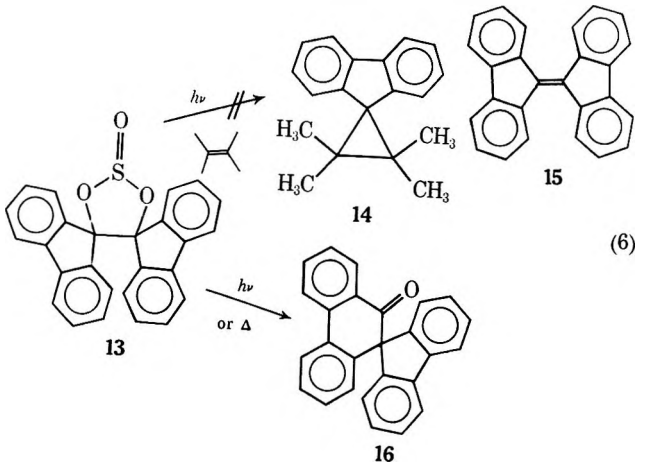
(13) (a) E. Wasserman, A. M. Trozzolo, W. A. Yager, and R. W. Murray, *J. Chem. Phys.*, **40**, 2408 (1964); (b) H. Kristinsson and G. W. Griffin, *J. Amer. Chem. Soc.*, **88**, 1579 (1966).

(14) Q. E. Thompson, M. M. Crutchfield, and M. W. Dietrich, *J. Org. Chem.*, **30**, 2696 (1965).

(15) M. V. Sargent and C. J. Timmons, *J. Chem. Soc.*, 5545 (1964).

(16) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 83.

lated to **7a**, was examined as a potential source of fluorenylidene, a species for which a limited number of shelf-stable precursors exist.[17] Substantial difficulty was encountered in the preparation of the corresponding bisfluorenylidene oxide,[18] which by analogy with other oxiranes should undergo [3 → 2 + 1] cycloelimination to fluorenylidene and fluorenone. In contrast the sulfite **13** was readily synthesized from fluorenopinacol in a manner similar to that described above for **7a**, and found to be stable when stored in a dark bottle at 5°. Upon irradiation (350 nm) in 2,3-dimethyl-2-butene, **13** undergoes photofragmentation to give sulfur dioxide; however, efforts to detect any of the anticipated 2,2,3,-3-tetramethylspiro[cyclopropane-1,9′-fluorene] (**14**) have proved unrewarding. Furthermore, the photostable, bright red bisfluorenylidene (**15**), a potential



(6)

[5 → 3 + 2] cycloelimination fragment, was conspicuously absent among the photoproducts.

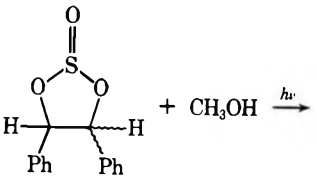
The principal photoproduct obtained from **13** is 9-diphenylenephenanthrone (**16**) formed by 1,2-aryl migration accompanied or preceded by elimination of sulfur dioxide. Furthermore, the spiro ketone **16** is the primary thermolysis product obtained from **13** at 145° and also has been obtained by both photolysis and thermolysis of the corresponding phosphorane.[6,19]

It is evident from the results cited above that the sulfites **7a** and **13** differ markedly in their respective modes of photofragmentation despite their structural similarities. In the case of **7a** cycloelimination is observed to give primarily diphenylcarbene (**8**). Formation of sulfur trioxide and 9,10-diphenylphenanthrene appears to be a competing reaction of secondary importance. In contrast, rearrangement to the spiro ketone **16** is the only significant photoreaction observed with **13** under the reaction conditions employed. In addition, a marked difference in their thermal behavior is also apparent; while similar thermolysis and photolysis products are obtained from **13**, such is not the case with **7a**. The reasons for these differences in behavior remain to be established.

In an attempt to characterize chemically carbenes produced as a result of photocycloelimination reactions of sulfites and to compare and contrast the properties of these species with those generated from other sources, a study of the hydrobenzoin sulfites (**17** and **18**, respectively) was initiated.[20] With these substrates it was also possible to investigate the effect of sulfite stereochemistry on the cycloelimination process by comparing the diastereomeric *meso*- and *dl*-pinacol sulfites (**17** and **18**, respectively).

The sulfites **17** and **18** were prepared by treatment of the corresponding hydrobenzoins with thionyl chloride according to the procedure given by Thompson, *et al.*[14] These investigators noted that geometrical isomerism is possible in the case of **17** as a result of the tetrahedral geometry assumed by the sulfur atom in the system. Two forms differing in the orientation of the exocyclic oxygen atom are isolable at 25°. The major and minor isomers are distinguishable by pmr spectroscopy and for convenience the major isomer has been used in these studies; however, photoequilibration of the isomeric sulfites **17** prior to cycloelimination has not been excluded.

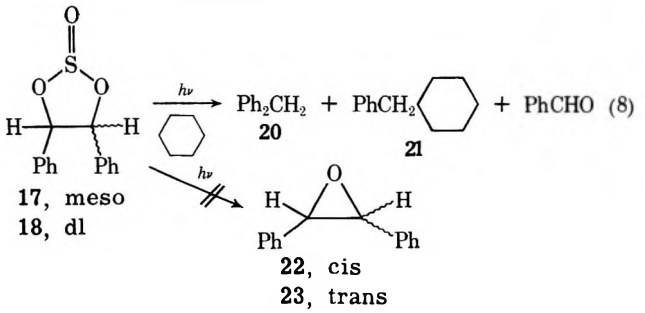
Preliminary chemical proof that phenylcarbene (**6**) is formed in the photocycloelimination reactions of the sulfites **17** and **18** was obtained by irradiating (254 nm) these substrates in methanol. As expected, benzylmethyl ether (**19**), sulfur dioxide, and benzaldehyde as well as diphenylmethane (**20**) are obtained from the photolysis mixtures of **17** and **18** (eq 7). Benzaldehyde



$$\underset{\textbf{19}}{PhCH_2OCH_3} + SO_2 + \underset{\textbf{20}}{Ph_2CH_2} + PhCHO \quad (7)$$

and diphenylmethane (**20**) were separated by preparative gas chromatography and their identity was established by comparison with authentic samples.

Irradiation (254 nm) of **17** or **18** in cyclohexane gave, as anticipated, the insertion product benzylcyclohexane (**21**) in high yield in addition to sulfur dioxide, benzaldehyde, and diphenylmethane (**20**) (eq 8). While the



mechanism of formation of **20** will be discussed later, it is significant that under the reaction conditions investigated no oxiranes are detected, *i.e.*, *cis*-2,3-diphenyloxirane (**22**) in the case of **17** or *trans*-2,3-diphenyloxirane (**23**) in the case of **18**, when the photoreactions were monitored using pmr and thin layer chromatographic techniques. Furthermore, the absence of detectable amounts of stilbene and its dehydrophotocy-

(17) Reference 16, p 87.
(18) E. Bergmann and J. Hervey, *Chem. Ber.*, **62**, 893 (1929).
(19) F. Ramirez and C. P. Smith, *Chem. Commun.*, 662 (1967).
(20) H. Dietrich, G. W. Griffin, and R. C. Petterson, *Tetrahedron Lett.*, 153 (1968).

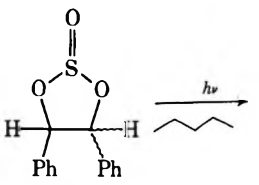
clization product phenanthrene among the reaction products indicates that [5 → 3 + 2] photocycloelimination does not occur to a significant extent with either **17** or **18**. This is in contrast to the behavior exhibited by **7a**, where formation of sulfur trioxide and 9,10-diphenylphenanthrene (**10**) competes with cycloelimination to give the carbene **8**. It is noteworthy that in this respect **17** and **18** behave in a manner similar to fluorenopinacol sulfite (**13**). Unlike **13**, however, the sulfites **17** and **18** were found to be photostable when irradiated in Pyrex vessels at 350 nm and could be recovered quantitatively in each case.

Although it is apparent from the chemical data that both **17** and **18** undergo [5 → 2 + 2 + 1] cycloeliminations to produce "free" carbene, the characteristic phenylcarbene epr signal could not be observed upon photolysis of these substrates for reasons yet undetermined.[21] Similar results were observed for 2,3-diphenyloxirane (**23**) and triphenyloxirane where no epr signal was detected for phenylcarbene (**6**) despite convincing chemical evidence to the contrary for its formation.[20,21] In the absence of direct epr and/or optical spectroscopic data, it was necessary to obtain further chemical proof for the contention that **17** and **18** are indeed phenylcarbene precursors.

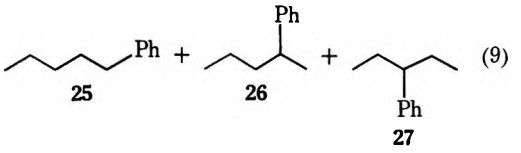
Competitive insertion experiments prove particularly useful as a method for comparing divalent carbon species generated from different sources such as **17** and **18**.[20,22] Gutsche and coworkers[22] have previously determined the insertion selectivity of phenylcarbene (**6**) generated from phenyldiazomethane (**24**). Additional data on the selectivity of **6** formed from the oxiranes **22** and **23** and the diazo compound **24** were reported by Griffin and coworkers.[20] A similar study was initiated of the insertion selectivity of **6** generated from the sulfites **17** and **18** and the conventional precursors **23** and **24** into primary and secondary C–H bonds of pentane.

Equimolar solutions of the compounds under study were made in *n*-pentane and photolyzed (254 nm) simultaneously under identical conditions using the "merry-go-round" technique in order to ensure uniform exposure. Insertion product ratios were determined gas chromatographically employing *n*-amylbenzene as an internal standard. Absolute yields were obtained by determination of the gas chromatographic response factors utilizing authentic mixtures of known concentration of the internal standard and reaction products. To ensure that the results obtained reflect initial insertion rates, relatively short irradiation times (25 min) were employed and the number of lamps in the light source was adjusted from 16 to 8 to reduce the light flux to a desired level.

In a typical case the three insertion products **25**, **26**, and **27** were obtained from *dl*-hydrobenzoin sulfite (**18**) (eq 9) and the relative ratios of these products were found to be 1.00:5.95:2.10, respectively. The ratio of the combined amounts of 2- and 3-benzylpentanes (**26** and **27**, respectively, formed by insertion into the six secondary C–H bonds) to 1-phenylhexane (**25**) (produced by attack at the six primary C–H bonds) was established from several determinations as 8.00 ± 0.16



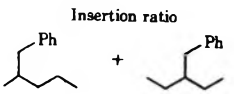
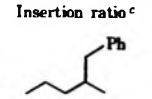
17 or **18**



25 **26** **27** (9)

(see Table I). The ratio of 2- to 3-benzylpentanes correspondingly is 2.90 ± 0.04, which when statistically corrected gives a selectivity factor for C_2 H or C_4H over C_3 H (all secondary) of 1.45 ± 0.05.

TABLE I
C–H INSERTION SELECTIVITY OF PHENYLCARBENE

Phenylcarbene precursor	Yields, % (254 nm, 8 lamps, 25 min)	Insertion ratio 	Insertion ratio[c] 
17	5.5	8.48 ± 0.24[a]	1.41 ± 0.05[a]
18	6.6	8.00 ± 0.18	1.45 ± 0.02
23	45.5	8.33 ± 0.14	1.35 ± 0.04
24	31.5	7.14 ± 0.14	1.31 ± 0.09
	18.3[b]	8.38 ± 0.19	1.33 ± 0.09

[a] Limits of error in all cases are standard deviations obtained on multiple integrations of several chromatograms. [b] 350 nm; 16 lamps; 4 hr. [c] Relative ratios corrected for number of hydrogens.

The results obtained in all cases substantiate the original proposal that the photolysis of cyclic sulfites may in fact give rise to species virtually indistinguishable chemically from those produced from conventional carbene precursors such as *trans*-2,3-diphenyloxirane (**23**) and phenyldiazomethane (**24**). Higher yields are obtained with the oxirane **23** and the diazo precursor **24** (Table I), which indicates that the rate of fragmentation of **23** (and **22**) exceeds that of **17** and **18**. It remains to be determined if the quantum yield is higher for the former pair or if the difference in rate is only a reflection of their higher extinction coefficients (Table II). The sulfites presently under examination do, of course, afford significantly higher yields of insertion products upon prolonged irradiation and are of preparative value; however, preservation of the initial selectivity factors was, of course, of paramount importance in the present study.

The stereochemistry of the cyclic sulfite precursors **17** and **18** exerts little or no influence upon the observed insertion selectivity factors, although the initial fragmentation rates for the *dl* isomer **18** may be slightly higher. This is not unexpected in view of the higher extinction coefficients observed for this diastereomer (Table II). The extinction coefficients differ significantly at 264 nm and studies are in progress to establish whether at this wavelength precise measurement of relative cycloelimination rates is feasible. Analysis of the reaction mixture at low conversions (10%) where

(21) We wish to thank Dr. Trozzolo and coworkers for their attempts to obtain the desired epr spectra.

(22) C. D. Gutsche, G. L. Bachman, and R. S. Coffey, *Tetrahedron*, **18**, 617 (1962).

TABLE II
ULTRAVIOLET SPECTRAL DATA FOR CYCLIC SULFITES

Sulfite	λ_{max}, nm[a]	ϵ
Benzopinacol (**7a**)	266	968
	261	1,031
	254	906
Fluorenopinacol (**13**)	288	14,700
	278	17,700
	269	16,100
	239	59,000
	232	56,400
meso-Hydrobenzoin (**17**)	268 sh	225
	264	398
	258	474
	252	396
dl-Hydrobenzoin (**18**)	269	292
	263	470
	257	502
	252	373
meso-4,4′-Dimethylhydrobenzoin (**36**)	273	322
	268	407
	263	576
	257	485
meso-2,2′-Dimethylhydrobenzoin (**37**)	273	687
	266	786
	260	620
meso-α,α'-Dimethylhydrobenzoin (**40**)	264	396
	258	504
	252	420
dl-α,α'-Dimethylhydrobenzoin (**41**)	263	388
	257	477
	252	366

[a] Determined in 90% ethanol.

shielding of the alternate isomer, if formed, should be relatively effective shows that within the limits of detectability (pmr and tlc) interconversion of the two diastereoisomers **17** and **18** does not occur. The presence of oxygen has no apparent effect on the selectivity factors exhibited by the carbenes generated photolytically from **17** and **18**. Neither *cis*- nor *trans*-2,3-diphenyloxirane (**22** nor **23**, respectively) could be detected among the reaction products by tlc. These results suggest that a stepwise mechanism involving the oxirane as an intermediate in the photolysis is improbable here as in the case of **7a**.

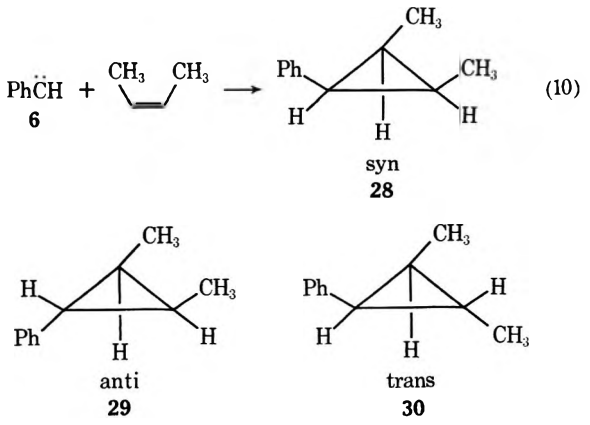
It is evident from the data presented in Table I that species showing similar discriminatory behavior are involved in the insertion reactions of **17**, **18**, **22**, and **23**. The lack of dependence of the insertion ratios on the prior history of the carbene may be interpreted in at least two ways: (a) the reaction is insensitive to energetic factors, *i.e.*, requires no activation energy which is unlikely, and/or (b) regardless of source, the carbenes formed are isoenergetic. Intuitively it is unreasonable that *nascent* phenylcarbene generated from such dissimilar precursors as oxiranes, sulfites, and diazo compounds should be isoenergetic, but perhaps thermal equilibration to a common vibrational level of the same state may be occurring prior to insertion. It is also interesting that the reactivity of the carbene from phenyldiazomethane (**24**) is affected by the nature of the radiation source as seen in Table I. Phenylcarbene (**6**) generated from **24** using a 254-nm source exhibits lower selectivity than that produced at a longer incident wavelength (>300 nm). Further speculation on the origin of these effects is unwarranted at this time in the absence of additional data, although it is noteworthy in this connection that the proportion of ground triplet state methylene produced in the primary photolysis of diazomethane is independent of wavelength at least over the range from 366 to 436 nm.[23]

Extensive effort has been devoted to characterizing the multiplicity of the reactive state(s) of phenylcarbene (**6**). A triplet ground state has been assigned to **6** on the basis of epr[13] and optical[8a] matrix isolation techniques. Calculations of the extended Hückel type support these experimental observations;[24] however, it is generally accepted that C–H insertion reactions of phenylcarbene involve a direct single step mechanism requiring the singlet state which reacts with the substrate more rapidly than interconversion occurs to the triplet ground state.[25,26] Furthermore, it is widely conceded that the stereochemistry of addition of phenylcarbene generated from a wide variety of precursors[20,23,27] is more easily rationalized on the basis of a singlet rather than a triplet mechanism; *i.e.*, when phenylcarbene reacts with an unsymmetrically substituted alkene such as 2-butene the stereochemical integrity of the alkene is maintained and high stereoselectivity (>95%) is observed.[22,27] Such results can only be accommodated by a triplet mechanism if the intermediate trimethylene diradical demanded by spin considerations undergoes cyclization at a rate sufficiently fast to preclude extensive rotamer equilibration; *i.e.*, the spin-imposed barrier to bond formation in the triplet state is surmounted by rapid intersystem crossing to the triplet state. In a recent reexamination of the phenylcarbene–2-butene reactions Moss and Dolling have demonstrated that less specific cyclopropanation occurs and increased abstraction recombination processes intervene when photolyses are conducted in frozen *cis*-butene matrices.[28] Although other explanations also are advanced it is inviting to accept their proposal that initially singlet carbene is formed but restricted in the matrix decays to the triplet ground state at a rate which is at least comparable with stereospecific addition to the matrix.

Since measurement of the discrimination exhibited by phenylcarbene (**6**) in the possible modes of addition to *cis*-2-butene (eq 10) has been widely employed as a sensitive method of comparing the properties of this species when generated from different sources, we have extended these studies to the cyclic sulfite substrates **17** and **18**.

Irradiations of equimolar amounts of **17**, **18**, **23**, and **24** were conducted in quartz Griffin–Worden pressure vessels[29] in *cis*-2-butene at 254 nm. The photolysis mixtures were analyzed by glc and the isomeric cyclopropanes **28**, **29**, and **30** were identified by comparison with authentic samples obtained by similar preparative scale photolysis. The identities of these cyclopropanes previously had been established by examination of the

(23) G. W. Taylor and J. W. Simons, *Can. J. Chem.*, **48**, 1016 (1970).
(24) R. Hoffmann, G. D. Zeiss, and G. W. VanDine, *J. Amer. Chem. Soc.*, **90**, 1485 (1968).
(25) W. v. E. Doering and L. H. Knox, *J. Amer. Chem. Soc.*, **83**, 1989 (1961).
(26) P. S. Skell and R. C. Woodworth, *ibid.*, **78**, 4496 (1956).
(27) (a) G. L. Closs, R. A. Moss, and J. J. Coyle, *J. Amer. Chem. Soc*, **84**, 4985 (1962); (b) G. L. Closs and R. A. Moss, *ibid.*, **86**, 4042 (1964).
(28) R. A. Moss and U.-H. Dolling, *ibid.*, **93**, 954 (1971).
(29) Kontes of Illinois, Evanston, Ill.; Worden Quartz Products, Inc., Houston, Tex.



(10)

pmr chemical shifts of the methyl protons and thus were readily identified from literature data.[27] The reactions were conducted using shorter irradiation times than those employed in the pentane insertion studies (*vide supra*) in order to preclude photoisomerization of the photolabile cyclopropanes subsequent to addition.[30-33] The reactions are highly stereoselective in each case (>95%) and from results of the comparative studies delineated in Table III it is clear that the

TABLE III

STEREOSELECTIVITY OF ADDITION OF PHENYLCARBENE FROM DIVERSE SOURCES TO *cis*-2-BUTENE

Phenylcarbene precursor	Syn:anti ratio[a]
17	1.17 ± 0.01
18	1.16 ± 0.01
23	1.19 ± 0.01
24	1.17 ± 0.01

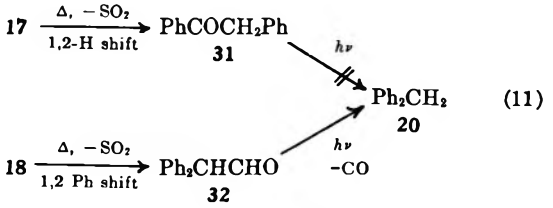
[a] Limits of error in all cases are standard deviations based on multiple integrations of several gas chromatograms.

stereochemistry of addition (syn/anti ratio) is essentially invariant regardless of source and in agreement with results previously reported by Closs and Moss.[27] In light of these factors and the comparative C–H insertion data (*vide supra*) little doubt remains that a common intermediate is involved which we believe is "free" phenylcarbene on the basis of the independence of chemical behavior on precursor structure. It must be assumed that phenylcarbene (6) is formed in the singlet state and adds to *cis*-2-butene faster than intersystem crossing to the triplet ground state can occur. However, it appears that a small amount of competitive intersystem crossing to triplet phenylcarbene must be occurring, since 2–5% of *trans*-2,3-dimethyl-1-phenylcyclopropane (30) has been observed in all cases studied. It is believed that this is a primary product of addition and not the result of subsequent product isomerization, since the major primary products, cyclopropanes 28 and 29, were found to be stable to the reaction conditions provided irradiation times are not prolonged (>9 min).

The observed predominance of the least stable syn isomer 28 in each case was first reported by Closs and coworkers[26] and confirmed by Griffin and Kristinsson.[31] A mechanistic interpretation of this phenomenon was advanced previously by Closs and coworkers.[27] It is proposed that a favorable transition state develops for syn addition in which the polarizable aryl electrons interact by London dispersion forces with the cis olefinic alkyl substituents.

The thermal behavior of the hydrobenzoin sulfites parallels that observed for fluorenopinacol sulfite (13) rather than benzopinacol sulfite. Price and Berti[34a] observed that 17 and 18 upon thermolysis at 240° do not form the corresponding oxiranes 22 and 23, but undergo conversion to deoxybenzoin (31) and diphenylacetaldehyde (32), respectively, in excellent yields. Similar results have recently been reported by Coxon and coworkers[34b] and confirmed in our laboratories. Bridged zwitterionic Ar_i-3[35] mechanisms leading to enol sulfite intermediates are proposed to rationalize these conversions. The enol sulfites may then undergo concerted or stepwise collapse to the observed products.

The isolation of the common photoproduct diphenylmethane (20) from the hydrobenzoin sulfites 17 and 18 also must be rationalized. In light of the thermochemistry of 17 and 18 it appeared likely that either 31 and/or 32 might be reasonable precursors for 20. In inde-



(11)

pendent experiments it was demonstrated that diphenylacetaldehyde (32) (a product of 1,2-phenyl migration) does undergo photodecarbonylation under the reaction conditions to give diphenylmethane (20).[8a,36] The formation of 32 from the sulfites 17 and 18 in a primary photochemical step is not unexpected in light of the previously reported analogous interconversion of fluorenopinacol sulfite (13) to the spiro ketone 16, which also requires 1,2-phenyl migration. Deoxybenzoin (31) (a product of 1,2-H migration) in contrast is not converted to 20, but as previously reported photolyzes to give mainly benzaldehyde and 1,2-diphenylethane.[37] Therefore 31 may be excluded as a source of 20 in the photofragmentation of 17 and 18. This is also supported by the fact that we were unable to detect more than trace amounts of 31 by capillary gas chromatographic analysis of the irradiation mixtures of 17 and 18. Our inability to detect substantial quantities of 32 is attributed to the extreme photolability of this aldehyde.

1,2-Phenyl migration is a process which is not without precedent in excited-state chemistry. For example, we have shown that 1,1,3,3-tetraphenylpropene is transformed into 1,1,2,3-tetraphenylcyclopropane, the product of photocyclization accompanied by phenyl mi-

(30) H. Kristinsson and G. W. Griffin, *J. Amer. Chem. Soc.*, **88**, 378 (1966).

(31) H. Kristinsson and G. W. Griffin, *Tetrahedron Lett.*, 3259 (1966).

(32) P. H. Mazzocchi, R. S. Lustig, and G. W. Craig, *J. Amer. Chem. Soc.*, **92**, 2169 (1970); G. W. Griffin and E. Waldau, unpublished results.

(33) E. W. Yankee and D. J. Cram, *J. Amer. Chem. Soc.*, **92**, 6328 (1970), and references cited therein.

(34) (a) C. C. Price and G. Berti, *ibid.*, **76**, 1211 (1954); (b) J. M. Coxon, M. P. Hartshorn, G. R. Little, and S. G. Maister, *Chem. Commun.*, 271 (1971).

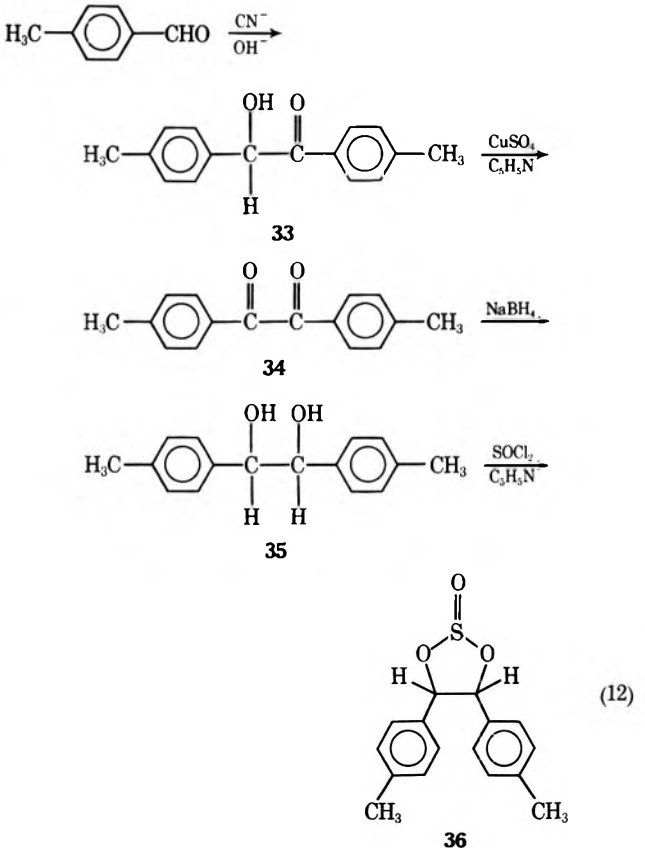
(35) R. Heck and S. Winstein, *J. Amer. Chem. Soc.*, **79**, 3105 (1957).

(36) M. Elam, P. Petrellis, H. Kristinsson, and G. W. Griffin, unpublished results.

(37) A. Schönberg, "Preparative Organic Photochemistry," Springer-Verlag, New York, N. Y., 1968, p 216.

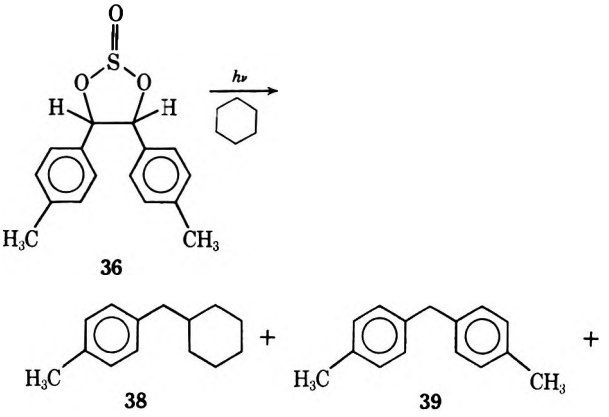
gration to the exclusion of H migration.[38] Preferential phenyl migration also occurs in the photocyclization of 1,1,3-triphenyl-3-methoxypropene to 1,1,2-triphenyl-3-methoxycyclopropane.[39] Other examples of predominance of phenyl over alkyl migration also are known.[40] While photochemical examples of 1,2-hydrogen migration have been reported, such processes are relatively inefficient.[38,41]

In order to determine the nature of the transition state in the photoinduced phenyl migrations observed with **17** and **18**, *meso*-4,4′-dimethylhydrobenzoin sulfite (**36**) and *meso*-2,2′-dimethylhydrobenzoin sulfite (**37**) were synthesized from the respective pinacols and photolyzed. The synthesis of the pinacol **35** was achieved by reduction of *p,p′*-bitolil (**34**) with sodium borohydride. The bitolil **34**, in turn, was obtained by oxidation of the corresponding benzoin **33** prepared from *p*-tolualdehyde, with copper sulfate and pyridine utilizing the method of Clarke and Dreger.[42] *meso*-4,4′-Dimethylhydrobenzoin (**35**) obtained in this way was converted to **36** in the usual manner with thionyl chloride.[14] *meso*-2,2′-Dimethylhydrobenzoin and its sulfite **37** were obtained from *o*-tolualdehyde in a manner analogous to that described for **36** in eq 12.



(12)

Upon irradiation (254 nm) of *meso*-4,4′-dimethylhydrobenzoin sulfite (**36**) in cyclohexane, *p*-tolylcarbene as well as sulfur dioxide and *p*-tolualdehyde are produced, as evidenced by formation of *p*-tolylcyclohexylmethane (**38**). The anticipated ditolylmethane possibly formed by photodecarbonylation of the intermediate rearrangement product, ditolylacetaldehyde, was shown by glc to be primarily the 4,4′-disubstituted isomer **39**, a result which is consistent with an Ar_1-3 transition state proposed for the corresponding thermal conversion (eq 13).[34,43]

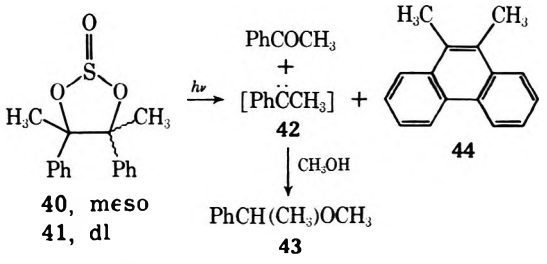


SO_2 + *p*-$CH_3C_6H_4CHO$ (13)

Similarly *meso*-2,2′-dimethylhydrobenzoin sulfite (**37**) upon irradiation (254 nm) in cyclohexane gave the anticipated product *o*-tolylcyclohexylmethane and di-*o*-tolylmethane accompanied by sulfur dioxide and *o*-tolualdehyde, providing further evidence supporting our mechanistic conclusions.

The photolysis of acetophenone pinacol sulfites was also studied in order to determine the effect of alkyl substitution on the cycloelimination reactions of cyclic sulfites and to provide additional precursors for methylphenyl carbenes.[44] The requisite *meso*- and *dl*-α,α′-dimethylhydrobenzoin sulfites (**40** and **41**, respectively) were synthesized in the conventional manner from the corresponding *meso*- and *dl*-α,α′-dimethylhydrobenzoins and thionyl chloride.[14] As anticipated, the sulfites **40** and **41** were found to undergo photocycloelimination upon irradiation (254 nm) to give the expected phenylmethylcarbene (**42**) which in methanol solvolyzes to α-phenethylmethyl ether (**43**) which is readily identified by glc and pmr spectroscopy. Other compounds detected among the photolytic products of **40** and **41** after separation by thick layer chromatography are acetophenone and 9,10-dimethylphenanthrene (**44**) (eq 14).

The formation of **44** suggest that [5 → 3 + 2] cycloelimination takes place with **40** and **41** to give sulfur trioxide and 1,2-dimethylstilbene(s). The latter sub-



(14)

(38) G. W. Griffin, A. P. Marcantonio, H. Kristinsson, R. C. Petterson, and C. S. Irving, *Tetrahedron Lett.*, 2951 (1965).

(39) J. J. Brophy and G. W. Griffin, *ibid.*, 493 (1970).

(40) E. Kristinsson and G. S. Hammond, *J. Amer. Chem. Soc.*, **89**, 5968 (1967).

(41) M. Pomerantz and G. W. Gruber, *ibid.*, **89**, 6798 (1967).

(42) H. T. Clarke and E. E. Dreger, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1964, p 87.

(43) The series of six possible isomeric ditolylmethanes have been synthesized and an attempt is presently being made to achieve total glc resolution, which has proved exceedingly difficult. A photolability study similar to that performed on the six isomeric dimethylbiphenyls is contemplated once resolution is achieved which will allow us to set limits on the homogeneity of the ditolylmethanes obtained from **36** and **37**. See U. Mende, J. L. Laseter, and G. W. Griffin, *Tetrahedron Lett.*, 3747 (1970).

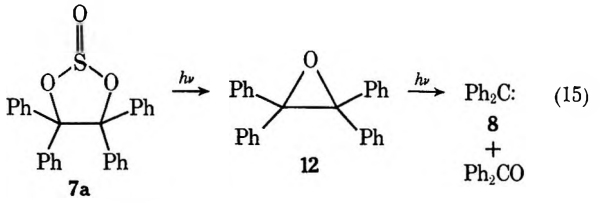
(44) H. Kristinsson, *ibid.*, 2343 (1966).

sequently undergo photodehydrocyclization to 9,10-dimethylphenanthrene (**44**). It was observed that smaller amounts of **44** are formed from **41** than **40**, which may be the case because concerted [5 → 3 + 2] cycloelimination with **41** would give *trans*-1,2-dimethylstilbene, which must undergo geometrical isomerization prior to dehydrocyclization. In contrast to the results obtained with the fluorenopinacol sulfite (**13**) and the hydrobenzoin sulfites (**17** and **18**) no rearrangement products were isolable from the irradiation mixtures obtained from **40** and **41**.

From the data compiled to date on the photochemical behavior of aryl-substituted cyclic sulfites it is apparent that these substrates may undergo [5 → 2 + 2 + 1] photocycloeliminations to carbenes, react in a [5 → 3 + 2] manner to give sulfur trioxide and aryl-substituted alkenes (which in turn under the reaction conditions are converted by photodehydrocyclization to phenanthrenes), and suffer rearrangement involving 1,2-aryl migration preceded or accompanied by loss of sulfur dioxide.

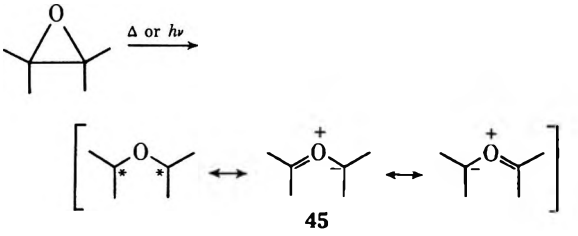
It has been demonstrated that all sulfites studied, with the exception of fluorenopinacol sulfite (**13**), fragment to arylcarbenes. It is evident from comparative C–H insertion selectivity and additional stereochemical studies that phenylcarbene (**6**) formed by cycloelimination from the diastereomeric hydrobenzoin sulfites **17** and **18** is probably singlet in character and identical with that obtained from more conventional precursors such as *trans*-2,3-diphenyloxirane (**23**) and phenyldiazomethane (**24**).

The results of earlier work in this laboratory confirm that suitably substituted oxiranes fragment upon irradiation to carbenes.[4,8] *A priori*, it appeared reasonable that carbene formation from sulfites might occur in a stepwise manner with formation of an oxirane upon loss of sulfur dioxide, which in turn could be the primary carbene precursor. This potential mode of fragmentation is exemplified for benzopinacol sulfite (**7a**) in eq 15. This reaction pathway remains subject



7a 12 (15)

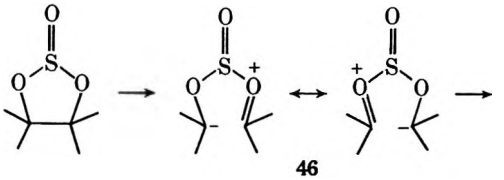
to consideration in view of the known thermal conversions of **7a** to **12** and the observation that the sulfites studied, when irradiated at −196° in a rigid matrix of 2-methyltetrahydrofuran, give colors reminiscent of those observed for the corresponding oxiranes under these conditions.[8,45a] The visible absorption spectra are essentially identical with those of the corresponding oxiranes with absorption maxima shifted by 1–5 nm. Such absorption maxima have been shown to exhibit a bathochromic shift with increasing irradiation times and hence it remains to be established how real these differences are.[45b] Thus caution must be exercised in attributing the photochromic behavior to the sulfites rather than to traces of oxirane generated under the low-temperature photolysis conditions. Direct spectroscopic comparison of the absorption intensity of the colored species obtained by these independent routes in rigid matrices is difficult since color development is not uniform and is restricted to the window surfaces. Thus absolute measurement of extinction coefficients is not feasible under these conditions. However, from a qualitative standpoint color development occurs more slowly in the case of the sulfites, which require longer irradiation times than needed for the corresponding oxiranes. Furthermore the color intensity is significantly lower for the former. Such differences would in fact be anticipated if initial oxirane formation is occurring and it is these species, produced in low concentration, which are actually responsible for the observed color. Although oxirane formation is not a detectable process at ambient temperatures (*vide supra*), it is conceivable that the [5 → 2 + 2 + 1] reaction of cyclic sulfites could occur in a concerted fashion at ambient temperatures without formation of the oxirane, and that the mechanistic process may be altered by sufficient cooling (−196°) so that discrete intermediates are stabilized. Under these conditions oxiranes may be implicated. The oxirane photochromism is believed to arise as a result of formation of oxoylides such as **45** formed by cleavage of the C–C bond[4,45] as shown in eq 16.



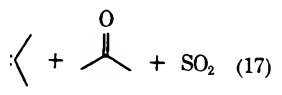
45 (16)

Huisgen and coworkers[46] have shown that in fact similar ylides when produced thermally from oxiranes may be trapped by dipolarophiles. These ylides may then fragment further in a thermal step or more likely by absorption of another photon to the carbene or alternatively recyclize reversibly to the oxirane. A detailed discussion of the probable reaction mechanism is given elsewhere.[4,8]

If the colored species obtained in the low-temperature irradiation of the sulfites are not identical with those obtained from the oxiranes, *i.e.*, if the 1–5 nm shift is a reflection of real differences in the structures, then perhaps ylides such as **46** may be formed by cleavage of the C–C bond as shown in eq 17 and then fragment further to give the carbene. This mode of opening seems unlikely in the absence of strain inherent in the corresponding oxiranes, but if such is the



46



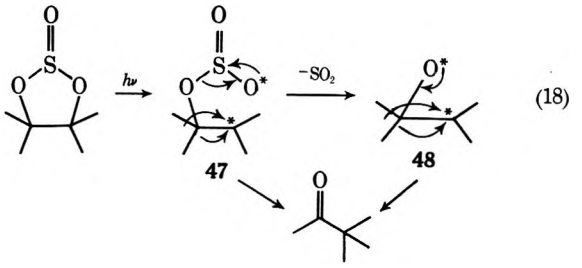
(17)

(45) (a) T. Do-Minh, A. M. Trozzolo, and G. W. Griffin, *J. Amer. Chem. Soc.*, **92**, 1402 (1970); (b) N. R. Bertoniere, Ph.D. Dissertation, Louisiana State University in New Orleans, 1971.

(46) H. Hamberger and R. Huisgen, *Chem. Commun.*, 1190 (1971); A. Dahmen, H. Hamberger, R. Huisgen, and V. Markowski, *ibid.*, 1192 (1971).

case alternate mechanistic pathways must be advanced to explain the occurrence of rearrangement products, *i.e.*, aryl migration as well as [5 → 3 + 2] cycloelimination to an alkene and sulfur trioxide.

The formation of rearrangement products is most economically rationalized on the basis of a mechanism involving a concerted Ar_1-3 migration after initial homolysis of the sulfite C–O bond to give **47**, although prior loss of sulfur dioxide and rearrangement *via* the intermediate **48** is not excluded (eq 18).



(18)

The intermediate **47** also may be invoked to explain the [5 → 3 + 2] cycloelimination reaction of sulfites to give sulfur trioxide, although a totally concerted elimination is certainly possible.

In summary, it is evident from this study that all of the cyclic sulfites examined with the exception of fluorenopinacol sulfite (**13**) are useful carbene precursors. It is also noteworthy that in all cases investigated excluding **13**, 1,2-aryl migration with loss of sulfur dioxide to give rearrangement products competes with carbene formation as does alkene formation with extrusion of sulfur trioxide.

From the considerations described above it appears that no single mechanism can satisfactorily explain the photochemical behavior of the sulfites and we believe that more than one process may be involved in the photofragmentation process. Further work is in progress to clarify these results.

Experimental Section

General.—All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 337 and 257 spectrophotometers. The ultraviolet spectra were determined on Perkin-Elmer 202 and 450 spectrophotometers and the molar extinction coefficients were obtained on a Cary Model 15 spectrophotometer. The proton magnetic resonance spectra were determined on a Varian A-60 spectrophotometer using deuteriochloroform as the solvent with 1% tetramethylsilane as the internal standard unless otherwise specified. The mass spectral studies were conducted using a Hitachi Perkin-Elmer RMU-6E spectrometer.

Analytical gas chromatograms were obtained on a Perkin-Elmer Model 900 gas chromatograph equipped with a flame ionization detector using Perkin-Elmer support coated opentubular (SCOT) capillary columns. Integration of peak areas was achieved either by multiplication of peak height by peak width at half height or by using a Hewlett-Packard Model 3370A electronic digital integrator. Preparative gas chromatographic separations were carried out on an Aerograph Model A-90P gas chromatograph using 0.25-in. columns. Silica gel G (PF_{254}, Brinkman Company) was used for thin and thick layer chromatographic separations.

Irradiations were conducted in serum capped 15 cm × 12.5 mm i.d. fused quartz tubes in a Rayonet photochemical reactor (The Southern New England Ultraviolet Co., Middletown, Conn.) using 16 8-W low pressure lamps unless otherwise specified. The lamps were either G8T5 (254 nm) or F8T5 (broad emission at 350 nm). A Rayonet MGR-100 Merry-Go-Round apparatus (The Southern New England Ultraviolet Co., Middletown, Conn.) was utilized in all kinetic studies to ensure uniform exposure of individual samples, which were rotated at 5 rpm. The solutions to be irradiated were degassed either by nitrogen sparging for 25 min or by the multiple freeze–thaw cycle technique.

Preparation of Benzopinacol Sulfite (7a).—A solution containing 1.4 g (12 mmol) of thionyl chloride in 5 ml of methylene chloride was added dropwise with stirring to a solution of 3.6 g (10 mmol) of benzopinacol in 20 ml of methylene chloride and 5 ml of pyridine. The reaction mixture was stirred at room temperature for 5 hr and the excess thionyl chloride was then destroyed by addition of water. The resulting mixture was treated with three 15-ml portions of hydrochloric acid (5%), and the organic phase was separated, washed repeatedly with water, and dried over anhydrous potassium carbonate. The residue remaining after removal of solvent under reduced pressure (3.0 g, 38%) was chromatographed on silica gel using benzene as the eluting solvent. The colorless crystals which deposited were recrystallized from ethanol to give the pure benzopinacol sulfite: mp 137–138°; ir 945, 1040 and 1240 cm^{-1}; pmr (CCl_4) τ 2.9 (m, aromatic); uv $\lambda_{max}^{C_2H_5OH}$ 266 nm (log ϵ 2.98), 261 (3.01), 254 (2.95); mass spectrum *m/e* 348, 332, 232, 182, and 105.

Anal. Calcd for $C_{26}H_{20}O_3S$: C, 75.72; H, 4.85. Found: C, 75.89; H, 4.72.

Preparation of 9-Fluorenopinacol.—9-Fluorenopinacol was prepared according to the procedure of Risinger and Eddy[47] by addition of zinc dust and sodium hydroxide to a solution of fluorenone cooled in ethanol to −5°. Recrystallization of the product from dilute ethanol gave the desired diol, mp 190–191° (lit.[48] mp 190–192°).

Preparation of 9-Fluorenopinacol Sulfite (13).—A solution of 0.6 g (5.0 mmol) of thionyl chloride in 5 ml of methylene chloride was added slowly with stirring to 9-fluorenopinacol (0.9 g, 3.0 mmol) at 0° in 10 ml of methylene chloride and 2 ml of pyridine. The resulting reaction mixture was stirred for 3 hr at room temperature and the product was isolated in the manner described earlier for **7a**. The crude product was recrystallized from methylene chloride–ethanol using Norit to give colorless needles: yield 0.7 g (70%); mp 175–178° dec; ir (KBr) 935 and 1215 cm^{-1}; pmr τ 2.7 (aromatic); uv $\lambda_{max}^{C_2H_5OH}$ 288 nm (log ϵ 4.16), 278 (4.29), 269 (4.20), 239 (4.77), 232 (4.75); mass spectrum *m/e* 344, 328, 316, 180, and 64.

Anal. Calcd for $C_{26}H_{16}O_3S$: C, 76.37; H, 3.92. Found: C, 76.02; H, 3.78.

Preparation of *meso*-Hydrobenzoin.—*meso*-Hydrobenzoin was prepared by sodium borohydride reduction of benzil employing the procedure described by Fieser,[49] mp 136–137° (lit.[49] mp 136–137°).

Preparation of *meso*-Hydrobenzoin Sulfite (17).—The procedure of Thompson and coworkers[14] was employed for the preparation of **17**. The crude product was crystallized from ether to yield the same major product reported by these investigators: mp 130–131° (lit.[14] mp 130–131°); ir ($CHCl_3$) 975, 1040, and 1210 cm^{-1}; pmr ($CDCl_3$) τ 3.0 (m, 10, aromatic), 3.85 (s, 2 methine); uv $\lambda_{max}^{C_2H_5OH}$ 268 nm (log ϵ 2.36), 264 (2.6), 258 (2.67), 252 (2.6); mass spectrum *m/e* 196, 180, 154, 126, and 105 (lit.[50] *m/e* 196, 180, 154, 126, and 105).

Preparation of *dl*-Hydrobenzoin.—*dl*-Hydrobenzoin was prepared according to the procedure outlined by Jenevein,[51] mp 120–121° (lit.[51] mp 120–121°).

Preparation of *dl*-Hydrobenzoin Sulfite (18).—*dl*-Hydrobenzoin sulfite was prepared by the same procedure employed for the meso isomer **17**. The crude product was recrystallized from ether–hexane, giving 0.8 g of white needles: mp 85–86° (lit.[14] mp 84–86°); ir (CCl_4) 965 and 1227 cm^{-1}; pmr ($CDCl_3$) τ 2.72 (m, 10, aromatic), 4.4, 4.85 (d, 2, benzylic); uv $\lambda_{max}^{C_2H_5OH}$ 269 nm (log ϵ 2.46), 263 (2.67), 257 (2.7), 252 (2.57); mass spectrum *m/e* 196, 180, 154, 126, and 105 (lit.[50] *m/e* 196, 180, 154, 126, and 105).

Preparation of *meso*-α,α′-Dimethylhydrobenzoin.—The meso

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(48) M. Gomberg and W. E. Bachmann, *J. Amer. Chem. Soc.*, **49**, 236 (1927).

(49) L. F. Fieser, "Organic Experiments," D. C. Heath, Boston, Mass., 1964, p 216.

(50) J. G. Pritchard and P. T. Funke, *J. Heterocycl. Chem.*, **3**, 209 (1966); P. Brown and C. Djerassi, *Tetrahedron*, **24**, 2949 (1968).

(51) R. M. Jenevein, Ph.D. Dissertation, Louisiana State University in New Orleans, 1969.

diol was obtained by addition of an excess of methyllithium to benzil as described by Stocker and coworkers.[52] Recrystallization from benzene–heptane yielded the pure *meso*-α,α'-dimethylhydrobenzoin, mp 120–121° (lit.[52] mp 120–121°).

Preparation of *meso*-α,α'-Dimethylhydrobenzoin Sulfite (40).—Thionyl chloride (3.6 g, 30 mmol) in 10 ml of methylene chloride was added slowly with stirring to 5.0 g (20 mmol) of *meso*-α,α'-dimethylhydrobenzoin in 20 ml of methylene chloride and 5 ml of pyridine at room temperature. After completion of the addition the reaction mixture was stirred for 4 hr and the excess thionyl chloride was removed by distillation under reduced pressure. The residue was dissolved in methylene chloride and the resulting solution was washed first with copper sulfate solution (5%) and then repeatedly with water. The organic phase was then dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The concentrate was chromatographed on alumina to give a viscous oil (4 g, 68%) which solidified on standing for 2 weeks. Recrystallization from methylene chloride–hexane gave the pure sulfite: mp 89°; ir ($CHCl_3$) 900, 1040, and 1222 cm^{-1}; pmr (CCl_4) τ 3.03 (m, 10, aromatic), 7.96 (s, 3, methyl), 8.16 (s, 3, methyl); uv $\lambda_{max}^{C_2H_5OH}$ 264 nm (log ϵ 2.59), 258 (2.72), 252 (2.62); mass spectrum *m/e* 224, 209, 181, 168, 126, 105, 104, 91, and 77.

Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.66; H, 5.55. Found: C, 66.43; H, 5.36.

Preparation of *dl*-α,α'-Dimethylhydrobenzoin.—This diol was prepared by the addition of freshly distilled 2,3-butanedione to phenyllithium as described by Stocker and coworkers.[52] The diol, mp 124–125° (lit.[52] mp 124–125°), was purified by recrystallization from heptane.

Preparation of *dl*-α,α'-Dimethylhydrobenzoin Sulfite (41).—*dl*-α,α'-Dimethylhydrobenzoin sulfite was prepared by addition of thionyl chloride (3.6 g, 30 mmol) in methylene chloride (10 ml) to the pinacol (5 g, 20 mmol) in 15 ml of methylene chloride and 5 ml of pyridine. The reaction mixture was worked up in a manner similar to that used for the meso isomer **40**. In this case, however, it was necessary to store the residual oil in the refrigerator for 6 weeks before solidification occurred (3.8 g, 85%). Purification of *dl*-α,α'-dimethylhydrobenzoin sulfite was achieved by recrystallization from aqueous methanol: mp 47–48°; ir ($CHCl_3$) 1223, 1070, 915 cm^{-1}; pmr (CCl_4) τ 2.6 (m, 10, aromatic), 8.38 (s, 3, methyl), 8.7 (s, 3, methyl); uv $\lambda_{max}^{C_2H_5OH}$ 263 nm (log ϵ 2.59), 257 (2.68), 252 (2.56); mass spectrum *m/e* 224, 208, 181, 168, 126, 105, 104, 91, and 77.

Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.66; H, 5.55. Found: C, 66.79; H, 5.65.

Preparation of Benzhydryl Methyl Ether (9).—The procedure of Gillis[53] was utilized for methylation of benzhydrol. Benzhydrol (5.0 g, 25 mmol) was added to a stirred suspension of 2.0 g (50 mmol) of finely powdered sodium hydroxide in 25 ml of dimethyl sulfoxide. To the resulting mixture was added 5.3 g (37 mmol) of methyl iodide and the solution was stirred for 3 hr. After dilution with 50 ml of water the product was extracted with ether, the organic phase was washed with water and dried over anhydrous sodium sulfate, and the volatile solvents were removed. The residual oil was then purified by distillation under reduced pressure, bp 105–106° (4 mm) [lit.[54] bp 146–148° (12 mm)].

Preparation of Benzyl Methyl Ether (19).—Benzyl alcohol (3.1 g, 30 mmol) was methylated in a manner similar to that used for benzhydryl alcohol. The benzyl methyl ether was purified by distillation at atmospheric pressure, bp 169–170° (lit.[55] bp 170°).

Preparation of Benzylcyclohexane (21).—Benzylcyclohexane was prepared as described by Smith[56] by treatment of cyclohexanone with benzylmagnesium bromide to give the 1-benzylcyclohexanol, which was subsequently dehydrated with iodine in toluene and then hydrogenated using palladium on charcoal as a catalyst. Purification was achieved by distillation, bp 141° (26 mm) [lit.[57] bp 133° (19 mm)].

Preparation of 2- and 3-Benzylpentane (26 and 27, Respectively).—To the Grignard reagent prepared from 10.2 g (60 mmol) of benzyl bromide and 1.45 g (0.06 g-atom) of magnesium turnings was added 5.0 g (58 mmol) of 2-pentanone to yield 7.2 g (65%) of 1-phenyl-2-methylpentanol. A mixture of the crude pentanol (4.8 g), 1.5 ml of hydriodic acid, and 1.5 g of red phosphorus was heated under reflux for 8 hr with occasional addition of hydriodic acid until an aliquot sample, after dilution with ether and treatment with aqueous sodium carbonate and sodium bisulfite, yielded a colorless solution (*i.e.*, no trace of free iodine). The reaction mixture was then diluted with water and extracted repeatedly with ether. The combined organic phases were washed with sodium carbonate solution (10%), sodium bisulfite (5%), and water and dried over anhydrous magnesium sulfate, and the volatile solvent was removed under reduced pressure. From the residual oil pure 2-benzylpentane was obtained by preparative glc using a 4 m × 6 mm Apiezon L on Chromosorb P column at 180°: pmr (CCl_4) τ 2.9 (s, 5, aromatic), 7.5 (d, 2, benzylic), 8.5–9.1 (m, 8, aliphatic), and 9.11 (d, 3, methyl); mass spectrum *m/e* 162 (molecular ion).

The same procedure with minor modifications was used for the preparation of 3-benzylpentane. The requisite 3-benzylpentane was purified by glc as before: pmr (CCl_4) τ 2.86 (m, 5, aromatic), 7.5 (d, 2, benzylic), 8.6 (q, 4, methylene), 9.12 (t, 6, methyl); mass spectrum *m/e* 162 (molecular ion).

1-Phenylhexane (**25**) was purchased from Aldrich Chemical Co., Inc., Milwaukee, Wis., and used without further purification.

Preparation of *syn*-, *anti*-, and *trans*-2,3-Dimethyl-1-phenylcyclopropane (28, 29, and 30, Respectively).—The authentic addition products derived from phenylcarbene (6) and *cis*-2-butene were prepared according to the method of Smith[56] by photolysis of *trans*-2,3-diphenyloxirane in *cis*-2-butene to give the syn and anti isomers. The trans isomer **30** was obtained in a similar manner from *trans*-2-butene: syn isomer, pmr (CCl_4) τ 2.8 (s, 5, aromatic), 9.05 (s, 6, methyl); anti isomer, pmr (CCl_4) τ 2.82 (m, 5, aromatic), 8.87 (s, 6, methyl); trans isomer, pmr (CCl_4) τ 2.92 (s, 5, aromatic), 9.22 (d, 6, methyl). The mass spectra of all three isomeric 2,3-dimethyl-1-phenylcyclopropanes exhibit the anticipated molecular ion at *m/e* 146.

Preparation of *o,o'*-Bitolil.—*o,o'*-Bitolil was prepared by oxidation of 2,2'-dimethylbenzoin with copper sulfate and pyridine according to the method employed by Clarke and Dreger[42] for the synthesis of the parent compound benzoin. The 2,2'-dimethylbenzoin was obtained in turn by condensation of *o*-tolualdehyde as described by Adams and Marvel.[58] The crude *o,o'*-bitolil was recrystallized from ethanol, mp 92° (lit.[59] mp 92°).

Preparation of *meso*-2,2'-Dimethylhydrobenzoin.—The *o,o'*-bitolil (4.6 g, 20 mmol) was reduced with sodium borohydride in a manner similar to that employed by Fieser[49] for *meso*-hydrobenzoin. The crude product was recrystallized from aqueous ethanol: mp 104–105°; pmr ($CDCl_3$) τ 2.84 (m, 4, aromatic), 4.84 [s (broad), 1, benzylic], 7.7 [s (broad), 1, hydroxyl], and 7.84 (s, 3, methyl).

Preparation of *meso*-2,2'-Dimethylhydrobenzoin Sulfite (37).—The sulfite **37** was prepared from 2.4 g (10 mmol) of the corresponding pinacol and 1.3 g (12 mmol) of thionyl chloride as described for **18** (*vide supra*). The crude product (1.8 g, 70%) was recrystallized from methylene chloride–hexane to give pure 2,2'-dimethylhydrobenzoin sulfite: mp 152–153°; ir (KBr) 1220, 930, 960, 740, and 770 cm^{-1}; pmr ($CDCl_3$) τ 2.9 (m, 8, aromatic), 3.54 (s, 2, benzylic), and 7.88 (s, 6, methyl); uv $\lambda_{max}^{C_2H_5OH}$ 273 nm (log ϵ 2.83), 266 (2.89), 260 (2.79); mass spectrum *m/e* 224, 208, 168, 140, 120, 119, 92, and 91.

Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.66; H, 5.55. Found: C, 66.81; H, 5.63.

Preparation of *p,p'*-Bitolil (34).—*p,p'*-Bitolil (**34**) was obtained by oxidation of 4,4'-dimethylbenzoin (**33**) with copper sulfate and pyridine.[42] The corresponding 4,4'-dimethylbenzoin was prepared by utilizing the benzoin condensation with *p*-tolualdehyde.[58] Purification was achieved by recrystallization from ethanol, mp 102–103° (lit.[60] mp 102–103°).

Preparation of *meso*-4,4'-Dimethylhydrobenzoin (35).—4,4'-

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(58) R. Adams and C. S. Marvel, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1964, p 94.

(59) M. S. Kharasch, W. Nudenberg, and S. Archer, *J. Amer. Chem. Soc.*, **65**, 495 (1943).

(60) M. Gomberg and W. E. Bachmann, *J. Amer. Chem. Soc.*, **50**, 2762 (1928).

Dimethylhydrobenzoin was prepared by sodium borohydride reduction of *p,p'*-bitolil: mp 144.5–145.5° (lit.[61] mp 145–146°); pmr ($CDCl_3$) τ 2.84 (s, 4, aromatic), 5.25 (s, 1, benzilic), 7.67 (s, 3, methyl), 7.9 [s (broad), 1, hydroxyl].

Preparation of *meso*-4,4'-Dimethylhydrobenzoin Sulfite (36).—The sulfite **36** was prepared in the usual manner from 2.4 g (10 mmol) of the diol **35** and 1.3 g (12 mmol) of thionyl chloride. The crude product was recrystallized from pentane to give the pure **36** (1.5 g, 50%): mp 82–83°; ir (KBr) 1220, 960, 840, and 780 cm^{-1}; pmr ($CDCl_3$) τ 3.1 (m, 8, aromatic), 3.95 (s, 2, methine), and 7.84 (s, 6, methyl); uv $\lambda_{max}^{C_2H_5OH}$ 273 nm (log ϵ 2.51), 268 (2.61), 263 (2.76), and 257 (2.68); mass spectrum *m/e* 224, 208, 168, 140, 120, 119, 92, and 91.

Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.66; H, 5.55. Found: C, 66.81; H, 5.76.

Preparation of *o*-Tolylcyclohexylmethane.—A solution of *o*-tolylcyclohexylmethanol (2.0 g, 10 mmol), prepared from cyclohexylmagnesium bromide and *o*-tolualdehyde, was heated under reflux with red phosphorus and hydriodic acid. The resulting crude *o*-tolylcyclohexylmethane was chromatographed over alumina after work-up in the manner previously described for **21** and the desired hydrocarbon was obtained as a colorless oil of sufficient purity for use: pmr (CCl_4) τ 3.1 (s, 4, aromatic), 7.6 (d, 2, benzylic), 7.7 (s, 3, methyl), and 8.7 (m, 11, cyclohexyl); mass spectrum *m/e* 188 (molecular ion).

Preparation of *p*-Tolylcyclohexylmethane (38).—A preparative procedure analogous to that described for the *o*-tolyl derivative was followed with the exception that *p*-tolualdehyde was used as the aldehyde substrate. The pure hydrocarbon was obtained as a colorless oil by preparative glc: pmr (CCl_4) τ 3.1 (s, 4, aromatic), 7.6 (d, 2, benzylic, J = 6 cps), 7.7 (s, 3, methyl), and 8.7 (m, 11, cyclohexyl); mass spectrum *m/e* 188 (molecular ion).

Preparation of Di-o-tolylmethane.—In a typical experiment 1.2 g (10 mmol) of o-tolualdehyde was added to the Grignard reagent prepared from 1.7 g (10 mmol) of *o*-bromotoluene and 0.26 g (0.01 g-atom) of magnesium and the reaction mixture was stirred for 12 hr at room temperature. The resulting mixture was hydrolyzed with dilute hydrochloric acid and extracted repeatedly with ether. The combined organic phases were washed with aqueous sodium carbonate and water, and finally dried over anhydrous sodium sulfate. The volatile solvents were then removed under reduced pressure and the resulting crude alcohol was crystallized from dilute ethanol to give the desired di-*o*-tolylcarbinol: mp 119–120° (lit.[62] mp 119–120°); yield 1.2 g (55%); pmr ($CDCl_3$) τ 2.7 (s, 8, aromatic), 3.88 (s, 1, benzylic), 7.74 (s, 6, methyl), and 8.00 [s (broad), 1, hydroxyl]. The alcohol (1.0 g, 5.0 mmol) prepared as described above was then heated under reflux with red phosphorus and hydriodic acid and the product was isolated and purified by chromatography on alumina: pmr (CCl_4) τ 3.0 (m, 8, aromatic), 6.18 (s, 2, benzylic), and 7.18 (s, 6, methyl); mass spectrum *m/e* 196 (molecular ion).

Preparation of Di-*p*-tolylmethane (39).—A preparative procedure similar to that employed for the analogous ortho-substituted hydrocarbon was used for the synthesis of di-*p*-tolylmethane from *p*-tolualdehyde and *p*-bromotoluene: mp 28° (lit.[63] mp 28.5°); pmr (CCl_4) τ 2.89 (s, 8, aromatic), 6.13 (s, 2, benzylic), and 7.74 (s, 3, methyl); mass spectrum *m/e* 196 (molecular ion).

Photolysis of Benzopinacol Sulfite (7a) in Methanol.—A solution of 0.10 g (2.5×10^{-4} mol) of benzopinacol sulfite (**7a**) dissolved in 10 ml of methanol was degassed utilizing the multiple freeze–thaw technique and irradiated for 12 hr in a quartz test tube.[64a] An absorption band at 1350 cm^{-1} characteristic of sulfur dioxide was observed in the infrared spectrum of an aliquot of the irradiated sample. The excess methanol was removed from the photolysis solution under reduced pressure and the components of the residual solid were separated by tlc (benzene–carbon tetrachloride, 65:35) into three fractions. The first fraction (12%) after recrystallization from ethanol (mp 235–236°) was found to be indistinguishable from 9,10-diphenylphenanthrene (**10**). An authentic sample of **10** was prepared by irradiation (254 nm) of tetraphenylethylene in methanol. The second fraction (40%) was shown to be benzhydryl methyl ether (**9**), spectroscopically identical with an authentic sample. The final fraction (15%) was identified as benzophenone by infrared spectroscopy. Under the conditions described no residual sulfite **7a** or tetraphenyloxirane (**12**) could be detected by tlc.

Relative Rates of Formation of Diphenylcarbene from Benzopinacol Sulfite (7a) and Tetraphenyloxirane (12).—In two identical quartz tubes were placed 3.0×10^{-2} mmol of benzopinacol sulfite (12.4 mg) and tetraphenyloxirane (10.44 mg) and each was dissolved in 10-ml aliquots of methanol containing 1.0×10^{-5} mol (1.6 mg) of phenylcyclohexane (Eastman Kodak Co., Rochester, N. Y.), which was employed as the internal standard. The tubes were sealed with rubber septa, degassed by nitrogen sparging, and irradiated[64b,d] for a total of 25 min. Aliquot samples (3 ml) were withdrawn after 4 and 13 min. The samples were analyzed by glc using a DC 550 SCOT 50-ft capillary column, temperature programmed from 110 to 140° at 5° per min. Enrichment techniques with authentic samples of benzhydryl methyl ether (**9**) and phenylcyclohexane (internal standard) permitted ready identification of the respective peaks in the chromatogram. Multiple runs of each sample were made and peak areas due to **9** and internal standard were determined by digital electronic integration. Their ratios were compared and absolute yields obtained from glc response factors were determined independently utilizing known solutions of **9** and phenylcyclohexane.

Irradiation of *meso*-Hydrobenzoin Sulfite (17) in Cyclohexane.—A solution of 0.065 g (0.25 mmol) of hydrobenzoin sulfite (**17**) in 10 ml of cyclohexane was irradiated for 15 hr.[64a] Analysis of the gaseous products by infrared and mass spectroscopy confirmed that sulfur dioxide is produced. The reaction mixture was concentrated under reduced pressure, and the residue was then separated preparatively into three main components by glc (Apiezon L, 0.25 in. × 12 ft column, 200°). The first component to emerge was found to be benzaldehyde, identical with an authentic sample. The second component was benzylcyclohexane (**21**), indistinguishable from an authentic sample. Diphenylmethane (**20**), having spectral characteristics identical with those of an authentic sample, was also separated. Examination of the reaction mixture by tlc confirmed that neither *trans*- nor *cis*-2,3-diphenyloxirane (**22** nor **23**) is produced in significant amounts.

Insertion Reactions of Phenylcarbene Generated from Diverse Sources in *n*-Pentane.—In each of four identical fused quartz tubes was placed 5.0×10^{-2} mmol of the carbene precursors to be compared. The specific amounts were 13.0 mg of *meso*-hydrobenzoin sulfite (**17**), 13 mg of *dl*-hydrobenzoin sulfite (**18**), 9.8 mg of *trans*-2,3-diphenyloxirane (**23**), and 5.9 mg of phenyldiazomethane (**24**). A 10-ml aliquot of a 1.0×10^{-5} *M* solution of amylbenzene (Aldrich Chemical Co., Inc., Milwaukee, Wis.) in 99% pure *n*-pentane (Columbia Organic Chemical Co., Inc., Columbia, S. C.) was transferred to each tube by means of a 10-ml pipette. The tubes were sealed with serum caps, degassed by nitrogen sparging using syringe needles, and irradiated[64b,d] for 25 min. A duplicate sample of phenyldiazomethane (**24**) was irradiated[64c,d] for 4 hr at 350 nm. The samples were then concentrated under reduced pressure and analyzed by glc. Satisfactory (base line) resolution of the benzyl pentanes **25**, **26**, and **27** was obtained using a DC 550 SCOT 50-ft capillary column which was temperature programmed from 75 to 145° at 1°/min from the time of injection of each individual run. Enrichment techniques employing authentic samples of the benzyl pentanes **25**, **26**, and **27** and the internal standard amylbenzene were used to establish the identity of these peaks in the resulting gas chromatograms. Multiple runs (4–6) were made for each sample and the requisite peak areas were determined by multiplying peak height by peak width at half peak height. In this manner areas of peaks corresponding to amylbenzene, **25**, **26**, and **27** were determined and the isomer ratios were then computed and tabulated for the individual carbene precursors (Table I). Absolute yields were obtained by determination of response factors utilizing standard solutions prepared from amylbenzene and authentic samples of the insertion products. Analysis by tlc (in benzene–carbon tetrachloride, 4:1) confirmed that no significant geometric isomerization of either the oxirane **23** or the sulfites **17** and **18** occurs under the reaction conditions and no detectable *cis*- or *trans*-diphenyloxirane (**22** or **23**) is formed in conjunction with the photocycloelimination reactions of the sulfite substrates.

(61) J. Grimshaw and J. S. Ramsey, *J. Chem. Soc. C*, 653 (1966).

(62) H. H. Hatt, *J. Chem. Soc.*, 1623 (1929).

(63) T. Reichstein and R. Oppenauer, *Helv. Chim. Acta*, **16**, 1373 (1933).

(64) Irradiations were conducted in serum-capped quartz or Pyrex tubes as specified using a Rayonet RPR 100 photochemical reactor (The Southern New England Ultraviolet Co., Middletown, Conn.) equipped with (a) 16 8-W low-pressure G8T5 lamps (254 nm); (b) eight 8-W low-pressure G8T5 lamps (254 nm); (c) 16 8-W low-pressure F8T5 lamps (350 nm) as a light source; (d) a Rayonet MGR 100 Merry-Go-Round apparatus (The Southern New England Ultraviolet Co., Middletown, Conn.) rotated at 5 rpm was utilized in all rate studies to ensure uniform exposure of individual samples.

Addition of Phenylcarbene Generated from Diverse Sources to *cis*-2-Butene. Stereospecificity of Cycloaddition.—Irradiations in this study were conducted in 150 × 24 mm i.d. fused quartz tubes which had been modified to accept an Aerosol Compatibility Head Assembly equipped with a valve (Fischer and Porter Co., Warminister, Pa.) (alternatively a Griffin–Worden Quartz Pressure Vessel[9]). The substrate to be photolyzed was placed in the quartz tube, the Aerosol Compatibility Head was secured, and the system was evacuated (~0.5 mm). The assembly was then immersed in a Dry Ice–acetone bath and sufficient *cis*-2-butene (99.91 mol %, Phillips Petroleum Co., Bartesville, Okla.) was admitted by means of a tygon tube to obtain approximately 5.0×10^{-3} *M* solutions. The specific weights of the compounds employed in the study were 13.0 mg (5.0×10^{-5} mol) of *meso*-hydrobenzoin sulfite (**17**), 13.0 mg (5.0×10^{-5} mol) of *dl*-hydrobenzoin sulfite (**18**), and 15.4 mg (7.88×10^{-5} mol) of *trans*-2,3-diphenyloxirane (**23**). The resulting solutions were degassed by the multiple freeze–thaw technique and irradiated[64b,d] for 9 min. Upon completion of the irradiations the excess *cis*-2-butene was collected by distillation into a cold trap.

Subsequent analysis of the *cis*-2-butene confirms that no geometric isomerization of this substrate takes place under the reaction conditions. A 1-ml aliquot of a standard (0.54 mg/ml, 3.34×10^{-6} mol) solution of phenylhexane (Matheson Coleman and Bell Co., East Rutherford, N. J.) in methylene chloride was added to each solution and the reaction mixture was then analyzed by glc. The isomeric cyclopropanes were resolved using two DC 550 SCOT 50-ft capillary columns in series and a program in which the temperature is varied from 100 to 130° at 0.5°/min. Enrichment techniques employing authentic samples of each of the isomeric 2,3-dimethyl-1-phenylcyclopropanes **28**, **29**, and **30** and phenylhexane, the internal standard, were used to confirm the identity of the peaks in the resulting gas chromatograms. Multiple runs (4–6) of each sample were made and the area of each peak was determined by multiplication of the peak height by the peak width at half height. The desired isomer ratios were calculated and compared for each of the phenylcarbene precursors. No concomitant geometric isomerization of the substrates occurs as indicated by tlc analysis.

Irradiation of Sulfites in Methanol at 350 nm.—Individual solutions (2.5×10^{-4} mol) of **7a**, **17**, **18**, **40**, and **41** in 10 ml of methanol contained in Pyrex tubes were degassed by nitrogen sparging and irradiated[64c] for 24 hr at 350 nm. After removal of the solvent under reduced pressure in each case the sulfites were recovered quantitatively and no methyl ether formation could be detected by tlc.

Irradiation of 9-Fluorenopinacol Sulfite (13) in 2,3-Dimethyl-2-butene at 350 nm.—A solution of 0.10 g (0.25 mmol) of 9-fluorenopinacol sulfite (**13**) in 10 g (0.13 mol) of 2,3-dimethyl-2-butene was irradiated[64c] for 5 hr after degassing by the multiple freeze–thaw technique. The solvent was removed from the resulting yellow solution by distillation and the residue upon recrystallization from methylene chloride–hexane gave colorless prisms, mp 260°, found to be indistinguishable from the 9-diphenylene-10-phenanthrone (**19**).[7,19] No evidence (tlc) was obtained for the formation of 2,2,3,3-tetramethylspiro[cyclopropane-1,9′-fluorene] (**14**).

Irradiation of *meso*- and *dl*-α,α′-Dimethylhydrobenzoin Sulfite (40 and 41, Respectively) in Methanol.—Solutions of 0.15 g (5.0×10^{-5} mol) of the *meso*- and *dl*-α,α′-dimethylhydrobenzoin sulfite (**40** and **41**) in 15 ml of methanol were photolyzed[64a] for 8 hr at 254 nm in a quartz tube after degassing by nitrogen sparging. After completion of the irradiation the effluent gas was analyzed by infrared and mass spectrometry and found to contain sulfur dioxide. The solutions were then concentrated under reduced pressure and the residue was separated into four fractions by tlc (benzene). The fourth fastest moving band was extracted and was found to be α-phenethylmethyl ether indistinguishable spectroscopically (ir, pmr) from an authentic sample. The third band on elution with chloroform yielded a colorless solid which crystallized from absolute ethanol to give colorless needles, mp 143–144° (12 mg, 12%), found to be indistinguishable from 9,10-dimethylphenanthrene (**44**). The remaining slowest moving fractions were found to contain primarily acetophenone and starting material. The presence of acetophenone was confirmed by enrichment techniques using glc analysis on a DC 550 SCOT 50-ft capillary column operated isothermally at 100°.

Irradiation of *meso*-4,4′- and *meso*-2,2′-Dimethylhydrobenzoin Sulfite (36 and 37, Respectively) in Cyclohexane at 254 nm.—Solutions of 0.10 g (3.5×10^{-4} mol) of the sulfites **36** and **37** in 25 ml of cyclohexane were degassed by the multiple freeze–thaw technique and irradiated[64a] in a quartz vessel at 254 nm for 8 hr. The solutions were then concentrated under reduced pressure and the residue was analyzed by glc using a DC 550 SCOT 50-ft capillary column operated at 130°. Compounds identified among the photoproducts of **36** by the enhancement technique utilizing authentic samples included *p*-tolualdehyde, *p*-tolylcyclohexylmethane (**38**), and di-*p*-tolylmethane (**39**), while *o*-tolualdehyde, *o*-tolylcyclohexylmethane, and di-*o*-tolylmethane were observed among the photolysis products of **37**. The analysis was conducted under conditions which would have permitted recognition of the di-*o*-tolylmethane from di-*p*-tolylmethane.

Irradiation of Deoxybenzoin (31) and Diphenylacetaldehyde (32).—Solutions of 0.2 g (1.2 mmol) of diphenylacetaldehyde and deoxybenzoin in 25 ml of cyclohexane were degassed by nitrogen sparging and irradiated[64b] at 254 nm for 8 hr. The solutions were then concentrated under reduced pressure and the residue was subjected to pmr analysis in carbon tetrachloride. Interpretation of pmr spectral data indicated that 70% of the diphenylacetaldehyde had been decarbonylated to diphenylmethane, while no diphenylmethane was observed in the photolysis of deoxybenzoin.

Thermolyses of Sulfites.—The thermolyses were carried out in boiling (a) xylene (140°), (b) decane (168°), and (c) hexadecane (275°). The solvent in each case was removed by distillation under reduced pressure and the residue was examined for products. Benzopinacol sulfite (**7a**) after 6 hr at 140° was converted cleanly into tetraphenyloxirane (**12**), mp 205–206° (from MeOH), indistinguishable from an authentic sample. After 6 hr at 140°, 9-fluorenopinacol sulfite (**13**) gave colorless prisms (from benzene), mp 260–261°, found to be identical with the spiro ketone 9-diphenylene-10-phenanthrone (**16**) obtained by photolysis of the sulfite **13**. The hydrobenzoin sulfites (**17** and **18**) were found to be stable at 140 and 168° (8 hr). At 275° (6 hr) the *dl* sulfite **18** was found to give mainly diphenylacetaldehyde while meso sulfite **17** gave no detectable quantities of this aldehyde (glc). The dimethylhydrobenzoin sulfites **40** and **41** were also found to be stable at 140° (12 hr).

Registry No.—**7a**, 34737-62-7; **10**, 602-15-3; **13**, 34737-64-9; **17**, 19455-94-8; **18**, 10359-60-1; **36**, 34737-67-2; **37**, 34712-68-0; **40**, 34737-68-3; **41**, 34737-69-4; **44**, 604-83-1; *meso*-2,2′-dimethylhydrobenzoin, 34737-70-7.

Acknowledgment.—The authors also wish to thank Dr. N. R. Bertoniere, Dr. E. Elder, Dr. R. L. Smith, and Mrs. J. Thompson for technical assistance in the preparation of the manuscript.

A Correction of the Literature Concerning Reactions of Polyarylated Carbinols. A Novel Suprafacial [1,5] Sigmatropic Rearrangement

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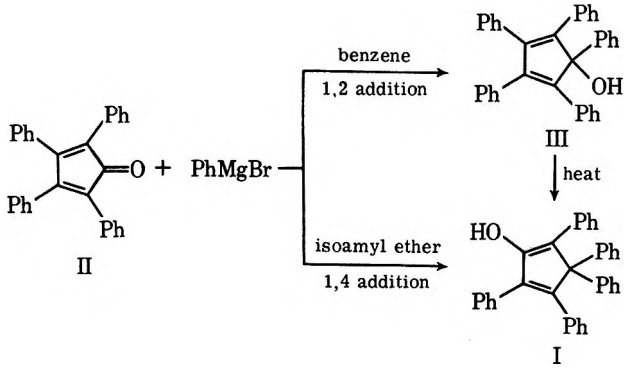
Received January 27, 1972

1,2 addition of phenylmagnesium bromide to tetraphenylcyclopentadienone in benzene affords the magnesium bromide salt of 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol. Replacing the benzene with isoamyl ether and refluxing for 8 hr converts the above salt into the magnesium bromide salt of 1,1,2,3,4-pentaphenyl-2,4-cyclopentadien-5-ol by a symmetry-allowed suprafacial [1,5] sigmatropic phenyl shift. Hydrolysis produced 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (IV) *via* the keto–enol tautomerization of the intermediate 1,1,2,3,4-pentaphenyl-2,4-cyclopentadien-5-ol (VII). Heating 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol in isoamyl ether for 6 hr produced IV *via* the same sigmatropic shift and enol intermediate VII. Investigation of the mechanism of this rearrangement in ionic solvents and in the presence of a radical inhibitor eliminated the possibility of any ionic or radical character to the rearrangement. Treatment of IV in acetic acid with 48% hydrobromic acid afforded 2,3,4,5,5-pentaphenyl-2-cyclopenten-1-one (VIII). Addition of phenylmagnesium bromide to VIII produced 1,2,3,4,5,5-hexaphenyl-2-cyclopenten-1-ol, which can be dehydrated with either acetyl chloride or acetic anhydride to produce 1,2,3,4,5,5-hexaphenyl-1,3-cyclopentadiene. This work is used to correct several errors in the existing literature.

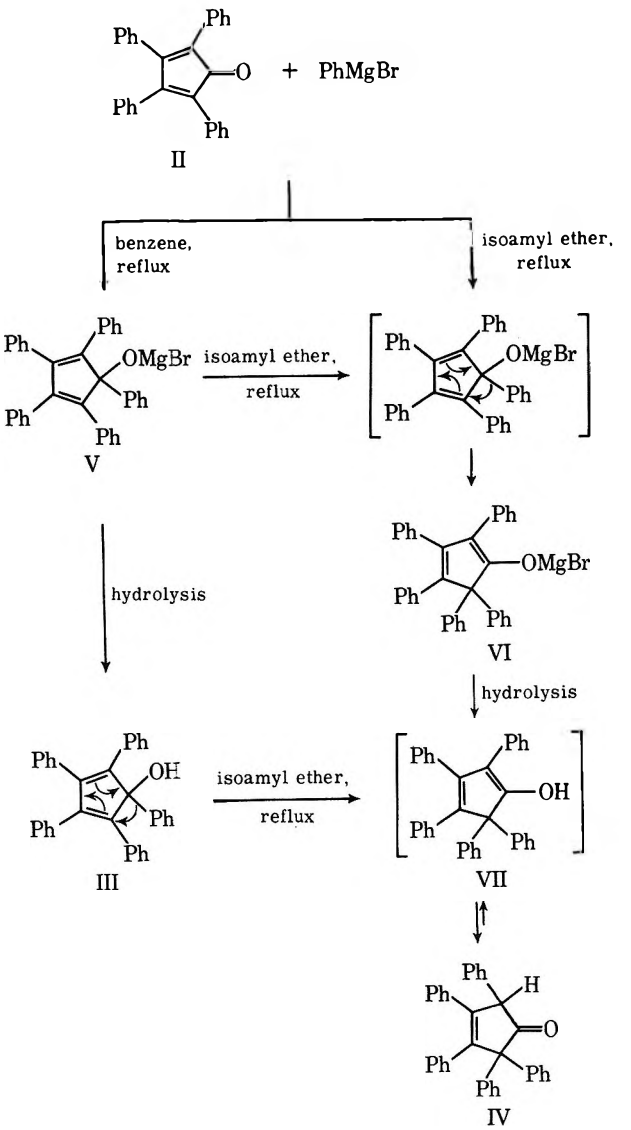
In 1943 Allen and VanAllan[1] reported that 2,3,3,4,5-pentaphenyl-1,4-cyclopentadien-1-ol (I) could be prepared by two methods: by direct 1,4 Grignard addition of phenylmagnesium bromide in isoamyl ether (isopentyl ether, bp 173°) to tetraphenylcyclopentadienone (tetracyclone, II), and by thermal isomerization of 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol (III) formed by 1,2 Grignard addition of phenylmagnesium bromide in benzene to tetracyclone (II). In 1961, Dufraisse, *et al.*,[2] reinvestigated the thermal isomerization of III, in the absence of solvent, and found that, in addition to two other minor products which were formed, the correct structure of the major product produced was not I but IV, 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one.[3] They explained the formation of IV *via* a pinacol rearrangement of III.



We have reinvestigated both the 1,4 Grignard addition of phenylmagnesium bromide to II and the thermal isomerization of III, and we have established that both reactions produce IV not *via* a pinacol rearrangement as previously reported, but *via* a symmetry-allowed suprafacial [1,5] sigmatropic phenyl shift. In addition we have repeated all the reactions which involve interconversions in the pentaphenylated cyclopentadienol system originally reported by Allen and VanAllan, and we have corrected the structures of all the products subsequently produced.

Addition of phenylmagnesium bromide in refluxing isoamyl ether to II, followed by hydrolysis, afforded a 65% yield of IV (Scheme I). The structural assignment of the product was aided by the spectral properties of a sample of IV independently synthesized[3] and by a mixture melting point comparison which showed

SCHEME I



(1) C. F. H. Allen and J. A. VanAllan, *J. Amer. Chem. Soc.*, **65**, 1384 (1943).

(2) C. Dufraisse, G. Rio, and A. Ranjon, *C. R. Acad. Sci.*, **253**, 2441 (1961).

(3) R. Breslow and H. W. Chang, *J. Amer. Chem. Soc.*, **83**, 3727 (1961).

no depression. To establish that IV is formed by thermal isomerization of the magnesium bromide salt V formed by 1,2 addition of phenylmagnesium bromide to II, we prepared V and investigated its reaction upon heating. Grignard addition of phenylmagnesium bromide to II in benzene afforded the desired magnesium bromide salt V, since quenching an aliquot of this solution afforded the dienol III. Replacing the solvent in the remaining unhydrolyzed reaction mixture with isoamyl ether and allowing the solution to reflux for 8 hr before hydrolysis and work-up afforded 65% (corrected for aliquot removed) of enone IV.

These results indicate that a direct 1,6 addition of phenylmagnesium bromide to II did not occur, but that the 1,2-addition product V initially formed when phenylmagnesium bromide is added to II thermally rearranges to VI. This rearrangement probably proceeds through a phenyl migration by a symmetry-allowed suprafacial [1,5] sigmatropic shift. This is the first such rearrangement reported for magnesium salts obtained from Grignard reactions and it is striking that such a rearrangement is so facile and that it affords such a good yield of rearranged product. Hydrolysis of the magnesium bromide salt VI affords only IV, probably through the dienol VII, which indicates that in this keto–enol tautomerization the keto form IV is highly favored (Scheme I).

In an effort to establish if such a sigmatropic shift is possible in the cyclopentadienol system we prepared III[1,3,4] by the 1,2 Grignard addition of phenylmagnesium bromide to II. Isolation of III (90%) and then placing it under reflux for 6 hr in isoamyl ether produced a 90% conversion of III to IV, probably through the dienol intermediate VII. The ease with which the dienol III is isomerized to the enone IV is very striking and it takes place much cleaner and in higher yield in the presence of solvent than in the absence[1,2] of solvent.

In order to study the mechanism of this phenyl shift and to establish that this rearrangement is indeed sigmatropic, and that it proceeds without any ionic or radical character, we performed the following reactions. Allowing III to reflux in isoamyl ether for 6 hr with a strong stream of oxygen bubbling through the refluxing solution continuously did not affect the yield of IV, since a 90% conversion of III to IV was again obtained. These results are exactly the same as those obtained when the reaction was performed without oxygen. This indicates that the observed phenyl shift is not radical in nature, since the presence of a radical inhibitor did not affect the yield of IV obtained. To eliminate the possibility of there being any ionic character to the rearrangement, we first allowed III to reflux in isoamyl ether for only 3 hr and by chromatography separated and isolated the ketone IV and the starting alcohol III. Under these conditions only 20% of IV was produced, while unrearranged alcohol III accounted for the remaining 80% of the reaction mixture. Repeating this reaction using dimethyl sulfoxide (DMSO) as the solvent and heating for 3 hr at 173°, followed by chromatography, afforded exactly the same yields of ketone IV and recovered unrearranged alcohol III, even though changing the solvent caused the reaction to be run in a medium of considerably increased dielectric constant: isoamyl ether, ϵ 2.82;[5] DMSO, ϵ 46.6.[6] These results indicate that it is highly unlikely that there is any ionic character to the phenyl migration observed. Having eliminated the possibility of any ionic or radical character to the observed rearrangement, it is left to be characterized as a [1,5] sigmatropic phenyl shift which must be suprafacial if it is thermally induced and if it is to obey the Woodward–Hoffmann rules.[7]

Once the correct structure of IV and its mechanism of formation was established, we turned our attention to its reactions. In Scheme II, we have listed the reactions performed and the structures assigned by Allen and VanAllan;[1] directly below their work we have represented the same reactions with the correct structures of the starting materials and products as established by this work. Attempted reaction of phenylmagnesium bromide with IV afforded only recovered starting material, as would be expected if our assigned structure (the presence of a proton α to the keto group) is correct for IV. Treatment of the unconjugated enone IV in glacial acetic acid with 48% hydrobromic acid afforded 73% of the conjugated enone 2,3,4,5,5-pentaphenyl-2-cyclopenten-1-one[2] (VIII). This product most likely arises from protonation of IV at C_3 followed by proton elimination from C_5.

The enone VIII was dissolved in benzene, added to a benzene solution of phenylmagnesium bromide, allowed to reflux overnight, and hydrolyzed to yield 85% of the enol IX, 1,2,3,4,5,5-hexaphenyl-2-cyclopenten-1-ol.

Dehydration of IX using excess acetyl chloride afforded 96% of X, 1,2,3,4,5,5-hexaphenyl-1,3-cyclopentadiene,[1] after refluxing for 24 hr, while dehydration of IX using acetic anhydride afforded 90% of X after refluxing for 3 days.

Experimental Section

1,2,3,4,5-Pentaphenyl-2,4-cyclopentadien-1-ol (III).—Into a 1-l., three-necked flask equipped with a mechanical stirrer and a reflux condenser was added 1.96 g (0.080 g-atom) of magnesium turnings and 13.36 g (0.080 mol) of bromobenzene in 150 ml of dry ether. After the reaction was complete, the ether was replaced by 50 ml of dry benzene and the mixture was brought to reflux. Tetracyclone (II, 7.70 g, 0.020 mol) dissolved in 100 ml of benzene was added dropwise to the refluxing Grignard solution. After the addition was complete the mixture was refluxed and stirred for 2 hr, cooled by means of an ice bath, and hydrolyzed with 200 ml of 10% ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted twice with 20-ml portions of benzene, and the benzene solutions were combined, washed with water, and dried over magnesium sulfate. Concentration of the benzene solution to essential dryness and recrystallization of the residue from petroleum ether (bp 30–60°) gave 8.40 g (0.0182 mol, 91%) of pale yellow crystals, mp 175–176° (lit.[4] mp 175–176°).

2,2,3,4,5-Pentaphenyl-3-cyclopenten-1-one (IV). A. By Grignard Reaction.—Using the same set-up and amounts of reagents as described above, an ether solution of phenylmagnesium bromide was prepared. After the reaction was complete, the ether was replaced with freshly distilled and dried isoamyl ether (isopentyl ether, bp 173°), the mixture was cooled to room temperature, and 3.84 g (10.0 mmol) of II was added as a solid. The mixture was then heated under reflux for 8 hr,

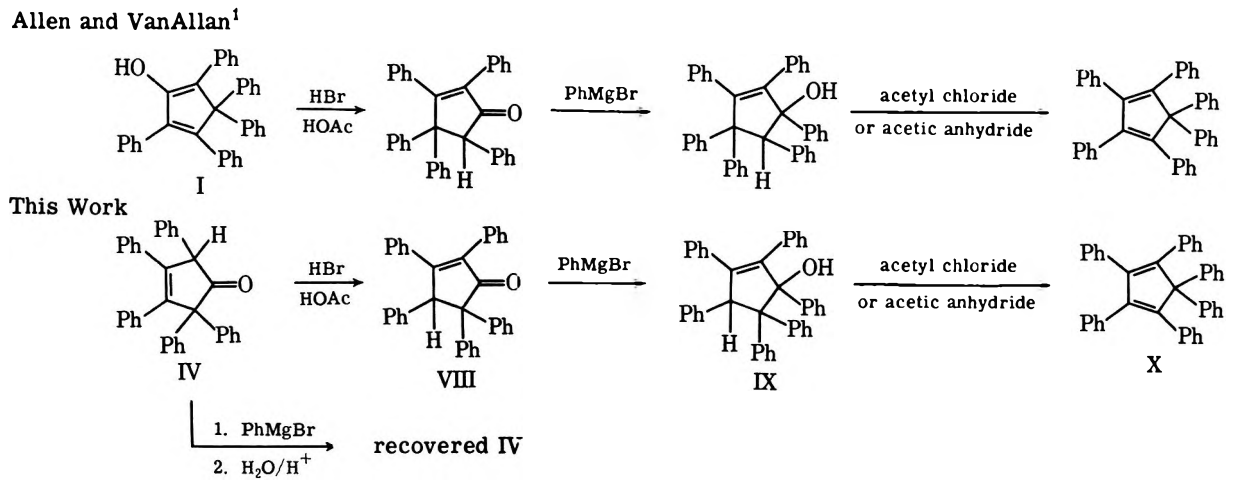
(4) K. Ziegler and B. Schnell, *Justus Liebigs Ann. Chem.*, **445**, 266 (1925).

(5) A. Weissberger, E. S. Proskauer, J. A. Riddick, and E. E. Toops, Jr., "Techniques of Organic Chemistry," Vol. VII, Interscience, New York, N. Y., 1955, p 123.

(6) E. M. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968, p 269.

(7) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970, pp 114–132.

SCHEME II



cooled by means of an ice bath, hydrolyzed, and worked up as described above. Removal of the solvent under vacuum afforded a viscous brown oil which was crystallized from benzene and petroleum ether to give 3.00 g (6.47 mmol, 64.7%) of white crystals, mp 194.5–196° (lit.[2,3] mp 194–195°). A mixture melting point with an authentic sample prepared as in D below showed no depression. The spectral data, ir,[2,3] uv,[2,3] and nmr,[3] for this compound agreed with the literature. The compound gave satisfactory carbon and hydrogen analyses and its molecular weight (mass spectrum) was 462 (calcd 462).

B. By Thermal Isomerization.—Into a 100-ml round-bottomed flask equipped with a condenser was placed 1.00 g (2.16 mmol) of III and 50 ml of isoamyl ether. The solution was refluxed for 6 hr and cooled, and the solvent was removed under vacuum to yield a viscous brown oil which was crystallized from benzene and petroleum ether to give 0.90 g (1.94 mmol, 90%) of white crystals identical in all respects with the product obtained in A above.

C. By Thermal Isomerization of the Intermediate Magnesium Bromide Salt.—Into a 500-ml three-necked round-bottomed flask equipped with a mechanical stirrer and a condenser was placed 0.96 g (0.039 g-atom) of magnesium turnings and 6.28 g (0.040 mol) of bromobenzene in 100 ml of ether and the mixture was stirred until the Grignard reagent had completely formed. The ether was then replaced with 100 ml of benzene, and 1.50 g (0.0039 mol) of II in 50 ml of benzene was added dropwise. When the addition was complete, the reaction mixture was refluxed for 2 hr, and a 20-ml aliquot was removed. Hydrolysis and work-up of the aliquot afforded 0.24 g (0.51 mmol, 13%) of III. The benzene in the remaining reaction mixture was replaced with isoamyl ether, refluxed with stirring for 8 hr, cooled by means of an ice bath, and hydrolyzed with 10% ammonium chloride solution. Work-up as described above afforded 0.97 g (2.1 mmol, 53%) of IV.

D. Independent Synthesis of IV.—Using the procedure described by Breslow, *et al.*,[3] afforded a pure sample of IV which was used to establish the structure of the product obtained from reactions A, B, and C above.

Thermal Isomerization of III in the Presence of a Radical Inhibitor.—Into a 250-ml three-necked round-bottomed flask equipped with a reflux condenser, a mechanical stirrer, and a gas-dispersion tube was placed 75 ml of isoamyl ether. The solvent was heated to reflux while a strong stream of oxygen was passed through the solution by means of the gas-dispersion tube which protruded below the surface of the solution. At this point 2.00 g (4.3 mmol) of III was added as a solid (which immediately dissolved), and the solution was refluxed for 6 hr while the oxygen stream was continued. After this time the oxygen stream was stopped, the solution was cooled to room temperature, and the solvent was removed under reduced pressure. This afforded a viscous brown oil which was crystallized from benzene and petroleum ether to give 1.80 g (3.88 mmol, 90%) of white crystals identical in all respects with the product obtained in A above.

Thermal Isomerization of III for Only 3 Hr. A. In Isoamyl Ether.—Into a 250-ml round-bottomed flask equipped with a condenser was placed 75 ml of isoamyl ether and the solvent was heated to reflux. At this point 2.00 g (4.3 mmol) of III was added as a solid (which immediately dissolved) and the mixture was refluxed for 3 hr. After this time the solution was cooled to room temperature and the solvent was removed under vacuum, affording a viscous brown oil which was taken up in carbon tetrachloride and chromatographed on Woelm acid alumina using carbon tetrachloride as eluent. Collection of the light yellow band which separated and concentration of the eluent afforded 0.40 g (0.86 mmol, 20%) of white crystals identical in all respects with the product obtained from A above. Changing the eluent to a 9:1 mixture of carbon tetrachloride–chloroform brought down a second yellow band. Concentration of the eluent afforded 1.59 g (3.43 mmol, 80%) of starting alcohol III.

B. In Dimethyl Sulfoxide.—This reaction was performed on the same scale, at the same temperature, and in the same manner as the one described above except that DMSO was used as the solvent. After the reaction was complete, the solution was cooled to room temperature, poured into 200 ml of water, and extracted three times with benzene. The benzene solutions were combined, washed three times with water, dried over anhydrous magnesium sulfate, and concentrated under vacuum to afford a yellow residue which was dissolved in carbon tetrachloride and chromatographed as described above. The first yellow band eluted with carbon tetrachloride afforded 0.40 g (0.86 mmol, 20%) of IV, while elution of the second yellow band with a 9:1 carbon tetrachloride–chloroform mixture afforded 1.59 g (3.43 mmol, 80%) of starting alcohol III.

Reaction of IV with Phenylmagnesium Bromide.—Into a 500-ml three-necked round-bottomed flask equipped with a condenser and a mechanical stirrer was placed 0.50 g (0.020 g-atom) of magnesium turnings and 3.14 g (0.020 mol) of bromobenzene in 100 ml of dry ether. After the Grignard reagent had completely formed the ether was replaced by 100 ml of benzene, and 8.31 g (0.018 mol) of IV in 75 ml of benzene was added slowly. After the mixture was refluxed for 20 hr, it was hydrolyzed and worked up in the usual manner to afford a quantitative recovery of IV.

2,3,4,5,5-Pentaphenyl-2-cyclopenten-1-one[2] (VIII).—Into a 50-ml round-bottomed flask equipped with a condenser was added 1.50 g (3.24 mmol) of IV, 2.5 ml of 48% hydrobromic acid, and 10 ml of glacial acetic acid and the mixture was refluxed for 3.5 hr. The reaction mixture was then cooled, poured into 500 ml of cold water, and extracted with benzene, and the benzene was separated and dried over anhydrous magnesium sulfate. Concentration of the benzene afforded a yellow oil which was crystallized from benzene and petroleum ether to give 1.10 g (2.37 mmol, 73%) of pale yellow crystals, mp 166–167° (lit.[2] mp 169–170°). The ir and uv spectral data for this compound agreed with the literature;[2] nmr (CCl_4) τ 2.79 (m, 15, ArH), 4.85 (s, 1, CH); mol wt (mass spectrum) 462 (calcd 462).

1,2,3,4,5,5-Hexaphenyl-2-cyclopenten-1-ol (IX).—Into a 500-ml three-necked round-bottomed flask equipped with a mechanical stirrer and reflux condenser was placed 0.96 g (0.040 g-atom) of magnesium turnings and 6.28 g (0.040 mol) of bromobenzene in 75 ml of dry ether. After the Grignard reagent had completely formed, the ether was replaced with 100 ml of benzene and 2.3 g (0.0050 mol) of VIII in 50 ml of benzene was added

slowly. The mixture was allowed to reflux overnight, hydrolyzed, and worked up in the usual manner to yield 2.29 g (0.0042 mol, 85%) of pale yellow crystals: mp 245–248°; ir (CCl_4) 3635 cm^{-1} (OH); nmr (CCl_4) τ 3.10 (m, 30, ArH), 4.50 (s, 1, OH), 7.26 (s, 1, CH).

Anal. Calcd for $C_{41}H_{32}O$: C, 91.07; H, 5.96; mol wt, 540. Found: C, 90.78; H, 6.06; mol wt, 540 (mass spectrum).

1,2,3,4,5,5-Hexaphenyl-1,3-cyclopentadiene[1] (X). A. Using Acetyl Chloride.—Into a 100-ml round-bottomed flask equipped with a condenser was placed 1.00 g (1.8 mmol) of IX and 25 ml of acetyl chloride, and the mixture was refluxed for 24 hr. After cooling to room temperature the mixture was carefully diluted with 100 ml of water and extracted with benzene and the benzene was dried over magnesium sulfate. Removal of the solvent under vacuum afforded a yellow oil which was crystallized from benzene and ethanol to yield 0.88 g (1.68 mmol, 96.5%) of white crystals: mp 175–177° (lit.[1] mp 172°); uv (CH_3CN) 335, 275 (sh), 247 mμ.

Anal. Calcd for $C_{41}H_{30}$: C, 94.21; H, 5.77; mol wt, 522. Found: C, 94.27; H, 5.93; mol wt, 522 (mass spectrum).

B. Using Acetic Anhydride.—Using the same procedure and amounts of reagents as described above but allowing the mixture to reflux for 3 days afforded 90% of product identical with that described above.

Registry No.—III, 2137-74-8; IV, 34759-47-2; VIII, 34759-48-3; IX, 34759-49-4; X, 34759-50-7.

Acknowledgments.—We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We also wish to thank the College of Arts and Sciences at VPI and SU for a Small Projects Grant which also helped support this research.

The Synthesis and Transformations of 2-Nitro-1-phenyl-1-hydroxyindene and Its Isomer

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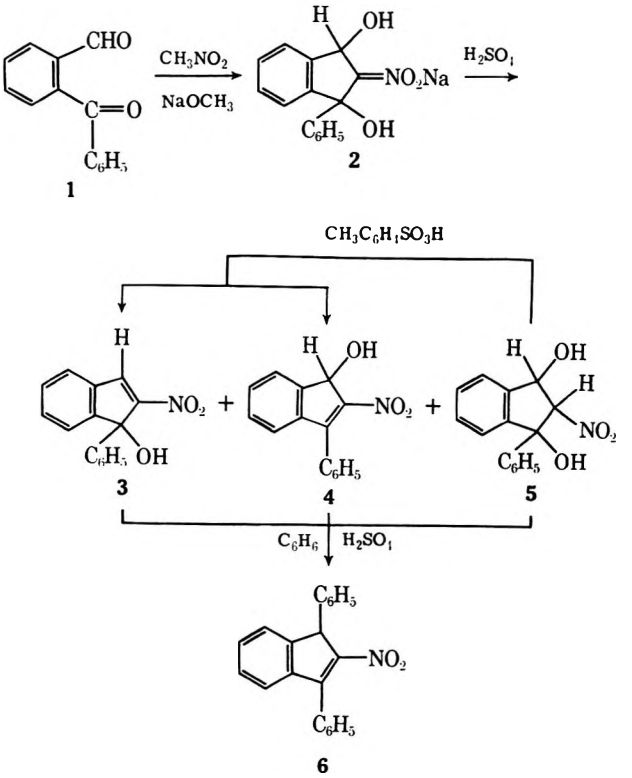
Received January 19, 1972

Condensation of 2-benzoylbenzaldehyde (1) with nitromethane in the presence of sodium methoxide gave, after acidification, 2-nitro-1-phenyl-1-hydroxyindene (3), 2-nitro-3-phenyl-1-hydroxyindene (4), and 2-nitro-1-phenyl-1,3-dihydroxyindan (5). The first two compounds were converted to the corresponding acetates 7 and 8, which on treatment with primary or secondary amines gave the nitroenamines 9 and the ammonium salts 11 of the 2-nitro-1-phenyl-3-indanone (12), respectively. Hydrolysis of 9 or 11 afforded 12. Treatment of the acetate 7 with alcohols yielded 2-nitro-3-phenyl-1-alkoxyindene (17). After prolonged reflux the isomeric 2-nitro-1-phenyl-3-alkoxyindene (18) was obtained. A catalytic amount of triethylamine rearranges 17 to 18.

The condensation of 1,4, 1,5, and 1,6 dialdehydes with nitromethane in an alkaline medium followed by acidification is a general method for the synthesis of five-, six-, and seven-membered ring systems.[1] However, little is known about the reactivity of diketones or keto aldehydes toward nitromethane.[1] This led us to study the condensation of *o*-benzoylbenzaldehyde[2] with nitromethane under alkaline conditions.

Treatment of *o*-benzoylbenzaldehyde with nitromethane in the presence of 1 equiv of sodium methoxide in methanol generated within 2 min a white, crystalline precipitate of the 1-phenyl-1,3-dihydroxy-2-acinitroindan sodium salt 2. Acidification of 2 with sulfuric acid in ice yielded two isomeric 2-nitrophenylhydroxyindenes (3 and 4) as well as 2-nitro-1-phenyl-1,3-dihydroxyindan (5). Structures were readily assigned from an interpretation of the nmr spectra for the three compounds. Dehydration of 5 with *p*-toluenesulfonic acid in refluxing benzene gave a mixture consisting mainly of 4 and a small amount of 3. Treatment of either 3, 4, or 5 with sulfuric acid in benzene as dehydrating agent gave 1,3-diphenyl-2-nitroindene (6)[3] (Scheme I).

SCHEME I



Acetylation of 3 was found to be temperature dependent. At −5°, the acetate 7 was obtained usually accompanied by 8. The thermodynamically more stable product 8 was produced either at room temperature from 3, by direct acetylation of 4, or by treatment of 7 with glacial acetic acid at room temperature (Scheme II).

Addition of primary or secondary amines to a solution of 7 resulted in an immediate color change from light yellow to green with the formation of nitroenamines of type 9.[4] Most likely Michael addition with

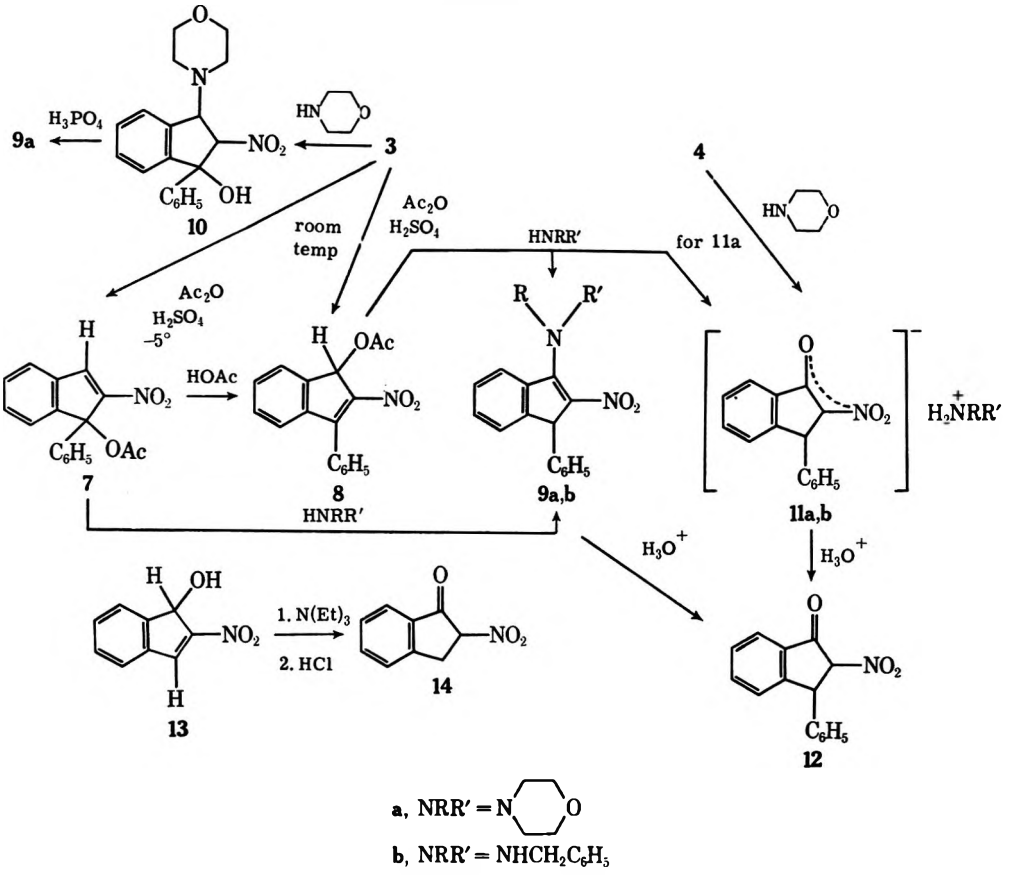
(1) F. W. Lichtenthaler, *Angew. Chem., Int. Ed. Engl.*, **3**, 211 (1964).

(2) W. Metlesics, T. Anton, M. Chaykovsky, V. Toome, and L. H. Sternbach, *J. Org. Chem.*, **33**, 2874 (1968).

(3) C. F. Koelsch, *ibid.*, **26**, 4238 (1961).

(4) See also F. W. Lichtenthaler and N. Majer, *Tetrahedron Lett.*, **411** (1969).

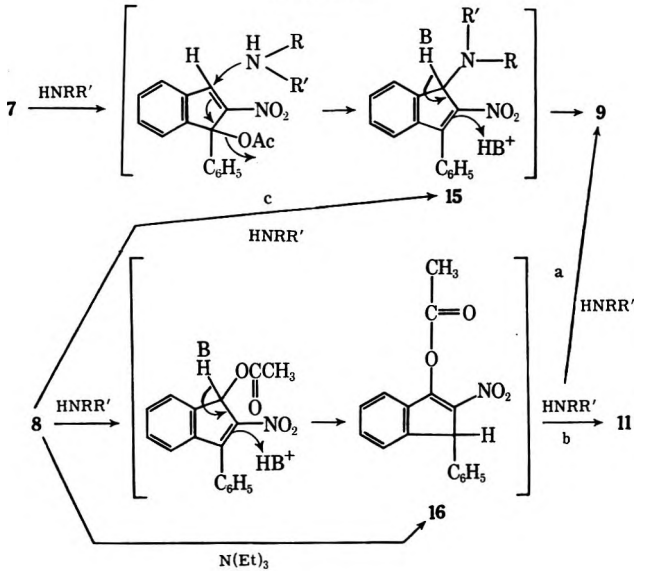
SCHEME II



a, NRR′ = N(morpholino)

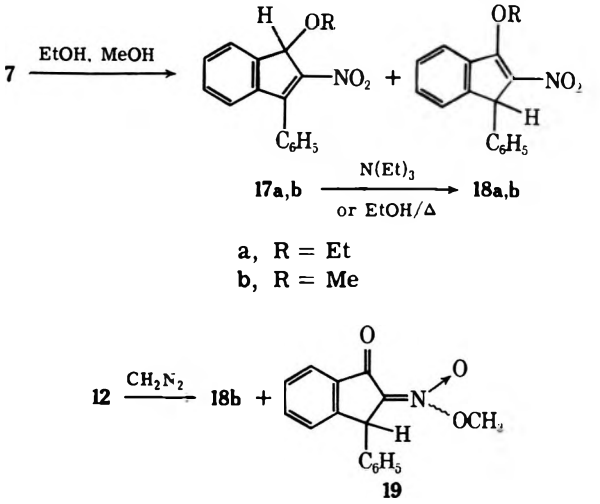
b, NRR′ = $NHCH_2C_6H_5$

SCHEME III



immediate loss of acetic acid leads to an intermediate like **15** (Scheme III) which then rearranges to **9**. If a leaving group less active than acetate is present, *e.g.*, the hydroxyl group in **3**, the reaction sequence stops at the Michael adduct. Thus, treatment of **3** with morpholine leads to compound **10**. However, the reaction will proceed to **9a** if the hydroxyl group is converted into a good leaving group by protonation with phosphoric acid. The transformation of intermediate **15** to compound **9** is facilitated by base[5] as was illustrated by the expeditious rearrangement of **17a** to **18a** in the presence of a catalytic amount of triethylamine (Scheme IV).

SCHEME IV



When the isomeric acetate **8** was treated with primary or secondary amines only a small amount of **9** was formed. The major products were the ammonium salts **11** of 2-nitro-1-phenylindanone (**12**). A possible reaction sequence is indicated in Scheme III with the initial formation of the enol acetate **16**, followed by ready cleavage to **9** or **11** by attack of the nucleophile of C_3 (path a) or on the carbonyl function of the acetoxy group (path b), respectively. Direct nucleophilic displacement of the acetoxy group in **8** would also lead to **9** (path c) *via* the intermediate **15**. These mechanisms

(5) A. M. Weidler, *Acta Chem. Scand.*, **17**, 2724 (1963); G. Bergson and A. M. Weidler, *ibid.*, **18**, 1487, 1498 (1964); C. Ohlson, J. Wollmark, and G. Bergson, *ibid.*, **20**, 750 (1966).

were clarified by the isolation of the unstable intermediate **16**, obtained by treatment of **8** with catalytic amounts of triethylamine. Reaction of **16** with morpholine gave exclusively **11a**. No trace of **9** could be detected by tlc, thereby excluding path a. Compound **11** must be derived from **8** as indicated by path c. The formation of the intermediate **16** is analogous to the facile rearrangement of **4** to **11a** with morpholine.

Hydrolysis of **9** or acidification of **11** led to **12**. We found that the unsubstituted 2-nitroindenone (**14**)[6] was also formed in fair yield by treatment of the 1-hydroxy-2-nitroindene (**13**)[7] with 1 equiv of triethylamine followed by immediate acidification.

The ease of formation of nitroenamines from **7** prompted us to investigate the products resulting from the treatment of this compound with alcohols. Two types of compounds were obtained, the adducts **17** and the rearranged compounds **18** (Scheme IV). Prolonged reflux of the reaction mixture led to a high percentage of the rearranged product. This transformation seems to proceed in polar solvents more rapidly than in nonpolar solvents. After 16 hr reflux in ethanol, a pure sample of **17a** was converted to **18a** in 77% yield, whereas reflux in toluene for the same period of time led to only 17% of the rearranged product as estimated by nmr. As mentioned above, this rearrangement was facilitated by the presence of a catalytic amount of triethylamine. The structural assignment for **18** was based on the signal for H_4 at 0.3 ppm downfield of the aromatic region in the nmr spectrum. This would be expected because of the presence of syn axial heteroatoms at C_3. In the case of the nitroenamines **9**, an even stronger deshielding of 0.4 ppm was observed. The structure of **18** was further substantiated by the methylation of **12** with diazomethane to give **18b** and the nitronic ester **19**.[8]

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. The uv spectra were determined on a Cary Model 14 spectrophotometer, nmr spectra with a Varian A-60 instrument, and the ir spectra on a Beckman IR-9 spectrophotometer. All spectra were compared in order to confirm or exclude the expected structural changes.

1,3-Dihydroxy-1-phenyl-2-acinitroindan Sodium Salt (2).—To a solution of 10.5 g (50 mmol) of *o*-benzoylbenzaldehyde and 6.1 g (100 mmol) of nitromethane in 50 ml of methanol was added 50 ml of 1 *N* sodium methoxide solution in methanol. The resulting white precipitate was stirred for 30 min, and after the addition of 100 ml of ether was collected on a funnel and washed with ether, uv max (0.01 *N* KOH) 256 mμ (ε 10,960), 268 (9800), 274.5 (10,200).

2-Nitro-1-phenyl-1-hydroxyindene (3). 2-Nitro-3-phenyl-1-hydroxyindene (4), and 2-Nitro-1-phenyl-1,3-dihydroxyindan (5).—The above prepared salt was suspended in 100 ml of water and, with stirring, 30 g of ice and 10 ml of concentrated sulfuric acid were poured into the reaction mixture. After 30 min of stirring, 100 ml of methylene chloride was added and the organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to a viscous oil. On addition of 30 ml of benzene and standing, a white solid appeared which was collected and rinsed with benzene to give 3.91 g (28.8%) of **5** as white rods, nmr ($CDCl_3$) δ 5.32 (s, 2, OH), 5.38, 5.68 (2 d, 2 × 1, CHCH), 7.15 (m, 9, ArH).

Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.16; H, 4.99; N, 5.13.

The filtrate was evaporated and treated with 15 ml of a mixture of hexane and ethyl acetate (2:1). The product formed yielded, after washing with the above mixture, 3.51 g of **3** as rectangular plates, mp 118.5–120°. Repetition of the above procedure gave an additional 1.44 g of **3**, mp 117–120°, for a combined yield of 4.95 g (39.1%), nmr ($CDCl_3$) δ 3.72 (broad s, 1, OH), 7.60 (m, 9, ArH), 8.01 (s, 1, vinyl H_3).

Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.08; H, 4.59; N, 5.69.

Evaporation of the above filtrate yielded an oil, which was extracted several times with 100-ml portions of boiling cyclohexane. The combined cyclohexane solutions were evaporated to a residue and barely dissolved in a small amount of methylene chloride. On addition of a mixture of hexane and ethyl acetate (2:1) and cooling, 390 mg (3.1%) of yellow, clustered prisms of **4** were collected, mp 121–124°, nmr ($CDCl_3$) δ 3.50 (broad s, 1, OH), 3.90 (s, 1, H_1), 7.57 (m, 9, ArH).

Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.44; H, 4.50; N, 5.47.

2-Nitro-3-phenyl-1-hydroxyindene (4).—A mixture of 12 g (44.3 mmol) of **5** and 1 g of toluenesulfonic acid was refluxed for 1.5 hr. After evaporation, the obtained residue was recrystallized from methylene chloride–hexane to give a mixture of **3** and **4** as the first crop. Concentration of the mother liquor yielded 5.55 g of **4**. Recrystallization from methylene chloride–hexane afforded 4.84 g (43.2%) of yellow prisms, mp and mmp 121–123.5°.

2-Nitro-1,3-diphenylindene (6).[9]—A solution of 250 mg (0.92 mmol) of **5** in 12 ml of benzene was mixed with 0.6 ml of concentrated sulfuric acid and refluxed for 1.25 hr. The cold solution was extracted three times with 70-ml portions of water, dried over sodium sulfate, filtered, and evaporated. The residue was recrystallized from ether–petroleum ether (bp 30–60°) to give 210 mg (73%) of **6** as yellow prisms, mp 105–107°, nmr ($CDCl_3$) δ 5.36 (1, s, H_1), 7.1–7.6 (m, 14, ArH).

Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.83; N, 4.47. Found: C, 80.56; H, 5.04; N, 4.43.

2-Nitro-1-phenyl-1-acetoxyindene (7).—A slurry of 40.5 g (160 mmol) of **3** in 100 ml of acetic anhydride was cooled to −5 to −10°, and then 1 ml of concentrated sulfuric acid was added to the vigorously stirred mixture. After 45 min, the temperature was allowed to rise to 0°. The yellow plates formed were collected and washed well with a mixture of hexane and ethyl acetate (2:1) to give 32.0 g (67.7%) of **7**, mp 140–144°. Recrystallization from benzene afforded the analytically pure material, mp 148–150°, nmr ($CDCl_3$) δ 2.17 (s, 3, CH_3), 6.3 (m, 9, ArH), 7.94 (s, 1, vinyl H_3).

Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.42; H, 4.36; N, 4.71.

2-Nitro-3-phenyl-1-acetoxyindene (8). A.—To a solution of 10 g (39.5 mmol) of **3** in 20 ml of acetic anhydride was added 0.1 ml of concentrated sulfuric acid at room temperature. The dark brown solution was stirred for 30 min and then evaporated. The residue was treated with ice and saturated sodium bicarbonate solution. The resulting precipitate was filtered, washed well with water, dissolved in methylene chloride, dried over anhydrous magnesium sulfate, filtered, and evaporated. Addition of ether afforded 8.3 g of **8**, mp 115–120°. Recrystallization from ethanol gave 6.2 g (53.2%) of dark yellow prisms, mp 128–131°, nmr ($CDCl_3$) δ 2.20 (s, 3, CH_3), 7.06 (s, 1, H_1), 7.5 (m, 9, ArH).

Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.10; H, 4.48; N, 4.64.

B.—To a solution of 200 mg (0.79 mmol) of **4** in 2 ml of acetic anhydride was added 1 drop of concentrated sulfuric acid at room temperature. After 20 min of stirring, the mixture was poured into ice and saturated sodium bicarbonate solution. The crystalline, orange precipitate, 210 mg, mp 119–123°, was recrystallized from methylene chloride–hexane to give 100 mg (42.9%) of **8**, mp and mmp 127–131°.

C.—A solution of 100 mg (0.34 mmol) of **7** in 3 ml of acetic acid was stirred overnight at room temperature. On dilution with ice and water, a reddish yellow crystalline solid (70 mg) was obtained, mp 120–126°, which on recrystallization from ethyl acetate and hexane gave **8**, mp and mmp 127–128.5°.

(6) T. Kametani, H. Sugakara, and S. Asagi, *Chem. Pharm. Bull.*, **14**, 1408 (1966); H. H. Baer and S. R. Naik, *J. Org. Chem.*, **35**, 2927 (1970).

(7) J. Thiele and E. Weitz, *Justus Liebigs Ann. Chem.*, **377**, 1 (1910); F. W. Lichtenthaler, *Tetrahedron Lett.*, 775 (1963); H. H. Baer and B. Achmatowicz, *J. Org. Chem.*, **29**, 3180 (1964).

(8) The stereochemistry of this compound has not been established.

(9) The formation of **6** was also observed from **3** and **4** under the same reaction conditions.

2-Nitro-1-phenyl-3-morpholinoindene (9a). A.—A solution of 8 g (27.1 mmol) of 7 in 60 ml of acetone was mixed with 4.7 g (54.5 mmol) of morpholine in 10 ml of acetone. After 45 min of stirring at room temperature, ice and water were added. The precipitate collected was recrystallized from methylene chloride–hexane to give 6.29 g (72.1%) of 9a as deep yellow prisms, mp 205–206° dec, nmr ($CDCl_3$) δ 3.92 (m, 8, aliphatic H), 5.18 (s, 1, H_1) 7.22 (m, 8, ArH), 7.72 (m, 1, H_4).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.92; H, 5.75; N, 8.64.

B.—A mixture of 550 mg (1.62 mmol) of 2-nitro-3-morpholino-1-hydroxy-1-phenylindane (10) and 3 g of 85% phosphoric acid was heated on the steam bath for 10 min until a clear brown solution was present. After dilution with water, insoluble solids were filtered off. The filtrate was made basic with concentrated sodium hydroxide solution and then extracted with 75 ml of chloroform. The organic layer was separated, dried over anhydrous sodium sulfate, and evaporated to dryness to give on addition of methanol 180 mg of yellow prisms, mp and mmp 208–210°. The above insoluble solid was dissolved in chloroform and washed with dilute sodium hydroxide solution. The organic layer was worked up as above to give 100 mg of crude material, mp and mmp 199–205°. A total of 280 mg (53.6%) of 9a was obtained.

2-Nitro-1-phenyl-3-benzylaminoindene (9b).—This compound was prepared using the same procedure as described for 9a, method A, in 91% yield as yellow prisms from methylene chloride–ethanol, mp 180–181°, nmr ($CDCl_3$) δ 5.10 (s, 2, CH_2), 5.20 (s, 1, H_1), 7.22, 7.40 (m, 13, ArH), 7.85 (m, 1, H_4), 10.28 (broad s, 1, NH).

Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.18; H, 5.30; N, 8.18. Found: C, 76.88; H, 5.24; N, 8.16.

2-Nitro-3-morpholino-1-hydroxy-1-phenylindan (10).—To a solution of 2.53 g (1 mmol) of 3 in 15 ml of tetrahydrofuran was added a small excess of morpholine in 5 ml of tetrahydrofuran. After 30 min of stirring at room temperature, the mixture was concentrated to *ca.* 1/3rd of the volume and diluted with 25 ml of ether. The product formed was collected to give 2.58 g (76%) of white prisms, mp 172° dec. Recrystallization of a sample from tetrahydrofuran–chloroform afforded the analytically pure product, mp 171–172° dec, nmr (DMSO) δ 2.52, 3.63 (m, 2 × 4, aliphatic H), 5.47 (s, 2, CHCH), 6.56 (s, 1, OH), 7.37 (m, 9, ArH).

Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.28; H, 5.96; N, 8.23.

Morpholinium 1-Phenyl-3-indanone-2-nitronate (11a). A.—A solution of 20 g (67.8 mmol) of 8 in 150 ml of methylene chloride was added dropwise to a solution of 12 g (138 mmol) of morpholine in 80 ml of methylene chloride. The thick white precipitate which formed was collected after 40 min and washed well with methylene chloride. The filtrate was set aside. The salt obtained (18.7 g) was recrystallized from hot dimethylformamide to give 12.9 g (56%) of 11a as white needles: mp 204° dec; ir (KBr) 2800–2480 cm^{-1} (amine salt); nmr (DMSO) δ 3.17, 3.83 (m, 2 × 4, aliphatic H), 4.96 (s, 1, H_1), 6.9–7.66 (m, 9, ArH).

Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 66.94; H, 6.00; N, 8.22.

The above filtrate was washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was recrystallized from methylene chloride–carbon tetrachloride to give 2.0 g (9%) of 9a as deep yellow prisms, mp and mmp 208–210° dec.

B.—A solution of 590 mg (2 mmol) of 2-nitro-1-phenyl-3-acetoxyindene (16) in a 5 ml of methylene chloride was added dropwise to a solution of 348 mg (4 mmol) of morpholine in 2 ml of methylene chloride. After 10 min, the precipitate was collected to give 622 mg (91.5%) of 11a as white needles, mp and mmp 196–199° dec.

The methylene chloride filtrate was washed with water and dried over anhydrous sodium sulfate. Tlc of this solution, compared with 9a using hexane–ethyl acetate (1:1) as eluent showed no trace of 9a.

C.—To a solution of 100 mg (0.39 mmol) of 4 in a minimum amount of tetrahydrofuran was added 86 mg of morpholine. After the solution had stood for 30 min, the white precipitate formed was filtered off and washed well with ether to give 135 mg (100%) of 11a, mp and mmp 198–199° dec.

Benzylammonium 1-Phenyl-3-indanone-2-nitronate (11b).—Following procedure A for 11a this compound was prepared similarly in 52.4% yield as pale yellow needles recrystallized from hot dimethylformamide: mp 200–203° dec; ir (KBr) 2800–2480 cm^{-1} (amine salt); nmr (DMSO) δ 4.10 (s, 2, CH_2), 4.98 (s, 1, H_1), 7.17, 7.38 (m, 14, Ar H), 8.62 (broad s, 3, NH_3).

Anal. Calcd for $C_{22}H_{20}N_2O_3$: C, 73.31; H, 5.59; N, 7.77. Found: C, 73.32; H, 5.61; N, 7.82.

A by-product, 9b, was obtained in 22.4% yield as yellow needles, mp and mmp 180–183° dec.

2-Nitro-1-phenyl-3-acetoxyindene (16).—To a solution of 2.95 g (10 mmol) of 8 in 10 ml of anhydrous methylene chloride was added 0.05 ml of triethylamine. The solvent was evaporated after 10 min. The residue was treated with ether and petroleum ether to give 2.44 g of a light tan solid. Recrystallization from methylene chloride–ether–petroleum ether afforded 1.35 g (45.8%) of 16 as colorless needles, mp 96–98° dec, nmr ($CDCl_3$) δ 2.37 (s, 3, CH_3), 5.23 (s, 1, H_1), 7.2–7.75 (m, 8, ArH), 7.95 (m, 1, H_4).

Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.34; H, 4.51; N, 5.04.

2-Nitro-1-phenyl-3-indanone (12). A.—A slurry of 500 mg (1.47 mmol) of 11a in 30 ml of ethanol and 50 ml of 2 *N* hydrochloric acid was warmed on the steam bath for 5 min. The organic solvent was evaporated and the aqueous residue was extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated. The residue obtained was recrystallized from ether–petroleum ether to give 270 mg (73%) of white rods: mp 93–96°; ir (KBr) 1745 cm^{-1} (CO); nmr ($CDCl_3$) δ 5.26, 5.40 (AB, J = 5 Hz, 2, CHCH), 7.0–8.0 (m, 9, Ar H).

Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.37; N, 5.53. Found: C, 71.15; H, 4.36; N, 5.53.

B.—A solution of 250 mg (0.77 mmol) of 9a in 50 ml of ethanol was treated with 100 ml of 2 *N* hydrochloric acid on the steam bath until the solution was completely discolored. The reaction was worked up as above to give 85 mg (44%) of crystalline material, mp and mmp 89–93°.

2-Nitro-1-indanone (14).—To a slurry of 3.54 g (20 mmol) of 2-nitro-1-hydroxyindene (13) in 13 ml of tetrahydrofuran was added 2.02 g (20 mmol) of triethylamine in 2 ml of tetrahydrofuran. After 4 min, 45 ml of water was added to the green solution and the pH was adjusted to 6 with 2 *N* aqueous hydrochloric acid. This solution was extracted three times with 30 ml of ether. The ethereal layers were discarded. The aqueous layer was cooled in an ice bath and acidified with 2 *N* hydrochloric acid to pH 2.5. A crystalline precipitate appeared and was collected to give 2.25 g, mp 70–75°. The solid was extracted into 1 l. of boiling petroleum ether (bp 60–90°), which was decanted from insoluble material and evaporated. Recrystallization of the residue from isopropyl alcohol–petroleum ether gave 1.05 g (30%) of pale yellow rods, mp 77–80°. A second crop of 300 mg, mp 75–77°, was obtained from the filtrates, nmr ($CDCl_3$) δ 3.78 (m, 2, CH_2), 5.48 (q, 1, H_2), 7.15–7.90 (m, 4, ArH).

Anal. Calcd for $C_9H_7NO_3$: C, 61.01; H, 3.98; N, 7.91. Found: C, 61.05; H, 4.03; N, 7.82.

2-Nitro-3-phenyl-1-ethoxyindene (17a). A.—A solution of 5.9 g (20 mmol) of 7 in 100 ml of ethanol was refluxed for 2 hr and then evaporated. The residue was taken up in 70 ml of ether and washed three times with 100-ml portions of water. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The product crystallized on addition of ether and petroleum ether. After two recrystallizations from ethanol, 2.6 g (46%) of 17a was obtained as yellow, clustered needles, mp 81.5–83°. From the filtrates, an additional 830 mg of less pure material, mp 79–81.5°, was isolated, nmr ($CDCl_3$) δ 1.25 (t, 3, CH_3), 3.75 (q, 2, CH_2O), 5.82 (s, 1, H_1), 7.58 (m, 9, ArH).

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.82; H, 5.48; N, 4.92.

2-Nitro-3-phenyl-1-methoxyindene (17b).—A solution of 10.6 g (36 mmol) of 7 in 150 ml of methanol was refluxed for 1.5 hr. On concentration and cooling, 7.88 g (82%) of 17b was collected as yellow rods, mp 113–114°. A second crop (630 mg) of less pure material, mp 112–113°, was obtained from the mother liquor. Recrystallization of a sample from methanol afforded an analytically pure product, mp 113–114.5°, nmr ($CDCl_3$) δ 3.41 (s, 3, CH_3O), 5.74 (s, 1, H_1), 7.49 (m, 9, ArH).

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.77; H, 5.01; N, 5.17.

2-Nitro-1-phenyl-3-ethoxyindene (18a). A.—A solution of

295 mg (1 mmol) of 7 in 30 ml of ethanol was refluxed for 23 hr. Evaporation of the solvent and crystallization of the residue from an ether–ethanol mixture gave 154 mg of a crude mixture of 17a and 18a (by nmr). Several recrystallizations from ethanol finally afforded a pure sample (29 mg, 10.3%) of 18a as yellow prisms, mp 88.5–90.5°, nmr ($CDCl_3$) δ 1.52 (t, 3, CH_3), 4.76 (AB of q, 2, CH_2O), 5.18 (s, 1, H_1), 7.29 (m, 8, ArH), 7.73 (m, 1, H_4).

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.49; H, 5.38; N, 5.01.

B.—To a solution of 50 mg (0.18 mmol) of 17a in 5 ml of methylene chloride was added 1 drop of triethylamine. The solvent was evaporated after 5 min and the crystalline residue was treated with ether and petroleum ether to give 35 mg (70%) of 18a as yellow prisms, mp and mmp 88–90°.

2-Nitro-1-phenyl-3-methoxyindene (18b). A.—**18b** was similarly prepared (see **18a**, procedure A) in 3.8% yield as yellow prisms, mp and mmp 99–102°, after several recrystallizations from ethanol.

B.—A solution of 5 g (19.75 mmol) of **12** in 100 ml of ether was treated with an excess of ethereal diazomethane solution until no more starting material was present as determined by tlc. Evaporation of the solvent gave an off-white, crystalline solid which on recrystallization from ethyl acetate–ether gave 0.85 g of pale yellow prisms, mp 121–122°, which were identified as 1-phenyl-2-methoxyimino-3-indanone *N*-oxide (**19**), ir ($CHCl_3$) 1700 cm^{-1} (CO), nmr ($CDCl_3$) δ 3.88 (s, 3, CH_3O), 5.07 (s, 1, H_1), 7.0–7.65 (m, 8, ArH), 7.90 (m, 1, H_4).

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90: H, 4.90; N, 5.24. Found: C, 72.03; H, 5.11; N, 5.25.

The residual mother liquors and filtrates were combined and evaporated and the residue was chromatographed on 400 g of silica gel using hexane–ethyl acetate (2:1) as the eluent. Removal of solvent from the first fractions, gave an additional 390 mg of **19**, for a combined yield of 1.24 g (23.5%), mp and mmp 121–122°. Later fractions gave, after removal of the solvent, 2.2 g (42%) of **18b** as yellow prisms (crystallized from ethyl acetate–ether), mp 91.5–93°, reset mp 101–102°, nmr ($CDCl_3$) δ 4.37 (s, 3, CH_3O), 5.10 (s, 1, H_1), 6.9–7.45 (m, 8, ArH), 7.70 (m, 1, H_4).

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.95; H, 4.94; N, 5.28.

Registry No.—**2**, 34764-52-8; **3**, 34764-53-9; **4**, 34764-54-0; **5**, 34764-55-1; **6**, 34764-56-2; **7**, 34764-57-3; **8**, 34789-54-3; **9a**, 34764-58-4; **9b**, 34764-59-5; **10**, 34764-60-8; **11a**, 34764-61-9; **11b**, 34764-62-0; **12**, 34764-63-1; **14**, 13943-70-9; **16**, 34764-65-3; **17a**, 34764-66-4; **17b**, 34764-67-5; **18a**, 34764-68-6; **18b**, 34764-69-7; **19**, 34764-70-0.

Acknowledgment.—The authors are indebted to the following members of the Physical Chemistry Department under the direction of Dr. P. Bommer: Dr. F. Scheidl for the microanalyses, Dr. T. Williams for the nmr spectra, Dr. V. Toome for the uv spectra, and Mr. S. Traiman for the ir spectra.

Thermodynamic and Kinetic Analysis of Meisenheimer Complex Formation

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Received February 22, 1971

The free-energy change for the reaction of sodium methoxide with 2,4,6-trinitroanisole (**3**) to give the Meisenheimer complex **2** has been measured and combined with the heat of this reaction to give the entropy change in DMSO–methanol mixtures. Using solubility measurements, the activity coefficients of **3** and the complex **2** have been determined. The free energy, enthalpy, and entropy of transfer of **3** and its complex **2** from pure methanol to methanolic dimethyl sulfoxide solutions have been calculated. The solvent effect on the thermodynamics of the reaction between sodium methoxide and **3** has been measured. The degenerate activity coefficients of sodium methoxide in methanol–DMSO mixtures have been obtained using an indirect method.

The chemistry of Meisenheimer or σ complexes, most of which are substituted cyclohexadienylide ions, has recently come under renewed scrutiny[2] and this research area has been quite active. Dipolar aprotic solvents have been found to enhance the stability of Meisenheimer complexes.[3–8] Indeed, this behavior has made possible the isolation of crystalline sodium and potassium cyclohexadienylides.[3–7] We have demonstrated recently that the increase in the equilibrium constant for the formation of sodium 1,1-dimethoxy-2,4-dicyano-6-nitrocyclohexadienylide (**1**) (eq 1) with increasing DMSO concentration in the DMSO–MeOH solvent system is due to an increase in the rate constant for complex formation (k_1) and a decrease in the rate constant for the decomposition of the complex (k_2).[6] These results have been rationalized using the differences in the hydrogen-bonding power of these solvents. Methoxide ions, being strong hydrogen bond acceptors, become considerably less solvated and, therefore, stronger nucleophiles in dipolar aprotic DMSO than in protic methanol[8,9] Since the 2,4,6-trinitroanisole is not effected strongly by this solvent change, k_1 increases with increasing DMSO concentration. The decrease in the rate constant for the decomposition of the complex (k_2) with increasing DMSO concentration is probably caused by the greater solvation of the highly delocalized negative charge of the complex in

(1) (a) Texas A & M University; (b) University of Tennessee.

(2) For recent reviews on Meisenheimer complexes and their relevance in nucleophilic aromatic substitution, see (a) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966); (b) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev., Chem. Soc.*, **22**, 123 (1968); (c) P. Buck, *Angew. Chem., Int. Ed. Engl.*, **8**, 120 (1969); (d) J. Miller, "Aromatic Nucleophilic Substitutions," Elsevier, Amsterdam, 1968; (e) M. R. Crampton, *Advan. Phys. Org. Chem.*, **7**, 211 (1969); (f) F. Pietra, *Quart. Rev., Chem. Soc.*, **23**, 504 (1969); (g) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).

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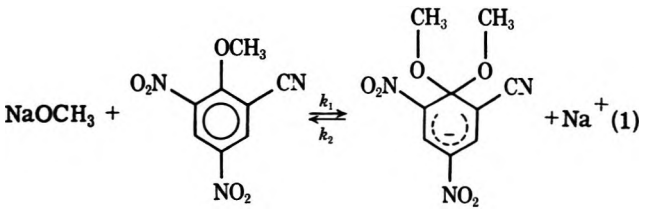
(9) A. J. Parker, *Quart. Rev., Chem. Soc.*, **16**, 163 (1962); *Advan. Org. Chem.*, **5**, 1 (1965); *Advan. Phys. Org. Chem.*, **5**, 173 (1967); *Chem. Rev.*, **69**, 1 (1969).



DMSO-rich solvents. These arguments are gross oversimplifications. Any serious consideration of solvent effects on reaction rates must include data on changes in the activity coefficients of the reactants and of the transition state as a function of solvent changes.[10] Even more valuable would be knowledge of the relative enthalpies and entropies of reactants and transition states, and therefore we have undertaken a systematic study of the reaction between 2,4,6-trinitroanisole (**3**) and sodium methoxide in methanol–DMSO mixtures in order to obtain these thermodynamic parameters. We have determined the rate constants for formation (k_1) and decomposition (k_2) of the sodium salt of the complex **2**, as well as measured mean ion activity coefficients of this species, activity coefficients of its parent ether, 2,4,6-trinitroanisole (**3**), heats of formation of the complex **2**, and heats of transfer for both the reactants and the complex. We have combined these data to calculate degenerate activity coefficients for sodium methoxide in methanolic dimethyl sulfoxide.

Experimental Section

The solvents and reagents were prepared, purified and standardized as previously described.[3,8,11]

The attainment of the equilibrium for the formation of **2** in methanol and in methanolic DMSO was followed at 495 nm in the thermostated cell compartment of a Beckman DU-2 spectrophotometer. The mixing techniques for fast reactions have been described previously.[4] Since the concentration of 2,4,6-trinitroanisole (**3**) was kept at least 20-fold smaller than that of the sodium methoxide, pseudo-first-order kinetics were observed and the corresponding rate constants, k_{obsd}, were calculated from the integrated first-order rate equation.

Rate constants for the decomposition of the complex (k_2) were determined directly by following the absorption decrease at 495 nm of dilute solutions (*ca.* 5×10^{-5} *M*) of solid **2** in the appropriate methanolic DMSO solutions as a function of time. At infinity time the absorption spectra of the solutions were identical with that of **3**.

Six solubility determinations were carried out in each solvent system for **2** and **3**. Three measurements were carried out by shaking solutions containing an excess of the solute at 25.0° and three by shaking saturated solutions at 30° and then cooling to 25.0°. The concentration of the solutes was determined spectrophotometrically. The error in the individual measurements is ±10%. In some cases, the concentration of the saturated solutions of **2** and **3** is greater than 1.0 *M* and thus these solutions are not ideal.

Calorimetric studies were carried out with a dual calorimeter similar to that described by Arnett, Bentrude, Burke, and Duggleby.[8,12] The apparatus was checked at least once a month by measuring the heat of solution of potassium chloride in water. The values obtained agreed within ±1% of the accepted value.[13] The application of these techniques to this system and the purification of reagents have been described previously.[8]

(10) A. J. Parker and R. Alexander, *J. Amer. Chem. Soc.*, **90**, 3313 (1968); R. Alexander, E. C. F. Ko, A. J. Parker, and T. J. Broxton, *ibid.*, **90**, 5049 (1968).

(11) We thank Dr. E. J. Fendler for samples of **1**, **2**, and **3**.

(12) E. M. Arnett, W. G. Bentrude, J. J. Burke, and P. M. Duggleby, *J. Amer. Chem. Soc.*, **87**, 1541 (1965).

(13) V. B. Parker, "Thermal Properties of Aqueous Uni-univalent Electrolytes," National Bureau of Standards, Washington, D. C., Patent N8RD8-NBS2.

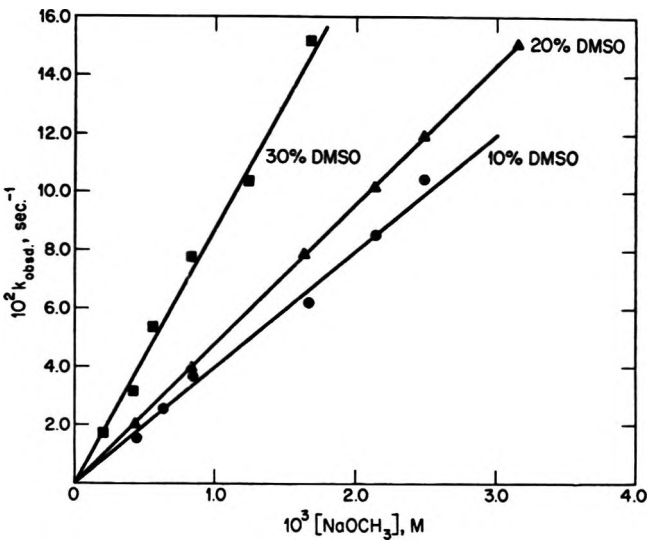
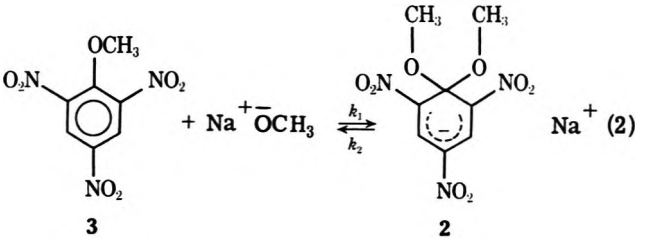


Figure 1.—The dependence of k_{obsd} for the equilibrium attainment of **2** (eq 3) on solvent and sodium methoxide concentration.

Results and Discussion

The addition of a solution of sodium methoxide ($[NaOCH_3] > 2 \times 10^{-4}$ *M*) to a solution of 2,4,6-trinitroanisole (*ca.* 10^{-5} *M*) in methanol or in methanolic DMSO results in the formation of complex **2** (eq 2).



In the methoxide ion concentration range of 2.0–3.0 × 10^{-4} *M* the observed pseudo-first-order rate constant for the equilibrium attainment, k_{obsd}, is given by eq 3,

$$k_{obsd} = k_1[NaOCH_3] + k_2 \quad (3)$$

where k_1 is the second-order rate constant for the formation of the complex and k_2 is the first-order rate constant for its decomposition. Figure 1 illustrates the relationship between k_{obsd} and $[NaOCH_3]$ according to eq 3. From the slopes of such plots values for k_1 have been obtained and are given in Table I. Values for k_2 are very small, and accurate interpolation from the intercepts of the plots illustrated in Figure 1 is impossible. However, we have obtained k_2 values directly from decomposition of solid **2** in the appropriate methanolic DMSO solution from which the equilibrium constant, $K = k_1/k_2$, can be calculated easily. These data are given in Table I. Also shown in Table I are the heats of the reaction from ref 8 and calculated values for ΔG and ΔS. It must be emphasized that the standard state for these values is dilute solution *in the indicated solvent*. The data in the different solvent systems cannot be compared directly, since each is referred to a different standard state. The data do show how the difference in ΔG or ΔH between the reactants and products (both in the same solvent) is changed as the amount of DMSO in the solvent increases. In the reaction between sodium methoxide and 2,4-dicyano-6-nitroanisole a linear de-

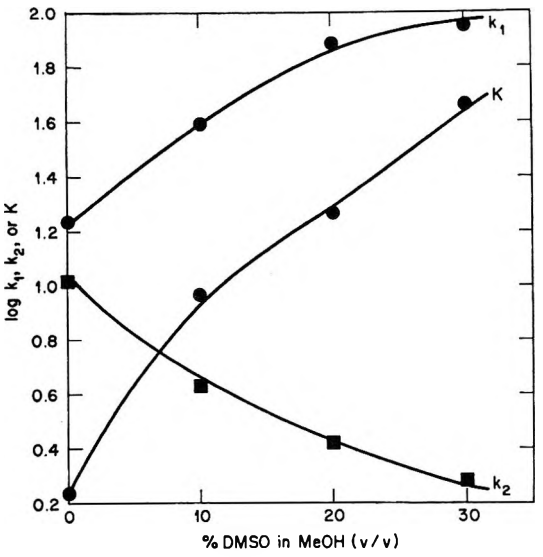


Figure 2.—Solvent effects on the rate constants for formation and decomposition of the Meisenheimer complex 2 and the equilibrium constant for its formation.

TABLE I

EFFECTS OF DIMETHYL SULFOXIDE ON THE KINETIC AND THERMODYNAMIC PARAMETERS FOR THE FORMATION AND DECOMPOSITION OF 2 AT 25.0°

	DMSO in MeOH (v/v), %			
	0.00	10.00	20.00	30.00
k_1, M^{-1} sec^{-1} [a]	17.3[b]	39.3	48.0	88.3
10^4k_2, sec^{-1} [c]	10.4[b]	4.25	2.60	1.90
$10^{-4}K$, M^{-1} [d]	1.70[b]	9.26	18.5	46.5
ΔG, kcal/mol[e]	−5.77	−6.77	−7.19	−7.74
ΔH, kcal/mol[e]	−4.86	−6.41	−6.98	−8.47
	±0.03[f]	±0.17	±0.22	±0.26
ΔS, eu[e]	+3.05	+1.21	+0.70	−2.45

[a] Calculated from the slopes of the lines in Figure 1. [b] Determined in ref 5. [c] Determined by decomposing 2 in the appropriate methanolic DMSO. Average of three runs (each within ±3%). [d] Determined from $K = k_1/k_2$ at 25.0°. [e] Thermodynamic parameters on the *equilibrium* for the formation of complex 2, uncorrected for the activity coefficients of 3 and complex 2. [f] Recent reestimated value of $-y$ kcal/mol [M. E. C. Biffin, J. Miller, A. Moritz, and D. B. Paul, *Aust. J. Chem.*, **22**, 2561 (1969)] is in good agreement with the experimental value reported here.

pendency of the logarithm of rate and equilibrium constants on the concentration of DMSO (in the DMSO–MeOH system) has been observed.[6] For complex 2 no such linear dependency was observed (Figure 2), illustrating the dangers inherent in attributing mechanistic significance to such plots. A nonlinear dependence of rate and equilibrium constants on solvent composition is not surprising.

To interpret the effects of solvent changes on the kinetics and equilibria of complex formation, the changes in the activity coefficients of the reactants, transition state, and products must be known. The easiest approach to this is to obtain the degenerate activity coefficients for the species involved. We shall adopt dilute solution in methanol as our standard state and determine the activity coefficients relative to this solvent for all the species in the other solvents. By microscopic reversibility, the transition states for the forward and reverse reaction are necessarily identical and are designated by $f'^{\ddagger}$.

Considering the reaction shown in eq 2, the rate constants for the formation of complex 2 in DMSO–MeOH solutions ($k_1^{\text{DMSO-MeOH}}$) are related to the same rate constant in pure methanol by (k_1^{MeOH}) by eq 4.

$$k_1^{\text{DMSO-MeOH}} = k_1^{\text{MeOH}} \frac{f'_3 f'_{\text{Na}^+} f'_{\text{OCH}_3^-}}{f'^{\ddagger}} \quad (4)$$

Similarly the rate constants for the decomposition of 2 in DMSO–MeOH ($k_2^{\text{DMSO-MeOH}}$) are related to that in pure methanol, k_2^{MeOH}, by eq 5. The degenerate

$$k_2^{\text{DMSO-MeOH}} = k_2^{\text{MeOH}} \frac{f'_2 f'_{\text{Na}^+}}{f'^{\ddagger}} \quad (5)$$

activity coefficients for sodium methoxide are necessary and can be determined in an indirect manner. In essence, since we know K in each of the solvents in addition to the activity coefficients for the reactants and products except for sodium methoxide, we can use these data to get the *relative* activity coefficients (degenerate activity coefficients) for sodium methoxide.

Dividing eq 4 by eq 5 and rearranging gives eq 6.

$$f'_{\text{NaOCH}_3} = \frac{K^{\text{DMSO-MeOH}} \times f'_2}{K^{\text{MeOH}} \times f'_3} \quad (6)$$

Since all of the quantities in the right-hand side of eq 6 are available, f'_{NaOCH_3} can be calculated easily. Note that the activity coefficient of sodium methoxide in each solvent (f_{NaOCH_3}) cannot be obtained using this method; only relative values can be obtained. However, this is the additional factor required to determine the effect on changing solvent in the kinetics and thermodynamics of this reaction.

In order to determine the effect of the increasing DMSO concentration on k_1 and k_2, the degenerate activity coefficients for 2, 3, and sodium methoxide and that for the transition state are necessary. Degenerate activity coefficients (f') are the activity coefficients for the species in the mixed solvent compared to pure methanol as the standard state ($f'_2 = f_2^{\text{DMSO-MeOH}}/f_2^{\text{MeOH}}$, $f'_3 = f_3^{\text{DMSO-MeOH}}/f_3^{\text{MeOH}}$, $f'_{\text{NaOCH}_3} = f_{\text{NaOCH}_3}{}^{\text{DMSO-MeOH}}/f_{\text{NaOH}_3}{}^{\text{MeOH}}$, and $f'^{\ddagger} = f^{\text{DMSO-MeOH}\ddagger}/f^{\text{MeOH}\ddagger}$). The most convenient way to obtain the necessary activity coefficients is by measuring the solubility of the reactants and product in each solvent, a standard technique.[14] If this is done, then the activity coefficient ratios are given by the solubility ratios; *e.g.*, eq 7, where S is the solubility

$$\frac{f_x^{\text{DMSO-MeOH}}}{f_x^{\text{MeOH}}} = \frac{S_x^{\text{MeOH}}}{S_x^{\text{DMSO-MeOH}}} \quad (7)$$

of species x. Due to the high solubility of sodium methoxide, we were able to obtain data only for 2,4,6-trinitroanisole and the complex 2. These data are given in Table II. The concentrations are sufficiently high so that the solutions are nonideal; nevertheless, reliable information about the direction and order of magnitude of the solvent effects can unquestionably be obtained from the data.

An independent check of the data in Table II as well as the assumption made in calculating f'_{NaOCH_3} exists. The degenerate activity coefficient of the transition state $f'^{\ddagger}$ can be calculated using k_1 and the activity coefficients for the starting materials or it can be derived from k_2 and the activity coefficient of the complex. Both values are given in Table II and the agreement is excellent.

The thermodynamic parameters for the reaction in

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TABLE II

EFFECTS OF DIMETHYL SULFOXIDE ON THE RELATIVE ACTIVITY COEFFICIENTS OF 2 AND 3 AND ON THE TRANSITION STATES FOR THEIR FORMATION AT 25.0°

	DMSO in MeOH (v/v), %			
	0.00	10.00	20.00	30.00
Solubilities (rel) of 3[a]	0.184	0.371	0.658	1.085
f'_3[b]	1.00	0.495	0.279	0.167
f'_{NaOCH_3}[c]	1.00	4.67	9.18	26.1
$f'^{\ddagger}$[d]	1.00	1.02	0.92	0.85
Solubilities (rel) of 2[a]	0.730	0.776	3.170	4.672
f'_2[e]	1.00	0.414	0.230	0.156
$f'^{\ddagger}$[f]	1.00	1.07	0.920	0.853

[a] Mean of six solubility determinations; see Experimental Section. [b] Degenerate activity coefficients of 3, $S_3^{MeOH}/S_3^{DMSO-MeOH} = f'_3$. [c] Derived from eq 6. [d] Degenerate activity coefficients for the transition state for formation or decomposition of complex 2. Derived from eq 4 and using f'_{NaOCH_3} values. [e] Degenerate activity coefficients of 2; $S_2^{MeOH}/S_2^{DMSO-MeOH} = f'_2$. [f] Degenerate activity coefficients for the transition state for formation or decomposition of complex 2 derived from eq 5.

TABLE III

THERMODYNAMICS OF TRANSFER OF THE INDICATED MOLECULES AND THE TRANSITION STATE FROM METHANOL TO METHANOLIC DIMETHYL SULFOXIDE AT 25.0°

	DMSO in MeOH (v/v), %			
	0	10	20	30
2,4,6-Trinitroanisole (3)				
ΔG_T,[a] kcal/mol	0	−0.42	−0.76	−1.06
ΔH_T,[b] kcal/mol	0	−0.91	−1.10	−1.24
ΔS_T,[a] eu	0	−1.6	−1.1	−0.60
$NaOCH_3$				
ΔG_T,[a] kcal/mol	0	+0.91	+1.31	+1.93
ΔH_T,[b] kcal/mol	0	+0.6	+1.3	+2.2
ΔS_T,[a] eu	0	−1.0	0	+0.9
Complex 2				
ΔG_T, kcal/mol	0	−0.52	−0.87	−1.10
ΔH_T,[a] kcal/mol	0	−1.86	−1.92	−2.65
ΔS_T, eu	0	−4.50	−3.52	−5.20
Transition State				
$\Delta G^{\ddagger}$,[b,c] kcal/mol	0	+0.01	−0.05	−0.09

[a] ΔG_T calculated from activity coefficients in Table II; $\Delta S_T = (\Delta H_T - \Delta G_T)/T$. [b] Taken from ref 8. [c] Calculated from $\Delta G_{T,\text{complex 2}}$ and $\Delta G^{\ddagger}$ from k_2.

TABLE IV

THERMODYNAMICS OF THE REACTION BETWEEN SODIUM METHOXIDE AND 2,4,6-TRINITROANISOLE AT 25.0°

	DMSO, %			
	0	10	20	30
$\delta\Delta G$, kcal/mol[a]	0	−1.01	−1.42	−1.97
$\delta\Delta H$, kcal/mol	0	−1.55	−2.2	−3.61
$\delta\Delta S$, eu	0	−1.9	−2.4	−5.5

[a] Calculated from the data in Table III. See discussion for details.

each of the solvents are given in Table I. In Table IV are these values recalculated using the data from Table III, *i.e.*, correcting the data in Table I for all activity coefficients. The changes are small. There is now enough data to allow examination of the effect of solvent changes on each of the species involved: sodium methoxide, 2,4,6-trinitroanisole, the transition state, and the Meisenheimer complex 2. Thus we can discover the source of the overall changes in the thermodynamics of the reaction shown in Table I. The necessary relative free energies calculated from the activity coefficients are shown in Table III. The necessary enthalpies of transfer were available from earlier work and the entropies were calculated. It is apparent that the largest change due to varying the solvent is the increase in the free energy of sodium methoxide. The contention that destabilization of sodium methoxide plays an important role in the formation of Meisenheimer complexes is substantiated. The thermodynamics of transfer of sodium methoxide is remarkable in that the variation in entropy is zero within the estimated error; thus $\Delta G_T = \Delta H_T$. This result is surprising, since generally enthalpy changes in a direction opposite to the entropy.[9]

The present thermodynamic data have implications for the derived extrathermodynamic relationship between heats of transfer of sodium and the H_- acidity function.[8] The derived relationship is eq 8. If for

$$H_- = \log \frac{a_{H^+}' a_{Na^+} f_{MeOH}}{a_{H^+} a_{Na^+}' f_{MeOH}} + \frac{\Delta H_{T,NaOH_3}}{2.3RT}(1 - T/\beta) \qquad (8)$$

sodium methoxide $\Delta G_T = \Delta H_T$, then β becomes quite large and $(1 - T/\beta) = 1$. Thus the slope of the line of H_- *vs.* $\Delta H_{T\ NaOCH_3}$ should be $1/2.3RT = 1.4$. The observed slope is 1.8.[8] This agreement is good considering the appoximations involved.

The transfer of 2,4,6-trinitroanisole is enthalpy controlled and there apparently exists a minimum in ΔS in the high methanol region. The transfer of the Meisenheimer complex is also enthalpy controlled. In both of these compounds, the entropy and enthalpy are changing in the opposite direction, tending to cancel. Interestingly, the free energy of the transition state is essentially completely insensitive to solvent. It would be nice to know whether this is due to a cancellation of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. Unfortunately, the data necessary for this analysis are not available.

As shown by the data in Table IV, the overall reaction is enthalpy controlled and the enthalpy and entropy changes are opposed. While the largest contribution is made by the changes in solvation of sodium methoxide, significant changes in the thermodynamic properties of 2,4,6-trinitroanisole and the complex are also occurring and there is no one overwhelming factor dominating the reaction in these solvent systems.

Registry No.—2, 12275-58-0; 3, 606-35-9; dimethyl sulfoxide, 67-68-5.

Acknowledgment.—Support of this work by the Research Corporation (J. W. L.) and the Atomic Energy Commission (J. H. F.) is gratefully acknowledged. The authors are grateful to a referee for his help in developing the thermodynamic analysis used here.

Kinetics and Mechanism of the Acid-Catalyzed Hydrolysis of α-Phenylvinyl Diethyl Phosphates

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Received December 20, 1971

The acid-catalyzed hydrolysis rates of a series of ring-substituted α-phenylvinyl diethyl phosphates in 0.1 *N* HCl–40% aqueous ethanol were measured at four different temperatures. The rate of hydrolysis was accelerated by electropositive substituents, whereas it was lowered by electron-withdrawing groups. From the rate data at different temperatures, the activation energies and activation entropies were calculated. Plots of log *k* at 85° against Brown's σ^+ substituent constants are linear with slope −1.69. The observed values of the activation parameters are consistent with an A-Se2 mechanism except for the para-nitro compound.

After the discovery of phosphoenolpyruvic acid (PEP) by Meyerhof and Lohmann,[1] vinyl phosphates acquired great importance in biochemistry.

In fact, PEP represents the last phosphorylated three-carbon-atom compound, both in glycolysis and in fermentation, and also seems to play a role in the fixation of carbon dioxide.[2]

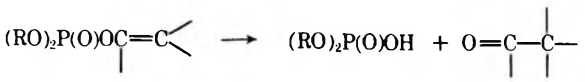
Owing to the difficulties in the preparation of PEP, no other vinyl phosphates had been synthesized until about 1950. However, after work establishing that certain organophosphorus compounds were very potent insecticides,[3] the chemistry of organophosphates developed enormously.

Recently in the acid-catalyzed hydrolysis of vinyl phosphates there has been a good deal of interest, since it has been considered as a model reaction for biological phosphorylations.[4]

It is known that the course of the acid-catalyzed hydrolysis of dialkyl vinyl phosphates is dependent upon the reaction conditions.

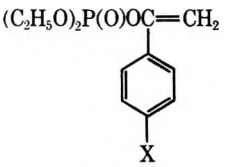
With HCl (1:1) at 100° total hydrolysis of all ester groups occurs, forming mainly alkyl chloride, phosphoric acid, and the corresponding ketone.[5,6]

Under milder conditions, however, selective hydrolysis of the vinyl ester group can be effected, yielding the dialkyl phosphate and the corresponding carbonyl compound[7-9] (see Experimental Section).



Recently, Bunton and Robinson[10] have shown that the acid-catalyzed hydrolysis of α-phenylvinyl diethyl phosphate follows an A-Se2 mechanism with slow proton addition to the vinylic double bond.

Although mechanistic studies have been carried out on acid-catalyzed hydrolysis of some vinyl phosphates, in the present paper, following our research work on phosphoric esters,[11] we wish to amplify the study examining the effect of the substituent para to the aromatic ring on the reaction rate of the acid-catalyzed hydrolysis in 0.1 *N* HCl–40% aqueous ethanol of vinyl phosphates previously synthesized[11] (I).



I

X = H, CH_3, CH_3O, Cl, NO_2

We find that the activation parameters are consistent with an A-Se2 mechanism, except for the para-nitro compound.

Results and Discussion

The acid-catalyzed hydrolysis was followed kinetically by titrating of the diethyl phosphate formed with 0.1 *N* NaOH (see Experimental Section).

TABLE I

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE ACID HYDROLYSIS OF α-PHENYLVINYL DIETHYL PHOSPHATE IN 0.1 *N* HCl–40% AQUEOUS ETHANOL AT 85°

Run no.	Initial concn, mol/l.	$k_1 \times 10^5$, sec^{-1}
1	0.0213	11.5
2	0.0245	11.2
3	0.0294	11.8
4	0.0315	11.9

TABLE II

ACID HYDROLYSIS OF α-PHENYLVINYL DIETHYL PHOSPHATE[a]

Elapsed time, min	0.1 *N* NaOH, ml	log $(a/a - x)$
0	0	0
30	1	0.0903
45	1.5	0.1436
60	1.7	0.1670
75	2.2	0.2180
90	2.55	0.2835
120	3	0.3606
150	3.4	0.4430
180	3.8	0.5445

[a] The data refer to the first kinetic run in Table I.

(1) O. Meyerhof and K. Lohmann, *Z.*, **293**, 60 (1934).

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TABLE III

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE ACID HYDROLYSIS OF α-PHENYLVINYL DIETHYL PHOSPHATES IN 40% AQUEOUS ETHANOL

		$k_1 \times 10^5$, sec^{-1}									
No.	Substituent	85°	80°	75°	70°	65°	60°	55°	50°	45°	40°
1	*p*-H	11.6		5.85		1.90		0.724			
2	*p*-CH_3	55.4[a]			14.1	9.91	6.64	3.41			
3	*p*-CH_3O	374[a]						35.5	22.1	14.4	8.82
4	*p*-Cl	5.91	3.95		1.33	1.05					
5	*p*-NO_2	0.927	0.653	0.499	0.401						

[a] Extrapolated values from their respective Arrhenius plots (Figure 1).

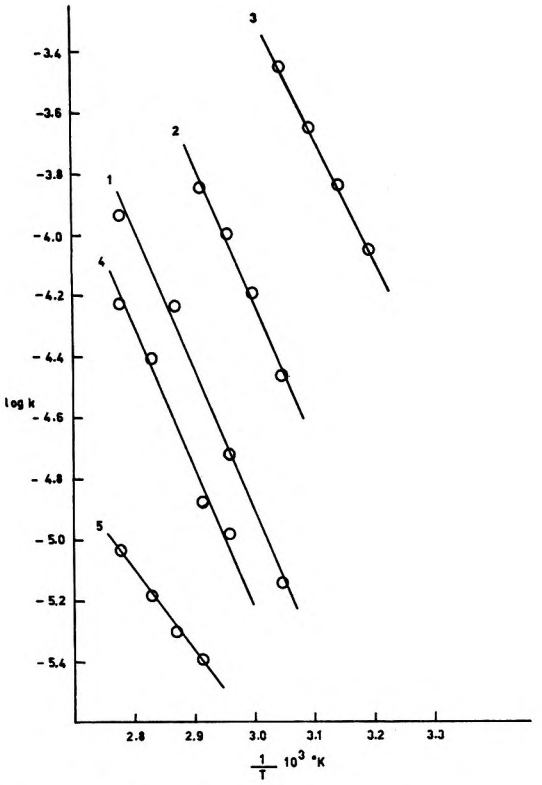

Figure 1.—The Arrhenius activation energy plots. The numbers on the curves refer to the series numbers in Table III.

The rate constants at 85° with varied initial concentrations of α-phenylvinyl diethyl phosphate (X = H), listed in Table I, clearly indicate that the reaction of hydrolysis is pseudo-first-order. A typical kinetic run is shown in Table II.

Considering the rate information at various temperatures, tabulated in Table III, it can be seen that the hydrolysis rate is increased by electropositive substituents, whereas it is decreased by electron-withdrawing groups.

The variation with temperature of the rates of hydrolysis gave the activation energies, activation entropies, and log *A* presented in Table IV and Figure 1.

These activation parameters are similar for all the compounds, except for the para-nitro compound, and

TABLE IV

ACTIVATION PARAMETERS FOR THE ACID HYDROLYSIS

Substituent	E_A, kcal/mol	ΔS, 85°, cal mol^{-1} °K^{-1}	log *A*
p-H	22.1	−16.8	9.62
p-CH_3	21.0	−17.1	9.57
p-CH_3O	18.5	−20.3	8.86
p-Cl	21.8	−19.2	9.10
p-NO_2	13.5	−46.1	3.23

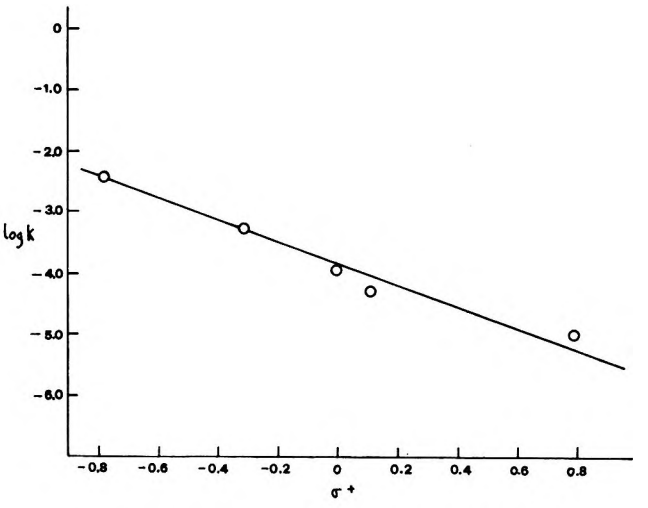

Figure 2.—Substituent effect on rate of hydrolysis.

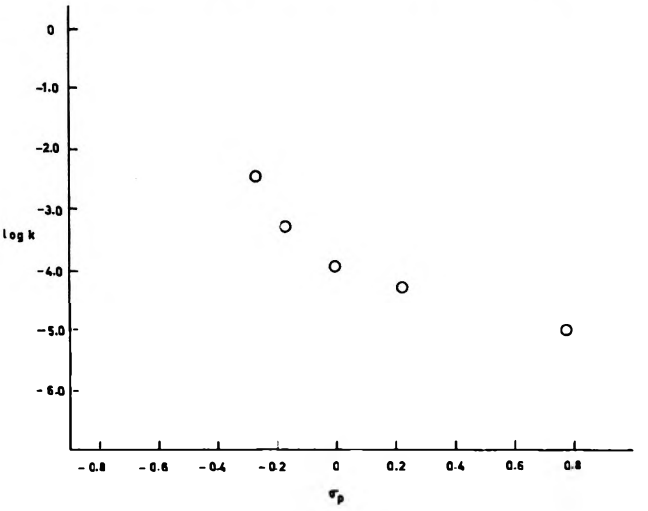

Figure 3.—Substituent effect on rate of hydrolysis.

are consistent with an A-SE2 mechanism involving a rate-determining protonation of the carbon–carbon double bond.[12–14]

Plots of log *k* at 85° against Brown's σ^+ substituent constants[15] are linear with a slope of −1.69 (Figure 2). The correlation with σ^+ constants is substantially better than with Hammett's σ_p constants[16] (Figure 3), indicating that electron deficiency in the transition state is conjugated with the substituent para to the aromatic ring.

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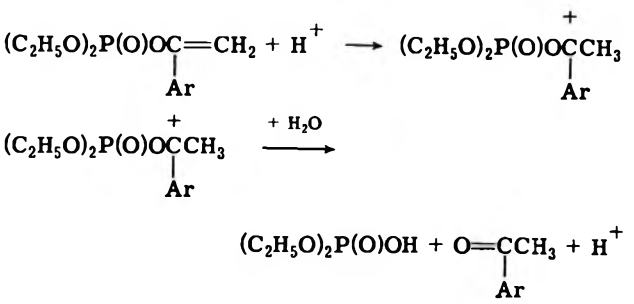
(16) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963.

SCHEME I



This ρ value is of the same order of magnitude as that found for other similar reactions that follow an A-Se2 mechanism.[12]

The data obtained, then, lead us to postulate that the acid-catalyzed hydrolysis of para-substituted α-phenylvinyl diethyl phosphates in 0.1 N HCl–40% aqueous ethanol follows an A-Se2 mechanism with initial protonation of the vinylic double bond followed by the attack by water and collapse to products (Scheme I).

The log A and ΔS^* values for the para-nitro compound, however, are considerably dissimilar. The log A values, in fact, are in the range expected for an A2 mechanism and the entropies of activation are characteristic of acid hydrolysis in which water molecules are closely bound into the transition state.[17]

However, the values of the activation parameters do not provide conclusive evidence that the para-nitro substituent causes the mechanism to change. Examination of the points of Figure 3 supports this possibility, and indicates that the gradient decreases at the higher values of T, and therefore the different values of the activation parameters found for the para-nitro compound may just be due to its slower rate requiring a higher temperature for conveniently measurable rates.

Experimental Section

Materials.—Preparation and purification of the vinyl phosphates have been elsewhere described.[11] Physical constants of the products used are listed in Table V.

Kinetic Procedure.—The reaction was performed with 0.1 N HCl–40% ethanol (95%), determining by titrating with 0.1 N NaOH the diethyl phosphate formed.

Aliquots of standardized aqueous ethanol, HCl, and vinyl ester (25 ml upon the whole) were mixed in glass-stoppered tubes and placed into a constant-temperature bath (±0.01°). The initial concentration of ester was 0.02 mol $l.^{-1}$.

Tubes were periodically removed from the constant-temperature bath and rapidly cooled in an acetone–solid carbon dioxide mixture, and the contents were poured into a beaker containing 25–30 ml of water. The diethyl phosphate formed was then titrated with standardized 0.1 N NaOH using phenolphthalein as indicator.

All rates were run in duplicate to at least 75% completion, with less than 3% deviation between the two rate constants in all cases.

All compounds gave excellent pseudo-first-order kinetics.

Rate constants were calculated by a least squares computer program with an Olivetti Programma 101.

Analysis of the Hydrolysis Products.—The appropriate vinyl phosphate (5 g) was mixed with 100 ml of 0.1 N HCl–40% aqueous ethanol in a glass-stoppered tube and maintained at the kinetic temperatures for several hours depending on the rate of the reaction, until complete hydrolysis. An aliquot of the solution was then neutralized to phenolphthalein with barium carbonate and baryta and warmed on the water bath. The barium salt was filtered, washed, and dried and then crystallized from 80% alcohol. The barium content, determined as barium sulfate, proved that the salt was in every case barium diethyl phosphate.[18]

The second aliquot of the solution was buffered with sodium acetate, and the corresponding para-substituted acetophenones were identified as p-nitrophenylhydrazones[19] (Table VI).

TABLE V

PHYSICAL CONSTANTS OF α-PHENYLVINYL PHOSPHATES USED IN THE ACID HYDROLYSIS

Substituent	Bp, °C (mm)	$n^{20}D$
p-H	117 (0.3)	1.4991
p-CH_3	119 (0.15)	1.4995
p-CH_3O	131 (0.15)	1.5114
p-Cl	123 (0.3)	1.5112
p-NO_2[a]		

[a] Mp 25°; recrystallized from anhydrous ether.

TABLE VI

PHYSICAL CONSTANTS OF p-NITROPHENYLHYDRAZONES[a]

No.	p-$XC_6H_4C(CH_3)$=$NNHC_6H_4NO_2$-p	Mp, °C	Ref
1	X = H	183–184	b
2	X = CH_3	196–198	b
3	X = CH_3O	193	b
4	X = Cl	238–139	b
5	X = NO_2	276–278	c

[a] All the compounds were crystallized from ethanol, except for the p-nitro derivative (compd no. 5), that was crystallized from dioxane. [b] A. Arcoria, *Ann. Chim. (Rome)*, **56**, 251 (1966). [c] A. Arcoria and S. Fisichella, *ibid.*, **57**, 1228 (1967).

The mixture melting point with authentic samples of p-nitrophenylhydrazones reveals no depression.

The reaction products from the acid hydrolysis of α-phenylvinyl diethyl phosphates in 0.1 N HCl–40% aqueous ethanol are, therefore, diethyl phosphate and the corresponding para-substituted acetophenones.

Registry No.—I (R = H), 1021-45-0; I (R = CH_3), 18276-76-1; I (R = CH_3O), 18275-67-7; I (R = Cl), 18276-77-2; I (R = NO_2), 34804-85-8.

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Transmission of Substituent Effects in Heterocycles. The Rates of Solvolysis of Substituted 1-(2-Thienyl)ethyl *p*-Nitrobenzoates[1]

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Received January 31, 1972

The rates of solvolysis of nine substituted 1-(2-thienyl)ethyl *p*-nitrobenzoates in 80% ethanol are well correlated by Brown's electrophilic substituent constants, σ_m^+ and σ_p^+ (correlation coefficient 0.993). An examination of the CNDO/2 molecular orbital parameters for 2-methylthiophene and 2-thienylmethyl cation reveal that this correlation is the result of the near coincidence of the regional charges at positions 4 and 5 in the thiophene moiety, with similar electron densities at the 3 and 4 positions of the benzene ring. The CNDO calculations carried out on thiophene appear to slightly underestimate the response of the system to changes in charge distribution. The slope of the correlation line (ρ) is -6.8 *vs.* σ_p^+, -7.1 against substituent constants determined by CNDO parameters, rather than -5.7 as observed for benzene systems.

Several studies have appeared recently which show that thiophene is more susceptible to electrophilic aromatic substitution than benzene. Marino and his coworkers have shown,[3] as have we,[4] that useful linear free energy relationships apply for electrophilic aromatic substitution reactions at the α and β positions of thiophene, and that the "Extended Selectivity" relationship holds.[3] Other recent studies[5,6] have shown that good correlation is observed for electrophilic reactions of a number of substituted thiophenes with Brown's σ^+ substituent constants.[7]

As there is a clear relationship between electrophilic substitution reactions and side chain solvolysis reactivity,[8-10] we have investigated solvolysis rates of substituted thiophene derivatives to gain information regarding the transmission of substituent effects in the thiophene ring system. In a previous study from these laboratories,[11] it was shown that this approach was useful in furan chemistry.

The solvolysis of 1-(2-thienyl)ethyl *p*-nitrobenzoate has a convenient rate near room temperature in 80% ethanol. The results of kinetic measurements on nine substituted derivatives are given in Table I. When these data are plotted against Brown's σ^+ constants, using σ_p^+ for 5 substituents and σ_m^+ for 4 substituents, an excellent correlation is obtained; ρ is -6.79 and the correlation coefficient is 0.993.

We have carried out a further investigation of these results to examine the potentialities of molecular orbital calculations to deal with these results. Recently, Butler[12] has reported that the observed values for the dissociation constants of substituted thienoic acids are well reproduced by the Dewar–Grisdale method,[13] using the SCF-π parameters of Summerfield and Kreevoy.[14] It should be further noted that there is high-quality correlation with the original Hammett substituent constants, as noted by Jaffé and Jones,[15] and more recently by Freeman[16] for the dissociation constants of the substituted thienoic acids. The calculated σ constants (Dewar–Grisdale) of Butler are very similar in value to the original Hammett σ values.

TABLE I

RELATIVE RATES OF SOLVOLYSIS OF SUBSTITUTED 1-(2-THIENYL)ETHYL *p*-NITROBENZOATES AT 25°

Compd	Rel rate	σ^+[a]	σ_{ij}^+[d]
5-OCH_3	1.61×10^5	−0.778	−0.728
5-Cyclopropyl	503	−0.410[b]	−0.399
5-Methyl	81	−0.311	−0.305
5-Phenyl	15.4	−0.179	−0.152
H	1.00	0.00	0.00
5-Bromo	0.137	0.150	0.207
4-Bromo	0.00187	0.405	0.416
4,5-Dibromo	0.000693	0.555[e]	0.623[e]
4-Ethoxycarbonyl	0.000705	0.366	0.382
5-Ethoxycarbonyl	0.000121	0.482	0.575

[a] From ref 7 unless otherwise noted; σ_p^+ used for 5 substituents, σ_m^+ for 4 substituents. [b] From L. B. Jones and V. K. Jones, *Tetrahedron Lett.*, 1493 (1966). [c] Sum of σ_m^+ and σ_p^+. [d] From eq 2, *vide infra*. [e] Sum of σ_{5-2}^+ and σ_{4-2}^+.

Bancroft and Howe[17] have shown that the Dewar–Grisdale equation,[13] when calibrated with Brown's σ^+ constants[7] rather than Hammett σ constants, gives greatly improved results in correlating the measured rates of detritiation of substituted naphthalenes. Eaborn and Fischer[18] have extended these observations.

Application of a modification of the Dewar–Grisdale equation successfully treats the substituent effects in the solvolysis of a variety of heteroarylmethyl compounds. The Dewar–Grisdale equation (1) possesses

$$(\sigma_{ij})_x = F_x/r_{ij} + q_{ij}M_x \qquad (1)$$

a term ($g_{ij}M_x$) representative of resonance effects. M_x is a parameter indicative of the resonance capability of substituent and g_{ij} is a measure of the transmission of resonance effects from a substituent attached to ring carbon i to the carbon (j) bearing the reaction center. The term g_{ij} is derived from Hückel molecular orbital

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.

(2) NIH Predoctoral Fellow, 1968–1970 (GM 41,892).

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theory. In solvolysis the delocalization of charge from the side chain to the carbon bearing the substituent, rather than polarization of the ring by the substituent, is of prime importance. Furthermore, the appreciable polarization of neutral heterocyclic systems necessitates consideration of the charge distribution of the un-ionized initial state as well. Accordingly, we define the term Δq_{ij} as the difference in regional charge[19] at atom i in the un-ionized molecule and the heteroarylmethyl cation. Use of the Δq_{ij} term in the framework of 1 gives the modified Dewar–Grisdale equation (2), in

$$(\sigma_{ij}^{+})_z = F_z^{+}/r_{ij} + \Delta q_{ij} M_z^{+} \quad (2)$$

which F^+ is a measure of the field set up by the substituent, M^+ is a measure of the capacity for resonance interaction of the substituent, and r_{ij} is the distance between atoms i and j. F^+ and M^+ constants are established for each substituent by the use of Brown's σ_p^+ and σ_m^+ constants in conjunction with $1/r_{ij}$ and Δq_{ij} values appropriate to the toluene–benzyl cation pair. Effective substituent constants, σ_{ij}^+, can then be calculated for any aromatic system from eq 2.

In practice the Δq_{ij} terms are obtained from molecular orbital calculations. The charge distributions of neutral compounds are computed with use of a methyl group as a side chain model; replacement of the methyl group with a planar methylene provides the computational model for the carbonium ion. The availability of standard programs for CNDO/2 and INDO all-valence electron molecular orbital models[20] made it feasible to compute Δq_{ij} values for a wide variety of heterocyclic systems. Such methods, by virtue of their uniquely defined heteroatom parameters and overall superiority to Hückel molecular orbital theory, are well suited to this application.

Two particular features of this approach are to be noted. The F^+_{INDO} and M^+_{INDO} values for typical substituents[21] show nearly complete separation into field ($\mathcal{F}$) and resonance ($\mathcal{R}$) terms when analyzed in terms of the Swain and Lupton model[22] (F^+_{INDO} = 91% $\mathcal{F}$, M^+_{INDO} = 95% $\mathcal{R}$). In addition, this approach is particularly suitable for predictions for new systems.

In the present instance, these methods show very clearly the reasons for the high quality of the correlation reported above with σ_p^+ and σ_m^+. This is the result of the near coincidence in the regional charges[20] at positions 4 and 5 in the thiophene ring, and the corresponding positions, meta or para, respectively, in benzene. Hence, the solvolysis reaction rate should respond to that blend of field and resonance interaction which is closely represented by σ_p^+ and σ_m^+.

The quality of the correlation using σ_{ij}^+ values from molecular orbital parameters is very similar to that using simply σ_p^+ and σ_m^+. Thus for the thiophene series the F^+, M^+, CNDO/2 method offers little advantage over the simple σ_p^+, σ_m^+ correlation. For furans, however, F^+, M^+, and CNDO/2 or INDO methods provide a clear improvement.[23]

The value of the correlation slope ρ for the CNDO/2 calculations is −7.14, somewhat more negative than the value (−5.7) typical of the solvolysis rates for secondary benzylic esters. In the case of furan[23] we observed that ρ was the same as for the benzene series within the experimental uncertainty; for benzofurans,[23] ρ is likewise the same for the benzyl compounds. It would thus appear that the CNDO calculations appropriately reproduce the balance of charge density at position 4 *vis-a-vis* position 5 in thiophene; however, it appears that the method slightly underestimates the magnitude of the charge induced on changing from the neutral methyl arene to the thienylmethyl cation.

Table II gives the results of the CNDO/2 calculations. The change in regional charge, Δq,[19] which results from the conversion of the methyl heteroarene to the heteroarylmethyl cation (A → B) is tabulated for benzene (toluene → benzyl) and for thiophene (2-methylthiophene → 2-thienylmethyl). The close similarity of the change in charge density is to be noted.

TABLE II
RESULTS OF CNDO/2 CALCULATIONS FOR BENZENE AND THIOPHENE

System	Position i	Position j	r	Δq	% $\mathcal{R}$
Benzene	3	1	1.732	0.0368	33
Benzene	4	1	2.000	0.2115	65
Thiophene	4	2	1.672	0.0395	~35
Thiophene	5	2	1.768	0.2051	65
Furan	4	2	1.605	0.0642	40

For typical substituents, one may calculate the ratio of the field and resonance components, using the Swain and Lupton approach.[22]

The percentage resonance predicted in the thiophene series (column 5, Table II) is nearly identical with the percentage resonance derived by Swain and Lupton from the σ^+ constants of Brown and Okamoto.

The differentiation between thiophene and furan derivatives is finally indicated by one entry for furan in Table II. The 4-substituted 2-furyl system is expected to show a greater resonance component, an expectation in accord with our observations.[23]

Experimental Section[24]

5-Bromo-2-acetylthiophene was prepared from 2-bromothiophene by the method of Hartough and Conley[25] in 88% yield, mp 87–89° (lit.[25] mp 94–95°).

5-Methyl-2-acetylthiophene was prepared from 2-methylthiophene by the method of Hartough and Kosak[26] in 71% yield, bp 90–92° (4 mm) [lit.[26] bp 84.5° (2 mm)].

5-Phenyl-2-acetylthiophene was prepared from 2-phenylthiophene[27] by the method of Hartough and Kosak[26] in 52% yield, mp 113–114° (lit.[28] mp 115–116°).

(19) Regional charge: The sum of the charges on a carbon atom and on any hydrogen atoms bonded to it. A. Streitwieser, Jr., and R. G. Jesaitis in "Sigma Molecular Orbital Theory," O. Sinanoglu and K. B. Wiberg, Ed., Yale University Press, New Haven, Conn., 1970, p 197.

(20) Programs available from the Quantum Chemistry Program Exchange, University of Indiana. We wish to express our appreciation to Professor Streitwieser and Dr. P. Mowery for providing us with the programs and in counsel in their use.

(21) A set including -OMe, $-CH_3$, $-C_2H_5$, -Cl, -Br, -H, $-CO_2Et$, -CN, $-CF_3$, and NO_2.

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(24) All melting points and boiling points are uncorrected. Routine nmr spectra were determined on a Varian A-60 instrument using tetramethylsilane as an internal standard. The elemental analyses were determined by the Microanalytical Laboratory, University of California, Berkeley.

(25) H. D. Hartough and L. G. Conley, *J. Amer. Chem. Soc.*, **69**, 3096 (1947).

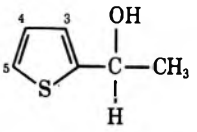
(26) H. D. Hartough and A. I. Kosak, *ibid.*, **69**, 3093 (1947).

(27) A. I. Kosak, R. J. F. Palchak, W. A. Steele, and C. M. Selwitz, *ibid.*, **76**, 4450 (1954).

(28) Y. Otsuji and E. Imoto, *Nippon Kagaku Zasshi*, **80**, 1199 (1959); *Chem. Abstr.*, **55**, 3194g (1961).

TABLE III

NMR CHEMICAL SHIFTS[a] AND COUPLING CONSTANTS[b] OF SUBSTITUTED 1-(2-THIENYL)ETHANOLS



Registry no.	Compd	Solvent	δ H_3	δ H_4	δ H_5	δ CH_3	δ CH	δ OH[c]	Additional data
2309-47-9	Unsubstituted	CCl_4	6.8 (m)	6.8 (m)	7.03 (m)	1.42 (d)	4.84 (q)	4.03 (s)	J_{CH_3-CH} = 7
34878-39-2	5-Cyclopropyl	CCl_4	6.58 (d)	6.46 (d)		1.44 (d)	4.82 (s)	3.32 (s)	J_{CH_3-CH} = 7; $J_{3,4}$ = 3.5; $CH_{(cyclopropyl)}$, δ 1.9 (m); $CH_{2(cyclopropyl)}$, δ 0.7 (m)
34878-40-5	5-Methyl	$CDCl_3$	6.62 (d)	6.48 (d)		1.41 (d)	4.83 (q)	4.15 (s)	J_{CH_3-CH} = 7; 5-CH_3, δ 2.33 (s); $J_{3,4}$ = 3.3
34878-41-6	5-Bromo	Neat	6.50 (d)	6.84 (d)		1.38 (d)	4.82 (q)	4.90 (s)	J_{CH_3-CH} = 7; $J_{3,4}$ = 3.5
1665-38-9	5-Phenyl	$CDCl_3$	6.83 (d)	7.06 (d)		1.57 (d)	5.00 (q)	3.12 (s)	J_{CH_3-CH} = 7; $J_{3,4}$ = 3.5; 5-phenyl, δ 7.3 (m)
34878-43-8	5-Ethoxycarbonyl	CCl_4	6.80 (d)	7.49 (d)		1.48 (d)	4.98 (q)	4.27 (s)	J_{CH_3-CH} = 7; $J_{3,4}$ = 3; $CH_{3(Et)}$, δ 1.33 (t); $CH_{2(Et)}$, δ 4.20 (q); $J_{CH_3-CH_2}$ = 7
34878-44-9	4,5-Dibromo	CS_2	6.60 (s)			1.42'(d)	4.78 (q)	4.28 (s)	J_{CH_3-CH} = 7
34878-45-0	4-Ethoxycarbonyl	CCl_4	7.09 (d)		7.73 (d)	1.48 (d)	4.85 (q)	4.16 (s)	J_{CH_3-CH} = 7; $J_{3,5}$ = 1.2 $CH_{3(Et)}$, δ 1.3 (d); $CH_{2(Et)}$, δ 4.18 (q); $J_{CH_3-CH_2}$ = 7
34878-46-1	4-Bromo	Neat	6.75 (d)		7.00 (d)	1.36 (d)	4.83 (q)	4.85 (s)	J_{CH_3-CH} = 7; $J_{3,5}$ = 2

[a] In parts per million (δ) from internal TMS. [b] J, the observed coupling constant, in cps. [c] Multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

4-Bromo-2-acetylthiophene and 4,5-dibromo-2-acetylthiophene were prepared from 2-acetylthiophene by the method of Gol'dfarb and Vol'kenshtein.[29] 4-Bromo-2-acetylthiophene was obtained in 51% yield, bp 132–134° (15 mm) [lit.[29] bp 133° (15 mm)]. The yield of 4,5-dibromo-2-acetylthiophene was 37% of white needles (ethanol), mp 83.5–84.5° (lit.[29] mp 85–86°).

4-Ethoxycarbonyl-2-acetylthiophene was prepared by a modification of the method of Farrar and Levine.[30] To 24.0 g (0.153 mol) of 3-ethoxycarbonylthiophene[31] in a three-neck 250-ml flask equipped with a reflux condenser and an overhead stirrer was added 18.15 g (0.178 mol) of acetic anhydride. To the stirred solution was added 4 ml of a 47% solution of boron trifluoride etherate by means of a hypodermic syringe. The flask was sealed and heated on a steam bath for 3 hr. The resulting black oil was poured into 1 l. of water and extracted with 3 × 50 ml of ether. The ether solution was washed with 2 × 50 ml of saturated sodium bicarbonate solution and once with 50 ml of water. After drying over anhydrous magnesium sulfate, the ether was stripped off on a rotary evaporator. Distillation at 5 mm gave 9.7 g of recovered starting material, bp 79–80°, and a fraction of a colorless oil, bp 140–144°, which soon solidified. Crystallization from hexane gave 6.8 g of colorless needles, mp 79.5–80.5°, of 4-ethoxycarbonyl-2-acetylthiophene. Imoto and coworkers[32] report the boiling point as 150–152° (6 mm).

2-Methyl-2-[2-(5-carboxythienyl)]-1,3-dioxolane was prepared by a modification of the method of Thames and McCleskey.[33] To 17.2 g (0.101 mol) of 2-methyl-2-(2-thienyl)-1,3-dioxolane dissolved in 150 ml of anhydrous ether under a nitrogen atmosphere was added 62.6 ml (0.101 mol) of *n*-butyllithium in hexane at room temperature. The solution gradually turned brown upon stirring for 1 hr. After cooling in an ice–salt bath for 10 min the brown solution was poured over freshly ground Dry Ice. The reaction mixture was allowed to warm until all the Dry Ice had evaporated. The organic layer was extracted with 200 ml of dilute sodium hydroxide solution. The aqueous solution was washed with 3 × 100 ml of ether which was backwashed with 50 ml of dilute sodium hydroxide solution. The aqueous portions were combined and cautiously acidified with concentrated hydrochloric acid to a pH of 3. Cooling of this acidic solution resulted in formation of a flocculent yellow solid. The solid was collected by suction filtration. The aqueous filtrate was extracted with 2 × 50 ml of ether. The ether solution was dried over anhydrous calcium chloride and the solvent was removed on the rotary evaporator. The resulting yellow solid was combined with that previously obtained to give 11.1 g of crude 2-methyl-2-[2-(5-carboxythienyl)]-1,3-dioxolane. The structure of the product was established by examination of the nmr spectrum. Less than 5% of an acetyl methyl peak resulting from hydrolysis of the dioxolane ring could be observed. The mixture of products was not separated but the crude material was directly used for the preparation of 5-ethoxycarbonyl-2-acetylthiophene.

5-Ethoxycarbonyl-2-acetylthiophene.—To a solution of 400 ml of absolute ethanol and 10 ml of concentrated sulfuric acid was added 10.8 g (0.05 mol) of crude 2-methyl-2-[5-carboxythienyl)]-1,3-dioxolane. The mixture was heated under reflux on a steam bath for 2.5 hr. The warm solution was poured into 1200 ml of sodium carbonate solution in a 3-l. separatory funnel. The flocculent yellow solid was taken up into 250 ml of ether. The aqueous ethanol phase was extracted with 4 × 50 ml of ether. The ether extracts were combined and dried over anhydrous calcium chloride. The solvent was removed under reduced pressure to give a yellow solid. Two recrystallizations gave 5.8 g (56%) of beige-colored 2-acetyl-5-ethoxycarbonylthiophene, mp 54–54.5°.

1(2-Thienyl)ethanols were prepared by reducing the ketones with sodium borohydride in anhydrous methanol for 1 hr at room temperature. Work-up in the usual fashion and removal of the solvent on a rotary evaporator generally yielded 90% of the carbinol. The 4- and 5-ethoxycarbonyl compounds were reduced in anhydrous ethanol instead of methanol to avoid transesterification. All the alcohols were characterized by nmr. The data are recorded in Table III.

1-(5-Methoxy-2-thienyl)ethanol was prepared from 2-methoxythiophene.[34] To 10.0 g (0.0885 mol) of 2-methoxythiophene in 250 ml of dry ether (dried over sodium) at 0° was added 57.5 ml

(29) Y. L. Gol'dfarb and Y. B. Vol'kenshtein, *Dokl. Akad. Nauk SSSR*, **128**, 536 (1959).

(30) M. W. Farrar and R. Levine, *J. Amer. Chem. Soc.*, **72**, 3695 (1950).

(31) C. C. Price, E. C. Mertz, and J. Wilson, *ibid.*, **76**, 5131 (1954).

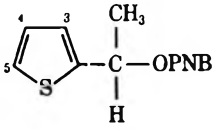
(32) Y. Otsuji, T. Kimura, Y. Sugimoto, E. Imoto, Y. Omoro, and T. Okawara, *Nippon Kagaku Zasshi*, **80**, 1021 (1959); *Chem. Abstr.*, **55**, 5467*b* (1961).

(33) S. F. Thames and J. E. McCleskey, *J. Heterocycl. Chem.*, **3**, 104 (1966).

(34) J. Sicé, *J. Amer. Chem. Soc.*, **75**, 3697 (1953).

TABLE IV

NMR CHEMICAL SHIFTS[a] AND COUPLING CONSTANTS[b] OF SUBSTITUTED 1-(2-THIENYL)ETHYL *p*-NITROBENZOATES



Registry no.	Compd	Solvent	δ H_2	δ H_4	δ H_5	δ CH_3	δ CH	δ C_6H_4	Additional data
23516-71-4	Unsubstituted	$CDCl_3$	7.1 (m)[c]	7.1 (m)	7.32 (q)	1.82 (d)	6.46 (q)	8.24 (s)	J_{CH_3-CH} = 7; $J_{4,5}$ = 5; $J_{3,5}$ = 1.5
34878-48-3	5-Methoxy	CS_2	6.62 (d)	5.89 (d)		1.76 (d)	6.12 (q)	8.07 (s)	J_{CH_3-CH} = 7; $J_{3,4}$ = 4; $CH_{3(OCH_3)}$, δ 3.77 (s)
34878-49-4	5-Cyclopropyl	CCl_4	6.79 (d)	6.50 (d)		1.74 (d)	6.24 (q)	8.10 (s)	J_{CH_3-CH} = 7; $J_{3,4}$ = 4; $CH_{(cyclopropyl)}$, δ 1.8 (m); $CH_{2(cyclopropyl)}$, δ 0.8 (m)
34878-50-7	5-Methyl	CS_2	6.82 (d)	6.53 (m)		1.70 (d)	6.25 (q)	8.12 (s)	J_{CH_3-CH} = 7; $J_{3,4}$ = 4; 5-CH_3, δ 2.40 (d); $J_{(5-CH_3-CH)}$ = 0.4
34878-51-8	5-Bromo	CS_2	6.80 (s)	6.80 (s)		1.73 (d)	6.20 (q)	8.10 (s)	J_{CH_3-CH} = 7
34878-52-9	5-Phenyl	CS_2	7.01 (s)	7.01 (s)		1.76 (d)	6.30 (q)	8.10 (s)	J_{CH_3-CH} = 7; 5-phenyl, δ 7.3 (m)
34878-53-0	5-Ethoxycarbonyl	$CDCl_3$	7.09 (d)[c]	7.64 (d)		1.81 (d)	6.38 (q)	8.23 (s)	J_{CH_3-CH} = 7; $J_{3,4}$ = 3.5; $CH_{3(Et)}$, δ 1.35 (t); $CH_{2(Et)}$, δ 4.32 (q); $J_{CH_3-CH_2}$ = 7
34878-54-1	4-Bromo	$CDCl_3$	7.06 (d)		7.18 (d)	1.78 (d)	6.36 (q)	8.23 (s)	J_{CH_3-CH} = 7; $J_{3,5}$ = 1.5
34878-55-2	4,5-Dibromo	$CDCl_3$	6.92 (s)			1.77 (d)	6.28 (q)	8.20 (s)	J_{CH_3-CH} = 7
34878-56-3	4-Ethoxycarbonyl	$CDCl_3$	7.46 (d)		7.92 (d)	1.79 (d)	6.29 (q)	8.08 (s)	J_{CH_3-CH} = 7; $J_{3,5}$ = 1.5; $CH_{3(Et)}$, δ 1.34 (t); $CH_{2(Et)}$, δ 4.26 (q); δ 4.26 (q); $J_{CH_3-CH_2}$ = 7

[a] In parts per million (δ) from internal TMS. [b] *J*, the observed coupling constant, in cps. [c] Multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

(0.0885 mol) of *n*-butyllithium (Foote Mineral) in hexane in a slow stream. The stirred solution was maintained under nitrogen for 10 min. To the solution was added dropwise 5.85 g (0.0885 mol) of acetaldehyde which had been precooled in the refrigerator. The solution was stirred at 0° for 40 min. The reaction mixture was then refluxed under a nitrogen atmosphere using a Dry Ice–isopropyl alcohol condenser for 3 hr. The red liquid was poured over crushed ice and the ether layer was extracted and dried over anhydrous sodium sulfate. Removal of the ether at room temperature gave an amber oil whose nmr spectrum showed it to be 89% of the desired alcohol and 11% 2-methoxythiophene. Stringent efforts to maintain anhydrous conditions during the reaction or changing the temperature to −70° did not affect the product ratio. The production of 2-methoxythiophene is the result of a competing reaction in which the 5-methoxy-2-thienyllithium abstracts an acidic hydrogen from the acetaldehyde.

The crude alcohol was warmed to 35° and all of the 2-methoxythiophene was removed at a pressure of 0.1 mm over a period of 48 hr. The alcohol proved to be thermally unstable under normal distillation conditions. It could be purified, however, by a bulb-to-bulb transfer in a sealed system which had been evacuated to 0.01 mm prior to heating. The crude alcohol was kept in one bulb over anhydrous sodium carbonate and was gently warmed between 60 and 80°. The receiving bulb was cooled in a liquid nitrogen bath. In this manner 9.0 g (65%) of pale yellow 1-(5-methoxy-2-thienyl)ethanol was obtained. The alcohol was immediately used for the preparation of the *p*-nitrobenzoate ester.

1-(5-Cyclopropyl-2-thienyl)ethanol was prepared from 2-cyclopropylthiophene.[35] To a solution of 4.103 g (0.033 mol) of 2-cyclopropylthiophene dissolved in 100 ml of anhydrous ether under a nitrogen atmosphere was added 20.46 ml (0.033 mol) of *n*-butyllithium in hexane. The *n*-butyllithium solution was added to the stirred solution at 0° in a steady stream. During the course of addition the solution turned a pale brown color. The ice bath was removed after 10 min, and the solution was stirred at room temperature for 5 hr. To the stirred solution was added 3.4 ml (0.06 mol) of acetaldehyde, which had been precooled to 0°, by means of a dry syringe which had also been cooled. The mixture was allowed to stir for 20 min and then was washed with 100 ml of water. The wash water was back extracted with 2 × 50 ml of ether. The combined organic extracts were finally washed with 50 ml of water. The solution was dried over anhydrous magnesium sulfate and the solvent was removed at room temperature under reduced pressure to give 5.2 g of a reddish oil. Examination of this oil by nmr showed it to be about 70% of the desired alcohol. Chromatography on silica gel gave 0.9 g of 2-cyclopropylthiophene, eluted with petroleum ether (bp 30–60°), and 3.3 g (59.5%) of 1-(5-cyclopropyl-2-thienyl)ethanol, eluted with chloroform.

Substituted 1-(2-Thienyl)ethyl *p*-Nitrobenzoates.—The appropriate 1-(2-thienyl)ethanol was dissolved in 20 ml of cold pyridine and treated with freshly recrystallized *p*-nitrobenzoyl chloride. After 6 hr at room temperature, the mixture was gently warmed with 100 ml of hexane for 10 min. The hexane–pyridine solution was decanted and filtered and then washed with 4 × 50 ml of warm water. The pyridine-free hexane solution was dried by filtering through a sodium chloride mat. Cooling of the hexane solution gave the crystalline *p*-nitrobenzoate ester. This work-up gave better results, as many *p*-nitrobenzoates have low melting points and readily form oils. The nmr data for the *p*-nitrobenzoates are recorded in Table IV. Table V tabulates melting points and analyses.

2-Vinylthiophene was prepared by the method of Emerson and Patrick[36] in 43% yield, bp 61–62° (45 mm) [lit. bp 65–67° (50 mm)].

Ethyl 1-(2-Thienyl)ethyl Ethyl Ether.—To a solution of 18.9 g (0.15 mol) of 2-acetylthiophene (Aldrich) dissolved in 100 ml of absolute ethanol at 0° was added 2.83 g (0.075 mol) of sodium borohydride. The solution was stirred at 0° for 0.5 hr and then at room temperature for 8.5 hr. The solution was acidified to

(35) Y. K. Yur'ev and D. Eckhardt, *Zh. Obshch. Khim.*, **31**, 3274 (1961); *Chem. Abstr.*, **57**, 4622*a* (1962).

(36) W. Emerson and T. Patrick, Jr., "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 980.

TABLE V
PROPERTIES OF SUBSTITUTED 1-(2-THIENYL)ETHYL *p*-NITROBENZOATES

Compd	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S
X = 5-OMe	66.8–67.6	54.72	4.26			54.66	4.18		
X = 5-c-C_3H_5	Oil								
X = 5-Me	48.5–49.0	57.72	4.50		11.01	57.53	4.70		11.05
X = 5-Ph	73.5–74.0	64.55	4.25			64.70	4.19		
X = H	64.5–65.8	56.31	4.00	5.05	11.56	56.33	4.24	5.06	11.50
X = 5-Br	99.0–100	43.80	2.81	(Br, 22.45)		43.68	2.95	(Br, 22.68)	
X = 4-Br	60.0–60.5	43.80	2.81	(Br, 22.45)		44.06	2.66	(Br, 22.24)	
X = 4,5-Br_2	99.0–99.7	35.88	2.08	(Br, 36.75)		35.82	2.25	(Br, 36.90)	
X = 4-COOEt	115.7–116.0	55.00	4.33			54.92	4.35		
X = 5-COOEt	91.5–92.0	55.00	4.33			55.22	4.15		

a pH of 2 with 2 *N* hydrochloric acid and then was refluxed overnight. The resulting yellow solution and white solid was poured into 1 l. of water which was extracted with 3 × 100 ml of ether. The ether extracts were dried (magnesium sulfate), and the ether was stripped off under vacuum at room temperature to give 21.1 g (90%) of a pale yellow oil. Analysis by nmr revealed only traces of 2-vinylthiophene. Fractional distillation gave 17.0 g of pure ethyl 1-(2-thienyl)ethyl ether, bp 93–93.5° (40 mm) [lit.[37] bp 78–79° (16 mm)].

Product Analysis.—Analysis of the products from the solvolysis of 1-(2-thienyl)ethyl *p*-nitrobenzoate in 80% aqueous ethanol at 60° was carried out by an adaptation of the glpc procedure of Buckson and Smith,[38] who analyzed the ethanolysis products from phenyldimethylcarbinyl chloride and the corresponding *p*-nitrobenzoate. Additional confirmatory data was provided by nmr spectroscopy.

1-(2-Thienyl)ethyl *p*-nitrobenzoate (0.015 *M*) in 80% ethanol was solvolyzed at 60° for 18 hr (*ca.* 10 half-lives). The solution was diluted with water and extracted with 6 × 50 ml of dichloromethane. The combined organic extracts were washed with 50 ml of saturated sodium bicarbonate solution and 50 ml of water. After drying over anhydrous magnesium sulfate, the solution was filtered and then concentrated to *ca.* 5 ml by distilling the solvent through a 12-in. Vigreux column.

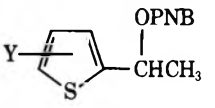
A portion (10 μl) of the remaining solution was injected into an Aerograph A90-P gas chromatograph equipped with a 5 ft × 0.25 in. 10% Carbowax on Chromosorb W column which had been treated with KOH. The column and injection port were kept at 114 and 147°, respectively. Ethyl 1-(thienyl)ethyl ether, 2-vinylthiophene, and 1-(2-thienyl)ethanol were shown to be completely stable under these conditions. The molar responses of the ether, alcohol, and 2-vinylthiophene were determined in separate experiments. In a control experiment a solution of the three compounds was subjected to the analysis procedure and the composition of the mixture was shown to be unchanged. In a separate experiment it was shown that 3% of 2-vinylthiophene could be observed in a mixture. Analysis of the solvolysis products and correcting for the molar responses showed the products to be 82 ± 10% ethyl 1-(2-thienyl)ethyl ether and 18 ± 10% 1-(2-thienyl)ethanol. No peak due to 2-vinylthiophene could be observed.

As an additional check on the nature of the solvolysis products the dichloromethane solution of the solvolysis products was examined with a Varian HA-100 nmr spectrometer. A quartet at δ 3.3 which could be assigned to the $-OCH_2CH_3$ methylene group of the ether product was clearly visible. Two superimposed doublets at δ 1.4 which could be assigned to the carbinyl methyl groups of the alcohol and ether were also observed. By integrating these peaks it was calculated that the solvolysis product consisted of 75 ± 10 mol % of the ether product and 25 ± 10 mol % of the alcohol product. No trace of the largest vinyl hydrogen peak in 2-vinylthiophene, which occurs at δ 5.8, could be observed.

Kinetic Procedures.—The kinetic solutions were prepared to be *ca.* 0.013 *M* *p*-nitrobenzoate in 80% aqueous ethanol. The solvent was prepared by mixing four parts of ethanol with one part of water by volume. The ethanol was purified by distilling commercial absolute ethanol twice from iodine-activated magnesium according to the method of Lund and Bjerrum.[39] The ethanol contained less than 0.05% water as determined by titration with Karl Fisher reagent. The water was laboratory distilled water. The volumes of the liquids were measured in pipettes and mixed at room temperature.

The kinetic samples were prepared by weighing 0.0013 mol

TABLE VI
EXPERIMENTAL RATE CONSTANTS FOR THE SOLVOLYSIS OF SUBSTITUTED 1-(2-THIENYL)ETHYL *p*-NITROBENZOATES IN 80% ETHANOL



Y	Temp, °C	Method[a]	k_1, sec^{-1}
5-Methoxy	13.40	Uv	6.73 ± 0.06 × 10^{-2}
	13.45	Uv	7.19 ± 0.23 × 10^{-2}
	13.45	Uv	6.88 ± 0.08 × 10^{-2}
	13.50	Uv	6.97 ± 0.04 × 10^{-2}
	13.50	Uv	6.80 ± 0.02 × 10^{-2}
	13.50	Uv	6.57 ± 0.08 × 10^{-2}
	0	PH-Stat	7.74 ± 0.15 × 10^{-3}
	0	pH-Stat	8.51 ± 0.17 × 10^{-3}
5-Cyclopropyl	25.00	T	1.15 ± 0.003 × 10^{-3}
	25.00	T	1.13 ± 0.004 × 10^{-3}
5-Methyl	44.63	Uv	1.62 ± 0.04 × 10^{-3}
	44.63	Uv	1.36 ± 0.06 × 10^{-3}
	45.00	T	1.32 ± 0.07 × 10^{-3}
	45.07	T	1.70 ± 0.03 × 10^{-3}
	25.00	Uv	2.39 ± 0.02 × 10^{-4}
	25.00	Uv	1.93 ± 0.01 × 10^{-4}
	25.00	T	1.78 ± 0.02 × 10^{-4}
	24.98	T	1.83 ± 0.02 × 10^{-4}
	24.98	T	1.81 ± 0.02 × 10^{-4}
5-Phenyl	45.00	Uv	4.98 ± 0.28 × 10^{-4}
	45.00	Uv	5.14 ± 0.33 × 10^{-4}
	45.00	Uv	5.02 ± 0.21 × 10^{-4}
	45.06	T	4.81 ± 0.05 × 10^{-4}
	24.98	T	3.23 ± 0.18 × 10^{-5}
	24.98	T	3.77 ± 0.15 × 10^{-5}
Hydrogen	45.00	T	2.61 ± 0.05 × 10^{-5}
	25.00	T	2.27 ± 0.04 × 10^{-6}
5-Bromo	75.00	T	1.14 ± 0.03 × 10^{-4}
	75.00	T	1.18 ± 0.02 × 10^{-4}
	44.93	T	4.31 ± 0.14 × 10^{-6}
	45.00	T	3.97 ± 0.10 × 10^{-6}
4-Bromo	75.00	T	6.55 ± 0.23 × 10^{-6}
	60.00	T	9.12 ± 0.53 × 10^{-7}
4,5-Dibromo	89.66	T	1.29 ± 0.04 × 10^{-5}
	75.00	T	2.24 ± 0.09 × 10^{-6}
4-Ethoxycarbonyl	89.66	T	1.57 ± 0.02 × 10^{-5}
	75.00	T	2.59 ± 0.08 × 10^{-6}
	75.00	T	2.68 ± 0.08 × 10^{-6}
5-Ethoxycarbonyl	110.00	T	1.18 ± 0.03 × 10^{-5}
	89.80	T	1.47 ± 0.09 × 10^{-6}

[a] T = trimetric.

(37) W. Emerson and T. Patrick, Jr., *J. Org. Chem.*, **13**, 729 (1948).
(38) R. L. Buckson and S. G. Smith, *ibid.*, **32**, 634 (1967).
(39) M. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931).

p-nitrobenzoate ester and dissolving the ester in 80 ml of absolute ethanol. For the faster runs this ethanol solution was thermostated in a volumetric flask in the temperature bath. To the thermostated solution was added 20 ml of distilled water at temperature, and, after temperature equilibration, aliquots were removed for titration. For the slower runs requiring higher temperatures, a sealed ampoule technique was used.

The aliquots from the kinetic runs were quenched in absolute ethanol and the liberated *p*-nitrobenzoic acid was titrated with *ca.* 0.0075 *M* potassium hydroxide in absolute ethanol on a Metrohm Potentiograph E336-A automatic recording titrator using the first derivative curve.

The solvolysis of 1-(5-methoxy-2-thienyl)ethyl *p*-nitrobenzoate at 13.5° was too rapid to be followed by the titration procedure. Instead an ultraviolet spectrophotometric procedure was used. The ultraviolet spectrum of the ester changed in a first-order manner to that of the reaction products if a slight amount of sodium bicarbonate was present to keep the liberated *p*-nitrobenzoic acid as the anion. A Gilford Model 2000 automatic recording spectrophotometer was used to follow the progress of the reaction. Rates were determined by both the ultraviolet spectrophotometric and titrimetric techniques for the 5-methyl and 5-phenyl compound under conditions which gave half-lives of 0.5 hr or less. The agreement in rates was quite satisfactory.

The rate of solvolysis of 1-(5-methoxy-2-thienyl)ethyl *p*-nitrobenzoate at 0.00° was slow enough to be followed by a titrimetric procedure. About 0.3 g of the ester was dissolved in 0.5 ml of dioxane. The dioxane solution was injected into 25 ml of 80% ethanol equilibrated at 0.00°. The solution was titrated with 0.66 *N* potassium hydroxide in 80% ethanol with a Radiometer SBR2 Titrigraph. The pH was kept constant at 7.6.

Measured rate constants are recorded in Table VI.

Registry No.—2-Acetyl-5-ethoxycarbonylthiophene, 33148-82-2.

Transmission of Substituent Effects in Heterocyclic Systems. The Solvolysis of Substituted 3-Furyl Derivatives[1]

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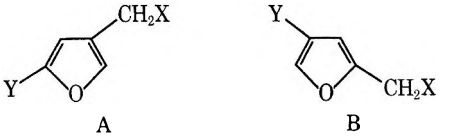
Received January 31, 1972

The rate of solvolysis of 2-(5-methyl-3-furyl)-2-propyl *p*-nitrobenzoate is substantially larger than the solvolysis rate for 2-(3-furyl)-2-propyl *p*-nitrobenzoate in 80% ethanol. The correlation of solvolysis rates for other 3-furyl systems is not satisfactory using pseudo meta relationships. However, generally useful and satisfactory correlations are obtained from consideration of CNDO/2 and INDO molecular orbital parameters for these systems. These parameters also provide an excellent basis for additional predictions.

In a previous paper it has been shown that the solvolysis rates of a number of 5-substituted 1-(2-furyl)-ethanol derivatives are satisfactorily correlated by the Hammett relationship, using Brown's σ_p^+ substituent constants.[3] Notable was the high sensitivity of the furan ring to the electronic effect of the substituent in such a correlation, with ρ being -8. These observations were largely limited to 5-substituted 2-furyl systems, because of the generally difficult accessibility of β-substituted furans. The 5-Y-2-furyl relationship may be thought of as a normally "conjugating" relationship as exemplified by consideration of valence bond resonance structures.

It was of interest to extend these observations on the mode of transmission of substituent effects to "nonconjugating" relationships in the furan system. Such systems, A and B, pose some problems in synthesis; as a consequence, we have therefore obtained a somewhat limited amount of information. Nonetheless, the pattern which emerges is quite clear, and points to some particularly interesting general conclusions.

Yur'ev, Gal'bershtam, *et al.*,[4,5] have reported that the rate of methanolysis of 2,5-dimethyl-3-chloromethylfuran is 18 times that of 2-methyl-3-chloromethylfuran. This striking rate increase for introduction of a methyl group in a "nonconjugating" position (*i.e.*, position 5)



is unusual; it is to be contrasted with the effect of a methyl group introduced in the meta position in benzene systems. For benzyl systems $k_{m\text{-Me}}/k_H$ ratios are typically 2 or 3.[6]

Our results show that this high ratio is characteristic of the furan system, and is not a singular or fortuitous result, due perhaps to ortho substitution. We have observed similar high rate ratios in both simple secondary and tertiary systems. From the results given in Table I, for the secondary systems **1** and **2**, the rate

TABLE I

RATE CONSTANTS FOR SOLVOLYSIS OF SOME SUBSTITUTED FURAN DERIVATIVES IN 80% ETHANOL

Compound solvolyzed	Temp, °C	k, sec^{-1}
1-(3-Furyl)ethyl *p*-nitrobenzoate (**1**)	75.00	8.18×10^{-6}
1-(5-Ethyl-3-furyl)ethyl *p*-nitrobenzoate (**2**)	75.00	7.24×10^{-5}
2-(3-Furyl)-2-propyl *p*-nitrobenzoate (**3**)	25.00	4.57×10^{-4}
	25.00	4.66×10^{-4}
2-(5-Methyl-3-furyl)-2-propyl *p*-nitrobenzoate (**4**)	25.00	2.75×10^{-3}

ratio k_{Et}/k_H is 8.85; in the tertiary systems, **3** and **4**, the rate ratio k_{Me}/k_H is 6.0.

A rational explanation of these observations comes

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.

(2) Graduate Fellow on the University of California–Chile Cooperative Program from funds provided by the Ford Foundation, 1966–1970.

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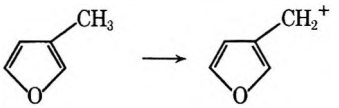
(5) M. A. Gal'bershtam, G. T. Khachaturova, N. E. Bairamova, K. Y. Novitskii, and Y. K. Yur'ev, *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.*, **11**, 1395 (1968); *Chem. Abstr.*, **71**, 21307b (1969).

(6) Exemplary are the following: cumyl chlorides, 2.0, 2.28 [Y. Okamoto, T. Inukai, and H. C. Brown, *J. Amer. Chem. Soc.*, **80**, 4972 (1958)]; benzhydryl chlorides, 2.1 [J. F. Norris and J. T. Blake, *ibid.*, **50**, 1808 (1928)]; benzyl tosylates, 2.65 [A. Streitwieser, *et al.*, *ibid.*, **92**, 5141 (1970)].

from consideration of the change in charge density at various positions within a heterocyclic nucleus which are induced by the change from a nonalternant hydrocarbon to the related cation, C → D.



C D

Discussion

It should be noted initially that furan represents a nonalternant hydrocarbon; as such, the charge density about the ring in the parent hydrocarbon is not equal at various carbon atoms, in contrast to benzene or other condensed polynuclear aromatic hydrocarbons. Hence any studies of the relationship of molecular orbital parameters with activity at these systems must consider the *change* in charge density at position *i*.

The availability of standard programs for CNDO/2 and for INDO calculations now make it feasible to carry out such calculations with reasonable facility. This we have done.[7,8] It has been recently shown by Streitwieser, *et al.*,[9] that the CNDO/2 method is superior to SCF-π and HMO methods for correlating the acetolysis rates of arylmethyl tosylates with ΔE values calculated for the transformation $ArCH_3 \rightarrow ArCH_2^+$. We have also compared CNDO/2 and INDO calculations concurrently. The pertinent results of these calculations of the change in regional charge,[10] Δq, are listed in Table II.

TABLE II
CHARGE DENSITIES AT VARIOUS POSITIONS FROM CNDO/2 AND INDO CALCULATIONS

System	Position	CNDO/2 Δq	INDO Δq	r^a	% $\mathfrak{R}$ calcd (INDO)
Toluene → benzyl cation	4	0.2114	0.2109	2.00	65
	3	0.0368	0.0353	1.732	30
2-Methylfuran → furfuryl cation	5	0.2763	0.2726	1.571	66
	4	0.0642	0.0696	1.605	39
3-Methylfuran → 3-furylmethyl cation	5	0.1076	0.1150	1.605	49

[a] Distance (in units of standard benzene bond length, 1.39 Å) from aromatic carbon to which side chain is attached to numbered carbon bearing substituent.

It is to be noted that the change in regional charge for position 5 in the 3-furylmethyl cation is strikingly larger than in the meta relationship in the case of toluene → benzyl. Hence one should not expect meta substituent constants to correctly represent the mode of response for this furyl system. However, for 2-methylfuran the change in regional charge at position 5 in going to the furfuryl cation is more nearly in accord with the para relationship in the case of toluene to benzyl. Hence, as previously reported,[3] para substituent constants, σ_p^+, should be reasonably good in correctly reproducing the observed results. This is in fact what we observed previously, namely, excellent correlation with σ para plus.[3] In order to relate these results of the change in charge density to substituent effects we need an appropriate method for calculating an effective substituent constant. Substituent constants have been treated as a blend of field and resonance contributions. Dewar and Grisdale[11] have been successful in treating the dissociation constants of naphthalene derivatives in this fashion and more recently Swain and Lupton[12] have shown that separation of substituent constants into $\mathfrak{F}$ and $\mathfrak{R}$ components successfully deals with the massive quantities of data in the literature.

Bancroft and Howe[13] have shown that the Dewar–Grisdale equation[11a] when calibrated with Brown's σ^+ constants[14] rather than Hammett σ constants gives greatly improved results in correlating the measured rates of detritiation of substituted naphthalenes. Eaborn and Fischer[15] have extended these observations. We make the further modification of using Δq_{ij} as the coefficient of the resonance term, and thus have the modified Dewar–Grisdale equation (1).

$$(\sigma_{ij}^+)_x = F^+_x/r_{ij} + \Delta q_{ij} M^+_x \quad (1)$$

The $1/r_{ij}$ and Δq_{ij} values for benzyl listed in Table II and the σ^+ values of Brown and Okamoto[14] define the parameters F^+ and M^+ for any substituent when related by eq 1. Thus follow eq 2–5.

$$F^+_{INDO} = 2.039\sigma_m^+ - 0.3548\sigma_p^+ \quad (2)$$

$$M^+_{INDO} = 5.568\sigma_p^+ - 4.822\sigma_m^+ \quad (3)$$

$$F^+_{CNDO} = 2.026\sigma_m^+ - 0.339\sigma_p^+ \quad (4)$$

$$M^+_{CNDO} = 5.546\sigma_p^+ - 4.803\sigma_m^+ \quad (5)$$

It is to be noted that both the CNDO/2 method and the INDO method give closely similar results.

The F^+ and M^+ substituent parameters then may be directly transcribed to give σ_{ij}^+ values for any heterocyclic system and any substitution pattern for which Δq values have been calculated. It should be noted that this approach does not have any arbitrary parameters introduced, save the standard parameters in the regular CNDO/2 or INDO program.

From the calculated σ_{ij}^+ values, predicted rates of reaction may be obtained from a modified Hammett equation (eq 6), using ρ for the corresponding solvolysis reaction in the benzene series.

$$\log k/k_0 = \rho\sigma_{ij}^+ \quad (6)$$

Comparisons involving 3-substituted furans are given in Table III.[16,17] It is evident that this approach

(7) We wish to express our appreciation to Professor Streitwieser and to Dr. P. Mowery for making available to us the QCPE program 142 suitably modified to use on the CDC 6400, and for counsel in use of this program.

(8) These calculations were carried out by Dr. R. W. Nichols with time donated by the University of California Computer Center. Further details will be available in a forthcoming paper by R. W. Nichols and D. S. Noyce.

(9) A. Streitwieser, Jr., H. A. Hammond, R. H. Jagow, R. M. Williams, R. G. Jesaitis, C. J. Chang, and R. Wolf, *J. Amer. Chem. Soc.*, **92**, 5141 (1970).

(10) Regional charge: the sum of the charges on a carbon atom and on any hydrogen atoms bonded to it. A. Streitwieser, Jr., and R. G. Jesaitis in "Sigma Molecular Orbital Theory," O. Sinanoglu and K. B. Wiberg, Ed., Yale University Press, New Haven, Conn., 1970, p 197.

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TABLE III

RELATIVE RATES AND SUBSTITUENT CONSTANTS FOR 5-SUBSTITUTED 3-FURYL SYSTEMS

System	Log k/k_0	$(\sigma_{3,3}{}^+)_{INDO}$	Calcd rate predicted
5-Me (4)	0.78[a]	−0.177	0.77[e]
5-Acetyl (5)	−2.53[a,b]	0.597[d]	−2.5[e]
5-Et (2)	0.95[c]	−0.169	0.96[f]

[a] At 25°. [b] $k = 1.36 \times 10^{-6}$ sec^{-1}, extrapolated. [c] At 75°. [d] $\sigma_p{}^+$ and $\sigma_m{}^+$ from ref 14. [e] Assuming $\rho = -4.34$. [f] Assuming $\rho = -5.7$ (ref 16 and 17).

satisfactorily accommodates the experimental data, both in the nature of the acceleration of rate of solvolysis caused by introduction of a 5-alkyl group and also in showing that this acceleration is greater in primary systems[4,5] than in secondary or tertiary systems.

Two additional features of this approach merit comment. For the effects of substituents in the 5 position in 3-furylmethyl systems, one may now calculate the percentage field and percentage resonance contributions which contribute to the total effect using Swain and Lupton's formulation.

For the three possible patterns of substitution in furan, these are given in the last column of Table II. Notable is the fact that the percentage resonance in 5-substituted furfuryl systems is 67%, almost identical with the corresponding value found by Swain and Lupton for para-substituted benzene derivatives, and defined by $\sigma_p{}^+$. For the 4 position in furfuryl systems, the percentage resonance is much less, but distinctly greater than for a meta position in a benzene ring. For 5-substituted 3-furylmethyl systems, the percentage resonance is 49%, and thus this increased resonance component is responsible for the sharp response of reaction rate to the introduction of a 5-methyl group.

Extending this analysis to an additional substituent, the 5-acetyl group, 2-(5-acetyl-3-furyl)-2-propyl *p*-nitrobenzoate (**5**), we find that the reaction rate is sharply depressed. For these three substituents, the correlation of reaction rate by a modified Hammett relationship is excellent.

Experimental Section[18]

1-(3-Furyl)ethyl *p*-Nitrobenzoate (1).—1-(3-Furyl)ethanol has been reported previously.[16,19,20] We observed that 1-(3-furyl)-ethanol is conveniently prepared from 3-bromofuran by the halogen metal interchange reaction with *n*-butyllithium at −78° followed by treatment with acetaldehyde, yield 73%, bp 92–93° (18 mm) [lit.[19] bp 55–60° (8 mm)].

To prepare the *p*-nitrobenzoate, the alcohol was converted to the lithium salt (*n*-butyllithium in hexane) and treated with *p*-nitrobenzoyl chloride. The ester was crystallized from hexane: mp 64–65°; ir ($CHCl_3$) 3016 (w), 1723 (s), 1612 (m), 1534 (s), 1277 (s), 873 (s), 660 cm^{-1} (m); nmr ($CDCl_3$) δ 1.68 (d, 3, $J_{CH_3,H}$ = 6.5 Hz, CH_3), 6.12 (q, 1, CHOPNB), 6.43 (dd, 1, 4-H), 7.31 (dd, 1, 5-H), 7.45 (dd, 1, 2-H), 8.15 (s, 4, phenyl H).

Anal. Calcd for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36. Found: C, 59.63; H, 4.48; N, 5.32.

4-Bromo-2-acetylfuran.—The preparation of 4,5-dibromo-2-acetylfuran by the method of Gol'dfarb and Tarasova[21] was improved to give a 75% yield using dibromomethane as solvent. Reduction with zinc in aqueous acetic acid afforded 4-bromo-2-acetylfuran in 77% yield, mp 68° (lit.[21] mp 68°).

4-Bromo-2-ethylfuran.—4-Bromo-2-acetylfuran was converted by Wolff–Kishner reduction to 4-bromo-2-ethylfuran in 79% yield: bp 78° (54 mm) [lit.[21] bp 56–57° (23 mm)]; nmr ($CDCl_3$) δ 1.21 (t, 3, J_{CH_3,CH_2} = 7.5 Hz, CH_3), 2.63 (m, 2, CH_2), 6.04 (m, 1, 3-H), 7.28 (d, 1, 5-H).

1-(5-Ethyl-3-furyl)ethanol.—To a solution of 4-bromo-2-ethylfuran (7.3 g) in 100 ml of anhydrous ether at −78° was added 1 equiv of *n*-butyllithium, precooled to −78°, over 30 min. After the addition was over the reaction mixture was stirred for 20 min at −78°. To this solution 5 ml of cold acetaldehyde was added by syringe. The reaction mixture was stirred for an additional 1 hr at −78°, the contents of the flask were poured over 400 ml of ice-cold water, and the mixture was carefully neutralized with 15% sulfuric acid. After work-up in the usual fashion, 1-(5-ethyl-3-furyl)ethanol (3.87 g, 66%) was obtained as a colorless liquid: bp 94–95° (14.5 mm); ir (CCl_4) 3571 (m, sh), 3436 (broad), 2985 (s), 1550 (m), 921 cm^{-1} (s); nmr ($CDCl_3$) δ 1.21 (t, 3, J_{CH_3,CH_2} = 7.5 Hz, CH_3CH_2), 1.42 (d, 3, $J_{CH_3,H}$ = 6.5 Hz, $CHOHCH_3$), 2.42 (s, 1, OH), 2.62 (q, 2, CH_2CH_3), 4.76 (q, 1, CHOH), 6.00 (d, 1, 4-H), 7.18 (d, 1, 2-H).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.86; H, 8.55.

1-(5-Ethyl-3-furyl)ethyl *p*-Nitrobenzoate (2).—From 1-(5-ethyl-3-furyl)ethanol and *p*-nitrobenzoyl chloride in the usual fashion,[3] **2** was obtained as white crystals from cold hexane: mp <25°; ir ($CHCl_3$), 1724 (s), 1610 (w), 1524 (s), 1337 (m), 1271 (s), 1117 (m), 1110 cm^{-1} (m); nmr ($CDCl_3$) δ 1.32 (t, 3, J_{CH_3,CH_2} = 7.5 Hz, CH_2CH_3), 1.82 (d, 3, $J_{CH_3,H}$ = 6.5 Hz, CH_3-CHOPNB), 2.80 (q, 2, CH_2CH_3), 6.15 (q, 1, CH_3CH), 6.40 (m, 1, 4-H), 7.44 (d, 1, 2-H), 8.10 (s, 4, phenyl H).

Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.27; H, 5.23; N, 4.84. Found: C, 61.98; H, 4.97; N, 4.98.

2-(3-Furyl)-2-propanol.—From methylmagnesium iodide and methyl 3-furoate the tertiary alcohol was obtained as a colorless liquid: bp 98° (19.5 mm) [lit.[19] bp 53–58° (8 mm)]; nmr (CCl_4) δ 1.48 (2, 6, CH_3), 2.69 (s, 1, OH), 6.32 (m, 1, 4-H), 7.25 (m, 2, 2-H and 5-H).

2-(3-Furyl)-2-propyl *p*-Nitrobenzoate (3).—From 2-(3-furyl)-2-propanol and *p*-nitrobenzoyl chloride in pyridine, **3** was obtained in the usual fashion as slightly yellow crystals from petroleum ether (bp 30–60°): mp 99.5–100.5°; ir ($CHCl_3$) 3021 (w), 1726 (s), 1610 (m), 1529 (s), 1351 cm^{-1} (s); nmr (CCl_4) δ 1.82 (s, 6, CH_3), 6.32 (m, 1, 4-H), 7.26 (m, 1, 2-H), 7.37 (m, 1, 5-H), 8.07 (d, 4, phenyl H).

Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 60.96; H, 4.50; N, 5.22.

4-Bromofurfural.—Bromination of furfural by the method of Gol'dfarb, *et al.*,[22] afforded 4,5-dibromofurfural, which was reduced with zinc dust in aqueous acetic acid[21] to 4-bromofurfural, mp 54.0–54.5° (lit.[23] mp 54°).

2-Methyl-4-bromofuran.—Wolff–Kishner reduction of 4-bromofurfural afforded 2-methyl-4-bromofuran in 61% yield: bp 132–134° [lit.[24] bp 60–62° (60 mm)]; nmr (CCl_4) δ 2.26 (d, 3, $J_{CH_3,3H}$ = 1 Hz, CH_3), 5.95 (m, 1, 3-H) 7.19 (d, 1, 5-H).

Anal. Calcd for C_5H_5BrO: C, 37.30; H, 3.13; Br, 49.63. Found: C, 37.31; H, 3.20; Br, 49.52.

2-(5-Methyl-3-furyl)-2-propanol.—To a solution of 14.3 g of 2-methyl-4 bromofuran in 200 ml of ether at −78° was added a precooled hexane solution of *n* butyllithium (1 equiv) over a period of 30 min. After an additional 30 min at −78° acetone (15 ml) was added, and the resulting mixture was maintained at −78° for 2 hr and then allowed to warm to room temperature. After working up in the usual fashion, there was obtained 9.3 g (74%) of 2-(5-methyl-3-furyl)-2-propanol as a colorless liquid: bp 58–60° (1 mm); nmr (CCl_4) δ 1.38 [s, 6, $(CH_3)_2$], 2.20 (d, 3, 5-CH_3), 2.45 (s, 1, OH), 5.88 (m, 1, 4-H), 7.02 (d, 1, 2-H).

2-(5-Methyl-3-furyl)-2-propyl *p*-Nitrobenzoate (4).—The above alcohol was converted directly to the ester using the pyridine method.[3] The crude ester, contaminated with *p*-nitrobenzoic acid, was used directly for kinetic measurements.

(18) Melting points and boiling points are uncorrected. Analyses are by the Microanalytical Laboratory, University of California, Berkeley. Spectra were recorded using Perkin-Elmer Model 237 (ir) or Varian A-60 (nmr) spectrometers.

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2-Acetyl-4-bromofuran Diethyl Ketal.—To a stirred solution of 2-acetyl-4-bromofuran (50.0 g) in 50 ml of absolute ethanol was added triethyl orthoformate (75.0 g) and 25 ml of a 9% (w/w) solution of dry hydrochloric acid in absolute ethanol. The reaction mixture was stirred at room temperature for 24 hr and, after it was neutralized with sodium ethoxide, the mixture was distilled to 85° to remove excess ethanol and ethyl formate. The residual dark liquid was distilled under reduced pressure. A forerun of triethyl orthoformate was collected and 33.0 g (90%) of 2-acetyl-4-bromofuran diethyl ketal was obtained as a colorless liquid: bp 119° (16 mm); bp 95° (3 mm); ir (CCl_4) 3155 (w), 2994 (s), 1370 (m), 1271 (s), 901 (s), 860 (s), 691 cm^{-1} (m) nmr (CCl_4) δ 1.13 (t, 6, J_{CH_3,CH_2} = 7 Hz, CH_2CH_3), 1.54 (s, 3, $=CCH_3$), 3.32 (dq, 4, CH_2), 6.34 (d, 1, $J_{3,5}$ = 0.9 Hz, 3-H), 7.40 (d, 1, 5-H).

2-(5-Acetyl-3-furyl)-2-propanol.—In a nitrogen-swept flask, immersed in an acetone–Dry Ice bath, was placed a solution of 2-acetyl-4-bromofuran diethyl ketal (26.3 g, 0.1 mol) in 250 ml of anhydrous ether. A precooled hexane solution of *n*-butyllithium (62.2 ml, 0.1 mol) was added over a period of 30 min. After the addition was complete the mixture was stirred at −78° for 1 hr and then 15 ml of acetone was added. The reaction mixture was stirred for 3 hr at −78° and for 2 hr at room temperature. The contents of the flask were poured into cold water and the mixture was extracted with ether. The ethereal solution was transferred to a flask, the ether was removed on a rotary evaporator, and the residual oil was hydrolyzed with 150 ml of water containing 3 ml of 3 *N* hydrochloric acid, at room temperature for 2 hr. The reaction mixture was extracted with ether. The ethereal solution was washed with 5% sodium bicarbonate and water, dried over anhydrous magnesium sulfate, and filtered. After removal of the ether on a rotary evaporator, 11.5 g (68%) of crude 2-(5-acetyl-3-furyl)-2-propanol remained as a pale yellow oil: ir (CCl_4) 3436 (broad), 2976 (m), 1681 (s), 1504 (m), 909 cm^{-1} (s); nmr (CCl_4) δ 1.46 (s, 6, CH_3), 2.34 (s, 3, $COCH_3$), 3.63 (s, 1, OH), 7.04 (d, 1, $J_{3,4}$ = 0.7 Hz, 4-H), 7.38 (d, 1, 2-H).

2-(5-Acetyl-3-furyl)-2-propyl *p*-nitrobenzoate (5) was prepared directly from the crude alcohol and *p*-nitrobenzoyl chloride using the pyridine method.[3] After two recrystallizations from ether–hexane, 2-(5-acetyl-3-furyl)-2-propyl *p*-nitrobenzoate was obtained as very pale yellow crystals: mp 108°; ir ($CHCl_3$) 3012 (w), 1725 (s), 1678 (s), 1613 (m), 1524 (s), 1279 cm^{-1} (s); nmr ($CDCl_3$) δ 1.94 (s, 6, CH_3), 2.48 (s, 3, $COCH_3$), 7.28 (d, 1, 3-H), 7.65 (d, 1, 5-H), 8.22 (d, 4, phenyl H).

Anal. Calcd for $C_{16}H_{15}NO_6$: C, 60.56; H, 4.76; N, 4.42. Found: C, 60.42; H, 4.69; N, 4.27.

Kinetic Methods.—Most of the kinetic procedures have been described previously.[3] Some of the individual experiments with **3** and **4** were carried out by measuring the kinetics at controlled pH, using a Radiometer Titrator (TTTlc), Autoburette (Type ABUlc), and a Titrigraph (Type SBR2c) maintaining the pH at 7.5. Additional kinetic data are recorded in Table IV.

TABLE IV

RATE CONSTANTS UNDER VARIOUS CONDITIONS

Compd	Temp, °C	Solvent	k, sec^{-1}
4	45.00	80% EtOH	4.49×10^{-3} [a]
	45.00	70% Dioxane	1.02×10^{-3}
5	75.00	80% EtOH	7.61×10^{-4}
	25.00	80% EtOH	1.36×10^{-6} [b]

[a] $\Delta H^{\pm}$ = 20.9 kcal; $\Delta S^{\pm}$ = −3.7 eu. [b] Extrapolated assuming $\Delta S^{\pm}$ = −4.0 eu.

Registry No.—**1**, 34878-28-9; **2**, 34878-29-0; **3**, 34878-30-3; **4**, 34878-31-4; **5**, 34878-32-5; 1-(5-ethyl-3-furyl)ethanol, 34878-33-6; 2-methyl-4-bromofuran, 24666-43-1; 2-(5-methyl-3-furyl)-2-propanol, 34878-35-8; 2-acetyl-4-bromofuran diethyl ketal, 34878-36-9; 2-(5-acetyl-3-furyl)-2-propanol, 34878-37-0.

Notes

Transmission of Substituent Effects in Heterocyclic Systems. The Application of Molecular Orbital Parameters to the Solvolysis of 4-Substituted 1-(2-Furyl)ethyl Systems[1]

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Received January 31, 1972

Recent studies from these laboratories[3-5] have shown that advanced molecular orbital calculations employing all-valence electron methods, such as CNDO/2 and INDO, provide a very useful foundation and framework for interpretation of substituent effects in heterocyclic systems.

It was shown[4] that equally good correlations were obtained for the rates of solvolysis of substituted 1-(2-thienyl)ethyl *p*-nitrobenzoates, using either Brown's electrophilic substituent constants[6] or substituent constants determined from CNDO/2 parameters incorporated in a modified Dewar–Grisdale equation. For 1-(3-furyl)ethanol derivatives only the substituent constants derived by the modified Dewar–Grisdale equation adequately accounted for the observed rates of solvolysis,[5] while for 5-substituted 1-(2-furyl)ethyl derivatives, excellent correlations are obtained with both σ^+ constants and CNDO/2 parameters. The modified Dewar–Grisdale approach is also particularly adaptable to predictions for other systems. It is the purpose of the present note to examine 1-(4-X-2-furyl)-ethanol derivatives in this context.

The equation (1) first proposed by Nichols[7] leads naturally to the predictions presented below.

$$\sigma_{ij}^{+} = F^{+}/r + \Delta q M^{+} \quad (1)$$

In eq 1, an electrophilic substituent constant, σ_{ij}^{+}, is determined for a substituent at a position i in a heterocyclic ring system, with reference to position j as

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.

(2) Graduate Fellow on the California–Chile Cooperative Exchange Program, from funds provided by the Ford Foundation, 1966–1970.

(3) D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, **34**, 1008 (1969).

(4) D. S. Noyce, C. A. Lipinski, and R. W. Nichols, *J. Org. Chem.*, **37**, 2615 (1972).

(5) D. S. Noyce and H. J. Pavez, *J. Org. Chem.*, **37**, 2620 (1972).

(6) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(7) R. W. Nichols, Ph.D. Dissertation, University of California, 1970.

TABLE I

SUBSTITUENT CONSTANTS IN HETEROCYCLIC SYSTEMS

Heterocyclic system	Substitution pattern[a]	r	Δq CNDO/2	Δq INDO	% $\mathcal{R}$ Calcd[b]	Typical substituent constants: CH_3	SCH_3	Br	COOEt
Thiophene	5,2	1.768	0.2051		66	−0.305		0.207	0.515
	4,2	1.672	0.0395		33			0.416	0.382
Furan	5,2	1.571	0.2763			−0.407	−0.803	0.182	0.617
				0.2726	66	−0.401	−0.783	0.187	0.621
	5,3	1.605	0.1076			−0.169	−0.115		
				0.1150	49	−0.177	−0.150		
	4,2	1.605	0.0642			−0.101	0.063	0.408	0.419
				0.0696	39	−0.114	0.047	0.404	0.423
Benzene	3,1	1.732	0.0368	0.0353	30	−0.069[c]	0.158	0.405	0.366
	4,1	2.00	0.2115	0.2109	65	−0.311[d]	−0.604	0.150	0.482

[a] First number is substituent position; second number is side chain position. [b] *Cf.* footnote 10. [c] By definition σ_m^+. [d] By definition. σ_p^+.

TABLE II

RATES OF SOLVOLYSIS OF 4-SUBSTITUTED 1-(2-FURYL)ETHYL *p*-NITROBENZOATES

Registry no.	Compd, 4 X	k, sec^{-1} (45.0°)	Log k, rel	Predicted relative rates: A[a]	B[b]	C[c]
18743-95-8	X = -H	1.30×10^{-4}	0.00	(0.0)	(0.0)	(0.0)
34858-73-6	X = $-SCH_3$	3.59×10^{-5}	−0.558	−1.264	−0.359	−0.268
18743-97-0	X = -Br	8.21×10^{-7}	−2.199	−3.443	−2.326	−2.303
18743-98-1	X = -COOEt	1.46×10^{-7} [d]	−2.949	−3.011	−2.338	−2.411

[a] Using σ_m^+ constants for 4 substituents, $\rho = -8.5$ (ref 3). [b] Using CNDO/2 σ_{ij}^+ constants as given in Table I; $\rho = -5.7$, as determined in ref 4. [c] Using INDO σ_{ij}^+ constants, $\rho = -5.7$. [d] Extrapolated from data at higher temperatures.

the locand of a reactive side chain, by the parameters F^+ and M^+ derived for that substituent from Brown's σ_m^+ and σ_p^+, and CNDO/2 (or INDO) determined regional charges, Δq,[8,9] for benzene.

From substituent constants thus determined,[10] it is also possible to determine the balance of resonance and field effects, % $\mathcal{R}$ and % $\mathcal{F}$, by relating these substituent constants to the Swain and Lupton treatment.[11] Relevant terms are presented in Table I.

It is to be noted that for the furan system, both the 3–5 relationship and the 2–4 relationship are suggested to show a larger response to the resonance capabilities of substituents than σ_m^+. This expectation was tested and found to be true for the 3–5 relationship in our previous paper.[5] Indications that this expectation shows up in the 2–4 relationship appear in limited data reported previously from these laboratories,[3] involving bromo and carboethoxy substituents.

To provide further data on this situation, we have synthesized and measured the rate of solvolysis of 1-(4-methylthio-2-furyl)ethyl *p*-nitrobenzoate (**1**). This ester solvolyzes somewhat more slowly than the parent 1-(2-furyl)ethyl *p*-nitrobenzoate. Table II presents these data, along with previous rates, and includes the expected rates on the basis of some other predications.

Column 3 in Table II gives the expected rates based on the use of σ_m^+ substituent constants, and the ρ of −8.5 as determined by Noyce and Kaiser. The match is relatively poor; in particular it is to be noted that σ_m^+ for -Br and -COOEt predict a relative rate sequence inverted from that observed. Further, the predicted rate for -SMe is much too slow. The situation is much improved using σ_{ij}^+ constants determined by either CNDO/2 or INDO calculations. The average deviation between calculated and observed rates is substantially reduced. The substituents now fall in the correct order.

Thus, these data show that the determination of electrophilic substituent constants by reference to CNDO/2 or INDO parameters in conjunction with a modified Dewar–Grisdale equation provides a much more satisfactory fit between observed and predicted rates of solvolysis. It suggests that this approach is a generally preferable one.

(8) Regional charge: the sum of the charges on a carbon atom and on any hydrogen atoms bonded to it. A. Streitwieser, Jr., and R. G. Jesaitis in "Sigma Molecular Orbital Theory," O. Sinanoglu and K. B. Wiberg, Ed., Yale University Press, New Haven, Conn., 1970, p 197.

(9) A more complete description of this derivation is given in ref 4.

(10) For a set of typical substituents: $-OCH_3$, $-CH_3$, $-C_2H_5$, -Cl, -Br, -H, $-CO_2Et$, -CN, $-CF_3$, and NO_2.

(11) C. G. Swain and E. C. Lupton, Jr., *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

Experimental Section[12]

4-Methylthio-2-acetylfuran.—In a nitrogen-swept flask, immersed in an acetone–Dry Ice bath, was placed a solution of 2-acetyl-4-bromofuran diethyl ketal[5] (18.8 g, 0.0715 mol) in 250 ml of anhydrous ether. To the well-stirred ethereal solution was added a precooled hexane solution of *n*-butyllithium (44.5 ml, 0.0715 mol) over a period of 30 min. After the addition was over the mixture was stirred at −78° for 1 hr and then dimethyl disulfide (6.735 g, 0.0715 mol) was added. The Dry Ice bath was removed and the reaction mixture was stirred for an additional 6 hr. The contents of the flask were poured into cold water and the mixture was extracted with ether. The ethereal solution was extracted with 20% sodium hydroxide and washed with water, and the ether was removed on a rotary evaporator. The residual oil was treated with 150 ml of water and 5 ml of 3 *N* hydrochloric acid, and the heterogeneous mixture was stirred and refluxed for 30 min. The reaction mixture was cooled, diluted with 150 ml of water, and extracted with ether. The ethereal solution was washed with 5% sodium bicarbonate and water, dried over anhydrous magnesium sulfate, and filtered. The ether was removed on a rotary evaporator and the residual liquid was distilled under reduced pressure. 4-Methylthio-2-acetylfuran (7.9 g, 71%) was obtained as a pale yellow oil, bp

(12) Melting points and boiling points are uncorrected. Nmr spectra were obtained using a VarianT-60 spectrometer. Analyses are by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.

125° (5 mm), which solidified on standing: nmr (CCl_4) δ 2.41 and 2.42 (2 singlets, 3 each, $-SCH_3$ and $COCH_3$), 7.08 (d, 1, 3-H), 7.40 (d, 1, $J_{3,5}$ = 0.9 Hz, 5-H).

Anal. Calcd for $C_7H_8O_2S$: C, 53.82; H, 5.16; S, 20.53. Found: C, 53.66; H, 5.26; S, 20.37.

1-(4-Methylthio-2-furyl)ethanol.—To a stirred solution of 4-methylthio-2-acetylfuran (7.81 g, 0.05 mol) in 75 ml of anhydrous methanol, placed in an ice water bath, was added sodium borohydride (1.41 g, 0.0374 mol) at a rate such that the temperature was kept below 20°. The mixture was stirred for 5 hr and worked up in the usual fashion to give 7.7 g (97%) of 1-(4-methylthio-2-furyl)ethanol as a pale yellow liquid: nmr (CCl_4) δ 1.40 (d, 3, CH_3), 2.27 (s, 3, SCH_3), δ 3.60 (s, 1, OH), 4.64 (q, 1, $J_{CH_3,H}$ = 6.5 Hz, CHOH), 6.11 (d, 1, 3-H), 7.13 (d, 1, $J_{3,5}$ = 0.9 Hz, 5-H).

1-(4-Methylthio-2-furyl)ethyl *p*-nitrobenzoate (1) was prepared from 1-(4-methylthio-2-furyl)ethanol (7.60 g, 0.048 mol) in 50 ml of pyridine, cooled in an ice water bath, and *p*-nitrobenzoyl chloride (8.907 g, 0.048 mol). After work-up in the usual fashion, 1-(4-methylthio-2-furyl)ethyl *p*-nitrobenzoate (8.0 g, 54%) was obtained as yellow crystals from hexane: mp 46°; nmr ($CDCl_3$) δ 1.80 (d, 3, $J_{CH_3,H}$ = 6.5 Hz, CH_3), 2.42 (s, 3, SCH_3), 6.26 (q, 1, CHOPNB), 6.53 (d, 1, $J_{3,5}$ = 0.85 Hz, 3-H), 7.38 (d, 1, 5-H).

Anal. Calcd for $C_{14}H_{13}NO_5S$: C, 54.71; H, 4.26; N, 4.56; S, 10.43. Found: C, 54.46; H, 4.08; N, 4.32; S, 10.28.

Kinetic Procedures.—Kinetic procedures have been described previously.[3-5]

Registry No.—4-Methylthio-2-acetylfuran, 934-64-5; 1-(4-methylthio-2-furyl)ethanol, 34858-77-0.

The Reaction of Some Acyclic α,β-Unsaturated Ketone Systems with *N*-Bromosuccinimide

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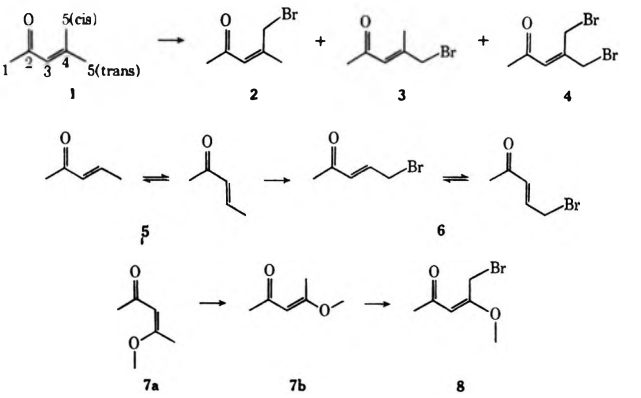
Received January 11, 1972

A preliminary communication by Buu-Hoi[1] in 1946 reported that mesityl oxide and 3-penten-2-one underwent bromination by *N*-bromosuccinimide (NBS) to give α-bromo ketones rather than allyl bromides; the unstable products of reaction were characterized purely on the basis of gross chemical reactivity such as ease of reaction with primary aromatic amines. These results were regarded with reservation by Djerassi,[2] who noted the possibility of allylic rearrangement of the primary products of reaction: *initial* formation of α-bromo ketones from acyclic α,β-unsaturated ketones would have belied experience to date, which indicated that substitution allylic to the olefinic bond was the general rule for cyclic systems. Later, the work of DePuy and coworkers[3] established unequivocally that 4-bromo-2-cyclopentenone was the exclusive product of reaction of 2-cyclopentenone with NBS under radical-promoting conditions.

Recent investigations of possible synthetic routes to models of the tetracycline A and B rings[4] have demonstrated that selective substitution allylic to the olefinic bond is achieved by similar bromination of cyclohex-2-enones and 3-methoxycyclohex-2-enones. It was noted also that the liquid 4-bromo-2-cyclohexenone slowly isomerized to roughly a 1:1 mixture of 6-bromo and 4-bromo ketones. In order to determine the effect of the greater conformational freedom of acyclic α,β-unsaturated ketones upon the pattern of bromine substitution and on the tendency of bromination products toward allylic rearrangement, mesityl oxide (**1**), 3-penten-2-one (**5**), and the methyl enol ethers (**7**) of acetylacetone[5] were brominated using NBS (Scheme I),

SCHEME I



and the products were subjected to detailed nmr spectroscopic analysis.

No product of bromine substitution α to carbonyl could be detected from the reaction of any of these four substrates, bromination allylic to the olefinic bond being the exclusive mode of substitution. *No evidence of allylic rearrangement could be perceived in the case of these acyclic allylic bromides.* All products of bromination are obviously predominantly in the s-cis conformation.

Assignment of both configuration and conformation was possible from a consideration of either benzene-induced solvent shifts (Table I) or $Eu(thd)_3$[6]-induced chemical shift data applying the carbonyl-plane rule in the former case[5] and assuming complexation at carbonyl oxygen in the latter.[7]

Mesityl oxide (**1**) reacted with 1 molar equiv of NBS to yield a mixture of approximately equal proportions of the isomeric allylic monobromides **2** and **3** (36 and 44%,[8] respectively), contaminated with an appreciable amount of the allylic dibromide **4** (20%[8]); **1** was readily and quantitatively converted to **4** by reaction with 2 molar equiv of NBS. Table II gives Δ_{Eu} values for **2**–**8**.

It is evident that the relative percentage of **2** and **3** represent an equilibrium ratio. The product mixture could be separated by thin layer chromatography (tlc) into three distinct bands corresponding to **2**, **3**, and **4**. However, isomerization of **2** and **3** was so rapid that the fractions obtained by elution of the chromatograms were invariably mixtures of the two compounds, although significantly enriched in the respective isomers (approximately 75 and 40%[8] of **3**). The equilibrium

(1) N. P. Buu-Hoi, *Experientia*, **2**, 310 (1946).
(2) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).
(3) C. H. DePuy, M. Isaks, K. L. Eilers, and G. F. Morris, *J. Org. Chem.*, **29**, 3503 (1964); C. H. DePuy, C. E. Lyons, and L. B. Rodewald, *J. Chem. Eng. Data*, **11**, 102 (1966).
(4) D. V. C. Awang, A. Vincent, W. L. Wilson, and H. W. Avdovich, *Can. J. Chem.*, **50**, 104 (1972).
(5) D. V. C. Awang, *ibid.*, **49**, 2672 (1971).
(6) Tris(2,2,6,6-tetramethyl-3,5-heptanedionato)europium(III), also referred to as tris(dipivalomethanato)europium(III), Eu(DPM)$_3$.
(7) H. Hart and G. M. Love, *Tetrahedron Lett.*, 625 (1971).
(8) Determined by integration of the areas of nmr signal peaks.

TABLE I

NMR CHEMICAL SHIFT[a,b] AND BENZENE SHIFT DATA FOR SUBSTRATES AND PRODUCTS OF BROMINATION

Compd		C_1H	C_3H	C_4H	cis[b] C_5H	trans[b] C_5H	OCH
1	CCl_4	2.07 (3 H)	6.02 (m, 1 H)		2.08 (d, 3 H) ($J_{3,5}$ = 1.5 Hz)	1.87 (d, 3 H) ($J_{3,5}$ = 1.5 Hz)	
	$\Delta_{C_6H_6}^{CCl_4}$	+0.22	+0.23		−0.02	+0.35	
2	CCl_4	2.13 (3 H)	6.06 (m, 1 H)		4.47 (2 H)	2.00 (d, 3 H) ($J_{3,5}$ = 1.8 Hz)	
	$\Delta_{C_6H_6}^{CCl_4}$	+0.23	+0.48		+0.13	+0.37	
3	CCl_4	2.13 (3 H)	6.25 (m, 1 H)		2.18 (d, 3 H) ($J_{3,5}$ = 1.8 Hz)	3.87 (2 H)	
	$\Delta_{C_6H_6}^{CCl_4}$	+0.23	+0.50		+0.13	+0.50	
4	CCl_4	2.22 (3 H)	6.30 (m, 1 H)		4.63 (2 H)	4.12 (2 H)	
	$\Delta_{C_6H_6}^{CCl_4}$	+0.32	+0.52		+0.11	+0.45	
5	CCl_4	2.12 (3 H)	6.00 (pq, 1 H) ($J_{3,4}$ = 16, $J_{3,5}$ = 1.5 Hz)	6.75 (pq, 1 H) ($J_{4,5}$ = 6.5 Hz)		1.90 (pd, 3 H)	
	$\Delta_{C_6H_6}^{CCl_4}$	+0.23	+0.12	+0.32		+0.47	
6	CCl_4	2.20 (3 H)	6.15 (d, 1 H) ($J_{3,4}$ = 16 Hz)	6.78 (pt, 1 H) ($J_{4,5}$ = 7 Hz)		6.00 (d, 2 H)	
	$\Delta_{C_6H_6}^{CCl_4}$	+0.48	+0.43	+0.47		+0.72	
7a	CCl_4	2.13 (3 H)	4.96 (1 H)			2.00 (3 H)	3.80 (3 H)
	$\Delta_{C_6H_6}^{CCl_4}$	−0.10	−0.15			+0.43	+0.52
7b	CCl_4	2.03 (3 H)	5.40 (1 H)		2.18 (3 H)		3.61 (3 H)
	$\Delta_{C_6H_6}^{CCl_4}$	+0.07	+0.17		−0.12		+0.43
8	CCl_4	2.14 (3 H)	5.48 (1 H)		4.43 (2 H)		3.70 (3 H)
	$\Delta_{C_6H_6}^{CCl_4}$	+0.28	+0.27		−0.03		+0.68

[a] Chemical shifts are in parts per million downfield relative to internal tetramethylsilane. [b] See illustration of 1 in Scheme I for clarification of notation: d, doublet; m, multiplet; pd, pair of doublets; pq, pair of quartets; pt, pair of triplets.

ratio was attained within hours of storage at room temperature of the nmr sample solutions.

Both methyl enol ethers of acetylacetone, **7a** and **7b**, were converted to allylic bromide **8** in quantitative yield upon treatment with 1 molar equiv of NBS. **7b** is probably an intermediate in the conversion of **7a** to **8**, since unreacted ether consists of only **7b** when reaction of **7a** was conducted with a deficiency of NBS or if the reaction was aborted before complete consumption of 1 molar equiv of the reagent; the mechanism of isomerization likely involves rapid and reversible addition of a bromine atom, by analogy with the generally accepted mechanism of olefin isomerization.[9]

3-Penten-2-one (**5**) underwent bromination to produce the allylic bromide **6**, which, like **5**,[11] apparently exists as a dynamic mixture of s-cis and s-trans conformers, since the shift data are not compatible with their representation as predominantly either one of the two species.

TABLE II

Δ_{Eu}[a] VALUES[b] FOR PROTONS OF SUBSTRATES AND PRODUCTS OF BROMINATION

Compd	C_1	C_3	C_4	cis C_5H	trans C_5H	OCH
2	2.9	1.5		2.1	0.9	
3	3.6	2.7		2.2	1.3	
4	3.3	2.5		3.0	1.3	
5	6.6	5.3	4.8		1.7	
6	4.2	3.8	3.3		0.8	
7a	5.0	6.3			1.8	2.0
7b	10.0	6.8		8.8		2.7
8	6.5	4.5		6.3		2.1

[a] Δ_{Eu} represents the slope of the straight line obtained from a plot of δ *vs.* Eu(thd)$_3$/substrate molar ratio [P. V. DeMarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, 92, 5734, 5737 (1970)]; the larger the Δ_{Eu} value the greater the particular proton or set of protons is shifted downfield by the shift reagent. [b] Because of limited solubility, reliable Δ_{Eu} values for 1 could not be obtained. However, the maximum displacements of chemical shift for the protons of this compound are consistent with the assignments made on the basis of all other criteria, being −1.57, 1.33, 1.17, and 0.55 ppm for C_1, cis C_5, C_3, and trans C_5 protons, respectively.

Experimental Section

Nmr spectra were recorded on a Varian A-60A spectrometer operated at an ambient probe temperature of 40 ± 2°.

Materials.—Mesityl oxide, 3-penten-2-one, and acetylacetone were obtained commercially and vacuum distilled before using. The methyl enol ethers of acetylacetone were prepared as previously described.[5]

General Bromination Procedure.—NBS brominations were conducted in the standard manner[12] employing a 100-W, Photoflood No. 2 lamp to maintain reflux of carbon tetrachloride while providing a catalytic radiative source. Irradiation was halted as soon as it was estimated, visually, that the NBS had been consumed. The reaction product was quickly cooled, succinimide was filtered off, and the filtrate was concentrated.

Nmr analysis of the filtrates indicated that better than 95% conversion to product was achieved in all cases.

Bromination products were isolated by preparative thin layer chromatography (tlc) on silica gel GF_{254} using benzene–ether (9:1).

Registry No.—NBS, 128-08-5; **1**, 141-79-7; **2**, 34764-74-4; **3**, 34764-75-5; **4**, 34764-76-6; **5**, 3102-33-8; **6**, 34764-77-7; **7a**, 10556-93-1; **7b**, 10556-94-2; **8**, 34764-80-2.

Acknowledgment.—The authors are grateful to Mr. H. W. Avdovich for recording of the nmr spectra and to

(9) P. S. Fredericks and J. M. Tedder, *J. Chem. Soc.*, **144** (1960); B. P. McGrath and J. M. Tedder, *Proc. Chem. Soc.*, 80 (1961). The possibility of hydrogen abstraction and isomerization of the mesomeric radical produced, followed by rehydrogenation, appears unattractive in the light of the observation by Wolfe and Campbell[10] that unreacted olefin in the NBS bromination of cyclohexane-*3,3,6,6-d*$_4$ is unisomerized.

(10) S. Wolfe and P. G. C. Campbell, *Can. J. Chem.*, **43**, 1184 (1965).

(11) J. Ronayne, M. V. Sargent, and D. H. Williams, *J. Amer. Chem. Soc.*, **88**, 5288 (1966).

(12) L. Horner and E. H. Winkelmann in "Newer Methods of Preparative Organic Chemistry," Vol. 3, W. Foerst, Ed., Academic Press, London, 1964, p 151.

Dr. W. L. Wilson for helpful discussions. We are indebted also to Mr. H. Séguin of the National Research Council of Canada for performing the elemental microanalyses.

Friedel–Crafts Isomerization of Tetramethylacetophenones

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Received December 16, 1971

In 1952 Baddeley and Pendleton[1] reported that, in the presence of excess aluminum chloride at 100°, acetyldurene (2,3,5,6-tetramethylacetophenone) (**1**) was converted to acetylprehnitine (2,3,4,5-tetramethylacetophenone) (**7**, 80%), aromatic hydrocarbon (10%), and diacetyldurene (**6**, 10%). The formation of the latter two products was ascribed to fission of the acetyldurene into durene and acetyl cation, followed by electrophilic attack on a second molecule of acetyldurene to produce diacetyldurene. Transfer of the acyl group from one aromatic nucleus to another would be analogous to the well-known Friedel–Crafts transalkylation reaction.[2] More recently nmr studies have been conducted on ketones in the presence of Friedel–Crafts catalysts. Treatment of aliphatic,[3] alicyclic,[4] and aromatic ketones[5] with such strong acids as fluorosulfuric acid, fluorosulfuric acid–antimony pentafluoride, and related systems led in all instances to the observation of O-protonation producing stable cation systems.

We felt that these data were inconsistent and set about trying to resolve the question. The inconsistency is centered about the facts that the nmr data[3–5] require that, in the presence of acid, acetyldurene and related systems are O-protonated, whereas the transacylation data require a second protonation (Scheme I).

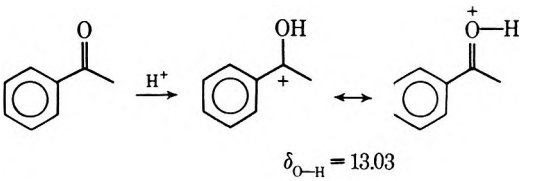
Although no benzenium ions such as **3** were observed by low-temperature nmr (protons in species such as **3** or **5** are observed at δ 4.5–5.5),[6] a small steady-state concentration would be stable under the reaction conditions. To effect transacylation **3a**, if present at all, must undergo the unlikely sequence outlined above: loss of $(CH_3CO)^+$ and H^+ followed by attack by the weak electrophile $(CH_3CO)^+$ on the *protonated* 2,3,5,6-tetramethylacetophenone to give **5** and finally **6**. On the other hand ions **3b–3d**, if present, are able to undergo intra- and intermolecular methyl shifts.

We have repeated the isomerization of acetyldurene with aluminum chloride with the results shown below.

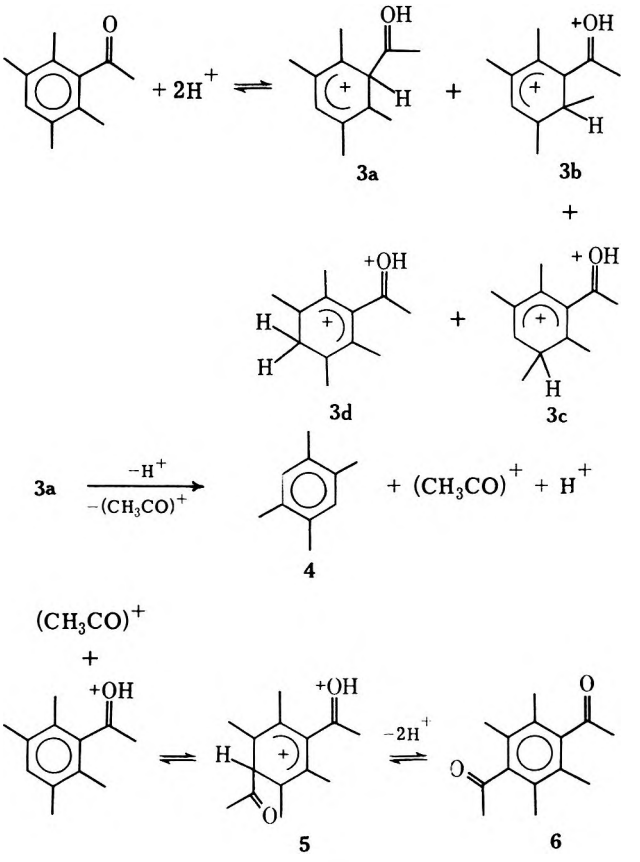
We observed no hydrocarbon or diacetyltetramethylbenzene product as was reported in the earlier study,

SCHEME I

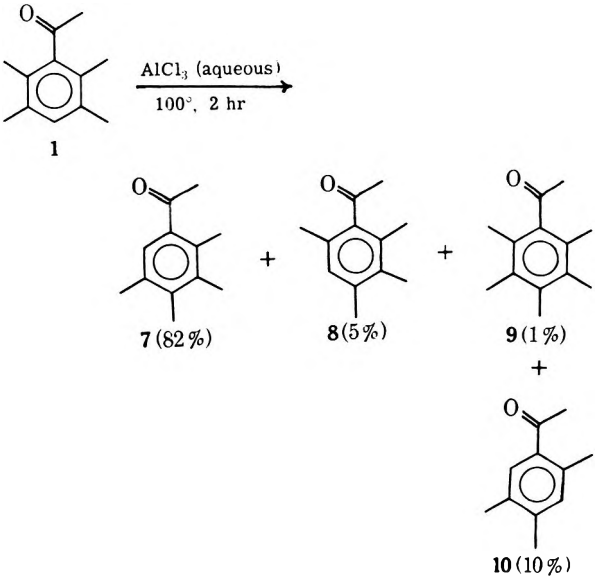
A. Nmr[5]



B. Transacylation[1]



and believe our results are consistent with the nmr data presented above. A combination of Friedel–Crafts transalkylation and isomerization reactions can account for all products formed. Scheme II, which presents one possible pathway, indicates that indeed when enough



(1) G. Baddeley and A. G. Pendleton, *J. Chem. Soc.*, 807 (1952).
(2) G. A. Olah, "Friedel-Crafts and Related Reactions," Vol. I, G. A. Olah, Ed., Wiley, New York, N. Y., 1963.
(3) G. A. Olah, M. Calin, and D. H. O'Brien, *J. Amer. Chem. Soc.*, **89**, 3586 (1967).
(4) G. A. Olah and M. Calin, *ibid.*, **90**, 938 (1968).
(5) G. C. Levy and S. Winstein, *ibid.*, **90**, 3574 (1968); M. Brookhart, G. C. Levy, and S. Winstein, *ibid.*, **89**, 1735 (1967); T. Birchall and R. J. Gillespie, *Can. J. Chem.*, **43**, 1045 (1965).
(6) G. A. Olah, *J. Amer. Chem. Soc.*, **87**, 1103 (1965).

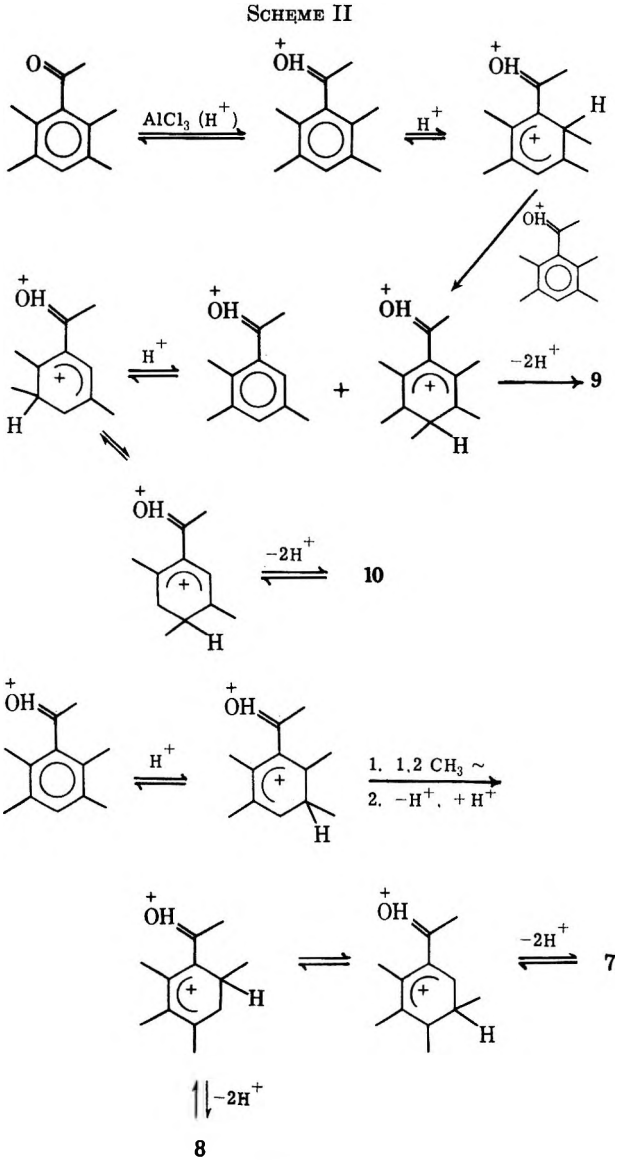
TABLE I

ACETYLATIONS OF POLYMETHYLBENZENES[a]

Substrate	Compd	$\nu_{C=O}$, cm^{-1}	Nmr: ArH, δ	Nmr: CH_3CO, δ	Nmr: CH_3, δ	Retention time, min[b]
1,2,3,4-Tetramethylbenzene	7	1694	7.23	2.45	2.09 (C_2, C_3, or C_4) 2.23 (C_3 or C_4) 2.35 (C_5)	5.9
1,2,3,5-Tetramethylbenzene	8	1695	6.78	2.30	2.08 (C_2) 2.13 (C_3) 2.20 (C_4, C_5)	4.2
1,2,4-Trimethylbenzene	10	1695	6.97 (H_3) 7.53 (H_6)	2.50	2.23 (C_2, C_4, or C_5) 2.55 (C_4 or C_5)	2.4
Pentamethylbenzene	9	1694 (CCl_4)		2.66	2.41 (C_2, C_5) 2.48 (C_3, C_5) 2.52 (C_4)	7.0

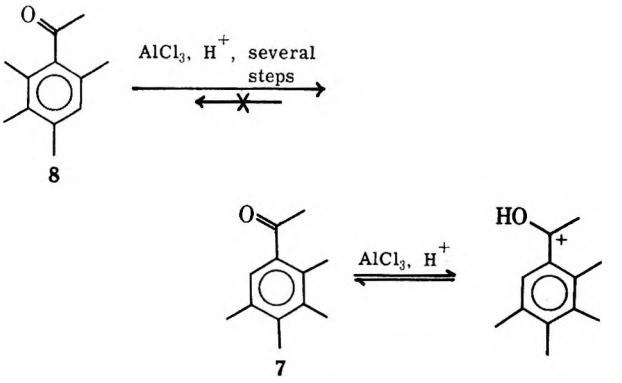
[a] All acetylations carried out as described for the acetylation of 1,2,4,5-tetramethylbenzene. [b] Retention times measured on a 150 ft MBMS capillary column at 160° and 30 psig He.

SCHEME II



methyl groups are present the ring is basic enough to be protonated despite the fact that the carbonyl is already protonated.

Two additional transacylations were attempted. Acetylprehnitine (**7**) was stable to the rection conditions, while 2,3,4,6-tetramethylacetophenone (**8**) was converted to **7** under the reaction conditions.



These results reflect the fact that under equilibrium conditions 2,3,4,5-tetramethylacetophenone is the most stable of the three tetramethylacetophenones.

With the above evidence in hand, we decided to further investigate the possibilites of Friedel–Crafts transacylations. The following ketone–aromatic hydrocarbon trapping agent mixtures were studied: acetophenone–anisole, acetophenone–naphthalene, acetyldurene–benzene, acetyldurene–anisole, 2-acetylthiophene–benzene, and 2-acetylfuran–benzene. A number of very strong acid catalysts were employed in these reactions, including aluminum chloride, aluminum chloride–water,[7] and 5:1 (mol/mol) hydrogen fluoride–antimony pentafluoride. Reaction temperatures were varied from 25 to 100° and ketone/aromatic hydrocarbon/catalyst ratios ranged from 1:1:0.1 to 1:1:1.5.

In no case were we able to detect any transacylation product under these conditions.

Experimental Section

All nmr spectra were obtained on a Varian Associates Model A-60 nmr spectrometer. All ir spectra were obtained on a Perkin-Elmer Model 700 spectrophotometer. All aromatic hydrocarbons were obtained from Aldrich Chemical Co., Milwaukee, Wis., and were used without further purification.

Acetylation of 1,2,4,5-Tetramethylbenzene.—A solution of 15.8 g (0.20 mol) of CH_3COCl in 15 ml of CH_2Cl_2 was added dropwise at 5° to a suspension of 26.6 g (0.20 mol) of anhydrous $AlCl_3$ in 15 ml of CH_2Cl_2 and the mixture was stirred for 10 min. At the same temperature, a solution of 26.8 g (0.20 mol) of 1,2,4,5-tetramethylbenzene in 50 ml of CH_2Cl_2 was added dropwise over 45 min. The mixture was stirred for 1 hr, poured onto ice, washed (H_2O, saturated $NaHCO_3$ and H_2O), and dried

(7) Water (0.005 mol) added as a promoter and to keep [H_2O] constant. See, *e.g.*, G. A. Olah and J. A. Olah, *J. Org. Chem.*, **32**, 1612 (1967).

(Na_2SO_4). After removal of the solvent *in vacuo* the yield of solid product was 20.4 g (0.114 mol, 58%) of a white substance, 2,3,5,6-tetramethylacetophenone (1), mp 72–73° (lit.[8] mp 73°), whose gc (150 ft MBMS capillary column at 160°, He pressure 30 psig) showed only a single peak (retention time 3.5 min). The compound gave an nmr spectrum (CCl_4) which consisted of singlets[9] at δ 2.05 (6 H, C_2 and C_6 methyls), 2.18 (6 H, C_3 and C_5 methyls), 2.32 (3 H, acetyl), and 6.85 (1 H, aromatic). The infrared spectrum (CCl_4) showed $\nu_{C=O}$ at 1698 cm^{-1}. Other acetylation data are summarized in Table I.

Isomerization of 2,3,5,6-Tetramethylacetophenone (1).—The procedure follows that of Baddeley and Pendleton.[1] 2,3,5,6-tetramethylacetophenone (1) (7.5 g, 0.043 mol), anhydrous $AlCl_3$ (15 g, 0.11 mol), H_2O (0.005 mol), and NaCl (1 g, 0.02 mol) were stirred together at 100° for 2 hr. The reaction mixture was cooled, poured onto ice, and neutralized with saturated $NaHCO_3$ solution. The organic material was extracted with a total of 30 ml of C_6H_6, washed (H_2O, saturated $NaHCO_3$ solution, and H_2O) and dried (Na_2SO_4). Analysis of the mixture by gc (150 ft MBMS column at 160°, He pressure 30 psig) showed five peaks: retention time 2.4 min (10%), 3.5 min (trace) 4.2 min (5%), 5.9 min (82%), and 7.0 min (1%). Comparison of retention time with that of authentic samples showed that these components were 2,4,5-trimethylacetophenone (10), starting material (1), 2,3,4,6-tetramethylacetophenone (8), 2,3,4,5-tetramethylacetophenone (7), and pentamethylacetophenone (9), respectively. Addition to this reaction mixture of pure samples of each of the components mentioned led to enhanced peak heights on the gas chromatogram.

Attempted Isomerization of 2,3,4,5-Tetramethylacetophenone (7).—Pure 7 was treated under the reaction conditions and was recovered intact as demonstrated by gc analysis.

Attempted Isomerization of 2,3,4,6-Tetramethylacetophenone (8)—Pure 8 was treated under the reaction conditions and gc analysis showed the conversion of 8 to 7.

Attempted Transacylation Reactions.—Typically, the attempted transacylations were run in the following manner illustrated for acetophenone–naphthalene. Acetophenone (1.20 g, 0.010 mol) and naphthalene (12.8 g, 0.10 mol) were mixed together in 20 ml of CCl_4. $AlCl_3$ (2.00 g, 0.015 mol) and water (0.005 mol)[7] were added and the reaction mixture was stirred at reflux overnight. The mixture was poured onto ice, washed (H_2O, saturated $NaHCO_3$ solution until basic, H_2O), dried (Na_2SO_4), and analyzed by gc (150 ft MBMS column at 100°, 20 psig He pressure). *In no case were any peaks observed except those for the starting materials.*

Registry No.—**1**, 2142-79-2; **7**, 34764-71-1; **8**, 2142-78-1; **9**, 2040-01-9; **10**, 2040-07-5.

Acknowledgments.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, to the State Universities of Wisconsin Research Fund, and to a National Science Foundation Institutional Grant for support of this research.

(8) L. I. Smith and G. Guss, *J. Amer. Chem. Soc.*, **59**, 804 (1937).

(9) All nmr spectra show slight broadening of ring methyls and ring hydrogens due to small long-range coupling.

Degradation of Solasodine

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Received December 23, 1971

A simple, high-yielding procedure for degrading solasodine (I) to 3β-acetoxy-5,16-pregnadien-20-one (VII) in steroid hormone production is desirable. It has previously been demonstrated[2] that I can be degraded in excellent overall yields (*ca.* 60%) to VII by conversion of the *O,N*-diacetate of the alkaloid with acid into the pseudoacetylamino derivative followed by oxidation and hydrolysis.

We have now found that the treatment of solasodine acetate (Ia) with phosgene in a basic milieu affords a number of intermediates which can be readily converted into a pseudoformamido derivative (VI) that can be transformed into VII.

Thus, when acetylsolasodine[3] (Ia) was treated with a cold benzene solution of phosgene and then refluxed with pyridine followed by a treatment with dimethylamine, two products were obtained. The analytical as well as spectroscopic data suggested the structure of the major product to be the epimino-*N*-carboxy compound V. This was confirmed by reduction of Va to the isomeric 5,6,22,23-tetrahydro derivatives, IX and IXa, the former of which agreed in properties with a synthetic specimen[3] prepared from phosgene and tetrahydrosolasodine acetate (VIII). The site of unsaturation in V, aside from the C-5 double bond, was placed at C-22 from nmr data. The spectra of both compound V and the product Va derived from the interaction of 5,6-dihydro-3β-acetylsolasodine (3β-acetylsoladulcidine) with phosgene–pyridine possessed a vinyl proton at 4.83 ppm[4] which was not present in the tetrahydro product IX. It is of some interest to note that the 16β,26-*N*-carboxy system in V proved refractory toward alkali or sodium borohydride reduction and only the C-3 free alcohol was obtained. The major product V (*ca.* 50%) was followed by about 15% of 26-*N'*,*N'*-dimethylcarbamido-5,20(22)-furostadien-3β-ol acetate (VI). The compound possessed a vinyl ether absorption[5] (1694 cm^{-1}) characteristic of a $\Delta^{20(22)}$-furostene structure and an amide-II band [3488 (NH), 1518, 1669 cm^{-1} (NNHCO)] in the infrared region. Chromic acid oxidation of the furostene derivative VI in aqueous acetic acid (80%) followed by hydrolysis of the acyloxy side chain with acetic acid[6] produced VII in good yield.

The reaction of solasodine acetate (Ia), on the other hand, with phosgene in triethylamine in lieu of pyridine proceeds to yield the very unstable *N'*,*N'*-dimethylaminoformylsolasodine acetate (II). The lability of the compound interfered in our attempts at purification and the structure was derived mainly from the infrared spectrum: 1735, 1245 (OAc), 1667 (–CON), 979, 911 cm^{-1} (spiro amino ketal linkage. A notable feature of compound II was its ease of isomerization to the pseudoformamido (furostadiene) derivative, VI, with glacial acetic acid. The second component, III, from the reaction mixture possessed an infrared spectrum quite similar to that of compound VI but exhibited a slightly less polar chromatographic behavior (tlc). It was assigned the isomeric $\Delta^{22(23)}$ structure III, since brief treatment with acetic acid or even hot methanol isomerized it readily to the pseudoformamido compound VI. In addition to II and III, a

(1) Visiting Scientist (1969–1971).

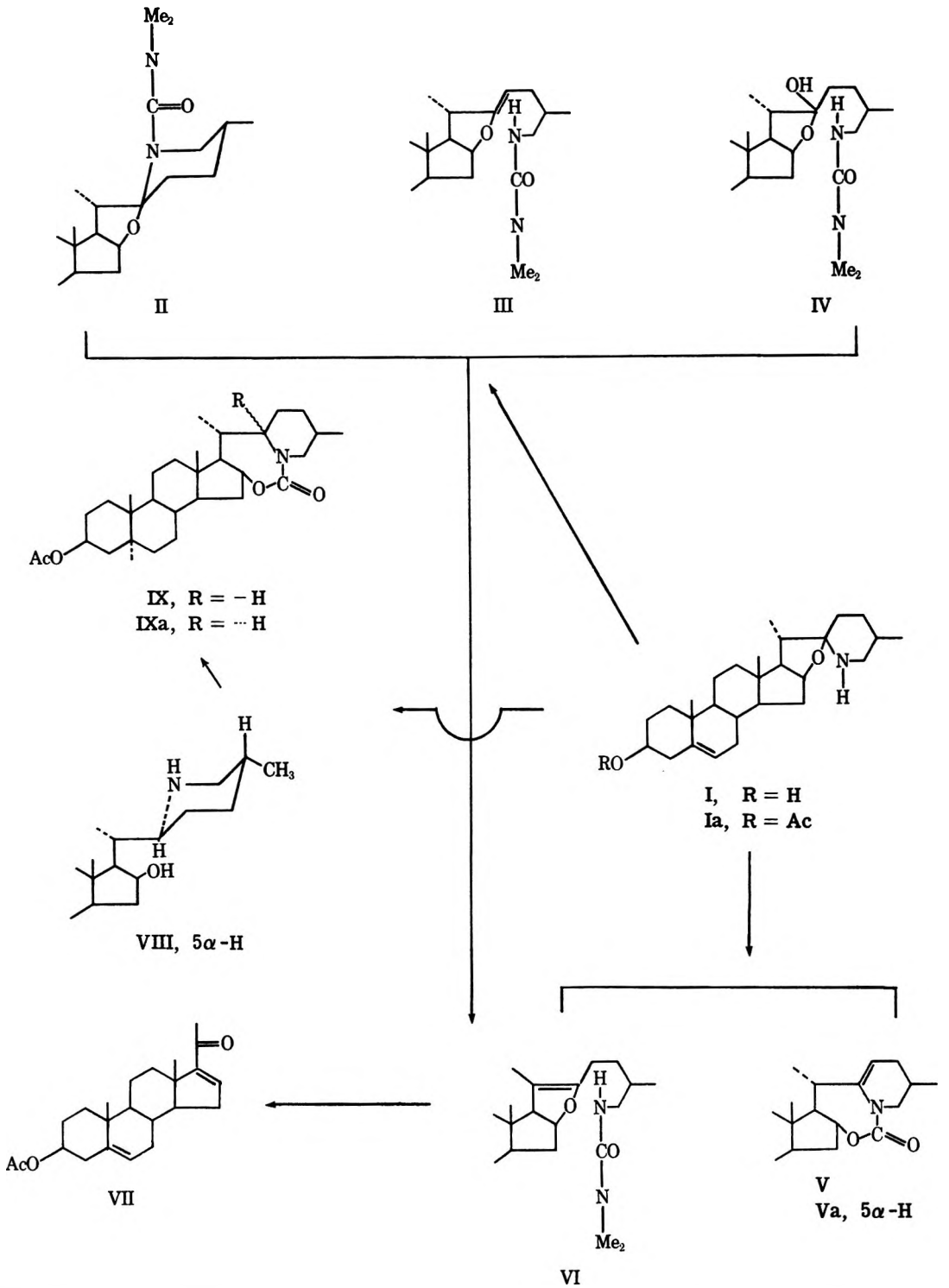
(2) Y. Sato, N. Ikekawa, and E. Mosettig, *J. Org. Chem.*, **25**, 783 (1960).

(3) G. Kusano, N. Aimi, and Y. Sato, *ibid.*, **35**, 2624 (1970).

(4) We are indebted to Dr. H. J. C. Yeh of the Microanalytical Services and Instrumentation Section of the Laboratory for taking the nmr spectra of compounds V, Va, and IX on the Varian HR-220 spectrometer.

(5) A. L. Hayden, P. B. Smeltzer, and I. Scheer, *Anal. Chem.*, **26**, 550 (1954).

(6) A. F. B. Cameron, R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, and A. G. Long, *J. Chem Soc.*, 2807 (1955).



small amount of C-22 hydroxy compound, IV, was obtained from the chromatography of the reaction mixture. The structural assignment was based mainly on the spectral data: mass spectrum *m/e* 526 ($M^+ - H_2O$); ir 3590 (OH), 3478 (NH), 1728, 1250 (OAc), 1643 cm^{-1} (-NHCO-). Like compounds II and III, product IV was converted into the furostadiene derivative VI by treatment with glacial acetic acid.

Thus for the preparation of VII, the crude reaction product from the interaction of solasodine acetate (Ia) and phosgene–triethylamine can be converted directly with glacial acetic acid into the crude pseudoformamido derivative, VI, and degraded oxidatively into the desired hormone intermediate. This alternative degradative procedure is somewhat comparable to the previously published method[2] for the degradation of solasodine in terms of yield and operation.

Experimental Section[7]

Reaction of Solasodine Acetate (Ia) with Phosgene–Pyridine.—Seven milliliters of a benzene solution of phosgene (0.3 g of phos-

(7) Melting points were determined on a Koffer hot stage and are uncorrected. Microanalyses were performed by the Microanalytic Services Unit of this laboratory. Infrared spectra were obtained with a Model 421 Perkin-Elmer spectrophotometer. Optical rotations were obtained in a 1-dm tube with a Model 141 Perkin-Elmer polarimeter. Nmr spectra were determined on the Model A-60 Varian Associates spectrometer, using $CDCl_3$ as solvent with tetramethylsilane as internal standard and are described in δ values (TMS, 0.0 ppm). The mass spectra in these experiments have been measured with a Hitachi Perkin-Elmer RMU-7 spectrometer. Tlc plates were precoated with silica gel G and purchased from Analtech, Inc., Wilmington, Del.

gene/ml of benzene) was added to 1.0 g of solasodine acetate (Ia) in 55 ml of benzene. Following the addition of 9 ml of pyridine, the reaction mixture was heated under reflux for 1 hr. An aqueous solution (25 ml) of dimethylamine (25%) was then added to the mixture with stirring and the reaction was continued for 15 min. The organic phase was washed with water, 2 *N* HCl, and again water. After removal of the solvent, the residue, twice crystallized from absolute EtOH, yielded needles of V (415 mg): mp 264–267°; $[\alpha]^{19}D$ −285° (*c* 1.0, $CHCl_3$); ir (CCl_4) 1732, 1240 (OAc), 1700, 1653 (-OCON<), 1335, 1316 cm^{-1}; nmr ($CDCl_3$) δ 4.06 (m, 1), 4.59 (m, 1), 4.72 (m, 1), 4.83 (t, 1, H-23), 5.37 (d, 1, H-6); mass spectrum *m/e* 481 (M^+).

Anal. Calcd for $C_{30}H_{43}O_4N$: C, 74.81; H, 9.00; N, 2.91. Found: C, 74.87; H, 8.81; N, 2.78.

The mother liquors were combined and evaporated to dryness. The residue was dissolved in pyridine (2.5 ml) and treated with acetic anhydride (1.0 ml). The mixture was then allowed to stand at room temperature for 1 day. After the usual work-up, the resinous residue was chromatographed on alumina (neutral, grade III, 30 g). Elution with toluene afforded a further crop of V (141 mg) and a subsequent fraction eluted with toluene and ethyl acetate (10%) yielded plates of the pseudoformamido compound VI (87 mg) from ethyl acetate: mp 154–159°; $[\alpha]^{18}D$ −30.2° (*c* 0.8, $CHCl_3$); ir (CCl_4) 3488 (NH), 1737, 1248 (OAc), 1694 (CCO), 1518, 1669 cm^{-1} (NHCO–); nmr ($CDCl_3$) δ 0.70 (s, 3), 0.92 (d, 3, J = 5.8 Hz), 1.04 (s, 3), 1.60 (s, 3), 2.02 (s, 3), 2.89 (s, 6), 3.12 (t, 2, J = 5.8 Hz), ~4.1 (m, 2), 5.38 (d, 1, J = 3.5 Hz); mass spectrum *m/e* 526 (M^+).

Anal. Calcd for $C_{32}H_{50}O_4N_2$: N, 5.32. Found: N, 5.45.

Reaction of 5,6-Dihydrosolasodine Acetate with Phosgene–Pyridine.—To 45 ml of a benzene solution of 5,6-dihydrosolasodine acetate (0.84 g) was added 4 ml of a benzene solution of phosgene (0.34 g of phosgene/ml of benzene) while the reaction flask was cooled in ice–water. After the reaction mixture had stood for 5 min at room temperature, 3 ml of pyridine was added and the mixture was refluxed for 1 hr. Then 20 ml of 25% aqueous dimethylamine was added to the cold reaction mixture with stirring and agitation for another hour. Following the addition of water, the reaction mixture was extracted with benzene. The benzene extract, after successively being washed with water, 2 *N* HCl solution, and water, yielded needles of Va (243 mg) from absolute EtOH: mp 288.5–291°; $[\alpha]^{18}D$ −225° (*c* 0.4, $CHCl_3$); ir 1735, 1245 (OAc), 1704, 1657 (NCOO–), 1339, 1321, 1189 cm^{-1}; nmr ($CDCl_3$) δ 4.06 (m, 1), 4.68 (m, 2), 4.82 (t, 1, H-23).

Anal. Calcd for $C_{30}H_{45}O_4N$: C, 74.49; H, 9.38; N, 2.90. Found: C, 74.62; H, 9.28; N, 2.86.

Reaction of Solasodine Acetate (Ia) with Phosgene–Triethylamine.—To 3 g of solasodine acetate (Ia) dissolved in 100 ml of benzene and 30 ml of triethylamine was added with stirring 20 ml of 12.5% phosgene in benzene during the course of 3 min while cooling the reaction flask in ice–water. After 1 hr at room temperature, 60 ml (25%) of aqueous dimethylamine was added with stirring and cooling of the reaction mixture. Vigorous stirring was continued for another hour. The benzene layer was successively washed with water, 2 *N* HCl, and water. The residue, after removal of the solvent, yielded a crude crystalline material [tlc, $CHCl_3$(2):EtOAc(1)] which was chromatographed on neutral alumina (95 g, grade III). Fractions eluted with benzene gave impure crystals of II: mp 160–170° (2.14 g); ir (CCl_4) 1735, 1245 (AOc), 1667 (-CON–), 979, 911 cm^{-1} (spiro amino ketal linkage). The compound is very unstable and attempts at purification by crystallization in acetone seemed to lead to diverse products. Therefore II was treated with 10 ml of boiling HOAc containing 0.1 ml of Ac_2O for 8 min, and the product after removal of the acid *in vacuo* was crystallized from EtOAc and then from aqueous CH_3OH to form plates (1.469 g), mp 158–161°. It was identical with VI (mixture melting point, ir, tlc).

Subsequent fractions eluted with 10% EtOAc in benzene gave rhombic crystals of III from ether: mp 132–140° (0.58 g); ir (CCl_4) 3445 (NH), 1736, 1243 (OAc), 1688 (C=CO), 1662, 1519 cm^{-1} (-NHCO–). Attempts to recrystallize the compound from hot CH_3OH isomerized it partially to VI. The same compound was obtained by treating 0.3 g of crude III with 1.5 ml HOAc containing 2 drops of Ac_2O under reflux for 10 min. The residue crystallized from aqueous CH_3OH to yield 0.17 g of VI melting at 151–156°. The ir spectrum was superposable with that of an authentic specimen. In another run of the same reaction, a 22ξ-hydroxy compound (IV) was obtained in poor yields from fractions eluted with 30% EtOAc in benzene. It melted at 163–172° and possessed the following spectral bands: ir 3590 (OH), 3478 (NH), 1728, 1250 (OAc), 1643, 1526 cm^{-1} (-NHCO–); mass spectrum *m/e* 526 ($M^+ - H_2O$). IV, like III and II, was converted into VI with HOAc.

Upon closer examination of the reaction products with tlc ($CHCl_3$:EtOAc, 20:1), small amounts of compounds V and VI were also detected. Although attempts were made to run the experiments under identical conditions, the production of the products, II, III, and IV, was always variable.

Reduction of Va.—Va (185 mg) was dissolved in 30 ml of AcOH and with 180 mg of Pd/C (180 mg) and hydrogenated for 2 days under atmospheric pressure at 25° when uptake ceased. The compounds were separated by preparative tlc with the solvent systems $CHCl_3$:EtOAc (20:1 and 10:1). Two compounds (IX and IXa) along with the starting material (Va) were obtained. Compound IX (18 mg), needles (CH_3OH), melted at 323.5–324.5°: ir (CCl_4) 1735, 1247 (OAc), 1697 cm^{-1} (OCON<). It was identical (melting points, mixture melting point, tlc, and ir) with the synthetic specimen. The isomeric IXa melted at 276–278° (8 mg): ir (CCl_4) 1736, 1248 (OAc), 1700 cm^{-1} (-OCON); mass spectrum *m/e* 485 (M^+, $C_{30}H_{47}NO_4$).

Hydrolysis of V.—V (36 mg) was dissolved in CH_3OH (4 ml) and a drop of water and 105 mg KOH were added. The mixture was refluxed for 2 hr. The free alcohol crystallized from MeOH as needles: mp <330°; $[\alpha]^{18}D$ −305° (*c* 0.4, $CHCl_3$); ir ($CHCl_3$) 3590 (OH), 1678, 1652 cm^{-1} (-OCON).

Anal. Calcd for $C_{28}H_{41}O_3N$: C, 76.49; H, 9.04; N, 3.19. Found: C, 76.57; H, 9.20; N, 3.10.

Sodium Borohydride Reduction of V.—V (150 mg) was dissolved in 2 ml of CH_2Cl_2 and treated with a solution of 300 mg of $NaBH_4$ in 8 ml of EtOH containing a few drops of water. After 4 hr of refluxing, the reaction mixture was acidified with 2 *N* HCl and extracted with $CHCl_3$. The residue, when crystallized, proved to be the C-3 alcohol as in the above hydrolysis.

Oxidation of VI to VII.—To 30 mg of VI dissolved in 2 ml of HOAc was added dropwise 1.8 ml of a solution (80% HOAc) of CrO_3 (11.4 mg, 2 molar equiv) with stirring while the reaction flask was being cooled with ice–water. The mixture was stirred at room temperature for 1 hr and then quenched with water followed by addition of a pinch of Na_2SO_3 to decompose the excess CrO_3. The reaction mixture was saturated with NaCl and extracted with ether. After removal of the ether the residue was dissolved in HOAc (5 ml) and refluxed for 2 hr. The HOAc was removed *in vacuo* and the dry residue was chromatographed on 2 g of alumina (neutral, grade I). Fractions eluted with benzene (40 ml) and benzene–ethyl acetate (23:2; 25 ml) were combined and twice crystallized from aqueous CH_3OH to yield needles, mp 172–175°, which agreed in properties (melting point, mixture melting point, and ir) with an authentic specimen of VII.

Registry No.—II, 34608-94-1; III, 34638-80-7; IV, 34638-81-8; V, 34638-82-9; Va, 34638-83-0; V free alcohol, 34638-84-1; VI, 34638-85-2; IX, 24694-77-7; IXa, 34638-87-4.

Studies on the Oxidation of Homosemibullvalene (Tricyclo[6.1.0.0^{4,9}]nona-2,6-diene). Photosensitized Oxygenation

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The dye-sensitized photooxygenation of organic compounds has been studied extensively by many workers and represents a very smooth method for introducing

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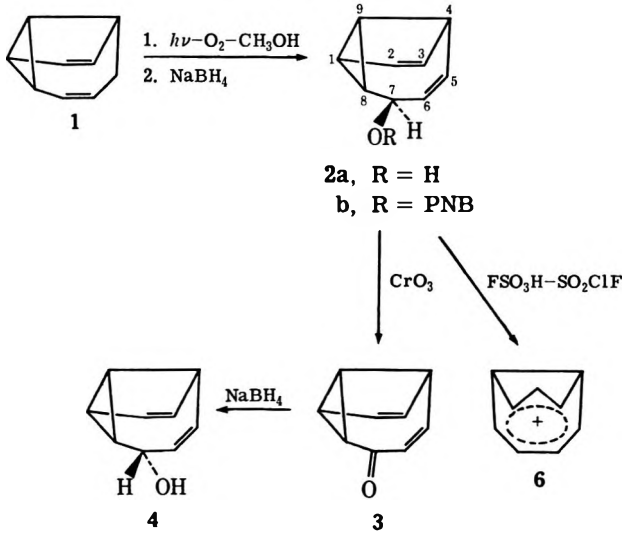
(2) Deceased Nov 23, 1969.

oxygen in a highly specific fashion into organic compounds.[3] Typically reactions of singlet oxygen with olefins have been studied with olefins possessing allylic hydrogen atoms.[4] It was suggested that the resulting allylic hydroperoxides arose through an "ene"-type mechanism.[5]

Now we wish to report the successful preparation of *exo*-tricyclo[6.1.0.0^{4,9}]nona-2,5-dien-7-ol (homosemibullvalenol) (**2a**),[6] an important intermediate from which 1,4-bishomotropylium ion (**6**) is formed, by singlet oxygen oxidation of tricyclo[6.1.0.0^{4,9}]nona-2,6-diene (homosemibullvalene) (**1**).[7] In our laboratory, we have recently prepared **6** by extraction of **2a** from a CD_2Cl_2 solution into a mixture of FSO_3H–SO_2ClF at $-135°$ and observed by nmr at $-125°$.[8]

When the photooxidation of **1** was conducted in methanol solution, **2a**, mp 88.5–89.5°, was obtained in 35% yield after $NaBH_4$ reduction of the hydroperoxide mixture (Scheme I). All photooxidations were performed at room temperature, using a 200-ml Pyrex immersion well apparatus fitted with an oxygen bubbler and a Sylvania DWY projection bulb. Rose bengal was used as dye sensitizer, and reagent grade anhydrous methanol was used as the solvent. The above-described reaction did not occur when oxygen, dye, or irradiation was omitted. Irradiation times varied from 55 min to 15 hr depending upon the concentration of **1**.

SCHEME I



The structure of the allylic alcohol **2a** was determined by its nmr spectrum, which consisted of a multiplet at τ 4.14 (2 H, olefinic), a doublet at τ 4.40 (1 H, olefinic), a doublet at τ 5.17 (1 H, olefinic), a multiplet at τ 6.52 (2 H, α-H and bisallylic), a sharp singlet at τ 7.55 (1 H, hydroxyl), and a multiplet at τ 7.92–8.88 (3 H, cyclopropyl), and by its mass spectrum, which showed a molecular ion peak at *m/e* 134 with isotope peak at *m/e* 135 (P + 1, 9.90) and 136 (P + 2, 0.65) of the appropriate intensities for the formula $C_9H_{10}O$.

Oxidation of **2a**, R_f[9] 0.31, ν_{max} 3601 cm^{-1} (CCl_4), with chromium trioxide in moist ether gave tricyclo[6.1.0.0^{4,9}]nona-2,5-dien-7-one (**3**) (R_f 0.81). Reduction of the ketone **3** with $NaBH_4$ in methanol provided only the new alcohol **4**, *endo*-tricyclo[6.1.0.0^{4,9}]nona-2,5-dien-7-ol, R_f 0.54, ν_{max} 3550 cm^{-1} (sharp, strong) (CCl_4), nmr τ 5.5 (α-H, $CDCl_3$). The endo configuration was assigned to **4** because of the very hindered hydroxyl group, as indicated by rapid elution from alumina, the strong 3550 cm^{-1} infrared absorption, and the deshielding of the α H from τ 6.5 in **2a** to 5.5 in **4**.

exo-Tricyclo[6.1.0.0^{4,9}]nona-2,5-dien-7-yl *p*-nitrobenzoate (**2b**), mp 138.5–139.5°, was prepared by the usual procedure and its structural assignment has been made from a 100-MHz nmr spectrum and a decoupling experiment. **2b** was decoupled by irradiating at the H_7 resonance, the H_4 resonance, and the H_1 resonance. The coupling constants shown in Table I were obtained from these experiments.

TABLE I
CHEMICAL SHIFTS (τ) AND COUPLING CONSTANTS (J) FOR **2b** ($CDCl_3$)

		J, Hz							
	τ	2	3	4	5	6	7	8	9
1	7.86	2.1	Small	0	0	0	0	8.0	7.5
2	4.20		5.0	1.5	0	0	0	0	0
3	5.00			1.0	0	0	0	0	0
4	6.26				7.0	0	0	0	7.0
5	3.83					9.2	2.5	0	0
6	4.09						1.0	1.0	0
7	5.16							1.7	0
8	8.53								8.0
9	8.16								
Aromatic	2.73								

The assignment of stereochemistry at C_7 is based on the vicinal coupling constants. **2b** has J_{76} = 1.0 and J_{75} = 2.5 Hz. The observed coupling constants are most consistent with the structure shown. The H_7–H_6 dihedral angle is *ca.* 90°, which should give a small coupling constant, whereas the H_7–H_5 angle is also *ca.* 90°, which should give a larger coupling constant because of allylic coupling.[10] This assignment corroborates the previous assignment by R_f, ν_{max} (OH), and τ (α H) values.

A number of other unsuccessful attempts (A–F) to prepare the allylic alcohol are outlined in Scheme II. No other products were detected by tlc or vpc in any of these systems.

The *p*-nitrobenzoate **2b** also might be a precursor for **6** and a full discussion of the solvolysis will be forthcoming.

(3) (a) K. Gollnick and G. O. Schenck in "1,4-Cycloaddition Reaction," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, p 225; (b) K. Gollnick and G. O. Schenck, *Pure Appl. Chem.*, **9**, 507 (1964); (c) E. J. Bowen, *Advan. Photochem.*, **1**, 23 (1963); (d) G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957).

(4) (a) C. S. Foote, *Accounts Chem. Res.*, **1**, 104 (1968); (b) K. Gollnick, *Advan. Photochem.*, **6**, 1 (1968); (c) K. Gollnick, "Oxidation of Organic Compounds," Vol. III, Advances in Chemistry Series, No. 77, American Chemical Society, Washington, D. C., 1968, p 78.

(5) (a) A. Nickon and J. F. Bogli, *J. Amer. Chem. Soc.*, **83**, 1498 (1961); (b) C. S. Foote, S. Waxler, and W. Ando, *Tetrahedron Lett.*, 4111 (1965).

(6) **2a**, **2b** and **4** are racemic and attempts to separate these into optically active components were not examined.

(7) **1** was prepared by Wolff–Kishner reduction of bicyclo[4.2.1]nona-2,4,7-trien-9-one: M. Sakai, D. L. Harris, and S. Winstein, *Chem. Commun.*, in press.

(8) P. Ahlberg, D. L. Harris, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 4454 (1970).

(9) See Experimental Section.

(10) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

SCHEME II

(A)[a] 1 + SeO_2 ⟶ Hydrocarbons and Polymers

(B)[b] 1 + t-BuO_2COPh ⟶ (OH⁻) ⟶ Seven Alcohols

(C) 1 + $Pd(OAc)_2$ ⟶ ($LiAlH_4$) ⟶ Hydrocarbons

(D)[c] 1 + NBS ⟶ (AgOAc) ⟶ (OH⁻) ⟶ Polymers

(E) 1 + $Hg(OAc)_2$ ⟶ Recovered 1

(F)[d] 1 + CrO_3–Py_2 ⟶ Recovered 1

[a] R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959). [b] H. L. Goering and U. Mayer, *J. Amer. Chem. Soc.*, **86**, 3753 (1964). [c] A. C. Cope, M. Brown, and H.-H. Lee, *ibid.*, **80**, 2855 (1958). [d] W. G. Dauben, personal communication.

Experimental Section

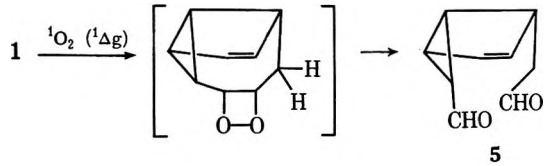
Melting points were taken in capillaries and are uncorrected.

exo-Tricyclo[6.1.0.0^{4,9}]nona-2,5-dien-7-ol (2a).—A solution of 2.0 g of 1 and 15 mg of rose bengal in 100 ml of anhydrous methanol was bubbled with oxygen and irradiated with a tungsten–iodine lamp until the absorption of oxygen ceased (calcd 200 ml, obsd 350 ml). The reaction mixture was reduced with 10 g of $NaBH_4$ at room temperature, quenched with 100 ml of 20% KOH solution, and then extracted with ether. The ether layer was dried over K_2CO_3 and evaporation of ether gave a viscous oil. This oil was chromatographed on a column of 100 ml of Silica AR with 10% ether–pentane, and divided into 20 fractions of 150 ml each. After evaporation of the solvent, fractions 6, 7, and 8 gradually crystallized on standing at room temperature to give white needles, mp 87.0–88.0°. These were recrystallized from pentane to give 800 mg (35%) of white needles: mp 88.5–89.5°; nmr, see text; ir (CCl_4) 3601 (m), 3360 (s), 3050 (s), 2915 (m), 2840 (w), 1586 (w), 1376 (m), 1341 (m), 1265 (m), 1038 (s), 997 (s), 970 (m), 956 (m), 942 (w), 919 (m), 910 (m), 892 (m), 853 (w), 727 (m) and 693 cm^{-1} (s); mass spectrum, parent peak at m/e 134 ($C_9H_{10}O^+$) and a base peak at m/e 43; R_f 0.31 (5 × 20 alumina coated plate eluted with 25% ether–pentane).

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.45; H, 7.56.

Fractions 1 and 2 consisted of a mixture of hydrocarbons (0.1 g). Combination of fractions 3, 4, and 5 yielded a viscous oil (0.5 g). The ir spectrum of this oil showed a characteristic aldehyde absorption at 2710 and 1730 cm^{-1}, a double bond absorption at 1650 cm^{-1}, and a cyclopropyl absorption at 3050 cm^{-1} (neat). We believe that this component is dialdehyde 5. A possible explanation for the unusual formation of this aldehyde is presented in Scheme III. $^1\Delta g$ oxygen reacts with 1 to form a

SCHEME III



5

1,2-dioxetane intermediate[11] which cleaves to 5. A more detailed report on further chemistry of 5 is forthcoming.

Fractions 9–15 consisted of viscous polymers (1.0 g). Fractions 16–20 consisted of small amounts of polymers and inorganic materials (0.1 g).

exo-Tricyclo[6.1.0.0^{4,9}]nona-2,5-dien-7-yl *p*-Nitrobenzoate (2b).—To a solution of 100 mg of 2a in 3 ml of dry pyridine was added 270 mg of *p*-nitrobenzoyl chloride at 0°. The solution was stirred for 0.5 hr at this temperature and then allowed to stand in the freezer for 6 hr. The mixture was decomposed with five drops of water at 0° and extracted with ether. The ether layer was washed with cold dilute HCl and saturated $NaHCO_3$, and then saturated NaCl. After drying over K_2CO_3, evaporation of the solvent gave a yellow solid, which was recrystallized from ether–pentane to give 190 mg of pale yellow leaflets, mp 138.5–139.5°, 91% yield.

Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63. Found: C, 67.69; H, 4.67.

Tricyclo[6.1.0.0^{4,9}]nona-2,5-dien-7-one (3).—To a solution of 50 mg of 2a in 10 ml of ether was added 0.5 g of CrO_3 in 6 ml of water. The mixture was stirred at room temperature for 3.5 hr. After usual work-up, the ketone 3 was collected by preparative tlc (Silica AR) with 25% ether–pentane (detected with uv lamp), ir (CCl_4) 1715 cm^{-1}, R_f 0.81.

Anal. Calcd for C_9H_8O: C, 81.79; H, 6.10. Found: C, 81.85; H, 6.01.

endo-Tricyclo[6.1.0.0^{4,9}]nona-2,5-dien-7-ol (4).—A solution of 28 mg of 3 in 2 ml of methanol was added to stirred $NaBH_4$ (80 mg) in 2 ml of methanol at room temperature. After the mixture had been stirred for 2 hr, the excess hydride was destroyed with 1 ml of 20% KOH solution. The aqueous layer was extracted with ether and the ether solution was washed with water and dried over K_2CO_3. Evaporation of the ether yielded a residue which was purified by preparative tlc (Silica AR) with 25% ether–pentane (detected with uv lamp): mp 111–112°; ir (CCl_4) 3550 cm^{-1} (OH); nmr ($CDCl_3$) τ 4.0–5.0 (4 H, multiplet, olefinic), 5.5 (1 H, narrow multiplet, α H), 6.70 (1 H, narrow multiplet, bisallylic), and 8.0–9.0 (3 H, multiplet, cyclopropyl); mass spectrum m/e 134 ($C_9H_{10}O^+$); R_f 0.54.

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.41; H, 7.52.

Registry No.—1, 30767-78-3; 2a, 34886-41-4; 2b, 34886-42-5; 3, 34886-43-6; 4, 34886-44-7.

Acknowledgment.—The authors gratefully acknowledge the help of Professor C. S. Foote, of the University of California at Los Angeles, with whom many fruitful discussions of this work were held.

(11) Numerous reports of 1,2-dioxetane intermediates have appeared in the literature: (a) P. D. Bartlett and A. P. Schaap, *J. Amer. Chem. Soc.*, **92**, 3323 (1970); (b) S. Mazur and C. S. Foote, *ibid.*, **92**, 3225 (1970); (c) C. S. Foote and J. W.-P. Lin, *Tetrahedron Lett.*, 3267 (1968); (d) W. Fenical, D. R. Kearns, and P. Radlick, *J. Amer. Chem. Soc.*, **91**, 3396 (1969); (e) H. E. O'Neal and W. H. Richardson, *ibid.*, **92**, 6553 (1970).

Twofold Redox Addition of Carbon Tetrachloride to Olefins

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Received December 20, 1971

The addition of haloalkanes to olefins, first described by Kharasch, has been known for a long time.[1] One of the drawbacks has been that with less reactive carbon halogen compounds, telomerization is observed rather than simple 1:1 addition. This difficulty has been overcome by a technique utilizing copper or iron salts as catalysts.[2-4] Even under these conditions some by-products of telomeric 2:1 structures have been reported.

We now show that under proper conditions products of "twofold" addition (not telomeric) can be obtained.

$$CCl_4 + 2CH_2{=}CHR \longrightarrow \underset{\text{twofold addition}}{RCHClCH_2CCl_2CH_2CHClR}$$
$$\searrow$$
$$\underset{\text{2:1 telomer}}{CCl_3CH_2CHRCH_2CHClR}$$

(1) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 957, pp 239–289.

(2) S. Murai, N. Sonoda, and S. Tsutsumi, *J. Org. Chem.*, **29**, 2104 (1964).

(3) R. K. Freidlina, E. T. Chukovskaya, and B. A. Englin, *Dokl. Akad. Nauk SSSR*, **159**, 1346 (1964).

(4) M. Asscher and D. Vofsi, *J. Chem. Soc.*, 1887 (1963).

This has now been demonstrated for methyl acrylate, ethylene, octene, and allyl alcohol. In addition, the possibility of combining two different functional groups by using two steps in the reaction has been shown. The yields are generally low, but that of dimethyl 2,4,4,6-tetrachloroheptanedioate (15%) is synthetically interesting. No effort has been made yet to optimize the yields.

The twofold addition products formed from carbon tetrachloride with ethylene and 1-octene were unsaturated, apparently from the loss of hydrogen chloride. This was even more noteworthy in that the products formed from carbon tetrachloride and allyl alcohol and methyl acrylate were saturated. One possible cause

$$CCl_4 + 2C_2H_4 \longrightarrow CH_2ClCH{=}CClCH_2CH_2Cl + HCl$$

of this difference is the solvent, which was isopropyl alcohol for the addition to ethylene, but acetonitrile for the addition to allyl alcohol, methyl acrylate, and octene. The loss of hydrogen chloride from the product derived from 1-octene could be thermal dehydrochlorination.

Products which are formed from isopropyl alcohol include isopropyl chloride, isopropyl ether, acetone, and propylene, which is converted to 1,1,1,3-tetrachlorobutane.

The nature of the solvent apparently plays a role in the reduction of carbon tetrachloride to chloroform,[5] since chloroform was not observed in experiments with allyl alcohol and methyl acrylate in acetonitrile,[6,7] but was isolated in the reactions of ethylene with carbon tetrachloride in isopropyl alcohol.

Twofold additions of carbon tetrachloride to allyl alcohol and methyl acrylate were carried out in acetonitrile to avoid some of the above-mentioned side reactions. The yields were low, 15% for methyl acrylate and 6.5% for allyl alcohol, but no effort was made to optimize them.

$$CCl_4 + CH_2{=}CHCH_2OH \longrightarrow HOCH_2CHClCH_2CCl_2CH_2CHClCH_2OH$$

$$CCl_4 + CH_2{=}CHCOOCH_3 \longrightarrow CH_3OCOCHClCH_2CCl_2CH_2CHClCOOCH_3$$

The reaction of 1-octene with carbon tetrachloride was also carried out in acetonitrile. The yield of twofold addition product was only 4%, and, similar to the results with ethylene, it was unsaturated. This, however, may have been due to thermal dehydrochlorination during isolation.

In order to show that products from two different olefins with carbon tetrachloride could be made, 1,1,1,3-tetrachloropropane was treated with octene in isopropyl alcohol. The desired mixed twofold addition product was formed, but loss of hydrogen chloride was extensive.[8]

$$CCl_3CH_2CH_2Cl + CH_2{=}CH(CH_2)_5CH_3 \longrightarrow CH_3(CH_2)_5CHClCH_2CCl_2CH_2CH_2Cl + C_{11}H_{19}Cl_3 + C_{11}H_{18}Cl_2$$

2.8% 8.4% 18%

(5) M. Asscher and D. Vofsi, *J. Chem. Soc.*, 2261 (1961).

(6) M. Asscher and D. Vofsi, *J. Org. Chem. USSR*, **2**, 370 (1966).

(7) R. K. Freidlina, E. T. Chukovskaya, and B. A. Englin, *ibid.*, **2**, 372 (1966).

(8) A similar reaction of 1,1,1,3-tetrachloropropane with ethylene has been carried out with $CuCl_2$ and ethanolamine as catalyst in methanol to give 22% of 1,3,3,5-tetrachloropentane and 14% of 1,3,3,7-tetrachloroheptane: D. W. Peck and H. E. Fritz, private communication.

Nmr Spectra.—Most characteristics of the nmr spectra are as expected. The notable characteristic is the separation of two methylene protons adjacent to an asymmetric center.[9] This is observed in all of the products derived from olefins $CH_2{=}CHR$ where R is not H. The most striking effect is observed in the nmr spectra of methyl 2,4,4,4-tetrachlorobutyrate and dimethyl 2,4,4,6-tetrachloroheptanedioate, where the nmr signals for the two methylene protons are not only well separated but couple with each other with J = 15 and 3 Hz, respectively.

Experimental Section

Addition of Carbon Tetrachloride to Ethylene.—A mixture of 1083 g of carbon tetrachloride, 871 g of isopropyl alcohol, 18.9 g of $FeCl_3 \cdot 6H_2O$, 15.75 g of benzoin, and 11.2 g of diethylamine hydrochloride was heated to 125° in a 1-gallon 316 stainless steel Parr Magnedash autoclave. The reactor was pressured to 2500 psig with ethylene and held at 125° for 4 hr. Distillation was used to separate 80 g of chloroform, 925 g of 1,1,1,3-tetrachloropropane,[3,4] nmr (CCl_4) δ 3.84 (t, 2), 3.18 (t, 2, J = 7.5 Hz), and 38 g of 1,1,1,3-tetrachlorobutane, bp 50–55° (10 mm), $n^{20}D$ 1.4795, nmr (CCl_4) δ 3.20 (2 d, 2, J = 5.5 Hz), 4.40 (m, 1), 1.70 (d, 3, J = 6.5 Hz). *Anal.* Calcd for $C_4H_6Cl_4$: C, 24.52; H, 3.09; Cl, 72.09. Found: C, 24.63; H, 3.11; Cl, 72.26.

The last part of the distillation provided a mixture of 18 g of 1,1,5-trichloro-1-pentene, 9 g of 1,3,5-trichloro-2-pentene, 17 g of 1,1,1,5-tetrachloropentane, and 7 g of 1,3,3,5-tetrachloropentane which were separated by gas chromatography for analysis.

1,1,5-Trichloro-1-pentene had nmr (CCl_4) δ 5.89 (t, 1, =CH–, J = 3.8 Hz), 2.35 (2 t, 2, J = 3.8 and 4.0 Hz), 1.88 (m, 2, J = 4.0, 3.1 Hz), 2.53 (t, 2, J = 3.1 Hz). *Anal.* Calcd for $C_5H_7Cl_3$: C, 34.62; H, 4.07; Cl, 61.31. Found: C, 34.52; H, 4.11; Cl, 61.40.

1,3,5-Trichloro-2-pentene had nmr (CCl_4) δ 4.20 (d, 2, =CH-CH_2Cl, J = 3.6 Hz), 5.88 (t, 1, =CH–, J = 3.6 Hz), 2.80 (t, 2, =$CClCH_2$–, J = 3.3 Hz), 3.70 (t, 2, –CH_2Cl, J = 3.3 Hz). *Anal.* Calcd for $C_5H_7Cl_3$: C, 34.62; H, 4.07; Cl, 61.31. Found: C, 34.73; H, 4.13; Cl, 61.03.

1,1,1,5-Tetrachloropentane had nmr (CCl_4) δ 2.71 (t, 2, CCl_3-CH_2–, J = 3.5 Hz), 1.92 (m, 4), 3.59 (t, 2, –CH_2Cl, J = 3.0 Hz).

1,3,3,5-Tetrachloropentane had nmr (CCl_4) δ 3.85 (t, 4, –CH_2Cl), 2.70 (t, 4, J = 4.0 Hz). *Anal.* Calcd for $C_5H_8Cl_4$: C, 28.61; H, 3.84; Cl, 67.55. Found: C, 28.45; H, 3.40; Cl, 66.98.

Addition of Carbon Tetrachloride to Methyl Acrylate.—A mixture of 30.8 g of carbon tetrachloride, 34.4 g of methyl acrylate, 8.2 g of acetonitrile, 0.21 g of benzoin, 0.22 g of diethylamine hydrochloride, and 0.17 g of $CuCl_2 \cdot 2H_2O$ was divided into three portions and charged to 45 ml polymerization tubes. The tubes were heated at 150° for 17 hr and cooled. Three water washes and steam distillation were used to separate 9 g (20%) of methyl 2,4,4,4-tetrachlorobutyrate, bp 46–53° (0.1–0.2 mm), $n^{20}D$ 1.4812,[4,10] nmr (CCl_4) δ 3.86 (s, 3), 4.61 (2 d, 1), 3.22 (2 d, 1), 3.83 (2 d, 1), and 10 g (15%) of dimethyl 2,4,4,6-tetrachloroheptanedioate, bp 140–141° (2.0 mm), $n^{20}D$ 1.4928, nmr (CCl_4) δ 3.82 (s, 3), 4.68 (t, 1), 2.92 (2d, 2). *Anal.* Calcd for $C_9H_{12}Cl_4O_4$: C, 33.16; H, 3.71; Cl, 43.50. Found: C, 33.42; H, 3.67; Cl, 43.28.

Addition of Carbon Tetrachloride to Allyl Alcohol.—This reaction was carried out as described above, except that 23.2 g of allyl alcohol was substituted for the methyl acrylate. The products were 10 g (24%) of 2,4,4,4-tetrachlorobutan-1-ol, bp 60–61° (0.15 mm), $n^{20}D$ 1.5042, nmr (CCl_4) δ 3.66 (s, 3, –OH), 3.29 (2 d, 2, CCl_3CH_2–), 4.39 (m, 1, –CHCl–), 3.9 (d, 2, –CH_2O–), and 3.5 g (6.5%) of 2,4,4,6-tetrachloroheptane-1,7-diol, bp 100–110° (4–7 mm), $n^{20}D$ 1.5113, nmr (CCl_4) δ 3.6 (s, 1, –OH), 3.26 (2 d, 2, –CCl_2CH_2–), 4.35 (m, 1, –CHCl–), 3.7 (d, 2, –CH_2O–). *Anal.* Calcd for $C_7H_{12}Cl_4O_2$: C, 31.15; H, 4.48; Cl, 52.53. Found: C, 30.81; H, 4.21; Cl, 53.05.

(9) For examples of nonequivalence to asymmetry see L. O. Moore, *J. Phys. Chem.*, **74**, 3603 (1970); G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 2628 (1964); E. I. Snyder, *ibid.*, **86**, 2624 (1963).

(10) M. de Malde, F. Minisei, U. Pallini, E. Voltena, and O. Quilico, *Chim. Ind. (Milan)*, **38**, 371 (1956).

Addition of Carbon Tetrachloride to 1-Octene.—This reaction was carried out as described above except that all reagents were doubled and 89.6 g of 1-octene was used in place of allyl alcohol. The mixture was heated in six 45-ml polymerization tubes. The products were 41 g (38.5%) of 1,1,1,3-tetrachlorononane,[4,11,12] bp 95–98° (1.7–2.0 mm), n^{20}D 1.4768, nmr (CCl_4) δ 3.2 (2 d, 2, $-CH_2CCl_3$), 4.2 (m, 1, -CHCl-), 1.85 (m, 2, $-CH_2CHCl-$), 1.36 (m, 8, $-CH_2-$), 0.9 (t, 3, $-CH_3$), and 5.5 g (4%) of 9,9,11-trichloro-7-heptadecene, bp 170° (2.0 mm), n^{20}D 1.4766, nmr (CCl_4) δ 0.9 (t, 3, $-CH_3$), 1.2–1.8 (m, 10, $-CH_2-$), 4 (m, 1, -CHCl-), 5.5 (d, 1, -CH=), 2.7 (d, 2, $=CClCH_2-$). *Anal.* Calcd for $C_{17}H_{31}Cl_3$: C, 59.74; H, 9.14; Cl, 31.12. Found: 59.37; H, 9.28; Cl, 31.11.

Addition of 1,1,1,3-Tetrachloropropane to 1-Octene.—A mixture of 42 g of 1-octene, 68 g of 1,1,1,3-tetrachloropropane, 40 ml of isopropyl alcohol, 0.9 g of $FeCl_3 \cdot 6H_2O$, 0.7 g of benzoin, and 0.5 g of diethylamine hydrochloride was refluxed at 85° for 20 hr. The mixture was washed twice with water and steam distilled. The residue was fractionated but the distillation cuts were mixtures as indicated by gas chromatography. Mass spectroscopy coupled to a gas chromatograph indicated that the three major components were 14.0% of $C_{11}H_{18}Cl_2$, 8.4% of $C_{11}H_{19}Cl_3$, and 2.8% of $C_{11}H_{20}Cl_4$.

Registry No.—Carbon tetrachloride, 56-23-5; ethylene, 74-85-1; 1,1,1,3-tetrachloropropane, 1070-78-6; 1,1,1,3-tetrachlorobutane, 13275-19-9; 1,1,5-trichloro-1-pentene, 2677-33-0; 1,3,5-trichloro-2-pentene, 34909-84-7; 1,1,1,5-tetrachloropentane; 2467-10-9; 1,3,3,5-tetrachloropentane, 24616-07-7, methyl methacrylate, 80-62-6; methyl 2,4,4,4-tetrachlorobutyrate, 25335-11-9; dimethyl 2,4,4,6-tetrachloroheptanedioate, 34909-87-0; allyl alcohol, 107-18-6; 2,4,4,4-tetrachlorobutan-1-ol, 3290-70-8; 2,4,4,6-tetrachloroheptane-1,7-diol, 34909-89-2; 1-octene, 111-66-0; 1,1,1,3-tetrachlorononane, 1070-27-5; 9,9,11-trichloro-7-heptadecene, 34909-90-5.

Acknowledgment.—Thanks are expressed to Dr. W. T. Pace for running the nmr spectra, to B. W. Wilkes for the mass spectra, and to Drs. J. P. Henry and J. T. Fitzpatrick for helpful discussions.

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Deoxygenations of 2-(D-*arabino*-Tetrahydroxybutyl)pyrazine 4-*N*-Oxide and 1-*N*-Oxide

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Received August 23, 1971

Deoxygenations of aromatic *N*-oxides[1] have been carried out with sulfur dioxide,[2] sulfurous acid,[3] phosphorus trichloride,[4] or phosphorus oxychloride[5] or by catalytic reduction over Raney nickel[6] or palladium carbon.[7] The reactions of pyrazine 1-*N*-oxide and pyrazine 1,4-di-*N*-oxide with phosphorus oxychloride have been reported to give 2-chloropyrazine and 2,6-dichloropyrazine in 25 and 40% yield, respectively.[8]

During the course of an investigation of heterocyclic compounds derived from carbohydrates, it was shown[9] that 2-amino-2-deoxy-D-glucose oxime (**1**) reacted with glyoxal to yield 2-(D-*arabino*-tetrahydroxybutyl)pyrazine 4-*N*-oxide (**2**) identical with that derived from 2-amino-2-deoxy-D-mannose oxime and glyoxal. The present report describes an investigation of the deoxygenations of carbohydrate-derived pyrazine *N*-oxides. The deoxygenation of 2-(D-*arabino*-tetraacetoxybutyl)-pyrazine 4-*N*-oxide (**3**) with phosphorus oxychloride yields the monochloropyrazine derivative **4**. In this case, the possible substitution position of chlorine is 3 or 5 on the pyrazine ring. The nmr spectrum of the crystalline monochloro tetraacetyl derivative **4** showed two singlets at τ 1.47 and 1.54 due to the uncoupled protons at C-3 and C-6 of the pyrazine ring. Thus it may be concluded that the position of chlorination is C-5 of the pyrazine ring (Scheme I).

On the other hand, the catalytic deoxygenation of 2-(D-*arabino*-tetrahydroxybutyl)pyrazine 4-*N*-oxide (**2**) was performed in methanol with palladium/carbon at room temperature by using a slightly positive pressure of hydrogen. The deoxygenated product **6** was oxidized with potassium permanganate to yield the pyrazinemonocarboxylic acid **7**, which showed an identical infrared spectrum, paper chromatographic R_f value,[10,11] and melting point with the authentic pyrazine-2-carboxylic acid. This fact shows that the 4-*N*-oxide **2** has been completely deoxygenated to 2-(D-*arabino*-tetrahydroxybutyl)pyrazine (**6**).

1-Amino-1-deoxy-D-fructose oxime (D-isoglucosamine oxime) (**9**) is an isomer of 2-amino-2-deoxy-D-glucose oxime (**1**) and can form a pyrazine 1-*N*-oxide derivative by the reaction with glyoxal. Little has been known of this sugar oxime and it was synthesized according to the procedure described by Breuer[12] from 1-amino-1-deoxy-D-fructose acetate (**8**)[13] and hydroxylamine. The condensation product **10** of this sugar oxime and glyoxal showed the identical molecular formula, ultraviolet maximum, and ultraviolet molecular absorption coefficient with those of 2-(D-*arabino*-tetrahydroxybutyl)pyrazine 4-*N*-oxide (**2**), but showed a quite different melting point and infrared spectrum from those of the latter. The deoxygenation by catalytic reduction of **10** was carried out according to the method used for the 4-*N*-oxide **2** and yielded the deoxygenated product **6**, which had identical physical constants and infrared spectrum with those of the deoxygenated product

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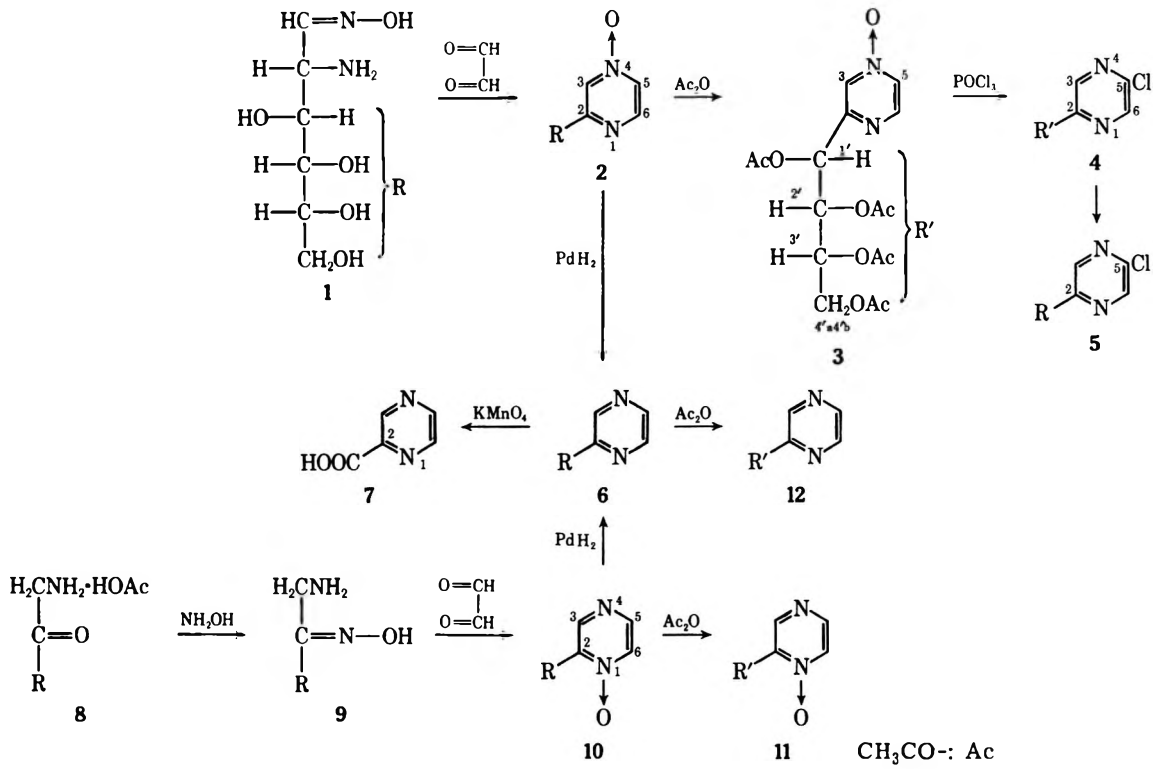
SCHEME I



of the 4-*N*-oxide **2**. Therefore, it can be concluded that the condensation product **10** is 2-(D-*arabino*-tetrahydroxybutyl)pyrazine 1-*N*-oxide.

Tetra-*O*-acetates **11** and **12** of the 1-*N*-oxide **10** and the deoxygenated product **6** were prepared with acetic anhydride and pyridine. Nmr studies on these materials (**4**, **11**, **12**) showed identical patterns in the region τ 3.4–5.8 with that of **3**.[9] The finding indicates that the deoxygenation conditions do not alter the conformation and configuration of these tetrahydroxybutyl side chains.

Experimental Section[14]

2-(D-*arabino*-Tetraacetoxybutyl)-5-chloropyrazine (4).—To 15 ml of phosphorus oxychloride, 5.7 g of 2-(D-*arabino*-tetraacetoxybutyl)pyrazine 4-*N*-oxide (**3**)[9] was added portionwise with stirring. After refluxing for 10 min, the solution was poured into ice water (200 g), and an aqueous solution of sodium hydroxide was added to make pH 9.0. The mixture was extracted several times with chloroform, and the combined extracts were washed with water, dried with sodium sulfate, and concentrated *in vacuo* to a syrup. It was dissolved with a little ether, and petroleum ether (bp 30–70°) was added to give crystals. They were recrystallized from ethyl acetate by adding ether and petroleum ether successively, giving 2.7 g (44.8%) of **4**: mp 72°; $[\alpha]^{25}D$ −7.8° (after 48 hr) (*c* 1.0, methanol); uv max (methanol) 210 and 276 mμ; nmr ($CDCl_3$) τ 8.06, 7.94, 7.90, 7.78 (s, 3 H, AcO-1′, AcO-2′, AcO-3′, and AcO-4′), 5.74 (m, 2 H, $J_{4'a4'b}$ = 12.5 Hz, H-4′), 4.72 (m, 1 H, $J_{3'4'a}$ = 3.0 Hz, $J_{3'4'b}$ = 4.0 Hz, H-3′), 4.35 (q, 1 H, $J_{2'3'}$ = 9.0 Hz, H-2′), 3.89 (d, 1 H, $J_{1'2'}$ = 2.5 Hz, H-1′), 1.54, 1.47 (s, 1 H, H-3 and H-6).

Anal. Calcd for $C_{16}H_{19}N_2O_8Cl$: C, 47.71; H, 4.76; N, 6.96; Cl, 8.80. Found: C, 47.56; H, 4.75; N, 6.89; Cl 8.70.

2-(D-*arabino*-Tetrahydroxybutyl)-5-chloropyrazine (5).—To a solution of 2.7 g of the tetra-*O*-acetate **4** in 100 ml of methanol, ammonia gas was passed through with cooling with ice water. After keeping overnight at room temperature, the reaction mixture was concentrated to separate a crystalline substance which was washed with ethahol, acetone, and ether. Recrystallization from water gave 900 mg (57.6%) of **5**: mp 172–173°; $[\alpha]^{15}D$ −70.0°, (after 48 hr) (*c* 1.0, water); ir (Nujol) 3280 cm^{-1} (OH); uv max (water) 277 mμ.

Anal. Calcd for $C_8H_{11}N_2O_4Cl$: C, 40.95; H, 4.78; N, 11.97; Cl, 15.11. Found: C, 40.71; H, 4.82; N, 11.86; Cl, 14.89.

2-(D-*arabino*-Tetrahydroxybutyl)pyrazine (6).—A suspension of 2 g (0.01 mol) of **2**[9] and 0.5 g of palladium/carbon in methanol was stirred for 60 hr at room temperature under a slightly positive pressure of hydrogen until the 4-*N*-oxide **2** was almost dissolved in methanol. After separation of the catalyst and the unchanged **2**, the methanolic solution was concentrated *in vacuo*, and the residue, 1.5 g (81.0%), mp 166–169°, was recrystallized from water to give 1.0 g (54.2%) of **6**: mp 168–170°; $[\alpha]^{14}D$ −66.7° (after 24 hr) (c 1.0, water); ir (Nujol) 3350 (OH) and 840 cm^{-1}; uv max (water) 266 mμ.

Anal. Calcd for $C_8H_{12}N_2O_4$: C, 47.99; H, 6.04; N, 14.00. Found: C, 47.74; H, 6.06; N, 13.95.

2-(D-*arabino*-Tetrahydroxybutyl)pyrazine 1-*N*-Oxide (10).—1-Amino-1-deoxy-D-fructose acetate (**8**) was obtained in 89% yield according to the method of Kuhn and Haas,[13] mp 136° (lit.[13] mp 137°). To the solution of 24 g (0.1 mol) of this acetate **8** in 1 *N* sodium methoxide (100 ml), a methanolic solution of hydroxylamine (0.15 mol) was added, and the mixture was kept overnight at room temperature. Concentration of the reaction mixture *in vacuo* and the addition of ethanol (*ca.* 400 ml) afforded an amorphous mass (**9**). It was dissolved in 100 ml of water, and 14 g (0.1 mol) of a 40% aqueous solution of glyoxal was added. The reaction solution was kept overnight at room temperature and passed through a column of Amberlite IR-120 (H^+) (100 ml). After the pH of washings became almost neutral, the adsorbed 1-*N*-oxide **10** was eluted with water (1.5 l.). The effluent was concentrated *in vacuo*, and the white crystalline substance formed was collected by filtration and washed with water–ethanol (1:1, v/v) to give 6.0 g of **10**. Recrystallization from water gave 5 g (23.1%): mp 197° (melt), 206° dec; $[\alpha]^{14}D$ 144.3° (after 24 hr) (*c* 1.0, water); ir (Nujol) 3350 (OH) 1610, and 1210 cm^{-1} (N→O); uv max (water) 218 mμ (ϵ 11,000), 265 (12,000).

Anal. Calcd for $C_8H_{12}N_2O_5$: C, 44.44; H, 5.60; N, 12.96. Found: C, 44.15; H, 5.40; N, 12.88.

Deoxygenation of 2-(D-*arabino*-Tetrahydroxybutyl)pyrazine 1-*N*-Oxide (10).—The deoxygenation of the 1-*N*-oxide **10** (2.0 g) was carried out according to the method described above, and 1.6 g

(14) Ultraviolet and 60-MHz nmr spectra were recorded with a Hitachi Perkin-Elmer 139 uv-visible spectrophotometer and a Varian Model A-60 spectrometer, respectively. Tetramethylsilane (τ 10.00) was used as the internal reference standard for nmr spectra. Melting points are not corrected. Pyridine–isoamyl alcohol–water (40:35:30, v/v) and Toyo Roshi No. 50 filter paper were used for descending paper chromatography.

(84.6%) of crude crystalline substance was obtained, which was recrystallized from water to give 1.1 g (59.3%) of **6**. This compound gave an identical ir spectrum and uv absorption pattern with those of **6** derived from 4-*N*-oxide **2**, mp 167–170°, $[\alpha]^{14}D$ −65.4° (after 24 hr) (*c* 1.0, water).

Anal. Calcd for $C_8H_{12}N_2O_4$: C, 47.99; H, 6.04; N, 14.00. Found: C, 48.25; H, 6.25; N, 14.20.

Pyrazine-2-carboxylic Acid (7).—To a solution of 2.2 g of **6** in 400 ml of water, 6.0 g of potassium permanganate was added in small portions with stirring at 90° for 5 hr. After addition of a small volume of methanol for digesting the excess of potassium permanganate, the precipitate was filtered off and washed with hot water. The filtrate and washings were combined and passed through a column of Amberlite IR-120 (H^+). Concentration of this effluent *in vacuo* and recrystallization of the residue from water yielded 760 mg (55.8%), mp 225° dec, ir (Nujol) 1710 cm^{-1} (C=O).

Anal. Calcd for $C_5H_4N_2O_2$: C, 48.39; H, 3.25; N, 22.28. Found: C, 48.40; H, 3.49; N, 22.28.

2-(D-*arabino*-Tetraacetoxybutyl)pyrazine 1-*N*-Oxide (11).—A mixture of **10** (3 g), acetic anhydride (50 ml), and pyridine (50 ml) was kept for 15 hr at room temperature and poured into ice water. The mixture was extracted with chloroform and the extract was treated as described for **3**.[9] The crystals from the chloroform extract were washed with ether and recrystallized with ethanol to give 4.1 g (76.8%) of **11**: mp 97°; $[\alpha]^{16}D$ −30.5° (*c* 1.0, methanol); ir (Nujol) 1745 (C=O), 1600, 1310 cm^{-1} (N→O); uv max (methanol) 224, 269 mμ; nmr ($CDCl_3$) τ 8.80, 7.95, 7.88, 7.78 (s, 3 H, AcO-1′, AcO-2′, AcO-3′, and AcO-4′), 5.74 (m, 2 H, $J_{4'a4'b}$ = 12.5 Hz, H-4′), 4.66 (m, 1 H, $J_{3'4'a}$ = 3.0, $J_{3'4'b}$ = 4.5 Hz, H-3′), 4.24 (q, 1 H, $J_{2'3'}$ = 9.0 Hz, H-2′), 3.43 (d, 1 H, $J_{1'2'}$ = 2.5 Hz, H-1′), 1.89 (q, 1 H, H-6 or H-5), 1.57–1.64 (m, 2 H, H-5 or 6 and H-3).

Anal. Calcd for $C_{16}H_{20}N_2O_9$: C, 49.98; H, 5.24; N, 7.29. Found: C, 49.70; H, 5.13; N, 7.18.

2-(D-*arabino*-Tetraacetoxybutyl)pyrazine (12).—A mixture of **6** (500 mg), pyridine (20 ml), and acetic anhydride (20 ml) was kept at 37° for 20 hr. From the reaction mixture tetra-*O*-acetate was extracted with chloroform and the extract was treated as described for **3**[9] to give 600 mg (61.5%) of **12**: mp 110–111°; $[\alpha]^{16}D$ −1.22° (after 48 hr) (*c* 1.0 methanol); ir (Nujol) 1740 mμ (C=O); nmr ($CDCl_3$) τ 8.11, 7.97, 7.90, 7.78 (s, 3 H, AcO-1′, AcO-2′, AcO-3′, and AcO-4′), 5.74 (m, 2 H, $J_{4'a4'b}$ = 12.0 Hz, H-4′), 4.71 (m, 1 H, $J_{3'4'a}$ = 2.5, $J_{3'4'b}$ = 4.0 Hz, H-3′), 4.31 (m, 1 H, $J_{2'3'}$ = 9.0 Hz, H-2′), 3.84 (d, 1 H, $J_{1'2'}$ = 2.5 Hz, H-1′), 1.43–1.50 (m, 3 H, H-3, 5, or 6).

Anal. Calcd for $C_{16}H_{20}N_2O_8$: C, 52.17; H, 5.47; N, 7.61. Found: C, 52.13; H, 5.41; N, 7.51.

Registry No.—**2**, 21537-56-4; **4**, 34546-42-4; **5**, 34546-43-5; **6**, 34546-44-6; **7**, 98-97-5; **10**, 34546-45-7; **11**, 34546-46-8; **12**, 34546-47-9.

Decarboxylation of Some Thallium(III) Carboxylates. A Mass Spectral Study

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Received December 21, 1971

Many heavy metal alkyl and aryl derivatives have been prepared by decarboxylation of the appropriate carboxylates.[3] The photolysis of primary, secondary, and tertiary carboxylic acids in the presence of thallium(III) has been studied, and the products are thallium(I) carboxylates and organic compounds derived from the radical R·.[4] No other such studies have been reported. Observation of the fragmentation of thallium(III) carboxylates in the mass spectrometer would shed some light on the nature of decarboxylation reactions.

Results and Discussion

Thallium(III) Acetate.—The ion of highest *m/e* value found in the mass spectrum of thallium(III) acetate is the molecular ion, $(CH_3COO)_3Tl^+$. It is clear that one of the major fragmentation pathways from the molecular ion is *via* successive loss of acetate groups and that this is substantiated by the observation of the appropriate metastable peaks (Table I).

TABLE I
MONOISOTOPIC MASS SPECTRA OF $(RCOO)_3Tl$ (R = CH_3 AND C_6H_5)

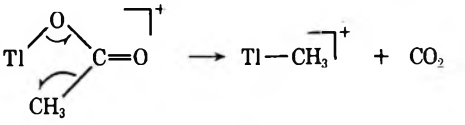
	R = CH_3		R = C_6H_5	
Ion	*m/e*	Rel intensity	*m/e*	Rel intensity
$(RCOO)_3Tl^+$	382	0.1	568	*a*
$(RCOO)_2TlH^+$	324	1.3		
$(RCOO)_2Tl^+$	323	51	447	0.1
$(RCOO)Tl(R)(H)^+$	280	0.1		
$(RCOO)TlR^+$	279	0.2	403	0.2
R_2Tl^+			359	0.2
$(RCOO)Tl^+$	264	0.8	326	8.6
RTl^+	220	0.4	282	19
$TlCO_2^+$	249	6.2	249	6.4
TlO^+	221	0.2		
Tl^+	205	100	205	100

Metastable Transitions

Process	*m/e* Obsd	*m/e* Calcd	Neutral fragment lost
	R = CH_3		
323 → 264	~216	215.8	CH_3COO
264 → 205	159.2	159.2	CH_3COO
	R = C_6H_5[b]		
326 → 282	243.9	243.9	CO_2
403 → 205	104.3	104.3	$C_6H_5COOC_6H_5$

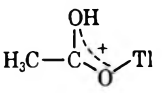
[a] Not observed. [b] Miscellaneous unassigned peak: ~174.

The formation of methylthallium species is probably associated with a rearrangement of the type



However, the possibility of thermal decarboxylation at the heated ion source cannot be ruled out, but seems less likely. It has previously been shown that the reverse reaction, *i.e.*, the insertion of carbon dioxide into the thallium–carbon bonds of trimethylthallium, does not occur at all at room temperature.[5]

Also present in the spectrum are the ions $(CH_3COO)_2TlH^+$ and $(CH_3COO)Tl(CH_3)H^+$, which are probably thallium hydride species, but the possibility of other structures such as



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cannot be excluded. For organothallium(III) compounds, only dimethylthallium phenoxide shows such species in its mass spectrum.[6]

Thallium(III) Benzoate.—The mass spectrum of thallium(III) benzoate (Table I) contains the ions $(C_6H_5COO)_nTl^+$ (n = 1 or 2), although the molecular ion is not observed. Multiplets attributable to species such as $(C_6H_5COO)TlC_6H_5^+$, $(C_6H_5)_2Tl^+$, and $C_6H_5Tl^+$, which are present in low abundance, are formed by elimination of carbon dioxide molecules from the ions $(C_6H_5COO)_nTl^+$ (n = 1 or 2). This is partly justified by the presence of a metastable ion at m/e 243.9 which may be related to the process

$$(C_6H_5COO)Tl^+ \longrightarrow C_6H_5Tl^+ + CO_2$$

Carbonation of triphenylthallium in refluxing xylene has been reported to give biphenyl and thallium(I) benzoate.[7]

On summation of the relative abundances of the phenylthallium species, it is apparent that the decarboxylation of thallium(III) benzoate in the mass spectrometer occurs more readily than does that of the acetate.

Thallium(III) Trifluoroacetate.—The molecular ion is absent in the mass spectrum of thallium(III) trifluoroacetate (Table II), which bears little or no resemblance to that of the acetate. The presence of dimeric species such as $(CF_3COO)_3Tl_2^+$ and $(CF_3COO)Tl_2^+$ suggests that the trifluoroacetate is polymeric or, more probably, dimeric in the gas phase.

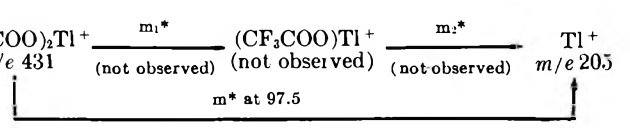
TABLE II

MONOISOTOPIC MASS SPECTRUM OF $(CF_3COO)_3Tl$[a]

m/e	Ion	Rel intensity
749	$(CF_3COO)_3Tl_2^+$	1.2
523	$(CF_3COO)Tl_2^+$	2.6
431	$(CF_3COO)_2Tl^+$	32
410	Tl_2^+	0.8
377[b]	$C_4F_4O_3Tl^+$	28
353[b]	$C_2F_4O_3Tl^+$	10
299	CF_2COOTl^+	4.3
275	$Tl(OF)_2^+$	1.2
249	$TlCO_2^+$	6.0
240	$TlOF^+$	0.9
221	TlO^+	2.2
205	Tl^+	100

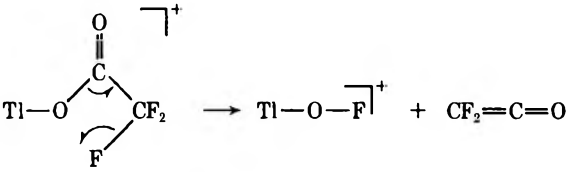
[a] The only metastable ion observed at m/e 97.5 corresponds to the process 431 → 205 (calculated m/e 97.5) with the loss of two CF_3COO groups. [b] See text.

Consecutive loss of two trifluoroacetate groups from the highly abundant ion, $(CF_3COO)_2Tl^+$, is confirmed by the presence of a metastable ion (m*) at m/e 97.5.



No other metastable peaks could be seen in the spectrum.

Another striking feature of the spectrum is the absence of both trifluoromethylthallium and thallium hydride species. The ion at m/e 353 would correspond to $(CF_3COO)TlOF^+$, but that at m/e 377 is of unknown structure. The formation of $(CF_3COO)TlOF^+$ and other unexpected ions such as $Tl(OF)_2^+$ and $TlOF^+$ may be attributed to a rearrangement of the following type.



All previous attempts to prepare trifluoromethylthallium(III) derivatives have failed.[8]

Experimental Section

Since the complexes are moisture sensitive, all manipulations were performed under a dry atmosphere of nitrogen.

Preparation of the Complexes.—Thallium(III) carboxylates were prepared by refluxing thallium(III) oxide (Johnson Matthey Chemicals) with the appropriate carboxylic acid in the presence of the corresponding acid anhydride.[9-12] Methyl benzoate was used as a solvent in the case of the benzoate. The reaction period ranges from 3 days to a week, until all the oxide had been consumed.

Mass Spectra.—The mass spectra were recorded on A. E. I. MS9 and MS12 spectrometers operating at source pressures of *ca.* 2×10^{-7} Torr, 70 eV ionizing energy, 100 μA ionizing current, resolution of 1000, and 8 kV accelerating voltage. Samples were introduced by direct insertion into the heated ion source (160°). The intensity of the multiplets of the metal-containing ions was normalized to the ^{205}Tl peak. The characteristic isotope pattern was observed for each thallium containing ion.

Registry No.—$(RCOO)_3Tl$ (R = CH_3), 2570-63-0; $(RCOO)_3Tl$ (R = C_6H_5), 14332-12-8; $(CF_3COO)_3Tl$, 23586-53-0.

Acknowledgments.—We are grateful to the British Council for financial support (to A. T. T. H.), the Salter's Company and King's College, Cambridge, for Research Fellowships (to A. G. L.), and Jesus College and the University, Cambridge, for studentships (to P. L. S.).

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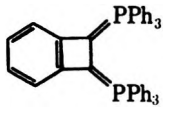
See Editorial, *J. Org. Chem.*, **37**, No. 13, 4A (1972).

Reductive Condensation of Unsaturated Phosphonium Salts with Carbonyl Compounds. Possible Generation of a Reactive 1,2-Bisylide

Summary: Reaction of 1,1,4,4-tetraphenyl-1,4-diphosphoniacyclohexene-2 dibromide with benzaldehyde and lithium affords 1,4-diphenylbutadiene, possibly *via* an intermediate 1,2-bisylide.

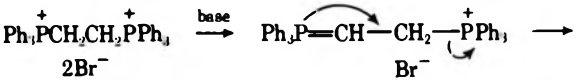
Sir: Phosphorus 1,3- and 1,4-bisylides are useful for double Wittig condensation,[1] but the analogous 1,2-bisylides have not been studied extensively. The only 1,2-bisylide known which is sufficiently reactive for Wittig condensation, 1,2-bis(triphenylphosphoranyl)benzocyclobutene[2] (I), can be prepared in the usual way from the bisphosphonium salt and base. However, attempted preparation of simpler 1,2-bisylides such as II by the above method affords triphenylvinylphosphonium halide and triphenylphosphine (*via* the monoylide III) at temperatures as low as −70°.[3-5]



I

$Ph_3P{=}CHCH{=}PPh_3$

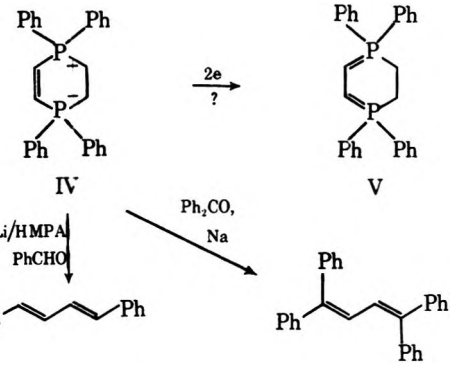
II



III

$Ph_3\overset{+}{P}{-}CH{=}CH_2$ Br^- + PPh_3

A potential route to 1,2-bisylides which avoids intermediates capable of elimination is based on the hypothesis that two-electron reduction of vinylene bisphosphonium salts would afford the desired bisylides. Thus, treatment of the known 1,1,4,4-tetraphenyl-1,4-diphosphoniacyclohexene-2 dibromide (IV)[6] with a reducing metal might be expected to form the cyclic bisylide V.[7]



IV V

In apparent agreement with the above proposal, treatment of IV with lithium/hexamethylphosphoramide in the presence of benzaldehyde, or with sodium and benzophenone in tetrahydrofuran, affords moderate yields of the expected Wittig products, *trans,-trans*-1,4-diphenylbutadiene and 1,1,4,4-tetraphenylbutadiene, respectively, in addition to complex polar products. However, we have been unable to obtain direct evidence that V is an intermediate in these reactions. Treatment of powdered IV with Li/HMPA at 20° slowly produces a characteristic orange solution, but subsequent addition of benzaldehyde to this solution does not afford any diphenylbutadiene. Furthermore, reaction of IV with Li/HMPA in the presence of cyclohexanone affords none of the derived Wittig product. Similar behavior has been noted for the 1,2-bisylide I which is also unstable at room temperature and does not form simple Wittig products with acetone.[2a]

Although the formation of dienes strongly implicates a Wittig betaine intermediate such as VI, we must note that other rationales can account for the generation of VI which do not involve the bisylide V. The reduction potentials of IV,[8] benzaldehyde, and benzophenone[9] are comparable; so it is possible that electron transfer to the carbonyl component is the first step. Nucleophilic addition of benzaldehyde radical anion to IV (by analogy to the addition of simpler nucleophiles[5,10]) would then produce a species VII which may react with a second mole of lithium and benzaldehyde to form VI (Scheme I).[11] On the basis of this rationale, the failure of cyclohexanone to form a Wittig product can be attributed to its unfavorable reduction potential.

Benzophenone ketyl also reacts with vinyltriphenylphosphonium bromide to form 1,1,4,4-tetraphenylbutadiene. According to the radical anion mechanism outlined in Scheme I, the ylide VIII is an intermediate, and Wittig condensation followed by dehydration leads to the observed diene. An alternate pathway involving electron transfer to the vinylphosphonium salt can also account for generation of VIII. We are not aware

(1) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, p 20.

(2) (a) A. T. Blomquist and V. J. Hruby, *J. Amer. Chem. Soc.*, **86**, 5041 (1964); *ibid.*, **89**, 4996 (1967). (b) P. J. Garratt and K. P. C. Vollhardt, *Chem. Commun.*, 1143 (1971).

(3) G. Wittig, H. Eggers, P. Duffner, *Justus Liebigs Ann. Chem.*, **619**, 10 (1958).

(4) Treatment of 1,2-bis(triphenylphosphonio)ethane dibromide with butyllithium at −70° in tetrahydrofuran followed by benzaldehyde affords ~10% 1-phenyl-1-heptene as the sole Wittig product. This substance results from addition of butyllithium to vinyltriphenylphosphonium bromide, by analogy to the work of Seyferth and Fogel.[5]

(5) D. Seyferth and J. Fogel, *J. Organometal. Chem.*, **6**, 205 (1966).

(6) A. M. Aguiar and H. Aguiar, *J. Amer. Chem. Soc.*, **88**, 4090 (1966).

(7) The recently reported electrochemical reduction of IV[8] to 1,1,4,4-tetraphenyl-1,4-phosphoniacyclohexane dibromide may prove to be the first example of generation of V. The protic solvent used is expected to protonate V to the observed saturated salt.

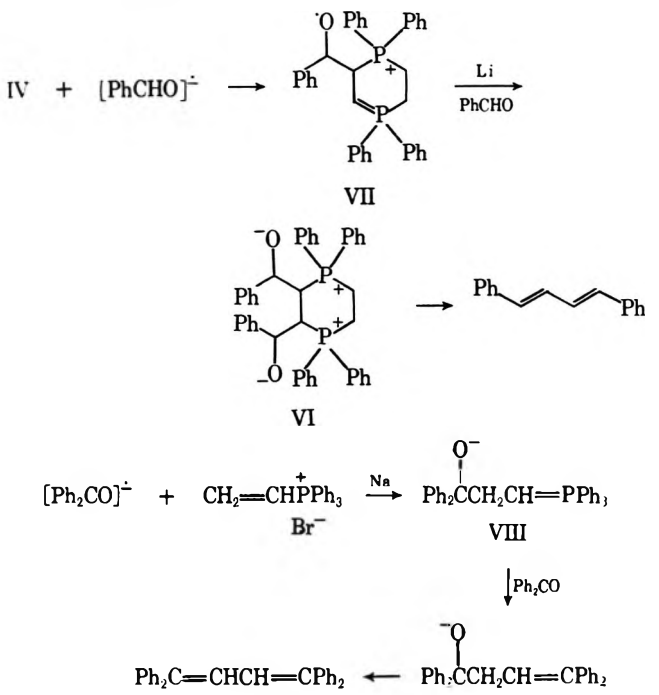
(8) J. H. Stocker, R. M. Jenevein, A. Aguiar, C. W. Prejean, and N. A. Portnoy, *Chem. Commun.*, 1478 (1971).

(9) P. H. Given and M. E. Peover, *J. Chem. Soc.*, 385 (1960).

(10) E. E. Schweizer and W. S. Creasy, *J. Org. Chem.*, **36**, 2244 (1971), and references therein; J. R. Shutt and S. Trippett, *J. Chem. Soc. C*, 2038 (1969).

(11) Alternately, nucleophilic addition of benzaldehyde or benzophenone dianion to IV could be invoked.

SCHEME I



of any direct analogy for the intermediate ylide radical (from one-electron transfer) or ylide anion (two-electron transfer) required for this mechanism.[12]

Studies are in progress to extend the scope of the diene synthesis to aliphatic carbonyl compounds. We are also exploring metal reductions of other vinyl-substituted tetravalent phosphorus compounds with the aim of devising reagents which are synthetically equivalent to phosphorus 1,2-bisylides.

Acknowledgment.—We thank the National Science Foundation for support of this research. We are also grateful to Professor A. M. Aguiar for his help with experimental procedures.

(12) The condensation of styrene radical anion and acetone constitutes a rather remote precedent for this rationale, although not for the organophosphorus intermediates: J. K. Kochi, *J. Org. Chem.*, **28**, 1960 (1963).

(13) Alfred P. Sloan Foundation Fellow, 1971–1973.

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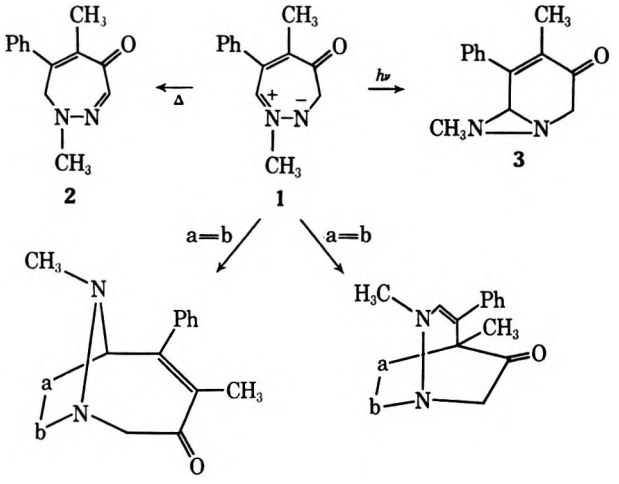
RECEIVED FEBRUARY 11, 1972

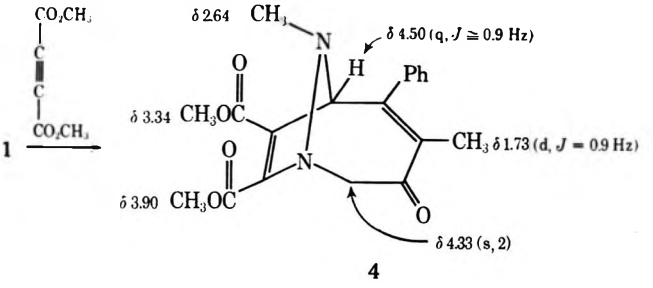
Heterocyclic Studies. 35. Cycloaddition Reactions of a 1,2-Diazepinium Betaine. 1,3- and 1,5-Dipolar Addition in a Vinylogous Azomethine Imine†[1]

Summary: Betaine **1** with acetylenedicarboxylic ester undergoes 1,3-cycloaddition, and with ketene or aryl isocyanates, 1,5-cycloaddition; the isocyanate products rearrange to 1,3 cycloadducts.

Sir: The 1-methyl-2,3-dihydrodiazepinium betaine **1** undergoes thermal sigmatropic rearrangement to the 1,7-dihydrodiazepinone **2** ($k_1^{MeOH,25°}$ 2.4 × 10^{-4} sec^{-1}) and a photochemical 4-π electrocyclic reaction to **3**.[2] In addition to these intramolecular processes, **1** presents the unusual possibility of dipolar cycloaddition reactions involving either the 4-π azomethine imine system or the 6-π system extending from C-5 to N-2. We now report both of these types of additions.



A mixture of the red betaine **1** [prepared in 90% yield by alkylation of the parent dihydrodiazepinone with $(CH_3)_3O^+BF_4^-$ in acetone][3] and excess dimethyl acetylenedicarboxylate was stirred for 30 min and the deep red solution was chromatographed on silicic acid. The colorless adduct **4**, mp 102°, was isolated in 33% yield. The bicyclic system of **4** was very sensitive to base but was quite stable to acid; heating in 12 *N* HCl led only to hydrolysis of one ester group.



The thermal rearrangement of **1** to **2** places a severe restriction on bimolecular reactions of **1**. With less reactive dipolarophiles such as methyl propiolate or methyl maleate, adducts were not obtained, and only **2** was isolated.

The possibility of addition to the extended π system of **1** in a [$_\pi6_s$ + $_\pi4_s$] process was explored with several dienes including furan and hexachlorocyclopentadiene, but again only **2** was formed and no adducts were detected. Another symmetry-allowed mode of cycloaddition for the extended azomethine imine would be a [$_\pi6_s$ + $_\pi2_a$] process, analogous to the numerous [$_\pi2_s$ + $_\pi2_a$) cycloaddition that have been observed with

† Attention is called to the possibility of including supplementary data; *e. g.*, see footnote 3 of this communication and editorial. F. D. G.

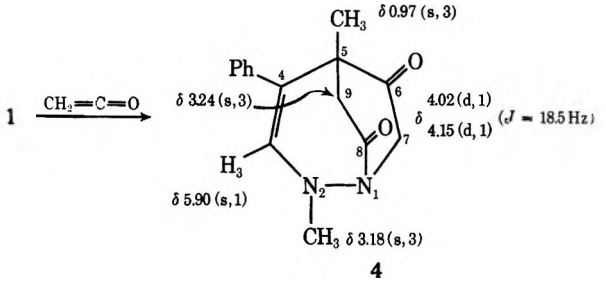
(1) Supported by Grant GP-9322 from the National Science Foundation.

(2) M. G. Pleiss and J. A. Moore, *J. Amer. Chem. Soc.*, **90**, 4738 (1968).

(3) Complete experimental details on all compounds described in this communication will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N. W., Washington D. C. 20036, by referring to code number JOC-72-2640. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

heteroallenes such as ketenes[4] and isocyanates.[5] This approach proved quite fruitful.

A solution of **1** in CH_2Cl_2 was decolorized in a few seconds by a stream of ketene, and evaporation gave the colorless adduct **5** (84%). Attachment of the ketene bridge at C-5 of **1** is clearly indicated by the high-field methyl signal. The only previous 1,5-dipolar cycloaddition of this type appears to be that observed in the reaction of *o*-diazo oxides and ketenes to give benzo-1,4,5-oxadiazepines;[6] in this case, however, 1,3-cycloaddition to the diazo group would give a nonbenzenoid product, and the 1,5-cycloaddition product is therefore strongly favored owing to product stability.



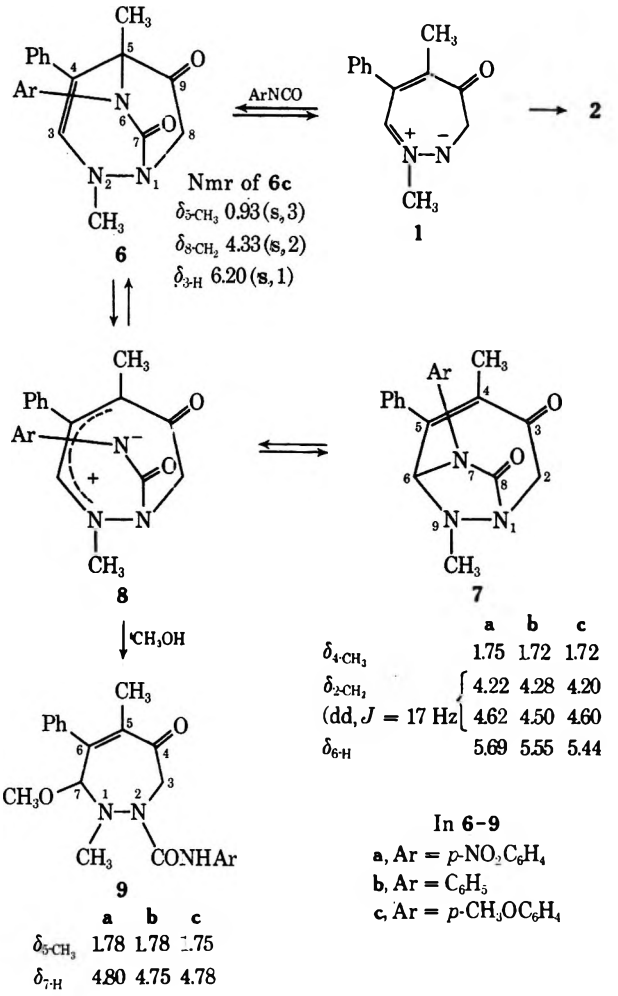
4

Reactions of **1** with aryl isocyanates at 25° gave the 1,3-dipolar adducts **7a–c** (50–70%); the relative rates were p-$NO_2 \gg p$-H $> p$-OCH_3. With *p*-methoxyphenyl isocyanate, a second compound was seen in the nmr spectrum of the reaction mixture, and an impure sample of this product was crystallized from a reaction at 0°. The nmr spectrum indicated the 1,5 cycloadduct **6c**. Solutions of **6c** at room temperature became orange in a few seconds and then faded; **7c** was then isolated. The nmr spectra of such solutions of **6c** initially showed small peaks due to the betaine **1** and then progressively the formation of **7c** and the rearrangement product **2** in a ratio of ~2.5:1. Reactions of **6c** and phenyl or *p*-nitrophenyl isocyanate gave the adducts **7b** and **7a**, respectively.

The presence of the other 1,5 adducts, **6a** and **6b**, was detected by nmr in solutions of **1** and isocyanates at −20°, but rearrangement to **7a,b** occurred rapidly on warming.

On heating the 1,3 adduct **7b** in a melt at 170°, phenyl isocyanate could be distilled, and the rearrangement product **2** was isolated in 66% yield.[7] The 1,3 adducts reacted in boiling methanol to give methoxy compounds considered to be **9**;[8] the relative rates were again p-$NO_2 > p$-H $> p$-OCH_3. Reaction of the 1,5 adduct **6c** in methanol at 25° gave the *p*-methoxy derivative **9c** and the 1,3 adduct **7c** (~2:1).

We interpret these observations in terms of a reversible concerted $[{}_\pi 6_s + {}_\pi 2_a]$ addition to form the 1,5 cycloadducts **6**, followed by rearrangement of **6** to the more stable 1,3 adducts **7** *via* the dipolar intermediate **8**. This intermediate presumably also gives rise to the methoxytetrahydrodiazepinones **9** by addition of methanol. The greater stability of the *p*-methoxyphenyl 1,5 adduct **6c** is attributed to the higher energy of intermediate **8c** relative to **8a** or **8b**. A similar sequence has been proposed for reactions of chlorosulfonyl isocyanate and dienes, which leads by $[{}_\pi 2_s + {}_\pi 2_a]$ addition to vinylazetidinones and thence by thermal rearrangement to dihydropyridones or dihydropyrans.[5]



According to the mechanism we suggest for the reactions of **1** with isocyanates, the $[{}_\pi 6_s + {}_\pi 2_a]$ addition to **6** is more rapid than $[{}_\pi 4_s + {}_\pi 2_s]$ addition leading directly to **7**, and the former process is presumably highly concerted. To assess the extent of charge developed in the isocyanate during these additions, the following second-order rate constants for the disappearance of **1** were measured in chloroform at 20° for five isocyanates.[9]

Ar	$k \times 10^2\ M^{-1}\ \text{sec}^{-1}$
p-CH_3O	1.62 ± 0.07
p-CH_3	1.37 ± 0.03
p-H	2.07 ± 0.06
m-Cl	3.68 ± 0.27
p-Cl	3.49 ± 0.26

From these data, a Hammett ρ value of 0.69 ± 0.13 was obtained with a correlation coefficient of 0.95. If the rate for *p*-methoxyphenyl isocyanate is omitted

(4) L. Ghosez, R. Montaigne, A. Roussel, H. Vanlierde, and P. Mollet, *Tetrahedron*, **27**, 615 (1971).

(5) E. J. Moriconi and W. C. Meyer, *J. Org. Chem.*, **36**, 2841 (1971), and many other references given there.

(6) W. Reid and R. Dietrich, *Ann.*, **666**, 113, 135 (1963); W. Reid and K. Wagner, *ibid.*, **681**, 45 (1965).

(7) Similar reversibility has been observed with 1,3-dipolar adducts from aryl isocyanates and azomethine imines derived from isoquinoline: R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 584 (1963).

(8) The 7-methoxy-1,2,3,7-tetrahydrodiazepinone structures **9** appear more compatible with the nmr values than the allylic isomers (5-methoxy-1,2,3,5-tetrahydrodiazepinone), but the latter alternative is not rigorously excluded by the data available.

(9) The reactions were run under pseudo-first-order conditions with isocyanate in excess, following the disappearance of **1** at 436 nm.

(*vide infra*), the data give a ρ value of 0.83 ± 0.13 and a correlation coefficient of 0.98. When compared with ρ values reported for the addition of alcohols to aryl isocyanates, 2.46 ± 0.16[10] and 1.98 ± 0.10,[11] the cycloadditions appear to involve very little (negative) charge development in the transition state, *i.e.*, a highly concerted reaction.

The rates of cycloaddition of aryl isocyanates to α,*N*-diphenylnitrone have a distinct minimum near $\sigma = 0$ with ρ values of -1.8 ± 1.1 and $+1.41 \pm 0.23$ for electron-donating and electron-withdrawing substituents, respectively.[12] These data have been interpreted as indicating a concerted but not synchronous addition mechanism,[12] and a similar conclusion may be drawn for the cycloadditions of **1**, in which *p*-anisyl isocyanate also reacts faster than *p*-tolyl isocyanate, and a significantly smaller ρ value is observed.

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RECEIVED MAY 18, 1972

(10) J. W. Baker and J. B. Holdsworth, *J. Chem. Soc.*, 743 (1947).
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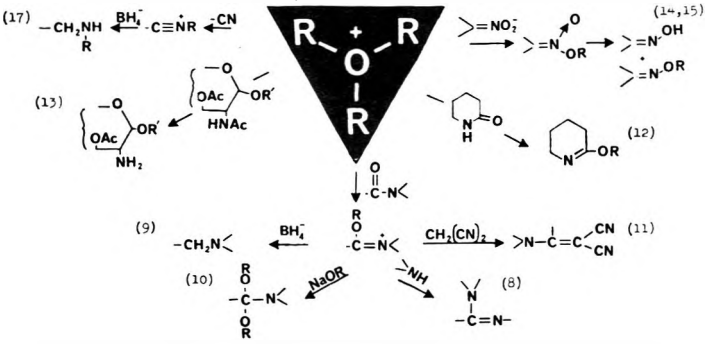
MEERWEIN SALTS

Versatile agents for O-, N-, P- and S-alkylation, ambident anion alkylation and hydride abstraction[1]



Hydroxy compounds such as alcohols, phenols and carboxylic acids (or their salts) react with trialkyloxonium salts to give O-alkyl derivatives. Such alkylations are especially useful for hindered alcohols, e.g., pinacolyl alcohol,[3] or when non-alkaline conditions are necessary, as in the case of chlorohydrins.[2] **Ethers** yield new trialkyloxonium salts. The product from **epoxides** depends on the initial structure, e.g., epichlorohydrin[4] gives a polymer and ethylene oxide affords dioxane. **Carbonyl compounds** can be O-alkylated in the order:[5] lactams > amides > lactones > esters > ketones > aldehydes. While most aldehydes and ketones yield only aldol condensation products some ketones, such as camphor,[2] can be O-alkylated. **α,β-Unsaturated ketones,** e.g. tropone,[6] are readily alkylated because of increased stabilization of the resulting cation. Esters are poorly alkylated but **carbonates**[7] which have additional stabilization can be alkylated. The O-alkylation of **amides** results in intermediates especially useful in organic synthesis. These imidate salts react with amines to yield **amidines**[8] and can be reduced[9] with $NaBH_4$ to amines. The salts of **tert**-amides can be reacted with NaOEt to give **amide acetals**[10] which are highly reactive to nucleophilic reagents, or these salts can be reacted directly with a nucleophile such as the anion of malononitrile to give N,N-disubstituted aminomethylenemalononitriles.[11] A similar product from the reaction[12] of a cyanoacetate with the iminoether of δ-valerolactam can be converted to 2-cyanomethylenepiperidine which can undergo **Michael type condensations** alpha to the nitrile. Imidate salts are easily hydrolyzed by water so that an **N-acetyl protecting group can be removed** readily without affecting other acetoxy groups.[13] Amine oxides and sulfoxides are readily O-alkylated as are phosphates.[1]

The sodium salt of nitro compounds can be alkylated to give **aci**-nitronic esters[14,15] which can rearrange to a mixture of oxime and oxime ether.

While in many instances nitrogen compounds can be alkylated with conventional reagents, cases exist where trialkyloxonium salts are needed. Thus, pyrazine and pyrimidine are alkylated to **bis-quaternary salts,**[16] and **nitriles** to nitrilium ions which can be reduced[17] with $NaBH_4$ to **sec**-amines. Phosphorous compounds such as triethylphosphite are alkylated[18] on P. Sulfides[19] readily yield sulfonium salts which have synthetic utility **via** the Stevens rearrangement.

Trialkyloxonium salts also can abstract hydride ions from acetals to give carbenium ions.[20]

The original trialkyloxonium complexes of Meerwein[2] were the tetrafluoroborate and the hexachloroantimonate. The former has only limited stability and generally must be freshly prepared and stored under ether, while the presently available hexafluorophosphates and hexachloroantimonates are stable crystalline solids at room temperature.

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