VOLUME 42 FEBRUARY 18, 1977 NUMBER 4 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

Published by the
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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.

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Easton, Pa. 18042
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Notice to Authors last printed in the issue of January 7, 1977

JOCEAH 42(4) 585–770 (1977)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 4 FEBRUARY 18, 1977

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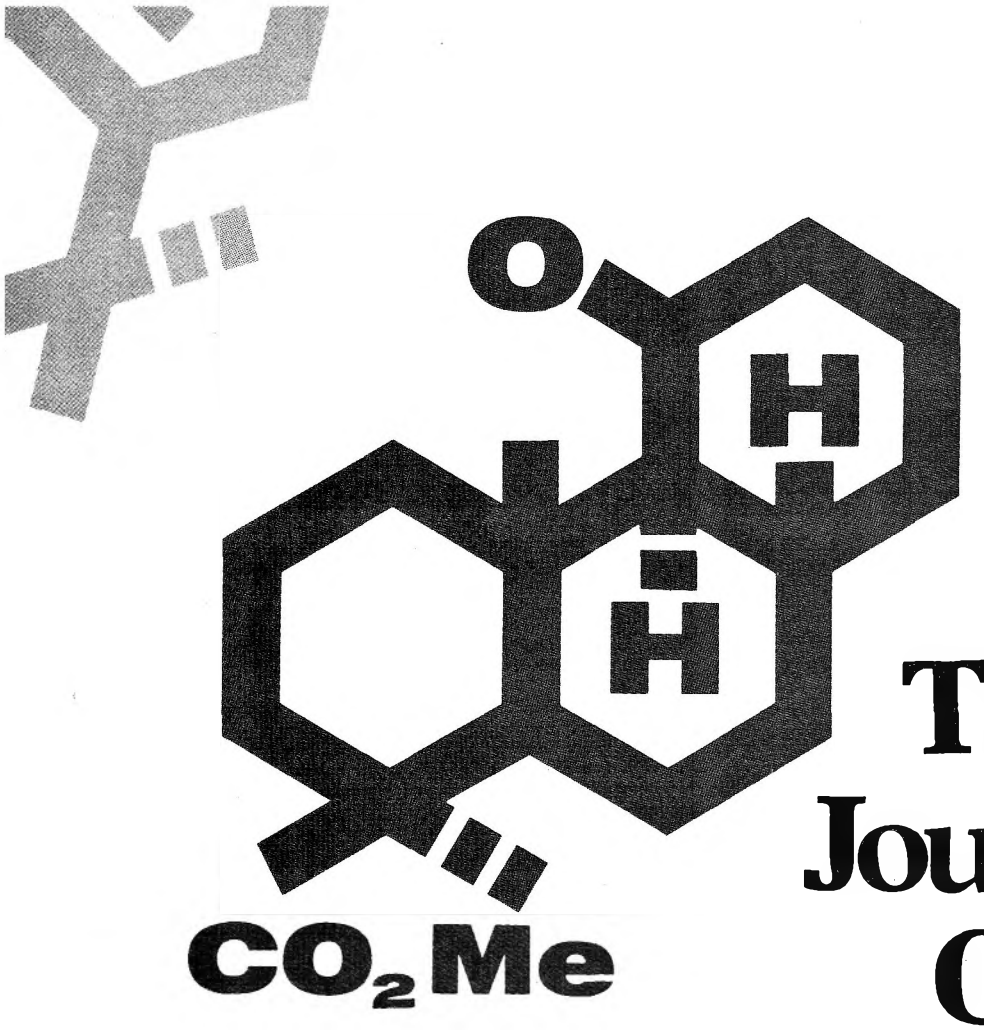

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AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 4

FEBRUARY 18, 1977

The Influence of the Neighboring Phenylthio Group on the Solvolytic Reactivity of Allylic Compounds. *An Example of an Internal S_N2' Reaction*

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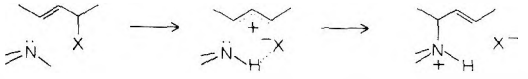
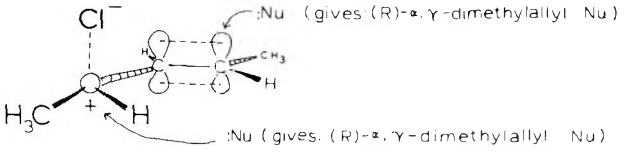
Received March 26, 1976

The rate and solvolysis products of *trans*-4-(phenylthio)-2-cyclohexenyl *p*-nitrobenzoate (**1b**), its cis isomer (**2b**), *trans*-6-(phenylthio)-2-cyclohexenyl *p*-nitrobenzoate (**3b**), and related compounds were investigated. The product compositions from **1b**, **2b**, and **3b** were quite similar and a common intermediate for all three was suggested. The solvolysis rate for **3b** was strongly accelerated, through sulfur participation, while the rates for **1b** and **2b** showed marginal acceleration. From these results it is inferred that S_N2' reactions, under conditions where the leaving group is the leading element of the reaction, are neither extremely facile nor stereospecific.

Since the pioneering paper of Stork and White,[2] there has been general acceptance[3] of the idea that the S_N2' reaction requires a syn (cis) relationship between entering and leaving groups. They found that *trans*-6-alkyl-2-cyclohexenyl 2,6-dichlorobenzoates underwent S_N2' reactions with piperidine and sodium malonate ester in a syn manner producing therefore *trans*-3-alkyl 4-substituted cyclohexenes. The reaction was second order and appeared not to involve rearrangement of starting material or products. Subsequently, theoretical agreements have been advanced to explain their observations.[4,5] More recently Bordwell et al.[6] have synthesized a number of γ-arylsulfonyl allylic halides which would seem to be well suited to S_N2' displacement by nucleophiles. They find, however, that these compounds are generally quite unreactive, a fact which has led them to question the attainability of the concerted S_N2' mechanism. They suggest that many of the reported examples may in fact proceed by mechanisms which involve carbonium ion type reactions and they classify the classic examples of Stork and White as S_Ni reactions (a variant of an ion pair mechanism) and picture them in the following manner.[6a] The importance of ion pairs



in displacement reactions of allylic substrate has also been recently emphasized by Sneen et al.[7] They report[7a] that the kinetic, product, and stereochemical data for the competitive substitution by solvent (alcohol or alcohol–H_2O) and external nucleophiles (N_3^- or NCS^-) on α,γ-dimethylallyl chloride are best accommodated by an ion pair mechanism. The evidence would indicate that the first formed intimate ion pairs are asymmetric and thereby give rise to an optically active product of assumed inverted configuration. The intimate ion pairs can interconvert or further dissociate to a meso solvent separated ion pair which rapidly collapses to give racemic product. It was not known whether the attack by external nucleophile took place at C-α (with assumed inversion) or at C-γ with a syn stereochemistry which would give the same stereochemical result, inversion.



In a companion study Sneen and Carter[7b] reported what appears to be an authentic example of an S_N2' reaction of phenoxide with α-methylallyl chloride. In this case the data pointed to a rate-determining displacement by phenoxide on a discrete intimate ion pair to give 17% S_N2' and 83% S_N2 type products. Although the stereochemistry of the S_N2' component was not determined, a recent theoretical study[5] of the S_N2' reaction by Epiotis et al. concluded that both nonbonded and electrostatic interactions favor syn over anti attack when the nucleophile is neutral and the leaving group departs as an anion. They expected these conclusions to hold regardless of whether one had a classical S_N2' reaction or an ion pair variant.

This study was undertaken to shed light on the stereochemistry and facility of S_N2' reactions conducted under ionizing conditions. In this paper we report our efforts to find evidence for sulfur participation in the solvolysis of compounds such as *trans*-4-(phenylthio)-2-cyclohexenyl *p*-nitrobenzoate (**1b**) and its cis isomer (**2b**). They contain a good internal nucleophile which is forced to participate in a predetermined manner, anti S_N2' for **1b** and syn S_N2' for **2b**. The phenylthio substituent (PhS) has previously been shown to be a good neighboring group by Goering and Howe,[8] who reported that the trans/cis rate ratio for the solvolysis (80% aqueous ethanol) of 2-(phenylthio)cyclohexyl chloride is

Table I. Solvolysis Rate Constants and Activation Parameters for *p*-Nitrobenzoates in TFE

a, X = OH
b, X = OPNB (*p*-nitrobenzoate)
c, X = ODNB (3,5-dinitrobenzoate)
d, X = OCH_2CF_3

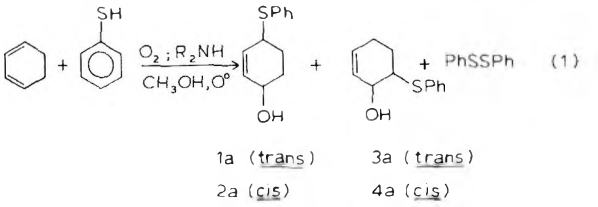
	1 (52939-10-3)[c]	2 (52939-09-3)	3 (60789-30-2)	5 (38313-01-8)	6 (60789-31-3)	7 (60789-32-4)	8 (60789-33-5)
k_{rel} (X = OPNB; 120 °C)	1.38	0.27	29.5	1.0	0.005	0.014	0.0016
$k \times 10^5$, s^{-1} (°C)[b]	2.00 (79.59)	1.52 (100.08)	9.08 (49.76)	1.57 (79.59)	0.0186 (120.0)[a]	0.562 (120.0)[a]	0.0063 (120)[b]
	4.95 (89.79)	3.62 (110.0)	20.2 (59.86)	4.03 (89.79)			
	11.36 (99.97)	10.19 (120.0)	31.0 (65.14)	8.55 (99.87)			
$\Delta H^{\ddagger}$, kcal/mol	21.7 ± 0.1	27.1 ± 2.6	16.6 ± 0.5	21.1 ± 0.1			
$\Delta S^{\ddagger}$, eu	−18.9 ± 0.3	−8.5 ± 6.8	−25.8 ± 1.6	−20.9 ± 2.9			

[a] Computed from the rate of the corresponding 3,5-dinitrobenzoate **6c** assuming $5.1k_{6b} = k_{6c}$ since $k_{5c}/k_{5b} = 5.1$ in TFE. The rate constant measured on **6b** at 20% reaction was ca. 2×10^{-7} s^{-1}. [b] The standard deviation for the rate constants are between 1 and 5% for all entries except for the last two under 5b, where they were ca. 8%, and 8b, whose rate could be measured only out to 10% reaction. [c] Registry no.

nearly 10^6. Our aim then was to see whether **1b** or **2b** would undergo solvolysis with sulfur participation, which could be detected either kinetically or by product analysis.

Results

The cooxidation[9] of thiophenol and 1,3-cyclohexadiene was expected to provide a high-yield synthetic route to 4-(phenylthio)- and 6-(phenylthio)-2-cyclohexen-1-ols (eq 1). Three

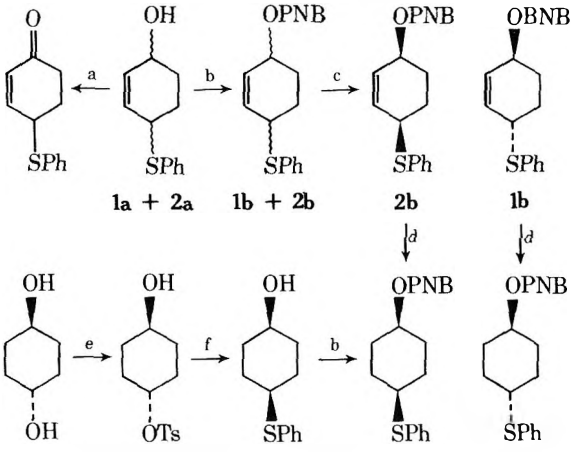


(1)

1a (trans) 3a (trans)
2a (cis) 4a (cis)

allylic alcohols were isolated in nearly equal amounts from this reaction mixture by column chromatography. One of these was shown to be **3a** by reduction to, and comparison with, an authentic sample of *trans*-2-(phenylthio)cyclohexanol (**7a**). The identities of the other two, **1a** and **2a**, were established by the route outlined in Scheme I. A careful search for **4a** was made

Scheme I. Stereochemical Assignment of *cis*- and *trans*-4-(Phenylthio)-2-cyclohexen-1-ol



a, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; b, *p*-nitrobenzoyl chloride, pyridine; c, chromatography and fractional recrystallization; d, H_2, $(C_6H_5P)_3Rh(I)Cl$, C_6H_6, C_2H_5OH; e, $CH_3C_6H_4SO_2Cl$, pyridine; f, C_6H_5SNa, H_2O–C_2H_5OH.

but none was detected (see Experimental Section for details).

trans-2-(Phenylthio)cyclohexanol (**7a**) was prepared from cyclohexene oxide and sodium thiophenoxide. The *p*-nitrobenzoates and 3,5-dinitrobenzoates used in this study were generally prepared from the corresponding alcohols by standard procedures. *trans*-4-Phenylsulfonyl-2-cyclohexenyl *p*-nitrobenzoate (**6b**) and 3,5-dinitrobenzoate (**6c**) were prepared by hydrogen peroxide oxidation of **1b** and **1c**, respectively. In a similar manner the cis isomer, **8b**, was prepared from sulfide **2b**.

The solvolysis rates were measured using the ampule technique in 2,2,2-trifluoroethanol (TFE).[10] Except as noted, good first-order plots were obtained for all compounds up to 75% reaction. The initial concentration of *p*-nitrobenzoate was kept below ca. 1.5×10^{-2} M, for at higher concentrations some autocatalysis was observed, as evidenced by an upward drifting of the first-order rate constant. Few 3,5-dinitrobenzoates were measured in TFE because of their low solubility. The solvolysis of sulfones **6b** and **8b** was quite slow in TFE and could be followed to only 20 and 10% reaction, respectively, after which severe discoloring of the medium and the production of an acidic by-product(s) occurred. A control ex-

periment showed that these acidic products were not the result of TFE decomposition at the elevated temperatures used for the solvolysis. As a cross-check the rate of the more reactive 3,5-dinitrobenzoate **6c** was also measured and corrected for the differences in leaving group ability as judged by k_{5c}/k_{5b} = 5.1 in TFE. The rate of **6b** obtained in this way was in good agreement with the value obtained directly. With the exception of **6b, 6c,** and **8b** experimental infinity titers were used to calculate all specific rate constants. The relative rates for all PNB's calculated at 120 °C, specific first-order rate constants, and activation parameters for the TFE runs are recorded in Table I.

Solvolysis products for **1b, 2b,** and **3b** were determined in TFE containing 2 equiv of 2,6-lutidine. In all three cases the ^{1}H NMR spectrum of the crude reaction mixture revealed the absence of elimination products. All three *p*-nitrobenzoates gave a similar product distribution consisting of **1d, 2d,** and **3d** in ca. 1:1:5 ratio. In addition, **3b** gave 7% of an internal return product, **1b.** In none of the preparative runs was anything isolated which could be assigned to either **4b** or **4d.** The products were identified by ^{1}H NMR spin–spin decoupling studies and comparison of these spectra to those of the corresponding alcohols and benzoate esters (see Experimental Section for details). The product mixtures are recorded in Table II.

Table II. Products Isolated from Preparative Solvolysis in TFE[a]

Starting material	Product ratios[b] 1d	2d	3d	% yield
1b	16	16	68	84
2b	16	12	72	68
3b	11	12	77	78[c]

[a] Buffered with 2 equiv of 2,6-lutidine. [b] The ratios were determined by careful integration of the appropriate ^{1}H NMR signals. The 1,4 isomers, **1d** and **2d,** were arbitrarily assigned. [c] *p*-Nitrobenzoate, **1b,** was also isolated (7%).

Discussion

As mentioned earlier, *trans*-2-(phenylthio)cyclohexyl chloride shows greatly enhanced reactivity [k(trans)/k(cis ≈ 10^6] due to sulfur participation. Of the seven *p*-nitrobenzoates studied in this paper, the analogous cyclohexenyl sulfide, **3b,** is the most reactive. This reactivity is most reasonably ascribed also to sulfur participation leading to ion **9.** The magnitude of the acceleration is certainly greater than 29.5 (k_{3b}/k_{5b}) because the rate of **5b** is certainly faster than that expected for unassisted **3b.** The rate constant k_{5b} can, however, be corrected for the retardation to be expected from a nonparticipating phenylthio group through a Hammett plot and thereby yield an estimate of k_{3b} (unassisted). Thus using the solvolysis rates of **5b** and **6b,** the known σ_I values[11] of $PhSO_2$ and PhS, and the assumption that the substituent effects at the α carbon of a developing allylic cation are similar to those at the γ carbon, one estimates that k_{3b} (observed)/k_{3b} (unassisted) is greater than 600. This strongly suggests sulfur participation during the initial ionization. The fact that the acceleration is considerably less in the cyclohexenyl system than in the cyclohexyl system is probably a reflection of the reduced electron demands in the allylic compound.[12]

9

The products isolated from the reaction are in accord with the postulated intermediate, **9,** since trans 1,2 ether, **3d,** but no cis 1,2 ether, **4d,** was isolated. Furthermore, if the intermediate were an open allylic cation, one might expect the amount of 1,4 products to exceed 1,2 products.[3] This is not the case; the major isolated product (ca. 73%) was trans 1,2 ether, **3d.** Thus sulfur bridging has apparently enhanced the formation of 1,2 products. Similar arguements have been used to explain the tendency toward the formation of 1,2-addition products in the reaction of halogens and sulfenyl chlorides with conjugated dienes under kinetically controlled conditions.[3,13]

Because of the magnitude of the rate acceleration for **3b** and the predominance of trans 1,2-substitution product, with the absence of cis 1,2-substitution product, we feel that the cis and trans 1,4 ethers **1d** and **2d** arise mainly from syn and anti S_N2' attack of solvent on bridged ion **9** rather than from a second open allylic cation. Their formation via the route **3b** → (**1b** + **2b**) → **1d** + **2d** is untenable, since **1b** and **2b** are stable under the reaction conditions. Thus the product data suggest that both syn and anti S_N2'-like processes are probably energetically comparable. A similar conclusion was recently expressed by Heasley *et al.*[13] based on stereochemical observations for the addition of bromine to dienes. In our case the mixture of 1,4 ethers probably results from a balancing of electrostatic repulsion between the positively charged sulfur and the developing positive charge on TFE's oxygen which favors anti solvent attack and nonbonded interactions which favor syn attack.[5]

The product distribution from all three sulfides, **1b, 2b,** and **3b,** are very similar. The fact that each gives approximately a 14:13:73 ratio of **1d**:**2d**:**3d** suggests that sulfur is participating in the 1,4 sulfides, **1b** and **2b,** just as it was in **3b.** Such participation does not, however, result in large rate accelerations for **1b** and **2b;** their rates are comparable to that of **5b.** The fact that PNB's **1b** and **2b** are about as reactive as the unsubstituted PNB, **5b,** does, however, suggest some sulfur assistance, since in the absence of participation, the electron-withdrawing effect of PhS should cause **1b** and **2b** to solvolyze more slowly than **5b.** Estimates of the unassisted rates for **1b** and **2b** were obtained via a Hammett plot using the rate data for model compounds **5b, 6b,** and **8b,** together with the known σ_I values for phenylthio (0.21) and phenylsulfonyl (0.52) groups.[11] The results suggest that the observed rate of **1b** is about 30 times faster than expected in the absence of participation and that the rate of **2b** is about 10 times faster. These rate accelerations are modest, and indicate that these internal S_N2' reactions show little stereospecificity and are not very facile. In fact, if one makes the reasonable assumption that **1b** and **2b** solvolyze by two pathways, a k_Δ pathway involving sulfur assistance and a k_s pathway involving solvent assistance,[14-16] one calculates that the amount of reaction which proceeds through the k_Δ pathway at 120 °C for **1b** is 96%[17] and for **2b** is 91%. The intervention of a small amount of a solvent assisted, k_s pathway could help explain the tendency of **1b** and **2b** to give less trans 1,2 ether, **3d,** and more 1,4 ethers, **1d** and **2d,** since k_s pathways would be expected to yield primarily unrearranged product of inverted configuration.

In recent years Bordwell[6] has searched, with little success, for examples of S_N2' reactions. His studies were conducted under conditions where substrate ionization was discouraged and nucleophilic attack encouraged. As a result of these studies, serious doubts concerning the attainability of concerted S_N2' reactions were raised. In this work we searched for intramolecular S_N2' reactions under conditions where the leaving group was the leading element of the reaction. Under these conditions one might expect that the incipient positive charge would encourage such a reaction. However, even under these apparently favorable conditions, we find, with our

substrate, that syn and anti S_N2' processes are energetically similar and that in either case they are not very facile.

Experimental Section

The ^1H NMR spectra were obtained on a Varian A-60 or JEOL MH-100 NMR spectrometer with Me_4Si as an internal standard. Infrared spectra were recorded with a Perkin-Elmer 337 spectrometer as neat liquids or as solutions as indicated. Gas–liquid partition chromatography was done on an Aerograph A90-P3 (thermal conductivity detector) gas chromatograph. All melting points are uncorrected.

Cooxidation of 1,3-Cyclohexadiene and Thiophenol. A modification of the procedure of Oswald[9] was used to prepare a mixture of 4- and 6-(phenylthio)-2-cyclohexenols. In a typical experiment 20.8 g (0.25 mol) of 1,3-cyclohexadiene and 2.9 g (0.04 mol) of freshly distilled diethylamine dissolved in 250 ml of methanol were cooled to 0 °C by means of an ice–water bath. Oxygen was bubbled through the solution and the flow adjusted so that the gas left the reaction mixture at a rate of 1 bubble every 10–15 s. Freshly distilled thiophenol (47.6 g, 0.43 mol) was added dropwise over a period of 8 h. The temperature was maintained at 0–5 °C for a total of 16 h and then allowed to warm to room temperature. The oxygen bubbling was continued for a total of 24 h.

The reaction mixture was cooled to −78 °C and the crystalline precipitate was filtered by suction, washed with a small amount of cold methanol, and dried to yield 29.5 g (97%) of diphenyl disulfide, mp 59–61 °C. The methanol solution was concentrated in vacuo and the residual product pumped out for 2 h at room temperature (0.2 mm) to remove any traces of solvent. The yield of unpurified alcohols was 29.2 g (99.0%).

The unpurified alcohols were chromatographed on a column of Florisil (Floridin C, 100/200 mesh) slurry packed in hexane. In a typical experiment, 4.1 g of unpurified alcohol was placed on the column (2.5 × 100 cm) and eluted with 1.5 l. of 50% benzene in hexane, 2.5 l. of 90% benzene in hexane, 1.5 l. of benzene, 1.5 l. of 8% ether in benzene, 1 l. of 50% ether in benzene, and 2.3 l. of 80% ether in benzene. Similar results could be obtained eluting first with hexane followed by 5% ether in hexane and gradually increasing the ether content.

Fractions of 20–25 ml were collected and analyzed by TLC on 10 × 20 cm silica gel HF plates using benzene and ether as the eluents.

Fraction 1: 0.18 g (3.7%); one spot on TLC, R_f 1 in benzene, identical with that of known diphenyl disulfide.

Fraction 2: 1.22 g (25.1%); one major spot with R_f 0.08–0.1 (benzene) and R_f 0.65 (ether). This fraction contains some material which has R_f values identical with those in fraction 3. ^1H NMR (100 MHz, $CDCl_3$) δ 1.40–2.44 (m, 4 H, $-CH_2-$), 3.08–3.88 (m, 2 H, CHS, OH–D_2O exchangeable), 4.13 (broad d, 1 H, J = 6 Hz, CHO), 5.42–6.04 (m, 2 H, vinyl), 6.84–7.88 (m, 5 H, ArH). This fraction was subsequently shown to be nearly pure **3a**.

Fraction 3: 2.32 g (47.8%); one spot when the TLC plate was developed in benzene (R_f 0.04). With ether development of the TLC plate two spots appeared (R_f 0.52 and 0.45). ^1H NMR (100 MHz, $CDCl_3$) δ 1.12–2.26 (m, 4 H, CH_2), 3.8 (s, 1 H, OH–D_2O exchangeable), 3.78 (broad s, 1 H, CHS), 4.18 (broad s, 1 H, CHO), 5.8–6.2 (m, 2 H, vinyl), 7.2–7.96 (m, SH, ArH). Fraction 3 was subsequently shown to be an approximately equal mixture of **1a** and **2a**.

Fraction 4: 0.32 g (6.5%); two spots with R_f (ether) 0.67 and 0.76. The spot at 0.76 did not absorb I_2 but did show under the UV lamp.

Fraction 5: 0.52 g (10.7%); one spot, R_f (ether) 0.79, which did not absorb I_2.

Fraction 6: 0.30 g (6.2%); contains series of components with R_f values (ether) ranging from 0 to 0.03 plus traces of fractions 2–5. It was a highly colored material.

The ^1H NMR spectra ($CDCl_3$) of fractions 4 and 5 showed none of the absorpiton shown in the spectra of fractions 2 and 3. No spectrum was run on fraction 6. Other column chromatography gave similar results.

Diimide Reduction of the Cooxidation Products. The procedure of Baird[18] was used to reduce the products of the cooxidation of 1,3-cyclohexadiene and thiophenol. To a stirred solution of the cooxidation reaction mixture (11.76 g, 0.057 mol, used without purification) and 58.2 g (0.3 mol) of potassium azodicarboxylate in 250 ml of methanol was added dropwise 36 g (0.6 mol) of acetic acid in 50 ml of methanol. As the addition proceeded, the temperature rose until the methanol gently refluxed. The reaction mixture was stirred for an additional 1 h after the acetic acid addition was complete. The ^1H NMR spectrum of an aliquot revealed the presence of vinylic absorption. An additional 42 g (0.216 mol) of potassium azodicarboxylate was added to the reaction mixture and 26.4 g (0.44 mol) of acetic acid added to the cooled reaction mixture. Stirring was continued for 5 h after the addition, during which time the mixture was allowed to warm to room temperature. A water-soluble white solid had formed during the reaction. Water was added to the reaction mixture to dissolve the solid and was extracted several times with ethyl ether. The combined ethereal extracts were washed ($NaHCO_3$, saturated NaCl solution), dried ($MgSO_4$), and concentrated in vacuo. The resulting solid was filtered and washed with ether. The ethereal filtrate was washed as before, dried, and concentrated. A ^1H NMR of the residue indicated the presence of vinyl protons. The integrated ratio of aromatic protons to vinyl protons was 3.2:1. This corresponds to a 25% reduction using azodicarboxylate.

Complete reduction of the mixture was accomplished with *p*-toluenesulfonylhydrazine[19] using a modification of the procedure described by Garbisch.[20] A solution of the residue for the azodicarboxylate reduction and 55.8 g (0.3 mol) of *p*-toluenesulfonylhydrazine (Aldrich Chemical Co.) in 300 ml of *p*-dioxane and 50 ml of triethylamine was refluxed under nitrogen for 24 h. The dioxane was removed in vacuo, and the residue taken up in ether. The ethereal solution was washed with 3 N potassium hydroxide, 3 N HCl, and 5% $NaHCO_3$, and dried over anhydrous $MgSO_4$. Removal of the ether in vacuo yielded 17.02 g (143%) of a dark brown liquid. ^1H NMR analysis indicated that the excess weight present in the reduced material came from unreacted *p*-toluenesulfonylhydrazine (or an impurity in that material) and dioxane.

GLC analysis of the reduction mixture on a 5-ft column of 5% Carbowax 20M on 60/80 mesh Chromosorb W at 190 °C showed two major peaks with retention times of 22.5 min for the 1,2 isomer and 53.7 min for the 1,4 isomers. The relative amount of the 1,2 and 1,4 isomers was obtained by cutting out and weighing the individual peaks. The average result of two determinations was that 34.5 ± 1.9% of the reduced alcohols were 1,2 isomer(s) and 65.5 ± 1.0% were 1,4 isomers. This is consistent with the results obtained in the column chromatography of the cooxidation reaction mixture (see above).

A similar tosylhydrazine reduction of fraction 2 from the cooxidation chromatogram gave **7a** with only traces of the 1,4 alcohols as established by GLC, ^1H NMR, and IR comparison with authentic **7a**.

***cis*-4-(Phenylthio)cyclohexanol).** The general method of Eliel[21] was used to prepare a 26% yield of *cis*-4-(phenylthio)cyclohexanol (mp 74–76 °C, lit.[22] 73–75 °C) from *trans*-4-hydroxycyclohexyl tosylate[23] and sodium thiophenolate. Spectral properties follow: IR ($CHCl_3$) 3600 (sharp), 3450 (broad), 2925, 1580, 1420, 1350, 1290, 1200 (broad), 1090, 1045, 1025, 995, 955, 885, 860 cm^{-1}.

***trans*-2-(Phenylthio)cyclohexanol (7a).** A solution of 27.5 g (0.25 mol) of thiophenol and 24.5 g (0.25 mol) of cyclohexene oxide in 75 ml of dry ethanol containing 0.5 g (0.22 g-atom) of sodium was allowed to stand with occasional swirling for 4 days. The reaction mixture was neutralized with CO_2 and few drops of water, filtered, and concentrated in vacuo. Distillation of the residue yielded 34.8 g (61.5%) of the desired product, bp 105–106 °C (0.25 mm) [lit.[24] 130–132 °C (1 mm)]. Slight cooling of the distillate induced crystallization of a solid (mp 37–42 °C) which did not remelt on warming to room temperature. Spectral properties follow: IR (thin film) 3450 (broad), 3050, 2925, 2850, 1580, 1470, 1430, 1380, 1350, 1260, 1230, 1195, 1150, 1120, 1070, 1040, 1025, 1010, 960, 890, 860, 845, 790, 750, 740, 690 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.62–7.17 (m, 5 H, ArH), 3.60–3.12 (m, 1 H, CHO) 3.14 (s, 1 H, OH, disappears with added D_2O), 3.05–2.45 (m, 1 H, CHS), 2.42–0.90 (m, 8 H, CH_2).

Anal. Calcd for $C_{12}H_{16}OS$: C, 69.19; H, 7.74. Found: C, 69.26; H, 7.82.

***cis*-2-(Phenylthio)cyclohexanol).** A very low yield of *cis*-2-(phenylthio)cyclohexanol was obtained from the free-radical addition of thiophenol to 1-cyclohexenyl acetate.[25] The addition was attempted by irradiating a 5:1 mole ratio solution of thiophenol and 1-cyclohexenyl acetate with a Sylvania sun lamp. Catalysis was also accomplished by benzoyl peroxide. Reaction times up to 200 h and temperatures up to 150 °C were employed. Neither method gave satisfactory yields and the product was contaminated by diphenyl disulfide.

The reaction mixture was taken up in ether, washed with excess 3 N NaOH, then with water, dried ($MgSO_4$), and concentrated. Distillation of the residue yielded three fractions boiling between 45 and 85 °C (2 mm). From the pot residue a small amount of the acetate was separated by preparative GLC (8-ft 25% SE-30 on 60/80 mesh Chromosorb P, 200 °C): 60-MHz ^1H NMR ($CDCl_3$) δ 7.62–7.11 (m, 18 H, ArH), 5.23–4.94 (m, 0.7 H, CHO), 3.60–3.26 (m, 1 H, CHS), 2.50–1.10

(m, 8 H, CH_2), 1.90 (s, 2.9 H, $OCOCH_3$). Even with preparative GLC the diphenyl disulfide was not completely eliminated.

GLC analysis on the 5-ft 5% Carbowax 20M column at 185 °C showed one peak with a retention time of 28.2 min, which was slightly longer than the retention time of the trans isomer.

Anal. Calcd for $C_{12}H_{16}OS$: C, 69.19; H, 7.74. Found: C, 60.33; H, 7.81.

Trimethylsilyl Ethers. To a solution of 2.5 mol of the appropriate alcohol in 10 ml of dry benzene containing 1 ml of dry pyridine was added by means of a hypodermic syringe 1.0 ml of trimethylchlorosilane (TMCS) (Pierce Chemical Co.). A white precipitate of pyridine hydrochloride formed immediately. After standing with occasional shaking for 5–10 min, the solution was centrifuged. The supernatant liquid was analyzed by gas–liquid partition chromatography on a 5-ft column of 5% Carbowax 20M on Chromosorb W 60/80 mesh. The sample was introduced directly onto the column.

GLC analysis of an authentic mixture of the trimethylsilyl ethers of *cis*- and *trans*-2-(phenylthio)cyclohexanol showed two peaks with the same retention time as the individual ethers. Under no conditions, however, was baseline separation achieved.

Cooxidation Reaction Reduction Products and Trimethylchlorosilane. GLC analysis of the trimethylsilyl ethers of the reduced (diimide) alcohols obtained from crude cooxidation reaction mixture showed two peaks with retention times of 9.4 (1,2 isomers, peak 1) and 16.0 min (1,4 isomers, peak 2) at 190 °C. A chromatogram run at 160 °C still exhibited just two peaks at 22.6 (1,2 isomers) and at 42.5 min (1,4 isomers). At 150 °C two peaks were again observed. The first was fairly sharp and had a retention time of 30.1 min which corresponds quite closely with the retention time (under the same conditions) of the known trans 1,2 isomer (31.8 min). No evidence of a peak corresponding to the cis 1,2 isomer (retention time of 35.4 min) was observed. The second peak observed in the chromatogram run at 150 °C was a very broad, unsymmetrical peak which began coming off the column after 45 min. The peak slowly increased to its maximum height which occurred after 60 min and then dropped sharply to the baseline. No resolution of the 1,4 isomers is possible under these conditions. Peaks were identified by comparison of retention times with those of authentic samples of the Me_3Si ethers prepared from **7a**, and *cis*- and *trans*-4-(phenylthio)cyclohexanol.

***trans*- and *cis*-4-(Phenylthio)-2-cyclohexenyl *p*-Nitrobenzoate (1b and 2b).** A solution of 8.25 g (0.04 mol) of *trans*- and *cis*-4-(phenylthio)-2-cyclohexenol (**1a** and **2a**, fraction 3 from cooxidation chromatogram) in 125 ml of dry pyridine was cooled to 0 °C. Then 7.45 g (0.04 mol) of *p*-nitrobenzoyl chloride was added and the solution stirred for 2 h. The reaction mixture was poured into ether, washed with cold 3 N HCl, 10% $NaHCO_3$, and saturated NaCl solution, and dried ($MgSO_4$). The ether was removed using a rotary evaporator at aspirator pressure to give 13.3 g (93%) of a pale yellow solid, mp 49–85 °C. TLC on silica gel (HF) revealed two spots (R_f 0.53 and 0.41) when eluted with 20% ethane in hexane (v/v).

The mixture was chromatographed on a 4.5 × 100 cm column slurry packed with silica gel in hexane, eluting with 5% ether in hexane (v/v). Fractions (50 ml) were collected and analyzed by TLC (20% ether in hexane, v/v). In any given run three major fractions were obtained. The first, accounting for between 20 and 25% of the total collected weight, was a yellow solid, mp 75–78 °C, and exhibited a single spot on TLC (R_f 0.53). The middle fraction (55–65% of the total) contained both isomers. The third fraction (15–20% of the total), also a yellow solid, mp 100–102 °C, was the other isomer (R_f 0.41). In separate experiments the compound with R_f 0.41 was shown to be the cis isomer (**2b**), thus identifying the other (R_f 0.53) as **1b** (see oxidation of **1a** and **2a**).

Recrystallization of **2b** from 1:1 ethyl acetate–hexane (v/v) yielded a yellow solid: mp 103–104 °C; IR (KBr) 3050, 2950, 2850, 1720, 1600, 1520, 1480, 1440, 1340, 1310, 1270, 1120, 1100, 940, 885, 870, 820, 770, 740, and 715 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.5–2.64 (m, 4 H, ring methylenes), 3.8–4.12 (broad s, 1 H, CHS), 5.44–5.76 (broad s, 1 H, CHO), 5.84–6.44 (m, 2 H, vinyl), 7.0–7.92 and 7.96–8.76 (m, 9 H, aromatic).

Oxidation of **1b** (1.0 g) with 2 equiv of hydrogen peroxide in glacial acetic acid gave 0.91 g of crude product which upon recrystallization from ethyl acetate gave 0.51 g (47%) of **6b** as a white, granular solid: mp 169–170 °C dec; IR ($CHCl_3$) 3020 (s), 1720 (s), 1605 (m), 1505 (s), 1440 (m), 1350 (s), 1310 (s), 1270 (s), 1145 (s), 1135 (s), 1115 (s), 1100 (s), 1085 (s), 904 (m), 895 (m), 710 (m), 690 (m), 635 (m), 615 cm^{-1} (m); ^1H NMR (100 MHz, $CDCl_3$) δ 1.44–2.6 (m, 4 H, ring methylenes), 3.78–4.16 (broad singlet, 1 H, $CHSO_2$), 5.36–5.64 (broad singlet, 1 H, CHOCO), 6.0–6.20 (m, 2 H, vinyl), 7.28–8.40 (m, 9 H, aromatic).

Anal. Calcd for $C_{19}H_{17}NO_6S$: C, 58.90; H, 4.42; N, 3.61. Found: C, 59.12; H, 4.37; N, 3.60.

Reduction of *cis*-4-(Phenylthio)-2-cyclohexenyl *p*-Nitrobenzoate (2b). A solution of 0.271 g (7.6×10^{-4} mol) of the *p*-nitrobenzoate with the smaller R_f value (which this experiment shows to be **2b**) in 10 ml of benzene was mixed with a solution of 0.15 g (1.6×10^{-4} mol) of tris(triphenylphosphine)rhodium(I) chloride and allowed to stir under 1 atm of hydrogen at room temperature for 15 h. The solvent was removed by rotary evaporation and the residue chromatographed on Florisil eluting with 10% by volume ether in hexane. A single fraction was obtained whose ^1H NMR spectrum ($CDCl_3$) was identical with that of authentic *cis*-4-(phenylthio)cyclohexyl *p*-nitrobenzoate. The TLC R_f value likewise was identical with that of the cis isomer.

***cis*- and *trans*-4-(Phenylthio)-2-cyclohexenyl 3,5-Dinitrobenzoate (2c and 1c).** A solution of 3.9 g (1.89×10^{-2} mol) of a 1:1 mixture of *cis*- and *trans*-4-(phenylthio)-2-cyclohexen-1-ol in 25 ml of dry pyridine was cooled to 0 °C. Then 4.7 g (2.0×10^{-2} mol) of 3,5-dinitrobenzoyl chloride was added slowly and the solution stored in the refrigerator for 48 h. Pouring the reaction mixture into ice-cold 3 N HCl resulted in the precipitation of a yellow solid, which was filtered, washed with 3 N HCl, water, 10% sodium bicarbonate solution, and finally water, and thoroughly dried to yield 6.9 g (91%) of crude ester.

Recrystallization of the crude material from 20% ethyl acetate in hexane (v/v) yielded 2.7 g of yellow needles, mp 118.5–120 °C. The analysis of this solid showed it to be nearly pure and based on the results of the *p*-nitrobenzoates, it was assumed (later proved correct) to be the trans isomer (**1c**).

The residue, dissolved in a small amount of carbon tetrachloride, was chromatographed on a silica gel column with elution by 1% ethyl acetate in carbon tetrachloride (v/v). Following their separation, each isomer was recrystallized. Recrystallization of **1c** from 20% ethyl acetate in cyclohexane (v/v) gave a yellow solid: mp 120.5–121.5 °C; IR ($CHCl_3$) 3100, 2960, 2890, 1720, 1620, 1525, 1460, 1350, 1280, 1160, 1090, 1075, 1025, 995, 895, 880 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 9.30–8.90 (m, 3 H, ArH), 7.55–7.15 (m, 5 H, ArH), 6.20–5.95 (m, 2 H, vinyl), 5.70–5.45 (m, 1 H, CHO), 4.10–3.80 (m, 1 H, CHS), 2.40–1.70 (m, 4 H, CH_2CH_2).

Anal. Calcd for $C_{19}H_{16}N_2O_6S$: C, 56.99; H, 4.03; N, 7.00. Found: C, 57.40; H, 4.27; N, 7.03.

Recrystallization of the other isomer from 1:1 carbon tetrachloride–cyclohexane gave **2c** as a yellow solid: mp 114.5–115.5 °C; IR ($CHCl_3$) 3100, 2960, 1720, 1620, 1550, 1350, 1270, 1160, 1075, 1000, 985, 900, 880 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 9.30–9.00 (m, 3 H, ArH), 7.55–7.10 (m, 5 H, ArH), 6.15–5.90 (m, 2 H, vinyl), 5.70–5.45 (m, 1 H, CHO), 3.95–3.70 (m, 1 H, CHS), 2.30–1.90 (m, 4 H, CH_2CH_2).

Anal. Calcd for $C_{19}H_{16}N_2O_6S$: C, 56.99; H, 4.03; N, 7.00. Found: C, 56.58; H, 4.17; N, 6.88.

Reduction of *cis*-4-(Phenylthio)-2-cyclohexenyl 3,5-Dinitrobenzoate (2c). The homogeneous catalytic reduction of *cis*-4-(phenylthio)-2-cyclohexenyl 3,5-dinitrobenzoate was effected as described for **2b** from 0.46 g (1.15×10^{-3} mol) of the ester with the smaller R_f value (vide supra) and 0.17 g of catalyst. Following reaction for 72 h and the usual workup, a yellow, crystalline solid was isolated which had mp 128–132 °C after recrystallization from 20% ethyl acetate in cyclohexane (v/v). TLC analysis after one elution (20% ether in hexane) showed a single spot with an R_f value identical with that of the known cis saturated ester. Multiple elutions showed two spots which could be ascribed to a mixture of the cis saturated ester and the cis unsaturated ester. No spot corresponding to **1c** was observed.

Oxidation of *trans*- and *cis*-4-(Phenylthio)-2-cyclohexenol (1a and 2a). A solution of 1.064 g (5.16×10^{-3} of a 1:1 mixture of **1a** and **2a** (fraction 3 from the cooxidation chromatogram) in 5 ml of dioxane was combined with a solution of 1.35 g (5.97×10^{-3} mol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 20 ml of dioxane in a 50-ml Erlenmeyer flask and stoppered. The reaction mixture was allowed to stand with occasional swirling for 48 h at room temperature. A solid formed which was filtered and the filtrate concentrated by rotary evaporation. Column chromatography of the residue on silica gel with elution by ether yielded 1.05 g (84%) of a colorless liquid: IR (thin film) 3050, 2950, 1860, 1690, 1590, 1490, 1440, 1380, 1250, 1210, 1120, 1090, 1070, 1025, 830, 750, and 695 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.15–6.75 (m, 5 H, ArH), 6.65–6.35 (q, 1 H, vinyl), 5.75–5.45 (q, 1 H, vinyl), 3.90–3.55 (m, 1 H, CHS), 2.80–1.80 (m, 4 H, CH_2).

Anal. Calcd for $C_{12}H_{12}OS$: C, 70.55; H, 5.92. Found: C, 70.64; H, 5.82.

The spectral data combined with the single TLC spot and a single GLC peak confirm that the product is the expected 4-(phenylthio)-cyclohex-2-enone. This experiment shows that fraction 3 contains two alcohols which are epimers. Since one of the two *p*-nitrobenzoates

derived from this fraction was shown to be the cis 1,4 isomer **2b** (see above), the identity of the other benzoate as **1b** is established.

***trans*-6-(Phenylthio)-2-cyclohexenyl *p*-Nitrobenzoate (3b).** The reaction of 2.74 g (1.83×10^{-2} mol) of *trans*-6-phenylthio-2-cyclohexenol with 3.80 g (1.9×10^{-2} mol) of *p*-nitrobenzoyl chloride was effected as described above. The product was recrystallized from absolute ethanol to yield 4.6 g (71%) of pale yellow needles: mp 95.5–97 °C; IR (KBr) 3100, 3075, 3030, 2960, 2910, 2840, 1710, 1600, 1590, 1510, 1475, 1440, 1310, 1250, 1165, 1095, 1020, 1010, 910, 870, 860, 780, 735, and 700 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.84 (m, 1 H), 2.28 (m, 3 H), 3.60 (m, 1 H, CHS), 5.6–6.24 (m, 3 H, CHO and vinyl), 7.24–7.64 (m, 5 H, ArH), 8.2 (A_2B_2, 4 H, NO_2ArH).

Anal. Calcd for $C_{19}H_{17}NO_4S$: C, 64.21; H, 4.82; N, 3.94. Found: C, 64.37; H, 4.75; N, 3.93.

***trans*-2-(Phenylthio)cyclohexyl *p*-Nitrobenzoate (7b).** *trans*-2-(Phenylthio)cyclohexyl *p*-nitrobenzoate was prepared in the usual way from 6.0 g (0.028 mol) of *trans*-2-(phenylthio)cyclohexanol and 6.0 g (0.032 mol) of *p*-nitrobenzoyl chloride. Recrystallization of the crude product yielded 5.6 g (56%) of white needles: mp 110.5–111.5 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 1.3–2.0 (m, 6 H, CH_2), 2.0–2.44 (m, 2 H, CH_2), 3.40 (m, 1 H, CHS, J = 9.2, 9.2, 4.1 Hz), 5.14 (m, 1 H, CHO, J = 9.2, 9.2, 4.1 Hz), 7.2–7.6 (m, 5 H, ArH), 8.16 (A_2B_2, 4 H, NO_2ArH); IR (KBr) 3065, 2925, 2850, 1715, 1600, 1515, 1465, 1435, 1340, 1315, 1265, 1125, 1095, 1025, 1010, 945, 935, 900, 865, 845, 825, 775, 750, 740, 710, 685 cm^{-1}.

Anal. Calcd for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.36; N, 3.92. Found: C, 63.84; H, 5.26; N, 3.95.

***cis*-4-(Phenylthio)cyclohexyl *p*-Nitrobenzoate.** In the usual manner, 2.0 g (9.6×10^{-3} mol) of *cis*-4-(phenylthio) cyclohexanol was reacted with 1.95 g (1.05×10^{-2} mol of *p*-nitrobenzoyl chloride to yield 2.1 g (61.5%) of white solid: mp 84.5–85 °C from absolute ethanol; IR (KBr) 3100, 3075, 2950, 1710, 1600, 1590, 1520, 1480, 1440, 1350, 1320, 1270, 1115, 1100, 1080, 930, 900, 870, 840, 805, 780, 745, and 715 cm^{-1}.

Anal. Calcd for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.36; N, 3.92. Found: C, 63.84; H, 5.46; N, 3.92.

***trans*-4-Phenylsulfonyl-2-cyclohexenyl 3,5-Dinitrobenzoate (6c).** Reaction of 2 equiv of H_2O_2 in glacial acetic acid with *trans*-4-(phenylthio)-2-cyclohexenyl 3,5-dinitrobenzoate (**1c**) prepared in the same manner as described for **1b** gave after recrystallization from acetone/water (9.5/0.5), 0.37 g (69%) of **6c** as pale yellow needles: mp 183–184 °C dec; IR (thin film) 3100 (m), 1330 (s), 1630 (m), 1550 (s), 1450 (m), 1345 (s), 1305 (s), 1275 (s), 1165 (s), 1145 (s), 1070 (m), 1000 (m), 885 (m), 725 (s), 690 cm^{-1} (s); ^1H NMR (100 MHz, $CDCl_3$) δ 1.6–2.6 (m, 4 H, ring methylenes), 3.95 (broad singlet, 1 H, $CHSO_2$), 5.52 (broad singlet, 1 H, CHOCO), 6.1–6.48 (m, 2 H, vinyl), 7.48–8.18 (m, 5 H, aromatic), 8.98–9.42 (m, 3 H, aromatic).

Anal. Calcd for $C_{19}H_{16}N_2O_8S$: C, 52.78; H, 3.73; N, 6.48. Found: C, 52.83; H, 3.52; N, 6.49.

Kinetic Procedures. Reaction rates were followed by titrating the production of *p*-nitrobenzoic acid or 3,5-dinitrobenzoic acid with NaOH (0.01 N) to the blue end point of bromothymol blue–bromocresol purple mixed indicator. Titration of standard solutions of either 3,5-dinitrobenzoic acid or *p*-nitrobenzoic acid in 2,2,2-trifluoroethanol (TFE) gave experimental titers that were within 4% of calculated titers. TFE was purified according to Dafforn and Streitweiser[26] and stored over 4A molecular sieves.

Solutions (0.01–0.15 M) were prepared by dissolving the weighed substrate and diluting with TFE in a 25-ml volumetric flask. Aliquots (2.5 ml) were transferred to ampules, sealed, and placed in a constant temperature bath. All temperatures from 50 to 100 °C are accurate to within ±0.05 °C while temperatures reported 110–120 °C are within ±0.2 °C. At appropriate time intervals, ampules were withdrawn and quenched in dry ice/acetone. After returning to room temperature, a 2-ml aliquot was pipetted into a 25-ml Erlenmeyer flask containing ca. 2 ml of H_2O and ca. 100 mg of indicator, and titrated with NaOH (0.01 N) to a light blue end point, the final volume in all cases being adjusted to 100 ml by addition of H_2O. All titrations were performed using a Koch self-filling microburet which could be read to 0.01 ml.

Excellent first-order rate plots were obtained to about 2–3 half-lives. Rate constants were computed from $\log (V_\infty - V_t) = -kt/2.03$ plots by the method of least squares. Unless otherwise noted, experimental infinity titers were used in all computations.

Product Studies. A. *trans*-6-(Phenylthio)-2-cyclohexenyl *p*-Nitrobenzoate (3b) in Buffered 2,2,2-Trifluorethanol. A solution (200 ml) of 1.401 g of **3b** (0.02 M) and 0.848 g of 2,6-lutidine (0.04 M) in TFE was sealed with a 300-ml round-bottom flask and heated at 65 °C for 10 half-lives. The solvent (TFE) was removed through a 10-cm Vigreux column until ca. 5 ml of liquid remained. The residue was taken up in ether (75 ml), washed twice with H_2O (15 ml), twice with 5% HCl (15 ml), and saturated $NaHCO_3$ (30 ml), and dried over K_2CO_3. Ether was removed through a 10-cm Vigreux column to give 2.535 g (ca. 60% TFE by ^1H NMR) of a pale amber-green liquid.

Table III. Chemical Shift Data and Splitting Patterns

Registry no.	Compd	Multiplicity[a]	δ_{CHS}[b]
60789-34-6	**3a**	Rough h	3.23
60789-35-7 (**1a**)	(**1a** + **2a**)	Broad s	3.78
60789-36-8 (**2a**)			
	3b	h	3.60
	1b	Broad s	3.96
	2b	Broad s	3.90
60789-37-9	**3d**	h	3.40
60789-38-0 (**1d**)	(**1d** + **2d**)	Broad s	3.82[c]
60789-39-1 (**2d**)			

[a] s = singlet, h = heptet. [b] Chemical shifts are in parts per million downfield from Me_4Si and the center of the signal is reported. [c] Estimated center.

The crude material was examined for the presence of elimination products (diene). The ^1H NMR of the crude material manifested the presence of an olefinic multiplet centered at ca. δ 5.9. The ratio of olefinic H to aromatic H to ring CH_2 was 2:5:4, as would be expected for the phenylthio substituted 2-cyclohexenyl trifluoroethyl ethers. No olefinic signals which could be ascribed to diene were present.

TLC analysis of the crude mixture on silica gel (5% ether/pentane, UV indicator) manifested the presence of three major components, R_f 0.49, 0.39, 0.16. Dry column chromatography (silica gel, 5% ether/pentane) and collecting the fractions by elution in the standard manner gave the separated components.

Fraction 1 (shown below to be a 10:10:80 mixture of **1d**, **2d**, and **3d**) consisted of 0.758 g (68% of theory) of a colorless liquid exhibiting two spots on TLC (R_f 0.49, 0.39); ^1H NMR (100 MHz, $CDCl_3$) δ 1.46–2.54 (m, 4 H, ring methylenes), 3.24–3.56 and 3.60–4.38 (heptet, overlapping quartets, J_{HF} = 8.7 Hz, and multiplets, methine and OCH_2CF_3, total of 4 H), 5.54–6.2 (m, 2 H, vinyl), 6.88–8.08 (m, 5 H, aromatic).

Anal. Calcd for $C_{14}H_{15}F_3OS$: C, 58.33; H, 5.25. Found: C, 58.50; H, 5.39.

Fraction 1 consisted of a mixture of 6- and 4-(phenylthio)-2-cyclohexenyl 2,2,2-trifluoroethyl ethers (**1d**, **2d**, and **3d**). Double resonance experiments were performed on fraction 1 in order to properly assign the spectrum. They rest on the fact that in **1d** and **2d** both the CHS and CHO protons are adjacent to vinyl protons but not to each other while in **3d** only the CHO and not the CHS proton is adjacent to a vinyl proton. These experiments are described below. Irradiation of the vinyl multiplet at 570, 580, or 587 Hz (note Hz × 0.01 = δ) had no effect on the heptet at δ 3.24–3.56 and conversely irradiation of the heptet at 338 Hz also had no affect on the multiplicity of the vinyl pattern. Irradiation of the ring methylenes at 204 Hz altered the multiplicity of the vinyl pattern and collapsed the heptet to a rough doublet, J = 6.0 Hz. The decoupling data were consistent with assigning the heptet at δ 3.24–3.56 to CHS of 6-(phenylthio)-2-cyclohexenyl 2,2,2-trifluoroethyl ether. Decoupling experiments performed with *trans*-6-(phenylthio)-2-cyclohexenol manifested the same behavior of CHS. Chemical shift data for CHS of **1a**, **2a**, and **1b** relative to CHS of **3a** and **3b**, respectively, supported the assignment. Thus the chemical shifts of the CHS protons in 1 (**a**, **b**, or **d**) and 2 (**a**, **b**, or **d**) are consistently further downfield than those of 3 (**a**, **b**, or **d**); see Table III.

Analysis of the coupling constants (–OCH^a–CH^bSPh–CH^cH^d–) for **3d** gave J_{ab} = 6.0, J_{bc} = 8.0, and J_{bd} = 2.8 Hz. The analogous set of coupling constants for **3b** is 7.0, 9.1, and 3.0 Hz, which supports the trans-diequatorial conformation for **3d**. Furthermore, these values are in agreement for those reported for shikimic acid.[27]

Thus the CHS heptet at δ 3.40 was assigned solely to *trans*-6-(phenylthio)-2-cyclohexenyl 2,2,2-trifluoroethyl ether (**3d**). Expansion and careful integration of the signals at δ 3.40–4.38 gave an 80/20 ratio of **3d** to (**1d** + **2d**).

Fraction 2 gave 0.028 g (2.5% of theory) of a liquid exhibiting one spot on TLC (silica gel, 5% ether/pentane UV indicator): R_f 0.39; ^1H NMR (100 MHz) δ 1.4–2.42 (m, 4 H, ring methylenes), 3.72–4.30 (multiplet and two quartets, J_{HF} = 9.0 Hz, 4 H, CHO, CHS, and OCH_2CF_3), 5.84–620 (m, 2 H, vinyl), 6.90–8.04 (m, 5 H, aromatic). Irradiation of 408 Hz (ca. center of CHO envelope) and 382 Hz (ca. center of CHS envelope) changed the multiplicity of the vinyl pattern

at δ 5.84–6.20, consistent with the allylic nature of both methine protons. The height ratio of the quartet signals (OCH_2CF_3) at δ 3.90 and 3.88 was 51/49. The ^1H NMR data were consistent with the presence of *cis*- and *trans*-4-(phenylthio)-2-cyclohexenyl 2,2,2-trifluoroethyl ethers (**2d** and **1d**) in ca. equal amounts (51:49).

Fraction 3 gave 0.100 g (7% of theory) of material that slowly solidified. It was identified as *trans*-4-(phenylthio)-2-cyclohexenyl *p*-nitrobenzoate (**1b**). The ^1H NMR was identical with that of authentic **1b** as were TLC data. Recrystallization from ethyl acetate/cyclohexane gave pale yellow needles, mp 75.5–77 °C (no depression upon mixing).

Fraction 4 gave 0.008 g of a residue that remained unidentified.

B. *trans*-4-(Phenylthio)-2-cyclohexenyl *p*-Nitrobenzoate (1b) in Buffered 2,2,2-Trifluoroethanol. A solution of 1.164 g of **1b** (0.022 M) and 0.703 g of 2,6-lutidine (0.044 M) in TFE was solvolyzed at 97 °C for 10 half-lives. The workup is the same as that described for A. No ^1H NMR evidence for diene formation was found.

Fraction 1 gave 0.764 g (81% of theory) of a liquid exhibiting two spots on TLC (R_f 0.49, 0.39). ^1H NMR analysis showed fraction 1 to consist of 71% of *trans*-6-(phenylthio)-2-cyclohexenyl 2,2,2-trifluoroethyl ether (**3d**) and 20% of *cis*- and *trans*-4-(phenylthio)-2-cyclohexenyl 2,2,2-trifluoroethyl ethers (**2d** and **1d** in a 1:1 ratio).

Fraction 2 gave 0.028 g (3% of theory) of a liquid exhibiting one spot on TLC (R_f 0.39). The ^1H NMR manifested the presence of *cis*- and *trans*-4-(phenylthio)-2-cyclohexenyl 2,2,2-trifluoroethyl ether (**2d** and **1d**) in a 50/50 ratio.

Fraction 3 gave 0.019 g of a residue that remained uncharacterized.

C. *cis*-4-(Phenylthio)-2-cyclohexenyl *p*-Nitrobenzoate (2b) in Buffered 2,2,2-Trifluoroethanol. A solution of 0.7185 g of **2b** (0.021 M) and 0.469 g of 2,6-lutidine (0.043 M) was solvolyzed at 110 °C for 8 half-lives. The workup is the same as that described for A. No ^1H NMR evidence for diene formation was found.

Fraction 1 gave 0.387 g (66% of theory) of a liquid which by TLC and ^1H NMR analysis was consistent with a mixture of 75% of *trans*-6-(phenylthio)-2-cyclohexenyl 2,2,2-trifluoroethyl ether (**3d**) and 25% of *cis*- and *trans*-4-(phenylthio)-2-cyclohexenyl 2,2,2-trifluoroethyl ethers (**2d** and **1d** in a 43/57 ratio).

Fraction 2 gave 0.017 g (3% of theory) of a liquid which by TLC and ^1H NMR analysis was consistent with a 43/57 mixture of *cis*- and *trans*-4-(phenylthio)-2-cyclohexenyl 2,2,2-trifluoroethyl ethers (**2d** and **1d**).

Product Stability. A solution of 0.204 g (0.02 M) of a mixture of 71% of **3d** and 29% of (**1d** and **2d**), 0.116 g (0.02 M) of *p*-nitrobenzoic acid, and 0.152 g (0.04 M) of 2,6-lutidine in TFE was sealed and heated at 110 ± 0.2 °C for 49.5 h. The solvent was removed under reduced pressure until ca. 5 ml of liquid remained. The residue was taken up into ether (40 ml), washed with H_2O (15 ml), 5% HCl (15 ml), and saturated $NaHCO_3$ (15 ml), and dried (K_2CO_3). Removal of ether under reduced pressure resulted in quantitative recovery of the isomeric ethers. The percentage remained constant at 71% of **3d** and 29% of (**1d** + **2d**).

In order to discount the possibility that the above product distribution of 71% of **3d** and 29% of (**1d** + **2d**) represented an equilibrium mixture of the diastereometric ethers, the following experiment was performed. A solution of 0.40 g (0.02 M) of a mixture of 80% of **3d** and 20% of 69 (**1d** + **2d**) (obtained at 65 °C, 0.124 g (0.021 M) of *p*-nitrobenzoic acid, and 0.168 g (0.042 M) of 2,6-lutidine in TFE was sealed and heated at 110 ± 0.2 °C for 49 h. After the usual workup, 0.196 g (93%) of the mixture consisting of 83% of **3d** and 17% of (**1d** + **2d**) was recovered.

***cis*-4-(Phenylsulfonyl)-2-cyclohexenyl *p*-Nitrobenzoate (8b).** Two equivalents of H_2O_2 was added to a cooled and stirred slush containing glacial acetic acid (2 ml) and *cis*-4-(phenylthio)-2-cyclohexenyl *p*-nitrobenzoate (0.362 g). More acetic acid (3 ml) was added after the mixture was allowed to come to room temperature, and the reaction was continued for another 4.5 h at 25 °C. The solution was placed on a steam bath for 1 h and poured into ice-cold H_2O (10 ml). The crude sulfone (0.317 g) was recrystallized from ethyl acetate/hexane (1:4) to give 0.18 g (46%) of **8b** as pale yellow flakes: mp 103.5–105.5 °C; IR (KBr) 1715 (s), 1515 (s), 1438 (m), 1342 (s), 1330 (s), 1298 (s), 1265 (s), 1226 (m), 1130 (s), 1115 (s), 1100 (s), 1082 (s), 989 (s), 908 (m), 870 (m), 852 (m), 745 (s), 717 (s), 690 (s), 585 (s), 528 cm^{-1} (s); ^1H NMR δ 1.56–2.2 (m, 4 H, CH_2), 3.66–3.96 (rough triplet, 1 H, J = 6 Hz, $CHSO_2$), 5.45 (broad singlet, 1 H, CHOCO), 6.0–6.34 (m, 2 H, vinyl), 7.1–8.68 (overlapping multiplets, 9 H, aromatic).

Anal. Calcd for $C_{19}H_{17}NO_6S$: C, 58.91; H, 4.42; N, 3.61. Found C, 58.92; H, 4.54; N, 3.62.

Acknowledgments. The authors gratefully acknowledge financial support of this work by the National Science Foundation and wish to thank Mr. David Baillargeon for preparation and solvolysis of **8b**.

Registry No. —**1c**, 60789-40-4; **2c**, 60789-41-5; **6c**, 60789-42-6; **7a**, 35550-80-2; 2,2,2-trifluoroethanol, 75-89-8; 4-(phenylthio)cyclohex-2-enone, 60789-43-7; 3,5-dinitrobenzoyl chlorid, 99-33-2; 1,3-cyclohexadiene, 592-57-4; thiophenol, 108-98-5; *cis*-4-(phenylthio)-cyclohexanol, 34209-61-5; cyclohexene oxide, 930-68-7; *cis*-2-(phenylthio)cyclohexanol, 60789-44-8; 1-cyclohexenyl acetate, 1424-22-2; *p*-nitrobenzoyl chloride, 122-04-3; *cis*-4-(phenylthio)cyclohexyl *p*-nitrobenzoate, 60789-45-9.

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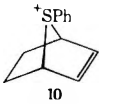

10

believe that this possibility is highly unlikely because of the overall similarity of the product ratios from **1b**, **2b**, and **3b**. Furthermore, the observed formation of cis **4** ether **2d** would not be expected from **10**.
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Iminosulfonium Salts and Iminosulfuranes from Thioethers, *N*-Chlorosuccinimide or *N*-Chlorobenzotriazole and Nitrogen-Containing Nucleophiles[1]

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Received August 27, 1976

A series of new *N*-alkyl-*S,S*-dimethyliminosulfonium and *N*-aralkyl-*S,S*-dimethyliminosulfonium salts (chlorides and picrates) has been prepared and characterized from alkyl- and aralkylamines, respectively, and dimethyl sulfide "activated" by *N*-chlorosuccinimide or *N*-chlorobenzotriazole. *N*-Chlorosuccinimide and *N*-chlorobenzotriazole have also been shown to be useful thioether "activators" for the preparation of *N*-aryliminosulfuranes, *N*-arylsulfonyliminosulfuranes, and *N*-acyliminosulfonium (and other) salts.

Although many types of N-substituted *S,S*-dialkyliminosulfonium salts and iminosulfuranes (sulfilimines) have been reported during the past decade, virtually no literature exists on the preparation and characterization of *N*-alkyl-*S,S*-dialkyliminosulfonium salts (**1**), $[R_2S^+NHR]\ A^-$.[2-5] Of the numerous methods available for preparing iminosulfonium salts and iminosulfuranes, the most important and general ones utilize sulfoxides or thioethers as starting materials. Sulfoxides[1b,6] and thioethers[7] are usually "activated" by certain electrophilic species at low temperatures followed by reaction with a nucleophilic nitrogen compound of low basicity. "Activation" consists in providing a leaving group attached to sulfur that can be readily displaced by nucleophiles at low temperatures (Scheme I).

In our earlier studies on the preparation of iminosulfonium salts and iminosulfuranes,[1b,6,7] we were unable to utilize primary aliphatic or aralkylamines successfully as the displacing nucleophiles with "activated" sulfoxides or thioethers. These amines, presumably as a result of their high basicity, are converted to salts, usually hydrochlorides, whereas the less basic arylamines, sulfonamides, and carboxamides effectively perform the nucleophilic displacement shown in Scheme I even though they are weak nucleophiles.

Almost simultaneously in 1972, Johnson, Bacon, and Kingsbury[5] and Vilsmaier and Sprügel[3] reported the reaction of *N*-chlorobenzotriazole (NCB) and *N*-chlorosuccinimide (NCS), respectively, with thioethers followed by reaction with amines to obtain N-substituted *S,S*-dialkyliminosulfonium salts. Although various amines were studied, cyclohexylamine[5] and benzylamine[3] were the only examples reported of the successful use of a primary aliphatic or aralkylamine for the preparation of **1** from "activated" thioethers.[8] In this paper we are reporting (a) the scope and limitations of the use of thioethers "activated" by NCB or NCS for the preparation of **1** and (b) an examination of the generality of NCB or NCS in the preparation of both known and previously unreported iminosulfuranes and iminosulfonium salts from arylamines, sulfonamides, or carboxamides and thioethers.[9]

Results and Discussion

Table I lists *N*-alkyl- and *N*-aralkyl-*S,S*-dimethylsulfonium salts (**2–14**) prepared (19–97% yields) either from NCS/dimethyl sulfide or NCB/dimethyl sulfide intermediates and alkyl- and aralkylamines. All salts were initially obtained as chlorides but in several cases it was necessary to convert them to picrates to reduce hygroscopicity and increase stability. Except in the cases of unstable compounds, correct elemental analyses were obtained (±0.3%).

With unstable and/or hygroscopic salts that could not be submitted for elemental analysis, NMR and IR spectra were run promptly; spectra were consistent with the proposed structures,[6,7] as was also the case with the compounds that analyzed correctly. Chlorides are water-soluble, white, crystalline solids; picrates are yellow, crystalline solids. Aqueous solutions of chlorides give an immediate precipitate with aqueous silver nitrate. All compounds listed in Table I are new with the exception of the *N*-benzylamine derivative. That compound was first reported by Vilsmaier and Sprügel[3] utilizing the NCS/dimethyl sulfide route but no spectral or analytical data were given. Their published melting point (71–72 °C) does not agree with ours (104–107 °C); they may not have been aware that the chloride is not only hygroscopic but is also difficult to separate from contaminating succinimide (see below).

The NMR spectra of the *N*-alkyl-*S,S*-dimethyliminosulfonium salts (**1**) clearly show that sulfur bears a high degree of positive charge which significantly deshields the *S*-methyl protons, thereby shifting the signals downfield to δ 3.0–3.4. This downfield shift of *S*-methyl protons is characteristic of iminosulfonium salts and iminosulfuranes.[6,7]

Scheme I

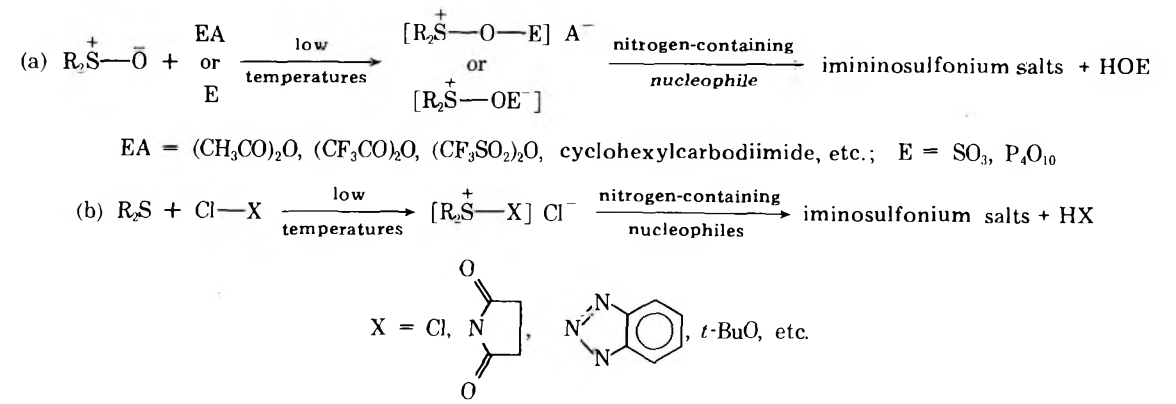
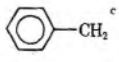
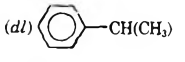
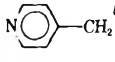


Table I. *N*-Alkyl and -Aralkyl-*S,S*-dimethyliminosulfonium Salts (1), $(CH_3)_2S^+NHR\ A^-$

Registry no.	R	(Compd)	A^-[a]	Yield, %	Mp (dec), °C	Remarks
60978-55-4	CH_3[b]	(2)	C	96	59–63	Hygroscopic; not analyzed
60978-57-6			P		185–190	Unstable; not analyzed
60978-86-1	CH_3CH_2[b]	(3)	C	85		Hygroscopic; not analyzed
60978-59-8			P	19	90–92	*d*
60978-60-1	$(CH_3)_2CH$[b]	(4)	C	63	55–58	Hygroscopic; not analyzed
60978-61-2			P		142–143	*d*
	$CH_3(CH_2)_3$[c]	(5)	C		Oil	Not analyzed
			P	42	Ill-defined	Not analyzed
60978-62-3	$(CH_3)_3C$[b]	(6)	C	58	164.5–165.5	*d*
60978-63-4	 [c]	(7)	C	78	150	*d*
60978-64-5	$(CH_3)_3C(CH_2)_4$[b]	(8)	C	80	108–110	*d*
60978-65-6	1-Adamantyl[c]	(9)	C	85	157.5–158.5	Hygroscopic; not analyzed
60978-67-8			P		188–189	*d*
60978-68-9	$CH_3(CH_2)_{15}$[b]	(10)	C	69	60	*d*
60978-69-0	$CH_3(CH_2)_{17}$[b]	(11)	C	66	70	*d*
35357-68-7	 [c]	(12)	C	80	104–107[e]	Hygroscopic; not analyzed
60978-71-4			P		112–113	*d*
60978-72-5		(13)	C	90+	168–169	*d*
60978-73-6	 [b]	(14)	C	83	95–96	Hygroscopic; unstable above −20 °C
60978-75-8			P		85–90	Unstable; not analyzed

[a] A^-: C = chloride; P = picrate. [b] NCB/$(CH_3)_2S$ used. [c] NCS/$(CH_3)_2S$ used. [d] Correct elemental analysis (±0.3%: C, H, N, S). [e] Lit[3] 71–72 °C. This compound is not stable.

In the preparation of 1 from thioethers and NCS or NCB, succinimide or benzotriazole is produced in equimolar quantities, respectively. This presented a separation problem with succinimide, whose solubility in many organic solvents parallels that of the desired salts. That difficulty could be overcome with stable chlorides by selectively extracting succinimide with ether from 1 in a Soxhlet extractor overnight. This separation procedure is fairly mild and protects hygroscopic salts from atmospheric moisture during workup. With unstable salts, however, the lengthy separation procedure is deleterious. In contrast, benzotriazole is usually easy to separate from 1 by fractional crystallization; thus, NCB is the reactant of choice in most cases. Although NCB is reported to be unstable, we have stored the pure compound in a refrigerator for many months without any detectable deterioration.

To explore the scope of the synthetic utility of NCS/thioether or NCB/thioether intermediates, a series of *N*-aryl-*S,S*-dimethyliminosulfuranes was prepared. Table II lists the compounds prepared (**15–19**) along with yields, melting points, and a comparison of the yields in appropriate cases with those obtained by our previously published Me_2SO/SO_3 procedure.[6] Table II also includes several *N*-aryl-*S,S*-dimethyliminosulfonium salts obtained (**20–23**) during the course of the study.

The NCS and NCB "activation" methods are clearly effective and useful in preparing *N*-aryliminosulfuranes and their salts. The aryl groups may contain electron-withdrawing or -donating substituents. In most cases yields are comparable with those obtained with Me_2SO/SO_3. The NCS/thioether and NCB/thioether procedures, however, require low temperatures whereas the Me_2SO/SO_3 procedure is operative at room temperature or only slightly below.

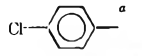
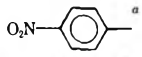
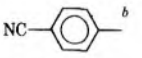
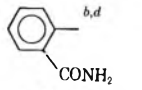
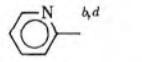
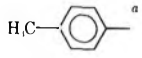
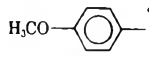
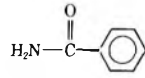
No reaction was obtained between 2,4,6-trichloroaniline or *o*-nitroaniline and the NCS/dimethyl sulfide intermediate; over 80% of the arylamines were recovered. Failure to obtain reaction is attributed to steric hindrance as *p*-nitroaniline reacts and we had shown earlier that bulky ortho substituents interfere with attack of nitrogen nucleophiles on an electrophilic sulfur atom.[6] In the preparation of the *N*-aryliminosulfuranes listed in Table II we have used aqueous base to remove the proton from nitrogen and simultaneously solubilize the by-product succinimide or benzotriazole.

Arylsulfonamides and carboxamides are compounds of low nucleophilicity (relative to arylamines); yet they react readily with the NCB/thioether intermediate. Sulfonamides (*p*-tolyl, phenyl, *p*-chlorophenyl) give generally good yields (40–90%) of *N*-arylsulfonyl-*S,S*-dimethyliminosulfuranes (Table III). Carboxamides (acetamide, benzamide) give only fair yields (40–45%) of *N*-acyl-*S,S*-dimethyliminosulfonium salts (Table IV). Acrylamide was recovered unchanged.

We did not explicitly study the relationship between nucleophilicity of amino (or amido) compound and rate of reaction with the NCB or NCS/thioether intermediate but we anticipated that amines would react more rapidly than amides.[1b] Evidence for different reaction rates was obtained by a study of the reaction of equimolar quantities of *o*-aminobenzamide (anthranilamide) with NCB/$(CH_3)_2S$. This reaction was carried out in a special all-glass apparatus[1b] which permitted formation of the reactive intermediate in one flask and then slow transfer of the intermediate at low temperature with stirring to another flask below it containing the anthranilamide, thereby avoiding an excess of reactive intermediate. The resultant iminosulfurane (18) was formed exclusively on the amino function, as expected (spectral characterization), although the yield was only fair.

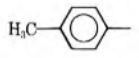
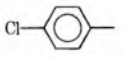
Thioethers other than dimethyl sulfide can also be used. With α-methylbenzylamine (*dl*, *l*, or *d*) as the model amine, we obtained excellent yields (40–96%) of iminosulfonium chlorides from NCS-"activated" diethyl sulfide and tetramethylene sulfide, as well as from dimethyl sulfide (Table V). Di-*tert*-butyl sulfide, diphenyl sulfide, and thiophene did not react with aniline, benzylamine, or α-methylbenzylamine, three amines that react satisfactorily with "activated" dimethyl sulfide. The amine (hydrochloride) was recovered. NCS-"activated" di-(*p*-methoxyphenyl) sulfide, bis(β-chlo-

Table II. *N*-Aryl-*S*,*S*-dimethyliminosulfuranes $(CH_3)_2S^+N^-R$, and *N*-Aryl-*S*,*S*-dimethyliminosulfonium Salts, $(CH_3)_2S^+NHR\ Cl^-$

Registry no.	R	(Compd)	Yield, %	Mp, °C	Me_2SO/SO_3 method[6] Yield, %	Me_2SO/SO_3 method[6] Mp, °C
		Iminosulfuranes				
60978-76-9		(15)	66	63–64	75	66.5–67.5
31896-57-8		(16)	80	162–163	90	168–170
60978-77-0		(17)	77	107–108	62	111–112
60978-78-1		(18)	25	120–131	*c*	*c*
60978-79-2		(19)	41	83–84	*c*	*c*
		Iminosulfonium Salts				
35357-64-3		(20)	85	110 dec (104–105)[3]	*c*	*c*
60978-80-5		(21)	67	111–112 dec	*c*	*c*
35357-66-5		(22)	68	128–130 dec (115–116)[3]	*c*	*c*
60978-81-6		(23)	43	152–153 dec	*c*	*c*

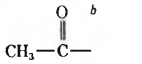
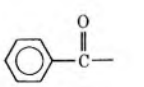
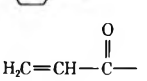
[a] $NCS/(CH_3)_2S$ used. [b] $NCB/(CH_3)_2S$ used. [c] Not studied. [d] Correct elemental analysis.

Table III. *N*-Arylsulfonyl-*S*,*S*-dimethyliminosulfuranes,[a] $(CH_3)_2S^+N^-SO_2R$

Registry no.	R	(Compd)	Yield, %	Mp, °C	Me_2SO/SO_3 method[6] Yield, %	Me_2SO/SO_3 method[6] Mp, °C
31657-41-7		(24)	89	156–158	80	156–158
60978-82-7		(25)	37	129–130	75	131
60978-83-8		(26)	70	113–115	91	122–123

[a] $NCB/(CH_3)_2S$ used.

Table IV. *N*-Acyl-*S*,*S*-dimethyliminosulfonium Salts,[a] $(CH_3)_2S^+NHR\ Cl^-$

R	(Compd)	Yield, %	Mp, °C	Lit. mp, °C
	(27)	45	124	131–133[3,11]
	(28)	42	105	108–109[12,16]
	No reaction			

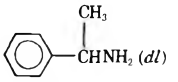
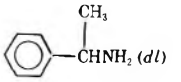
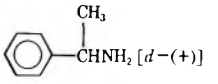
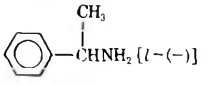
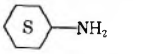
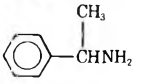
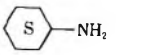
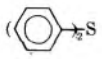
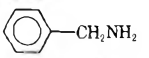
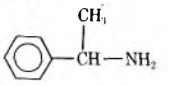
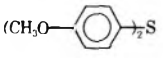
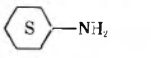
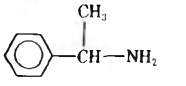
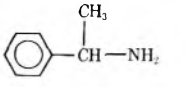
[a] $NCB/(CH_3)_2S$ used. [b] The acetamide–chloroform solution used in this preparation must be carefully dried.

roethyl) sulfide, and bis(β-cyanoethyl) sulfide yielded unstable products that decomposed in a complex way on reaction with cyclohexylamine and α-methylbenzylamine (Table V).

Failure of di-*tert*-butyl sulfide to react was anticipated as we had observed such behavior before.[7,13] Earlier findings of Kingsbury and Johnson[14] had shown that di-*tert*-butyl sulfide is not converted to sulfoxide by NCB in methanol. We attribute failure to react a result of steric hindrance to attack on the bulky thioether by the large activating species (NCB). Failure of diphenyl sulfide or thiophene to react is attributed to reduction in nucleophilicity of the sulfur atom by the aromatic ring(s). To overcome the effect of reduced electron density on sulfur in aromatic thioethers we prepared di(*p*-methoxyphenyl) sulfide. This thioether seemed to form an "activated" intermediate and yielded an iminosulfonium salt when treated with cyclohexylamine but the resulting product was quite unstable.

Comparison of the NCB or NCS/thioether procedure with numerous literature methods for preparing iminosulfuranes shows that this procedure is equal to or superior to previously described methods.[1b,6,10] In addition, the NCB and NCS procedures now make readily available a variety of *N*-alkyl-

Table V. Miscellaneous *S,S*-Dialkyliminosulfonium Chlorides[a]

Thioether	Amine	Iminosulfonium chloride Yield, %	(Compd)	Mp, °C
$(C_2H_5)_2S$		44	(29)	110
(352-93-2)[d]	(618-36-0)[d]		(60978-84-9)[d]	
		95	(30)	174–175 dec
(110-01-0)			(60978-85-0)	
		95	(31)	172–173 dec
	(3886-69-9)		(61045-15-6)	
		95	(32)	172–173 dec
	(2627-86-3)		(61045-16-7)	
$(CH_3)_2S$[b]		78	(7)	150
$(CH_3)_2S$[b,c]		90+	(13)	168–169 dec
$[(CH_3)_3C]_2S$		No reaction		
		No reaction		
		No reaction		
		Decomposition		
$(ClCH_2CH_2)_2S$		Decomposition		
$(CNCH_2CH_2)_2S$		Decomposition		

[a] NCS/thioether "activation," except where indicated. [b] See Table I. Listed here for comparison purposes. [c] NCB "activation." [d] Registry no.

and -aralkyliminosulfonium salts, compounds difficult, if not impossible, to obtain by older methods.

Experimental Section[15]

***N*-Alkyl-*S,S*-dimethyliminosulfonium Salts (Table I). A. *N*-Cyclohexyl-*S,S*-dimethyliminosulfonium Chloride (7).** Dimethyl sulfide (2.0 ml, 27.5 mmol, 10% excess) was dissolved in CH_2Cl_2 (75 ml) and cooled to −50 to −60 °C in a 250-ml, three-neck flask fitted with a stirrer, dropping funnel, thermometer, and drying tube. NCS (3.38 g, 25 mmol) dissolved in CH_2Cl_2 (50 ml) was added dropwise; a dense white precipitate formed. Stirring was continued for 1 h below −40 °C followed by the dropwise addition of cyclohexylamine (3.05 ml, 25 mmol) dissolved in CH_2Cl_2 (10 ml). After an additional 1 h of stirring below −40 °C, the reaction mixture was allowed to warm to room temperature and all volatiles were then removed in a rotary evaporator. The residue was transferred to the cup of a Soxhlet extractor and extracted overnight with ether. The white, insoluble solid residue (3.75 g, 78%) of crude **7**, mp 141–142 °C dec, was recrystallized to constant melting point from CH_2Cl_2/ether: mp 150 °C dec (single TLC spot); NMR ($CDCl_3$) cyclohexyl H (δ 1.0–2.2, broad s, 11 H); $^+S(CH_3)_2$ (3.42, s, 6 H); NH (7.92, d, 1 H). The NH signal disappeared upon addition of D_2O. Anal. Calcd for $C_8H_{18}ClNS$: C, 49.1; H, 9.27; N, 7.16; S, 16.4. Found: C, 49.2; H, 9.08; N, 7.19; S, 16.2.

B. *N-tert*-Octyl-*S,S*-dimethyliminosulfonium chloride (8) was prepared from dimethyl sulfide (2.0 ml, 27.5 mmol), NCB (3.84 g, 25 mmol), *tert*-octylamine (3.23 g, 25 mmol), and CH_2Cl_2 (170 ml) except that the reaction solution was not evaporated to dryness but to a volume of about 100 ml, followed by addition of ether to the cloud point. Storage of the mixture overnight at −20 °C yielded a precipitate of crude **8** (5.0 g, 90%), mp 102–104 °C dec, which was recrystallized to constant melting point from CH_2Cl_2/ether: mp 108–110 °C dec (single TLC spot); NMR ($CDCl_3$) $C(CH_3)_3$ (δ 0.85, s, 9 H), CH_2 (1.37, m, 8 H), $^+S(CH_3)_2$ (3.44, s, 6 H), NH (7.97 broad s, 1 H). Anal. Calcd for $C_{10}H_{24}ClNS$: C, 53.2; H, 10.7; N, 6.20; S, 14.2. Found: C, 53.4; H, 10.8; N, 6.19; S, 13.9.

C. *N*-Benzyl-*S,S*-dimethyliminosulfonium chloride and picrate (12) were prepared as in A from dimethyl sulfide, NCS, benzylamine, and CH_2Cl_2 (160 ml). The crude chloride (4.62 g, 80%), mp 100–102 °C dec, remaining in the Soxhlet cup was recrystallized to constant melting point from CH_2Cl_2/ether: mp 104–107 °C dec (single TLC spot) (lit.[3] 71–72 °C; see Table I and text); NMR ($CDCl_3$) $^+S(CH_3)_2$ (δ 3.14, s, 6 H), CH_2 (4.14, d, 2 H), aromatic H (7.26, broad s, 5 H), NH (8.48, broad s, 1 H) (the NH signal disappeared on addition of D_2O); IR (KBr) 2780 and 700 cm^{-1} (strong).

As the chloride is hygroscopic, a portion was converted to the picrate by treatment of an aqueous solution with saturated aqueous picric acid. The yellow crstals that formed on cooling were recrystallized from absolute ethanol, mp 112–113 °C dec. Anal. Calcd for $C_{15}H_{16}N_4O_7S$: C, 45.5; H, 4.07; N, 14.1; S, 8.09. Found: C, 45.8; H, 4.09; N, 14.1; S, 7.86.

D. Miscellaneous Preparative Details. With the exceptions noted in Table I (**6, 7, 8, 10, 11, 13**), chlorides were too hygroscopic or unstable to be submitted for analysis. Picrates were less hygroscopic and more stable, and satisfactory analyses could be obtained in some cases (**3, 4, 9, 12**). Compounds **2, 5,** and **14,** as chlorides or picrates, were not analyzed but their NMR spectra were consistent with the

proposed structures. Picrates were usually prepared from methanol or ethanol solutions of the chlorides and an excess of a saturated solution of picric acid in the same solvent. Chlorides (**10, 11**) prepared from hexadecyl- and octadecylamines were waxy solids of somewhat ill-defined melting points. They appeared to be stable and relatively nonhygroscopic but they (as well as other stable chlorides) were stored in a desiccator over a drying agent as a routine precaution. Aqueous solutions of chlorides gave an immediate precipitate on addition of silver nitrate solution.

***N*-Aryliminosulfuranes and *N*-Aryliminosulfonium Chlorides (Table II). A. *N*-*p*-Chlorophenyl-*S,S*-dimethyliminosulfurane (15).** **15** was prepared from dimethyl sulfide, NCS, *p*-chloroaniline, and CH_2Cl_2 (200 ml) except that excess aqueous NaOH (50 ml of 1 N) was added to the reaction mixture after it had reached room temperature. The CH_2Cl_2 solution was separated, washed with water (50 ml), dried ($MgSO_4$), and evaporated to dryness in a rotary evaporator. The residue (6.0 g), a yellow oil, showed only two spots on TLC examination, R_f 0.28 (identical with authentic **15**)[6] and 0.65 (succinimide). Crystallization from ether/hexane yielded pure **15** (3.1 g, 68%), mp 63–64 °C (lit.[6] 66–67 °C) (NMR and IR identical with those of an authentic sample).

B. *N*-*p*-Nitrophenyl-*S,S*-dimethyliminosulfurane (16) was similarly prepared using *p*-nitroaniline instead of *p*-chloroaniline and acetonitrile/CH_2Cl_2 (1:1) instead of CH_2Cl_2 to assist the dissolution of the amine at low temperatures. Crude **16** (3.96 g, 80%), mp 156–158 °C, was crystallized from ethyl acetate/pentane, mp 162–163 °C (lit.[6] 168–170 °C) (NMR and IR identical with those of an authentic sample).

C. *N*-*p*-Cyanophenyl-*S,S*-dimethyliminosulfurane (17) was prepared from dimethyl sulfide, NCB, *p*-cyanoaniline, and CH_2Cl_2 (180 ml). Crude **17** (4.8 g) was crystallized from CH_2Cl_2/ether, mp 107–108 °C (lit.[6] 111–112 °C) (3.4 g, 77%) (NMR and IR identical with those of an authentic sample).

D. *N*-2-Pyridino-*S,S*-dimethyliminosulfurane (19) was prepared from dimethyl sulfide, NCB, 2-aminopyridine, and CH_2Cl_2 (140 ml). Crude **19** was dissolved in chloroform (100 ml) and washed with dilute aqueous NaOH and then with water to remove benzotriazole contaminant. The chloroform solution was dried ($MgSO_4$), ether was added to the cloud point, and the mixture was cooled overnight at −20 °C. Pure **19**, mp 83–84 °C, was isolated by filtration (1.58 g, 41%): NMR ($CDCl_3$) $^+S(CH_3)_2$ (δ 2.66, s, 6 H), aromatic H (7.22–7.92, m, 4 H). Anal. Calcd for $C_7H_{10}N_2S$: C, 54.5; H, 6.53; N, 18.2. Found: C, 54.5; H, 6.58; N, 17.9.

E. *N*-*o*-Carboxamidophenyl-*S,S*-dimethyliminosulfurane (18) was prepared using the "inverse addition" technique and dual reaction flask apparatus previously reported by us.[1b] Dimethyl sulfide (2.0 ml, 27.5 mmol) was dissolved in acetone (25 ml) in the upper flask and the solution was cooled to −50 to −60 °C with stirring followed by dropwise addition of NCB (3.84 g, 25 mmol), dissolved in acetone (30 ml). A dense white precipitate formed and stirring was continued for 1 h below −40 °C. The slurry was then added slowly with stirring to the lower flask which contained *o*-aminobenzamide (3.4 g, 25 mmol) dissolved in acetone (100 ml) and cooled to −50 to −60 °C. After 1 h, triethylamine (3.5 ml, 25 mmol) dissolved in acetone (20 ml) was added and the reaction mixture was then allowed to warm to room temperature. Triethylamine hydrochloride was filtered off and the filtrate was evaporated to dryness in a rotary evaporator yielding crude **18** as a light tan solid (mp 108–110 °C). It was dissolved in CH_2Cl_2 and treated with activated carbon, and ether was added to the cloud point. Cooling to 0 °C yielded analytically pure **18**: mp 130–131 °C (1.2 g, 25% yield) [single spot on TLC, R_f 0.375 (silica gel/acetone)]; NMR (D_2O) $^+S(CH_3)_2$ (δ 2.68, s, 6 H), aromatic H (6.76–8.16, m, 4 H); IR (KBr) 753, 792, 921, 1162, 1222, 1262, 1480, 1640, 3250 cm^{-1}. The position of the C=O absorption was the same as that in *o*-aminobenzamide, thus demonstrating that ylide formation had *not* occurred on the carboxamido group. Anal. Calcd for $C_9H_{12}N_2OS$: C, 55.1; H, 6.16; N, 14.3; S, 16.3. Found: C, 55.1; H, 6.14; N, 14.1; S, 16.5.

F. *N*-Phenyl-*S,S*-dimethyliminosulfonium chloride (20) was prepared from dimethyl sulfide, NCS, aniline, and CH_2Cl_2 (135 ml). Extraction of crude **20** with ether in a Soxhlet extractor yielded **20** (4.03 g, 85%), mp 110 °C dec, a hygroscopic, somewhat unstable compound that did not yield an insoluble picrate: NMR ($CDCl_3$) $^+S(CH_3)_2$ (δ 3.38, s, 6 H), aromatic H (7.22, broad s, 5 H).

G. *N*-*p*-Tosyl-*S,S*-dimethyliminosulfonium chloride (21) and *N*-*p*-methoxyphenyl-*S,S*-dimethyliminosulfonium chloride (22) were prepared in the same way as **20** except for the use of *p*-toluidine and *p*-anisidine, respectively. Both salts are unstable. NMR: compound **21** ($CDCl_3$/Me_2SO-d_6), $ArCH_3$ (δ 2.34, s), $^+S(CH_3)_2$ (3.44, s), aromatic H (7.14, 7.44, dd); compound **22** (Me_2SO-d_6), $^+S(CH_3)_2$ (δ 3.48, s, 6 H), CH_3O (3.76, s, 3 H), aromatic H (6.84, 7.10, dd, 4 H), NH (9.89, broad s, 1 H).

H. *N*-*p*-Carboxamidophenyl-*S,S*-dimethyliminosulfonium chloride (23) was prepared from dimethyl sulfide, NCB, *p*-aminobenzamide (125 ml of acetonitrile was used to dissolve the amide), and CH_2Cl_2 (100 ml): NMR (D_2O) $^+S(CH_3)_2$ (3.39, s, 6 H), aromatic H (7.24, 7.84, dd, 4 H).

***N*-Arylsulfonyl-*S,S*-dimethyliminosulfuranes (24–26) (Table III). *N*-*p*-Toluenesulfonyl-*S,S*-dimethyliminosulfurane (24)** was prepared from dimethyl sulfide, NCB, and CH_2Cl_2 (125 ml); *p*-toluenesulfonamide (25 mmol) dissolved in acetone (50 ml) was added to the CH_2Cl_2 solution of the "activated" thioether. After 1 h at −40 °C, the reaction mixture was allowed to warm to room temperature and aqueous NaOH (50 ml, 25 mmol) was added. Crude **24** isolated by evaporation was dissolved in CH_2Cl_2, ether was added to the cloud point, and the mixture was cooled overnight to −20 °C. Pure **24** was isolated by filtration (5.12 g, 89%), mp 156–158 °C (lit.[6] 156–158 °C), identical in every respect with an authentic specimen.

Compounds **25** (*N*-benzenesulfonyl-) and **26** (*N*-*p*-chlorophenylsulfonyl-) were similarly prepared in 37 and 70% yields, respectively, except that benzenesulfonamide was added in 1:1 acetone/CH_2Cl_2 (50 ml) and *p*-chlorobenzenesulfonamide was added in CH_2Cl_2 solution (50 ml).

***N*-Acyliminosulfonium Salts (27 and 28) (Table IV). *N*-Acetyl-*S,S*-dimethyliminosulfonium chloride (27)** was prepared from dimethyl sulfide, NCB, and acetamide in chloroform (50 ml; solution carefully dried) and CH_2Cl_2 (100 ml). After reaching room temperature, the reaction mixture was concentrated under vacuum to ca. 100 ml followed by addition of ether to the cloud point. The mixture was cooled to −20 °C and crystalline **27** (hygroscopic) was isolated by filtration (1.75 g, 45%), mp 124 °C (lit.[3,11] 131 °C). The NMR and IR spectra were virtually identical with those of an authentic specimen of the corresponding bromide[11] and confirmed the structure.

The *N*-benzoyl analogue (**28**) was similarly prepared except that benzamide was added in CH_2Cl_2 (50 ml) and the crude product was extracted overnight with ether in a Soxhlet extractor. The insoluble residue consisted of pure **28** (2.3 g, 42%), mp 105 °C (lit.[12,16] 108 °C). NMR and IR were consistent with the structure.

Miscellaneous Iminosulfonium Chlorides (Table V). A. *N*-(*dl*)-α-Methylbenzyl-*S,S*-diethyliminosulfonium chloride (29) was prepared from diethyl sulfide (2.97 ml, 27.5 mmol, 10% excess) in CH_2Cl_2 (75 ml) cooled to −50 °C to which NCS (3.34 g, 25 mmol) was added (a dense white precipitate formed) followed after 1 h by (*dl*)-α-methylbenzylamine (3.23 ml, 25 mmol), dissolved in CH_2Cl_2 (20 ml). After an additional 1 h below −40 °C, the reaction mixture was allowed to warm to room temperature and the solvent was evaporated in a rotary evaporator. The residual oil was dissolved in acetone and ether was added to the cloud point. The mixture was cooled overnight at −20 °C and the white, crystalline product (**29**) was collected by filtration (2.7 g, 44%), mp 110 °C. The product was hygroscopic but stable: NMR ($CDCl_3$) CH_3CH_2 (δ 1.20, 1.44, t, t, 6 H), CCH_3 (1.68, d, 3 H), CH_3CH_2 (3.52, 3.90, m, m, 4 H); CH (4.16, m, 1 H); aromatic H (7.40, broad s, 5 H), NH (8.52, broad s, 1 H). Anal. Calcd for $C_{12}H_{20}ClNS$: C, 58.7; H, 8.20; N, 5.70; S, 13.1. Found: C, 58.8; H, 8.13; N, 5.69; S, 13.2.

B. *N*-(*dl*)-α-Methylbenzyl-*S,S*-tetramethyleneiminosulfonium chloride (30) was prepared as described in A but substituting tetramethylene sulfide for diethyl sulfide and extracting the crude solid residue with ether in a Soxhlet extractor overnight. Crude residual **30** (4.96 g, 95%), mp 161–163 °C, was recrystallized from CH_2Cl_2/ether to yield the analytically pure salt, mp 174–175 °C. Its NMR spectrum ($CDCl_3$), although complex, could be readily interpreted and the integrated values for all of the protons were correct. The signal for the NH proton disappeared upon addition of D_2O. Anal. Calcd for $C_{12}H_{18}ClNS$: C, 59.1; H, 7.44; N, 5.75; S, 13.2 Found: C, 59.3; H, 7.33; N, 5.86; S 13.4.

Compounds **31**, mp 172–173 °C dec, and **32**, mp 172–173 °C dec, were prepared in the same way in over 95% yields utilizing the enantiomeric (*d*)- and (*l*)-α-methylbenzylamines. The specific rotations were $[+0.43°]^{25}_{D,CH_3OH}$ and $[-0.47°]^{25}_{D,CHOH}$, respectively. Their NMR spectra (DCl_3) were virtually identical with that of **30**.

Acknowledgment. This investigation was supported in part by Grants 07803, 05280, and 12227, awarded by the National Cancer Institute, DHEW, and the Samuel S. Fels Fund. One of us (A.D.D.) thanks the Armstrong Cork Co. for a research fellowship.

Registry No.—Dimethyl sulfide, 75-18-3; cyclohexylamine, 108-91-8; *tert*-octylamine, 60996-53-4; benzylamine, 100-46-9; hex-

adecylamine, 143-27-1; octadecylamine, 124-30-1; *p*-chloroaniline, 106-47-8; *p*-nitroaniline, 100-01-6; *p*-cyanoaniline, 873-74-5; 2-aminopyridine, 504-29-0; aniline, 62-53-3; *p*-toluidine, 106-49-0; *p*-anisidine, 104-94-9; *p*-aminobenzamide, 2835-68-9; *p*-toluenesulfonamide, 70-55-3; benzenesulfenamide, 98-10-2; *p*-chlorobenzenesulfonamide, 98-64-6; NCS, 128-09-6; NCB, 128-08-5; methylamine, 74-89-5; ethylamine, 75-04-7; isopropylamine, 75-31-0; butylamine, 109-73-9; *tert*-butylamine, 75-64-9; 1-adamantylamine, 768-94-5; 4-aminomethylpyridine, 3731-53-1; 2-aminobenzamide, 88-68-9.

References and Notes

(1) (a) Parts of this paper have been presented at the 9th Middle Atlantic Regional Meeting of the American Chemical Society, Wilkes-Barre, Pa., April 1974; VIth International Symposium on Sulfur Chemistry, Bangor, Wales, July 1974; and 7th Central Regional Meeting of the American Chemical Society, Morgantown, W.Va., May 1975; taken from the Ph.D. Thesis of A. D. Dawson, Temple University, 1975. (b) This is part 16 in the Iminosulfuranes series. Part 15: A. K. Sharma, T. Ku, A. Dawson, and D. Swern, *J. Org. Chem.*, **40**, 2758 (1975).

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(3) E. Vilsmaier and W. Sprügel, *Tetrahedron Lett.*, 625 (1972).

(4) C. R. Johnson, J. J. Rigau, M. Haake, D. McCants, Jr., J. Keiser, and A. Gertsma, *Tetrahedron Lett.*, 3719 (1968).

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(6) T. E. Varkey, G. F. Whitfield, and D. Swern, *J. Org. Chem.*, **39**, 3365 (1974), and literature cited therein.

(7) G. F. Whitfield, H. S. Beilan, D. Saika, and D. Swern, *J. Org. Chem.*, **39**, 2148 (1974), and literature cited therein.

(8) Knoll, Mueller-Kalben, and Appel[2b] prepared three *N*-alkyl-*S,S*-dialkyliminosulfonium hexachloroantimonates in good yield from dimethyl (or methyl ethyl) chlorosulfonium hexachloroantimonates and isopropylamine or 1,2-ethylenediamine; melting points, NMR spectra, and elemental analyses were given. Appel and Büchner[2a] mentioned the preparation of *N*-cyanoethyl-*S,S*-diethyliminosulfurane (but not its salts) from diethylsulfilimine and acrylonitrile but without supporting details or characterization (W. Büchner, Dissertation, University of Heidelberg, 1960; not available to us). M. Haake and H. Benack, *Synthesis*, 308, 310 (1976), recently reported the preparation of alkyl(aryl)dialkylaminosuccinimidosulfonium salts from sulfenamides and NCS, and have also prepared ylides from the salts.

(9) After our study had been completed, P. Claus, W. Rieder, P. Hofbauer, and E. Vilsmaier, *Tetrahedron*, **31**, 505 (1975), reported the use of NCS for the efficient preparation of *N*-arylsulfilimines (*N*-aryliminosulfuranes) and their picrates from thioethers and arylamines. In the few cases where duplication of compounds exists, their results and ours agree. However, as we had reported earlier,[1a] the NCS and NCB pathways can also be employed with sulfonamides and carboxamides.

(10) D. S. Tarbell and C. Weaver, *J. Am. Chem. Soc.*, **63**, 2939 (1941).

(11) H. Kise, G. Whitfield, and D. Swern, *Tetrahedron Lett.*, 1761 (1971).

(12) W. Ando, N. Ogino, and T. Migito, *Bull. Chem. Soc. Jpn.*, **44**, 2278 (1971).

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(14) W. D. Kingsbury and C. R. Johnson, *Chem. Commun.*, 365 (1969).

(15) Dimethyl sulfide, diethyl sulfide, diphenyl sulfide, tetramethylene sulfide, and thiophene (Aldrich) were dried with freshly activated (450 °C, 12 h) Linde molecular sieves before use. β,β'-Dicyanodiethyl sulfide (Aldrich) was used as received. Triethylamine (Aldrich) was purified by fractional distillation from phenyl isocyanate. *N*-Chlorosuccinimide (Arapahoe or Aldrich) was recrystallized from hot water. *N*-Chlorobenzotriazole was prepared by the literature procedure.[5] Methylamine and ethylamine (MCB) were condensed from cylinders. Isopropylamine, butylamine, benzylamine, cyclohexylamine, α-methylbenzylamine, *o*- and *p*-nitroaniline, *p*-chloroaniline, *p*-toluenesulfonamide, *p*-chlorobenzenesulfonamide (Eastman), *d*- and *l*-α-methylbenzylamine, adamantylamine, *p*-aminobenzonitrile, *o*-aminobenzamide (Aldrich), *tert*-octylamine (Rohm and Haas), hexadecylamine, octadecylamine (Armour), and benzenesulfonamide (MCB) were used as received; in all cases purity was 97% or greater. All solvents were the purest and driest grades; they were purified when necessary. For IR, a Perkin-Elmer Infracord 137B or Pye Unicam SP 1000 were used. For NMR, a Varian A-60A or XL-100 with tetramethylsilane or 2,2-dimethyl-2-silapentane-5-sulfonate (Norell) as internal standards were used. Melting points (uncorrected) were taken on a Thomas-Hoover capillary apparatus. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Del. For TLC, Eastman silica gel Chromagrams or Analtech prescored silica gel plates with fluorescent indicator were used. Spots were visualized under UV or by development in a closed chamber containing iodine crystals.

(16) J. E. Moffatt and U. Lerch, *J. Org. Chem.*, **36**, 3391 (1971).

Synthesis of 2,4,6-Trinitrobenzenesulfenyl Chloride and Derivatives[1a]

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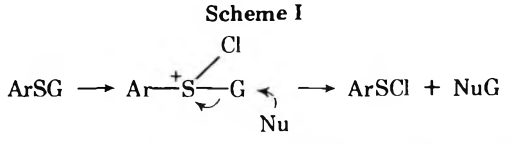
Received August 10, 1976

The synthesis of 2,4,6-trinitrobenzenesulfenyl chloride was accomplished by chlorinolysis of phenyl 2,4,6-trinitrophenyl disulfide which could be prepared by reaction of potassium thiopicrate with benzenesulfenyl chloride. The sulfenyl chloride reacted with alcohols, secondary amines, and the silver salts of N-alkylsulfonamides to afford, respectively, sulfenate esters, sulfenamides, and sulfenylsulfonamides.

Nitrobenzenesulfenyl chlorides are well known and the subjects of an extensive literature.[2] The *o*- and *p*-nitrobenzenesulfenyl chlorides are easily prepared and have received considerable attention. The synthesis of 2,4-dinitrobenzenesulfenyl chloride is the subject of an *Organic Syntheses* preparation[3] and is readily available from commercial sources. It has found application not only in synthetic and analytical chemistry, but also in natural product chemistry as a protecting group for the hydroxyl function and numerous derivatives have been characterized.[4] By contrast, 2,4,6-trinitrobenzenesulfenyl chloride (1) heretofore has been a completely unknown compound. In the course of our investigations of the dynamic stereochemistry of sulfenamides,[5] we became interested in 1 and have directed our efforts to its synthesis and the preparation of some of its derivatives.[6]

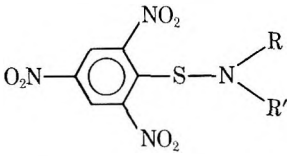
The mononitro- and dinitrobenzenesulfenyl chlorides are readily prepared by chlorinolysis of the corresponding thiols, symmetrical disulfides, or sulfides using chlorine gas or sulfuryl chloride as the chlorinating agent.[2,3] All of these reactions presumably involve electrophilic attack at sulfur followed by nucleophilic displacement of the sulfenyl chloride as a neutral leaving group (Scheme I).

Scheme I



This sequence requires that the sulfur atom act as a nucleophile in the initial step leading to the formation of the chlorosulfonium ion and the presence of an additional ortho nitro group suggests that this step should be less favorable for the synthesis of 1 as compared with its mono- and dinitro analogues. In accord with this expectation, Kharasch et al. were unable to prepare 1 by chlorinolysis of benzyl 2,4,6-trinitrophenyl sulfide (2) using sulfuryl chloride, although this

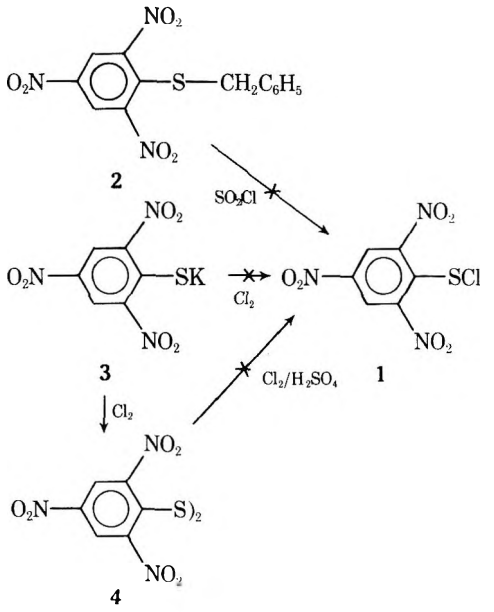
Table I. *N,N*-Dialkyl(aryl)-2,4,6-trinitrobenzenesulfenamides



Registry no.	R	R'	Yield, %	Mp, °C	Anal. Found (calcd) C	H	N	S
60882-81-7	$CHMe_2$	CH_2Ph	66	151–152	49.10 (48.98)	3.95 (4.11)	14.40 (14.28)	8.40 (8.17)
60882-82-8	$CHMe_2$	$CHMe_2$	72	108–109	41.87 (41.86)	4.66 (4.68)	16.19 (16.27)	9.61 (9.31)
60882-83-9	CH_2Ph	$2,4,6\text{-}Me_3C_6H_2$	19	164–165	56.33 (56.40)	4.48 (4.30)	12.00 (11.96	6.71 (6.84)

reaction readily affords 2,4-dinitrobenzenesulfenyl chloride from benzyl 2,4-dinitrophenyl sulfide[7] (Scheme II). Our initial

Scheme II

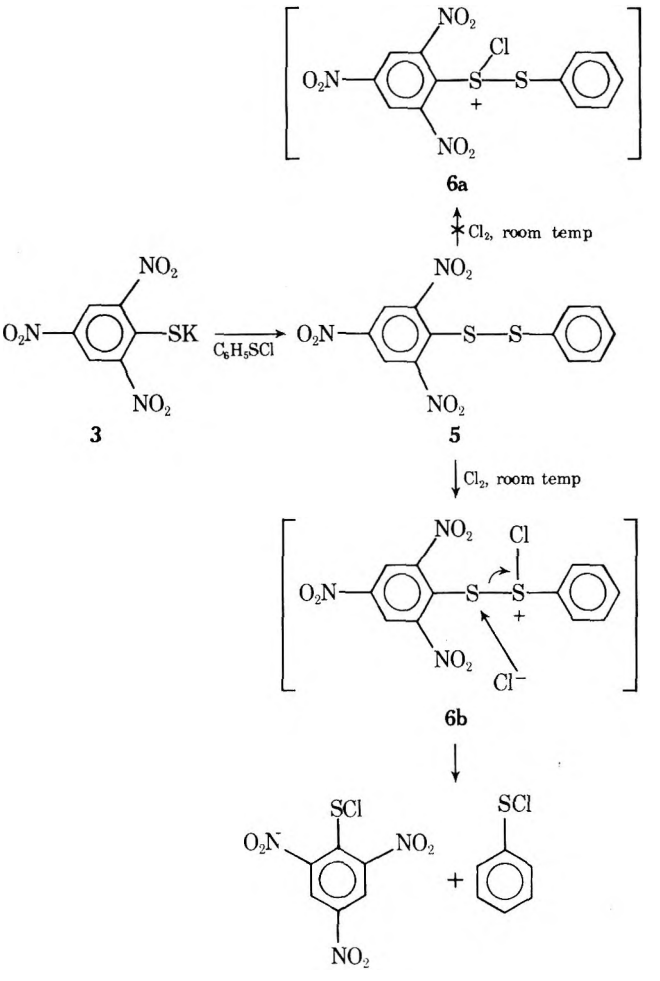


effort involved the chlorination of the potassium thiolate, **3**,[8] reasoning that the negatively charged thiolate anion would be sufficiently nucleophilic to undergo reaction. While reaction did occur, the product obtained was the symmetrical disulfide 4 rather than the desired **1**. This result is not surprising since the chlorination of thiols to yield sulfenyl chlorides is thought to proceed via the symmetrical disulfides as intermediates.[2] The disulfide, in this case, resisted further chlorinolysis even in the presence of oleum, which is recommended by Kharasch in the chlorinolysis of bis(2,4-dinitrophenyl) disulfide.[9]

Since we associated the refractory nature of **4** with the very low nucleophilicity of a sulfur attached to a trinitrophenyl ring, we reasoned that chlorination of a mixed disulfide, such as **5**, might provide a successful route to **1**. Although the formation of intermediate **6a** would be prevented by the trinitrophenyl ring, another more favorable chlorosulfonium ion, **6b**, would be possible which should undergo facile nucleophilic displacement (possibly aided by the electron-withdrawing nitro groups) (Scheme III).

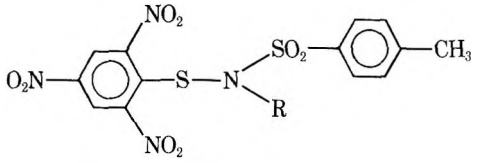
In the fact, this route proved successful. Thus, phenyl 2,4,6-trinitrophenyl disulfide (**4**), prepared by reaction of benzenesulfenyl chloride with **3**, reacted smoothly with chlorine gas at room temperature to afford a mixture of sulfenyl chlorides. The desired product could be isolated from this mixture by selective crystallization. 2,4,6-Trinitrobenzenesulfenyl chloride seems to be rather sensitive to moisture but can be stored for periods of more than 1 month at 5 °C. Longer storage can probably be accomplished by using a sulfenamide as a storage compound,[2] although this was not attempted. The regeneration of the sulfenyl chloride by treatment of a sulfenamide with HCl would not require electrophilic attack on sulfur and should take place readily.

Scheme III



The sulfenyl chloride **1** reacts with nucleophiles, alcohols and amines yielding stable derivatives, sulfenate esters and sulfenamides. Reaction with benzyl alcohol in the presence of pyridine afforded benzyl 2,4,6-trinitrobenzesulfenate. Upon treatment with secondary amines in the presence of a suitable base (pyridine, triethylamine, or an excess of the secondary amine) at room temperature, the corresponding sulfenamides (Table I) are formed from **1**.

Table II. *N*-*p*-Toluenesulfonyl-*N*-alkyl-2,4,6-trinitrobenzenesulfenamides



Registry no.	R	Yield, %	Mp, °C	Anal. Found (calcd) C	H	N	S
60882-84-0	CH_2Ph	48	152–153	47.61 (47.62)	3.23 (3.20)	11.22 (11.11)	12.47 (12.71)
60882-85-1	$CHMe_2$	42	144–146	42.10 (42.10)	3.54 (3.53)	12.44 (12.28)	13.96 (14.05)
60882-86-2	CHMePh	48	167–169	48.59 (48.64)	3.46 (3.50)	10.98 (10.81)	12.43 (12.37)
60882-87-3	CMe_2CH_2OMe	22	158–160	43.46 (43.20)	3.96 (4.03)	11.16 (11.19)	12.55 (12.81)

Synthesis of *N*-arenesulfonyl-*N*-alkyl-2,4,6-trinitrobenzenesulfenamides required a modification in our previous procedure used for obtaining mononitro and dinitro analogues. Previously, we had prepared sulfenylsulfonamides by reaction of the sulfenyl chloride with the lithium salt of the *N*-alkylsulfonamide, which had been prepared in situ by treatment of the sulfonamide with butyllithium.[5] This method, however, was not applicable in the present case; tar formation occurred and no desired product could be isolated. Possibly, electron transfer occurs from the sulfonamide anion to the highly electron-deficient trinitrobenzene ring leading to a radical cation and a radical anion which can undergo subsequent reaction. The use of the corresponding silver salt of the sulfonamide was considered since the greater covalent character of the Ag–N bond would hinder electron transfer. Addition of aqueous silver nitrate to an aqueous solution of the sodium salt of the sulfonamide resulted in the precipitation of the silver salt as a white to gray powder which appeared to be stable to air and moisture. Although further purification and definite characterization were not attempted, the infrared spectra exhibited no absorption which could be associated with the stretching of an N–H bond. Treatment of these silver salts with **1** in benzene at room temperature yielded the desired sulfenylsulfonamides in moderate yield (Table II).

Reaction of **1** with olefins, such as cyclohexene and stilbene, resulted in formation of addition products as indicated by NMR spectra of the reaction mixtures, but isolation of crystalline products has not yet been successful.

Experimental Section

Bis(2,4,6-trinitrophenyl) Disulfide (4). An unsuccessful attempt at preparing the sulfenyl chloride by direct action of chlorine gas on potassium 2,4,6-trinitrobenzenethiolate[8] was made. Thus, chlorine gas was introduced to a dark red suspension of potassium 2,4,6-trinitrobenzenethiolate in dichloromethane at room temperature. Reaction occurred instantaneously, the dark red solid disappeared, and a yellowish solid, probably potassium chloride, formed. After completion of the reaction, the solid was removed by filtration and the solution was evaporated, affording yellow crystals, mp 179–180 °C dec (from tetrahydrofuran–hexane). Elemental analysis and mass spectrometry indicated that the compound was the symmetrical disulfide; no M^+, base peak $M^+/2$. Anal. Calcd for $C_{12}H_4N_6O_{12}S_2$: C, 29.52; H, 0.82; N, 17.21; S, 13.13. Found: C, 29.92; H, 0.73; N, 17.50; S, 12.92.

The disulfide was rather unstable and prolonged heating in tetrahydrofuran afforded the corresponding monosulfide, mp 224–225 °C (lit. mp 228–228.5 °C[10]).

Chlorinolysis of the disulfide was tried using fuming sulfuric acid as a catalyst without success.[11]

Phenyl 2,4,6-Trinitrophenyl Disulfide (5). A solution of 14.5 g of freshly prepared benzenesulfenyl chloride in 20 ml of benzene was added dropwise during the course of 1.5 h to an ice-cold suspension of potassium 2,4,6-trinitrobenzenethiolate,[8] prepared from 24.8 g (0.1 mol) of picryl chloride and 22.0 g (0.11 mol) of freshly prepared potassium sulfide pentahydrate ($K_2S·5H_2O$),[13] in 100 ml of benzene. The reaction mixture was stirred at 5 °C for 1 h. The solid formed was filtered off and washed with 30 ml of benzene. The combined benzene solution was concentrated to a volume of 50 ml using a rotary evaporator. After addition of 20 ml of hexane, the solution was kept overnight in a refrigerator, affording 24.2 g (69%) of yellow crystals, mp 87–88 °C (from tetrahydrofuran–hexane): NMR ($CDCl_3$) δ 7.30 (5 H, s), 8.79 (2 H, s).

Anal. Calcd for $C_{12}H_7N_3S_2O_6$: C, 40.79; H, 2.00; N, 11.89, S, 18.15. Found: C, 40,82; H, 1.90; N, 11.98; S, 18.31.

2,4,6-Trinitrobenzenesulfenyl Chloride (1). Chlorine gas was slowly introduced from a cylinder and through sulfuric acid to a magnetically stirred suspension of 10.6 g (30 mmol) of **5** in 200 ml of carbon tetrachloride. A slight evolution of heat was detected. Introduction of the gas was continued for 20 min after the solid disulfide had completely dissolved and a clear orange solution had been obtained. Completion of the reaction was determined by observing the NMR spectrum of the reaction mixture; signals of the starting disulfide [δ 7.14 (5 H, s) and 8.82 (2 H, s)] were completely replaced by the product signals [δ 7.3–8.0 (5 H, m) and 9.1 (2 H, s)]. The excess chlorine and a large part of the solvent were evaporated using a rotary evaporator, to a volume of ca. 30 ml. The red-orange oily solution was kept in a freezer at −20 °C overnight and afforded yellow crystals in a yield of 7.2 g (86%), mp 61–63 °C (from benzene–hexane), NMR (CCl_4) δ 8.95 (s).

Anal. Calcd for $C_6H_2N_3O_6SCl$: C, 25.77; H, 0.72; N, 15.03; S, 11.47; Cl, 12.68. Found: C, 25.83; H, 0.65; N, 14.90; S, 11.85; Cl, 13.25.

Benzyl 2,4,6-Trinitrobenzenesulfenate. A solution of 2,4,6-trinitrobenzenesulfenyl chloride (1.40 g, 5 mmol) in 25 ml of benzene was added dropwise to a solution of benzyl alcohol (0.54 g, 5 mmol) and pyridine (0.40 g, 5 mmol) in 50 ml of benzene at room temperature. Precipitation of a solid (pyridine hydrochloride) occurred immediately. The mixture was stirred for 30 min, filtered, and evaporated. The residual oil was chromatographed through a silica gel column with benzene as an eluent. Pale yellow crystals, mp 100 °C dec (from tetrahydrofuran–hexane), were obtained, which were sparingly soluble in chloroform but soluble in benzene and dimethyl sulfoxide: NMR (dimethyl sulfoxide) δ 4.82 (2 H, s), 7.39 (5 H, s), and 9.12 (2 H, s). Anal. Calcd for $C_{13}H_9N_3SO_7$: C, 44.45; H, 2.58; N, 11.96; S, 9.13. Found: C, 44.40; H, 2.3; N, 12.00; S, 9.39.

This compound decomposed rapidly in moist dimethyl sulfoxide but quite slowly in dry dimethyl sulfoxide.

***N,N*-Dialkyl-2,4,6-trinitrobenzenesulfenamides.** A solution of 10 mmol of 2,4,6-trinitrobenzenesulfenyl chloride in 20 ml of benzene was added dropwise to a solution of 20 mmol of a secondary amine in 50 ml of benzene. The mixture was stirred at room temperature for 5 h, the solid was filtered off, and the solution was evaporated. The residue was chromatographed on silica gel with hexane–benzene (9:1) as an eluent. The pure products were obtained by recrystallization from tetrahydrofuran–ethanol (Table I).

Preparation of Silver Salts of *N*-Alkyl-*p*-toluenesulfonamides. To an ice-cold solution of 10 mmol of an *N*-alkyl-*p*-toluenesulfonamide in 20 ml of methanol was added 10 ml of 1 N aqueous sodium hydroxide and the mixture was stirred for 2 h. A solution of 10 mmol of silver nitrate in 3 ml of water and 10 ml of methanol was added dropwise to the above solution. By the end of addition, white

to slightly gray powdery solid had formed. The mixture was stirred for a further 30 min and filtered. The solid was dried in vacuo in a desiccator ($CaCl_2$), yield 95–99%. Infrared spectra indicated the absence of the N–H group.

***N*-Alkyl-*N*-*p*-toluenesulfonyl-2,4,6-trinitrobenzenesulfenamides.** A solution of 3.5 mmol of 2,4,6-trinitrobenzenesulfenyl chloride in 10 ml of benzene was added to a magnetically stirred suspension of 4 mmol of a silver salt of *N*-alkyl-*p*-toluenesulfonamide in 30 ml of benzene and the mixture was stirred at room temperature for 48 h. After filtration of the solid, the solution was evaporated and the residue chromatographed on silica gel with benzene–hexane (2:1) as an eluent. The products were purified by recrystallization from tetrahydrofuran–hexane (Table II).

Registry No. —**1**, 60882-88-4; **3**, 16158-74-0; **4**, 60882-89-5; **5**, 60882-90-8; NHR_1R_2 (R_1 = $CHMe_2$; R_2 = CH_2Ph), 102-97-6; NHR_1R_2 (R_1 = $CHMe_2$; R_2 = $CHMe_2$), 108-18-9; NHR_1R_2 (R_1 = CH_2Ph; R_2 = 2,4,6-$Me_3C_6H_2$), 60882-91-9; *p*-$MeC_6H_4SO_2NHR$ (R = CH_2Ph)·Ag, 60882-92-0; *p*-$MeC_6H_4SO_2NHR$ (R = CH_2Me_2)·Ag, 60882-93-1; *p*-$MeC_6H_4SO_2NHR$ (R = CHMePh)·Ag, 60882-94-2; *p*-$MeC_6H_4SO_2NHR$ (R = CMe_2CH_2OMe)·Ag, 60882-95-3; benzenesulfenyl chloride, 931-59-0; benzyl 2,4,6-trinitrobenzenesulfenate, 60882-96-4; benzyl alcohol, 100-51-6.

References and Notes

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Derivatives of 4-Chloro-3,5-dinitrobenzotrifluoride. 2. Synthesis of 2-(Trifluoromethyl)-4-nitrobenzimidazo[2,1-*b*]benzothiazole and Related Compounds[1]

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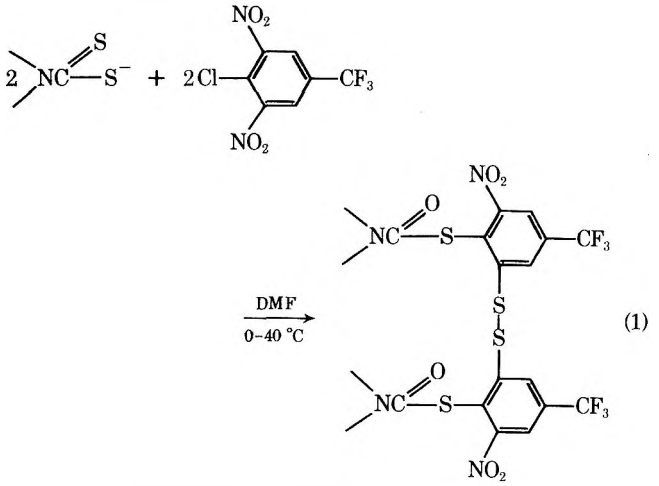
Received July 6, 1976

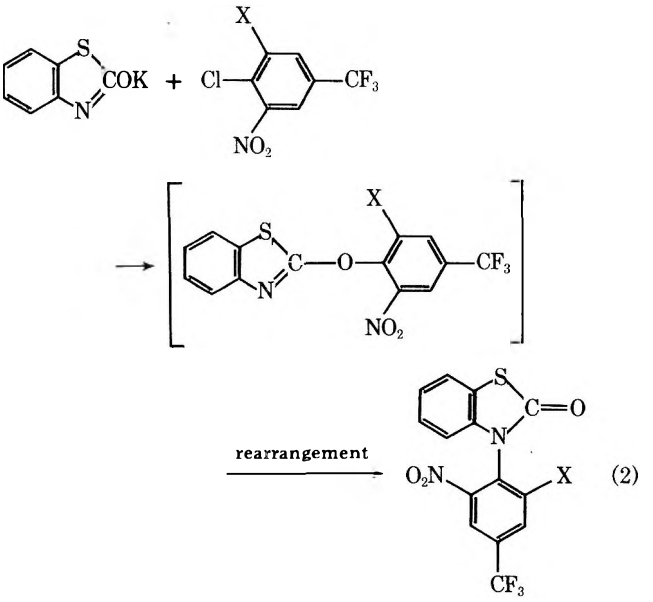
Depending on reaction temperatures the reaction of potassium 2-mercaptobenzimidazole with 4-chloro-3,5-dinitrobenzotrifluoride afforded either the expected 2-(2,6-dinitro-4-trifluoromethylphenylthio)benzimidazole (**3**) or the unexpected 4-nitrobenzimidazo[2,1-*b*]benzothiazole (**5**). Possible mechanism and supporting NMR, IR, and mass spectral data are discussed.

In a previous communication[2] we reported that the reaction of sodium or triethylamine salts of disubstituted dithiocarbamic acids with 4-chloro-3,5-dinitrobenzotrifluoride afforded the product as illustrated by reaction 1. Thus it appeared desirable to replace the above anion with other nucleophiles.



(1)

The reaction of potassium 2-benzothiazolol with 4-chloro-3,5-dinitrobenzotrifluoride or 4-chloro-3-nitrobenzotrifluoride in dimethylformamide at 90–100 °C afforded 3-(2,6-dinitro-4-trifluoromethylphenyl)-2-benzothiazolinone (**1**) and 3-(2-nitro-4-trifluoromethylphenyl)-2-benzothiazolinone (**2**),



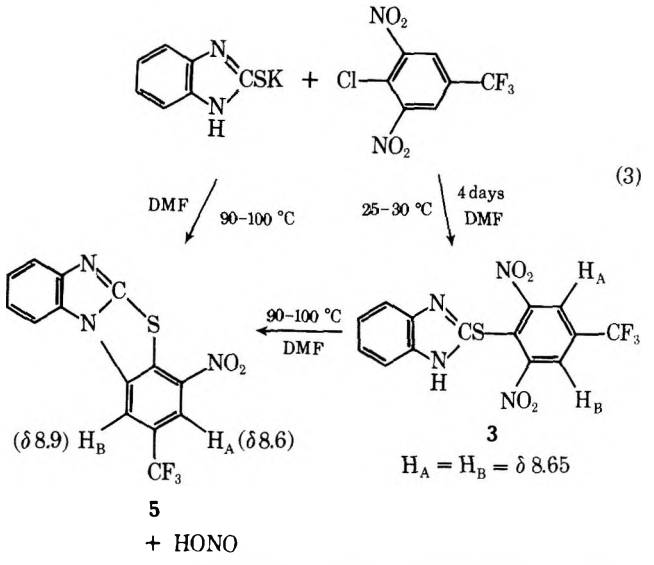
(2)

1, X = NO_2; **2**, X = H

respectively (reaction 2). The NMR, IR, and mass spectral data for **1** and **2** were in agreement for the proposed structures.

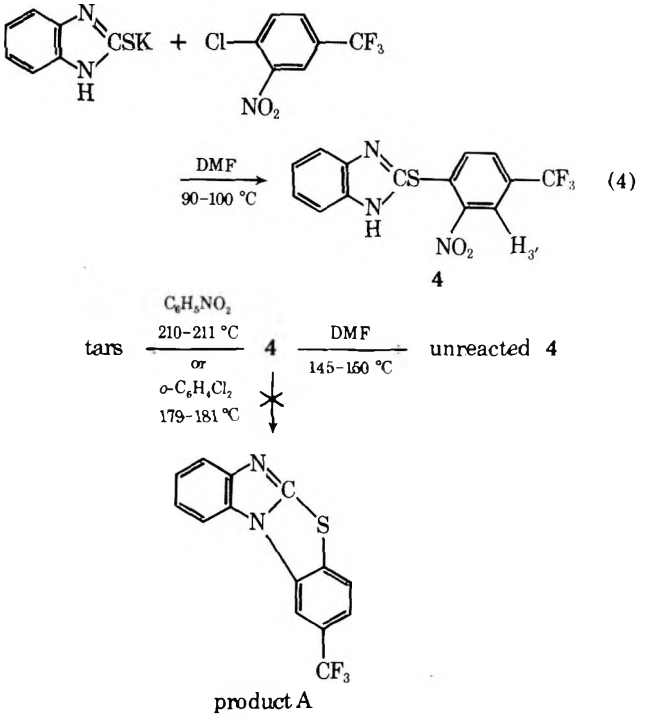
Depending on reaction temperatures, the reaction of potassium 2-mercaptobenzimidazole with 4-chloro-3,5-dinitrobenzotrifluoride in dimethylformamide afforded either the

expected product, 2-(2,6-dinitro-4-trifluoromethylphenylthio)benzimidazole (3), at 25–30 °C or the cyclized product, 2-(trifluoromethyl)-4-nitrobenzimidazo[2,1-*b*]benzothiazole (5), at 90–100 °C. Heating 3 in dimethylformamide at 90–100 °C also furnished 5 (reaction 3). The reaction of potassium



(3)

2-mercaptobenzimidazole with 4-chloro-3-nitrobenzotrifluoride in dimethylformamide at 90–100 °C did not afford the expected cyclized product A but instead furnished 2-(2-nitro-4-trifluoromethylphenylthio)benzimidazole (4). The heating of 4 in various solvents at reflux temperatures either gave unreacted 4 or decomposed products (reaction 4). Proof of structure for 3, 4, and 5 was based on elemental analysis,

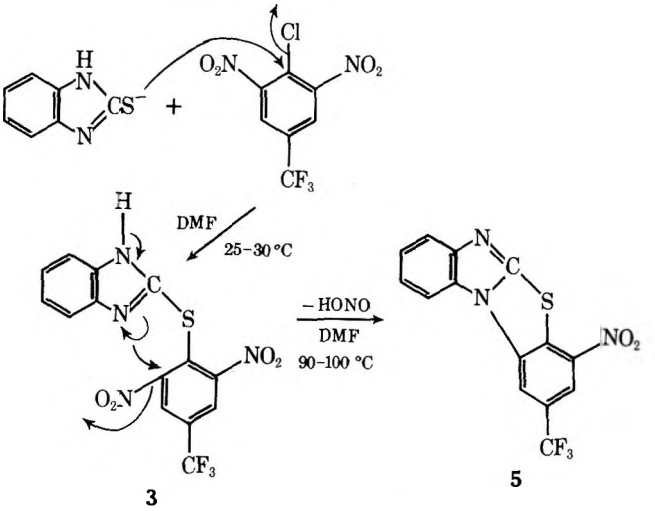


(4)

NMR, IR, and mass spectral data. It is noteworthy to contrast the chemical shift for the aromatic protons (H_A and H_B) in 3 and 5. The H_A and H_B protons in 3 are equivalent and appeared at δ 8.65 whereas in 5 H_A H_B protons are nonequivalent and appeared at δ 8.6 and 8.9, respectively. The assignment of H_A and H_B protons in 5 seems logical since one would not expect the chemical shift of H_A to change significantly when 3 is converted to 5. However, the environment of the H_B proton changed markedly from 3 to 5. In 5, the H_B proton resides in the plane of the heteroaromatic moiety and would be expected to be deshielded with respect to its position in 3. This downfield shift of 0.25 ppm for H_B in 5 lends support for the cyclization reaction. Interpretation of the mass fragmentation patterns for 3, and 5 are depicted in Schemes I and II, respectively. See microfilm edition for these schemes.[3]

Fused rings containing the benzothiazolyl and benzimidazolyl moieties as in 5 have been prepared by other routes.[4]

We would like to propose the following scheme for the cyclization reaction:



Experimental Section

NMR spectra were obtained with a Varian A-60 NMR spectrometer. The chemical shifts are reported in δ, using tetramethylsilane as reference. All melting points were taken upon a Fisher-Johns block and are uncorrected. The mass spectra of 1–5 were determined with a Varian-MAT CH-7 mass spectrometer operating at an ionizing potential of 70 eV using the direct insertion probe technique with a source temperature of 250 °C. The infrared spectra of 2, 2, and 5 were obtained with a Beckman IR-12 spectrophotometer.

3-(2,6-Dinitro-4-trifluoromethylphenyl)-2-benzothiazolinone (1) and 3-(2-Nitro-4-trifluoromethylphenyl)-2-benzothiazolinone (2). To a stirred solution containing 15.1 g (0.1 mol) of 2-benzothiazolol and 6.6 g (0.1 mol) of 85% potassium hydroxide in 200 ml of DMF and 10 ml of water, 0.1 mol of 4-chloro-3,5-dinitrobenzotrifluoride or 4-chloro-3-nitrobenzotrifluoride was added in one portion. An exothermic reaction set in causing a temperature rise from 25 to 35 °C. The stirred reaction mixture was heated at 90–100 °C for 24 h. After cooling to 30 °C, 800 g of ice water was added and stirring continued at 0–10 °C for 1 h. The solids were collected by filtration, washed with water until the washings were neutral to litmus, and air dried at 25–30 °C. The crude product (1), mp 220–224 °C, was obtained in 73% yield. After recrystallization from toluene, 1 melted at 233–234 °C; NMR ($CDCl_3$) δ 7.05–7.70 (m, 4, H-4 to H-7), 8.66 (s, 2); IR (CSI) 3090 (ArC–H), 1695 and 1675 (C=O), 1560–1550 (NO_2 asymmetric), 1400–1100 (C–F), 1320–1310 (NO_2 symmetric), and 700–600 cm^{-1} (C–S); mass spectrum *m/e* (rel intensity) 385 (100), 366 (2), 339 (5), 311 (25), 293 (15), 265 (47), 253 (32), 196 (31), 96 (22), and 69 (19).

Anal. Calcd for $C_{14}H_6F_3N_3O_5S$: C, 43.64; H, 1.57; N, 10.91; S, 8.32. Found: C, 43.58; H, 1.57; N, 10.93; S, 8.41.

The crude product (2), mp 168–170 °C, was obtained in 78% yield. After recrystallization from isopropyl alcohol and heptane (2:1), 2 melted at 195–196 °C; NMR ($CDCl_3$) δ 6.55–8.70 (m, 7); IR (KBr) 3130 (ArC–H), 1690 (C=O), 1540 (NO_2 asymmetric), 1180–1125 (C–F), and 1330 cm^{-1} (NO_2 symmetric); mass spectrum *m/e* (rel intensity) 341 (17.3), 340 (100), 294 (59.6), 267 (14.4), 266 (97.6), 222 (13.6), 197 (13.9), 96 (23.8), 69 (24.9), and 45 (16.9).

Anal. Calcd for $C_{14}H_7F_3N_2O_3S$: C, 49.42; H, 2.07; F, 16.75; N, 8.23; S, 9.42. Found: C, 49.31; H, 2.06; F, 16.68; N, 8.15; S, 9.63.

2-(2,6-Dinitro-4-trifluoromethylphenylthio)benzimidazole (3). To a stirred solution containing 30 g (0.2 mol) of 2-mercaptobenzimidazole, 13.2 g (0.2 mol) of 85% potassium hydroxide, 200 ml of DMF, and 20 ml of water, 54 g (0.2 mol) of 4-chloro-3,5-dinitrobenzotrifluoride was added in one portion. An exothermic reaction set in causing a temperature rise from 25 to 47 °C. Immediately the reaction mixture was cooled to 30 °C and stirred at 25–30 °C for 4 days. After cooling to 10 °C, 800 g of ice water was added and stirring continued at 0–10 °C for 1 h. The solid was collected by filtration, washed with water until the washings were neutral to litmus, and air dried at

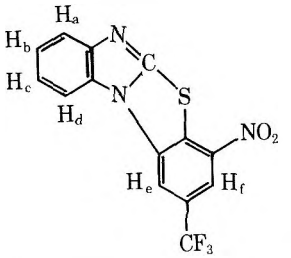
25–30 °C. The crude product, **3**, mp 247–249 °C, was obtained in 94% yield. After recrystallization from isopropyl alcohol **3** melted at 248–250 °C; NMR (Me_2SO-d_6) δ 6.90–7.60 (m, 4), 8.65 (s, 2); mass spectrum *m/e* (rel intensity) 384 (38), 338 (57), 292 (60), 274 (30), 251 (15), 223 (18), 133 (100), 106 (21), 102 (12), and 90 (23).

Anal. Calcd for $C_{14}H_7F_3N_4O_4S$: C, 43.76; H, 1.84; F, 14.83; N, 14.58; S, 8.38. Found: C, 43.85; H, 1.81; F, 14.70; N, 14.54; S, 8.57.

2-(2-Nitro-4-trifluoromethylphenylthio)benzimidazole (4). The procedure was identical with that described for product **3** except that 0.2 mol of 4-chloro-3-nitrobenzotrifluoride was substituted for the 4-chloro-3,5-dinitrobenzotrifluoride and the stirred reaction mixture was heated at 90–100 °C for 24 h. The crude product (4), mp 214–215 °C, was obtained in 95% yield. After recrystallization from *methyl alcohol* **4** melted at 218 °C; NMR (Me_2SO-d_6) δ 7.00–8.10 (m, 6), 8.45 (s, 1, $H_{3'}$); mass spectrum *m/e* (rel intensity) 339 (54.1), 294 (17.3), 293 (100), 292 (22.2), 206 (35.4), 133 (50.7), 122 (17.5), 106 (16.4), 90 (23.0), and 63 (21.0).

Anal. Calcd for $C_{14}H_8F_3N_3O_2S$: C, 49.56; H, 2.38; F, 16.80; N, 12.38; S, 9.45. Found: C, 49.50; H, 2.27; F, 17.06; N, 12.30; S, 9.50.

2-(Trifluoromethyl)-4-nitrobenzimidazo[2,1-*b*]benzothiazole (5). Method I. The charge and procedure were identical with those described for **3** except that after the addition of 4-chloro-3,5-dinitrobenzotrifluoride the stirred reaction mixture was heated at 90–100 °C for 24 h. During this heating period a brownish-yellow gas was liberated. The crude product, mp 26–269 ° C, was obtained in 86% yield. After recrystallization from DMF it melted at 275 °C; NMR (Me_2SO-d_6) below (sample was run on 90 MHz at ambient temperature with time averaging for 340 scans; a computer simulation was obtained of the four-spin system with assignments taken from the experimental spectrum); IR (CsI) 3090 (ArC–H), 1690–1480 (C=N), 1545(NO_2 asymmetric), 1400–1100 (C–F), 1295 (NO_2 symmetric), and 700–600 cm^{-1} (C–S); mass spectrum *m/e* (rel intensity) 337 (100), 318 (3), 291 (78), 279 (5), 271 (2), 247 (7), 227 (5), 222 (3), 178 (2), 168.5 (5), and 69 (7).



δ H_a 2143 Hz (8.7 ppm) J_{ab} = +7 Hz
δ H_b 2038 Hz (7.5 ppm) J_{bc} = +7 Hz
δ H_c 2028 Hz (7.4 ppm) J_{cd} = +7 Hz
δ H_d 2062 Hz (7.8 ppm) J_{ac} = +1.5 Hz
δ H_e 2168 Hz (8.9 ppm) J_{bd} = +1.5 Hz
δ H_f 2134 Hz (8.6 ppm) J_{ad} = 0

Method II. A stirred charge containing 19.2 g (0.05 mol) of **3** in 100 ml of DMf was heated at 90–100 °C for 24 h. During this heating period a brownish-yellow gas was liberated. After cooling to 30 °C, 400 ml of water was added and stirring continued for 1 h. The solid was collected by filtration, washed with water until the washings were neutral to litmus, and dried at 25–30 °C. The crude product, mp 272–274 °C, was obtained in 83% yield. After recrystallization from DMF it melted at 275 °C. A mixture melting point with the product obtained from method I was not depressed and the NMR and IR spectra of the two were superimposable.

Anal. Calcd. for $C_{14}H_6F_3N_3O_2S$: C, 49.86; H, 1.79; F, 16.90; N, 12.46; S, 9.51. Found: C, 49.94; H, 1.80; F, 16.73; N, 12.43; S, 9.46.

Attempted Cyclization of 4. A stirred mixture containing 34 g (0.1 mol) of **4** and 100 ml of dimethylformamide, o-dichlorobenzene, or nitrobenzene was heated at reflux temperatures for 24 h. During this heating period no gas was liberated and the solution became black. The first solvent furnished unchanged **4** and the latter two solvents afforded decomposed **4** (tars).

Registry No.—**1**, 60968-20-9; **2**, 60968-21-0; **3**, 60968-22-1; **4**, 60968-23-2; **5**, 60968-24-3; 2-benzothiazolol, 934-34-9; 4-chloro-3,5-dinitrobenzotrifluoride, 393-75-9; 4-chloro-3-nitrobenzotrifluoride, 121-17-5; 2-mercaptobenzimidazole, 583-39-1.

Supplementary Material Available. Mass spectral fragmentation routes for **3** and **5** (2 pages). Ordering information is given on any current masthead page.

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(3) See paragraph at end of paper regarding supplementary material.
(4) (a) G. F. Buffin and J. D. Kendall, *J. Chem. Soc.*, 361 (1956); (b) J. A. Van Allan, *J. Org. Chem.*, **21**, 24 (1956); (c) J. J. D'Amico, R. H. Campbell, and E. C. Guinn, *ibid.*, **29**, 865 (1964).

Syntheses and Some Properties of 4-Acyl-1-methyl-2-azathiabenzene 1-Oxides

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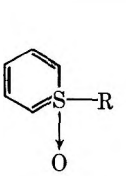
Received June 22, 1976

A series of 4-acyl-1-methyl-2-azathiabenzene 1-oxides have been prepared by base-catalyzed cyclization of *N*-(β,β-diacylvinyl)dimethylsulfoximines which, in turn, were obtained by the reactions of 3-ethoxymethylene-2,4-pentanedione, diethyl ethoxymethylenemalonate, ethyl 2-(ethoxymethylene)acetoacetate, and 2-acetyl-3-methoxy-2-cyclohexen-1-one with dimethylsulfoximine. Comparison of the physical and chemical properties of the azathiabenzene 1-oxides with those of the corresponding 4-acyl-1-methylthiabenzene 1-oxides suggests that both *the ylidic and betainelike properties of the 2-azathiabenzene 1-oxides are much lower than those of the latter.*

Thiabenzene 1-oxides (**1**) are of substantial intrinsic interest as heterocycles containing six π electrons in a cyclic conjugated ring system; if the 6π electrons can delocalize in the ring through sulfur, they are expected to be aromatic. Previous syntheses and studies of the properties of such 6π heterocycles,[1-5] however, have demonstrated that they can be best represented as cyclic ylidic structures.

The introduction of a heteroatom into the thiabenzene 1-oxides ring system is expected to alter significantly the electronic structure of **1**. Cram and Williams[6] have recently synthesized 3,5-diphenyl-1-methyl-2-azathiabenzene 1-oxide (**2**) and suggested that it is not aromatic on the basis of NMR



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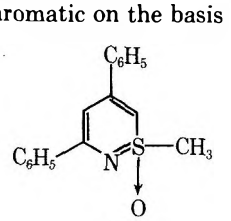
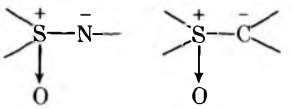


2

spectral data. However, because there is still limited information available concerning the properties of this heterocyclic system, we have now prepared a series of 4-acyl-1-methyl-2-azathiabenzene 1-oxides,[7,8] and compared their physical and chemical properties with those of the corresponding 4-acyl-1-methylthiabenzene 1-oxides.[4]

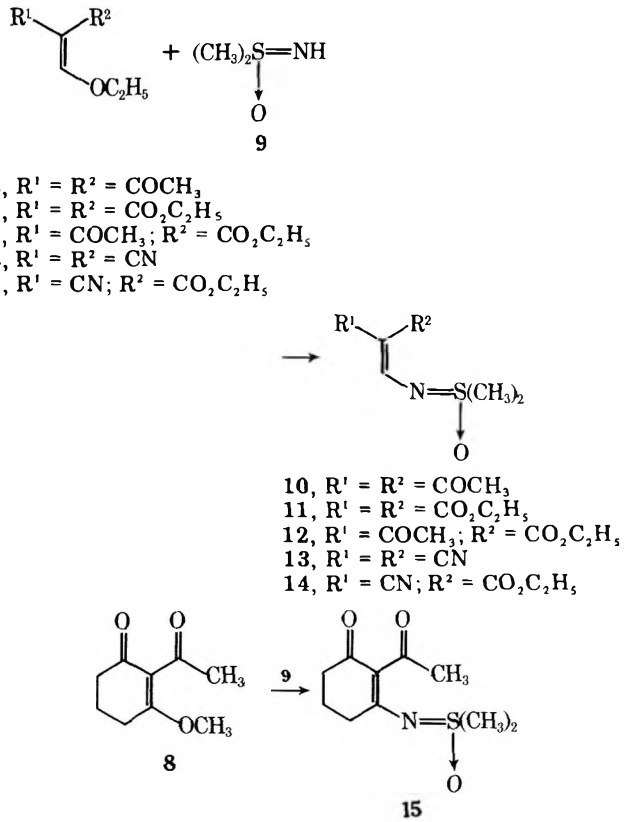
Syntheses. The 4-acyl-1-methyl-2-azathiabenzene 1-oxides were synthesized by application of the route used for the syntheses of 4-acyl-1-methylthiabenzene 1-oxides.[4] When 3-ethoxymethylene-2,4-pentanedione (**3**) was treated with dimethylsulfoximine (**9**) in chloroform at room temperature, there formed in 75% yield *N*-(β,β-diacetylvinyl)dimethylsulfoximine (**10**). Compounds **11**–**15** were also obtained in good yield from the reactions of diethyl ethoxymethylenemalonate (**4**), ethyl 2-(ethoxymethylene)acetoacetate (**5**),[9] ethoxymethylenemalononitrile (**6**), ethyl ethoxymethylenecyanoacetate (**7**), and 2-acetyl-3-methoxy-2-cyclohexen-1-one (**8**), respectively, with **9**. The structures of these new derivatives of sulfoximines were assigned on the basis of elemental and spectral data (see Experimental Section). The most striking feature of the NMR spectrum of **10** is that the two acetyl methyl groups give lines of equal intensity (δ 2.42 and 2.30) whose coalescence temperature is about 120 °C.[10] Similarly the signals due to the ethoxy methylene groups of **11** have different chemical shifts (δ 4.52 and 4.20), which remained invariant over a substantial temperature range (35–160 °C). These phenomena are in analogy to those observed with dimethyloxosulfonium 3,3-dicarbethoxy- and 1-carbethoxy-3,3-diacetylallylides,[4b] but in contrast to those observed with dimethylsulfonium 1-carbethoxy-4,4-diacetylallylide,[4b] 2,2-diacyl-*N*-(1-pyridinio)vinylaminides,[11] and 3,3-diacyl-(1-pyridinio)prop-2-enides,[11] in which the resonance due to two acetyl or ethoxy methylene groups is averaged owing to rapid rotation of these groups about the partial double bond.[12] The restricted rotation observed with the sulfoximines and oxosulfonium ylides suggests that structures are characterized by the presence of considerable bond localization. It is possible that such bond localization results from strong pπ–dπ bonding (contribution from ylene structures) in bonds i and ii, respectively.



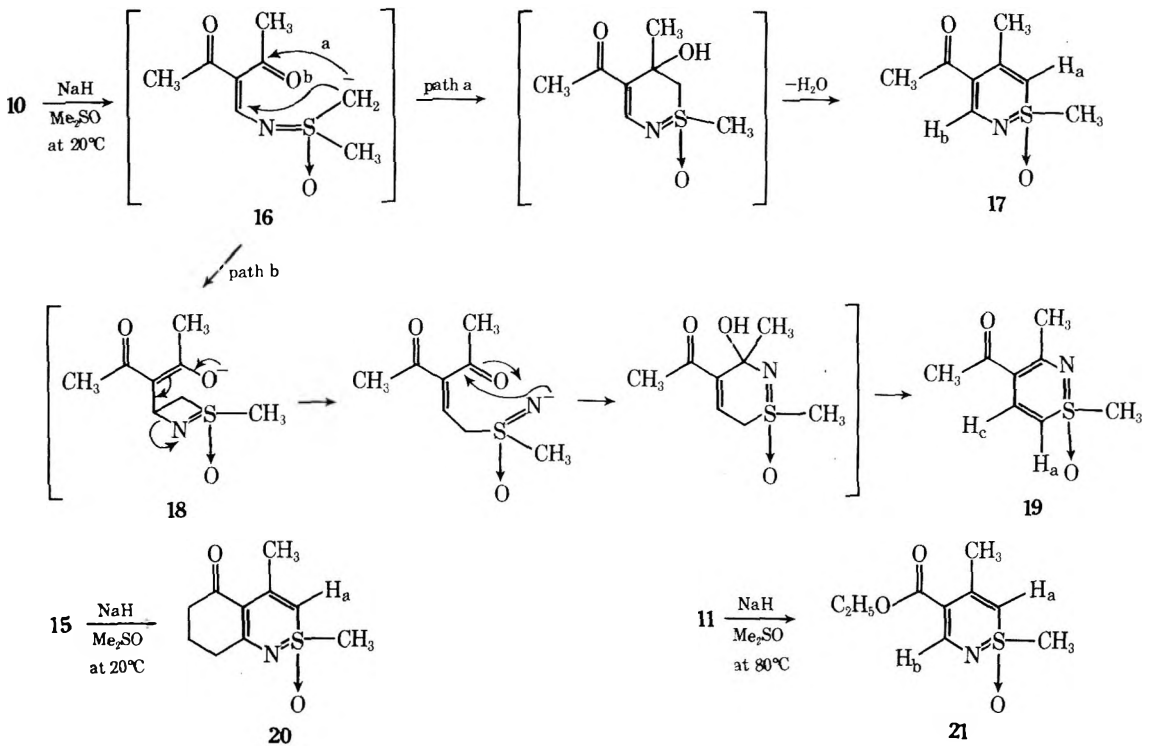
i ii

In the cases of **12** and **14**, the possibility of geometrical isomerism arises. In fact, the NMR spectrum of a freshly prepared deuteriochloroform solution of **12** shows signals for one of the isomers, but, after ca. 10 min, new signals corre-

Scheme I



Scheme II



sponding to the other isomer appear. At equilibrium the mixture consists of two isomers in a ratio of 1:1. Compound **14** was shown to exist as either one of the isomers by its NMR spectrum. In this case no isomerization took place.

The next step was the cyclization of these sulfoximines **10–15**. Treatment of **10** with sodium hydride in dimethyl sulfoxide for 3 h at room temperature gave two isomeric products **17** and **19** in 30 and 18% yields, respectively, whose structures were assigned on the basis of the elemental analyses and spectroscopic data (vide infra). This transformation can be formulated as shown in Scheme II. The initially formed ylidic anion **16** undergoes an intramolecular cyclization followed by dehydration to give **17** (path a). If the ylidic anion **16** competitively undergoes an intramolecular Michael addition reaction (path b), a four-membered ring intermediate **18** would be formed. This step may be followed by a C–N bond cleavage, cyclization, and dehydration to lead to **19.**

Similar treatment of **15** gave a bicyclic compound **20** in 73% yield. Compound **11** was less reactive and did not cyclize at room temperature, but gave **21** in 60% yield when the reaction mixture was heated at 80 °C for 5 min.

The cyclization of **12** was found to be markedly affected by the reaction temperature. Thus, after 3 h at room temperature **12** gave a mixture of three products, **22** (35%), **23** (13%), and **24** (7%), whereas in 5 min at 80 °C it gave a mixture of four products, **25** (41%), **22** (8%), **23** (13%), and **24** (1%). The structures of **22** and **25** were readily assigned by spectral comparison with those of **17** and **21,** respectively. The structure of **23** was confirmed by alkaline hydrolysis of **22** into **23.** Compound **24** was shown to be dimeric by mass spectrometry (M^+, *m/e* 430) and examination of the IR, UV, and NMR spectra enabled us to assign structure **24.** The IR spectrum shows two carbonyl absorption at 1710 and 1700 cm^{-1} and its UV spectrum closely resembles that of **22.** The NMR spectrum (90 MHz) reveals H_a and H_b at δ 6.33 and 8.39 (singlets), H_c and H_d at δ 3.67 as a doublet (2 H, J = 6 Hz), H_e at δ 5.14 as a broad signal, and H_f and H_g at δ 3.60 as an AB quartet with a further small splitting (J = 18 Hz). Irradiation of H_e resulted in collapse of the doublet at δ 3.67 (H_c and H_d) into a singlet. The remaining signals indicate the presence of two ethoxyl groups, one *S*-methyl group, and two *C*-methyl groups.

The main reaction course of the cyclization of **12** at room temperature involves the cyclization at the acetyl carbonyl groups, while the reaction at higher temperature resulted in formation of a product derived from the cyclization at the ester carbonyl group. Since the acetyl carbonyl group is more reactive than the ester carbonyl group as shown by the cycli-

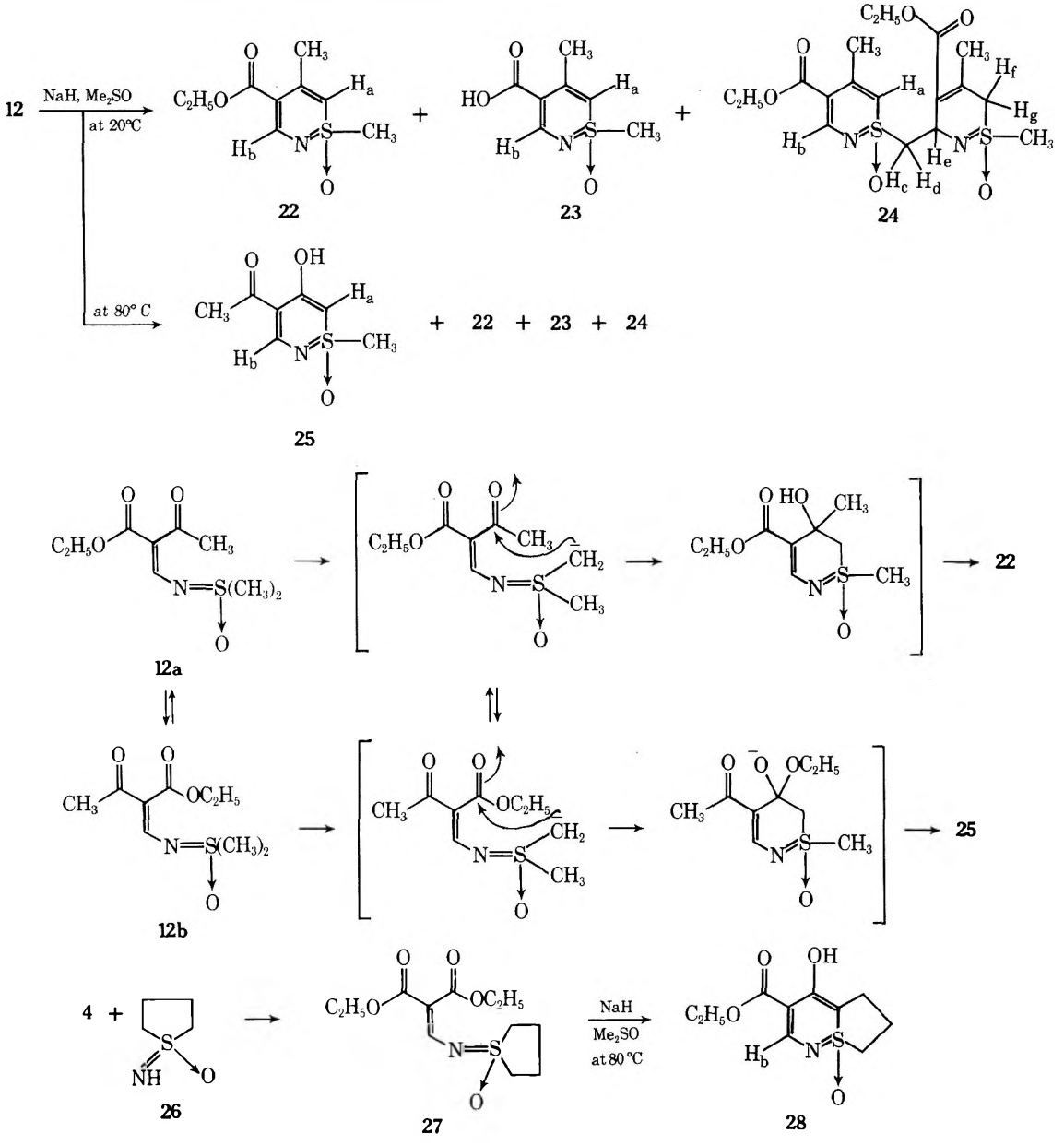


Table I. NMR Data (60 MHz, in $CDCl_3$) of 2-Azathiabenzene 1-Oxides

Registry no.	Compd	$H_a(H_a')$	H_b	H_c	SCH_3	CCH_3	Other protons
49836-29-5	17	5.81 (m)	8.26 (bs)		3.34 (s)	2.48 (d) J = 1 Hz	2.36 ($COCH_3$)
60803-98-7	19	5.93 (d) J = 10 Hz		7.78 (d) J = 10 Hz	3.35 (s)	2.58 (s)	2.35 ($COCH_3$)
49836-31-9	20	5.74 (bs)			3.23 (s)	2.46 (d) J = 1 Hz	1.65–2.85 (m) [$-(CH_2)_3-$]
60803-99-8	22	5.80 (m)	8.43 (bs)		3.34 (s)	2.46 (d) J = 1 Hz	4.24 (q), 1.33 (t) (OCH_2CH_3)
49836-26-2	29	5.45–5.72 (m)	7.76		3.44 (s)	2.51 (bs)	2.31 ($COCH_3$)
49836-27-3	30	5.42–5.78 (m)	8.00		3.46 (s)	2.53 (bs)	4.20 (q), 1.32 (t) (OCH_2CH_3)
49836-34-2	31	5.50 (s) 5.36 (s)			3.37 (s)	2.53 (bs)	1.70–2.80 (m) [$-(CH_2)_3-$]

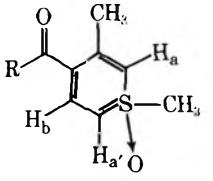
zation reaction of **10** but not **11** at room temperature and because **12** exists as an equilibrium mixture of two geometrical isomers in solution at room temperature, it is not unexpected that the products **22** and **23** were predominantly formed at room temperature. At higher temperature, however, it is reasonably assumed that the cyclization at the ester carbonyl group may compete with the cyclization at the acetyl carbonyl group to lead to formation of **25**. One possible rationalization for the formation of **24** may involve a Michael addition of a carbanion derived from either **12** or **22** to **12** followed by cyclization.

As a further extension of this method, we applied it to the synthesis of a 2-azathiabenzene 1-oxide containing a sulfur atom at a bridgehead position. Thus, sulfoximine **27** obtained from **4** and tetramethylenesulfoximine **26** was treated with sodium hydride in dimethyl sulfoxide to give **28**, whose structure was readily assigned by a comparison of the spectral data with those of **21**.

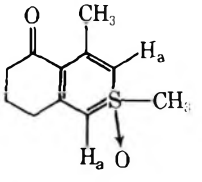
Lastly, cyano-substituted sulfoximines **13** and **14** did not give cyclized products under the reaction conditions we used and the starting material was recovered.

Physical Properties of 2-Azathiabenzene 1-Oxides. Comparison of the NMR spectra of 2-azathiabenzene 1-oxides **17**, **19**, **20**, and **22** with those of **29–31** (Table I) indicates that the signals due to S-CH_3, C-CH_3, and $COCH_3$ or $CO_2C_2H_5$ appear essentially at the same positions. However, the ring proton signals (H_a and H_b) of the 2-azathiabenzene 1-oxides are slightly shifted to lower field than those of the corresponding thiabenzene 1-oxides. The shift of H_a may be associated with less carbanionic character at this position and the shift of H_b may be attributed mainly to an electronegative effect of the nitrogen atom.

The IR carbonyl absorption bands of **17**, **19**, **20**, and **22** appear at 1658, 1655, 1645, and 1692 cm^{-1}, respectively, which are higher than those of the corresponding thiabenzene 1-oxides **29** (1641 cm^{-1}), **30** (1632 cm^{-1}), and **31** (1686 cm^{-1}),



29, R = CH_3
30, R = OC_2H_5



31

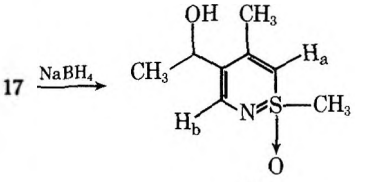
suggesting that the betainelike character (a polarization of the carbonyl group) of 2-azathiabenzene 1-oxides is considerably lower than that of the thiabenzene 1-oxides.

The electronic spectra of the 2-azathiabenzene 1-oxides **17**, **19**, and **20** have a major absorption band at 270–275 nm, which is slightly hypsochromic compared to the corresponding absorption band of thiabenzene 1-oxides **29** and **31** (297–299 nm).[4] Of particular interest is that the position of the absorption maximum was affected neither by the solvent used nor by addition of ethanolic 6 N hydrochloric acid. This is in contrast to the cases of thiabenzene 1-oxides **29** and **31**, in which protonation takes place at the carbonyl oxygen atom under acidic conditions and a new absorption band appeared at 320–330 nm. This difference appears to reflect the decreased basicity of the 2-azathiabenzene 1-oxides.

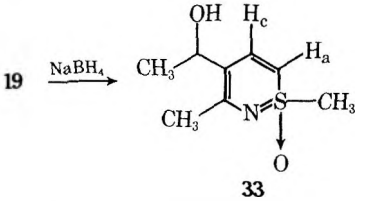
Chemical Properties of 2-Azathiabenzene 1-Oxides. Deuterium Exchange. In a deuteriochloroformic solution containing deuterium oxide at 35 °C, no significant exchange of any protons of 2-azathiabenzene 1-oxides **17** or **22** occurred. However, when **17** or **22** was dissolved in deuteriochloroform containing acetic acid-d_4, a slow decrease in the intensity of the H_a signal was observed, and ca. 50% of H_a was exchanged after 1 week at 35 °C. In the presence of trifluoroacetic acid-*d*, **17** or **22** had exchanged at H_a by the time the NMR spectrum could be measured. In comparison, thiabenzene 1-oxides **29** and **30** exchanged at H_a and H_a' completely after 8 h at 35 °C under the neutral conditions[4] and underwent complete exchange rapidly in the presence of acetic acid-d_4.

The less facile exchange of the ring protons in 2-azathiabenzene 1-oxides than in thiabenzene 1-oxides is attributed to the lower carbanionic character of the former, in agreement with the NMR findings.

Reduction with Sodium Borohydride. Sodium borohydride reduction of **17** in ethanol produced a colorless oil **32**



32



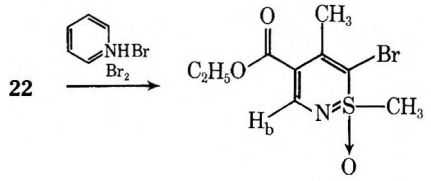
33

displaying the correct molecular ion peak at *m/e* 187 in its mass spectrum and IR absorption at 3280 cm^{-1} due to a hydroxyl group. The NMR spectrum shows a doublet (J = 7 Hz) at δ 1.43 attributable to CH_3CHOH, a broad quartet at δ 4.72 (CH_3CHOH), and a broad singlet at δ 2.53 (OH). In addition, an *S*-methyl singlet is displayed at δ 3.27, and a ring methyl signal (δ 2.25, d, J = 1 Hz), H_a (δ 5.78), and H_b (δ 7.43) are also seen.

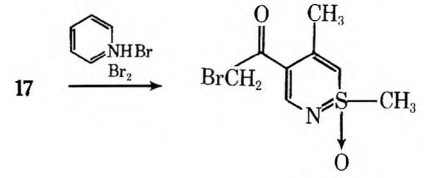
Similarly, **19** was reduced to alcohol **33** in 66% yield.

By contrast, thiabenzene 1-oxide **29** was found to be inert to $NaBH_4$ reduction.

Bromination. When **22** was treated with pyridine bromide perbromide in acetic acid at room temperature, monobromo derivative **34** was obtained in 58% yield. Under similar conditions, **17** gave a less stable compound which we consider to be most likely **35** on the basis of the NMR data.



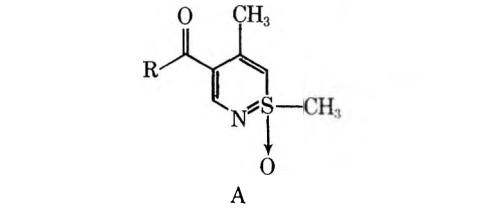
34



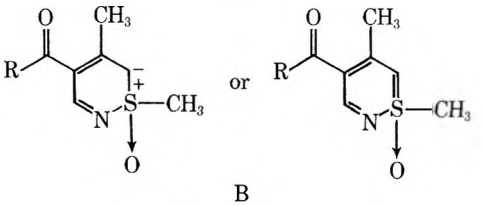
35

Structure of 2-Azathiabenzene 1-Oxides. As noted previously,[4] thiabenzene 1-oxides **29–31** are best regarded as the stabilized cyclic ylides, in which both the carbanionic and betainelike properties are lowered compared with the corresponding acyclic oxosulfonium ylides. These properties can be understood by consideration of the charge delocalization in the ring (but no conjugation through sulfur) and the contribution of $p\pi$–$d\pi$ bonding in the C_2–S–C_6 bond.[13]

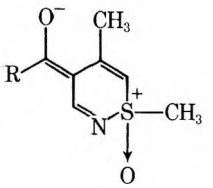
Comparison of the physical and chemical properties of 2-azathiabenzene 1-oxides with thiabenzene 1-oxides demonstrated that both the carbanionic (contribution from structure B) and betainelike properties (contribution from structure C) in the former are much lower than those of the latter. It is possible that the contribution from canonical form A in which the carbonyl group and double bonds exist in a localized state is considerably greater in 2-azathiabenzene 1-oxides. In this arrangement an appreciable negative charge will reside on the nitrogen atom presumably owing to the strong $p\pi$–$d\pi$ bonding between the sulfur and nitrogen.[14]



A

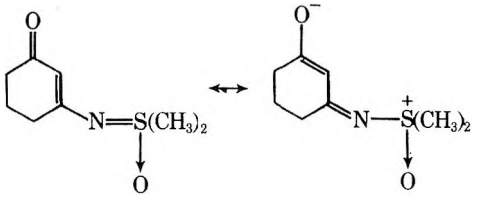


B

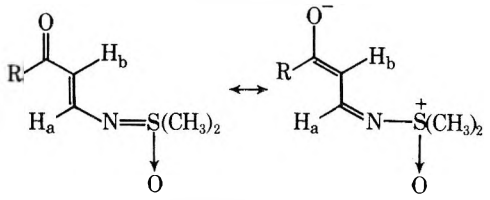


C

In this connection, it should be noted that a similar difference in the extent of delocalization of the negative charge is also seen in acyclic systems. UV and NMR spectral investigations of the electronic structures of sulfoximine **36** and oxosulfonium ylide **39** have revealed that the negative charge of the latter is well delocalized over the enone system while in the former the polarization is relatively small.[15] Comparison of the wavelengths of the carbonyl absorption of the sulfoximines with those of the corresponding oxosulfonium ylides in the infrared spectra provides further support for their

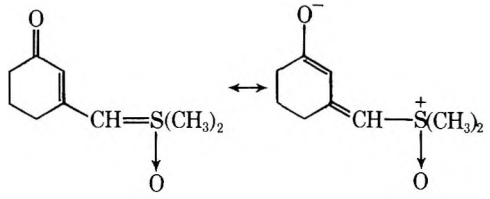


36 (1624 cm^{-1})[15]

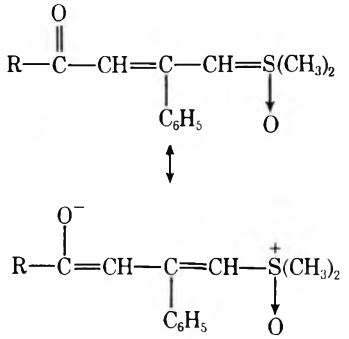


37, R = CH_3 (1658 cm^{-1})[16]
38, R = OC_2H_5 (1685 cm^{-1})[16]

electronic structures; the carbonyl bands of **36–38** are shifted to higher frequency when compared with those of **39–41**.



39 (1589 cm^{-1})[15]



40, R = t-C_4H_9 (1597 cm^{-1})[1]
41, R = OC_2H_5 (1670 cm^{-1})[2]

These results can also be rationalized if we assume that $p\pi$–$d\pi$ bonding in i is stronger than in ii.

Further studies on the electronic structures of both thiabenzene 1-oxides and 2-azathiabenzene 1-oxides using x-ray analysis are in progress.

Experimental Section

Melting points are uncorrected. NMR spectra were determined with Hitachi R-20A (60 MHz) and R-22 (90 MHz) spectrometers using tetramethylsilane as an internal standard. IR spectra were recorded

with a Hitachi EPI-G3 spectrophotometer and UV spectra with a Hitachi 124 spectrophotometer. Mass spectra were obtained with a Hitachi RMU-6D with a direct inlet system operating at 70 eV.

***N*-(2,2-Diacetylvinyl)dimethylsulfoximine (10).** To a solution of 3.12 g (0.02 mol) of **3** in 10 ml of $CHCl_3$ was added 1.86 g (0.02 mol) of dimethylsulfoximine (**9**). The reaction was slightly exothermic. After 30 min, the reaction mixture was scratched. A precipitated white solid was collected and recrystallized from AcOEt to yield 3.58 g (75%) of **10**: mp 165 °C; IR ($CHCl_3$) 1650, 1530 cm^{-1}; UV max (EtOH) 297 nm (log ϵ 4.32), 258 (3.89); NMR ($CDCl_3$) δ 8.10 (s, 1, olefinic proton), 3.27 [s, 6, $S(CH_3)_2$], 2.42 (s, 3, $COCH_3$), 2.30 (s, 3, $COCH_3$); mass spectrum *m/e* 203 ($M^{\cdot+}$).

Anal. Calcd for $C_8H_{13}NO_3S$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.15; H, 6.48; N, 6.83.

***N*-(2,2-Dicarbethoxyvinyl)dimethylsulfoximine (11).** A mixture of 1.86 g (0.02 mol) of **9** and 4.3 g (0.02 mol) of **4** was heated at 130–140 °C while slowly distilling ethanol out of the reaction mixture. Heating was continued until no more ethanol distilled (ca. 30 min). The resulting oil was passed through a short column of alumina with *n*-hexane–AcOEt as solvent to give 3.7 g (70%) of **11** as a yellow solid: mp 67–69 °C (from ether); IR ($CHCl_3$) 1725, 1700, 1595 cm^{-1}; UV max (EtOH) 281 nm (log ϵ 4.48), 218 (3.81); NMR ($CDCl_3$) δ 7.98 (s, 1, olefinic proton), 4.26 (q, 2, J = 7 Hz, OCH_2CH_3), 4.20 (q, 2, J = 7 Hz, OCH_2CH_3), 3.21 [s, 6, $S(CH_3)_2$], 1.33 (t, 3, J = 7 Hz, OCH_2CH_3), 1.29 (t, 3, J = 7 Hz, OCH_2CH_3); mass spectrum *m/e* 263 ($M^{\cdot+}$).

Anal. Calcd for $C_{10}H_{17}NO_5S$: C, 45.61; H, 6.51; N, 5.32. Found: C, 45.67; H, 6.50; N, 5.56.

***N*-(2-Acetyl-2-carbethoxyvinyl)dimethylsulfoximine (12).** A mixture of 1.86 g (0.02 mol) of **9** and 3.72 g (0.02 mol) of **5** was heated at 90 °C for 3 h. After cooling, the reaction mixture solidified. Recrystallization of the solid from *n*-hexane–AcOEt gave 3.76 g (81%) of **12**: mp 97–97.5 °C; IR (KCl) 1720, 1620, 1580 cm^{-1}; UV max (EtOH) 293 nm (log ϵ 4.23), 230 (3.78); the NMR spectrum taken immediately after dissolving **12** in $CDCl_3$ showed the following signals, δ 8.06 (s, 1, olefinic proton), 4.28 (q, 2, J = 7 Hz, OCH_2CH_3), 3.27 [s, 6, $S(CH_3)_2$], 2.28 (s, 3, $COCH_3$), 1.34 (t, 3, J = 7 Hz, OCH_2CH_3). After 10 min, new signals appeared at δ 4.20 (q, J = 7 Hz, OCH_2CH_3), 2.39 (s, $COCH_3$), and 1.30 (t, J = 7 Hz, OCH_2CH_3); mass spectrum *m/e* 233 ($M^{\cdot+}$).

Anal. Calcd for $C_9H_{15}NO_4S$: C, 46.33; H, 6.48; N, 6.01. Found: C, 46.17; H, 6.57; N, 6.20.

***N*-(2,2-Dicyanovinyl)dimethylsulfoximine (13).** A solution of 0.93 g (0.01 mol) of **9** and 1.22 g (0.01 mol) of **6** in 20 ml of $CHCl_3$ was heated at 70 °C for 10 min and then cooled. The precipitated solid was collected and recrystallized from methanol to yield 1.5 g (89%) of **13**: mp 187 °C; IR (KCl) 2200, 1550 cm^{-1}; UV max (EtOH) 283 nm (log ϵ 4.42); NMR (Me_2SO-d_6) δ 8.19 (s, 1, vinyl proton), 3.55 [s, 6, $S(CH_3)_2$]; mass spectrum *m/e* 169 ($M^{\cdot+}$).

Anal. Calcd for $C_6H_7N_3OS$: C, 42.59; H, 4.17; N, 24.84. Found: C, 42.75; H, 4.13; N, 24.91.

***N*-(2-Cyano-2-carbethoxyvinyl)dimethylsulfoximine (14).** Us.ng a similar procedure to that described for **13**, **14** was obtained from 0.93 g (0.01 mol) of **9** and 2.02 g (0.01 mol) of **7** in 87% yield: mp 188 °C (from ethanol); IR (KCl) 2200, 1680, 1570 cm^{-1}; UV max (EtOH) 286 nm (log ϵ 4.42); NMR (Me_2SO-d_6) δ 8.34 (s, 1, vinyl proton), 4.11 (q, 2, J = 7 Hz, OCH_2CH_3), 3.50 [s, 6, $S(CH_3)_2$], 1.20 (t, 3, J = 7 Hz, OCH_2CH_3); mass spectrum *m/e* 216 ($M^{\cdot+}$).

Anal. Calcd for $C_8H_{12}N_2O_3S$: C, 44.44; H, 5.60; N, 12.96. Found: C, 44.70; H, 5.50; N, 12.80.

***N*-(2-Acetyl-3-oxo-1-cyclohexenyl)dimethylsulfoximine (15).** Using a procedure similar to that previously described for **11**, compound **15** was obtained from 1.86 g (0.02 mol) of **9** and 3.4 g (0.02 mol) of **8** in 85% yield (3.9 g): mp 126–126.5 °C (from AcOEt); IR ($CHCl_3$) 1692, 1630, 1564 cm^{-1}; UV max (EtOH) 296 nm (log ϵ 4.34); NMR ($CDCl_3$) δ 3.13 [s, 6, $S(CH_3)_2$], 2.8–1.7 [m, 6, $(CH_2)_3$], 2.22 (s, 3, $COCH_3$); mass spectrum *m/e* 229 ($M^{\cdot+}$).

Anal. Calcd for $C_{10}H_{15}NO_3S$: C, 52.39; H, 6.60; N, 6.11. Found: C, 52.21; H, 6.57; N, 5.90.

Cyclization of 10. A. A solution of 1.02 g (5 mmol) of **10** in 10 ml of dry Me_2SO was added to a stirred suspension of NaH (0.26 g, ca. 1.1 equiv, as a 50% oil dispersion, washed with dry petroleum ether before use) in 10 ml of Me_2SO at room temperature under nitrogen. After stirring for 3 h at room temperature, the reaction mixture was poured into water and extracted thoroughly with $CHCl_3$. The extract was washed with a saturated NaCl solution and dried ($MgSO_4$). Evaporation of the solvent in vacuo gave a brown oil, which was chromatographed on a short column of silica gel with ether as solvent to yield 0.28 g (30%) of **17** as a solid: mp 94–95 °C (from ether–*n*-hexane); IR ($CHCl_3$) 1658, 1569 cm^{-1}; UV max (EtOH) 300 nm (log ϵ 3.94), 272 (4.17); mass spectrum *m/e* 185 ($M^{\cdot+}$).

Anal. Calcd for $C_8H_{11}NO_2S$: C, 51.88; H, 5.99; N, 7.56. Found: C, 52.16; H, 6.05; N, 7.66.

The aqueous layer from the $CHCl_3$ extraction was slightly acidified with 10% HCl solution and extracted with $CHCl_3$. The extract was washed with water, dried ($MgSO_4$), and concentrated to give a brown oil which was chromatographed on silica gel with *n*-hexane–AcOEt as solvent to yield 0.17 g (18%) of **19** as a solid: mp 150 °C (from acetone); IR ($CHCl_3$) 1655, 1550 cm^{-1}; UV max (EtOH) 305 (log ϵ 3.96), 270 nm (4.19); mass spectrum *m/e* 185 ($M^{\cdot+}$).

Anal. Calcd for $C_8H_{11}NO_2S$: C, 51.88; H, 5.99; N, 7.56. Found: C, 52.00; H, 5.99; N, 7.61.

B. When the same reaction mixture of **10** and NaH in Me_2SO was heated at 80 °C for 5 min under nitrogen, followed by the same workup as described above, **17** and **19** were obtained in 22 and 26% yields, respectively.

Cyclization of 15. In the same way as described above, a stirred suspension of 1.15 g (5 mmol) of **15** and NaH (0.26 g as a 50% oil dispersion) in 10 ml of Me_2SO was heated at 80 °C for 3 min under nitrogen. After workup, the crude product was passed through a short column of silica gel with ether as solvent to give 0.77 g (73%) of **20** which was recrystallized from ether: mp 97–97.5 °C; IR ($CHCl_3$) 1645, 1551 cm^{-1}; UV max (EtOH) 297 sh nm (log ϵ 3.92), 275 (4.26); mass spectrum *m/e* 211 ($M^{\cdot+}$).

Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.58; H, 6.21; N, 6.48.

Cyclization of 11. A solution of 1.32 g (5 mmol) of **11** in 10 ml of dry Me_2SO was added to a stirred suspension of NaH (0.26 g as a 50% oil dispersion) in 10 ml of Me_2SO under nitrogen and the reaction mixture was heated at 80 °C for 5 min. After cooling, the reaction mixture was poured into ice–water and a solution was acidified with 10% HCl solution and extracted with $CHCl_3$. The extract was washed with a saturated NaCl solution, dried ($MgSO_4$), and concentrated in vacuo to give 0.65 g (60%) of **21** as a yellowish solid, which was recrystallized from ether: mp 94–95 °C; IR ($CHCl_3$) 3685, 1670, 1605 cm^{-1}; UV max (EtOH) 295 nm (log ϵ 3.36), 250 (3.70), 230 (4.08); NMR ($CDCl_3$) δ 11.94 (s, 1, OH), 8.37 (s, 1, H_b), 5.39 (s, 1, H_a), 4.32 (q, 2, J = 7 Hz, OCH_2CH_3), 3.33 (s, 3, SCH_3), 1.36 (t, 3, J = 7 Hz, OCH_2CH_3); mass spectrum *m/e* 217 ($M^{\cdot+}$). This compound gave a brown color with a ferric chloride solution.

Anal. Calcd for $C_8H_{11}NO_4S$: C, 44.23; H, 5.10; N, 6.45. Found: C, 44.07; H, 5.10; N, 6.45.

Cyclization of 12. A. A solution of 1.17 g (5 mmol) of **12** in 10 ml of dry Me_2SO was added to a stirred suspension of NaH (0.26 g as a 50% oil dispersion) in 10 ml of Me_2SO at room temperature under nitrogen. After 3 h, the reaction mixture was poured into ice–water and extracted with $CHCl_3$. The extract was washed with a saturated NaCl solution, dried ($MgSO_4$), and concentrated to give an oily mixture of two products, which was separated by column chromatography on alumina. Elution with *n*-hexane–AcOEt (1:1) yielded 0.38 (35%) of **22**, which was recrystallized from ether–*n*-hexane: mp 70 °C; IR ($CHCl_3$) 1692, 1570 cm^{-1}; UV max (EtOH) 295 nm (log ϵ 3.46), 245 (4.08); mass spectrum *m/e* 215 ($M^{\cdot+}$).

Anal. Calcd for $C_9H_{13}NO_3S$: C, 50.21; H, 6.08; N, 6.51. Found: C, 50.47; H, 6.16; N, 6.43.

Further elution with the same solvent gave 0.16 g (7%) of **24**, which was recrystallized from benzene–*n*-hexane: mp 153–155 °C; IR ($CHCl_3$) 1710, 1700, 1570 cm^{-1}; UV max (EtOH) 295 nm (log ϵ 3.17), 247 (3.89); NMR ($CDCl_3$, 90 MHz) δ 8.39 (bs, 1, H_b), 6.33 (m, 1, H_a), 5.26–5.04 (m, 1, H_e), 4.30 (q, 2, J = 7 Hz, OCH_2CH_3), 4.22 (q, 2, J = 7 Hz, OCH_2CH_3), 3.67 (d, 2, J = 6 Hz, H_c and H_d), 3.60 (q, 2, J = 18 Hz, H_f and H_g), 3.12 (s, 3, SCH_3), 2.46 (s, 3, ring CH_3), 2.09 (d, 3, J = 1 Hz, vinyl CH_3), 1.38 (t, 3, J = 7 Hz, OCH_2CH_3), 1.24 (t, 3, J = 7 Hz, OCH_2CH_3); mass spectrum *m/e* 430 ($M^{\cdot+}$).

Anal. Calcd for $C_{18}H_{26}N_2O_6S_2$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.44; H, 6.12; N, 6.52.

The aqueous layer of the $CHCl_3$ extraction was acidified with a 10% HCl solution and extracted with $CHCl_3$. The extract was washed with a saturated NaCl solution, dried ($MgSO_4$), and concentrated to give a crude solid, which was recrystallized from acetone to yield 0.12 g (13%) of **23**; mp 197–199 °C; IR (KCl) 1685, 1570 cm^{-1}; UV max (EtOH) 295 nm (log ϵ 3.39), 244 (3.99); NMR (Me_2SO-d_6) δ 8.28 (bs, 1, H_b), 6.31 (m, 1, H_a), 3.49 (s, 3, SCH_3), 2.39 (s, 3, ring CH_3); mass spectrum *m/e* 187 ($M^{\cdot+}$).

Anal. Calcd for $C_7H_9NO_3S$: C, 44.92; H, 4.82; N, 7.48. Found: C, 44.87; H, 4.85; N, 7.56.

B. A stirred suspension of 1.16 g of **12** and NaH (0.26 g as a 50% oil dispersion) in Me_2SO was heated at 80 °C for 5 min under nitrogen. After workup as described above, the basic extract was chromatographed on alumina with *n*-hexane–AcOEt as solvent to give **22** and **24** in 8 and 1% yields, respectively. Chromatography of the acidic

extract on silica gel with AcOEt gave 0.12 g (13%) of **23** and 0.44 g (47%) of **25.** Recrystallization of the latter from MeOH gave white crystals: mp 181 °C; IR (KCl) 3400, 1630, 1575 cm^{-1}; UV max (EtOH) 294 nm (log ϵ 3.84), 268 (3.99), 244 (4.13); NMR (Me_2SO-d_6) δ 13.76 (bs, 1, OH), 8.52 (s, 1, H_b), 5.75 (bs, 1, H_a), 3.48 (s, 3, SCH_3), 2.40 (s, 3, $COCH_3$); mass spectrum *m/e* 187 ($M^{\cdot+}$). This compound gave a brown color with a ferric chloride solution.

Anal. Calcd for $C_7H_9NO_3S$: C, 44.92; H, 4.82; N, 7.48. Found: C, 44.94; H, 4.93; N, 7.47.

Hydrolysis of 22. A solution of 0.86 g of **22** and 0.24 g of NaOH in 15 ml of ethanol was refluxed for 5 h. After cooling, the solution was concentrated in vacuo, acidified with 10% HCl, and extracted with methylene chloride. The extract was washed, dried ($MgSO_4$), and concentrated to give 0.43 g (58%) of **23,** mp 197–199 °C (from acetone).

***N*-(2,2-Dicarbethoxyvinyl)tetramethylenesulfoximine (27).** Using a similar procedure to that described for the preparation of **11,** compound **27** was obtained from 1.04 g (0.01 mol) of tetramethylenesulfoximine (**26**) and 2.15 g (0.01 mol) of **4** in 79% yield (2.15 g) as a colorless oil: IR ($CHCl_3$) 1695, 1590 cm^{-1}; UV max (EtOH) 283 nm (log ϵ 4.14), 233 (3.65); NMR ($CDCl_3$) δ 8.00 (s, 1, olefinic proton), 4.28 (q, 2, J = 7 Hz, OCH_2CH_3), 4.22 (q, 2, J = 7 Hz, OCH_2CH_3), 3.50–3.15 [m, 4, $S(CH_2)_2$], 2.48–2.05 [m, 4, $(CH_2)_2$], 1.84 (t, 3, J = 7 Hz, OCH_2CH_3), 1.29 (t, 3, J = 7 Hz, OCH_2CH_3). This compound was used without further purification.

Cyclization of 27. Using the same procedure described for **21,** compound **28** was obtained from 0.45 g (1.3 mmol) of **27** and NaH (0.65 g as a 50% oil dispersion) in 10 ml of Me_2SO in 53% yield (0.16 g): mp 87–89 °C (from ether); IR ($CHCl_3$) 3685, 1665, 1620 cm^{-1}; UV max (EtOH) 286 nm (log ϵ 3.58), 263 (3.74), 236 (4.26); NMR ($CDCl_3$) δ 11.72 (s, 1, OH), 8.35 (s, 1, H_b), 4.38 (q, 2, J = 7 Hz, OCH_2CH_3), 3.90–2.95 [m, 4, $(CH_2)_2$], 2.35–2.08 (m, 2, CH_2), 1.42 (t, 3, J = 7 Hz, OCH_2CH_3); mass spectrum *m/e* 243 ($M^{\cdot+}$). This compound gave a brown color with a ferric chloride solution.

Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.38; H, 5.39; N, 5.76. Found: C, 49.37; H, 5.38; N, 5.80.

Deuterium Exchange Experiments. A. Under Neutral Conditions. To a solution of 0.1 mmol of a sample of **27** in 0.4 ml of $CDCl_3$ was added 1 drop of D_2O and the mixture was shaken well and kept at 35 °C.

B. With Acid Catalysis. To a solution of 0.1 mmol of a sample in 0.4 ml of $CDCl_3$ was added 1 drop of acetic acid-d_4 or trifluoroacetic acid-d.

The exchange was followed by NMR spectroscopy.

$NaBH_4$ Reduction of 17. To a solution of 185 mg of **17** in 10 ml of ethanol was added 40 mg of $NaBH_4$ and the mixture was stirred at room temperature for 8 h. The mixture was diluted with water, extracted with $CHCl_3$, washed, and dried ($MgSO_4$). Evaporation of the solvent gave 143 mg (77%) of **32** as a colorless oil: IR ($CHCl_3$) 3280, 1585 cm^{-1}; UV max (EtOH) 317 nm (log ϵ 3.25), 220 nm sh (3.16); NMR ($CDCl_3$) δ 7.43 (m, 1, H_a), 5.78 (m, 1, H_b), 4.72 (bq, 1, J = 7 Hz, CH_3CHOH), 3.27 (s, 3, SCH_3), 2.53 (bs, 1, OH), 2.25 (d, 1, J = 1 Hz, ring CH_3), 1.43 (d, 1, J = 7 Hz, CH_3CHOH); mass spectrum *m/e* 187 ($M^{\cdot+}$).

$NaBH_4$ Reduction of 19. Using a similar procedure to that described above for **32, 33** was obtained by reduction of 185 mg of **19** with 40 mg of $NaBH_4$ in 66% yield (123 mg): a colorless oil; IR ($CHCl_3$) 3600, 1600, 1575 cm^{-1}; UV max (EtOH) 321 nm (log ϵ 3.12), 220 (3.23); NMR ($CDCl_3$) δ 7.42 (d, 1, J = 1 Hz, H_a), 5.90 (d, 1, J = 10 Hz, H_c), 4.92 (q, 1, J = 7 Hz, CH_3CHOH), 3.31 (s, 3, SCH_3), 2.25 (s, 3, ring CH_3), 1.60 (s, 1, OH), 1.35 (d, 3, J = 7 Hz, CH_3CHOH); mass spectrum *m/e* 187 ($M^{\cdot+}$).

Bromination of 22. A solution of 0.22 g (1 mmol) of **22** and 0.29 g (1.5 mmol) of pyridine bromide perbromide in 20 ml of acetic acid was stirred at room temperature. After 1 h, the reaction mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with a saturated $NaHCO_3$ solution and a saturated NaCl solution, dried ($MgSO_4$), and concentrated to give a red-brown oil which was submitted to preparative TLC using $CHCl_3$ as solvent to afford 0.17 g (58%) of **34** as a brown solid: mp 64 °C (from *n*-hexane); IR ($CHCl_3$) 1700, 1560 cm^{-1}; NMR ($CDCl_3$) δ 8.17 (s, 1, H_b), 4.22 (q, 2, J = 7 Hz, CH_3CH_2), 3.49 (s, 3, SCH_3), 2.57 (s, 3, ring CH_3), 1.28 (t, 3, J = 7 Hz, CH_3CH_2).

Anal. Calcd for $C_9H_{12}BrNO_3S$: C, 36.74; H, 4.11; N, 4.76. Found: C, 36.83; H, 4.42; N, 4.91.

Bromination of 17. Under similar conditions used for bromination of **22** (except for 15 h at room temperature), 185 mg of **17** gave 160 mg of a crude oily material which liberated bromine during purification procedure: NMR ($CDCl_3$) δ 8.32 (bs, 1, H_b), 5.95 (m, 1, H_a), 4.22 (AB q, 2, J = 11 Hz, $BrCH_2$), 3.38 (s, 3, SCH_3), 2.45 (d, 3, J = 1 Hz, ring CH_3).

Registry No.—**3,** 33884-41-2; **4,** 87-13-8; **5,** 3788-94-1; **6,** 123-06-8; **7,** 94-05-3; **8,** 21014-78-8; **9,** 1520-31-6; **10,** 60804-00-4; **11,** 60804-01-5; **12,** 60804-02-6; **13,** 60804-03-7; **14,** 60804-04-8; **15,** 60804-05-9; **21,** 60804-06-0; **23,** 60804-07-1; **24,** 60804-08-2; **25,** 60804-09-3; **26,** 50578-18-2; **27,** 60804-10-6; **28,** 60804-11-7; **32,** 60804-12-8; **33,** 60804-13-9; **34,** 60804-14-0; **35,** 60804-15-1; pyridine bromide perbromide, 39416-48-3.

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Photoelectron Spectra of Cyclic Azo *N*-Oxides and Azo *N,N'*-Dioxides

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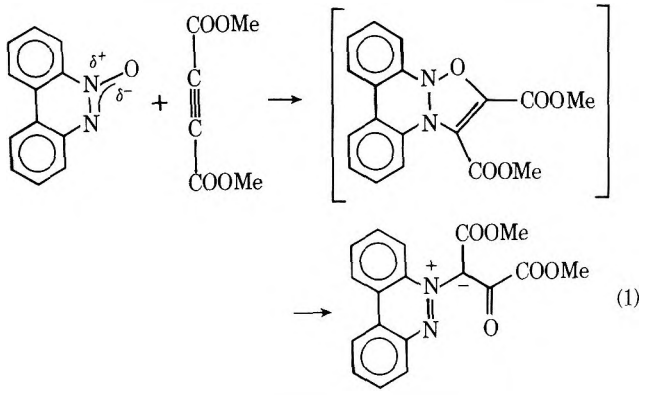
Received February 11, 1976

The photoelectron spectra of 3,3,4,4-tetramethyldiazetine (1), 3,3,4,4-tetramethyldiazetine *N*-oxide (2), 3,3,4,4-tetramethyldiazetine *N,N'*-dioxide (3), 3,3,6,6-tetramethyl-1,2-diazacyclohexene (4), 3,3,6,6-tetramethyl-1,2-diazacyclohexene *N*-oxide (5), and 3,3,6,6-tetramethyl-1,2-diazacyclohexene *N,N'*-dioxide (6) have been measured and the ionization potentials have been interpreted in terms of molecular orbitals with the assistance of INDO calculations. The energy of the highest occupied π orbital increases along the series azo > azo oxide > azo dioxide, a result consistent with expectations based on simple perturbation theory. The relationships between the molecular orbital energies and the chemistry of azo *N*-oxides and azo *N,N'*-dioxides are discussed.

Azo *N*-oxides and azo *N,N'*-dioxides, formally obtained by stepwise oxidation of azo compounds, have many interesting physical and chemical properties such as the valence isomerization of azo *N*-oxides to oxadiaziridines[1] and the dissociation/dimerization of azo dioxide/nitroso alkanes.[2] While studing these two reactions we prepared a number of cyclic azo, azo *N*-oxide, and azo *N,N'*-dioxide compounds. Herein we report the photoelectron spectra of these compounds and calculations of the electronic structures of azo *N*-oxides and azo *N,N'*-dioxides by the INDO–SCFMO method.

Azo *N*-oxides, like azomethine ylides, azomethine imines, nitrones, azimines, and nitroalkanes, are 1,3 dipoles having nitrogen as the central atom[3]. In this series of 1,3 dipoles, reactivity in cycloaddition reactions varies from very high (azomethine ylides) to undetectable (nitroalkanes), with azo *N*-oxides being among the less reactive compounds. Rees and co-workers have reported that the reaction of benzo[c]cinnoline *N*-oxide and dimethyl acetylenedicarboxylate at 190 °C gives an ylide, presumably through rearrangement of an initially formed cycloadduct (eq 1).[4] The reactivity of 1,3 di-

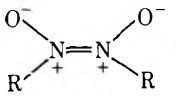


(1)

poles in cycloaddition reactions has been correlated with the electronic structure of the 1,3 dipole,[5] as will be elaborated upon later.

Azo *N*-oxides are thermally more stable than the corresponding azo compounds. In cases where the rates of extrusion of N_2O and N_2 from azoxy alkanes and azo alkanes have been measured the ratio of the rate constants is on the order of $k_{azoxy}/k_{azo} = 10^{-16}$.[6] The difference in the rates of these reactions has been attributed to a symmetry-induced barrier to reaction in the azo *N*-oxide due to the perturbing effect of the oxygen on the MO's of the reactant.[6]

The chemistry of azo *N,N'*-dioxides has many aspects of interest, including the thermal dissociation of the azo dioxide to the corresponding nitroso alkane, in the formal sense cleavage of a double bond under very mild conditions (eq 2). Rates and equilibria of the reaction have been measured for a number of cyclic and acyclic systems.[2,7,8] The mechanism

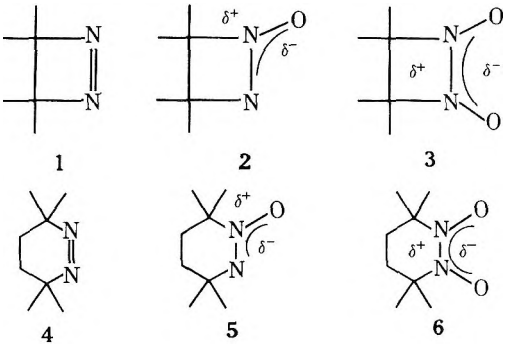


2RNO (2)

of the dimerization/dissociation process has been studied by Hoffmann, Mallory, and Gleiter; they suggested a non-least-motion path for the dimerization reaction, the least-motion path being symmetry forbidden.[9] Their ideas have received experimental support in the work of Greene and Gilbert on cyclic azo dioxides.[8]

In those azo dioxides which do not dissociate, the chemistry of the azo dioxide functional group can be observed. Azo dioxides can be reduced to azo *N*-oxides and azo compounds, but they are resistant to further oxidation.[8] Azo dioxides react photochemically to give nitroxyls (loss of NO).[8,10] In a thermal reaction, 3,3,4,4-tetramethyldiazetine *N,N'*-dioxide (3) gives 2,3-dimethyl-2-butene and NO.[11] Overall, azo dioxides are a relatively inert functional group.

Herein we report the photoelectron spectra of a series of cyclic azo, azo *N*-oxide and azo *N,N'*-dioxide compounds and molecular orbital calculations on the electronic structures of these molecules. The reactivity of azo *N*-oxides in 1,3-dipolar cycloaddition reactions and the oxidation–reduction chemistry of azo *N,N'*-dioxides have received particular attention as we are interested in relationships between molecular orbital theory, photoelectron spectroscopy, and chemical reactivity.



1 2 3

4 5 6

Experimental Section

The spectra were run on a PS-18 spectrometer (Perkin-Elmer) with a standard inlet for liquid and solid samples. The spectra were calibrated with argon as an internal standard. The ionization potentials reported in Table I are the average values from three or more spectra; single values were reproducible to ±0.05 eV. All compounds were prepared as previously reported.[8] For the solid samples the probe was heated to increase the count rate: 36 °C for **2**, 65 °C for **3**, 50 °C for **5**, and 80 °C for **6**, all ±5 °C.

PE Spectra. The PE spectra of the four-membered ring series 3,3,4,4-tetramethyldiazetine (1), 3,3,4,4-tetramethyldiazetine *N*-oxide (2), and 3,3,4,4-tetramethyldiazetine *N,N'*-dioxide (3) are presented in Figure 1. The PE spectra of the six-membered ring series 3,3,6,6-tetramethyl-1,2-diazacyclohexene (4), 3,3,6,6-tetramethyl-1,2-di-

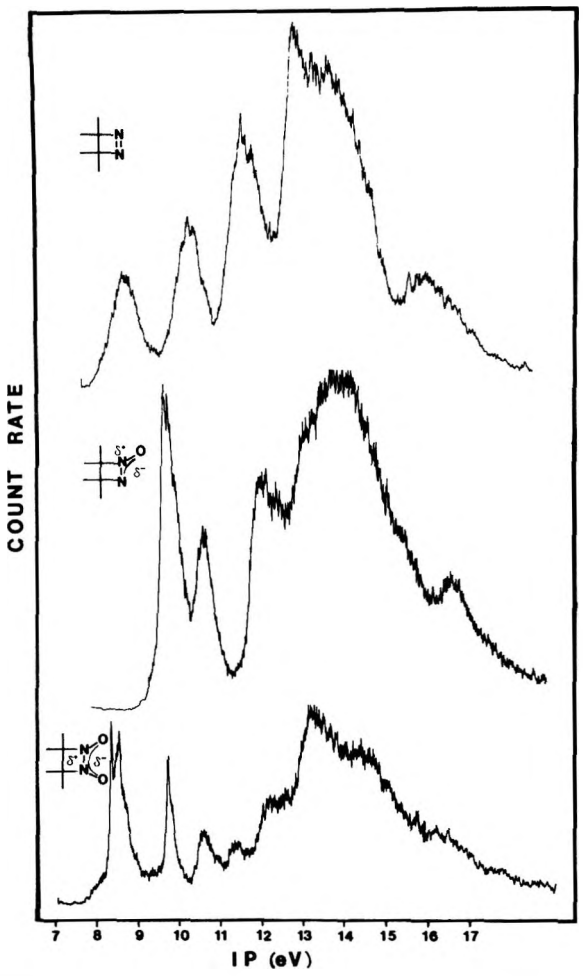


Figure 1. Photoelectron spectra of four-membered ring series (**1**, **2**, and **3**).

Table I. Ionization Potentials (eV) of Compounds 1–6[a]

Compd	1st	2nd	3rd
1	8.77	10.24	11.5
2		9.82[b]	10.8
3	8.52	9.73	10.6
4	7.85	10.7[c]	
5		9.20[b]	10.1
6	8.19	9.58	10.7

[a] The spectra were calibrated with argon as a single internal standard (see Experimental Section). As a referee has pointed out, care must be taken when using this technique that the linearity of the spectral range not change with time; otherwise ionization potentials in the 8-eV region will be inaccurate. The reproducibility of our results suggests that we have not encountered this problem. (For a comparison, see ref 29, Table I). [b] The first two bands overlap and a precise assignment is not possible; see text for discussion. [c] Broad, diffuse band, assignment accurate to only ±0.1 eV.

azacyclohexene *N*-oxide (**5**), and 3,3,6,6-tetramethyl-1,2-diazacyclohexene *N,N'*-dioxide (**6**) are presented in Figure 2. The corresponding vertical ionization potentials of compounds **1–6** are given in Table I. These potentials refer to the positions of the corresponding maxima of the Frank–Condon envelopes.

Results and Discussion

INDO Calculations. Calculations of the electronic structures of azo *N*-oxides and azo *N,N'*-dioxides by the INDO–SCFMO[12] method were investigated to aid interpretation of the photoelectron spectra.[13] Initially we sought a model system which would reproduce the significant trends in the photoelectron spectra. Calculations were performed on diimide (**7**), diimide *N*-oxide (**8**), and diimide *N,N'*-dioxide (**9**) with the HNNH angle fixed to reproduce either the four-membered ring series (95°) or the six-membered ring series (120°). The calculations on this model system were checked against similar calculations on the four-membered ring series compounds **1**, **2**, and **3** (methyl groups included): for **1**, **2**, and **3** standard bond lengths and angles (except within the ring) were used and the total energy was minimized with respect to the NN bond length for **1** and with respect to the NN and NO bond lengths for **2** and **3**.[14] The results are summarized in Table II. Since the model system reproduces the geometries

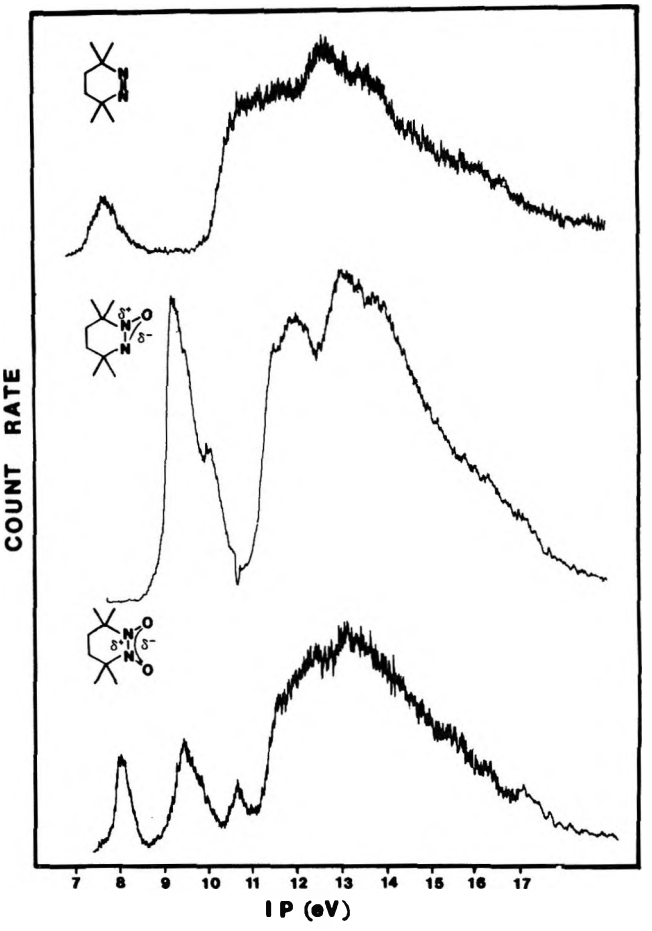


Figure 2. Photoelectron spectra of six-membered ring series (**4**, **5**, and **6**).

Table II. Geometries of 1–3 and the Models for 1–6 Calculated by the INDO Method

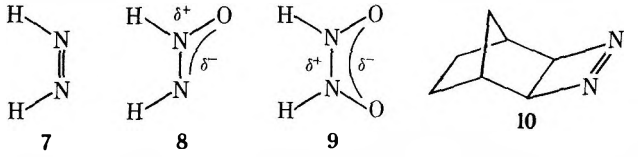
Compd	<CNN, deg[a]	<HNN, deg	R_{NN}, Å	R_{NO}, Å
1	95		1.26	
7		95	1.26	
7		120	1.22	
2	95		1.29	1.23
8		95	1.29	1.23
8		120	1.26	1.23
3[b]	95		1.32	1.24
9		95	1.32	1.24
9		120	1.29	1.24

[a] These CNN angles were found by minimizing the total energy with respect to the NN bond length for **1**, and with respect to the NN and NO bond lengths for **2**. These values were then used for <HNN in the calculations on **7–9**. [b] Calculations for **3** were not carried to the full energy minimization.

Table III. Orbital Coefficients in the Azo *N*-Oxides

Compd	π_2			n_+		n_-	
	O	N_1	N_2	O	N_2	O	N_2
2	−0.67	0.13	0.66	0.39	0.43	−0.66	0.29
8 (95°)	−0.73	0.11	0.68	0.66	0.23	−0.52	0.60
8 (120°)	−0.75	0.09	0.66	0.62	0.32	−0.55	0.63

of **1**, **2**, and **3**, we assume that this model system will delineate the significant trends in shape, electron density, and energy of the molecular orbitals of compounds **1**–**6**. One limitation of calculations based on the protio models **7**–**9** is that they cannot assess the effects of the carbon skeleton on the MO trends. Comparison of the calculations on the four-membered ring compounds **1**–**3** and the protio models **7**–**9** revealed no



7 **8** **9** **10**

significant differences in the trends we were interested in—the ordering of the molecular orbitals and the prediction of ionization potentials. The ionization potentials calculated, based on these model compounds and Koopmann's theorem,[15] will not correspond to the observed ionization potentials in absolute value, but significant trends in the ordering of the molecular orbitals and in relative energy differences between orbitals should be preserved.

Azo Compounds 1 and 4. The PE spectra of azo compounds have been extensively studied and the assignments of the first three ionization potentials to ionization from the antisymmetric (n_-) and symmetric (n_+) combinations of lone pair orbitals on the nitrogens and to the π orbital are well established.[16] The first three bands in the PE spectrum of **1** (Figure 1) at 8.77, 10.24, and 11.5 eV are accordingly assigned to the n_-, n_+, and π orbitals, respectively. The observed ionization potentials and assignments are in excellent agreement with the results of Heilbronner, Lemal, et al., for 3,4-diazatricyclo[4.2.1.$0^{2,5}$]non-3-ene (**10**).[17] The splitting between the π orbital and the σ levels is much greater in **1** than in **10** and allows a more precise assignment of the ionization for the π level in the four-membered-ring azo compounds.

The PE spectrum of azo compound **4** has recently been reported by Houk, Engle, and Chang[18] and our results are identical with theirs. The first ionization potential, at 7.85 eV, is broad and structureless and has been assigned to ionization from the n_- orbital. The second band was not well defined and has been assigned an ionization potential of 10.7 ± 0.1 eV.

Azo *N*-Oxides 2 and 5. Oxidation of an azo group to an azo *N*-oxide changes the ethylenic π system of the azo group to an allyl π system in the azo *N*-oxide, and changes the lone pair interaction from a 1,2 interaction of orbitals of equal energy (azo) to a 1,3 interaction of orbitals of unequal energy (azo *N*-oxide: O_p and N_p). All 1,3 dipoles have a three-atomic-orbital system containing four electrons, and thus π_1 and π_2 are filled in the azo *N*-oxides (see Figure 3).[3] The point of interest for interpreting the PE spectra is the relative ordering of π_2 and the two lone pair orbitals. It is difficult to assess the effect of the difference in energy of the oxygen and nitrogen p orbitals on the relative ordering of the three orbitals of interest. INDO calculations on **2** and **8** were studied as a function of both the CNN or HNN angles and the NNO angle. With the HNN angle of **8** fixed at either 95° or 120°, the ordering of the molecular orbitals was π_2, n_+, and n_- for an NNO angle of 120°. The energy of the π_2 orbital was insensitive to the NNO angle while the relative energies of the lone pair orbitals were calculated to cross at an NNO angle of 115°. The π_2 orbital

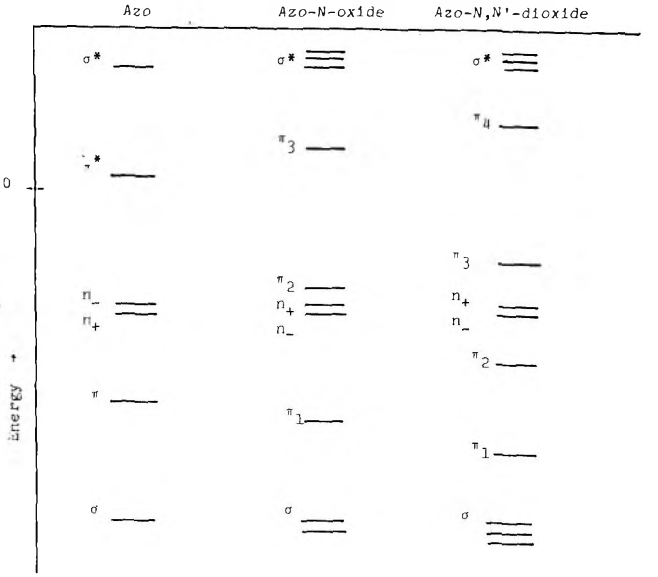
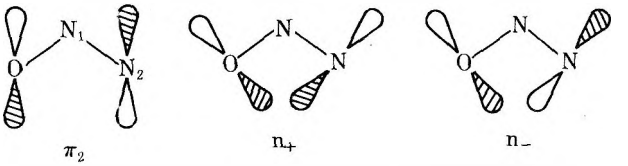


Figure 3. Schematic diagram of the orbital levels in the azo, azo *N*-oxide, and azo *N,N'*-dioxide compounds based on INDO calculations.

had most of the electron density on the two end atoms with a node between O and N_1. The lone pair orbitals are shown below and the orbital coefficients are given in Table III.



π_2 n_+ n_-

In all the calculations on azo *N*-oxides with the NNO angle fixed at 120° the ordering of the MO's was π_2, n_+, and n_-. The difference in energy between the π and n_+ orbitals was calculated to be 1.3 eV for **8** with an HNN angle of 95°, 1.5 eV for an HNN angle of 120°, and 0.6 eV for **2**. These results are based on Koopman's theorem.[14] We also have calculated the total energy of the radical cation formed by loss of an electron from a specified orbital in the ground state molecule, and from this calculated total energy we subtracted the calculated total energy of the ground state molecule; in this way we have taken some account of electron reorganization which must occur during ionization and thus have circumvented some of the problems inherent in Koopman's theorem.[19,20] With this method the calculated energy differences between the π_2 and n_+ MO's in **8** were 0.4 eV for HNN = 95° and 0.3 eV for HNN = 120°; convergence problems complicated calculations on **2**. We expect to see two closely spaced bands in the PE spectra of azo *N*-oxides corresponding to ionization from the π_2 and n_+ orbitals with the n_- orbital coming at higher energy.

The PE spectrum of **2** showed a broad, intense first band capped by two sharp spikes. Whether the two sharp peaks at 9.75 and 9.9 eV should be assigned to separate ionization potentials or to vibrational fine structure is not clear from the spectrum. Further work at higher resolution than we have obtained, or on more tractable analogous compounds (such as the perfluoro derivatives), would be required to resolve this

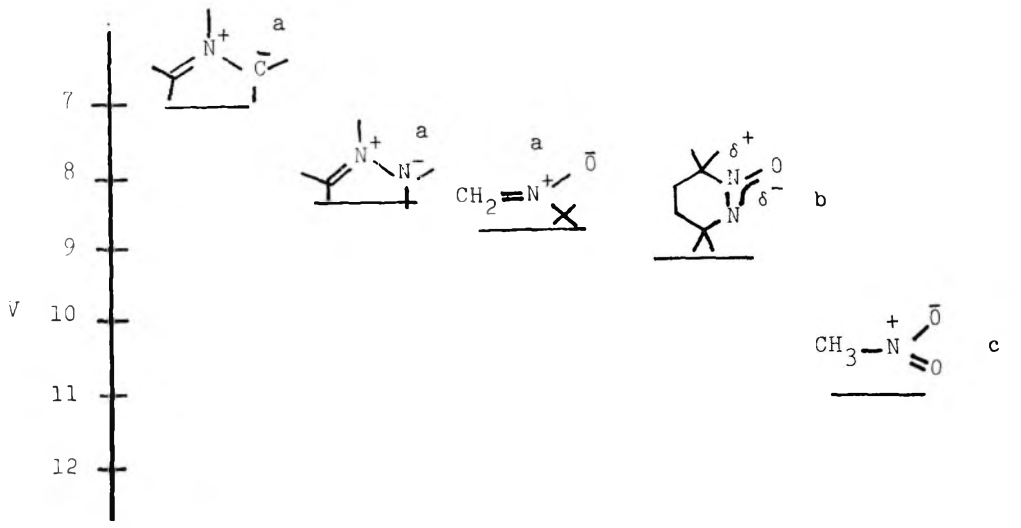


Figure 4. HOMO energies of the series of nitrogen-centered 1,3 dipoles taken from (a) ref 5, (b) this work, and (c) M. J. S. Dewar, M. Shanshal, and S. D. Worley, *J. Am. Chem. Soc.*, **91**, 3590 (1969).

uncertainty. Tentatively, we would assign the π_2 and n_+ molecular orbitals to the first band based upon the calculations and upon the high intensity of the band. The third band in the spectrum at 10.8 eV was assigned to the n_- orbital.

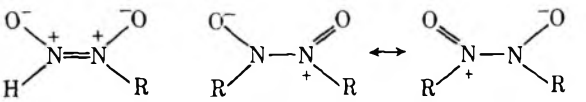
The PE spectrum of **5** shows a broad first band which could not be resolved into separate peaks. This was not unexpected since the energy differences predicted were smaller in this system, and because increasing the size of a molecule usually results in less well defined peaks. We have assigned two ionization potentials, π_2 and n_+, to this first band for the same reasons given for the four membered ring compound **2**. The band at 10.1 eV was assigned to the n_- MO.

The effect of oxidizing an azo system is to raise the energy of the π orbital and to interchange the energy of the n_- and n_+ orbitals.[22]

Houk and co-workers have correlated the energies of the highest occupied π orbitals with reactivity in 1,3-dipolar cycloaddition reactions for a series of 1,3 dipoles.[5] Application of perturbation theory to 1,3-dipolar cycloaddition reactions led them to conclude that reactivity in 1,3-dipolar cycloadditions would increase as the dipole LU was lowered and the dipole HO increased.[5] Since the changes in the HO level are larger than changes in the LU level, they proposed that reactivity would correlate with the HOMO level.[5] Their work did not include azo *N*-oxides, probably owing to lack of information.

In Figure 4 we have plotted the HOMO energies of several 1,3 dipoles. Along the series azomethine ylide, azomethine imine, nitrone, azo *N*-oxide, and nitroalkane the reactivity in 1,3-dipolar cycloaddition reactions decreases. The ionization potential of azo *N*-oxides, measured here, would suggest very little reactivity in cycloaddition reactions for the azo *N*-oxides, as has been observed experimentally.[4,8] The only reported case is that of Rees and co-workers referred to above.[4] This type of negative evidence is not conclusive, but it is consistent with the ideas of Houk et al.[5]

Azo *N,N'*-Dioxides 3 and 6. Oxidation of an azo *N*-oxide to an azo *N,N'*-dioxide changes the allyl π system of the monooxide to a butadiene-like π system in the dioxide, and the 1,3 lone pair interaction into a 1,4 lone pair interaction between orbitals of equal energy. Previous SCF calculations on azo dioxides have emphasized that the major contributor to the electronic structure of azo dioxides is I, with some contribution from structure II to reduce the positive charge on the adjacent nitrogens.[24,25] Our results suggest that this simple type of valence bond picture may not be a good representation



I II

for azo dioxides and that a MO picture might be more accurate.

Calculations by the INDO method on **3** and on **9** predict the NO bond length to be shorter than the NN bond length as has been observed by DeBoer and Turley.[26] The calculated charges on the nitrogens of diimide *N,N'*-dioxide were +0.29 and on the oxygens −0.35. For comparison the calculated charge on the nitrogen of nitromethane was +0.615. A simple valence model predicts a charge of ±0.5 to +1.0 for the nitrogens of an azo dioxide. The lower value predicted by INDO calculations is supported by the ESCA results, which have been interpreted as a measure of the charge on an atom.[8,27] Calculations based on the MO picture correctly reproduce the geometry of the azo *N,N'*-dioxides and the trends in the ESCA results.[8]

INDO calculations predict the HOMO to be a π orbital similar to χ_3 of butadiene with a node between the oxygens and nitrogens, and of low energy (IP = 8–8.5 eV). The χ_3 orbital of butadiene is antibonding. Replacing the carbons of butadiene with nitrogen and oxygen to give the azo dioxide should stabilize this orbital due to the higher core charges of nitrogen and oxygen. The PE spectrum of 3,3,4,4-tetramethyldiazetine *N,N'*-dioxide (**3**) has a first band at 8.37 eV. The first band in the PE spectrum of 3,3,6,6-tetramethyl-1,2-diazacyclohexene *N,N'*-dioxide (**6**) was at 8.19 eV. Both azo dioxides have a first ionization potential at low energy, much lower than the first ionization potentials of either azo or azoxy compounds, and well in accord with the calculations.

The energies of the lone pair orbitals will be determined by the magnitude of the 1,4-through bond interaction. The lone pair orbitals on the oxygens combine to form a symmetric and an antisymmetric orbital of approximately equal energy. However, these lone pair orbitals can interact with the NN σ and σ^* orbitals and this will give rise to the characteristic through bond interaction (see Figure 5).[28] The symmetric lone pair orbital mixes into the NN σ orbital, of the same symmetry, in an antibonding fashion and goes to higher energy. The antisymmetric lone pair orbital mixes into the NN σ^* orbital in a bonding fashion and goes to lower energy. The calculated

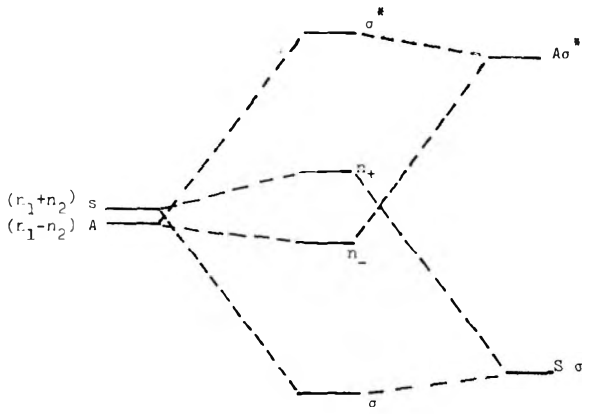


Figure 5. 1,4-Through bond interaction of oxygen lone pairs with the σ and σ^* NN bonds in the azo dioxides.

splitting between the lone pair orbitals is 1.75 eV for **9** (95°) and 1.2 eV for **9** (120°). The observed splittings were 1.1 eV for **3** and 0.9 eV for **6**. Thus, the MO picture successfully reproduces the major features of the photoelectron spectra of azo dioxides.

In summary the photoelectron spectrum of azo dioxide **3** was assigned as π orbital 8.37, n_+ 9.73, and n_- 10.6 eV; and the spectrum of **6** was π 8.19, n_+ 9.58, and n_- 10.7 eV.

The general features of the molecular orbital structure of azo dioxides do not account for the known oxidation–reduction chemistry of azo dioxides. The low ionization potential of the π orbital suggests that it would readily give up an electron and be oxidized, while the high energy of the LUMO would argue against further reduction. Compound **6** has been reduced with Si_2Cl_6 and $LiAlH_4$, but it was not oxidized by a variety of reagents, including $KMnO_4$.[8]

The correlation of chemical reactivity and photoelectron spectral data is in the early stages of exploration, and definitive results are not yet available. The correlation of cycloaddition reactivity with the HOMO energy in the nitrogen-centered 1,3 dipoles suggests that PE data may be useful in the design of organic syntheses. The greater understanding of molecular properties, such as oxidation and reduction potentials, which can be obtained with PE data is another area that will be useful to all organic chemists.

Acknowledgment. This work was supported in part by the National Science Foundation through Grant GP-40933X. I thank Dr. John Baldwin for many helpful discussions, and Drs. Thomas Koenig and Richard Wielesek and Mr. William Snell for help in obtaining the photoelectron spectra.

Registry No.—**1**, 54166-22-2; **2**, 40543-89-3; **3**, 34493-89-5; **4**, 19403-24-8; **5**, 54143-34-9; **6**, 54143-35-0.

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Photoelectron Spectra of Bicyclic Azo *N*-Oxides and Azo *N,N'*-Dioxides[1]

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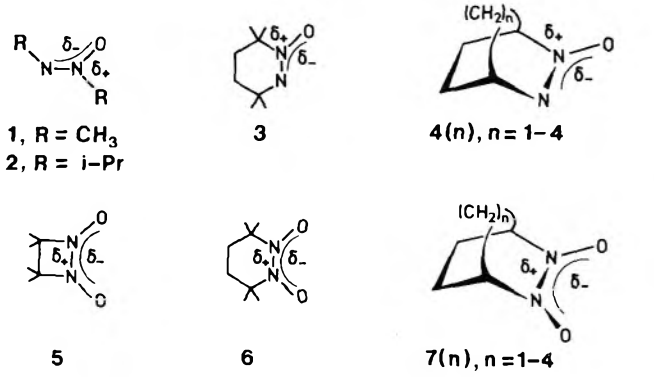
Received April 29, 1976

The photoelectron (PE) spectra of a series of cyclic azo *N*-oxides and azo *N,N'*-dioxides have been measured. For the former the highest lying molecular orbitals are assigned in order of decreasing energy: π(NNO) ~ n_+(NNO) > n_-(NNO). For the latter a π(ONNO) > n_+(OO) > n_-(OO) series is obtained. The assignments are based on empirical correlation including well-resolved fine structure in several cases and on semiempirical calculations involving three separate parameterizations. The molecular orbital correlation for the redox series azoalkane, azo *N*-oxide, and azo *N,N'*-dioxide is delineated.

The recent interest in the electronic structure of azo *N*-oxides and azo *N,N'*-dioxides[2-5] prompts us to present some preliminary results we have obtained in the course of our systematic investigation of the chemical,[6] thermochemical,[7] and electronic properties of acyclic, bicyclic, and polycyclic azo *N*-oxides and azo *N,N'*-dioxides. Here we report the He I photoelectron spectra of 2,3-diazabicyclo[2.2.*n*]alk-2-ene 2-oxide [**4**(*n*)], 2,3-diazabicyclo[2.2.*n*]alk-2-ene 2,3-dioxide [**7**(*n*)], and the reference compounds **1**–**3** and **5**–**6**.



The spectra are interpreted on the basis of empirical correlation and by CNDO–MO calculations for **4**(1,2), **5**, and **7**(1,2) employing several parameterizations.[8]

Experimental Section

The compounds were prepared and purified as previously described.[6] The PE spectra were recorded on a PS-18 spectrometer (Perkin-Elmer, Beaconsfield, England) and calibrated with a mixture of argon and xenon gases introduced to the target chamber *simultaneously* with the sample. The reported ionization potentials (Table I) are averages of three to six determinations. Slow scanning of the spectra with narrow slits and low vapor pressure in the target chamber enabled us to obtain well-resolved vibrational fine structure for the first bands of **6** and **8**(2). A more diffuse structure was observed for the other compounds.

Discussion

Typical spectra for the azo *N*-oxides **1** and **4**(1) are given in Figures 1 and 2, respectively. The first five experimental IP's for the compound series studied are listed in Table I.

The two highest levels are predicted by all parameterizations to be π(NNO) and n_+(NNO) (cf. Figure 5)[9] and to be very close in energy by CNDO/B. The former is in agreement with reported calculations for azoxymethane[10] and 3,3,4,4-tetramethyldiazetine *N,N'*-dioxide (**5**).[5] Indeed the first band in the PE spectra of compounds **1**–**3** is very intense and seems to contain two ionizations.[11] Careful scrutiny of expanded spectra of this band reveals a diffuse vibrational structure but no conclusion regarding the exact IP of each orbital can be drawn. A clearer situation is encountered in the series **4**(*n*). The PE spectrum of diazanorbornene *N*-oxide **4**(1) (Figure 2) shows two ionization bands at 9.48 and 9.72 eV (predicted splitting: 0.17 eV, CNDO/B). The energy difference between π(NNO) and n_+(NNO) decreases when the size of the molecule increases. We were able, however, to resolve the two bands for the other three bicycles and to estimate their respective fine structure (cf. Table I). The calculations suggest the third IP to be associated with ionization from n_-(NNO) consistent with the findings for pyrimidine and pyrazine *N*-oxides.[2,3]

The question as to whether the π(NNO) orbital lies above n_+(NNO) remains. We cannot rely exclusively on MO calculations since the energy difference is small, the calculations were performed with estimated geometries, and, further, the strict validity of Koopmans' theorem would be required in order to compare the experimental IP's with the calculated energies. Population analysis for **4**(1) and **4**(2) reveals that

Table I. First Five Experimental Vertical Ionization Potentials (IP's, eV)[a] of Some Azo *N*-Oxides

IP	1	2	3	4(1)	4(2)	4(3)	4(4)
1				9.48 (1200)	9.30 (~1000)	9.21 (~1000)	9.13 (~1000)
	10.07[b]	9.60[b]	9.13[b]				
2				9.72 (800)	9.42 (~1000)	9.30 (~1100)	9.24 (~1000)
3	11.06	10.33	9.88	10.75	10.28	10.09	10.00
4	13.02[c]	11.8[d]	11.4[d]	12.17	11.41	11.45	11.10
5	14.1	12.2[e]	11.8[e]	13.1	11.87	11.8[c]	11.5[d]

[a] Key: ±0.03 or ±0.1 eV. The vertical IP's are taken as the maxima of the Frank–Condon envelopes. The numbers in brackets represent the vibrational fine structure, ±50 or ±100 cm^{-1}. [b] The first two IP's interpenetrate and show diffuse vibrational structure; a precise assignment is not possible. The number indicates the maximum of the band. [c] This band exhibits a complex fine structure (~1350 and ~1000 cm^{-1}). [d] Shoulder. [e] Broad band which contains more than one IP.

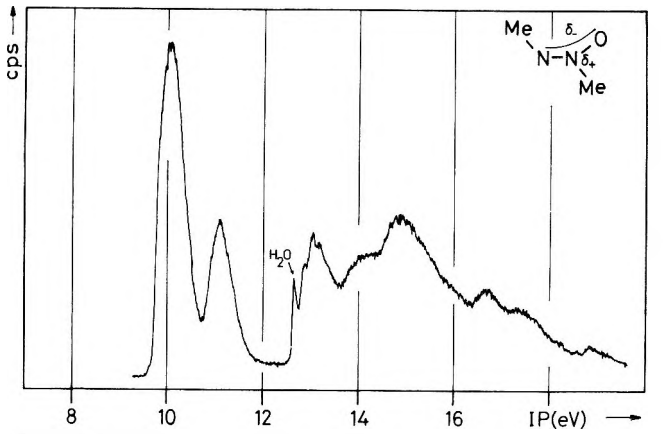


Figure 1. Photoelectron spectrum of **1**.

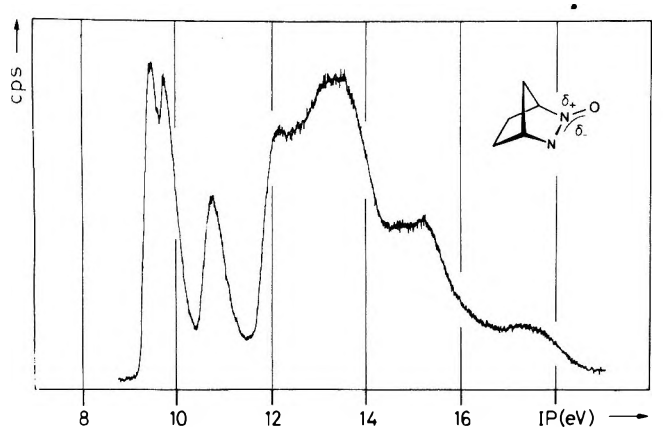


Figure 2. Photoelectron spectrum of **4**(1).

Table II. First Five Experimental Vertical Ionization Potentials (IP's, eV)[a] of Some Azo *N,N'*-Dioxides

IP	5	6	7(2)	7(3)	7(4)
1	8.23 (750, 1050)	7.86 (~900)	8.04 (680)	8.04 (~800)	8.03 (~800)
2	9.45 (800)	9.33	9.44 (800)	9.48	9.46
3	10.42	9.5[b]	9.88	9.7[b]	9.7[b]
4	11.25	10.57	10.75	10.77	10.58
5	12.1	11.6[b]	11.7	11.7	11.4

[a] See Table I. [b] Shoulder.

both π(NNO) and n_+(NNO) orbitals are NN bonding and NO antibonding. The former is quite localized on the NNO moiety whereas the latter mixes more with other MO's. It might be expected that the vibrational frequency will be reduced to a greater extent for n_+(NNO) than for π(NNO). However, the NN and NO stretches (1508 and 1200 cm^{-1}, respectively, in the neutral molecule[12]) are probably strongly coupled so that a more detailed analysis will be required in order to make a secure assignment.

The addition of a second oxygen atom to the NNO group leads to a more symmetrical moiety whose characteristic high-lying orbitals are a ONNO antibonding π orbital and two oxygen lone pair orbitals, n_+ and n_- (cf. Figure 5). Typical spectra are shown on an expanded scale for **5** and **7**(2) in Figures 3 and 4, respectively. The experimental first five IP's of the compounds studied are collected in Table II.

Again the CNDO/B, CNDO/S and CNDO/2 methods used here and other work[5,10] agree that the antibonding π(ONNO) orbital is the HOMO. We thus assign the first band in all the spectra to this energy level. Although no explicit calculations

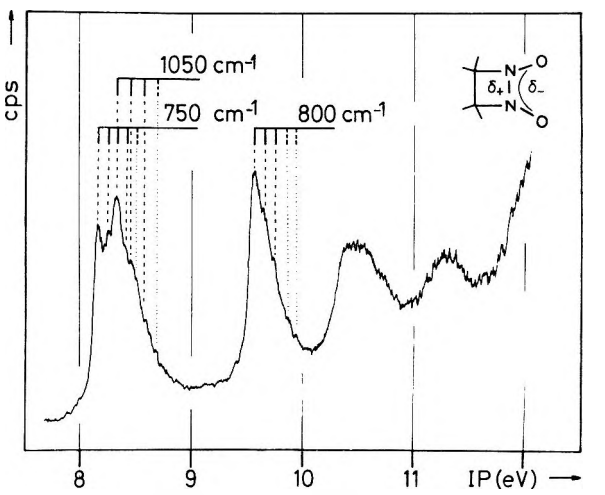


Figure 3. Photoelectron spectrum of **5** (expanded scale).

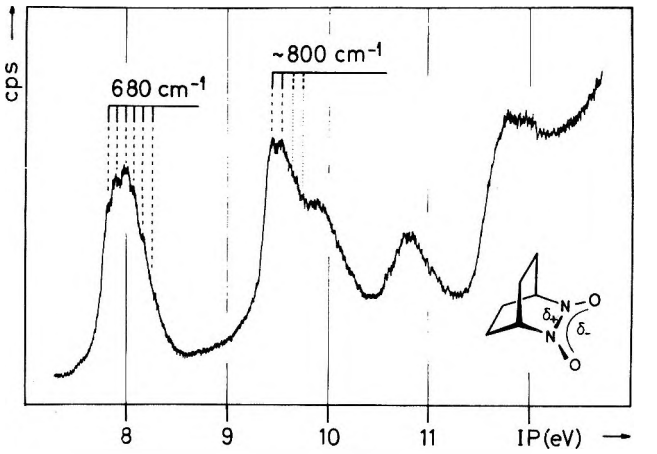


Figure 4. Photoelectron spectrum of **7**(2) (expanded scale).

were carried out for dioxide **6**, the analogous assignment is supported by the similarity of observed fine structure for **6** and **7**(n)[13] (680–900 cm^{-1}). In the case of **5** two progressions are observed, one of which (1050 cm^{-1}) could arise from the NO stretching vibration (1320 and 1450 cm^{-1} in neutral *cis*-nitroso dimers[14]). The next two bands are assigned to the symmetrical and antisymmetrical lone pair combinations, respectively. The observed splitting, $\epsilon(\Delta n) = \epsilon(n_+) - \epsilon(n_-)$, amounts to 0.96 eV for **5**. According to the CNDO calculations, it is mainly through-bond dominated owing to an appreciable contribution of the cyclobutane ring orbitals to the n_+ and n_- orbitals. The situation changes in going to the six-membered ring. Through-bond and through-space interactions almost cancel each other leading to $\epsilon(\Delta n) \simeq 0.17$ eV (calculations predict it to be five times smaller than for **5**). That two ionizations are contained in the second band of **6** is not very obvious; however, the situation is clear for **7**(2) where the two bands are well separated. For **7**(3) and **7**(4) we observe only shoulders.

In summary the oxidation of an azo alkane perturbs both the lone-pair and the π system in a straightforward fashion as illustrated by the [2.2.2]-bicyclic example in Figure 5. The strong 1,2-azo lone pair interaction [$\epsilon(\Delta n) \simeq 3.0$ eV][15] is replaced by the reduced 1,3-nitrogen–oxygen interaction in the *N*-oxides [$\epsilon(\Delta n) = 0.98$ eV]. The splitting is further diminished in the *N,N'*-dioxide where the oxygen lone pairs experience a 1,4 relationship [$\epsilon(\Delta n) = 0.44$ eV]. The center of gravity of the lone pair splittings is not a simple function of the atoms involved. It arises in part from orbital mixing with framework MO's. Changes in the IP's of the π levels are understood by considering the second order perturbation of π(NN)/azo with

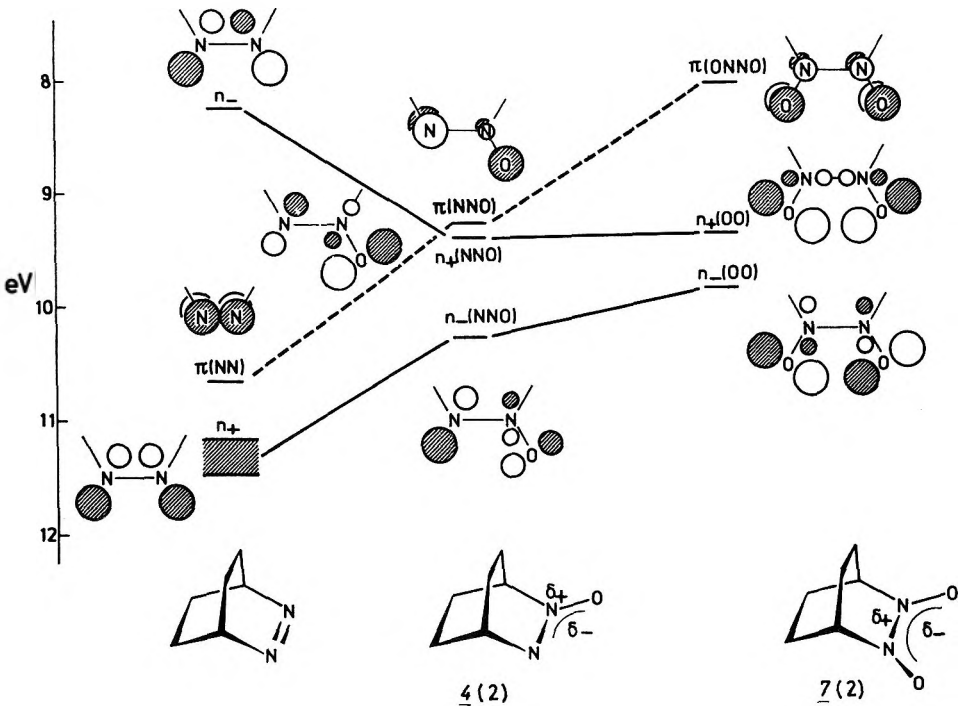


Figure 5. Correlation diagram for the high-lying MO's of azoalkanes, azo *N*-oxides, and azo *N,N'*-dioxides as represented by the experimental IP's for 2,3-diazabicyclo[2.2.2]oct-2-ene,[15] **4**(2), and **7**(2). The assignment $\pi(NNO) < n_+(NNO)$ is speculative and is based on semiempirical calculations.[8]

π(pO). The former is raised in energy and the resulting π(NNO) contains a node between N and O. Addition of a second π(pO) by oxidation to the *N,N'*-dioxide lifts the π orbital still further [π(ONNO)].

Efforts are underway to determine unambiguously the sequence for the azo *N*-oxide π(NNO) and n_+(NNO) orbitals. When this has been accomplished, our MO calculations will be described in detail and the implications of the relationships shown in Figure 5 for the relative chemical behavior of azo alkanes, azoxy alkanes, and azo *N,N'*-dioxides will be discussed.

Acknowledgment. This work was supported by grants from the Danish Research Council (511-5153) and from the University of Lausanne. We thank Dr. K. Müller (ETH, Zürich, Switzerland) for use of his PS-18 spectrometer, and Drs. P. Iversen (Århus University, Århus, Denmark), P. Singh (Syntex Corp., Palo Alto, Calif.), and M. Heyman (University of Copenhagen) for generous gifts of oxides **1**, **3**, and **6** respectively. We are likewise grateful to Dr. K. E. Gilbert for permitting us access to his manuscript prior to publication. H. O. thanks Professor J. F. M. Oth (ETH, Zürich) for his hospitality while the measurements were being taken.

Registry No.—1, 54168-20-6; 2, 35216-94-5; 3, 54143-34-9; 4(1), 22509-00-8; 4(2), 25926-96-9; 4(3), 26081-83-4; 4(4), 25926-97-0; 5, 34493-89-5; 6, 54143-35-0; 7(2), 36479-80-8; 7(3), 54143-30-5; 7(4), 54143-31-6.

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Photorearrangement of *N*-Chlorophosphoramidates

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Received April 27, 1976

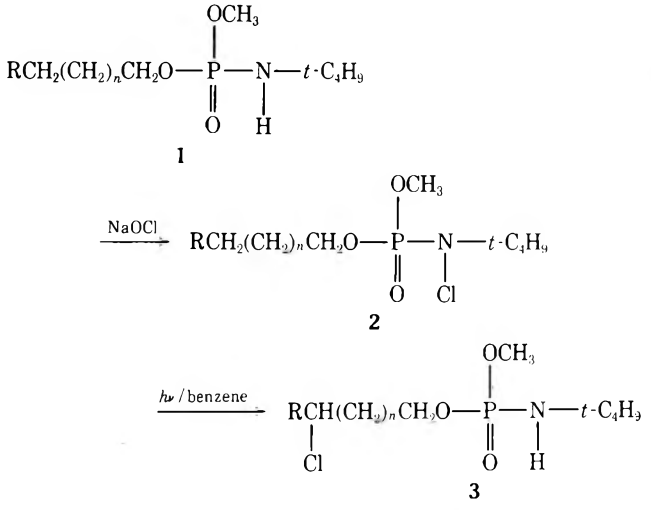
The photodecomposition of alkyl methyl *N*-chloro-*N*-*tert*-butylphosphoramidates in benzene with or without scavenger was attempted with a view to ascertaining the ability of hydrogen abstraction by phosphoramidate radical. In the photodecomposition of *N*-chlorophosphoramidates in benzene, the rearrangement products, *O*-monochloroalkyl isomers, were obtained in high yield but their isomer compositions were almost the same as those of photochlorination products of original phosphoramidates. On the other hand, in the reactions with scavengers of chlorine atoms or hydrogen chloride, such as dichloroethylene or 2,4,6-trimethylpyridine, the fairly selective rearrangements were observed. The major product was the 3-chloralkyl derivative in the phosphoramidates having *O*-butyl or *O*-pentyl group. The regioselective rearrangements observed in this investigation clearly suggest the intramolecular hydrogen abstraction by phosphoramidate radicals via the seven-membered-ring transition state.

Addition to the double bonds and hydrogen abstraction from alkyl chains are the main possible reactions of nitrogen radicals derived from *N*-halo compounds.[1,2]

Until now, rearrangements via intramolecular hydrogen transfer by nitrogen radicals have been investigated on many *N*-halo compounds such as *N*-halo amines,[3-5] *N*-haloamides,[6-11] *N*-halosulfonamides,[13-17] and others.[17]

N,N-Dihalophosphoramidates, a relatively new class of pseudohalogens, have recently been reported to add to olefins and dienes by Zwierzak et al.[18-24] However, it has not yet been determined whether the phosphoramidate radical is capable of abstracting hydrogen atoms from alkyl chains.

To verify the ability of the phosphoramidate radical to abstract hydrogen, photodecomposition of alkyl methyl *N*-chloro-*N*-tert-butylphosphoramidates was attempted.



Reaction products halogenated in the *O*-alkyl chain were obtained in high yield from the above rearrangement which were fairly selective under the proper conditions to eliminate or control the hydrogen atom abstraction by the chlorine atom. The major rearrangement product was the 3-chloroalkyl derivative thought to be derived from intramolecular 1,6-hydrogen transfer of phosphoramidate radicals except in the case of methyl propyl *N*-chloro-*N*-*tert*-butylphosphoramidate (**2a**), in which the 3 position is substituted exclusively by primary hydrogens.

Among the rearrangement products, the 2- and 3-chloroalkyl derivatives are intermediates for the synthesis of cyclophosphorine derivatives such as 1,3,2-oxazaphospholidines[25-28] and 1,3,2-oxazaphosphorines.[25,27] From the standpoint of synthetic interest, the reaction was investigated in detail.

Results and Discussion

Alkyl methyl *N*-chloro-*N*-*tert*-butylphosphoramidates (**2a**, R = H, n = 1; **2b**, R = CH_3, n = 1; **2c**, R = C_2H_5, n = 1) were prepared by the chlorination of the corresponding phosphoramidates (**1a–c**) with chlorine in a buffered solution.

Their photodecomposition was carried out in benzene using a high-pressure mercury arc lamp and the rearrangement products were analyzed by GLC. In the gas chromatogram of **3a**, three peaks were observed. The first and the last peak were identified as **1a** and propyl methyl 3-chloro-*N*-tert-butylphosphoramidate, respectively, by comparing their retention times with those of authentic compounds. The main component (the second peak) was separated by preparative GLC and identified by ^1H NMR as propyl methyl 2-chloro-*N*-*tert*-butylphosphoramidate.

In the gas chromatogram of **3b**, four peaks were found. The first and the last peak were identified as **1b** and butyl methyl 4-chloro-*N*-*tert*-butylphosphoramidate, respectively, comparing their retention times with those of the authentic compounds. The third peak (major component) and the second peak were separated by preparative GLC and identified as the 3- and 2-chlorobutyl isomers, respectively. Five peaks in the GLC of **3c** were identified as **1c** and pentyl methyl 2-, 3-, 4-, and 5-chloro-*N*-*tert*-butylphosphoramidate, respectively, in order of increasing retention time in accordance with reported results on various chlorinated aliphatic compounds.[29-32] The isomer composition of the rearrangement and photochlorination products are summarized in Table I.

As shown in Table I, no marked differences are observed between the isomer composition of the rearrangement products and the free-radical chlorination products. Whether phosphoramidate radicals are involved in these reactions could not be ascertained.

However, these results may be explained if it is assumed that phosphoramidate radicals cannot compete with chlorine atoms in hydrogen abstraction because the latter are far more reactive.

To substantiate the above assumption, photodecomposition of *N*-chlorophosphoramidate (**2a–c**) was conducted in the presence of dichloroethylene, which is known to be a potential chlorine atom trap.[33,34]

As shown in Table II, considerable changes in the isomer composition of the rearrangement products are observed when over 5 mol of dichloroethylene are added to 1 mol of *N*-chlorophosphoramidates.

Furthermore, **2a**, **2b**, and **2c** were photodecomposed in the presence of 2,4,6-trimethylpyridine (TMP), reported by Johnson and Greene[11,12] to be an effective scavenger of hydrogen chloride generated in the chlorine atom chain reaction.

Table I. Photodecomposition (A) of Alkyl Methyl *N*-Chloro-*N*-*tert*-butylphosphoramidates (2a, 2b, 2c) and Photochlorination (B) of Alkyl Methyl *N*-*tert*-Butylphosphoramidates (1a, 1b, 1c) in Benzene

Sample	Reaction type	Concn, mol	Reaction time, h	Recovery, %	Chlorine content, % (calcd)	Isomer composition, %[a,b] 1-	2-	3-	4-	5-
2a	A	0.05	1.0	93	11.7 (14.5)	0	86	14		
1a	B	0.2	0.2		7.1 (14.5)	0	85	15		
2b	A	0.1	3.0	98	11.4 (13.8)	0	19	72	9	
1b	B	0.1	0.1		3.5 (13.8)	0	22	70	8	
2c	A	0.08	3.0	95	11.9 (13.0)	0	10	38	47	5
1c	B	0.1	0.1		3.0 (13.0)	0	6	38	53	3

[a] Analyzed by GLC, 20% Carbowax 1000 on Celite 545, 1 m, at 165 °C for **3a, 3b;** 30% Carbowax 20M on Celite 545, 2 m, at 185 °C for **3c.** [b] 10–20% of unsubstituted phosphoramidate (**1a, 1b, 1c**) was detected in the rearrangement products.

Table II. Photodecomposition of Alkyl Methyl *N*-Chloro-*N*-*tert*-butylphosphoramidates in Benzene in the Presence of Dichloroethylene (DCE)[a]

N-Chloro compd	Mole ratio DCE[b]/2	Reaction time, h	Recovery,[c] %	Chlorine content,[c] % (calcd)	Isomer composition, %[d,e] 1-	2-	3-	4-	5-
2a	5	1.5	102	14.6 (14.5)	0	72	28		
2b	5	2.0	98	14.0 (13.8)	0	13	74	13	
2c	2	2.5	99	13.7 (13.8)	0	16	38	38	8
2c	5	3.0	102	13.5 (13.8)	0	17	54	21	8
2c	10	5.0	103	13.7 (13.8)	0	16	55	21	8

[a] Concentration, 0.1 mol, 15 ± 2 °C under nitrogen. [b] *cis*-Dichloroethylene. [c] The crude products contained small amounts of chlorine-containing compounds derived from dichloroethylene. [d] Analyzed by GLC; see Table I. [e] 10–15% of unsubstituted phosphoramidate (**1a–c**) was found in the products.

Table III. Photodecomposition of Alkyl Methyl *N*-Chloro-*N*-*tert*-butylphosphoramidates in Benzene in the Presence of 2,4,6-Trimethylpyridine (TMP)[a,b]

N-Chloro compd	Concn, mol	Reaction time, h	Recovery, %	Chlorine content, % (calcd)	Isomer composition, %[c,d] 1-	2-	3-	4-	5-
2a	0.10	4.5	85	9.6 (14.5)	0	73	27		
2b	0.19	2.5	60	13.2 (13.8)	0	16	77	7	
2c	0.10	2.5	86	12.9 (13.1)	0	20	64	16	0

[a] Photolysis at 20 ± 2 °C under nitrogen. [b] Mole ratio, TMP:*N*-chloro compound 2:1. [c] Analyzed by GLC; see Table I. [d] 5–10% (**2b, 2c**) and 40% (**2a**) of unsubstituted phosphoramidate was found in the crude products.

In the rearrangement of **2a,** the active chlorine persisted for a long period and relatively large amounts of TMP hydrochloride were isolated from the reaction, while the photodecomposition of **2b** and **2c** proceeded rapidly. The crude rearrangement products were analyzed by GLC and ^{1}H NMR. The results of GLC analyses are shown in Table III.

In the NMR of the crude rearrangement product (**3a**), a doublet at δ 1.52, assigned to the terminal methyl protons of the 2-chloropropyl isomer, and a quintet at δ 2.10, assigned to the center methylene protons of the 3-chloropropyl isomer, were observed in a ratio of 3:1, along with the other expected signals.

In the NMR of **3b,** a doublet at δ 1.55 (2.5 H based on *tert*-butyl protons), multiplets centered at δ 2.0 (2.0 H) and 4.2 (2.9 H), and small triplets at δ 1.07 (0.35 H) and 0.93 (0.3 H) were observed together with the signals of *tert*-butyl protons (δ 1.28, s, 9 H) and *O*-methyl protons (δ 3.70, d, 3 H). The signals at δ 1.55 and 1.07 were assigned to the terminal methyl protons of the 3- and 2-chlorobutyl isomers, respectively. The triplet at δ 0.93 may be assigned to the terminal methyl protons of the 4-chlorobutyl isomer and unsubstituted phosphoramidate (**1b**), though the content of the former is small.

Also, in the NMR of **3c,** a doublet at δ 1.52, assigned to the terminal methyl protons of the 4-chloropentyl derivative, was small (0.5 H) and a large triplet (δ 1.04, 1.8 H), assigned to the terminal methyl protons of the 3-chloropentyl derivative, was observed.

Although a few small unidentified peaks were found in some gas chromatograms of the rearrangement products, besides the identified main peaks, no indication of substitution of the chlorine atom on an *O*-methyl or *tert*-butyl group was found in the NMR spectra.

The isomer composition estimated by NMR analyses showed good agreement with GLC results. Striking differences in isomer composition were noted between rearrangements in the presence or absence of DCE or TMP.

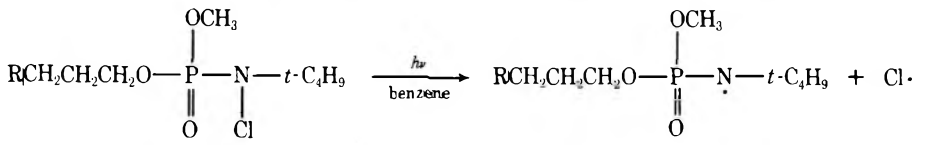
In addition, it was found that in rearrangements with scavengers, substitution at the 3 position of the *O*-alkyl chain was most preferred in **2b** and **2c.** Even in **2a** in which the 3 position contains only primary hydrogens, the content of the 3-chloropropyl isomer increased considerably.

Based on the above results, a reaction pathway is proposed in Scheme I.

In the rearrangements without scavengers, a chlorine atom chain reaction may be the main process due to the higher rate of hydrogen atom abstraction by chlorine atoms. However, in the rearrangements with scavengers, the influence of chlorine atoms is suppressed and phosphoramidate radicals are by far the most important hydrogen atom abstracting agents.

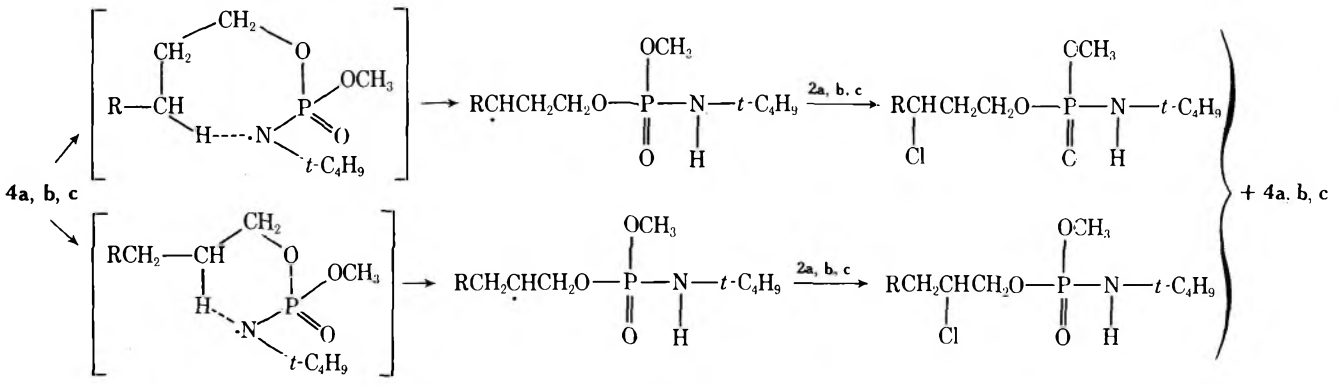
The observed remarkable selectivity at the 3 position seems to be clear evidence of intramolecular hydrogen abstraction by phosphoramidate radicals. If the reaction were intermolecular, the electrophilic nitrogen radicals would allow the

Scheme I. Proposed Pathway of Photodecomposition of *N*-Chloro-*N*-*tert*-butylphosphoramidates



2a, b, c 4a, b, c

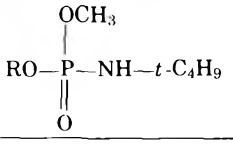
1. Intramolecular hydrogen abstraction by phosphoramidate radical



a, R = H; b, R = CH_3; c, R = C_2H_5

2. Intermolecular hydrogen abstraction by phosphoramidate radical
3. Hydrogen abstraction by chlorine atom

Table IV. Analytical and Physical Data of Alkyl Methyl *N*-*tert*-Butylphosphoramidates[a]



Compd	R	Yield, %	Bp, °C (mm)	IR (neat), cm^{-1}	NMR (CCl_4), δ
1a	*n*-C_3H_7	78	90–92 (0.5)	3220, 2980, 1245, 1200, 1050, 1005	0.98 (t, 3 H), 1.20 (s, 9 H), 1.64 (sextet, 2.1 H), 3.59 (d, 3 H), 3.85 (q, 2 H), 4.75 (d, 0.9 H)
1b	*n*-C_4H_9	54	124–125 (2.0)	3220, 2980, 1245, 1205, 1030–1060, 985	0.96 (t, 3 H), 1.19 (s, 9 H), 1.30–1.78 (m, 4 H), 3.58 (d, 3 H), 3.90 (q, 2 H), 4.78 (d, 1 H)
1c	*n*-C_5H_{11}	73	*101–102 (0.5)*	*3220, 2980, 1250,* 1205, 1030–1065, 1000	*0.92 (t, 3 H), 1.19 (s, 9 H), 1.34* (m, 4 H), 1.60 (m, 2 H), 3.59 (d, 3 H), 3.88 (q, 2 H), 4.76 (d, 1 H)

[a] Satisfactory analytical data (±0.3% for C, H, N) were obtained for all compounds.

preferential substitution of the secondary hydrogens farthest from the electron-attracting substituent.[2,36] However, in intramolecular hydrogen abstraction by nitrogen radicals, such as amminium,[3,35] amydyl,[8-11] and sulfonamide radicals,[13-17] a six-membered-ring transition state is known to be far more preferable to a seven-membered ring. The distinct preference of the latter to the former observed in this investigation is extraordinary and suggests significant differences in the transition states due to the –O–P–N– bond in the phosphoramidate radicals.

Experimental Section[37]

Alkyl Methyl *N*-*tert*-Butylphosphoramidate (1a–c). Alkyl methyl *N*-*tert*-butylphosphoramidates were prepared by the reaction of alkylmethyl phosphite[38] and *tert*-butylamine according to the procedure of Todd.[39] They were purified by distillation at reduced pressure; purity of all compounds was checked by GLC and ^1H NMR (Table IV).

Alkyl Methyl *N*-Chloro-*N*-*tert*-butylphosphoramidates (2a–c). To a mixture of *n*-pentyl methyl *N*-*tert*-butylphosphoramidate (**1c**, 4.7 g, 0.021 mol), sodium acetate (18 g), glacial acetic acid (1.8 g), and water (40 ml), chlorine gas was introduced with stirring and cooling (10–15 °C) until the solution had a yellow color. After the reaction, excess chlorine was expelled by nitrogen and the yellow, oily product was multiply extracted with dichloromethane. The extracts were combined, washed with water, and dried over magnesium sulfate. The solvent was removed in vacuo to leave an almost colorless liquid (**2c**, 5.87 g, 86%). Active chlorine, 13.0% (calcd, 13.1%).

Similarly, n-butyl methyl N-chloro-N-tert-butylphosphoramidate (**2b**, active chlorine, 13.6%) and *n*-propyl methyl *N*-chloro-*N*-*tert*-butylphosphoramidate (**2a**, active chlorine, 14.2%) were obtained in ca. 90% yields.

Photodecomposition of *N*-Chlorophosphoramidates (2a–c) in Benzene. *N*-Chlorophosphoramidate (0.018 mol) was dissolved in 180 ml of benzene and nitrogen was slowly bubbled through the solution for 20 min before irradiation. The solution was irradiated with a high-pressure mercury arc lamp at 20 ± 2 °C under nitrogen until the active chlorine content became negligible. After irradiation, the solvent was removed under reduced pressure; the crude rearrangement product (**3a–c**) was obtained as a viscous, orange oil. The rearrangement products were analyzed by GLC (Table I) and some of the isomers were isolated in pure form by preparative GLC.

Propyl Methyl 2-Chloro-*N*-*tert*-butylphosphoramidate. ^{1}H NMR (CCl_4) δ 1.21 (s, 9 H), 1.53 (d, 3 H), 3.64 (d, 3 H), 3.86–4.23 (complex overlapped multiplets, 3 H), 4.60 (d, 0.9 H).

Anal. Calcd for $C_8H_{19}ClNO_3P$: C, 39.43; H, 7.88; N, 5.75; Cl, 14.55. Found: C, 39.30; H, 8.08; N, 5.61; Cl, 14.30.

Butyl Methyl 2-Chloro-*N*-*tert*-butylphosphoramidate. ^{1}H NMR (CCl_4) δ 1.08 (t, 2.5 H), 1.24 (s, 9 H), 1.65–2.05 (m, 2 H), 3.65 (d, 3 H), 3.90–4.18 (m, 3 H), 4.35 (bs, 1 H).

Anal. Calcd for $C_9H_{21}ClNO_3P$: C, 41.95; H, 8.21; N, 5.44; Cl, 13.76. Found: C, 42.02, H, 8.29; N, 5.48.

Butyl Methyl 3-Chloro-*N*-*tert*-butylphosphoramidate. ^{1}H NMR (CCl_4) δ 1.21 (s, 9 H), 1.55 (d, 3 H), 2.00 (m, 2 H), 3.61 (d, 3 H), 3.90–4.25 (m, 3 H), 4.58 (bs, 1 H).

Anal. Found: C, 41.94; H, 8.45; N, 5.51.

Pentyl Methyl 2-Chloro-*N*-*tert*-butylphosphoramidate. ^{1}H NMR (CCl_4) δ 0.97 (t, 2.7 H), 1.23 (s, 9 H), 1.40–1.90 (m. 4.2 H), 3.62 (d, 3 H), 3.82–4.25 (m, 3.8 H).

Anal. Calcd for $C_{10}H_{23}ClNO_3P$: C, 44.20; H, 8.53; N, 5.15; Cl, 13.09. Found: C, 43.65; H, 8.60; N, 5.30.

Pentyl Methyl 3-Chloro-*N*-*tert*-butylphosphoramidate. ^{1}H NMR (CCl_4) δ 1.07 (t, 2.5 H), 1.22 (s, 9 H), 1.50–2.15 (m, 4.1 H), 3.60 (d, 3.2 H), 3.80–4.20 (m, 3.2 H), 4.70 (bs, 0.5 H).

Anal. Found: C, 44.23; H, 8.51; N, 5.38.

Pentyl Methyl 4-Chloro-*N*-*tert*-butylphosphoramidate. ^{1}H NMR (CCl_4) δ 1.21 (s, 9 H), 1.50 (d, 3 H), 1.60–2.00 (m, 4.2 H), 3.58 (d, 2.7 H), 3.80–4.20 (m, 3.3 H), 4.45 (bs, 0.5 H), and small signals supposed due to the impurities (δ 1.0 and 2.07).

Photochlorination of Alkyl Methyl *N*-*tert*-Butylphosphoramidates (1a–c) with Chlorine. 1b (**1a**, **1c**) (0.016 mol) was dissolved in 160 ml of benzene and chlorine gas was introduced to the solution for 6 min at 20 °C under irradiation by a tungsten lamp. The crude chlorination products were analyzed by GLC. Results are summarized in Table I.

Photodecomposition of *N*-Chlorophosphoramidates (2a–c) in the Presence of Dichloroethylene. 2b (0.015 mol) and 0.03–0.15 mol of *cis*-dichloroethylene were dissolved in 150 ml of benzene and the solution was irradiated under nitrogen as described above. **2a** and **2c** were also photodecomposed and the results of analyses of the crude reaction products by GLC are summarized in Table II. The major component in **3c** was separated by GLC and characterized as pentyl methyl 3-chloro-*N*-*tert*-butylphosphoramidate, a colorless, viscous liquid, Cl, 13.3 (calcd, 13.1): IR (neat) 3240, 1250, 1200, 1070, 1025 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.08 (t, 3 H), 1.24 (s, 9 H), 1.50–2.20 (m, 4 H), 3.60 (d, 3 H), 4.10 (multiplets, 4 H).

Photodecomposition of *N*-Chlorophosphoramidates in the Presence of 2,4,6-Trimethylpyridine (TMP). 2b (4.84 g, 0.019 mol) and TMP (4.56 g, 0.038 mol) was dissolved in 100 ml of benzene and solution was irradiated under nitrogen at 20 ± 2 °C until the active chlorine content was negligible. After irradiation, benzene was removed in vacuo and ether was added to the residue. Insoluble TMP hydrochloride (0.24 g) was filtered off and the filtrate was washed with dilute hydrochloric acid and water successively. The ether solution was dried over anhydrous magnesium sulfate and the solvent was removed, leaving a red, viscous liquid (**3b**, 2.92 g), Cl, 13.2. ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 0.3 H), 1.07 (t, 0.35 H), 1.28 (s, 9 H), 1.55 (d, 2.5 H), 1.8–2.3 (m, 2 H), 3.70 (d, 3 H), 4.2 (m, 2.9 H).

In a similar procedure, **2c** (5.22 g, 0.017 mol) afforded 4.50 g of **3c** and TMP hydrochloride (0.18 g), Cl, 12.9. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 0.3 H), 1.04 (t, 1.8 H), 1.26 (s, 9 H), 1.52 (d, 0.5 H), 1.55–2.30 (complex multiplets, 4.1 H), 3.68 (d, 3 H), 3.83–4.38 (m, 3.1 H). Also, **3a** (3.30 g, Cl, 9.6) and TMP hydrochloride (0.60 g) were obtained from the reaction of **2a** (3.90 g, 0.016 mol). ^{1}H NMR (CCl_4) δ 0.97 (t, 1.2 H), 1.22 (s, 9 H), 1.52 (d, 1.2 H), 1.63 (sextet?, 0.8 H), 2.10 (quintet 0.4 H), 3.53–3.68 (complex signals, 3.4 H), 3.74–4.20 (complex signals, 2.8 H), 4.50 (bs, 1 H).

Authentic Compounds. Propyl Methyl 3-Chloro-*N*-*tert*-butylphosphoramidate. 3-Chloropropyl methyl phosphite was synthesized by the reaction of dimethyl phosphite (27.5 g, 0.25 mol) and 3-chloropropanol (23.6 g, 0.25 mol) at 115–130 °C for 4 h. The crude product was purified by vacuum distillation: bp 88–89 °C (1.0 mm); yield 11.7 g; Cl, 20.4 (calcd, 20.5). 3-Chloropropyl methyl phosphite (6.85 g, 0.04 mol) was dissolved in 50 ml of CCl_4 and a CCl_4 solution of *tert*-butylamine (8.0 g/25 ml) was added dropwise with stirring and cooling. The crude reaction product (6.95 g) was distilled at reduced pressure and the pure compound (4.23 g, 42%) was obtained as a colorless liquid: bp 105–107 °C (0.17 mm); IR (neat) 3240 m, 2970 s, 1482 w, 1440 m, 1398 m, 1370 m, 1310 w, 1245 s, 1200 s, 1050 s, 1025 s, 970 s, 880 w, 793 m, 655 cm^{-1} w; ^{1}H NMR (CCl_4) δ 1.22 (s, 9 H), 2.10 (quintet 2 H), 3.55–3.70 (d + t?, 5 H), 4.03 (d + t?, 2 H), 4.65 (d, 1 H).

Anal. Calcd for $C_8H_{19}ClNO_3P$: C, 39.43; H, 7.88; N, 5.75; Cl, 14.55. Found: C, 39.27; H, 8.15; N, 5.69; Cl, 14.34.

Butyl Methyl 4-Chloro-*N*-*tert*-butylphosphoramidate. 4-Chloro-1-butanol was prepared by the method of Kerner.[40] Transesterification of 4-chloro-1-butanol (7.0 g) and dimethyl phosphite (10 g) was carried out at 110–130 °C and the crude 4-chlorobutyl methyl phosphite was purified by distillation in vacuo, a colorless liquid, 2.8 g, Cl, 18.5 (calcd, 19.0). Butyl methyl 4-chloro-*N*-*tert*-butylphosphoramidate (0.7 g) was obtained by the reaction of phosphite (0.5 g) and *tert*-butylamine (1.2 g) in CCl_4, Cl, 13.5 (calcd, 13.8): IR (neat) (major absorptions) 3220, 2970, 1250, 1200, 1050 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.20 (s, 9 H), 1.83 (m, 4 H), 3.45–3.68 (d + t, 5 H), 3.90 (q, 2 H), 4.50 (bs, 1 H).

Pentyl Methyl 5-Chloro-*N*-*tert*-butylphosphoramidate. The pure compound was obtained by the reaction of 5-chloropentyl methyl phosphite, which was prepared by transesterification of dimethyl phosphite with 5-chloro-1-pentanol, and *tert*-butylamine in the presence of CCl_4, Cl, 12.8 (calcd, 13.1): IR (neat) 3220, 2960, 1250, 1200, 1040 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.21 (s, 9 H), 1.50–1.95 (m, 6 H), 3.50 (t, 2 H), 3.63 (d, 3 H), 3.92 (q, 2 H), 4.38 (d, 1 H).

Acknowledgment. The authors wish to thank Professor D. Swern, Temple University, for advice and helpful discussion.

Registry No.—**1a**, 61047-44-7; **1b**, 61047-45-8; **1c**, 61047-46-9; **2a**, 61047-47-0; **2b**, 61047-48-1; **2c**, 61047-49-2; **3** (R = CH_3; *n* = 0), 61047-50-5; **3** (R = C_2H_5; *n* = 0), 61047-51-6; **3** (R = CH_3; , *n* = 1), 61047-52-7; **3** (R = C_3H_7; *n* = 0), 61047-53-8; **3** (R = C_2H_5; *n* = 1), 61047-54-9; **3** (R = CH_3; *n* = 2), 61047-55-0; **3** (R = H; *n* = 1), 61047-56-1; **3** (R = H; *n* = 2), 61047-57-2; **3** (R = H; *n* = 3), 61047-58-3; 3-chloropropyl methyl phosphite, 61047-59-4; dimethyl phosphite, 868-85-9; 3-chloropropanol, 627-30-5; *tert*-butylamine, 75-64-9; 4-chloro-1-butanol, 928-51-8; 4-chlorobutyl methyl phosphite, 61047-60-7; 5-chloropentyl methyl phosphite, 61047-61-8; 5-chloro-1-pentanol, 5259-98-3.

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Photochemical Rearrangements of an Unsaturated Nitro Compound. Mechanistic and Exploratory Organic Photochemistry[1,2]

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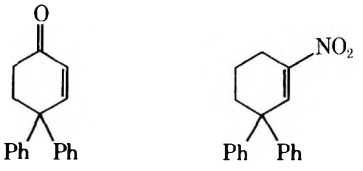
Received July 13, 1976

3,3-Diphenyl-1-nitrocyclohexene was synthesized for photochemical study in order to compare nitro n–π^* photochemistry with carbonyl n–π^* reactivity. Both direct and sensitized irradiations in benzene gave rise to *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane; the preference for formation of trans product was shown to be kinetic. Additionally, the photolysis afforded 3,3-diphenylcyclohexanone. Quantum efficiencies were determined, and these were found to be quite low compared with the corresponding enone analogue. Thus, for formation of bicyclic nitro compound the unsensitized and sensitized efficiencies were found to be $\phi = 3.05 \times 10^{-4}$ and 4.52×10^{-4} (acetophenone). Evidence favoring triplet multiplicity of the rearranging species is discussed as is the low reaction efficiency. It was observed that irradiation in isopropyl alcohol gave rise to 3,3-diphenylcyclohexanone oxime as the major product with the oxime to bicyclic product ratio increasing with increasing isopropyl alcohol concentration in isopropyl alcohol–benzene mixtures. Finally, *cis*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane was independently synthesized by reaction of 2-phenyl-1-nitrocyclopentene with diphenylsulfonium benzylide. This stereoisomer was converted, both in direct and sensitized irradiations, to the trans stereoisomer with a steady state favoring trans isomer over 1000:1.

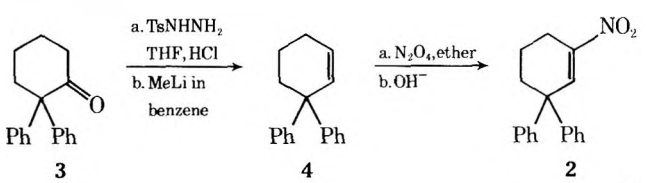
Some of our previous studies[3-6] have involved the n–π^* triplet photochemical rearrangement of 4,4-diphenylcyclohexenone (1) and substituted derivatives. The evidence favored promotion of a nonbonding (i.e., p_y or n) electron to the antibonding π system with rearrangement involving bonding of a γ aryl group to the β carbon.

Nitroalkenes also have an n–π^* triplet as their lowest electronic excited state, although the literature on the subject is sparse.[7] Thus we were interested in seeing if the photochemistry of a nitro analogue of 4,4-diphenylcyclohexenone (1) would prove parallel to that of the ketone. For this study we selected 3,3-diphenyl-1-nitrocyclohexene (2).



1 2

Synthesis of the Photochemical Reactant. The synthesis utilized 3,3-diphenyl-1-cyclohexene[8] (4) which was prepared from 2,2-diphenylcyclohexanone (3) using the method of Dauben.[9] Reaction of the diphenylcyclohexene 4 with nitrogen tetroxide in ether followed by hydroxide treatment gave a 19% yield of the desired 3,3-diphenyl-1-nitrocyclohexene (2), mp 106–107 °C. Note eq 1.



3 4 2 (1)

Exploratory Photochemistry. Exploratory irradiations were carried out using a 450-W medium-pressure immersion lamp along with either a Pyrex or a circulating sodium metavanadate filter, thus using light above 290 or 330 nm. A slow reaction was observed and could be monitored with analytical GC; two products were observed and these appeared linearly with time.

Preparative isolation employed column chromatography on Florisil. One product proved to be the known 3,3-diphenylcyclohexanone.[10] The major product, 5, was a solid, mp 127.5–129 °C; at the end of 10 h a 9% yield of this photoproduct was formed. The minor diphenylcyclohexanone product was found in 0.5% yield. Thus, qualitatively, this contrasts with the very facile rearrangement of 4,4-diphenylcyclohexenone (1) where a similar conversion is complete in ca. 0.5 h.

Photoproduct Structure Elucidation. The first evidence regarding photoproduct 5 was the appearance of 6.59- and 7.37-μ bands in the infrared suggesting that this was a nitro compound. Substantial further evidence derived from the 270-MHz ^{1}H and 67.9-MHz ^{13}C NMR spectra (Tables I and II). The first point noted was the presence of two unsplit ^{13}C peaks at 79.8 and 53.3 ppm downfield from Me_4Si, indicating the presence of two quaternary carbons. The low field of the former suggested that it bore the nitro group (i.e., a C–NO_2 group present). Additionally, the doublet at 38.6 ppm proved suggestive of a benzylic cyclopropyl group (i.e., CHPh) bearing a hydrogen. Finally, the ^{1}H and ^{13}C NMR spectra both suggested the presence of three methylene groups (i.e., CH_2) and the former suggested that these formed a contiguous chain of three ($-CH_2CH_2CH_2-$); thus these are mutually coupled as indicated in Table II.

With evidence for these structural moieties in hand and with the course of the rearrangement of 4,4-diphenylcyclohexenone[3] in mind, a tentative assignment of 5 as *cis*- or *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane was made.

It seemed desirable to have the model compounds *cis*- and *trans*-1,6-diphenylbicyclo[3.1.0]hexane[8] (8 and 7, respectively), so these were prepared from the *cis*- and *trans*-5,6-

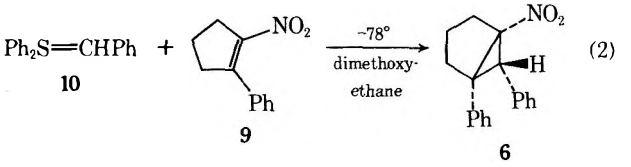
Table I. 67.9-MHz ^{13}C NMR Data

Compd	Carbon	Multiplicity	Chemical shift, ppm	$^1J_{^{13}CH}$, Hz
5	1	s	79.8	
	2	d of d	35.1	131
	3	d of d	21.1	132
	4	d of d	28.4	134
	5	s	53.3	
	6	d	38.6	155
6	1	s	79.7	
	2	d of d	40.8	132
	3	d of d	19.4	132
	4	d of d	33.3	134
	5	s	47.4	
	6	d	37.5	158
7	5	d	31.3	164
	2	d of d	26.4	130
	3	d of d	23.3	130
	4	d of d	31.8	129
	1	s	38.8	
	6	d	33.7	155
8	5	d	31.2	162
	2	d of d	28.5	128
	3	d of d	21.8	130
	4	d of d	36.8	130
	1	s	42.4	
	6	d	30.0	158

diphenylbicyclo[3.1.0]hexan-2-ones of known[3] structure. Synthetic details are given in the Experimental Section and the NMR spectra are detailed in Tables I and II. These spectra can be seen to show remarkable parallelism with that of photoproduct **5**.

With the preceding evidence in hand, we proceeded to obtain an unambiguous structure proof. This was obtained by synthesis of the stereoisomer of the photoproduct.

The reaction of 2-phenyl-1-nitrocyclopentene[11] (**9**) with diphenylsulfonium benzylide[12] (**10**) led to a product (**6**), mp 110–111.5 °C. The infrared spectrum again revealed the presence of a nitro group and was reminiscent of, but different from, that of the photoproduct (**5**). The ^{13}C NMR spectrum of this product was exceptionally similar to that of the photoproduct; note Table I. Literature analogy[13] had suggested that the nitrocyclopentene plus sulfonium benzylide reaction should lead to three-ring formation as shown in eq 2. Thus,



(2)

it was apparent that the synthesis had led to the stereoisomer (i.e., **6**) of the photoproduct (i.e., **5**).

Table II. 270-MHz ^1H NMR Data[b]

Compd	Proton	Multiplicity	Chemical shift, τ	Coupling constants, Hz[a]
5	a	16-line mult	9.61	$J_{ab} = -13.7$, $J_{ac} = 8.5$, $J_{ad} = 11.2$, $J_{ae} = 8.3$, $J_{af} = 11.2$
	b	d of t	8.39	$J_{bc} = 0.3$, $J_{bd} = 9.1$, $J_{be} = 0.1$, $J_{bf} = 9.4$
	c	d of d	7.75	$J_{cd} = -14.0$, $J_{ce} = 0.0$, $J_{cf} = 0.0$,
	d	mult	7.63	$J_{de} = 0.0$, $J_{df} = 0.5$
	e	d of d	7.58	$J_{ef} = -13.6$
	f	pseudo q	6.73	
	g	s	5.70	
	Arom	10 H mult	2.64	
6	a	16-line mult	8.35	$J_{ab} = -13.8$, $J_{ac} = 11.8$, $J_{ad} = 8.0$, $J_{ae} = 8.3$, $J_{af} = 11.3$
	b	mult	8.06	$J_{bc} = 8.5$, $J_{bd} = 0.7$, $J_{be} = 0.4$, $J_{bf} = 8.6$
	c	mult	7.75	$J_{cd} = -13.1$, $J_{ce} = 0.0$, $J_{cf} = 0.0$
	d	mult	7.72	$J_{de} = 0.0$, $J_{df} = 0.0$
	e	d of d	7.23	$J_{ef} = -12.9$
	f	d of d of d	7.08	
	g	s	6.91	
	Arom	2 H d of d	3.09	$J = 7.5, 1.0$
	Arom	5 H mult	2.80	
	Arom	3 H mult	2.72	
7	a	16-line mult	9.80	
	b	mult	8.64	
	c, d	1 H d of d	8.11	$J = 11.4, 8.5$
	e, f, h	4 H mult	7.87	
	g	d	7.65	$J = 8.46$
	Arom	10 H mult	2.93–2.91	
8	a	16-line mult	8.47	
	b	d of t	8.19	$J = 14.8, 8.1$
	c, d	mult	7.87–8.07	
	e, f, h	d of d	7.69	$J = 12.7, 8.1$
	g	d	7.77	$J = 3.7$
	Arom	2 H d of d	3.78	$J = 8.5, 1.0$
	Arom	8 H mult	3.55	

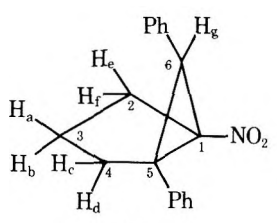
[a] The coupling constants listed for the methylene protons of compounds **5** and **6** are those obtained from a reiterative computer simulation of the observed spectrum. See the Experimental Section for details. [b] The observed and simulated methylene regions of the 270-MHz spectra of compounds **5** and **6**, along with a more complete discussion of their comparisons with the spectra of **7** and **8**, are given in the Ph.D. Thesis of L. C. Roberts, University of Wisconsin, 1976.

Table III. Summary of Quantum Yield Data

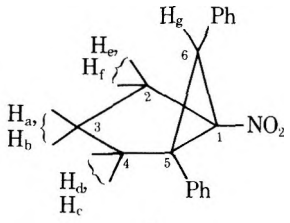
Concn of reactant, M	Added reagent (M)	λ_{irrad}, nm	Φ_r[a] bicyclic	Φ_r[b] ketone	Conversion, %
3.20×10^{-3}	None	317	3.06×10^{-4}	3.97×10^{-5}	3.240[c]
3.20×10^{-3}	None	317	3.03×10^{-4}	3.75×10^{-5}	1.630
3.20×10^{-3}	None	317	3.04×10^{-4}	2.63×10^{-5}	0.759
3.20×10^{-3}	None	317	3.05×10^{-4}	1.61×10^{-5}	0.361
1.00×10^{-3}	Acetophenone (5.25×10^{-1})	337	3.90×10^{-4}	4.22×10^{-4}	0.867
1.00×10^{-3}	Acetophenone (5.25×10^{-1})	337	4.37×10^{-4}	2.07×10^{-4}	0.343
1.00×10^{-3}	Acetophenone (5.25×10^{-1})	337	4.33×10^{-4}	1.65×10^{-4}	0.181

[a] Linear extrapolation to 0% conversion gave $\Phi_r = 3.05 \times 10^{-4}$ and $\Phi_r = 4.52 \times 10^{-4}$ for the formation of the bicyclic photoproduct in the direct and sensitized photolyses, respectively. [b] Linear extrapolation to 0% conversion gave $\Phi_r = 1.18 \times 10^{-5}$ and $\Phi_r = 8.70 \times 10^{-5}$ for the formation of the ketone in the direct and sensitized photolyses, respectively. [c] This run is less reliable than the others since at this extent of conversion the bicyclic photoproduct could have been absorbing up to 1% of the light.

The assignment of stereochemistry to the two stereoisomers derives nicely from comparison of the ^1H NMR spectra of these compounds with those of the model compounds **7** and **8** of known stereochemistry. Primarily, the hydrogens labeled a in Table II, corresponding to the endo hydrogen at C-3, are shifted markedly upfield in photoproduct **5** and in model compound **7**. Since the latter is known to have an endo C-6 phenyl configuration, we can conclude that the upfield shift is due to the high field hydrogen being in the shielding cone of the phenyl group. Also we can conclude that photoproduct **5** has the endo configuration. Stereochemical assignments are thus:



5



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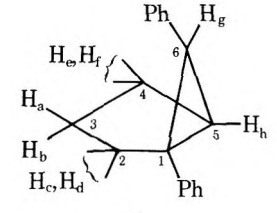

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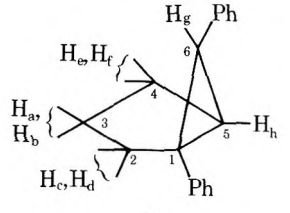


8

Final proof of the structure of photoproduct **5** derived from its formation in the acetophenone sensitized irradiation of the synthetically derived cis bicyclic isomer **6**. Such stereoisomerization has literature precedent in the photochemical interconversion of cis and trans isomers of 5,6-diphenylbicyclo[3.1.0]hexan-2-one[14] and also of the cis and trans isomers of 2,3-diaryl-1-benzoylcyclopropanes.[15-17] Even in the absence of conjugating carbonyl or similar chromophores, diaryl cyclopropanes are known[18-20] to cis–trans isomerize photochemically.

Multiplicity and Quantum Efficiency Studies. One of the first questions of interest was whether the reaction would proceed via the triplet (i.e., under sensitized conditions). Accordingly, using the 450-W immersion apparatus and a combination Pyrex–copper–cobalt–nickel filter (290–390 nm bandwidth), an acetophenone-sensitized run was carried out. It was determined that minimally 99% of the light was captured by acetophenone sensitizer. From this run the same trans bicyclic photoproduct **5** was obtained (12% yield) along with 3,3-diphenylcyclohexanone (**11**) (14%) and recovered unphotolyzed reactant (23%).

For more quantitative studies the Black Box apparatus[21] was employed along with a narrower bandwidth solution filter of nickel–cobalt–copper (see Experimental Section for details). The conversions were monitored by GC. Under mild conditions (170 °C, SE-30, see Experimental Section) each of the compounds of interest—nitroalkene reactant **2**, cis and trans bicyclic nitro compounds **5** and **6**, 3,3-diphenylcyclohexanone, and tetraphenylethylene internal standard—gave nicely separable peaks. Ferrioxalate actinometry was used along with an integrating digital photometer.[22] The results are compiled in Table III. These runs were made from 3.2 to 0.4% completion in the direct irradiations and from 0.9 to 0.2% in the sensitized runs. Linear extrapolation to zero time gave nitrobicyclic quantum yields of $\phi = 3.05 \times 10^{-4}$ and 4.52×10^{-4} for the direct and sensitized runs, respectively. A major dependence of quantum yield on extent conversion was observed for 3,3-diphenylcyclohexanone product. Since this quantum yield increased with time, it seems unlikely that this ketone is a primary photoproduct.

An additional effort dealing with the nature of the excited state present was undertaken. This utilized the addition of isopropyl alcohol in order to determine if an efficient hydrogen abstracting excited state was present. With the addition of 10% isopropyl alcohol to the benzene solvent, a new product was obtained in addition to those ordinarily found. This proved to be 3,3-diphenylcyclohexanone oxime (**12**). Runs in pure isopropyl alcohol afforded oxime **12** as the major photoproduct (oxime **12**:bicyclic **5**:ketone **11**, 5.7:1:0); note eq 3, Table IV, and the Experimental Section.

Interpretative Discussion. The first clear point deriving from the present study is the occurrence of a phenyl migration rearrangement parallel to that of enones [e.g., 4,4-diphenylcyclohexenone (**1**)]. In analogy to the ketone photochemistry,[3-6] it is the trans diphenyl product which is kinetically preferred. In the present instance this corresponds to inversion of configuration of C-3 during phenyl migration and bonding of C-3 to C-1.

The second point of interest is that the reaction appears to utilize an excited triplet, again in analogy to the ketone photochemistry.[3-6] Thus, successful rearrangement on sensitization means that, minimally, one knows that the triplet is capable of undergoing the rearrangement. The only uncertainty is whether the species involved in the direct irradiations is also the triplet. That the quantum yield in the direct runs is two-thirds of the sensitized runs is suggestive. Were these the same, one would tend to conclude that the same excited

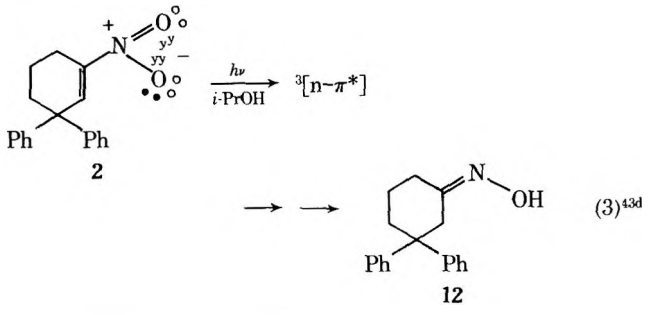
Table IV. Photolysis of 3,3-Diphenyl-1-nitrocyclohexene in Isopropyl Alcohol

Reactant (M)	Added reagent (M)	Solvent	λ_{irrad},[a] nm	Photolysis time, min	Conversion, %	Ratio of products[b]
Nitro olefin (3.58×10^{-3})	None	*i-PrOH*	>290	150	66.4	5.7:1.0:0
Nitro olefin (3.58×10^{-3})	None	10% *i*-PrOH in benzene	>290	150	19.5	0.9:1.0:-[c]
Nitro olefin (3.11×10^{-3})	None	10% *i*-PrOH in benzene	>330	150	15.5	1.3:1.0:0.2
Nitro olefin (3.11×10^{-3})	None	10% *i*-PrOH in benzene	>330	30	3.3	0.8:1.0:0.2
Nitro olefin (3.11×10^{-3})	Naphthalene (0.1)	10% *i*-PrOH in benzene	>330	150	13.0	1.0:1.0:0.2

[a] The filters used were Pyrex, for light of wavelength greater than 290 nm, and a combination of Pyrex and sodium metavanadate solution, for light of wavelength greater than 330 nm. [b] The ratio given is the mole ratio of 3,3-diphenylcyclohexanone oxime to *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane to 3,3-diphenylcyclohexanone, determined by NMR, using hand integrations of the expanded spectra. [c] Not detected by NMR at normal amplitude.

state species was rearranging in both direct and sensitized runs (i.e., the "fingerprint method" [6] type reasoning) and that intersystem crossing occurs with unit efficiency. With the two quantum yields being potentially orders of magnitude different but actually being not too different, the simplest conclusion is that the direct irradiations also involve the triplet but that the formation of triplet is only 67% efficient. Coincidentally, the intersystem crossing efficiency of nitrobenzene has been reported[23] to be 0.67.

The hydrogen abstraction reaction with isopropyl alcohol (note eq 3) seems ascribable to the n–π^* triplet. Thus, irra-



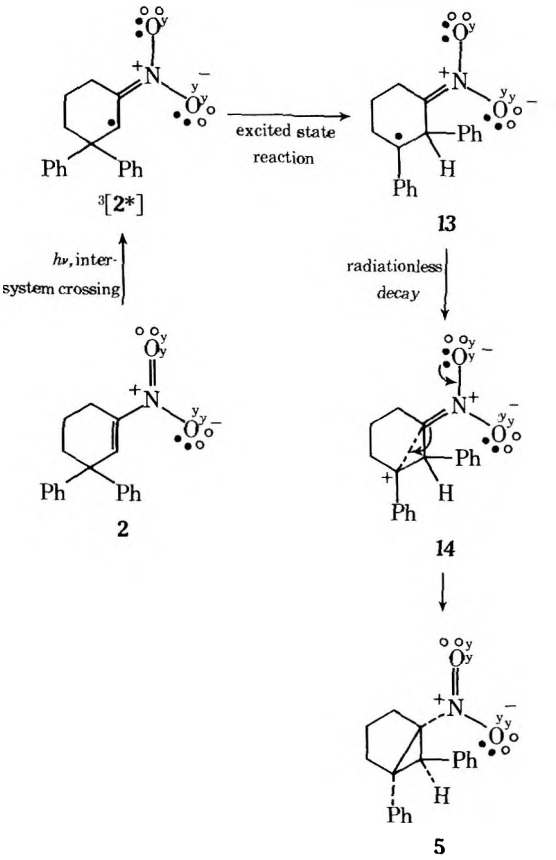
diation of nitro compounds in isopropyl alcohol has been reported[24] to give hydrogen abstraction via the n–π^* triplet. Hence, in the photochemistry under discussion evidence is available that the n–π^* triplet is present in solution.

Still another point is the dramatically lowered quantum efficiencies of the nitroalkene rearrangement compared with the 0.043 efficiency[3b] observed for 4,4-diphenylcyclohexenone in a parallel process.

The last point before proceeding to consideration of an overall mechanism is that formation of 3,3-diphenylcyclohexanone (*11*) is unusual. The more common reaction of a nitroalkene is formation of the oximino ketone.[25]

A reasonable mechanism for formation of the rearranged, bicyclic photoproduct **5** is depicted in Chart I. The scheme in Chart I is quite analogous to that[3] given for the corresponding ketone rearrangement and conforms to the general scheme proposed by us 16 years ago.[26] The step we termed "rebonding" or "bond alteration" in the early days of our studies now corresponds to the triplet state reaction to give species **13**. However, **13** is still a triplet and clearly a multiplicity change is needed to get to ground state product. This is written as a separate step giving zwitterion **14** in Chart I; **14** then bonds to afford photoproduct **5**. However, it is conceivable that multiplicity change and radiationless conversion may lead **13** directly to photoproduct **5**; thus the zwitterions in the enone photochemistry we reported[3] have never been intercepted by nucleophiles. This contrasts with the case of dienone photo-

Chart I. Rearrangement Mechanism

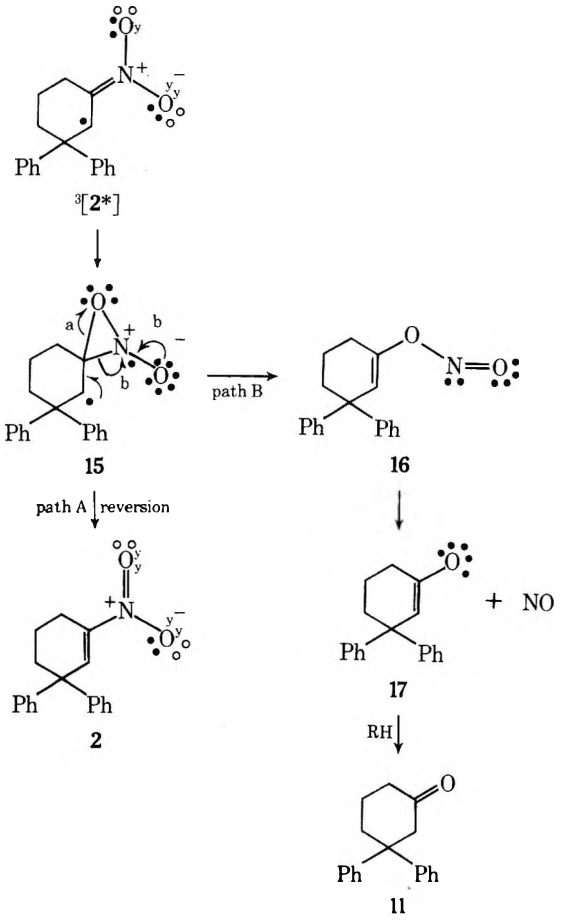


chemistry where numerous examples of intercepting[27] and generating[28,29] zwitterions have been reported. Thus, the stepwise nature of the reaction has not been defined with certainty.

The formation of ketone **11** seems most likely to involve the initial steps of the Chapman reaction[7e,25] except that with carbon 2 being quite hindered (adjacent to two phenyl groups), it seems more likely that the enoloxy radical **17** hydrogen abstracts to give enol which then affords the observed ketonic product. Note Chart II. This chart also includes a potential source of energy dissipation by reversion of the Chapman intermediate **15**. This would then account for the low reaction efficiency.

We conclude by noting that nitroalkene photochemistry does parallel enone photochemistry in specialized, optimum cases such as that presently investigated. However, the availability of an efficient mode of energy dissipation derives from the capability of n–π^* nitro moieties to attack π systems.

Chart II. Mechanism of Formation of 3,3-Diphenylcyclohexanone



This leads to intrusion of an efficient competing reversion process and a lower efficiency.

Experimental Section[30]

2,2-Diphenylcyclohexanone. This compound was prepared by the method of Zaugg et al.[31] from cyclopentanone in an overall yield of 58%, after crystallization from hexane, mp 100.2–101.8 °C (lit.[3] 97–99 °C).

3,3-Diphenylcyclohexene. This compound has been previously reported by Dauben[8] and was prepared from 2,2-diphenylcyclohexanone by his general method.[9] A detailed procedure follows. A 50.1-g (0.20 mol) sample of 2,2-diphenylcyclohexanone was converted to its tosylhydrazone by refluxing for 26 h with 37.2 g (0.20 mol) of *p*-toluenesulfonylhydrazine in 400 ml of THF containing 0.6 ml of concentrated hydrochloric acid. Benzene (1.5 l.) was added, and the solvent distilled off at atmospheric pressure until the temperature of the distillate stabilized at 79 °C. The mixture was then cooled to 0 °C, mechanically stirred, and treated with 260 ml of a 1.7 M solution of methyllithium in ether over 40 min. The resulting solution was stirred at room temperature for 1.5 h, treated with 80 ml of water, poured into 400 ml of water, and extracted with pentane. The pentane was dried and concentrated in vacuo to give 51.0 g (0.20 mol) of 3,3-diphenylcyclohexene, pure by NMR, which was distilled to give 37.5 g (0.16 mol, 80%) of 3,3-diphenylcyclohexene, bp 115–145 °C (0.0025 mm). Recrystallization from pentane and then from methanol, at −78 °C, gave an analytical sample, mp 44–45 °C (lit.[8] 31–32 °C).

The spectral data follow: IR ($CHCl_3$) 3.27, 3.32, 3.40, 3.49, 3.51, 5.12, 5.31, 5.50, 6.27, 6.71, 6.92, 7.45, 8.46, 8.70, 9.01, 9.35, 9.71, 9.98, 10.88, 11.11, 11.68, 14.39 μ; 60-MHz ^{1}H NMR ($CDCl_3$) τ 2.80 (10 H, m, aromatic), 3.99 (2 H, m, vinyl), 7.40–8.81 (6 H, m, CH_2); UV (cyclohexane) 260 nm (ϵ 325), 254 (416), 250 (481), 269 (342).

Anal. Calcd for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.30; H, 7.65.

3,3-Diphenyl-1-nitrocyclohexene.[32] A 25-ml (393 mmol) sample of dinitrogen tetroxide was vacuum distilled at 0.05 mm from a steel cylinder (Matheson Gas) into a trap cooled to −196 °C. The material was then allowed to thaw, and was passed, in a stream of dry air, into a stirred solution of 22.5 g (96.2 mmol) of 3,3-diphenylcyclohexene in 400 ml of dry ether at 0 °C. After all of the gas had been added (4 h), the reaction mixture was allowed to warm to room temperature and stir for 24 h. The resulting dark mixture was cooled to 0 °C and treated with 62 g (1.55 mol) of sodium hydroxide in 400 ml of water. The two-phase mixture was then magnetically stirred at room temperature for 24 h. The resulting mixture was ether extracted, and the ether solutions washed with water, dried, and concentrated in vacuo to give 17.8 g of a brown solid. Crystallization from hexane and then recrystallization from methanol gave 6.83 g (24.5 mmol, 25.4%) of 3,3-diphenyl-1-nitrocyclohexene, mp 104.0–106.5 °C, pure by NMR. Additional recrystallization from ether–hexane, treatment with Norit in refluxing methanol, crystallization from methanol, and recrystallization from ether–hexane gave 5.19 g (18.6 mmol, 19.3%) of pale yellow prisms of 3,3-diphenyl-1-nitrocyclohexene, mp 106.0–107.0 °C, >99.99% pure by GC (0.5% Carbowax 20M, 5% QF-1, and 5% SE-30).

The spectral data follow: IR (KBr) 3.26, 3.29, 3.38, 3.40, 3.48, 5.08, 5.26, 5.45, 5.63, 5.98, 6.25, 6.54, 6.67, 6.88, 6.94, 7.42, 8.26, 8.64, 9.26, 9.71, 10.70, 10.93, 11.63, 12.09, 12.99, 13.16, 13.51, 13.95, 14.22, 15.67, 16.39 μ; 100-MHz ^{1}H NMR ($CDCl_3$) τ 2.30 (1 H, br s, vinyl), 2.60–3.00 (10 H, m, aromatic), 7.40 (2 H, m, CH_2 adjacent to nitro substituted vinyl), 7.73 (2 H, m, CH_2CPh_2), 8.28 (2 H, m, CH_2); 15-MHz ^{13}C NMR ($CDCl_3$) 18.73 (br d of d, central CH_2), 24.20 (d of d, CH_2), 34.75 (d of d, CH_2 adjacent to nitro vinyl), 49.22 (s, Ph_2C), 126.73 (aromatic), 127.56 (aromatic), 128.55 (aromatic), 139.38 (d, vinyl β to nitro), 146.17 (s, tertiary aromatic), 149.60 ppm (s, nitro vinyl); UV (hexane) 244 nm (ϵ 8520), 325 sh (138); (95% ethanol) 253 nm (ϵ 7950); mass spectrum *m/e* (rel intensity) 279.12615 (0.5, calcd for $C_{18}H_{17}O$, 279.12593), 250 (0.2), 249.12840 (76.2, calcd for $C_{18}H_{17}O$, 249.12794), 234 (23.8), 233 (100.0), 205 (13.3), 204 (9.8), 203 (11.9), 202 (11.9), 193 (6.0), 192 (6.7), 191 (10.2), 190 (4.8), 189 (6.7), 180 (4.3), 179 (7.4), 178 (12.9), 177 (3.6), 165 (14.3), 156 (7.4), 155 (38.1), 154 (4.8), 153 (7.4), 152 (9.8), 130 (8.3), 129 (54.0), 128 (13.8), 127 (10.0), 117 (11.7), 116 (7.1), 115 (27.9), 105 (15.2), 91 (61.2), 77 (21.4).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.16; H, 6.30; N, 4.92.

Degradation of 3,3-Diphenyl-1-nitrocyclohexene. A 174-mg (0.623 mmol) sample of 3,3-diphenyl-1-nitrocyclohexene was reduced with zinc in acetic acid by the general method of Hassner.[34] The nitro olefin was dissolved in 15 ml of acetic acid containing 0.5 ml of water at 40 °C. Then 800 mg (12.2 g-atoms) of zinc dust was added portionwise over a period of 5 h. The mixture was heated to reflux, boiled for 4 h, stirred at room temperature for 10 h, reheated to 40 °C, and filtered hot. The zinc was washed with hot acetic acid, the acetic acid solutions diluted with 200 ml of water, ether extracted, and the extracts neutralized with saturated sodium bicarbonate solution, washed with saturated sodium chloride solution, dried, and concentrated in vacuo to give 116 mg (0.463 mmol, 74.4%) of 3,3-diphenylcyclohexanone, pure by NMR, whose spectral data were identical with those of a known sample of 3,3-diphenylcyclohexanone.[35] Recrystallization from ether gave 49 mg (0.175 mmol) of colorless crystals, mp 113–116 °C (lit.[10] 114–115 °C).

Previously unreported spectral data follow: 15-MHz ^{13}C NMR ($CDCl_3$) 210.0 (carbonyl), 147.3 (tertiary aromatic), 128.4 (aromatic), 126.9 (aromatic), 126.2 (aromatic), 53.7 (CH_2), 40.7 (CH_2), 35.8 (CH_2), 21.1 ppm (CH_2); UV (cyclohexane) 243 nm (ϵ 213), 250 (329), 255 (442), 259 (497), 263 (523), 270 (414), 283 (29), 291 (32), 298 (32), 308 (24), 320 (12); mass spectrum *m/e* (rel intensity) 251 (19.9), 250.13573 (100.0, calcd for $C_{18}H_{18}O$, 250.13576), 208 (12.2), 207 (40.4), 194 (17.4), 193 (98.8), 181 (5.3), 180 (31.2), 179 (22.0), 178 (26.6), 173 (10.1), 167 (9.3), 165 (21.5), 117 (6.5), 116 (5.5), 115 (34.3), 103 (12.9), 91 (25.0), 89 (8.6), 83 (8.4), 77 (14.0), 70 (22.6), 57 (9.9), 55 (25.2), 51 (6.9), 43 (15.0), 42 (53.2), 41 (11.0), 39 (5.9).

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.55; H, 7.22.

Preparative Photolysis of 3,3-Diphenyl-1-nitrocyclohexene. A 435-mg (1.56 mmol) sample of 3,3-diphenyl-1-nitrocyclohexene in 500 ml of purified benzene was purged with vanadous-purified nitrogen[36] for 1 h prior to and during photolysis. The solution was irradiated through a 2-mm Pyrex filter with a 450-W Hanovia medium pressure mercury arc lamp, monitoring by GC (5% QF-1). After 9.75 h, the irradiation was discontinued, and concentration in vacuo gave 435 mg of dark orange oil. Chromatography on a 2.8 × 80 cm Florisil (Fisher, 60–100 mesh) column containing 2% of Sylvania no. 290 red phosphor, slurry packed with 1% ether in hexane, gave the following: fraction 1, 400 ml, 1% ether in hexane, 9.1 mg of unidentified oil; 2, 500 ml, 5% ether in hexane, 0.7 mg of unidentified oil; 3, 525 ml, 10% ether in hexane, 1.4 mg of unidentified oil; 4, 600 ml, 10% ether in hexane, 382 mg of 3,3-diphenyl-1-nitrocyclohexene and *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane, in a ratio of 9:1; 5, 600 ml, 15%

ether in hexane, 4.3 mg of unidentified oil; 6, 1000 ml, ether, 10.6 mg of 3,3-diphenylcyclohexanone; 7, 1000 ml, ether, 4.6 mg of an unidentifiable mixture. All fractions were analyzed by NMR and GC (5% QF-1).

Fraction 4 was rechromatographed on a 2.8 × 80 cm basic alumina (Fisher, 80–200 mesh, Brockman activity I) column containing 3% of Sylvania no. 290 red phosphor, packed in 1% ether in hexane, to give 40.7 mg of *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane (pure by NMR) upon elution with 50% ether in hexane. The 3,3-diphenyl-1-nitrocyclohexene could not be recovered, probably owing to decomposition or permanent adsorption on the alumina. Recrystallization from ether–hexane gave 18.6 mg of analytically pure colorless crystals of *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane, mp 127.5–129.0 °C.

The spectral data follow: IR (KBr) 3.26, 3.30, 3.36, 3.38, 3.40, 3.48, 5.10, 5.30, 5.51, 5.69, 6.24, 6.59, 6.91, 7.37, 7.54, 8.22, 9.28, 9.75, 9.92, 10.57, 10.86, 11.20, 11.74, 12.35, 12.87, 13.11, 13.64, 14.20, 14.77, 16.69 μ; 100-MHz ^{1}H NMR ($CDCl_3$) τ 2.64 (10 H, br s, aromatic), 5.72 (1 H, s, benzylic), 6.74 (1 H, m, CH_2), 7.65 (3 H, m, CH_2), 8.42 (1 H, m, CH_2), 9.64 (1 H, m, CH_2); UV (cyclohexane) 253 nm (ϵ 3936); (acetonitrile) 259 nm (ϵ 3240); mass spectrum *m/e* (rel intensity) 249 (6.5), 233.13322 (100.0, calcd for $C_{18}H_{17}$, 233.13302), 155 (29.4), 154 (2.2), 153 (5.0), 152 (6.1), 130 (5.0), 129 (38.1), 128 (13.1), 127 (8.0), 117 (10.9), 116 (6.1), 115)22.2), 105 (12.6), 91 (71.3), 77 (17.4).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.63; H, 6.25; N, 5.20.

Fraction 6 was rechromatographed on a 1.2 × 21 cm basic alumina (Fisher, 80–200 mesh) column deactivated with 10% water and containing 5% of Sylvania no. 290 red phosphor, packed in hexane to give 5.8 mg of 3,3-diphenylcyclohexanone upon elution with 85 ml of hexane and then 50 ml of ether. Trituration with chloroform gave 5.0 mg of colorless crystals, mp 110.5–113.5 °C, whose spectral data were identical with those of a known sample of 3,3-diphenylcyclohexanone.[35]

Preparative Photolysis of 3,3-Diphenyl-1-nitrocyclohexene for Quantitative Recovery. A 1.00-g (3.58 mmol) sample of 3,3-diphenyl-1-nitrocyclohexene in 1 l. of purified benzene was purged with vanadous-purified nitrogen[36] for 1 h prior to and during photolysis. The solution was irradiated through a 2-mm Pyrex filter and 4 mm of a 0.025 M solution of sodium vanadate in 0.05 M sodium hydroxide (circulated as lamp coolant) with a 450-W medium pressure mercury arc lamp, monitoring by GC (0.25% Carbowax). The Pyrex-vanadate filter transmitted light of wavelength above 330 nm. The irradiation was discontinued after 10 h 40 min, and the photolysate was concentrated and dried in vacuo to give 1.00 g of yellow oil. (The UV spectra of the photolysate and filter solution were not changed during photolysis.) Chromatography of the crude residue on a 3.4 × 28 cm Florisil (Fisher, 60–100 mesh) column, containing 2% of no. 2282 green Sylvania phosphor, slurry packed in hexane, collecting 1-l. fractions, gave the following: fraction 1, hexane, 1.4 mg of unidentifiable oil; 2, 2% ether in hexane, 0.8 mg of unidentifiable oil; 3–4, 2% ether in hexane, 732.4 mg of 3,3-diphenyl-1-nitrocyclohexene; 5, 2% ether in hexane, 19.2 mg of 3,3-diphenyl-1-nitrocyclohexene and 28.9 mg of *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane; 6–11, 2% ether in hexane, 60.7 mg of *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane; 12–15, 4–32% ether in hexane, 5.5 mg of overlap; 16, 64% ether in hexane, 4.8 mg of 3,3-diphenylcyclohexanone; 17–30, 33.3 mg of unidentified oil; 31–35, 3–40% methanol in ether, 106.7 mg of unidentified oil. Thus, the mass balance is 100%.[37]

2-Phenyl-1-nitrocyclopentene. The procedure of Bordwell[11] was followed to convert 15.1 g (105 mmol) of 1-phenylcyclopentene to 3.69 g (19.5 mmol, 18.6%) of 2-phenyl-1-nitrocyclopentene, mp 50.5–51.5 °C (lit.[11] 51.5–52.5 °C) after chromatography.

***cis*-5,6-Diphenyl-1-nitrobicyclo[3.1.0]hexane.** To a −77 °C slurry of 1.16 g (3.26 mmol) of benzyldiphenylsulfonium tetrafluoroborate[12] in 7.50 ml of dry DME was added, dropwise, 2.00 ml (2.94 mmol) of a 1.47 M solution of butyllithium in hexane. The resulting light orange suspension was treated dropwise with a solution of 309 mg (1.63 mmol) of 2-phenyl-1-nitrocyclopentene in 2.00 ml of dry DME. The dark orange mixture was then stirred under nitrogen at −77 to −78 °C for 102 h, monitoring by TLC. The reaction mixture was then diluted with 50 ml of water and ether extracted. The extracts were washed with water, dried, and concentrated in vacuo to give an orange oil. NMR analysis placed an upper limit of 1% on the possible yield of *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane, relative to the cis isomer. Chromatography on a 2.8 × 90 cm silica gel (Davison, 60–200 mesh) column containing 3% of Sylvania no. 290 red phosphor, slurry packed in hexane, gave the following: fraction 1, 2000 ml, hexane, 492 mg of diphenyl sulfide; 2, 1350 ml, 1% ether in hexane, nil; 3, 225 ml, 1% ether in hexane, 52.1 mg of 2-phenyl-1-nitrocyclopentene with several unidentified compounds; 4, 1875 ml, 1% ether in hexane, 265 mg of 2-phenyl-1-nitrocyclopentene and *cis*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane. All fractions were analyzed by GC (5% QF-1). The material from fraction 4 was recrystallized from ether–hexane to give 180 mg (0.645 mmol, 39.5%) of colorless prisms, mp 110.0–111.5 °C, identified as *cis*-5,6-diphenyl-1-nitrobicyclo-[3.1.0]hexane.

The spectral data follow: IR (KBr) 3.26, 3.30, 3.36, 3.37, 3.41, 3.48, 6.24, 6.61, 6.68, 6.91, 7.44, 8.31, 8.51, 9.64, 10.41, 12.02, 12.63, 13.14, 13.48, 14.10, 14.31, 15.22 μ; 100-MHz ^{1}H NMR ($CDCl_3$) τ 2.60–3.20 (10 H, m, aromatic), 6.95 (1 H, s, benzylic cyclopropyl), 7.20 (2 H, m, CH_2 adjacent to nitrosubstituted bridgehead), 7.74 (2 H, m, CH_2 adjacent to phenyl-substituted bridgehead), 8.26 (2 H, m, central CH_2 of three-bridge); UV (cyclohexane) 253 nm (ϵ 2668); mass spectrum *m/e* (rel intensity) 249 (23.7), 233.13256 (72.9, calcd for $C_{18}H_{17}$, 233.13302), 155 (28.8), 129 (67.8), 128 (16.9), 117 (13.6), 115 (30.5), 105 (28.8), 91 (100.0), 77 (23.7), 74 (28.8).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13, N, 5.01. Found: C, 77.59; H, 6.11; N, 5.03.

270-MHz ^{1}H NMR Spectra and Simulated Spectra of *cis*- and *trans*-5,6-Diphenyl-1-nitrobicyclo[3.1.0]hexane.[38] GC pure samples of both *cis*- and *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]-hexane were analyzed by 270-MHz NMR.

The spectral data are given in Table II.

The methylene regions of the 270-MHz NMR spectra of both *cis*- and *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane were simulated using the self-iterative computer program mentioned above.[30]

It should be noted that the <1.0 Hz coupling constants are necessary to make the simulated spectrum identical with the observed one, but the relative error is ca. 0.5 Hz.

Isomerization of *cis*-5,6-Diphenyl-1-nitrobicyclo[3.1.0]hexane to *trans*-5,6-Diphenyl-1-nitrobicyclo[3.1.0]hexane. A 100-mg (0.358 mmol) sample of *cis*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane and 11.7 ml(12.0 g, 100 mmol) of acetophenone in 100 ml of purified benzene was purged with vanadous-purified nitrogen[36] for 1 h prior to and during photolysis. The solution was irradiated through a 2-mm Pyrex filter with a 450-W Hanovia medium pressure mercury arc lamp, monitoring by GC (0.25% Carbowax). The concentration of acetophenone was such that it absorbed >99% of the ultraviolet light incident on the solution. After 25 min of irradiation, all of the starting cis isomer had been consumed. The solvent and sensitizer were removed to give 132 mg of dark orange oil, and NMR analysis of the crude photolysate showed *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]-hexane to be the only identifiable product. No 3,3-diphenyl-1-nitrocyclohexene was present either by NMR or GC. The crude product was dissolved in ether and filtered through a 1.2 × 5 cm silica gel column. Removal of the solvent gave 104 mg of an oil which was chromatographed on a 1.2 × 26 cm silica gel (Davison, 60–200 mesh) column containing 2% of no. 2282 green Sylvania phosphor, slurry packed in hexane. Elution, collecting 50-ml fractions, gave the following: fraction 1, hexane, nil; 2, 1% ether in hexane, nil; 3, 2% ether in hexane, 15.9 mg (0.0569 mmol, 15.9%) of *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane, mp 122–127 °C, after trituration with pentane. Recrystallization from hexane–ether gave 5.0 mg of colorless prisms, mp 127.0–129.0 °C. The IR, NMR, and mass spectrum were all identical with those of the major photoproduct of 3,3-diphenyl-1-nitrocyclohexene, previously identified as *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane (vide supra).

Photolysis of 3,3-Diphenyl-1-nitrocyclohexene to Extended Conversion. A 100-mg (0.358 mmol) sample of 3,3-diphenyl-1-nitrocyclohexene in 100 ml of purified benzene was purged with vanadous-purified nitrogen[36] for 1 h prior to and during the photolysis. The solution was irradiated through a 2-mm Pyrex filter with a 450-W Hanovia medium pressure mercury arc lamp, monitoring by GC (5% QF-1). The irradiation was discontinued after 19.0 h, when the ratio of major product to starting nitro olefin had reached 0.5:1. The only primary products seen were *trans*-5,6-diphenyl-1-nitrobicyclo-[3.1.0]hexane and 3,3-diphenylcyclohexanone. The solvent was then removed, and the residue was analyzed by GC (0.5% Carbowax). There was no *cis*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane, although as little as 0.1% (relative to the trans isomer) would have been detected by GC.

Photostationary State of *trans*- and *cis*-5,6-Diphenyl-1-nitrobicyclo[3.1.0]hexane. A mixture of 9.54 mg (0.0341 mmol) of *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane and 1.93 mg (0.00692 mmol) of *cis*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane in 50 ml of benzene was purged with vanadous purified nitrogen[36] for 1 h prior to and during photolysis. The solution was irradiated through a 2-mm Pyrex filter with a 450-W Hanovia medium pressure mercury arc lamp, monitoring by GC (0.25% Carbowax). The relative amount of

the cis isomer rapidly decreased as the irradiation progressed, until, after 10 h, it was no longer present. (As little as 0.03% would have been detected.) Thus, the ratio of the cis isomer to the trans isomer is essentially zero at the potostationary state.

***cis*- and *trans*-5,6-Diphenylbicyclo[3.1.0]hex-2-ene.** These compounds were prepared by the general method of Dauben[9] from *cis*- and *trans*-5,6-diphenylbicyclo[3.1.0]hexan-2-one using a procedure very similar to that of Zimmerman and Epling.[39]

***cis*-1,6-Diphenylbicyclo[3.1.0]hexane.**[40] A 88-mg (0.379 mmol) sample of *cis*-5,6-diphenylbicyclo[3.1.0]hex-2-ene and 1.75 g (9.01 mmol) of dipotassium azodicarboxylate in 20 ml of dry pyridine were treated at room temperature with 2.00 ml (32.5 mmol) of acetic acid in 10 ml of pyridine during 6 h. The resulting mixture was then stirred for 27 h, treated with 2.00 ml more of acetic acid over 1.25 h, stirred for 23 h, treated with a third 2.00-ml portion of acetic acid, and stirred for 4 h. The reaction mixture was then poured into 150 ml of water and pentane extracted. The extracts were washed with 10% hydrochloric acid, dried, and concentrated in vacuo to give 73.6 mg (0.314 mmol, 82.9%) of *cis*-1,6-diphenylbicyclo[3.1.0]hexane, pure by NMR. Chromatography on a 2.8 × 11 cm silica gel (Davison, 60–200 mesh) column, slurry packed in hexane, eluting with 750 ml of hexane, gave 69.7 mg (0.279 mmol, 78.3%) of colorless crystals, mp 74–77 °C (lit.[8] 66–68 °C), identified as *cis*-1,6-diphenylbicyclo[3.1.0]hexane. One crystallization from methanol sharpened the melting point to 73–75 °C and gave 56.1 mg.

The spectral data follow: IR (KBr) 3.27, 3.38, 3.46, 5.13, 5.32, 6.22, 6.63, 6.84, 6.86, 7.59, 7.81, 8.13, 8.25, 8.50, 9.03, 9.09, 9.18, 9.51, 9.55, 10.22, 10.55, 10.80, 11.31, 12.25, 12.84, 12.99, 13.87, 14.01, 16.47 μ; 100-MHz ^{1}H NMR ($CDCl_3$) τ 2.80–3.40 (10 H, m, aromatic), 7.60–8.80 (8 H, m, CH_2 and cyclopropyl); mass spectrum *m/e* (rel intensity) 235 (12.6), 234.14121 (58.9, calcd for $C_{18}H_{18}$, 234.14085), 207 (7.3), 206 (15.5), 193 (5.0), 192 (6.3), 191 (10.5), 179 (4.1), 178 (8.5), 177 (1.6), 165 (9.1), 157 (7.9), 156 (24.0), 155 (14.9), 152 (4.7), 144 (14.3), 143 (51.0), 131 (5.5), 130 (46.7), 128 (23.3), 119 (4.6), 117 (44.9), 116 (9.4), 115 (23.7), 105 (3.0), 104 (5.5), 103 (7.7), 102 (9.9), 101 (8.9), 92 (8.7), 91 (100.0), 89 (11.8), 79 (5.1), 78 (7.0), 77 (16.6), 65 (11.1), 63 (6.4), 51 (10.9).

Anal. Calcd for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.20; H, 7.84.

***trans*-1,6-Diphenylbicyclo[3.1.0]hexane.**[40] A 272-mg (1.17 mmol) sample of *trans*-5,6-diphenylbicyclo[3.1.0]hex-2-ene and 1.49 g (7.67 mmol) of dipotassium azodicarboxylate in 37 ml of dry pyridine were treated at room temperature with 1.5 ml (26 mmol) of acetic acid in 7 ml of pyridine over 0.5 h and then stirred for 43 h. Another portion (3.76 g, 19.4 mmol) of dipotassium azodicarboxylate was added to the colorless slurry, followed by the addition of 1.5 ml (26 mmol) of acetic acid in 7 ml of pyridine over a period of 4 h. The resulting mixture was stirred for 7.5 h, treated with a final 1.60-ml (29 mmol) portion of acetic acid in 7 ml of pyridine, and stirred for 25 h. The colorless reaction mixture was then poured into 150 ml of water and pentane extracted. The extracts were washed with 10% hydrochloric acid, washed with saturated sodium bicarbonate solution, dried, and concentrated in vacuo to give 248 mg (1.06 mmol, 90.5%) of a colorless oil, pure by NMR and TLC. The oil was chromatographed on a 2.8 × 17 cm silica gel (Davison, 60–200 mesh) column, slurry packed in hexane, eluting with 700 ml of hexane, to give 228 mg (0.973 mmol, 83.2%) of analytically pure (GC on 5% QF-1 and 0.25% Carbowax 20M) *trans*-1,6-diphenylbicyclo[3.1.0]hexane.

The spectral data follow: IR (neat) 3.23, 3.27, 3.30, 3.37, 3.41, 3.49, 5.14, 5.32, 5.53, 5.69, 6.02, 6.24, 6.34, 6.67, 6.78, 6.89, 7.47, 7.61, 7.89, 8.01, 8.33, 8.47, 8.64, 9.12, 9.32, 9.73, 10.78, 11.01, 11.48, 11.89, 12.74, 13.23, 13.79, 13.97, 14.37, 14.97, 15.70 μ; 100-MHz ^{1}H NMR ($CDCl_3$) τ 2.60–3.10 (10 H, m, aromatic), 7.70 (1 H, d, benzylic cyclopropyl, J = 8 Hz), 7.80–8.40 (5 H, m, CH_2 and cyclopropyl methine), 8.70 (1 H, m, central CH_2 of three-bridge, exo proton), 9.73 (1 H, m, central CH_2 of three-bridge, endo proton); UV (cyclohexane) 253 nm (ϵ 789), 260 (743), 267 (614), 276 (281); mass spectrum *m/e* (rel intensity) 235 (20.9), 234.14099 (100.0, calcd for $C_{18}H_{18}$, 234.14085), 207 (11.8), 206 (25.4), 193 (8.5), 192 (11.0), 191 (33.7), 189 (11.6), 179 (6.3), 178 (14.8), 176 (2.7), 165 (14.6), 157 (12.8), 156 (38.2), 155 (26.3), 152 (8.7), 144 (22.3), 143 (85.6), 131 (8.7), 130 (79.9), 128 (28.1), 118 (7.4), 117 (76.1), 116 (16.7), 115 (43.4), 105 (6.4), 104 (8.7), 103 (13.9), 102 (15.7), 101 (13.9), 92 (16.0), 91 (90.5), 89 (21.6), 79 (8.8), 78 (13.3), 77 (30.9), 65 (21.5), 63 (11.2), 51 (21.0).

Anal. Calcd for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.35; H, 7.70.

270-MHz ^{1}H NMR Spectra of *cis*- and *trans*-1,6-Diphenylbicyclo[3.1.0]hexane. Analytically pure samples of both *cis*- and *trans*-1,6-diphenylbicyclo[3.1.0]hexane (vide supra) were analyzed by 270-MHz NMR. The spectral data are given in Table II.

Preparative Sensitized Photolysis of 3,3-Diphenyl-1-nitrocyclohexene. A 212-mg (0.759 mmol) sample of 3,3-diphenyl-1-nitrocyclohexene in 650 ml of purified benzene containing 50 ml (0.428 mol) of acetophenone was purged with vanadous-purified nitrogen[36] for 1 h prior to and during photolysis. The solution was irradiated through a 2-mm Pyrex filter with a 450-W Hanovia medium pressure mercury arc lamp. Additional filtration of the light was accomplished by circulating the following filter solution[4] around the lamp as coolant: 20.0 g of cupric sulfate pentahydrate, 157 g of nickelous sulfate hexahydrate, 300 g of cobaltous sulfate heptahydrate, and 23.5 g of potassium nitrate in 1 l. of distilled water. The concentrations of nitro olefin and acetophenone were such that the acetophenone absorbed >99% of the light incident on the photolysis solution. After 8.5 h, secondary photolysis began to be apparent, monitoring by GC, 0.25% Carbowax, so the irradiation was discontinued and the solvent was removed in vacuo. The bulk of the acetophenone was removed by distillation at 40–50 °C (0.8–0.1 mm), and the residue was analyzed by GC (0.25% Carbowax) for the possible presence of *cis*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane. None of the cis bicyclic was detected although as little as 0.1%, relative to the trans isomer, would have been seen. Chromatography of the ether-soluble portion of the crude photolysate on a 2.8 × 86 cm Florisil (Fisher, 60–100 mesh) column containing 2% of Sylvania no. 2282 green phosphor, slurry packed in hexane, collecting 1-l. fractions, gave the following: fraction 1, hexane, nil; 2–4, 1% ether in hexane, nil; 5–8, 1% ether in hexane, 47.9 mg of 3,3-diphenyl-1-nitrocyclohexene; 9–10, 1% ether in hexane, 2.0 mg of overlap; 11–13, 2% ether in hexane, 25.7 mg of *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane; 14–20, 2% ether in hexane, 5.3 mg of an unidentified mixture; 21, 8% ether in hexane, 8.2 mg of an unidentified mixture; 22–23, 32% ether in hexane, 27.1 mg of 3,3-diphenylcyclohexanone; 24–26, 32% ether in hexane, 15.8 mg of an unidentified mixture. All fractions were identified by GC (0.25% Carbowax) and NMR.

Preparative Photolysis of 3,3-Diphenyl-1-nitrocyclohexene in Isopropyl Alcohol. A 75.6-mg (0.271 mmol) sample of 3,3-diphenyl-1-nitrocyclohexene in 115 ml of isopropyl alcohol (Mallinckrodt Reagent) was purged with vanadous-purified nitrogen[36] for 1 h prior to and during photolysis. The solution was irradiated with a 450-W Hanovia medium pressure mercury arc lamp, monitoring by GC (0.25% Carbowax). The irradiation was discontinued after 150 min, and the solvent was removed in vacuo to give 84.5 mg of an oil which was almost totally a single compound, by NMR. Trituration with ether and crystallization from ether gave 16.4 mg (0.062 mmol, 22.8%) of 3,3-diphenylcyclohexanone oxime, mp 181–191 °C, which had all spectral data identical with those of a known sample (vide infra). Chromatography on a 1.2 × 10 cm Florisil (Davison, 60–100 mesh) column, eluting with 10% ether in hexane, followed by recrystallization from methanol gave an analytical sample, mp 190–199 °C.

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22. Found: C, 81.29; H, 7.17.

3,3-Diphenylcyclohexanone Oxime. A 100-mg (0.399 mmol) sample of 3,3-diphenylcyclohexanone was stirred for 12 h with 277 mg (3.99 mmol) of hydroxylamine hydrochloride and 41 mg (0.5 mmol) of sodium acetate in ethanol–water (5:1 v/v). The reaction mixture was then poured into water, ether extracted, dried, and concentrated in vacuo to give 64.0 mg of a colorless, crystalline solid. Recrystallization of 55 mg from methanol gave 46 mg (0.173 mmol, 51.8% based on total crude product) of colorless crystals, mp 191–199 °C.

The spectral data follow: IR (KBr) 3.08, 3.17, 3.26, 3.37, 6.17, 6.68, 6.90, 7.40, 7.51, 7.74, 7.92, 8.06, 9.17, 9.64, 10.08, 10.49, 10.72, 10.95, 11.98, 13.00, 13.18, 14.03, 14.27 μ; 60-MHz NMR ($CDCl_3$) τ 1.92 (1 H, br s, OH), 2.80 (10 H, m, aromatic), 6.84 (2 H, s, CH_2), 7.20–7.80 (4 H, m, CH_2), 8.00–8.60 (2 H, m, CH_2); UV (95% ethanol) 262 nm (ϵ 519), 268 (377); mass spectrum *m/e* (rel intensity) 266 (19.7), 265.14652 (100.0, calcd for $C_{18}N_{19}NO$, 265.14666), 249 (21.5), 248 (96.9), 193 (23.5), 191 (22.7), 179 (14.3), 178 (27.2), 170 (24.5), 167 (17.3), 165 (24.0), 130 (16.5), 129 (52.0), 128 (10.9), 115 (46.7), 105 (19.1), 103 (12.4), 98 (10.4), 91 (58.5), 77 (21.2).

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22. Found: C, 81.32; H, 7.22.

Photolysis of 3,3-Diphenyl-1-nitrocyclohexene in Isopropyl Alcohol. A 200-mg (0.716 mmol) sample of 3,3-diphenyl-1-nitrocyclohexene in 200 ml of isopropyl alcohol was purged with vanadous-purified nitrogen[36] for 1 h prior to and during photolysis. The solution was irradiated with a 450-W Hanovia medium pressure mercury arc lamp, through a 2-mm Pyrex filter, monitoring by GC (0.25% Carbowax). After 150 min of irradiation, the solvent was removed in vacuo to give a yellow oil which was analyzed by NMR and found to contain

3,-diphenylcyclohexanone oxime, *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane, and 3,3-diphenyl-1-nitrocyclohexene in a ratio of 5.73:1.00:3.40. The product ratio was determined by hand integration of the expanded 100-MHz NMR spectrum. If any 3,3-diphenylcyclohexanone were present, it was not present in sufficient amount to be detected. Crystallization of the crude product from methanol, treatment with Norit, and a second crystallization from methanol gave 89.2 mg (0.336 mmol, 46.9%) of 3,3-diphenylcyclohexanone oxime, mp 184–195 °C.

Photolysis of 3,3-Diphenyl-1-nitrocyclohexene in 10% Isopropyl Alcohol. A solution of 3,3-diphenyl-1-nitrocyclohexene in 10% isopropyl alcohol in benzene (v/v) was purged with vanadous-purified nitrogen[36] for 1 h prior to and during the photolysis. In runs 1–3 the solution was irradiated with a 450-W Hanovia medium pressure mercury arc lamp through 2 mm of Pyrex and a 4-mm thickness of 0.025 M sodium vanadate in 0.05 M sodium hydroxide, circulated as lamp coolant. In run 4, only Pyrex was used as a filter. The filters were such that the light transmitted was of wavelength longer than 330 or 290 nm, respectively. The nitro olefin absorbed >99% of the incident UV light, relative to any other species in solution. After the irradiation, the photolysate was concentrated in vacuo and (in the quenched run) the naphthalene was removed by sublimation at 40 °C (0.05 mm). The ultraviolet spectrum of the photolysate and filter were the same before and after photolysis. By a combination of NMR and GC analysis (tetraphenylethylene internal standard) the quantities of *trans*-5,6-diphenyl-1-nitrobicyclo[3.1.0]hexane, 3,3-diphenylcyclohexanone, and 3,3-diphenylcyclohexanone oxime produced were determined. The details of each run are given below.

Run 1. Starting nitro olefin, 0.358 mmol in 115 ml of 10% isopropyl alcohol in benzene; 150 min photolysis time; bicyclohexane formed, 0.0225 mmol; cyclohexanone formed, 0.0045 mmol; oxime formed, 0.0284 mmol; 15.5% conversion.

Run 2. Starting nitro olefin, 0.358 mmol in 115 ml of 10% isopropyl alcohol in benzene containing 0.1 M naphthalene; 150 min photolysis time; bicyclohexane formed, 0.0207 mmol; cyclohexanone formed, 0.00456 mmol; oxime formed, 0.0213 mmol; 13.0% conversion.

Run 3. Starting nitro olefin, 0.358 mmol in 115 ml of 10% isopropyl alcohol in benzene; 30 min photolysis time; bicyclohexane formed, 0.00578 mmol; cyclohexanone formed, 0.00121 mmol; oxime formed, 0.00488 mmol; 3.3% conversion.

Run 4. Starting nitro olefin, 0.358 mmol in 100 ml of 10% isopropyl alcohol in benzene; 150 min photolysis time; ratio of oxime to bicyclohexane, 0.94:1.00; 19.5% conversion.

Apparatus for Quantum Yields. The quantum yield photolyses were run on the "Black Box" apparatus.[21] Light output was measured by ferrioxalate actinometry.[41] The light absorbed in the reaction cell was determined by the splitting ratio technique.[21] The light was filtered through a three-compartment cell containing one of the following solution filter combinations. Filter A, (a) 0.1 M cupric sulfate pentahydrate in 1% sulfuric acid, (b) 1.0 M cobaltous sulfate heptahydrate in 5% sulfuric acid, (c) 2.0 M nickelous sulfate hexahydrate in 5% sulfuric acid; this combination gave a maximum transmission (39%) at 317 nm and was opaque below 280 nm and above 360 nm. Filter B, (a) 1.0 M cupric sulfate pentahydrate in 5% sulfuric acid, (b) 2.0 M cobaltous sulfate heptahydrate in 5% sulfuric acid, (c) 0.5 M nickelous sulfate hexahydrate in 1.5% sulfuric acid; this combination gave a maximum transmission (24%) at 337 nm and was opaque below 310 nm and above 375 nm.

Direct Quantum Yields. The direct photolyses for quantum yield determinations were run in purified benzene. The photolysis solution was purged with vanadous-purified nitrogen[36] for 1 h prior to and during irradiation. The photolysates were analyzed by GC on a 4 ft × 0.25 in. column of 5% SE-30 on Varaport 30, 100/120 mesh, at 170 °C using tetraphenylethylene as internal standard. Data for the quantum yields are as follows.

Run 1. Filter A; starting nitro olefin, 2.40 mmol in 750 ml; 225.1 mEinsteins absorbed; bicyclohexane formed, 0.0688 mmol; Φ = 0.000306; ketone formed, 0.00895 mmol, Φ = 0.0000397; 3.24% conversion.

Run 2. Filter A; starting nitro olefin, 2.40 mmol in 750 ml; 110.4 mEinsteins absorbed; bicyclohexane formed, 0.0335 mmol, Φ = 0.000303; ketone formed, 0.00414 mmol, Φ = 0.0000375; 1.63% conversion.

Run 3. Filter A; starting nitro olefin, 2.40 mmol in 750 ml; 54.65 mEinsteins absorbed; bicyclohexane formed, 0.0166 mmol, Φ = 0.000304; ketone formed, 0.00162 mmol, Φ = 0.0000263; 0.759% conversion.

Run 4. Filter A; starting nitro olefin, 2.40 mmol in 750 ml; 26.96 mEinsteins absorbed; bicyclohexane formed, 0.00822 mmol, Φ = 0.000305; ketone formed, 0.000440 mmol, Φ = 0.0000161; 0.361% conversion.

Sensitized Quantum Yields. The sensitized photolyses for quantum yield determinations were run in purified benzene containing enough acetophenone to absorb >99% of the light incident on the solution. The photolysis solution was purged with vanadous-purified nitrogen[36] for 1 h prior to and during irradiation. The acetophenone was removed in vacuo (0.04 mm) at 40–50 °C before GC analysis, performed as in the direct quantum yields. Data for the quantum yields are as follows.

Run 1. Filter B; starting nitro olefin, 0.752 mmol in 750 ml; 8.03 mEinsteins absorbed; bicyclohexane formed, 0.00313 mmol, Φ = 0.000390; ketone formed, 0.00339 mmol, Φ = 0.000422; 0.867% conversion.

Run 2. Filter B; starting nitro olefin, 0.749 mmol in 750 ml; 3.99 mEinsteins absorbed; bicyclohexane formed, 0.00174 mmol, Φ = 0.000437; ketone formed, 0.000826 mmol, Φ = 0.000207; 0.343% conversion.

Run 3. Filter B; starting nitro olefin, 0.751 mmol in 750 ml; 2.27 mEinsteins absorbed; bicyclohexane formed, 0.000982 mmol, Φ = 0.000433; ketone formed, 0.000375 mmol, Φ = 0.000165; 0.181% conversion.

Acknowledgment. Support of this research by the National Science Foundation is gratefully acknowledged.

Registry No.—**2**, 60934-67-0; **4**, 31158-25-5; **5**, 60909-09-3; **6**, 60965-82-4; **7**, 31186-81-9; **8**, 31186-82-0; **11**, 17245-76-0; 11 oxime, 56740-40-0; dinitrogen tetroxide, 10544-72-6; benzyldiphenylsulfonium BF_4^-, 1763-99-1; 2-phenyl-1-nitrocyclopentene, 29787-31-3; *cis*-5,6-diphenylbicyclo[3.1.0]hex-2-ene, 27995-70-6; *trans*-5,6-diphenylbicyclo[3.1.0]hex-2-ene, 27995-69-3.

References and Notes

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9-*tert*-Butyl-9-azabicyclo[3.3.1]nonan-3-one

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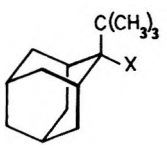
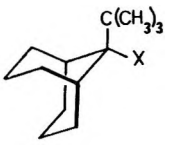
Received August 13, 1976

The title compound **7** has been synthesized by reaction of *tert*-butylamine with cycloocta-2,7-dienone. ^{13}C NMR and pK_a measurements of **7** show that the nitrogen atom of **7** is either a flattened pyramid or planar.

Six-membered cyclic compounds in chair conformations bearing axial *tert*-butyl groups are rare, as would be anticipated based upon the severe 1,3-diaxial steric interactions inherent in such conformations.[1] For instance, in order to avoid having an axial *tert*-butyl group, twist boat conformations are preferred for *trans*-1,3-di-*tert*-butylcyclohexane,[2a-c] *cis*-1,4-di-*tert*-butylcyclohexane,[2c,d] and *cis,trans*-1,3,5-tri-*tert*-butylcyclohexane;[2e] however, for both *cis*- and *trans*-1,2-di-*tert*-butylcyclohexane chair conformations with axial *tert*-butyl groups have been found to be important.[2f,g] Other carbocyclic examples are 2-*tert*-butyladamantane (**1c**),[3a] 2-*tert*-butyladamantan-2-ol (**1a**),[3b] and 9-*tert*-butylbicyclo[3.3.1]nonan-9-ol (**2a**).[3c] The corresponding *p*-nitrobenzoates **1b** and **2b** exhibit extraordinarily high solvolytic reactivities due to relief of strain during ionization.[3b-d]



1a-c

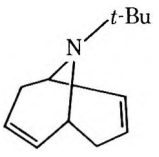


2a,b

a, X = OH
b, X = *p*-$NO_2C_6H_4CO_2$
c, X = H

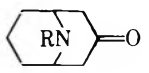
Heterocyclic compounds[4,5] such as *cis*-2-alkyl-5-*tert*-butyl-1,3-dioxanes[4a] and 5-*tert*-butyl-1,3,2-dioxaphosphorins[5e] with axially disposed *tert*-butyl groups have also been described. In these molecules the severe 1-*tert*-butyl-3-hydrogen diaxial interactions present in carbocyclic compounds are absent.[6]

Recently Cuthbertson and MacNicol have reported the preparation of 9-*tert*-butyl-9-azabicyclo[3.3.1]nona-2,6-diene (**3**),[7] a compound in which the 1,3-diaxial interactions are



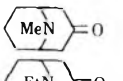
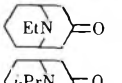
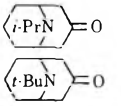
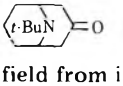
3

diminished by flattening of the carbon bridges. We now report the synthesis and interesting properties of 9-*tert*-butyl-9-azabicyclo[3.3.1]nonan-3-one (**7**). For comparison we have also prepared the *N*-methyl, *N*-ethyl, and *N*-isopropyl analogues **4**–**6**. We were intrigued with the possibility of detecting a flattening of the nitrogen pyramid to relieve some of the steric



4, R = Me
5, R = Et
6, R = *i*-Pr
7, R = *t*-Bu

Table I. Carbon-13 Chemical Shifts of *N*-Alkylnorpseudopelletierines[a]

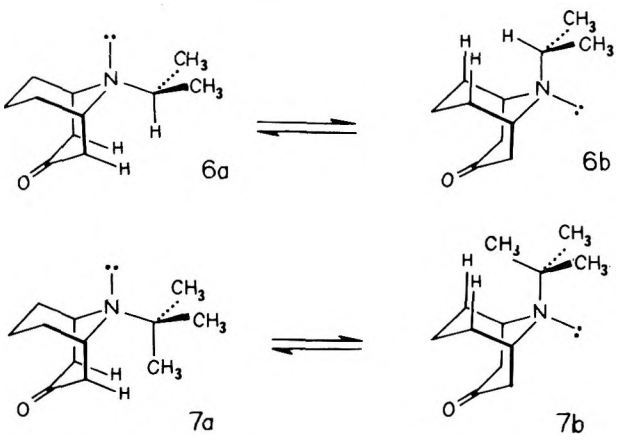
Registry no.	Compd	C-1	C-2	C-3	C-6	C-7	NCC	NCC
552-70-5	4 	55.8	41.8	210.0	29.7	16.1	41.1	
27092-59-7	5 	53.6	42.4	210.1	30.0	16.8	46.4	13.7
56258-85-6	6 	50.6	42.7	211.3	30.3	16.6	47.5	21.9
56258-86-7	7 	48.4	47.0	212.7	32.3	17.2	54.1	30.0

[a] $CDCl_3$ solution, downfield from internal Me_4Si.

interactions of the axial *tert*-butyl group. Amine rehybridization as a consequence of geometric factors has been observed previously.[8]

The approach chosen for the synthesis of norpseudopelletierine derivatives **4–7** was the double Michael addition[9,10] of the appropriate primary amine to cycloocta-2,7-dienone[11] according to the procedures of Kashman and Cherkez.[10b] The reactions with methylamine, ethylamine, and isopropylamine gave high yields of amino ketones **4–6.** The reaction with *tert*-butylamine proceeded more slowly but gave mainly **7** with four or five minor products which were not investigated. The yield of **7,** after purification by preparative VPC, was 32%.

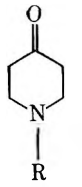
To evaluate the consequences of steric interaction in compounds **4–7,** we have relied on carbon-13 nuclear magnetic resonance spectroscopy[12] and pK_a measurements. Table I collects the chemical shifts for the various carbon atoms; shielding assignments were made on the basis of relative signal intensities and with the aid of coupled spectra.[13] Particularly revealing are the chemical shifts of the carbons 2(4) and 6(8), which endure only small (nominally 0.3 ppm) downfield shifts as two of the methyl hydrogens of pseudopelletierine (**4**) are sesquentially exchanged for methyl groups. Upon substitution of the final hydrogen by methyl to provide the *tert*-butyl derivative **7,** these carbons experience substantial downfield shifts (4.3 and 2.0 ppm). The origin of the observed shifts is certainly steric in nature, and the direction (downfield) and magnitudes of the shifts are in agreement with Stothers' results for δ steric effects.[14] The *N*-ethyl and *N*-isopropyl amino ketones **5** and **6** can adopt preferred conformations in which the methyl groups lie away from the axial hydrogens at carbons 2, 4, 6, and 8, as illustrated in **6a** and **6b.** When the last



methyl group is added to give **7,** interaction of one of the methyl groups with the axial hydrogens becomes obligatory. To relieve the severity of this steric interaction, the *tert*-butyl group must be tilted away from a purely axial orientation, and the nitrogen pyramid must be flattened toward planarity. Probably the nitrogen atom is not completely planar (sp^2 hybridization) because of the repulsion of the nitrogen lone pair for the carbon ligands.[15] We draw attention to the fact that the shift increments per methyl group are greater, especially for *tert*-butyl amino ketone **7,** at carbons 2 and 4 than at carbons 6 and 8. Assuming that the deshielding effects (δ effect) of the methyl groups are approximately the same for the two types of conformations, this indicates that conformations with the *N*-alkyl groups axial to the piperidone rings are preferred to conformations with the *N*-alkyl group axial to the piperidine rings. This preference is probably the result of the presence of the trigonal carbon atom in the ketonic bridge, permitting greater flattening of that bridge and concomitant movement of the axial hydrogens at C-2 and C-4 away from the axial *N*-alkyl group.[15]

With each additional methyl group the likelihood of a γ-steric interaction between the bridgehead carbons and the methyl carbons also is enhanced. Such γ-steric effects[17] result in the signals of the bridgehead carbon atoms being shifted progressively upfield by approximately 2.5 ppm for each additional methyl group. This finding is in accord with the results reported by Grant and Cheney,[18] who have advanced a steric polarization mechanism to account for such γ upfield shifts. Additional support for this interpretation is available from the ^1H NMR data (see Experimental Section) for the bridgehead positions which undergo increasing deshielding as the number of methyl groups increases.[19]

The basicity data (Table II) for these bicyclic amines are also quite interesting. Usually the basicity of amines is enhanced by increasing β substitution. For example, the conjugate acids of trimethylamine, dimethylethylamine, dimethylisopropylamine, and dimethyl-*tert*-butylamine have pK_a values of 9.81, 10.16, 10.47, and 10.69, respectively.[21a] Recently measured pK_a values for the conjugate acids of 4-piperidone (**8a**), *N*-methyl-4-piperidone (**8b**), *N*-ethyl-4-



8a, R = H
b, R = Me
c, R = Et
d, R = *t*-Bu

piperidone (**8c**), and *N*-*tert*-butyl-4-piperidone (**8d**) are 8.6, 8.1, and 8.3, and 9.0, respectively.[21b]

The pK_a values for the conjugate acids of amino ketones **4–7** measured in 35:64 (v/v) ethanol–water are near 7. Amino ketones **4–6** show the normal trend of increased basicity paralleling increased β substitution. However, *tert*-butyl amino ketone **7** is *less* basic than **5** and **6.** Such a decrease in basicity would be expected to accompany a change in nitrogen hybridization toward sp^2. Flattening of the nitrogen pyramid to

Table II. Basicity and UV Absorption Data for *N*-Alkylnorpseudopelletierines

Compd	pK_a'[a]	λ_{max} (ϵ)[b]	λ_{max} (ϵ)[b]
4	6.90	206 (1400)	246 (770)
5	7.24	208 (1780)	242 (825)
6	7.46	201 (2190)	246 (1020)
7	7.05	202 (1690)	230 (1580)[c]

[a] pK_a' of the conjugate acid determined in 36:64 (v/v) ethanol–water at 25.0 °C. [b] Pentane solution. [c] There is also a shoulder at ca. 265 nm.

relieve the interactions of the *tert*-butyl group with the axial hydrogens at carbons 2, 4, 6, and 8 would impart greater p character to the lone pair orbital. Protonation of the nitrogen lone pair would localize the lone pair to one side of the nitrogen atom and would require more s character in the N–H bond than in the original lone pair orbital, thus imparting more p character to the three N–C bonds. Because the protonated *tert*-butyl amino ketone experiences greater steric interactions than the free amine its pK_a is lowered.

The ultraviolet absorption spectra of compounds **4–6** are also of interest (Table II). The observed short wavelength maxima (ca. 205 nm) are typical of tertiary amines,[8b] and the long wavelength maxima (ca. 245 nm) are consistent with those found for other β-amino ketones in which σ-coupled charge transfer transitions give rise to similar values.[22] The *tert*-butyl derivative **7** behaves somewhat anomalously since it displays a maximum at 230 nm. Perhaps this indicates that on account of rehybridization at the nitrogen atom the lone pair of electrons is geometrically less suitable for through-bond coupling with the carbonyl group. Palacek[23] and Hudec[22b] have demonstrated that σ coupling is quite dependent upon the orientation of the lone pair of electrons relative to the carbonyl group.[23]

We are continuing active investigation of this and other hindered amines and hope to determine the precise geometry about the nitrogen atoms of sterically crowded amines.

Experimental Section

Melting points (taken on a Thomas-Hoover capillary apparatus) and boiling points are uncorrected. pK_a' determinations were carried out according to the procedure of Thomson[24] using an Instrument Laboratory Model 265 Electrometer. Ultraviolet spectra were recorded with a Cary Model 14 spectrophotometer. Infrared spectra were obtained on a Perkin-Elmer Model 457 spectrophotometer. Proton magnetic resonance spectra were obtained with a Varian Associates T-60 instrument. ^{13}C NMR spectra were measured with a JEOL JNM PS-100 spectrometer interfaced with a Digilab Nova 1200 computer. Vapor phase chromatographic analyses and collections were performed with a Varian Aerograph Model 90-P instrument employing a 0.25 in. diameter by 6 ft column packed with 5% SE-30 on Chromosorb G. Mass spectra were obtained on an Associated Electrical Industries MS-902 spectrometer. Elemental analyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Pseudopelletierine (4). Method C of Kashman[10b] was followed. To a stirred solution of 2.92 g (0.0433 mol) of methylamine hydrochloride in 45 ml of absolute methanol at room temperature was added 4.6 g of anhydrous sodium carbonate, followed by 5.28 g (0.0433 mol) of cycloocta-2,7-dienone.[11] After 22 h VPC, NMR, and IR indicated that the reaction was 95% complete. Workup consisted of filtering the yellow mixture and concentrating to a semisolid, which was taken up in methylene chloride and filtered. The filtrate was extracted with 6 M aqueous HCl solution; the combined extracts were basicified, extracted with methylene chloride, and dried (Na_2SO_4), and the bulk of the solvent removed by atmospheric distillation using a 16-in. Vigreux column. The remainder of the solvent was removed on a rotary evaporator to provide 5.79 g of a yellow, waxy solid which was sublimed (52–54 °C, 0.25 Torr) to give 4.57 g (69%) of slightly yellow solid, mp 46–55 °C (lit.[10a] 62–64 °C). Analysis by VPC showed a single peak.

***N*-Ethylnorpseudopelletierine (5).** Method A of Kashman[10b] was used. To stirred solution of 1.22 g (0.0100 mol) of cycloocta-2,7-dienone[11] in 2 ml of methanol at room temperature was added through a serum cap by means of a syringe 0.5 g (0.73 ml, 0.0110 mol) of ethylamine. When an NMR spectrum of an aliquot indicated the absence of cyclooctadienone, the solution was concentrated on a rotary evaporator, and the liquid residue distilled (bp 62 °C, 0.07 Torr; lit.[23] 90–95 °C, 0.1 Torr) to afford 1.43 g (85%) of **5**. VPC analysis showed only one peak.

***N*-Isopropylnorpseudopelletierine (6).** The procedure used for the preparation of **5** was employed, except that 0.841 g (0.0069 mol) of cycloocta-2,7-dienone and 0.455 g (0.5 ml, 0.0076 mol) of isopropylamine were used to give 1.14 g (91%) of crude **6** which on VPC analysis showed only one peak. Samples for spectra, pK_a' determination, and analysis were obtained by preparative VPC: mp 57.5–59.5 °C; NMR ($CDCl_3$) 3.67 br, 2 H, 1.17 d (J = 6 Hz), 6 H; IR ($CHCl_3$) 1691 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 181 (45), 166 (100), 138 (53), 124 (61), 123 (23), 122 (26), 96 (36), 82 (30), 80 (46), 79 (28), 70 (26), 55 (28), 52 (25), 50 (26), 44 (31), 43 (40), 42 (38), 41 (77).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.90; H, 10.51; N, 7.82.

***N*-*tert*-Butylnorpseudopelletierine (7).** The procedure used for **5** was followed, substituting 0.85 g (1.22 ml, 0.0110 mol) of *tert*-butylamine for ethylamine. Preparative VPC afforded 0.620 g (32%) of liquid **7**: NMR ($CDCl_3$) 3.82 br, 2 H, 1.23 s, 9 H; IR (neat) 1700 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 195 (22), 180 (100), 96 (31), 82 (31), 43 (31), 41 (25).

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.83; H, 10.88; N, 7.09.

Acknowledgment. This work was supported by a grant from the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—Cycloocta-2,7-dienone, 1073-76-3; isopropylamine, 75-31-0; *tert*-butylamine, 75-64-9.

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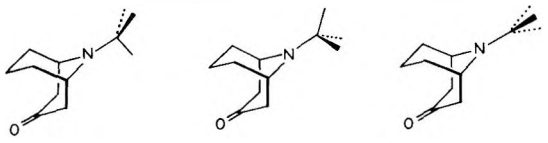
(15) The experimental data do not exclude the possibility that the nitrogen atom in **7** is planar. For example, the NMR spectrum can be explained on the

basis of an equilibrium of N-planar conformations **7c**, **7d** (and **7e**) with **7c** predominating over **7d**. Carbons 2 and 4 would be deshielded by the δ effect in **7c** and carbons 6 and 8 would be deshielded in **7d**. An attempt to resolve



7c 7d 7e

the question by low temperature ^{1}H NMR was unsuccessful. While some changes were evident, the spectra were not sharp enough to permit any rigorous conclusions.[16]

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Terpenes and Related Systems. 16.[1] Fate of Representative Bicyclic Sesquiterpenes in Strong Acid Medium. A General Rearrangement of Hydroazulene Sesquiterpenenes to Decalin Types

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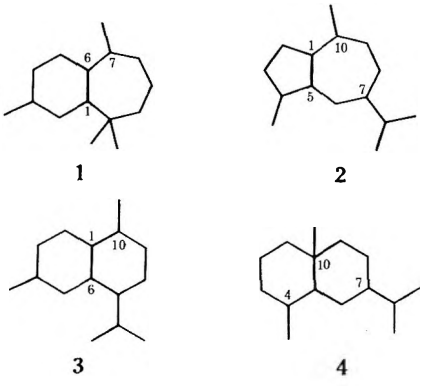
Received August 23, 1976

Rearrangement of several naturally occurring bicyclic sesquiterpenes of himachalane (**1**), guaiane (**2**), cadalane (**3**), and eudesmane (**4**) types has been studied in strong acid medium under stable carbocation conditions. The structures of the carbocations (**8** and **40**) formed from α- and β-himachalenes (**5** and **6**) and from selinenes (**38**), respectively, have been deduced from ^{1}H NMR spectral data. Quenching of these cationic solutions provides convenient preparation of conjugated dienes **9**, **10**, and **28**. A novel and general rearrangement of guaiane-type hydroazulenic sesquiterpenes to (+)-10-epizonarene (**22**), a naturally occurring heteroannular diene of the cadalane family, has been discovered. (−)-γ-Murrolene (**33**) has been found to rearrange stereospecifically to another heteroannular diene, (−)-zonarene (**34**), of cadalane type. Probable mechanisms for the rearrangements encountered in the present study are discussed.

Acid-catalyzed rearrangements of polyisoprenoids have been extensively investigated by organic chemists since the dawn of this century.[2] This high level of interest has been sustained by the unraveling of numerous unique rearrangements that are synthetically useful and mechanistically fascinating.[3] Furthermore, the recognition[4a-d] that cationic cyclizations play a key role in the biogenesis of isoprenoids has provided the impetus to mimic[4e,f] many of these rearrangements in the laboratory by generating appropriate carbonium ions. Isoprenoids in particular, as they contain tertiary carbon centers and double bonds, are highly amenable to deep-seated structural changes on creation of an electron-deficient site.[2-4] Over the years, a variety of media have been employed to study the acid-catalyzed rearrangements of terpenoid substrates. The recent advent of carbonium ion stabilizing solvents,[5-7] e.g., H_2SO_4, FSO_3H, etc., has opened new possibilities for deflecting the normal course of terpene rearrangements, under stable carbonium ion conditions.[5,6]

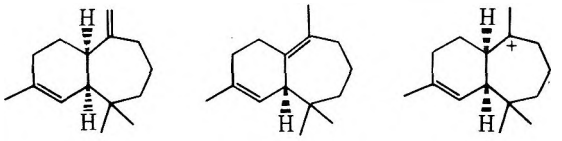
The dichotomy in the behavior of carbonium ions under varying acidity of the medium has been demonstrated in many cases. Perhaps the earliest example[8] in the field of isoprenoids is the conversion of camphor to β-camphorsulfonic acid in sulfuric acid and camphor-π-sulfonic acid in fuming sulfuric acid. Recently, Deno[9] and Sorenson[10] have extensively studied the rearrangements of monoterpenes camphene, fenchol, and borneol in sulfuric acid and fluorosulfonic acid and shown that stable cyclohexenyl cations are formed in this medium, in direct contrast[2,11,12] to their behavior in weakly acidic media. A similar dependence of the mode of rearrangement on the acidity of the reaction medium has been demonstrated by us[13,15,17,18] in the rearrangements of sesquiterpene hydrocarbons humulene[13,14] and longifolene[15,16] as well as abietic-type[17-19] diterpene resin acids. This ability of polyisoprenoids to undergo novel molecular rearrangements[9,10,13,15,17-20] in strong acid medium, under the conditions salubrious to the formation of stable carbocations, has encouraged us to in-



1 2 3 4

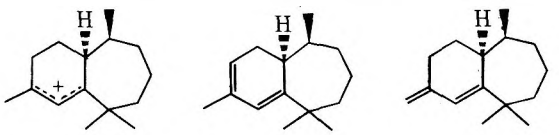
vestigate the rearrangement of representative bicyclic sesquiterpenes in strong acid medium. Consequently, the fate of several naturally occurring bicyclic sesquiterpene hydrocarbons[21] belonging to himachalane (**1**), guaiane (**2**), cadalane (**3**), and eudesmane (**4**) types in concentrated H_2SO_4 has been studied. The highlight of these studies is the discovery[22] of a facile and general rearrangement (**2** → **3**) of perhydroazulenes to decalinic ring systems. These results are discussed here.

The Cation from Himachalenes and Its Quenching Products. α- and β-himachalenes (**5**, **6**)[23] are the major sesquiterpene hydrocarbons of *Cedrus deodar* Loud, and are



5 **6** **7**

widely distributed in nature. Their acid-catalyzed rearrangements are of considerable interest as the cation **7** derived from **5** and **6** has been implicated[4c,d] in the biogenesis of several tri- and tetracyclic sesquiterpenes. However, no report concerning the cationic cyclization or acid rearrangement of **5** and **6** has appeared in the literature. When a solution of either α- or β-himachalene (**5** or **6**) in methylene chloride was rapidly dispersed in concentrated H_2SO_4 (97–99%) at 0–5 °C, a clear orange solution [λ_{max} (H_2SO_4) 340 nm] was obtained. This solution exhibited a reasonably clean ^1H NMR spectrum with a singlet at δ 7.6 corresponding to a central hydrogen of a cyclohexenyl cation, a broad singlet at δ 2.87 due to a methyl attached to the termini of an allylic cation, a pair of singlets at δ 1.45 and 1.63 due to the geminal dimethyl, and a doublet at δ 0.97 (J = 7 Hz) due to the tertiary methyl group. These data are consistent with the reasonable structure **8** for the

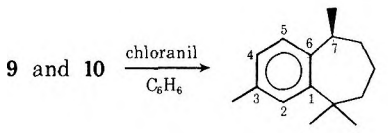


8 **9** **10**

cation, mechanistically accessible from either **5** or **6** via a couple of 1, 2- or a 1,3-hydride shift.

Further confirmation of the carbon skeleton of the cation **8** came from the quenching products obtained by careful destruction of the cation in aqueous sodium carbonate at 0 °C. A 90% yield of a light yellow oil containing more than 66% of a 4.5:1.5:1 mixture of **9**, **10**, and **11** was obtained. The mixture could be conveniently separated by column chromatography over $AgNO_3$ impregnated silica gel. The structures of dienes **9** and **10** were easily deduced from their spectral characteristics. The major component **9** was a homoannular diene [λ_{max} (MeOH) 274 nm] and exhibited in its ^1H NMR spectrum two dienylic hydrogens (δ 5.73, 1 H, s, and 5.17, 1 H, m), along with a vinylic methyl (δ 1.67, 3 H, s), a nonequivalent geminal dimethyl group (δ 1.05 and 1.15, 3 H, s), and a tertiary methyl group (δ 0.90, d, J = 7 Hz). The minor diene **10** was heteroannular [λ_{max} (MeOH) 249 nm] and its IR spectrum revealed the presence of a terminal methylene group (3120, 1630, and 885 cm^{-1}) and trisubstituted olefinic linkage (860 cm^{-1}). The ^1H NMR spectrum displayed an olefinic proton singlet at δ 6.1 and a terminal methylene doublet at δ 4.60 and 4.68 along with methyl singlets at δ 1.01 (3 H, s), 1.18 (3 H, s), and 0.81 (3 H, d, J = 7 Hz). The third component was readily identified as *ar*-himachalene **11** by comparison of its spectral data with those of an authentic[24,25] specimen.

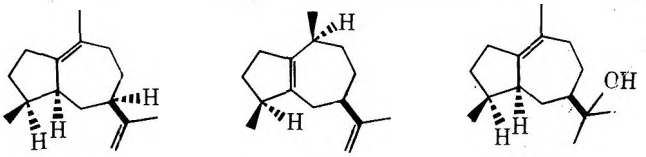
Both the dienes **9** and **10** were smoothly aromatized by chloranil in refluxing benzene to (+)-*ar*-himachalene (**11**).[24]



11

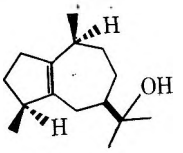
This conversion establishes the *S* configuration of the chiral center at C_7 in **9** and **10** as the $[\alpha]_D$ +3.8° of **11** prepared from these dienes is comparable to the $[\alpha]_D$ +5.90° of (+)-*ar*-himachalene (**11**) prepared[24] from (+)-*ar*-turmerone, a compound of well-established absolute stereochemistry. The ring junction hydrogen at C_6 in dienes **9** and **10** is tentatively assigned α-H stereochemistry from mechanistic considerations. The conformation[26] of α- and β-himachalenes (**5** and **6**) would be expected to favor protonation from the α face to give the common cation **7**, which can undergo either a series of 1,2-hydride shifts or a direct 1,3-hydride shift leading to cation **8** with the assigned C_6 stereochemistry. It remains to be seen whether the dienes **9** and **10** prepared in this work will be found to occur in nature. However, it may be noted that conjugated dienes with disposition of double bonds as in **9** and **10** have been known in the cadinane and bisabolane[27] framework for long time.

The Cation from Guaiane-Type Sesquiterpenes and Its Quenching Product. Among the guaiane family of sesquiterpene, α-bulnesene (**12**), α-guaiene (**13**), α-bulnesol (**14**), and



12 **13** **14**

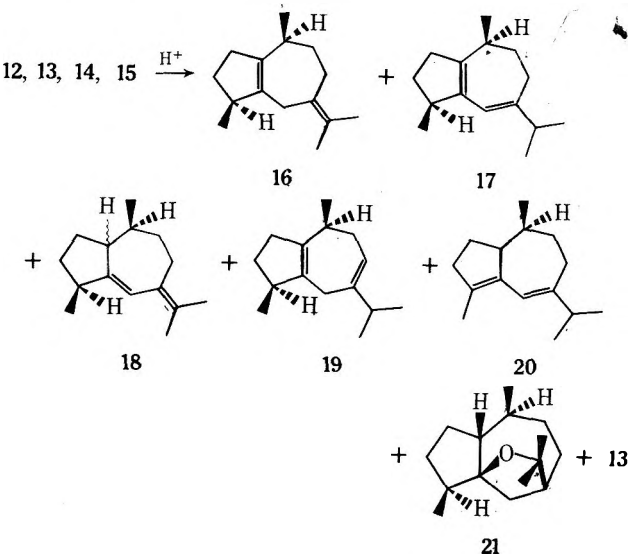
guaiol (**15**) are commonly encountered[21] in nature and **14** and **15** are considered biogenetically important.[4c,d] Acid-catalyzed



15

reactions of **12**–**15** have been extensively studied[28] using a variety of acid catalysts and shown to lead to the formation of an equilibrium mixture of various guaiene isomers (**16**–**20**) and guaioxide (**21**), depending on the reaction conditions, without any skeletal rearrangement (Scheme I).

Scheme I



16 **17** **18** **19** **20** **21**

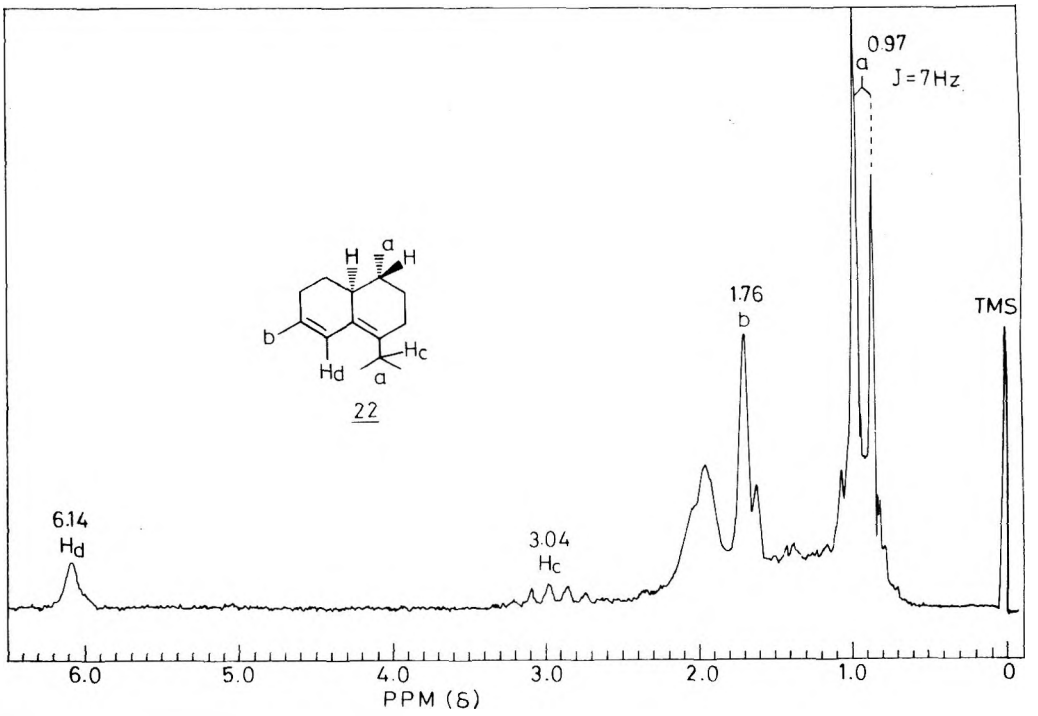
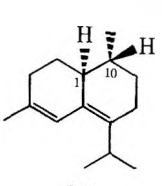


Figure 1. ^{1}H NMR spectrum of (+)-10-epizonarene (**22**).

When a solution of either guaiol (**15**), α-bulnesene (**12**), or α-guaiene (**13**) in concentrated H_2SO_4 (97–99%) was prepared at 0–5 °C, a clear orange-brown solution [λ_{max} (H_2SO_4) 330 nm] was obtained. The ^{1}H NMR spectrum of this solution, although indicative of the formation of an enylic cation, was not sufficiently clean to make any definite structural assignment. Quenching of the sulfuric acid solution in iced aqueous sodium carbonate led to the recovery of 80–95% organic material. Analysis by GLC and $AgNO_3$–silica gel TLC indicated the presence of a major component which was readily separated and obtained pure in 30–40% isolated yield. Several minor products were present but could not be obtained pure and characterized owing to extensive and rapid polymerization. The major product was indicated to be a heteroannular diene [λ_{max} (MeOH) 249 nm], whose structure was more clearly defined by its ^{1}H NMR spectrum (Figure 1, an isopropyl group, a tertiary methyl group, a vinylic methyl, and an olefinic proton). These gross structural features at first sight pointed to the structure of iso-α-gurjunene (**20**),[28f,29] but a comparison with an authentic sample showed that they were indeed not identical. Perusal of literature data for several sesquiterpene heteroannular dienes and mechanistic considerations then led to the characterization of this diene as (+)-10β*H*-murrola-4,6-diene[30,31] (*ent*-10-epizonarene, **22**). A direct spectral comparison[34] established the identity of **22**



22

with the naturally occurring 10-epizonarene. Furthermore, the optical rotation (Table I) of **22** obtained from various precursors delineates its absolute stereochemistry.[31] However, the optical activity of **22** obtained from different precursors varies significantly and appears to be considerably racemized compared to the natural product.

The generality of the rearrangement of guaiane sesquiterpenes to (+)-10-epizonarene was further demonstrated by the

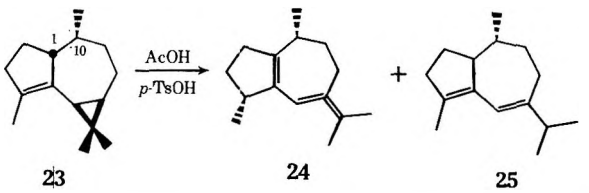
Table I. Rearrangement of Guaiane-Type Sesquiterpenes to (+)-10-Epizonarene (22) in Concentrated H_2SO_4 at 0–5 °C

Starting olefin	Yield[a] of 10-epizonarene, %	$[\alpha]^{21}_D$ ($CHCl_3$)	Ref
α-Bulnesene **12** $[\alpha]_D$ ±0°	30–35	+24	Present work
α-Guaiene **13** $[\alpha]_D$ −22.4°	30	+4	Present work
Guaiol **15** $[\alpha]_D$ −32°	25	+80	Present work
α-Gurjunene **23** $[\alpha]_D$ −180°	50	+125	Present work
Chamaecyparis nooktkatensis		+175	31

[a] Isolated yield from several experiments.

smooth rearrangement of (−)-α-gurjunene **23** to **22** in concentrated sulfuric acid in 50% yield (Table I). This result again contrasts[28f,35] with the behavior of α-gurjunene **23** in less acidic nucleophilic medium, when a mixture of isogurjunene A (*ent*-γ-guaiene, **24**) and iso-α-gurjunene B (**25**) is obtained (Scheme II). Similarly, bicyclohumulene (**27**), an acid rearrangement product[14] of the monocyclic sesquiterpene humulene (**26**), further rearranged to a new heteroannular diene in concentrated sulfuric acid medium. This diene [UV λ_{max} (MeOH) 241, 249, and 256 nm; ^{1}H NMR isopropyl group (δ 1.06, 6 H, d, J = 7 Hz), quaternary methyl group (δ 0.92, 3 H, s), vinylic methyl group (δ 1.67, 3 H, br s), and olefinic proton

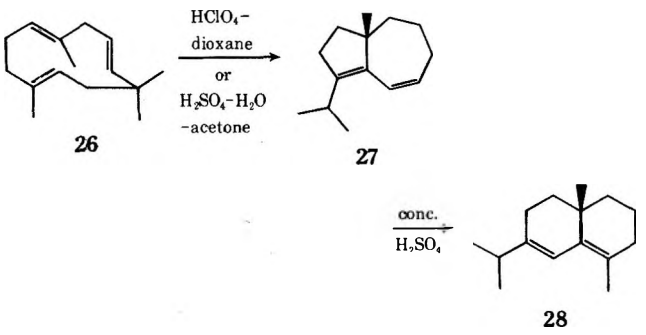
Scheme II



23 **24** **25**

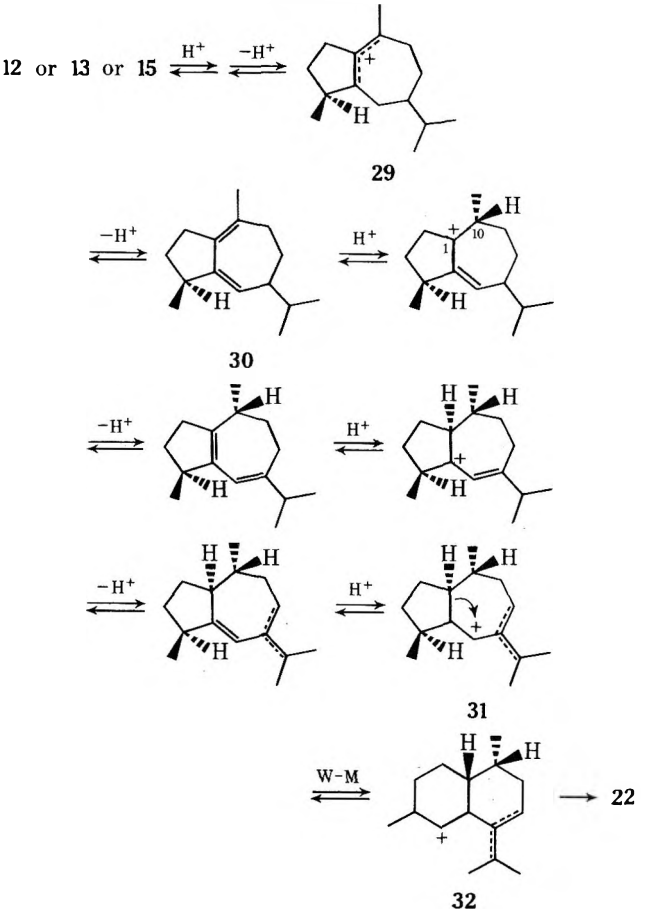
(δ 6.17, 1 H, s)], as expected, turned out to be identical[36] with δ-selinene (28) (Scheme III). The identity of 28 was further established through a direct spectral comparison.

Scheme III

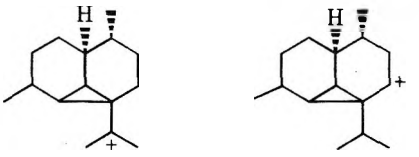


Although the course of rearrangement of perhydroazulenes (12, 13, 15, 23, and 27) to the decalin system (22 and 28) is for the most part mechanistically unexceptional, there are a few stereochemical features that elicit interpretive comment. Firstly, the exclusive formation of *ent*-10-epizonarene (22) from α-guaiene (13) and guaiol (15) indicated that the C_{10} methyl group had epimerized (from β to α) during the rearrangement process. Secondly, C_1 and C_{10} centers are stereoselectively protonated from the β face and α face, respectively, to generate the relative stereochemistry of C_1 and C_{10} present in 22. We would like to visualise this rearrangement as proceeding through a common intermediate (e.g., carbonium ion 29 and diene 30) derivable from 12, 13, and 15 though a protonation–deprotonation sequence (Scheme IV). An exami-

Scheme IV

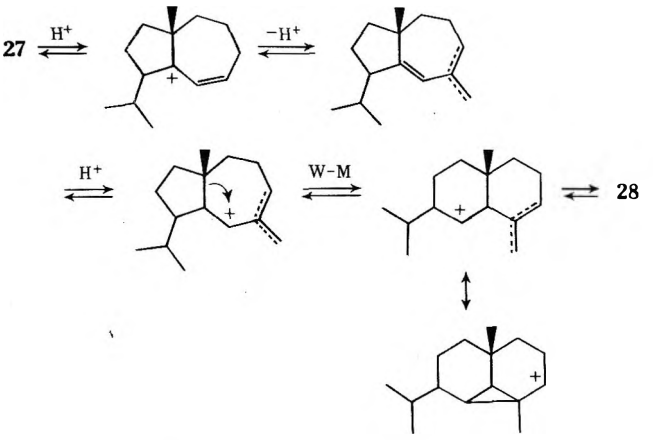


nation of a Drieding model of either 29 or 30 revealed only marginal steric preference for the observed protonation (at C_1 and C_{10}) and therefore much racemization could be anticipated in this step. This is borne out by the low optical purity of (+)-10-epizonarene (22) obtained in this rearrangement (Table I). Finally, in case of (−)-α-gurjunene (23) the C_1 stereochemistry is reversed from β- to α-H but the C_{10} stereochemistry is retained and the product obtained has high chiral retention (Table I). The ease of rearrangement of 31 to 32 is somewhat unexpected as it involves an uphill climb from a conjugated, substituted allyl cation 31 to an unconjugated secondary cation 32. However, it is reasonable to speculate that the activation energy for the rearrangement may be lowered through contribution from structures such as 32a and 32b.

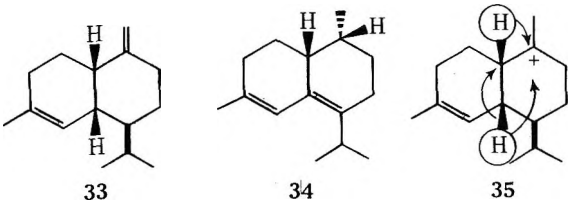


The interesting rearrangement of bicyclohumulene[14] (27) to δ-selinene (28), constituting a fascinating overall humulene (26) → δ-selinene (28) conversion,[13] is analogous to the guaiane → cadalane type transformation. A plausible mechanism is depicted in Scheme V.

Scheme V



The Cation from Cadinane Types and Its Quenching Product. Acid-catalyzed rearrangement of several cadinanic sesquiterpenes has been studied[31,37] previously. These studies have essentially resulted in isomerization of double bonds, disproportionation, and aromatization to calamenenes. Presently, we have looked into the behavior of (−)-γ-murrolene (33) in strong acid medium. Extraction of 32 into con-



centrated H_2SO_4 (96–98%) from a methylene chloride solution at 0–5 °C furnished an orange-colored solution having intense UV absorption [λ_{max})h_2SO_4) 340 nm]. Quenching of the acid solution into iced aqueous sodium carbonate furnished an oily product (85%) consisting of a major component which was separated by $AgNO_3$–silica gel column chromatography in 40% yield. The spectral characteristics [UV λ_{max} (MeOH) 249 nm; ^1H NMR (Figure 2) δ 0.72 (3 H, d, J = 7 Hz, tertiary methyl), 0.90 (6 H, d, J = 6.5 Hz, isopropyl methyls), 1.71 (3 H, br s, vinylic methyl), 6.08 (1 H, br s, olefinic proton)] indicated its

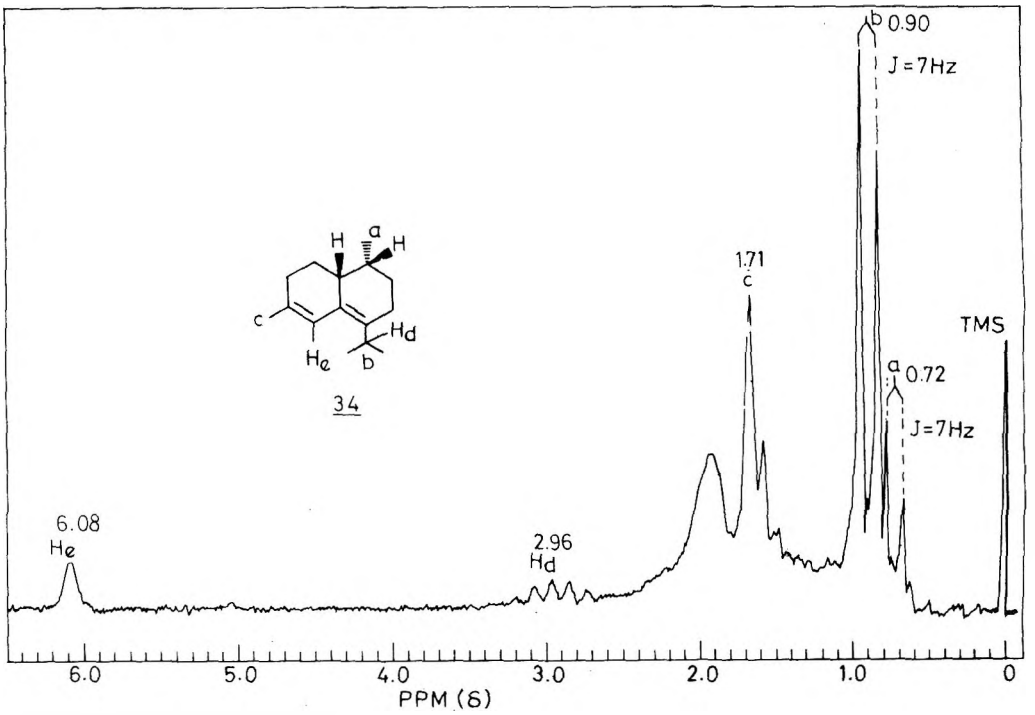
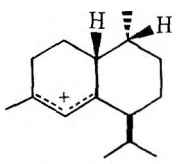
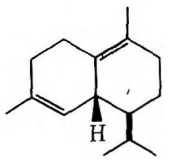


Figure 2. ^{1}H NMR spectrum of (−)-zonarene (**34**).

structure as (−)-10βH-murrola-4,6-diene (zonarene, **34**) and a direct spectral comparison with the natural product[31,32,34] unambiguously established its formulation. The stereospecific transformation of (−)-γ-murrolene (**33**) to (−)-zonarene (**34**) can be accounted for in terms of either 1,2-hydride shifts (1, 10 and 6, 1) or a direct 1,3-hydride shift (6, 10) in the initially formed cation **35** and eventuating in the formation of stable cyclohexenyl cation **36**. The stereospecificity of the **33** → **34**



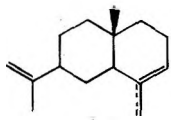
36



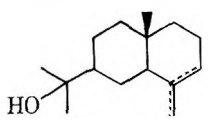
37

rearrangement is particularly noteworthy in view of the recently reported[31] isomerization of (+)-δ-cadinene (**37**) to (+)-10-epizonarene (**22**) of low optical purity.

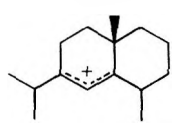
The Cation 40 from Eudesmane (Selinane) Types and Its Quenching Product. The α- and β-selinenes (**38**) as well as α- and β-eudesmols (**39**) are known to isomerize to δ-selinene (**28**) with acidic reagents.[38] Extraction of **38** and **39** from



38, α-endocyclic β-exocyclic



39, α-endocyclic β-exocyclic



40

methylene chloride solutions into sulfuric acid at 0–5 °C effected facile isomerization to the cyclohexenyl cation **40** whose structure was evident from its ^{1}H NMR spectrum (δ 7.53, s, central proton of an enylic cation, 1.48 d, J = 7 Hz, isopropyl methyls, 1.53, s, quaternary methyl, and 1.53, d, J = 6.5 Hz, tertiary methyl group) and intense UV absorption [λ_{max} (H_2SO_4) 340 nm]. Destruction of the cation **40** in iced aqueous sodium carbonate led to near-quantitative recovery of a single diene identified as δ-selinene (**28**) by spectral comparison.[36] The formation of **40** is simply accommodated by either 1,2-hydride shifts or a protonation–deprotonation sequence leading to a stable enylic cation.

Conclusions

It has been demonstrated that a variety of bicyclic sesquiterpene hydrocarbons form stable enylic cations in strong acid medium whose structures can be examined by ^{1}H NMR spectroscopy. There is a marked propensity for the formation of stable 1,3-dialkylated cyclohexenyl carbonium ions of the type **8**, **36**, and **40** and the rearrangement of perhydroazulenic dienes to the decalinic system is the outcome of this favorable stability change. The guaiane → cadalane rearrangement observed here establishes the first direct correlation between the two most abundantly distributed sesquiterpene carbon skeletons and may be of some biogenetic significance. Quenching of the stable carbonium ion solutions with base provides a preparatively useful method for the synthesis of conjugated sesquiterpene dienes, many of which occur widely in nature.

Experimental Section[39]

Starting Materials. Samples of natural products, procured from various sources, were purified via column chromatography followed by distillation or crystallization and adequately characterized through spectral methods. Sulfuric acid (AR grade, BDH, 98%) was used for the preparation of carbonium ion solutions.

Preparation and Quenching of Stable Carbocations in Sulfuric Acid. General Procedure. In the preparative experiments the carbocations were prepared by adding 10% solutions of the natural products in methylene chloride dropwise to a well-stirred solution of sulfuric acid (98%) which had been cooled in an ice bath (0–5 °C). The resultant carbocation solutions were usually 10% with respect to the organic cation. Aliquots from this solution were withdrawn and used for UV and ^{1}H NMR determinations. After stirring for about 30 min at 0–5 °C the cation solution was added dropwise to a vigorously stirred mixture of petroleum ether and aqueous sodium carbonate containing crushed ice. The general apparatus used for these operations was a slight modification of that described earlier.[15] The petroleum ether extract and washings from the quenching solution were dried and evaporated to dryness on a rotary evaporator. The residual oils were analyzed by TLC on 15% silver nitrate impregnated silica gel plates and GLC on a 10-ft Carbowax 20% on Chromosorb P column at 145 °C.

The Cation 8 from Himachalenes 5 and 6. Preparation of

Dienes 9 and 10. Following the above general procedure, a CH_2Cl_2 solution (15 ml) of α-himachalene **5** or β-himachalene[42] **6** (3 g, 15 mmol) in sulfuric acid (30 ml) afforded the cation **8** as an orange solution: UV λ_{max} (H_2SO_4) 340 nm; ^1H NMR (H_2SO_4) δ 0.98 (CH_3CH, 3 H, d, J = 7 Hz), 1.45 (>CCH_3, 3 H, s), 1.63 (>CCH_3, 3 H, s), 2.86 ($CH_3C{=}C^+{=}C<$, 3 H, s), 7.6 (>$C{=}CH^+{=}C<$, 1 H, s). Quenching of the cation in iced aqueous sodium carbonate (75 g in 500 ml of water), extraction with petroleum ether, washing, and drying furnished 2.7 g (90%) of a yellow oil. Distillation at 100–110 °C (2 mm) yielded 2.0 g (66%) of a colorless oil and left behind a viscous polymeric residue. GLC analysis coupled with TLC ($AgNO_3$–SiO_2) resolved the distilled oil into three main components. Efficient separation was achieved by column chromatography on a $AgNO_3$–silica gel column (80 g, 60 × 2 cm). The first of these (64% by GLC), **9** [bp 90–100 °C (1 mm) $n^{30}D$ 1.5170] showed the following spectral properties: UV λ_{max} (MeOH) 274 nm (ϵ 5200); IR 1670, 1601, 860, and 782 cm^{-1} (trisubstituted olefin); ^1H NMR (CCl_4) δ 0.90 (CH_3CH, 3 H, d, J = 7 Hz), 1.05 and 1.15 (CH_3CCH_3, 3 H, s), 1.67 ($CH_3C{=}C<$, 3 H, s), 5.17 ($HC{=}C<$ 1 H, m), 5.73 ($HC{=}C<$, 1 H, s). Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.18; H, 11.77. The second component (21% by GLC), **10** [bp 95–100 °C (2 mm), $n^{30}D$ 1.5145], showed the following spectroscopic properties: UV λ_{max} (MeOH) 248 nm (ϵ 18 400); IR 3120, 1630, 885 (exocyclic methylene), 1595, 860 cm^{-1} (trisubstituted olefin); ^1H NMR (CCl_4) δ 0.81 (CH_3CH, 3 H, d, J = 7 Hz), 1.0 (>CCH_3, 3 H, s), 1.09 (>CCH_3, 3 H, s), 4.60 and 4.68 ($H_2C{=}C<$, 2 H, d), 6.1 ($HC{=}C<$, 1 H, s). Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 89.06; H, 11.40. The last component (14% by GLC), **11** [bp 110–115 °C (2 mm), $n^{30}D$ 1.5285, $[\alpha]_D$ +3.8°, c 2.3] exhibited IR 3010, 1620, 1580, 1450, 810 cm^{-1} (aromatic); ^1H NMR (CCl_4) δ 1.26 (CH_3CH, 3 H, d, J = 7 Hz), 1.30 (>CCH_3, 3 H, s), 1.38 (>CCH_3, 3 H, s), 2.26 ($ArCH_3$, 3 H, s), 6.98 (Ar, 3 H, m). The IR and ^1H NMR spectra of **11** were superimposable with those of an authentic specimen.[24,25] The literature[24] records $[\alpha]_D$ +2.92° (c 1.7) for the naturally occurring material and $[\alpha]_D$ +5.90° (c 1.04) for the (+)-*ar*-himachalene **11** obtained from (+)-*ar*-tumerone. Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 88.90; H, 10.60.

Aromatization of Dienes 9 and 10 with Chloranil. A mixture of dienes **9** and **10** (1.5 g) and 3 g of chloranil in dry benzene (60 ml) was refluxed for 6 h under a nitrogen blanket. The precipitate was filtered and washed with 10 ml of benzene. The solvent was stripped off on a rotary evaporator and the residual oil dissolved in aqueous acetone (25 ml). Powdered potassium permanganate was added pinch by pinch to destroy any olefinic impurity. When no more of the oxidant was being consumed, the reaction mixture was diluted with water (30 ml), extracted with petroleum ether, washed, and dried. Filtration through a silica gel (20 g) column yielded (0.8 g, 55%) pure **11** identical in all respects with an authentic sample.[24,25]

Rearrangement of Guaiol (15), α-Guaiene (13), and α-Bulnesene (12) in Sulfuric Acid. Preparation of (+)-10-Epizonarene (22). Following the general procedure, guaiol[43] (**15,** 2 g, 9 mmol) in CH_2Cl_2 (15 ml) was dispersed in sulfuric acid (20 ml) to furnish an orange-brown solution, UV λ_{max} (H_2SO_4) 330 nm. This solution did not exhibit any well-defined signals in the ^1H NMR spectrum. Quenching of the sulfuric acid solution in iced aqueous sodium carbonate (50 g in 500 ml of water), extraction with petroleum ether (50 ml × 3), washing, and drying furnished 1.4 g (70%) of a colorless oil. GLC analysis in conjunction with $AgNO_3$–silica gel TLC revealed the presence of one major component (~50%) together with several minor products which rapidly became viscous on standing or on passage through a $AgNO_3$–silica gel column. The major product **22** was, however, eluted from a $AgNO_3$–silica gel column (50 g, 40 × 2 cm) with petroleum ether–benzene (9:1) and obtained pure in 20–25% yield. The diene **22** (bp 100–105 °C (2 mm), $n^{31}D$ 1.5145, $[\alpha]_D$ +80°, c 2.8) exhibited the following spectral characteristics: UV λ_{max} (MeOH) 249 nm (ϵ 15 600); IR 1645, 1610, 861 cm^{-1} (trisubstituted olefin); ^1H NMR (CCl_4) δ 0.97 (CH_3CHCH_3 and CH_3CH, 9 H, d, J = 7 Hz), 1.76 ($CH_3C{=}C<$, 3 H, br s), 3.04 (CH_3CHCH_3, 1 H, septet, J = 7 Hz), 6.14 ($HC{=}C<$, 1 H, s) and led to its identification[31,34] as (+)-10-epizonarene. The IR and ^1H NMR spectrum of **22** was indistinguishable from that of the natural product.[31,34] Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.41; H, 11.40. Similarly, preparation of the cation solution from α-guaiene[44] (**13,** 1.5 g, 7.3 mmol) in sulfuric acid (15 ml) followed by quenching and usual workup led to the isolation of yellow, oil material (1.4 g, 93%). Distillation at 100–110 °C (2 mm) furnished 0.95 g (63%) of a colorless oil and a dark brown resinous material remained in the distillation bulb. GLC and TLC ($AgNO_3$–silica gel) indicated the presence of one major product (50%), **22,** which was isolated by column chromatography on $AgNO_3$–silica gel and resulted in the isolation (30%) of pure (+)-10-epizonarene **22,** $[\alpha]_D$ +4.00°. In an identical fashion α-bulnesene[44] (**12,** 0.8 g, 3.9 mmol) was dispersed in sulfuric acid (10 ml) and after usual quenching and workup furnished a colorless oil (0.75 g, 95%). Column chromatography on a $AgNO_3$–silica gel column yielded pure **22,** $[\alpha]_D$ +24.2° (c 1.97), in 30–35% yield.

Rearrangement of α-Gurjunene[45] (23) in Sulfuric Acid. Formation of (+)-10-Epizonarene (22). α-Gurjunene (**23,** 1.5 g, 7.3 mmol) in methylene chloride (15 ml) was dispersed in sulfuric acid (15 ml) as described above. Quenching the sulfuric acid solution in iced aqueous sodium carbonate (40 g in 300 ml of water), extraction with petroleum ether, and usual workup yielded 1.4 g (93%) of a yellow oil. Distillation at 100–110 °C (2 mm) gave 1 g (66%) of a colorless oil. GLC and TLC indicated the presence of one major compound **22,** which was isolated (50% yield) by column chromatography on a $AgNO_3$–silica gel column (20 g, 40 × 1.4 cm) and elution with petroleum ether–benzene mixture (9:1). The spectral (IR, ^1H NMR) characteristics of **22,** $[\alpha]_D$ +125° (c 2.9), were identical with those of (+)-10-epizonarene.

Rearrangement of Bicyclohumulene (27) in Sulfuric Acid to δ-Selinene (28). Bicyclohumulene[46] (**27**) was prepared from humulene[47] (**26**) according to the procedure of Dauben et al. A methylene chloride (10 ml) solution of **27** (0.3 g, 1.5 mmol) was added to sulfuric acid (4 ml) as described earlier. Quenching the solution in iced aqueous sodium carbonate (15 g in 100 ml of water) and usual workup led to the isolation of 0.2 g (65%) of a labile mixture of dienes as a colorless oil. Column chromatography on a $AgNO_3$–silica gel column (20 g, 40 × 1.4 cm) and elution with petroleum ether–benzene mixture (9:1) led to the isolation of pure δ-selinene (**28**) in 20–25% yield. The diene **28** was characterized through its spectral characteristics [UV λ_{max} (MeOH) 249 nm (ϵ16 500); IR 1620, 872 cm^{-1} (trisubstituted olefin); ^1H NMR (CCl_4) δ 0.92 (>CCH_3, 3 H, s), 1.06 (CH_3CHCH_3, 6 H, d, J = 7 Hz), 1.67 ($CH_3C{=}C<$, 3 H, s), 6.17 ($HC{=}C<$, 1 H, s)] and direct comparison with the reported spectra.[36]

Rearrangement of (−)-γ-Murrolene (33) in Sulfuric Acid to (−)-Zonarene (34). (−)-γ-Murrolene[48] (**33,** 0.5 g, 2.5 mmol) in methylene chloride (5 ml) was rapidly dispersed in sulfuric acid (5 ml) as described in the general procedure. Quenching in iced sodium carbonate (15 g in 100 ml of water), extraction with petroleum ether (25 ml × 2), and workup as described above furnished 0.42 g (85%) of an oily product. This product was charged on a $AgNO_3$–silica gel column (20 g, 30 × 1.4 cm) and elution with petroleum ether–benzene mixture (9:1) yielded 0.2 g (40%) of pure diene **34.** The diene **34** [bp 90–100 °C (2 mm), $[\alpha]_D$ −89° (c 1.2)] was identified as (−)-zonarene on the basis of the spectral data [UV λ_{max} (MeOH) 249 mm (ϵ 18 000); IR 1645, 1610, 864, 840 cm^{-1} (trisubstituted olefin); ^1H NMR (CCl_4) δ 0.72 (CH_3CH, 3 H, d, J = 7 Hz), 0.90 (CH_3CHCH_3, 6 H, d, J = 7 Hz), 1.71 ($CH_3C{=}C<$, 3 H, s), 2.96 (CH_3CHCH_3, 1 H, septet, J = 7 Hz), 6.08 ($HC{=}C<$, 1 H, s)] and direct spectral comparison with the natural product.[31-34]

The Cation 40 from Selinenes (38) and Eudesmols (39). Preparation of δ-Selinene (28). A mixture of α- and β-selinene (**38,** 3 g, 15 mmol) in methylene chloride (25 ml) was dispersed in sulfuric acid (30 ml) to give an orange-brown solution of cation **40,** UV λ_{max} (H_2SO_4) 340 nm; ^1H NMR (H_2SO_4) δ 1.48 (CH_3CHCH_3, 6 H, d, J = 7 Hz), 1.53 (>CCH_3, 3 H, s), 1.53 (CH_3CH, 3 H, d, J = 7 Hz), and 7.53 (>$C{=}C^+{=}C<$). Quenching the cation **40** in aqueous sodium carbonate (80 g in 500 ml of water), extraction with petroleum ether (50 ml × 3), washing, drying, and removal of solvent furnished 2.8 g (93%) of a pale yellow oil. Column chromatography on a $AgNO_3$–silica gel column (80 g, 50 × 2 cm) and elution with petroleum ether–benzene (9:1) furnished 1.6 g of pure δ-selinene (**28**) in 53% yield. In an identical experiment, a mixture of α- and β-eudesmols (**39,** 1 g) furnished 0.48 g (50%) of δ-selinene (**28**), which was identified by spectral comparison with an authentic sample.[36]

Acknowledgment. The authors would like to express their sincere thanks to Professor G. B. Singh (BHU, India) and Dr. S. Raghu (Michigan State University) for the ^1H NMR spectral data reported in this paper.

Registry No.—**5,** 3853-83-6; **6,** 1461-03-6; **8,** 60909-18-4; **9,** 60909-27-5; **10,** 60909-28-6; **11,** 19419-67-1; **12,** 3691-11-0; **13,** 3691-12-1; **15,** 489-86-1; **22,** 41702-63-0; **23,** 489-40-7; **27,** 60909-26-4; **28,** 28624-23-9; **33,** 24268-39-1; **34,** 41929-05-9; α-**38,** 473-13-2; β-**38,** 17066-67-0; β-**39,** 473-16-5; β-**39,** 473-15-4; **40,** 60909-17-3.

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(30) Recently, two heteroannular dienes of cadalane skeleton, (−)-zonarene (**33**) and 10-epizonarene (**22**), in both its enantiomeric forms have been shown to occur widely in several essential oils[31] and brown seeweed[32] *Dictyopteris zonariodes*. Both **22** and **33** have also been obtained in racemic form as the minor products of cyclization[33] of farnesol with boron trifluoride etherate. Andersen et al.[31] have elucidated the absolute configuration of zonarenes from the CD data by the application of transoid diene chirality rule.
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(43) (−)-Guaiol (**15**, $[\alpha]_D$ −32°) was kindly supplied by Dr. W. Bruhn (Dragoco, Holzmindent) and Professor S. C. Bhattacharya (IIT, Bombay).
(44) (−)-α-Guaiene (**13**) and α-bulnesene (**12**, $[\alpha]_D$ 0) were isolated from commercial patchouli oil supplied by Fritzsche Brothers, Inc., New York, N.Y.
(45) (−)-α-Gurjunene (**23**, $[\alpha]_D$ −180°) was kindly provided by Professor G. Ourisson.
(46) We would like to thank Professor W. Parker (Sterling, U.K.) for the spectra of bicyclohumulene (**27**).
(47) Humulene (**26**) was isolated from wild ginger oil, kindly supplied by Drs. S. Dev and B. A. Nagasampagi.
(48) (−)-γ-Murrolene (**33**, $[\alpha]_D$ −3°) was kindly provided by Professor V. Herout (Prague, Czechoslovakia).

Thermolysis of Arenediazonium Ions in Acidic Methanol. Evidence for Competing, Independent Ionic and Radical Mechanisms[1]

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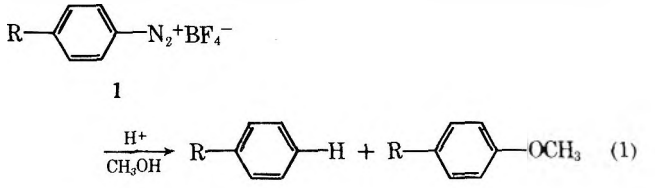
Received July 29, 1976

Thermolysis of *p*-bromo- or *p*-methoxybenzenediazonium ions in acidic methanol affords products of protodediazoniation (ArH) and methoxydediazoniation ($ArOCH_3$), mainly the former under N_2, mainly the latter under O_2. In our experiments, both rates and products are determined from events within a single sealed ampule. Overall rate constants are dissected into components k_r and k_i in proportion to the yields of ArH and $ArOCH_3$, respectively. Changing the atmosphere from N_2 to O_2 depresses k_r by two orders of magnitude but has no significant effect on k_i. The results are intelligible in terms of competing, independent radical and ionic mechanisms, the former severely inhibited by O_2, the latter unaffected. There is no need to invoke an earlier hypothesis that the radical and ionic mechanisms involve a common intermediate.

In 1970, Broxton, Bunnett, and Paik[3] entitled a communication: Do Radical and Ionic Pathways of Decomposition of Arenediazonium Ions in Acidic Methanol proceed via a Common Intermediate? We have carefully restudied the matter, and our data provide an answer to that question. The answer is that in two representative cases rate and product data are entirely consistent with a model of competing, independent ionic and radical mechanisms. We find no need to invoke the unusual hypothesis earlier suggested.

The phenomenon of interest was first described by DeTar and Kosuge:[4] certain substituted benzenediazonium ions, such as those with *p*-bromo and *p*-methoxy substituents, decompose in acidic methanol *under nitrogen* to give mainly protodediazoniation products (bromobenzene and anisole, respectively), but in the same solutions *under oxygen* to afford principally products of methoxydediazoniation (*p*-bromoanisole and *p*-dimethoxybenzene, respectively); see eq 1.



a, R = Br; b, R = CH_3O

Broxton, Bunnett, and Paik[3] confirmed the essential observations of DeTar and Kosuge, and adduced evidence of several sorts that radical intermediates and a radical chain mechanism are involved in formation of protodediazoniation products **2a** and **2b**. However, they found no evidence for radical intermediates in the reactions leading to methoxydediazoniation products **3a** and **3b**.

The reason that Broxton, Bunnett, and Paik[3] suggested that the radical and ionic pathways might share a common first step was a striking confrontation of product with kinetic data. Although changing the atmosphere from N_2 to O_2 caused a drastic change in product composition, the measured diminution in rate was relatively modest, so that it was difficult to account for the change in product composition in terms merely of suppression by O_2 of a fast radical mechanism leading to **2a** or **2b** so as to allow a slow ionic process to prevail.

Subsequent observations by Ohmori[5] motivated our reexamination of the thermolysis of **1a** and **1b**. We noted that the rate and product determinations of Broxton, Bunnett, and Paik[3] were made in separate experiments under similar but not exactly identical conditions. For example, in Paik's experiments[6] each ampule in kinetic runs contained 5 ml of reaction solution while each ampule for product determination contained 10 ml of similarly prepared solution. Conceivably the difference in sample volume or some other minor variation caused the kinetic and product data to be not quite strictly comparable.

An obvious way to avoid such doubts is to perform both rate and product determinations on portions of the very same solution which has undergone reaction in a single sealed ampule. That is what we have now done, but we hasten to point out that this straightforward approach is not simple in its execution. For an estimate of rate to be meaningful, reaction must have occurred only partially by the time of measurement, but the unreacted diazonium ion complicates determination of the yields of, say, bromobenzene and *p*-bromoanisole by GLC. Our response to this challenge was to combine the partially reacted solution with excess phenol in alkaline aqueous medium, allowing azo coupling to occur, and then to extract with ether to remove the bromobenzene and *p*-bromoanisole for GLC analysis.

Experimental Section

Materials. *p*-Bromo- and *p*-methoxybenzenediazonium fluoroborates were prepared by diazotization of the redistilled primary amines in 24% fluoroboric acid solution below 5 °C by addition of an equimolar amount of sodium nitrite. The crystalline diazonium salt was collected and purified by dissolving it in a minimum amount of acetone and reprecipitating by addition of diethyl ether. Before each set of experiments, each diazonium salt was repurified by three cycles of solution in acetone and precipitation by ether.

Commercial *p*-toluenesulfonic acid was recrystallized from 37% hydrochloric acid and the resulting hydrate was dehydrated by keeping it at reduced pressure over KOH and P_2O_5; the anhydrous acid was stored at reduced pressure over P_2O_5.

Methanol was purified by the magnesium method.[7] Bromobenzene, *p*-bromoanisole, anisole, *p*-dimethoxybenzene, and *m*-dichlorobenzene were purified by redistillation before use. α-Naphthylamine *p*-toluenesulfonate was prepared as described elsewhere.[8]

GLC Determinations. An Aerograph Model 200 instrument equipped with flame ionization detector and disk integrator was used. An aluminum column, 3.2 mm i.d. by 183 cm long, packed with 4% Carbowax 20M on Chromosorb G was used. The column temperature was 70 °C for analysis of bromobenzene, anisole, and *m*-dichlorobenzene, 120 °C for *p*-dimethoxybenzene, and 130 °C for *p*-bromoanisole. Molar response factors, relative to *m*-dichlorobenzene (the internal standard), were determined for all products by repeated analysis of standard mixtures.

General Experimental Procedure. A solution of the diazonium salt (**1a** or **1b**) and *p*-toluenesulfonic or sulfuric acid in dry methanol was prepared by mixing measured amounts of the ingredients at 0 °C. Aliquots (5 ml) were transferred to "5-ml" ampules (total volume to seal-off point about 7.6 ml) by pipet, the ampules were cooled to <−50 °C by partial immersion in a slurry of solid carbon dioxide in 2-propanol, and each ampule was gently bubbled for 15–20 min either with oxygen gas or with deoxygenated nitrogen or argon, the gas being passed through methanol at the same temperature before entering the solution in the ampule. Immediately after the bubbling treatment,

Table I. Thermolysis of *p*-Bromobenzenediazonium Fluoroborate in Acidic Methanol at 56 °C: Some Representative Experiments[a]

Expt no.	Atmosphere	Time, min	Reaction by GLC, %	$10^5 k_g$,[b] s^{-1}	Product ratio[c]	$10^5 k_r$, s^{-1}	$10^5 k_i$, s^{-1}	Reaction, photometric, %	$10^5 k_c$,[d] s^{-1}
89	N_2	15	60.6	103	28.8	100	3.47	62.0	108
90	N_2	15	67.1	124	35.6	120	3.38	68.9	130
91	N_2	20	66.5	91.2	29.4	88.2	3.00	65.8	89
92	N_2	20	84.3	154	45.2	151	3.34	82.3	144
93	N_2	25	81.9	114	24.2	110	4.53	88.6	145
94	N_2	25	80.1	108	31.1	104	3.35	80.3	108
95	N_2	400	95.8		36.8				
96	N_2	0						0.2	
105	O_2	200	37.5	3.92	1/5.13	0.64	3.28	46.2	5.17
106	O_2	200	41.4	4.46	1/5.54	0.68	3.78	44.5	4.90
107	O_2	230	45.9	4.46	1/7.31	0.54	3.92	49.0	4.88
108	O_2	230	44.9	4.31	1/7.51	0.51	3.80	49.7	4.98
109	O_2	260	51.4	4.63	1/10.1	0.42	4.21	55.0	5.12
110	O_2	260	55.3	5.16	1/8.62	0.54	4.62	55.0	5.12
111	O_2	3000	83.0		1/17.7				
112	O_2	0						0	

[a] In these experiments, $[H_2SO_4] = 0.108$ M. [b] Pseudo-first-order rate constant from GLC product data. [c] Molar ratio of C_6H_5Br to *p*-bromoanisole. [d] Pseudo-first-order rate constant from photometric data.

Table II. Thermolysis of *p*-Bromobenzenediazonium Fluoroborate in Acidic Methanol at 56 °C: Resume of Kinetic Data

Expt no.	Atmosphere	[TsOH],[a] M	$10^5 \bar{k}_g$,[b] s^{-1}	10^5 s.d. in k_g, s^{-1}	Mean product ratio[c]	s.d. in product ratio	$10^5 \bar{k}_r$, s^{-1}	10^5 s.d. in $\bar{k}_r$, s^{-1}	$10^5 \bar{k}_i$, s^{-1}	10^5 s.d. in $\bar{k}_i$, s^{-1}	$10^5 \bar{k}_c$,[d] s^{-1}	10^5 s.d. in $\bar{k}_c$, s^{-1}
25–28	N_2	0.0098	120	8	28	3	116	8	4.13	0.28	116	10
33–36	N_2	0.0098	111	14	27	5	107	15	4.08	0.46	123	9
42–49	N_2	0.101	33	3	7.6	0.7	29	3	3.79	0.21	40	6
60–64	N_2	0.100	28	3	6.6	1.5	25	3	3.82	0.50	29	3
81–86	N_2	0.0010	81	7	23	3	77	7	3.45	0.42	89	12
89–94	N_2	0.108[e]	116	22	32	7	112	22	3.51	0.52	121	22
116–127	Degassed	0.100	48	9	9.8	2.4	43	9	4.50	0.71	38	12
134–137	Ar	0.100	24	1.7	4.4	0.4	19.5	1.5	4.45	0.34	34	6
	Average of 49 expt under N_2, Ar, or degassed								**4.00**	0.61		
29–30	O_2	0.0098	5.80	0.32	1/8.9	0.9[f]	0.58	0.02	5.21	0.34	6.52	0.02
37–39	O_2	0.0098	5.99	0.68	1/7.2	1.0[f]	0.74	0.10	5.26	0.63	6.46	0.24
51–58	O_2	0.101	4.14	0.48	1/10.1	1.6[f]	0.38	0.03	3.76	0.48	4.77	0.09
67–72	O_2	0.100	5.32	0.51	1/4.4	0.7[f]	0.98	0.07	4.34	0.52	5.15	0.11
97–102	O_2	0.0010	4.01	0.39	1/2.9	0.2[f]	1.03	0.13	2.98	0.28	9.65	0.20
105–110	O_2	0.108[e]	4.49	0.41	1/7.4	1.9[f]	0.55	0.10	3.94	0.45	5.03	0.12
	Average of 31 expt under O_2								**3.99**	0.82		

[a] *p*-Toluenesulfonic acid, except as otherwise indicated. [b] Average total rate constant, from GLC data. [c] Molar ratio of C_6H_5Br to *p*-bromoanisole. [d] Average total rate constant, from photometric data. [e] Sulfuric acid. [f] Standard deviation in the mean ratio of *p*-bromoanisole to C_6H_5Br.

each ampule was sealed with a torch and retained in the cold bath until a set of ampules could be placed all at once in the thermostat at 56 or 80 °C. Single ampules were removed from the thermostat at recorded times, thrust directly into an ice–water slurry to terminate thermolysis, and then stored in a solid CO_2–2-propanol slurry until analysis of the contents was undertaken.

Events in each ampule constitute a separately numbered experiment for tabulation purposes. Inasmuch as several ampules were supplied with aliquots from the same batch of reaction solution on a given day, some being bubbled with nitrogen, some with oxygen, our experiments occur in sets of common origin. These sets comprise experiments 17–24, 25–32, 33–41, 42–58, 60–74, 81–88 plus 97–104, 89–96 plus 105–112, 116–128, 130–139, M1–M21, M22–M42, M43–M53, and M54–M65. Between sets of experiments some days or weeks passed. Moreover, they were based on separate repurifications of diazonium salt and sometimes involved different tanks of sweep gases or different batches of methanol solvent.

In all experiments the diazonium salt concentration was 0.01 M. Hydrogen ions were provided by *p*-toluenesulfonic acid, for experiments with **1a** at concentrations indicated in Table II, but 0.100 M for all experiments with **1b**, except that sulfuric acid (0.108 M) was used for the experiments listed in Table I.

For analysis of the contents of ampules, somewhat different procedures were employed for **1a** reactions than for **1b** reactions. This was learned by experience; the cause is apparently a great difference in electrophilic reactivity between **1a** and **1b**.[9]

Ampules for **1a** reactions were brought to 0 °C by immersion in an ice–water slurry, opened, and a measured volume (0.1 or 0.2 ml) was removed by pipet and discharged into 2 ml of a solution of α-naphthylamine *p*-toluenesulfonate (0.017 M) in methanol in a 25-ml volumetric flask at 0 °C. After swirling, the resulting solution of azo dye was allowed to stand for 20 min, then acidified by addition of 0.5 ml of 12 M HCl and diluted to the mark with methanol. The absorbance at 540 nm was measured by means of a Gilford spectrophotometer. This method for determination of unreacted diazonium salt was calibrated by analysis of a series of solutions of **1a** of varying concentration, and it was shown that absorbance is linearly related to diazonium ion concentration.

Immediately following withdrawal of the aliquot for colorimetric determination of unreacted diazonium salt, another aliquot (1.0 ml) was withdrawn by pipet and discharged into 1 ml of an aqueous solution of phenol, adjusted to pH 10 by external spotting of pH indicator paper, contained in a 10-ml test tube and held at 0 °C. After 2 or 3 h at that temperature, 1 ml of 0.5 M NaOH in water and 0.1 ml

Table III. Thermolysis of *p*-Methoxybenzenediazonium Fluoroborate in Acidic Methanol at 80 °C. Resume of Kinetic Data[a]

Expt no.	Atmosphere	$10^5 \bar{k}_g$, s^{-1}	10^5 s.d. in $\bar{k}_g$, s^{-1}	Mean product ratio[b]	s.d. in product ratio	$10^5 \bar{k}_r$, s^{-1}	10^5 s.d. in $\bar{k}_r$, s^{-1}	$10^5 \bar{k}_i$, s^{-1}	10^5 s.d. in $\bar{k}_i$, s^{-1}	$10^5 \bar{k}_c$, s^{-1}	10^5 s.d. in $\bar{k}_c$, s^{-1}
M1–M8	N_2	34	10	8.4	1.1	30	8	3.77	1.41	33	10
M23–M28	N_2	112	37	53	8	110	36	2.05	0.52	140	70
M43–M51	N_2	26	2.5	7.6	1.2	23	2.5	3.10	0.29	27	2.4
	Average of 23 expt under N_2							**3.06**	1.09		
M12–M20	O_2	4.34	0.30	1/3.5	0.5[c]	0.99	0.15	3.35	0.20	4.22	0.24
M33–M40	O_2	3.67	0.37	1/3.9	1.0[c]	0.80	0.26	2.87	0.18	4.48	0.19
M54–M63	O_2	3.20	0.36	1/16	2.0[c]	0.19	0.03	3.01	0.34	3.71	0.15
	Average of 27 expt under O_2							**3.08**	0.32		

[a] *p*-Toluenesulfonic acid, 0.100 M, present in all experiments; rate constant symbols as in Table II. [b] Molar ratio of anisole to *p*-dimethoxybenzene. [c] Standard deviation in the mean ratio of *p*-dimethoxybenzene to anisole.

of a standard solution of *m*-dichlorobenzene in methanol were added. The resulting solution was extracted six times with 6-ml portions of diethyl ether and the combined ether extracts were dried over anhydrous $CaCl_2$ overnight. The extract was passed through a small column (7 mm diameter, 60 mm long) packed with basic alumina to remove traces of azo dye, concentrated by distillation of the ether to a volume of about 1 ml, and analyzed by GLC as described above.

The procedure was similar for ampules for **1b** reactions. The chief differences were that the original 0.1- or 0.2-ml portion of an ampule's contents was discharged into 2 ml of a methanol solution 0.06 M in α-naphthylamine and 0.05 M in *p*-toluenesulfonic acid, that absorbance was measured at 570 nm, and that the subsequent coupling with phenol was conducted at pH 9.0 during 2 or 3 h at room temperature.

Calculation and Presentation of Results. This experimental procedure gave two measures of the extent of reaction: the amount of diazonium salt unreacted, and the amount of products **2a** and **3a** or **2b** and **3b** formed. From the amount of **1a** or **1b** unreacted and the relevant time of heating, a rate constant (symbolized k_c) for the total rate of thermolysis of the diazonium salt was reckoned, it being assumed that first-order kinetics prevailed and that the ampule attained thermostat temperature immediately upon immersion. Earlier work[3,6] showed that first-order kinetics are obeyed accurately by these reactions under oxygen and approximately by those under nitrogen. From the sum of the amounts of **2a** and **3a** or of **2b** and **3b** formed, a rate constant (symbolized k_g) for the total rate of thermolysis was calculated on the basis of the foregoing assumptions and the further assumption that **2a** and **3a** or **2b** and **3b** were the sole products formed. k_g values were then separated into parts relevant to the formation of **2a** or **2b** (symbolized k_r) and of **3a** or **3b** (symbolized k_i) in proportion to product yields. In Table I results are fully tabulated for a set of experiments with **1a** that happen to involve sulfuric acid as the source of protons but which are otherwise representative. For other sets of data, only mean values for sets are presented in print, in Tables II and III, but results are fully tabulated in Table IV and V, which appear in the supplementary material.

Several sets of experiments included ampules that were not heated or which were heated for a very long time in order to effect complete thermolysis of the diazonium salt. Those that were not heated were shown by photometric analysis to contain within experimental error all the diazonium salt originally present. Those heated until "infinity" contained no diazonium salt according to the photometric analysis but the combined yields of **2a** and **3a** or of **2b** and **3b** totaled less than 100%. Specifically, infinity total yields of **2a** plus **3a** totaled 95–98% for reactions under N_2 or Ar, and 83, 80, and 60% under O_2, while infinity total yields of **2b** plus **3b** totaled 85–92% under N_2 and 83–87% under O_2. These totals are similar to those observed by Paik.[6]

Inasmuch as infinity total yields of **2a** plus **3a** or **2b** plus **3b** are less than 100%, we infer that the summed yields of these products as measured for interrupted reactions (most of our experiments) underestimate the extent of reaction that had occurred. Indeed, most (but not all) of our k_g values are lower than the k_c values for the same experiments. However, our method for dividing k_g values into k_r and k_i components, which ignores miscellaneous by-products, considerably compensates for that underestimate. The extent of compensation is better the more nearly the summed yields of **2a** and **3a** or **2b** and **3b** approach the actual percent of thermolysis of the diazonium salt. It is also better the lower the percent of thermolysis at the time of interrupting the reaction. Sample calculations show that at 30% thermolysis k_r or k_i is underestimated by 2.0% if the summed yields of the two products represent 90% of the actual thermolysis, or by 3.9% if they represent 80% of it. At 60% thermolysis, k_r or k_i is underestimated by 5.8 or 10.8%, respectively, if the summed yields of the two products represent 90 or 80% of the actual thermolysis. The shortfall in the summed yields of **2a** plus **3a** or **2b** plus **3b** was worse in our experiments under O_2 than under N_2, but the percent thermolysis at the time of interruption was in general lower for the experiments under O_2. With attention to the sample calculations mentioned, we judge that our estimates of k_i and k_r are low at most by about 10%. This is less than the random error in our measurements, but must be recognized as a systematic factor affecting experiments under all atmospheres.

For experiments 97–102, under O_2, the k_c values derived from our data are more than double the k_g values. Another extraordinary measurement in the same set is the very low percent of thermolysis at infinity (expt 103) as determined by GLC, namely, 60.2%. One might think the cause to be an erroneously low measurement of the amount of **1a** used, but that is unlikely to be the case because for experiments under N_2 in the same set, based on the same master batch of reaction solution, there is reasonably good agreement between k_c and k_g for expt 81–86, and the summed yields of **2a** and **3a** in expt 87 are 95.8%.

For each set of kinetic-product experiments, mean values of product ratios (**2a/3a** or **2b/3b**) and the several rate constants were reckoned, together with standard deviations, by means of a Texas Instruments SR-51A calculator preprogrammed for these calculations. The standard deviation (abbreviated s.d.) is calculated with $n - 1$ weighting:

$$\text{s.d.} = \left[\sum_{i=1}^{n} (x_i - \bar{x})^2/(n-1) \right]^{1/2}$$

These mean values and standard deviations are listed in Tables II and III. Product ratios for reactions under O_2 are listed as the reciprocals of the **3a/2a** or **3b/2b** ratios, and the standard deviations refer to mean values of the latter ratios. In Tables II and III also listed are mean values and standard deviations of k_i for all kinetic-product experiments under O_2 and for all those under N_2, Ar, or degassed.

Results

Each of our experiments involved determination of rate and product composition from events in a single ampule with a specified atmosphere heated for a measured period of time. Detailed data for a representative set of experiments are displayed in Table I, and averaged data for sets of experiments are set forth in Tables II and III. Each "set" of experiments utilized aliquots from a single master batch of reaction solution.

In all cases rates under N_2, Ar, or in degassed ampules were higher than under O_2. For experiments within a set, overall rates under N_2 are at least sixfold greater than under O_2, and at most 53-fold greater (in terms of k_g values). Within a set, under either atmosphere the standard deviation in the mean k_g value is about 10%, but between sets there are great variations of overall rates under N_2 while variations of overall rates under O_2 are moderate, at the level of ±20%.

For reactions of **1a**, the effect of changing hydrogen ion concentration was explored, but pH (within the range 1–3) had little bearing on rates or product compositions. Thus, for runs under N_2 hydrogen ion concentration was about 0.001 M in expt 81–86, 0.01 M in expt 25–28 and 33–36, and 0.1 M in expt 42–49, 60–64, and 89–94, and average k_g values bear no consistent relationship to acid concentration. It appears to matter little whether hydrogen ions are provided by sulfuric acid (expt 89–94 and 105–110) or *p*-toluenesulfonic acid (the rest).

Turning attention now to product ratios, we see immediately the gross difference first noted by DeTar and Kosuge,[4] namely, the preponderance of protodediazoniation leading to **2a** or **2b** under N_2, Ar, or degassed conditions but of methoxydediazoniation leading to **3a** or **3b** under O_2. Looking more closely, we see marked differences in product ratio between sets of experiments under the same atmosphere but lesser differences between experiments in the same set. Significant differences in the product ratio between sets are observed for reactions under O_2 as well as under N_2.

As to the k_r and k_i obtained by dissection of k_g values, the k_r differ enormously—by two orders of magnitude—between atmospheres, and substantially between sets of experiments under a given atmosphere, but the k_i show only moderate variation between sets of experiments or even between N_2 and O_2 atmospheres. *The average k_i value under N_2, Ar, or in degassed conditions is virtually identical with the average k_i under O_2.* As shown in Tables II and III, this important finding emerges from our studies either on **1a** or **1b**, spectacularly in either case.

Discussion

Broxton, Bunnett, and Paik[3,10] present evidence that radical intermediates are involved in the reaction of **1a** under N_2 that leads predominantly to protodediazoniation product **2a**. The reaction of **1a** under O_2 leading mainly to **3a** does not respond to tests for the intermediacy of radicals. The present results show that the rate of formation of methoxydediazoniation product **3a** is unaffected by the atmosphere. The rate of transformation of **1b** to **3b** is also independent of the atmosphere.

Methoxydediazoniation thus behaves as expected of an ionic mechanism. With attention to evidence concerning the mechanism of hydroxydediazoniation in water,[11–13] we propose that reaction occurs via aryl cation intermediates (eq 2). The huge depression in the rate of protodediazoniation as the atmosphere is changed from N_2 to O_2 is then attributed to scavenging by O_2 of radical intermediates in a radical chain mechanism.

$$ArN_2^+ \rightarrow N_2 + Ar^+ \xrightarrow{CH_3OH} ArOCH_3 + H^+ \qquad (2)$$

There is no need to invoke the hypothesis, tentatively advanced by Broxton, Bunnett, and Paik,[3] that the radical pathway to **2a** or **2b** and the ionic pathway to **3a** or **3b** involve a common intermediate.

How then did the data of Broxton, Bunnett, and Paik[3] cause them seriously to formulate that hypothesis? Their kinetic data (at 65 °C) are not directly comparable with ours, but the present total photometric rate constants (k_c) under O_2 are in good agreement with those extrapolated or interpolated from data of Paik[6] at other temperatures; in units of $s^{-1} \times 10^{-5}$, our average k_c for **1a** at 56 °C is 6.15 while 6.27 is extrapolated from Paik, and our average k_c for **1b** at 80 °C is 4.14 while 4.13 is interpolated from his measurements. The product ratios of Broxton, Bunnett, and Paik[3] fall within or very close to the range of our measurements. The chief difference between their data and ours lies in the rate measurements under N_2; whereas they reported ratios of k_c (N_2) to k_c (O_2) of about 2, we find such ratios ranging from 5.6 to 24.0 for **1a** and from 7.3 to 31.2 for **1b**. We surmise that some feature of the experimental technique employed by Broxton, Bunnett, and Paik[3] allowed a significant amount of O_2 to be present in the ampules used in kinetic studies under N_2, causing substantial depression of the reaction rate.

As to the mechanism of the radical reaction that predominates under N_2, we find the propagation sequence postulated by DeTar and co-workers[4,14] to be attractive and compatible with the evidence available; it comprises steps 3, 4, and 5.

$$Ar\cdot + CH_3OH \rightarrow ArH + \cdot CH_2OH \qquad (3)$$

$$\cdot CH_2OH + ArN_2^+ \rightarrow ArN{=}N\cdot + CH_2OH^+ \qquad (4)$$

$$ArN{=}N\cdot \rightarrow Ar\cdot + N_2 \qquad (5)$$

Actually, steps 4 and 5 were earlier[4,14] amalgamated as one, but subsequent work[15] indicates that the phenylazo radical can have discrete existence as such.

The nature of the initiation and termination steps is less clear. The very considerable variation of the observed k_r value between sets of our experiments based on different repurifications of diazonium salts and sometimes on different batches of solvent or different tanks of N_2 suggests that unidentified, adventitious impurities play significant roles either in initiation or in termination steps. Our experiments do, however, allow rejection of one conceivable initiation hypothesis, namely, that a neutral, covalent arylazo methyl ether (Ar-N=NOCH$_3$) initiates protodediazoniation by homolysis to arylazo (ArN=N·) and methoxyl radicals. The fact that arylazo methyl ethers are detectable in methanol solutions only if they are alkaline[16] indicates that the azo ether conjugate acids are prone to dissociate to diazonium ions and methanol molecules (eq 6). Because of this equilibrium and the acid–

$$ArN{=}N{-}\underset{H}{O^+}{-}CH_3 \rightleftharpoons ArN_2^+ + CH_3OH \qquad (6)$$

base equilibrium between arylazo methyl ethers and their conjugate acids, the concentrations of arylazo methyl ethers in acidic methanol solutions should be inversely proportional to the hydrogen ion concentration. Accordingly the rate of initiation via arylazo methyl ether homolysis should vary 100-fold between 0.1 and 0.001 M *p*-toluenesulfonic acid, but we find no correlation of k_r with hydrogen ion concentration within this range.

Initiation by homolysis of the conjugate acids of arylazo methyl ethers is not excluded by our data, nor is initiation by electron transfer from methanol to diazonium ion, forming directly arylazo radicals. Intuitively, we favor the latter possibility.

Protodediazoniation under Oxygen. Arguing that an atmosphere of O_2 should suppress radical mechanisms, DeTar and Kosuge[4] suggested that the formation of protodediazoniation products under O_2 may occur by a heterolytic mechanism, namely, by hydride ion abstraction from methanol by aryl cations (eq 7).

$$Ar^+ + CH_3OH \rightarrow ArH + CH_2OH^+ \qquad (7)$$

In our experiments we find substantial variation of k_r and the product ratio from one set of experiments to another, even under O_2 (see Tables II and III). It is unlikely that the rate of an ionic process, or the ratio of rates of two ionic processes, would vary so much between experiments set up to be identical or nearly identical. Moreover, Broxton, Bunnett, and Paik[3,10] have shown that the proportion of protodediazoniation under O_2 is further reduced, sometimes to the point of undetectability, by addition of 2-methyl-2-nitrosopropane as a supplementary radical scavenger. We judge, therefore, that protodediazoniation under O_2 occurs by a radical

mechanism very similar to that under N_2, and that inhibition by O_2 is not totally efficient.

Registry No.—**1a**, 673-40-5; **1b**, 459-64-3; **2a**, 108-86-1; **2b**, 100-66-3; **3a**, 104-92-7; **3b**, 150-78-7; *p*-toluenesulfonic acid, 104-15-4; sulfuric acid, 7664-93-9; methanol, 67-56-1.

Supplementary Material Available. Tables IV and V give detail for all experiments similar to that given for a few in Table I (11 pages). Ordering information is given on any current masthead page.

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Thermolysis of Arenediazonium Salts in Acidic Methanol. Effects of Substituents, Atmospheres, and Added Substances on the Competition between Ionic and Radical Mechanisms[1]

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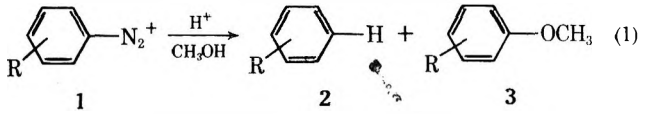
Received July 29, 1976

Thermolysis of benzenediazonium ions in acidic methanol gives either protodediazoniation or methoxydediazoniation. Several types of evidence, including the identity of minor by-products, experiments to trap radical intermediates, and the effects of added substances on product compositions, indicate competition between independent radical (giving protodediazoniation) and ionic (giving methoxydediazoniation) mechanisms. The radical mechanism is repressed by O_2 and certain other radical scavengers. For the *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, and *p*-OCH_3 substituted benzenediazonium salts the radical mechanism predominates under a N_2 atmosphere and the ionic mechanism predominates under O_2. For the H, *p*-CH_3, *m*-CH_3, and *m*-OCH_3 compounds the ionic mechanism predominates under both atmospheres while for the *p*-NO_2 compound the radical mechanism predominates under both.

The main products from the thermolysis of diazonium salts in acidic methanol (at pH 1–3) are benzene derivatives (**2**) resulting from protodediazoniation and aryl methyl ethers (**3**) that represent methoxydediazoniation (eq 1).



(1)

1 **2** **3**

a, R = H
b, R = *m*-Br
c, R = *p*-Br
d, R = *m*-Cl
e, R = *p*-Cl
f, R = *m*-CH_3
g, R = *p*-CH_3
h, R = *m*-OCH_3
i, R = *p*-OCH_3
j, R = *p*-NO_2

DeTar and Kosuge[2] made the striking observation that for two diazonium salts (**1c** and **1i** bisulfates) the former type of product (**2**) predominates when the atmosphere above the reacting solution is nitrogen but that under oxygen principally the aryl methyl ether is formed. Arguing mainly from that evidence, they suggested that methoxydediazoniation occurs by an ionic mechanism, via aryl cation intermediates, and that protodediazoniation occurs for the most part by a radical mechanism. However, for the rather small component of protodediazoniation observed under O_2, where a radical mechanism was expected to be suppressed, they suggested an ionic mechanism involving abstraction of hydride ion from the α position of the alcohol by aryl cations.[3]

We have reinvestigated these phenomena, partly to extend description of them, partly to apply various tests of mechanism, and for the most part the evidence we have obtained supports the mechanistic suggestions of DeTar and Kosuge. However, we find no support for their suggestion of a minor ionic protodediazoniation pathway. We have given a preliminary account[4] of some of our work, but in one respect our present interpretation differs from that offered earlier.

Certain other studies bear directly on our work. Melander[5] investigated the dediazoniation of *o*- and *m*-nitrobenzenediazonium sulfates in acidic tritium-labeled methanol and ethanol, and found that the hydrogen atom that takes the place vacated by the diazonio group comes from the α position of the alcohol, not from the hydroxy group. Horner and Stöhr[6] found that thermolysis of unsubstituted benzenediazonium sulfate in methanol gave mainly anisole under either N_2 or O_2 and that benzene, formed in small amount (4%) under N_2, did not appear under O_2. The kinetics of protodediazoniation of benzene-1,4-bisdiazonium ion in aqueous 2-propanol were studied by Lewis and Chalmers.[7] The photolytic and radiolytic decomposition of *p*-toluenediazonium ion in water solutions of methanol and other alcohols was studied by Packer and co-workers;[8] the chief product is toluene, quantum yields as high as 8 have been measured for photolysis, and inhibition by O_2 is strong, all consistent with a radical chain mechanism.

Zollinger and associates[9] studied the thermolysis of benzenediazonium ion in 2,2,2-trifluoroethanol solutions; they found evidence of an ionic mechanism via phenyl cation except when a radical pathway was catalyzed by a substance

Table I. pH Effects on Rates and Products from Thermolysis of Benzenediazonium and *p*-Bromobenzenediazonium Fluoroborates in Methanol

Substituent	Temp, °C	Acid[a] or base	Atmosphere	$10^4 k_\psi$, s^{-1}	Products, % 2	3
H	29.8	TsOH, 0.01 M	N_2	2.0		
	65	TsOH, 0.1 M	N_2		0	88
	29.8	TsOH, 0.01 M	O_2	2.0[b]		
	65	TsOH, 0.1 M	O_2		0	92
	30	Nil	N_2	2.0	3	66
	30.1	CH_3ONa, 0.1 M	N_2	200		
	30	CH_3ONa, 1.1 M	N_2		64	0
p-Br	65.2	TsOH, 0.01 M	N_2	3.6–8.6[c]		
	65	TsOH, 0.1 M	N_2		73[d]	19[d]
	65.2	TsOH, 0.01 M	O_2	2.2[e]		
	65	TsOH, 0.1 M	O_2		4[d]	72[d]
	30	Nil	N_2	0.15	82	5
	30	CH_3ONa, 0.1 M	N_2	69		
	30	CH_3ONa, 0.01 M	N_2		66	0

[a] TsOH is *p*-toluenesulfonic acid. [b] Extrapolated from higher temperatures. [c] Extremes of the range of 18 observations are given; from measurements at 65.2 °C and other temperatures, the extrapolated k_ψ at 30 °C is 4.4×10^{-6} s^{-1}. [d] Average of determinations listed in Table II. [e] Average from three runs.

Table II. Product Compositions from Thermolysis of Substituted Benzenediazonium Fluoroborates under Nitrogen and under Oxygen at 65 °C

Registry no.	Substituent	Under N_2 2, %[a]	Under N_2 3, %[a]	Under O_2 2, %[a]	Under O_2 3, %[a]
369-57-3	H	0[b]	88, 89[c]	0,[b] 3	92,[c] 94
500-25-4	*m*-Br	38, 36, 39,[c] 68[c]	59, 52, 61,[c] 21[c]	4,[c] 0[d]	84,[c] 89[d]
673-40-5	*p*-Br[e]	68, 74, 63, 84, 78,[c] 85,[f] 94[g]	16, 20, 23, 16, 18,[c] 3,[f] 4[g]	3, 3, 4, 6[c]	69, 81, 70, 70[c]
456-39-3	*m*-Cl	44, 51, 55, 92, 84[c]	40, 36, 38, 9, 13[c]	6,[c] 0[d]	86,[c] 92[d]
673-41-6	*p*-Cl	71, 94, 84,[c] 90[c]	14, 8, 8,[c] 11[c]	5,[c] 13[c]	54,[c] 57[c]
1422-76-0	*m*-CH_3	0[b]	94, 95, 100[c]	0[b]	100,[c] 90[d]
459-44-9	*p*-CH_3	0[b]	93, 93, 90[c]	0	95[c]
17569-84-5	*m*-OCH_3	6, 6, 6[c]	85, 86, 90[c]	6,[c] 0[d]	86,[c] 91[d]
459-64-3	*p*-OCH_3[e]	80,[c] 76[c]	18,[c] 24[c]	22,[c] 8	62,[c] 78
456-27-9	*p*-NO_2	86, 92	0[b]	35, 40	7, 0.4

[a] Each entry in a column represents a different experiment, or the average of two concordant experiments; experiments are entered in the same order in the columns for % 2 and % 3. [b] Only traces if any detected in any experiment. [c] Average of two concordant experiments utilizing the same batch of reacting solutions. [d] At 50.6 °C, with 0.01 M *p*-toluenesulfonic acid. [e] For more extensive data, see ref 12. [f] 30 °C. [g] 27 °C.

such as pyridine. Indeed, the discovery of isotopic exchange with added N_2 and of capture of added carbon monoxide ultimately to form trifluoroethyl benzoate point definitively to the intermediacy of phenyl cation.[10] In this connection, Swain, Sheats, and Harbison[11] adduced several types of evidence showing that aryl cation intermediates are intermediates in the thermal hydroxydediazoniation of diazonium salts in water.

Bunnett and Yijima[12] determined rates and products of the thermolysis of *p*-bromo- and *p*-methoxybenzenediazonium fluoroborates in acidic methanol under N_2 and under O_2. Their data show variation of product composition with atmosphere much as reported by DeTar and Kosuge,[2] and that the rate of methoxydediazoniation is independent of the atmosphere. An oxygen atmosphere specifically represses the rate of protodediazoniation.

Results

Gross pH Effects on Rates and Products. Some representative data are set forth in Table I. Unsubstituted benzenediazonium ion undergoes mainly methoxydediazoniation in acidic methanol under either O_2 or N_2 and its proclivity to this mode of reaction is such that anisole is the main product even in initially neutral methanol under N_2. The rate also is the same under these three sets of conditions. However, with methanolic sodium methoxide the rate is much greater and the product is mainly benzene,[13] no anisole being detectable. Indeed, in experiments with several diazonium salts (mostly not reported here) we have never observed any methoxydediazoniation to occur in methanol containing methoxide ion in substantial concentration (0.001 M or higher).

The rate–product pattern with *p*-bromobenzenediazonium ion is different; in acidic methanol the product composition and total thermolysis rate change sharply as the atmosphere is changed from N_2 to O_2. As with benzenediazonium ion itself, the rate of thermolysis in strongly basic methanol is much greater than in the absence of sodium methoxide and only protodediazoniation is observed.

Variation of Product Composition with Atmosphere. We determined the percentages of protodediazoniation (2) and methoxydediazoniation (3) products formed from several diazonium salts in acidic methanol under N_2 or under O_2. Our results are summarized in Table II. In the cases of the *p*-bromo- and *p*-methoxybenzenediazonium ions, Bunnett and Yijima[12] have performed this type of experiment more ex-

tensively and their data are qualitatively similar to those now reported.

Three diazonium salts, benzenediazonium fluoroborate (**1a**) and its *m*-methyl (**1f**) and *p*-methyl (**1g**) derivatives, undergo virtually exclusive methoxydediazoniation under either atmosphere, only traces of benzene or toluene being detectable as products. The behavior of the *m*-methoxy substrate (**1h**) is similar, only about 6% of protodediazoniation product being detectable even under N_2. At the other extreme is *p*-nitrobenzenediazonium fluoroborate (**1j**), which gave no methoxydediazoniation product (**3j**) under N_2 and very little of it under O_2.

The product compositions from the other diazonium salts are strongly dependent on the atmosphere, mainly protodediazoniation occurring under N_2 and mainly methoxydediazoniation under O_2.

We call attention to the variability of the product compositions observed from thermolysis of the *m*-bromo and *m*-chloro substrates under N_2. Although in some experiments protodediazoniation predominated just as for their para isomers, in others the two modes of reaction occurred in rather similar amounts. Essentially the same technique was used in all these cases.

Our results for the *p*-bromo and *p*-methoxy substrates are qualitatively similar to those of DeTar and Kosuge.[2] However, they differ appreciably in the case of *p*-nitrobenzenediazonium ion; the earlier workers reported about 40% of *p*-nitroanisole to be formed under either atmosphere. They also differ for *p*-toluenediazonium ion; the earlier report was that substantial amounts of toluene were formed under N_2, more at 25 °C than at 65 °C. In this case we also examined the thermolysis reaction under N_2 at 25 °C and at 46 °C and obtained results nearly the same as listed in Table II for 65 °C. DeTar and Kosuge determined product compositions by UV spectrophotometric analysis; the apparent errors in their determinations may be attributed to limitations of that method.

Formaldehyde as a By-Product. *p*-Bromobenzenediazonium fluoroborate (**1c**) was allowed to decompose completely in acidic methanol under N_2, and the resulting solution was treated with tetrahydrophthalazine; the expected product of condensation with formaldehyde[14] was obtained. However, by the same method no formaldehyde could be found as a product of thermolysis of **1c** in acidic methanol under O_2.

Minor Products from *p*-Bromobenzenediazonium Fluoroborate. Large-scale thermolysis reactions of this substrate (0.01 M) in methanol 0.1 M in H_2SO_4 were conducted under N_2 and O_2 atmospheres in order to provide substantial amounts of minor by-products for ease of determination and identification. Under N_2, besides 70.6% of bromobenzene and 14.5% of *p*-bromoanisole, we obtained 0.6% of *p*-bromobenzyl alcohol, 0.4% of *p*-bromophenol, 0.3% of 4,4′-dibromobiphenyl, and indications of traces of 4,4′-dibromoazobenzene. Under O_2, in addition to 4.2% of bromobenzene and 71.9% of *p*-bromoanisole, we got 6.4% of *p*-bromophenol and 0.3% of 4,4′-dibromobiphenyl. Although these product yields sum to less than 90% in both cases, we were unable despite assiduous search to find tangible amounts of other products.

Experiments to Trap Intermediates. Benzenediazonium fluoroborate was subjected to thermolysis under N_2 in methanol-*O*-*d* containing 0.1 M D_2SO_4 and also in initially neutral CH_3OD; the benzene obtained was virtually deuterium free in both cases. *p*-Bromobenzenediazonium fluoroborate thermolysis under the same two sets of conditions likewise furnished bromobenzene containing 1.5 mol % or less of deuterium. Thus the hydrogen atom that takes the place of the diazonio group in protodediazoniation comes from the methyl group of the methanol solvent, not from the hydroxy group.

Inasmuch as aryl radicals readily abstract iodine atoms from aryl iodides,[15] the obtaining of ArI from thermolysis of ArN_2^+ in the presence of Ar′I would constitute evidence for the intermediacy of Ar· radicals. We observed that thermolysis (at 65 °C) of *p*-bromobenzenediazonium fluoroborate in acidic methanol under N_2 in the presence of iodobenzene (0.24 M) afforded 40% of *p*-bromoiodobenzene. However, a similar reaction under O_2 gave no detectable amount of *p*-bromoiodobenzene. Thermolysis of benzenediazonium fluoroborate (at 30 °C) in acidic methanol under N_2 in the presence of *m*-chloroiodobenzene (0.21 M) yielded only 4% of iodobenzene. This criterion indicates that *p*-bromophenyl radicals are formed abundantly in the thermolysis of **1c** under N_2 but not under O_2, and that few phenyl radicals are generated during thermolysis of **1a** under N_2.

Thermolysis of *p*-bromobenzenediazonium fluoroborate in acidic methanol containing I_2 (0.009 M) under O_2 afforded 11% of bromobenzene, 5% of *p*-bromoanisole, and 37% of *p*-bromoiodobenzene.

Product Effects of Diverse Substances. Table III summarizes the effects of several substances on product yields, mainly from *p*-bromobenzenediazonium ion (**1c**). For each substrate and atmosphere, the average product composition in the absence of added substances (from Table II) is also shown.

For thermolysis of **1c** under N_2, sharply increased proportions of **3c**, at the expense of **2c**, were obtained when 2-methyl-2-nitrosopropane (*t*-BuNO), ferrous sulfate, or nitrous acid was present. Phenylazotriphenylmethane (PAT) and galvinoxyl had the opposite effect. Anthraquinone-2-sulfonic acid had, within experimental error, no effect. The effects of cuprous chloride and 2,2′-dipyridyl were slight and similar, being to increase somewhat the proportion of **2c** formed. It is noteworthy that at 35.2 °C **2c** remains the preferred product rather than **3c** despite the presence of 0.01 M nitrous acid; in the absence of nitrous acid the predominance of **2c** is also greater at the lower temperature, as may be seen in Table II.

For thermolysis of **1c** under O_2, added substances have qualitatively similar effects but they appear more subtly in the data. Certainly *t*-BuNO and perhaps nitrous acid operate further to repress formation of **2c**. Azobisisobutyronitrile (AIBN) causes the yield of **2c** actually to surpass that of **3c** under O_2 but the sum of the yields of the two products is only about 50%. The other added substances have effects indistinguishable from experimental error.

Considering now the other diazonium salts in Table III, we see that the effects of PAT and *t*-BuNO are qualitatively similar to those on thermolysis of **1c**. Especially to be noted is the cooperativity of the effects of O_2 and *t*-BuNO on thermolysis of *p*-nitrobenzenediazonium ion (**1j**); whereas this substrate forms no **3j** under N_2 and very little under O_2, the combination of O_2 and *t*-BuNO enables **3j** to become the predominant product, although the yields of **2j** and **3j** total only 37%.

Product Effect of Illumination. A few experiments were conducted in a Rayonet photochemical reactor equipped with "300-nm" (broad band) fluorescent lamps, the temperature of the reacting solution being 28 °C. Photolysis of **1c** under N_2 gave 77% of **2c** but no **3c**; under O_2 14% of **2c** and 25% of **3c** were formed, and it is unclear what happened to the rest of the **1c** under O_2. Comparison with thermolysis experiments at about the same temperature suggests that product patterns from the two modes of decomposition are rather similar.

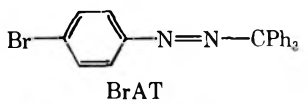
Atmosphere Effects on the Thermolysis of *p*-Bromophenylazotriphenylmethane (BrAT). These experiments have been performed to test the possibility that O_2 might affect product formation from **1c** by oxidizing *p*-bromophenylazo or *p*-bromophenyl radical to some precursor of **3c**.

Table III. Effects of Diverse Substances on Product Composition in Thermolysis of Substituted Benzenediazonium Fluoroborates in Acidic Methanol

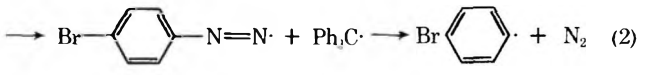
Substituent	Added substance	Temp, °C	Atmosphere	Products, % 2[a]	Products, % 3[a]
p-Br		65	N_2	74[b]	18[b]
	t-BuNO,[c] 0.005 M	65	N_2	12, 9, 33	45, 67, 45
	$FeSO_4$, 0.00125 M	65.8	N_2	20[d]	70[d]
	HNO_2, 0.01 M	78.4	N_2	14	63
	HNO_2, 0.001 M	55.6	N_2	13	67
	HNO_2, 0.005 M	55.6	N_2	19, 32,[d] 20	56, 44,[d] 42
	HNO_2, 0.01 M	55.6	N_2	9, 23	63, 60
	HNO_2, 0.01 M	35.2	N_2	56, 49	26, 13
	Galv,[e] 0.005 M	65.8	N_2	94[d]	2[d]
	Anq,[f] 0.002 M	55.6	N_2	66	16
	Anq, 0.004 M	55.6	N_2	78	10
	PAT,[g] 0.005 M	65.4	N_2	99	0
	Dipy,[h] 0.001 M	65	N_2	74	7
	CuCl, 2×10^{-5} M	65.2	N_2	77	6
	CuCl, 0.001 M	65.2	N_2	76[d]	4[d]
p-Br		65	O_2	4[b]	72[b]
	t-BuNO, 0.005 M	65	O_2	1[d]	68[d]
	$FeSO_4$, 0.00125 M	65.8	O_2	6[d]	74[d]
	HNO_2, 0.01 M	78.4	O_2	4	78
	HNO_2, 0.001 M	55.6	O_2	0	68
	HNO_2, 0.005 M	55.6	O_2	4[i]	73[i]
	HNO_2, 0.01 M	55.6	O_2	3	73
	HNO_2, 0.01 M	35.2	O_2	15, 8	47, 41
	Galv, 0.005 M	65.8	O_2	18	40
	Anq, 0.002 M	55.6	O_2	5	67
	Anq, 0.004 M	55.6	O_2	4	67
	Dipy, 0.001 M	65	O_2	4	73
	CuCl, 2×10^{-5} M	65.2	O_2	9	54
	CuCl, 0.001 M	65.2	O_2	5	54
	AIBN,[j] 0.04 M[k]	70	O_2	32	20
	AIBN, 0.06 M[k]	70	O_2	31	16
p-Cl		65	N_2	86[b]	10[b]
	PAT, 0.005 M	65.4	N_2	95[d]	0[d]
p-OCH_3		65	N_2	78[b]	21[b]
	t-BuNO, 0.005 M	65.5	N_2	24	49
		65	O_2	17[b]	67[b]
	t-BuNO, 0.005 M	65.5	O_2	3	62
	t-BuNO, 0.01 M	65.5	O_2	11	60
p-NO_2		65	N_2	89[b]	0[b]
	t-BuNO, 0.01 M	65.5	N_2	43	16
		65	O_2	38[b]	4[b]
	t-BuNO, 0.01 M	65.5	O_2	6	31

[a] Each entry in a column represents a different experiment, or the average of two or more concordant experiments; experiments are entered in the same order in the columns for % 2 and % 3. [b] Average value from Table II. [c] "*t*-BuNO" is 2-methyl-2-nitrosopropane. [d] Average of two concordant experiments. [e] "Galv" is galvinoxyl. [f] "Anq" is anthraquinone-2-sulfonic acid. [g] "PAT" is phenylazotriphenylmethane. [h] "Dipy" is 2,2′-dipyridyl. [i] Average of four concordant runs. [j] "AIBN" is azobisisobutyronitrile. [k] *p*-Toluenesulfonic acid, 0.01 M.

Thermolysis of BrAT under N_2 afforded **2c** in 70% yield. Under O_2 the same product was formed in 46% yield. In neither case was any **3c** obtained. Other products were not sought.



BrAT



(2)

The thermolysis of BrAT was also carried out in methanol containing 0.24 M iodobenzene. Under N_2 14% of **2c** and 29% of *p*-bromoiodobenzene were formed; under O_2 these yields sank to 10 and 18%, respectively. The formation of *p*-bromoiodobenzene is attributed to iodine atom abstraction from iodobenzene by the *p*-bromophenyl radical, formed as in eq 2.[16]

Discussion

The primary question to which this research was addressed was why changing the atmosphere from N_2 to O_2 should cause the course of thermolysis of several diazonium salts in acidic methanol to switch from mainly protodediazoniation to mainly methoxydediazoniation. The present results, together with the kinetic data of Bunnett and Yijima,[12] provide a clear answer: there are competing radical chain and ionic mechanisms of thermolysis; in some cases the balance of rates is such that the radical chain mechanism predominates under N_2 but is suppressed under O_2 sufficiently so that the slower ionic mechanism prevails. The radical mechanism leads principally to protodediazoniation products (**2**) and the ionic mechanism to aryl methyl ethers (**3**).

The present work also provides information about the effects of substituents on the relative rates of the two reaction pathways.

Evidence That Protodediazoniation Occurs by a Rad-

ical Mechanism. Most of the evidence relates to experiments with *p*-bromobenzenediazonium ion (**1c**).

Protodediazoniation is stimulated by the addition of good radical sources. Whereas thermolysis of **1c** under N_2 gives a mixture of mainly **2c** and some **3c**, thermolysis in the presence of PAT affords **2c** without **3c**. A parallel observation was made in respect to thermolysis of **1e** (Table III). PAT is known to undergo homolysis, in the manner of eq 2, to form phenyl radicals.[16,17] The phenyl radicals so formed initiate a radical chain mechanism which leads to **2c**, and the rate of initiation is so great that the slow ionic mechanism can no longer noticeably compete.

AIBN is also a familiar radical source.[18] Its effect, observed for thermolysis under O_2 (Table III), is qualitatively similar to that of PAT. Whereas thermolysis of **1c** under O_2 normally leads mainly to **3c**, with AIBN more of **2c** than of **3c** is formed. The yields of **2c** and **3c** total only about 50%; it is not surprising that a great deal of the reaction was diverted to other products, for a radical chain reaction occurring under O_2 would often be intercepted to form other products.

The minor products found from thermolysis of **1c** under N_2 indicate the intermediacy of *p*-bromophenyl radicals. 4,4′-Dibromobiphenyl is presumably obtained by dimerization of *p*-bromophenyl radical; we note that biphenyl was earlier observed[19] as a product from the thermolysis of **1a** in acetate-buffered methanol. *p*-Bromobenzyl alcohol formation can be ascribed to colligation of a *p*-bromophenyl and a hydroxymethyl radical. Under O_2, the chief minor product is *p*-bromophenol, the genesis of which is doubtless combination of *p*-bromophenyl radical with O_2 to form the *p*-bromophenylperoxy radical, $p\text{-}BrC_6H_4O_2\cdot$, followed by further steps not entirely clear.

The fact that thermolysis of **1c** under N_2 in the presence of iodobenzene forms a substantial amount of *p*-bromoiodobenzene further indicates the intermediacy of *p*-bromophenyl radicals, for aryl radicals are known to abstract iodine atoms from aryl iodides.[15]

Our finding that protodediazoniation in acidic CH_3OD affords products virtually deuterium free recalls Melander's similar observations for tritium-labeled methanol of a quarter century ago,[5] and is consistent with the intermediacy of aryl radicals. Aryl radicals are known to abstract hydrogen from the α carbon of methanol much faster than the hydroxy group.[20,21]

The fact that protodediazoniation is suppressed under an O_2 atmosphere is likewise consistent with a radical chain mechanism, for O_2 is a prominent scavenger of radicals.[22] Another scavenger that has qualitatively the same effect, as may be seen in Table III, is 2-methyl-2-nitrosopropane (*t*-BuNO).[23,24] Moreover, *t*-BuNO reinforces the effect of O_2; see especially in Table III the cooperative effects of *t*-BuNO and O_2 on the thermolysis of the *p*-bromo and *p*-nitro substrates.

Nature of the Radical Mechanism. Our observations are consistent with the propagation and termination steps of a radical chain mechanism for protodediazoniation proposed by DeTar and Turetzky.[19] The propagation cycle, slightly modified in view of evidence that arylazo radicals may have independent existence,[25] is sketched in Scheme I. Several

Scheme I

$$Ar\cdot + CH_3OH \rightarrow ArH + \cdot CH_2OH \quad (3)$$

$$\cdot CH_2OH + ArN_2^+ \rightarrow ArN{=}N\cdot + CH_2OH^+ \quad (4)$$

$$ArN{=}N\cdot \rightarrow Ar\cdot + N_2 \quad (5)$$

features of this mechanism are substantiated by studies of Beckwith and Norman[26] in which reactive intermediates or spin-trapped derivatives thereof were observed by means of their ESR spectra.

The minor products of thermolysis of **1c** under N_2 are indicative of termination steps, namely, dimerization of aryl radicals and colligation of aryl with hydroxymethyl radicals.

The nature of initiation is, however, unclear. Bunnett and Yijima[12] have discussed the problem; they favor initiation by electron transfer directly from methanol to the diazonium ion, forming thereby an arylazo radical which enters the propagation cycle at step 5.

Nature of the Ionic Mechanism. With attention to evidence that the thermolysis of diazonium ions in water occurs via aryl cation intermediates,[10,11,27] we suggest that methoxydediazoniation occurs by heterolysis of the diazonium ion to generate an aryl cation, followed by its coordination with methanol and finally expulsion of a proton, as sketched in eq 6.

$$ArN_2^+ \longrightarrow N_2 + Ar^+ \xrightarrow{CH_3OH} ArOCH_3 + H^+ \quad (6)$$

Effects of Other Additives. Nitrous acid under N_2 has an effect qualitatively similar to that of *t*-BuNO: it changes the products of **1c** thermolysis from mainly **2c** to mainly **3c**. It appears to suppress the radical chain mechanism. Nitrous acid is known to decompose on heating to release nitric oxide, NO,[28] which is an odd electron species and an effective scavenger of reactive radicals.[29]

It is noteworthy that under other circumstances nitrite ion acts to catalyze the formation of aryl radicals from diazonium salts. Addition of sodium nitrite to solutions of benzenediazonium fluoroborate and a monosubstituted benzene in dimethyl sulfoxide causes instantaneous reaction with evolution of N_2 and formation of biaryls of isomer ratio indicating the intermediacy of phenyl radicals.[30] In this situation nitrite ion acts to generate radicals and any inhibiting effect of the byproduct NO_2 molecules is of secondary significance.

Galvinoxyl operates, surprisingly, somewhat to increase the proportion of **2c** formed from **1c** under either N_2 or O_2. It is often employed as a radical scavenger,[31] but in the present system if anything it appears to have a mildly beneficial effect on the radical chain mechanism, perhaps by assisting initiation in some fashion that is not immediately obvious.

Ferrous sulfate under N_2 strongly represses protodediazoniation, changing the product composition approximately to that found under O_2. The probable agent of repression is ferric ion present as a contaminant or formed in the course of the reaction. Investigations by Norman and West[32] and by Walling[33] indicate that ferric ion effectively oxidizes hydroxymethyl radicals, thereby terminating radical chain reactions involving them. We did not investigate the effect of ferric ion as such, but are struck by the fact that under O_2, where one would anticipate a greater extent of oxidation of ferrous to ferric ion, the product ratio in the presence of added ferrous sulfate was much the same as in its absence. Years ago Waters[34] explained that the redox potential of the ferrous/ferric ion couple is such that ferrous salts cannot directly transfer an electron to diazonium ions.

Effect of Temperature. In Table II one can see that *p*-bromobenzenediazonium ion under N_2 gives an enhanced proportion of **2c** at 27 or 30 °C as compared to 65 °C. In Table III it is reported that under either N_2 or O_2 the proportion of protodediazoniation in the presence of 0.01 M nitrous acid is greater at 35 °C than at 55.6 °C. All these data indicate that the enthalpy of activation for the ionic mechanism leading to **3c** is greater than for the radical mechanism leading to **2c**.

Alternative Mechanistic Hypotheses. In 1970 we suggested the possibility that the radical and ionic pathways

leading, say, from **1c** to **2c** and **3c**, respectively, might proceed via a common intermediate.[4] That tentative hypothesis arose from consideration of product data in comparison with kinetic data, as they varied from N_2 to O_2 atmosphere. The kinetic/product study of Bunnett and Yijima,[12] which utilizes a different experimental design that enables a more straightforward interpretation, affords data that can be interpreted simply in terms of competing radical and ionic mechanisms without need to invoke the hypothesis of a common intermediate. The present product study likewise provides no cause to invoke that unusual hypothesis.

In view of the rich chemistry of copper-catalyzed diazonium salt reactions[35] and the profound effects that traces of copper ions can have in other systems,[36] we studied the effect of adding cuprous chloride. It had no appreciable effect on product composition under either N_2 or O_2 atmosphere. We also probed the effect of adding 2,2′-bipyridyl, which complexes ferrous ion strongly in acidic solution and certain other metal ions considerably.[37] It also had no effect under either atmosphere. These experiments indicate that transition metal ions are not centrally involved in the phenomena which are our present interest.

DeTar and Kosuge[2] suggested that the formation of protodediazoniation products under O_2 occurred via an ionic mechanism in which aryl cations abstracted hydride ions from the methyl group of methanol. They were inclined to believe that the radical mechanism was suppressed almost completely under O_2. Our finding, for diazonium salts **1c**, **1i** and **1j** that *t*-BuNO reinforces O_2 in suppressing protodediazoniation indicates that the radical mechanism is not entirely blocked by the O_2 atmosphere, and that what remains is further retarded by a second radical scavenger. Although we do not feel that the ionic mechanism of protodediazoniation can be totally dismissed, we find no support for it.

Substituent Effects. The product compositions listed in Table II represent the outcome of competition between radical and ionic mechanisms. The rates of both in principle may be influenced by substituents. Except for *p*-nitrobenzenediazonium ion, methoxydediazoniation strongly predominates under O_2, and the rates under O_2 for the most part report substituent effects on the ionic mechanism. These rates correlate very well with rates of hydroxydediazoniation in water,[4] but they do not correlate with Hammett σ values.[1b] Thus, reaction is fast with certain substituents (e.g., *m*-CH_3 and *m*-OCH_3) that have positive or negative σ values of small magnitude, and slow with others (e.g., *p*-NO_2 and *p*-OCH_3) that have positive or negative σ values of larger magnitude. (For the *p*-nitro substrate, rates were not measured in methanol under O_2; the statement is based on measurements in water solution.[38])

Substituent effects on the competition between mechanisms appear to be determined in large part by the strong substituent dependence of the rate of the ionic mechanism. In methanol under O_2, the *m*-methoxy substrate (the fastest) reacts more than 11 000 times faster than its para isomer (the slowest).[1b] Those diazonium salts that give mainly or entirely methoxydediazoniation even under N_2 (**1a**, **1f**, **1g**, and **1h**) are the four that react fastest under O_2.

However, there is more to it than that. Under O_2 the *p*-methyl, *m*-bromo, and *m*-chloro substrates react at nearly the same rate but under N_2 the first undergoes only methoxydediazoniation whereas the latter two give mainly protodediazoniation products. It follows that the *m*-bromo and *m*-chloro substituents are more favorable to the radical mechanism than is *p*-methyl. Furthermore, although the ionic mechanism in water goes about 80 times faster for the *p*-nitro than for the *p*-methoxy substrate, the radical mechanism in methanol is nevertheless more pronounced for the former. Clearly the *p*-nitro substituent has an especially beneficial influence on the radical mechanism. In general, electron-withdrawing substituents appear to assist it.

From gross rate data for a radical chain mechanism it is hard to say why substituent effects are as they are. The overall reaction rate is composite, and in principle substituents may differently affect initiation, propagation, and termination rates.

The fact (Table II) that for the *m*-bromo and *m*-chloro substrates under N_2 product compositions varied widely between intended replicate determinations suggests a great sensitivity of the radical mechanism to inhibition by O_2. We surmise that minor contamination by O_2 occurred in some experiments, despite careful flushing with N_2, and considerably suppressed reaction by the radical pathway.

Experimental Section

Diazonium Salts. *m*-Bromo-, *m*-chloro-, *m*-methoxy-, and *m*-methylanilines, as well as aniline itself, were commercial products repurified by distillation at reduced pressure. *p*-Bromo-, *p*-chloro-, *p*-methoxy-, *p*-methyl-, and *p*-nitroanilines were reagent grade materials used without further purification. To 30 ml of 48% HBF_4 and 30 ml of water in a 200-ml polyethylene beaker, 0.1 mol of aromatic primary amine was slowly added. The mixture was cooled to below 5 °C by external cooling with an ice–NaCl mixture. With mechanical stirring, a solution of 0.1 mol of $NaNO_2$ in 30 ml of water was added slowly so that the temperature did not exceed 5 °C, and stirring was continued 5 min after completion of addition. The solid diazonium fluoroborate was collected and purified by three cycles of solution in a minimum amount of acetone and then flocculation by addition of diethyl ether, and then air dried. All were white except *m*-methoxybenzenediazonium fluoroborate, which was light yellow. Decomposition points were as follows: H, 108–110 °C; *m*-Br, 139–140 °C; *p*-Br, 137–138 °C; *m*-Cl, 146–148 °C; *p*-Cl, 136–137 °C; *m*-CH_3, 97–101 °C; *p*-CH_3, 109–111 °C; *m*-OCH_3, 87–88 °C; *p*-OCH_3, 142 °C; and *p*-NO_2, 157–158 °C. These are mostly very close to those reported by Schulte-Frohlinde and Blume.[38]

Methanol. Reagent grade methanol was repurified by the magnesium method.

Nitrogen. Commercial nitrogen gas was deoxygenated by passing it through columns packed with activated copper metal on an inert support (BASF Catalyst R 3-11).

2-Methyl-2-nitrosopropane (*t*-BuNO). *tert*-Butylamine was oxidized to 2-methyl-2-nitropropane after Kornblum and Clutter;[39] the latter was reduced to *tert*-butylhydroxylamine after Kamm;[40] and the last was oxidized to *t*-BuNO after Emmons.[41]

***p*-Bromophenylazotriphenylmethane (BrAT).** The procedure of Cohen and Wang[42] was used; the product had mp 109–110 °C dec.

General Procedure for Product Determinations Summarized in Tables II and III. The diazonium fluoroborate (2.50×10^{-4} mol) was dissolved in 25 ml of methanol 0.1 M in *p*-toluenesulfonic acid (or in a few cases 0.5 M); the resulting solution was 0.01 M in diazonium salt. By pipet, 10 ml was transferred to a thin-walled, flat-bottomed glass ampule rated as "10 ml" but having total volume to the seal-off point about 14.0 ml. The solution in the ampule was bubbled gently with a stream of O_2 or of deoxygenated N_2, the bubbling tube was removed, a small piece of plastic film (Parafilm) was placed temporarily over the open end, and the ampule was sealed with a torch. In the case of O_2 ampules, the methanol solution was frozen by cooling with liquid nitrogen before sealing. The ampule was placed in a thermostat bath and left there for 10 or more half-lives as estimated from kinetic studies carried on concurrently.[1b]

Ampules removed from the thermostat were cooled, rinsed externally, and opened, and their contents were transferred to a 25-ml volumetric flask. To each flask, 5 ml of an 0.02 M solution of either iodobenzene or *m*-dichlorobenzene in methanol was added, and finally methanol to the mark. GLC analysis was conducted by means of an Aerograph Model 200 gas chromatograph equipped with flame ionization detector and disk integrator. The column was 3.2 mm i.d. by 183 cm long, packed either with 10% Carbowax 20M on Chromosorb P or with 4% Carbowax 20M on Chromosorb G. Molar response factors for products of type **2** and **3** against iodobenzene or *m*-dichlorobenzene as internal standard were redetermined in connection with each set of determinations and used in evaluating the GLC data.

Minor Products from *p*-Bromobenzenediazonium Fluoroborate. In 1 l. of 0.1 M sulfuric acid in methanol contained in a 2-l. single-neck flask, 2.71 g (0.01 mol) of the substrate was dissolved. The solution was bubbled for 2 h with either O_2 or deoxygenated N_2, the

space above the liquid was flushed with the relevant gas, and a condenser was installed with an arrangement at the top to provide a small positive pressure of the relevant gas. The solution was heated in a thermostat bath at 65.4 °C for about 40 h, cooled, and equipped for distillation and the volume reduced to about 300 ml by slow distillation. Water saturated with NaCl (100 or 150 ml) was added and the mixture was thrice extracted with diethyl ether. The combined ether layers were dried over anhydrous sodium sulfate and concentrated by distillation, heat being provided by an oil bath at 45 °C. The resulting product mixture was yellow for the reaction under N_2 and red for that under O_2.

Product yields were determined by GLC, with *m*-dichlorobenzene and *p*-bromobiphenyl being used as internal standards, and molar response factors being evaluated with use of authentic samples except for *p*-bromobenzyl alcohol (for which the same factor as for *p*-bromophenol was assumed) and for 4,4′-dibromoazobenzene (which was not detectable in quantitative GLC). By means of elution chromatography from silica gel, the crude product mixtures were separated into fractions eluted with petroleum ether and with diethyl ether–acetone. Each of these fractions was further fractionated by preparative GLC, and components were identified by the following evidence: bromobenzene, GLC t_R* (retention time) and IR* (the asterisk means spectrum identical with that of an authentic sample); *p*-bromoanisole, GLC t_R,* IR,* and NMR;* 4,4′-dibromobiphenyl, GLC t_R,* MS, and IR;* *p*-bromophenol, GLC t_R,* MS, and IR;* *p*-bromobenzyl alcohol, MS and IR (in agreement with the published spectrum[43]); and 4,4′-dibromoazobenzene, MS and mp 202–205 °C (lit.[44] mp 202–204 °C).

Experiments in Methanol-*O*-*d*. About 0.2 g of benzenediazonium fluoroborate or its *p*-bromo derivative was dissolved in 10 ml of CH_3OD[45] and (for runs in acidic CH_3OD) one drop of D_2SO_4 was added. For the bromo compound, the solution was placed in an ampule and bubbled with N_2. The ampule was sealed and heated in a thermostat at 65 °C overnight. The ampule was cooled, its contents added to 20 ml of cold water, and the mixture extracted with 30 ml of pentane. The pentane extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated to about 1 ml. The mass spectrum was obtained by means of an Hitachi RMU-6E mass spectrometer. Deuterium content was judged from the relative magnitudes of the M + 1 and M peaks, after correction for normal isotopic abundance of carbon-13 and deuterium. For benzenediazonium fluoroborate, the method was the same except that the reaction was carried out in a 10-ml volumetric flask kept overnight in a thermostat at 30 °C.

Reactions in the Presence of Aryl Iodides. Reactions were conducted as indicated in the text in the presence of 0.01 M *p*-toluenesulfonic acid for a time sufficient to ensure complete decomposition of the diazonium salt, as indicated by kinetic measurements. Products were determined by GLC, the method being calibrated both as to retention times and molar response factors with use of authentic samples.

Detection of Formaldehyde. A solution of *p*-bromobenzenediazonium fluoroborate (0.098 M) in methanol 0.1 M in *p*-toluenesulfonic acid was bubbled with N_2, sealed in an ampule, and heated at 65 °C for 19 h. The ampule was opened and 2 ml of its contents combined with 1 ml of aqueous acetate buffer and a solution of 0.07 g of tetrahydrophthalazine[14] in 2 ml of water. A precipitate formed; after 10 min, it was collected and dried; weight 0.0077 g (27%). A similar run was conducted under O_2, but no precipitate formed after addition of tetrahydrophthalazine. However, upon addition of a small amount of authentic formaldehyde, a precipitate formed.

Kinetic Determinations. In a 100-ml volumetric flask, a solution of ca. 1×10^{-4} mol of diazonium salt in methanol sometimes containing acid or base (as indicated in Table I) was prepared. For runs at ca. 30 °C, the solution was prepared at thermostat temperature with use of solvent or reagent solutions previously flushed with the indicated gas, and samples were taken at recorded times by means of a 5-ml pipet. For runs at 65 °C, 5-ml aliquots of the reaction solution were transferred to ampules which were bubbled with the indicated gas and then sealed; for runs under O_2 the contents of each ampule were frozen by external cooling with liquid nitrogen before sealing. The sealed ampules for a run at 65 °C were all placed at once in the thermostat, and single ampules were removed at recorded times and plunged into ice-cold water. The pipetted samples from 30 °C runs or the entire contents of ampules for 65 °C runs were discharged into 100-ml volumetric flasks containing 5 ml of an 0.02 M solution of α-naphthylamine in methanol and (for the neutral and $NaOCH_3$ reactions) 1 ml of concentrated hydrochloric acid. The flasks were filled to the mark with methanol and after 15 min the absorbance of the resulting azo dye was measured at 525 nm for **1a** and 540 nm for **1c**. Plots of ln A_t vs. time were linear for reactions in acidic solution under O_2 and at least approximately so in other cases.

Experiments with *p*-Bromophenylazotriphenylmethane (BrAT). Solutions of 10 ml volume, containing 0.01 M BrAT and 0.1 M *p*-toluenesulfonic acid and in some cases 0.24 M iodobenzene, were placed in ampules and bubbled with the gas indicated in the text. The ampules were sealed and heated overnight or longer at 65 °C. They were opened, a measured volume of a standard solution of *m*-dichlorobenzene was added to serve as internal standard, and GLC analysis was conducted. Retention times and molar response factors were independently determined with use of authentic samples.

Registry No.—BrAT, 53034-21-2; *p*-toluenesulfonic acid, 104-15-4; methanol, 67-56-1.

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(1) (a) Research supported in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and in part by the National Science Foundation; (b) based in part on the Ph.D. Thesis of C. H. Paik, University of California, SANTA Cruz, June 1972.
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Syntheses of β-Diamines and β-Amino Alcohols from α,β-Unsaturated Ketones and Aldehyde, Methylamine, and Borohydride Reducing Agents

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Received June 18, 1976

The reduction of three α,β-unsaturated ketones and one aldehyde by sodium borohydride and/or sodium cyanoborohydride in the presence of methylamine produced β-diamines and β-amino alcohols in variable yields. Thus, the maximum yields obtained follow: from crotonaldehyde, 40% *N,N'*-dimethyl-1,3-butanediamine (**1**) and 5% 3-methylamino-1-butanol (**4**); from methyl vinyl ketone, 15% **1** and 5% 4-methylamino-2-butanol (**5**); from 3-penten-2-one, 50% *N,N'*-dimethyl-2,4-pentanediamine (**2**) and 60% 4-methylamino-2-pentanol (**6**); and from mesityl oxide, less than 5% *N,N'*-dimethyl-2-methyl-2,4-pentanediamine (**3**) and 70% 4-methylamino-2-methyl-4-pentanol (**7**). A reaction mechanism of initial addition of amine followed by reduction of one or both of the carbonyl–imine (or iminium ion) equilibrium species is discussed.

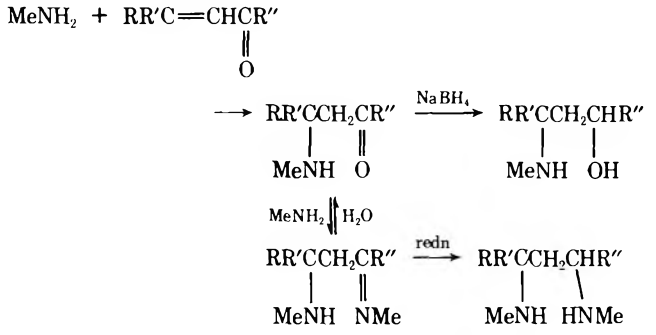
During the pursuit of our research we found that the availability of β-disubstituted secondary amines such as **1–3** (see Table I) would be highly desirable. Although procedures for the preparations of primary amine analogues have been established,[1] the same techniques are not always applicable for the secondary amines. Only compound **1** of **1–3** has been reported and it was obtained as a by-product in less than 15% yield.[2] The development of reliable syntheses for these types of compounds was therefore undertaken.

This paper reports the procedures and results obtained employing four α,β-unsaturated carbonyl compounds (crotonaldehyde, methyl vinyl ketone, 3-penten-2-one, and mesityl oxide), two borohydride reducing agents ($NaBH_4$ and $NaBH_3CN$), and methylamine. In addition to obtaining the desired secondary diamines (although in highly variable yields), proper control of reaction conditions resulted in the preparation of β-amino alcohols.

Results and Discussion

The results of these and previously reported syntheses are summarized in Table I. In none of the reactions reported here were by-products readily identifiable, although NMR spectra and elemental analyses were consistent with the formation of some triamines. The majority of the by-products (30% and more of the total product weight, depending on the starting material) were viscous, polymeric materils.

It is proposed that the reactions to produce compounds **1–7** proceed by the mechanism depicted below (where R, R', and R'' are H or Me as defined in Table I). The addition of methylamine was likely the first step followed by reduction of one or more of the carbonyl–imine equilibrium species. This mechanism is consistent with the experimental results. (Although imines are depicted above as being the species reduced to amines by both reagents, Borch, Bernstein, and Durst have reported that iminium ions are the actual species reduced by sodium cyanoborohydride.[3])



Reduction of crotonaldehyde, methyl vinyl ketone, and mesityl oxide with sodium borohydride by procedures 3 and/or 4 (see Experimental Section) gave the amino alcohols **4, 5,** and **7,** respectively. In each case the hydroxyl function was attached to the carbon atom that was formerly a part of the carbonyl group. This suggests that the initial step in each of the reactions was addition of amine to form the Mannich base. The preparations of compounds **8** and **9** substantiate this.

8 **9**

When crotonaldehyde, dimethylamine hydrochloride, and sodium cyanoborohydride were sequentially added to a solution of ammonia in methanol, 1-dimethylamino-3-aminobutane (**8**) was obtained. The reverse deployment of amine reagents, addition of crotonaldehyde to dimethylamine followed by ammonium chloride and sodium cyanoborohydride, produced 1-amino-3-dimethylaminobutane (**9**). In neither case was the other compound obtained.

The second step of the mechanism, establishment and reduction of a ketone–imine or aldehyde–imine (or iminium ion) equilibrium, has precedence.[4] Indeed, it is the selective reduction of such equilibrium species that has led to the use of sodium cyanoborohydride for reductive amination. Although at pH values of 4 or less aldehydes and ketones are reduced to alcohols by sodium cyanoborohydride, they are reduced only slowly at values of 6 and above.[3] At the higher pH values sodium cyanoborohydride thus functions selectively by reducing the iminium ions of the carbonyl–iminium ion equilibrium.[3] The fact that diamines were obtained in the reactions reported here indicates that such equilibria also exist in this system. The reactions of 3-penten-2-one with sodium borohydride to produce **2** and **6** exemplify the presence and importance of these equilibria. The ratio of amino alcohol (**6**) to diamine (**2**) obtained (see Table I) was substantially increased when the relative amount of methylamine was reduced (procedure 2 vs. 3) and when additional quantities of water were introduced prior to reduction (procedure 3 vs. 4).

The mechanism involved in the reactions to form diamines and amino alcohols thus appears to be unambiguous, but the large variations in yields among the three diamines and four amino alcohols cannot be rationalized with certainty since the compositions of the by-products and the mechanisms of their formation are not known. Based on the results for **2** and **6** discussed above, however, the carbonyl–imine equilibrium appears to be an important consideration. From the mesityl oxide reductions, for example, the consistently poor yields of diamine **3** compared to those of amino alcohol **7** suggest that the ketone–imine equilibrium lay far to the ketone side under all of the conditions employed. Thus, in contrast to the 3-

Table I. Table of Compounds and Yields

RR'CCH$_2$CHR''
MeNH X

Compd	R	R'	R''	X	Yield, % 1[a]	2[c]	3[a]	4[a]	Lit.
1	Me	H	H	HNMe	40[b]	35[b]	0[b]	c	<15[d]
					15[e]	5[e]	0[e]	0[e]	
2	Me	H	Me	HNMe	20	50	30	5	
3	Me	Me	Me	HNMe	<5	0	0	0	
4	Me	H	H	OH	0	0	5	c	64[f] <30[d]
5	H	H	Me	OH	0	0	5	5	
6	Me	H	Me	OH	0	5	35	60	35[g]
7	Me	Me	Me	OH	0	60	70	70	80[h]

[a] See Experimental Section for description of procedures 1, 2, 3, and 4. [b] From crotonaldehyde as starting material. [c] Crotonaldehyde is incompatible with procedure 4. [d] From crotonaldehyde, methylamine, and sodium amalgam (ref 2). [e] From methyl vinyl ketone as starting material. [f] From methyl crotonate, methylamine, and LiAlH$_4$: H. Schonenberg, H. Vogel, and E. Bamann, *Arch. Pharm. (Weinheim, Ger.)*, **298**, 371 (1965). [g] From 3-penten-2-one, methylamine, and sodium amalgam (ref 7). [h] From mesityl oxide, methylamine, and sodium amalgam (ref 7 and 9).

penten-2-one and sodium borohydride system (vide supra), variations in the relative methylamine quantities and the presence of additional water did not greatly affect the product distributions when mesityl oxide was reduced with sodium borohydride. In fact, the diamine was observed only when sodium cyanoborohydride was employed (procedure 1) and then it was obtained in very poor yield. An equilibrium lying far to the ketone side can be rationalized in terms of the greater steric requirements of the additional methyl group in mesityl oxide compared to 3-penten-2-one.

Experimental Section

Chemicals. With the exception of crotonaldehyde, obtained from Eastman Chemical, reagents were obtained from Aldrich Chemical and were used without further purification.

Analyses. Microanalyses were obtained from Midwest Microlabs, Inc., Indianapolis, Ind.

Syntheses of Secondary Amino Compounds. The general preparative procedures are described below. Yields of the individual compounds are summarized in Table I. NMR, analytical, and derivative data for the individual compounds follow the general procedures.

1. Procedure 1. Reduction of a 2:1 mole ratio of amine to α,β-unsaturated ketone or aldehyde with sodium cyanoborohydride.

The following procedure was modeled after that of Borch.[5] To a solution of 33.3 g (0.50 mol) of MeNH$_2$·HCl and 200 ml of MeOH contained in a 500-ml round-bottom flask equipped with a magnetic stirring system, ice bath, addition funnel, and nitrogen inlet was added all at once 11.2 g (0.20 mol) of KOH. Although KCl precipitated, it caused no interference. When the KOH had completely reacted, 0.20 mol of α,β-unsaturated ketone or aldehyde dissolved in 40 ml of methanol was added dropwise. After completion of addition, the suspension was stirred for 0.5 h and a solution of 5.23 g (25% excess of 0.067 mol) of NaBH$_3$CN dissolved in 40 ml of MeOH was added dropwise. (This procedure using crotonaldehyde required the immediate addition of the reducing agent rather than allowing the solution of crotonaldehyde, MeNH$_2$, and MeNH$_2$·HCl to stir for 0.5 h. Failure to begin the addition immediately resulted in discoloration of the solution and eventual formation of a brown oil.) The suspension was stirred overnight and allowed to warm to room temperature. The KCl was removed by filtration, and 16.8 g (0.30 mol) of KOH was added to the filtrate. After the KOH had completely dissolved and reacted, the suspension was filtered again. It was found that these two filtrations were more efficient than a single filtration after the latter portion of KOH had been added to the original suspension. The MeOH was then removed by rotary evaporation until about 50 ml of solution was left. The remaining solvent was distilled at atmospheric pressure. The product was removed from the viscous material remaining by crude vacuum distillation (0.8–0.1 mm) requiring pot temperatures of up to 100 °C, and a heat lamp on exposed pot and distillation head glassware. The receiving flask was kept in a dry ice-2-propanol bath. These drastic conditions were necessary to remove the product from the increasingly viscous residue. Any water in the product was removed by benzene azeotrope employing a Dean-Stark apparatus. The benzene was then removed by distillation and the product was distilled at either atmospheric pressure or under vacuum.

2. Procedure 2. Reduction of a 2:1 mole ratio of amine to α,β-unsaturated ketone or aldehyde with sodium borohydride.

The same general procedures were employed as in 1 above with the exception that 4.4 g of NaBH$_4$ dissolved in a solution of 3–4 pellets of KOH and 40 ml of water was used instead of NaBH$_3$CN in methanol.

3. Procedure 3. Reduction of a 1:1 mole ratio of amine to α,β-unsaturated ketone or aldehyde with sodium borohydride.

The procedures were similar to 2 above. Only 16.2 g (0.25 mol) of MeNH$_2$·HCl and 13.6 g (0.24 mol) of KOH were used for 0.2 mol of aldehyde or ketone. After stirring overnight the KCl was filtered, but no further addition of KOH was necessary.

4. Procedure 4. Reduction of a 1:1 mole ratio of amine to α,β-unsaturated ketone with sodium borohydride in the presence of additional water.

The procedure differed from 3 above only in that an additional 50 ml of water was added after the ketone-containing solution, and the suspension was allowed to stir 0.5 h before addition of the reducing agent. This procedure is $_2$·HCl discolored and eventually formed a brown oil unless the reducing agent addition was begun immediately.

***N,N'*-Dimethyl-1,3-butanediamine (1):** bp 61 °C (10 mm), 152 °C (740 mm); NMR (CDCl$_3$) δ 1.12 (d, 3, CH$_3$), 1.30 (m, 4, CH$_2$), 1.67 (s, 2, NH), 2.45 (s, 3, NCH$_3$), 2.48 (s, 3, NCH$_3$) and 2.7 (m, 3, CH and CH$_2$). The dioxalate derivative had mp 192–192.5 °C dec (lit.[2] mp 193 °C dec).

***meso*- and *dl*-*N,N'*-Dimethyl-2,4-pentanediamine (2).** Two points in the preparation should be mentioned. It was found during the crude distillation that when a yellow, higher boiling, more viscous compound began to distill, the desired product was completely removed and the distillation could be stopped. In those preparations where the amino alcohol 6 was also obtained (procedures 2, 3, and 4), the two compounds could be separated by vacuum distillation through a 10-cm Vigreux column: bp 52 °C (6 mm); NMR (CDCl$_3$) δ 0.88 (d, 6, CH$_3$), 1.1 (m, 2, CH$_2$), 1.29 (s, 2, NH), 2.22 (s, 6, NCH$_3$), and 2.45 (m, 2, CH). The dipicrate derivative of the isomeric mixture had mp 210 °C.

Anal. Calcd for dipicrate C$_{19}$H$_{24}$N$_8$O$_{14}$: C, 38.78; H, 4.11 N, 19.04. Found: C, 39.36; H, 4.20; N, 18.76.

***N,N'*-Dimethyl-2-methyl-2,4-pentanediamine (3):** bp 48 °C (10 mm); NMR (CDCl$_3$) δ 1.32 (s, 6, CH$_3$), 1.47 (d, 3, CH$_3$), 1.6 (m, 2, CH$_2$), 2.21 (s, 6, NCH$_3$), 2.3 (m, 1, CH), and 2.98 (s, 2, NH).

Anal. Calcd for C$_8$H$_{20}$N$_2$: C, 66.61; H, 13.97; N, 19.42. Found: C, 66.49; H, 13.90; N, 19.11.

3-Methylamino-1-butanol (4): bp 63 °C (13 mm) [lit.[6] 65 °C (14 mm)]; NMR (CDCl$_3$) δ 1.10 (d, 3, CH$_3$), 1.63 (m, 2, CH$_2$), 2.25 (s, 2, NH and OH), 2.48 (s, 3, NCH$_3$), 2.6 (m, 1, CH), 3.33 (m, 2, CH$_2$).

4-Methylamino-2-butanol (5): bp 78 °C (8 mm); NMR (D$_2$O) δ 1.23 (d, 3, CH$_3$), 1.70 (m, 2, CH$_2$), 2.32 (s, 3, NCH$_3$), 2.61 (m, 2, CH$_2$), 3.85 (m, 1, CH).

Anal. Calcd for C$_5$H$_{13}$NO: C, 58.21; H, 12.70; N, 13.58. Found: C, 58.31; H, 12.53; N, 13.65.

***erythro*- and *threo*-4-Methylamino-2-pentanol (6)** (see additional comments under 2 above): bp 63 °C (6 mm) [lit. 75.5–76 °C (14 mm),[7] 80–82 °C (17 mm)[8]]; NMR (CDCl$_3$) δ 1.04 (4 sets of d, 6, CH$_3$),

1.3 (m, 2, CH_2), 2.30 (s, 6, NCH_3), 2.53 (m, 1, CH), 3.1 (s, 2, NH and OH), and 3.83 (m, 1, CH). A picrate derivative of the isomeric mixture had mp 87–89 °C (lit.[7] threo mp 103.5–105 °C, erythro mp 86–87 °C).

Anal. Calcd for picrate $C_{12}H_{18}N_4O_8$: C, 41.62; H, 5.24; N, 16.18. Found: C, 41.76; H, 5.52; N, 16.20.

4-Methylamino-4-methyl-2-pentanol (7): bp 70 °C (10 mm) [lit. bp 115 °C (16 mm),[7] 184.5–185.5 °C (750 mm)[9]]; NMR (D_2O) δ 1.27 (s, 6, CH_3), 1.28 (d, 3, CH_3), 1.63 (m, 2, CH_2), 2.32 (s, 3, NCH_3), 4.07 (m, 1, CH). A picrate derivative had mp 154 °C (lit.[7,9] mp 156–158 °C).

1-Dimethylamino-3-aminobutane (8). The procedure was similar to procedure 1 above. Thus, 10.6 g (0.20 mol) of NH_4Cl was dissolved in 200 ml of methanol and cooled with ice, and 11.2 g (0.20 mol) of KOH was added all at once. After all of the KOH had reacted, 16.2 ml (0.20 mol) of crotonaldehyde dissolved in 40 ml of methanol was added dropwise. That addition was immediately followed by the addition of 16.2 g (0.20 mol) of Me_2NH·HCl and then the dropwise addition of a solution of 5.23 g (25% excess of 0.067 mol) of $NaBH_3CN$ in 40 ml of MeOH. The product was worked up in the manner described under 1 above except that no attempt was made to dry it. A yield of 40% was estimated by NMR after distillation through a 10-mm Vigreux column. Traces of water and MeOH remained in the product: bp of mixture 93 °C (740 mm) [lit.[10] bp 55 °C (16 mm)]; NMR ($CDCl_3$) δ 1.21 (d, 3, CH_3), 1.68 (m, 2, CH_2), 2.32 (s, 6, NCH_3), 2.4 (m, 3, CH_2 and CH), and 3.37 (s, 2, NH_2). A picrate had mp 180 °C (lit.[10] mp 181 °C).

1-Amino-3-dimethylaminobutane (9). The preparation of **9** was the same as for 8 above except that the introductions of the NH_4Cl and Me_2NH·HCl were reversed. After the product had been crudely distilled, it was dried employing a benzene azeotrope as in procedure 1 above. A yield of 15% was obtained: bp 46 °C (10 mm) [lit.[11] bp 154–156 °C (pressure not given)]; NMR ($CDCl_3$) δ 1.03 (d, 3, CH_3), 1.63 (m, 2, CH_2), 1.08 (s, 2, NH_2), 2.30 (s, 6, NCH_3), 2.6 (m, 3, CH_2 and CH). A picrate derivative had mp 204 °C (lit.[11] mp 204 °C).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Ball State University Research Committee for support of this research. The authors thank Drs. T. L. Kruger and B. N. Storhoff for their discussions and suggestions.

Registry No.—**1**, 57757-16-1; *meso*-**2**, 60978-26-9; *dl*-**2**, 60978-27-0; *meso*-**2** dipicrate, 60978-28-1; *dl*-**2** dipicrate, 60978-29-2; **3**, 60978-30-5; **4**, 2704-55-4; **5**, 42142-55-2; *erythro*-**6**, 53019-16-2; *threo*-**6**, 53089-02-4; *erythro*-**6** picrate, 60978-31-6; *threo*-**6** picrate, 60978-32-7; **7**, 42142-50-7; **8**, 13022-87-2; **9**, 60978-33-8; crotonaldehyde, 4170-30-3; methyl vinyl ketone, 78-94-4; mesityl oxide, 141-79-7; dimethylamine HCl, 506-59-2; dimethylamine, 124-40-3; 3-penten-2-one, 625-33-2.

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Migration of Acyl Groups in *o*-Aminophenol. 1. The Acetyl–Benzoyl, Acetyl–*p*-Nitrobenzoyl, and Acetyl–Propionyl Systems

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Received July 19, 1976

The synthesis and characterization of six mixed diacyl derivatives of *o*-aminophenol is described. It is shown that the rearrangements which have created so much uncertainty in this area in the past are actually solvent-catalyzed isomerizations which were minimized in this work by the proper choice of reaction and recrystallization solvents. In pyridine and in ethanol, isomerization resulted in the formation of dynamic equilibrium mixtures in accord with the theoretical predictions of Le Rosen and Smith in 1949. The compositions of the equilibrium mixtures and of the mixtures of monoacyls obtained on saponification were also in general agreement with the theoretical predictions of these authors. However, the failure to obtain isomerization in acetone, ether, water, or acetic acid solvents appears to cast doubt on their assumption of a general acid–base catalyzed isomerization mechanism. Further work to test this mechanism was deferred because of inconsistencies in the isomerization rates which appear to be due to the presence of unknown trace impurities.

The rearrangements occurring in *N,O*-diacyl derivatives of o-aminophenol wherein the two acyl groups are different (mixed diacyls) have been studied extensively in the older literature.[1-4] A 1968 Russian review article lists 228 references dealing with these migrations and related phenomena.[5] As noted in this review, these reactions are of theoretical interest as well as being of considerable practical importance in organic synthesis. In general, the mechanism of these reactions has remained obscure because of the inability of these earlier workers to separate and analyze the labile product mixtures which they obtained.

Le Rosen and Smith were the first workers to provide quantitative results for one of these systems (acetyl–benzoyl) and their work strongly indicated that the rearrangements were actually isomerizations of the mixed diacyls caused by the catalytic influence of the solvents used in preparing and purifying these products.[6] They further showed that isomerization was rapid in alkaline medium so that saponification in dilute base gave a mixture of the two possible monoacyl products. A theoretical explanation of their findings was presented which seemed to clarify the reasons for the many conflicting results reported to that time. They suggested that the isomerizations were general acid or base catalyzed so that an equilibrium mixture of the mixed diacyls was formed in

Table I. Approximate Times for Equilibrium to Be Reached and Composition of Equilibrium Solutions

	Alcohol		Pyridine	
	Time, h	% NA[a]	Time, h	% NA[a]
o-Acetamidophenyl benzoate	20	83	240	83
o-Benzamidophenyl acetate	24	83	580	81
o-Acetamidophenyl p-nitrobenzoate	32	66		
o-(p-Nitrobenzamido)phenyl acetate	24	65		
o-Acetamidophenyl propionate	50	63	30	61
o-Propionamidophenyl acetate	50	63	30	62

[a] Calculated weight percent of the more stable *N*-acetyl mixed diacyl isomer.

acidic or basic solvents. The principle of "minimum charge concentration" was developed to predict the more stable isomer and thereby the approximate composition of the expected equilibrium mixtures.

The reinvestigation of past work in this field called for by Le Rosen and Smith was halted by the untimely death of Dr. Le Rosen. Apparently, other workers failed to pursue the leads provided by Le Rosen and Smith because of the formidable analytical problems involved. A great deal of expertise in columnar chromatography was required at that time, and it was thought that the required pure mixed diacyls could be obtained only by means of preparative chromatography. Accordingly, despite the theoretical and practical importance of this work, the field remained dormant since 1949 except for a recent article by Amundsen and Ambrosio on rearrangements with *N,O*-acyl–alkoxycarbonyl derivatives of o-aminophenol.[7]

With the recent advent of modern high-performance liquid chromatography (HPLC) the way was at last cleared to performing the separations and analyses of the labile mixed diacyl products. It is the purpose of this article to present preliminary findings with three acyl systems chosen to test the hypotheses proposed by Le Rosen and Smith.

Results and Discussion

A. Preparation and Isomerization of Mixed Diacyls. The work of Le Rosen and Smith showed that isomerization of the mixed diacyls was catalyzed by pyridine and by ethanol. The first solvent was generally used by earlier workers in the synthesis of the mixed diacyls and the second was frequently used in recrystallization of the crude products. Thus, mixtures of the two possible mixed diacyls were usually obtained and, when ethanol was used for recrystallization, the same equilibrium mixture resulted so that it appeared that only one mixed diacyl could be prepared. In this work, initial attempts to prepare the mixed diacyls in the absence of pyridine were unsuccessful in that very low conversions were obtained. However, it was found that the second acylation could be carried out at room temperature in ether or acetone containing minor amounts of pyridine (2–10%). Under these conditions, little isomerization occurred and the pure mixed diacyls were isolated by recrystallization of the crude products from benzene or hexane.

Since Le Rosen and Smith had proposed that the isomerizations were instances of general acid–base catalysis, it was surprising to find that these isomerizations were not catalyzed by ether or acetone (Lewis bases). It was even more surprising to find that isomerization did not occur in glacial acetic acid and that this solvent could be used without incorporation of a basic catalyst in the synthesis of o-benzamidophenyl acetate from o-benzamidophenol. Finally, it was found that the water-soluble acetyl–propionyl mixed diacyls isomerized very slowly in water or in dilute hydrochloric acid solution. While these observations cannot be said to completely invalidate the assumption of a general acid–base catalysis mechanism, they do strongly suggest that this assumption must be tested further. However, it was decided that such work should be deferred because of the anomalous isomerization behavior of the "crude" mixed diacyls discussed below.

The approximate time required for equilibrium to be established and the concentration of the more stable o-acetamidophenyl esters obtained at these times in absolute ethanol and in pyridine solutions are summarized in Table I for the six recrystallized mixed diacyls studied in this work. The values given in this table represent the averaged results obtained from several isomerizations carried out at room temperature (about 25 °C) with 0.5–2.0% solutions of the indicated mixed diacyl. As a first approximation, the isomerizations appeared to be first-order reactions, but no attempt has yet been made to obtain rigorous kinetic data for these isomerizations. This is primarily because it was discovered that the isomerization rates were greatly influenced by the presence of unknown trace impurities. For example, a "crude" sample of o-acetamidophenyl benzoate precipitated from aqueous pyridine still contained 98% of the unrearranged isomer after 71 h in absolute alcohol. The liquid chromatographic analysis of this "crude" sample showed it to be nearly pure with only traces of the opposite isomer and unreacted o-acetamidophenol present. This anomalous behavior was noted with other crude mixed diacyl isomers studied herein and tests showed that this behavior was not attributable to residual pyridine since similar results were obtained with "crude" mixed diacyl samples precipitated from acetic acid. It was also shown that addition of 0.5% pyridine or hydroquinone caused recrystallized p-nitrobenzamidophenyl acetate to isomerize appreciably faster in alcohol than in the absence of these free-radical inhibitors. These observations are very puzzling and may provide a valuable clue to the overall reaction mechanism. Meanwhile, however, the main value of the results listed in Table I was to show that acyl migrations were indeed isomerizations caused by the influence of certain solvents such as alcohol and pyridine.

With the acetyl–p-nitrobenzoyl mixed diacyls, the results of isomerization in 90% aqueous ethanol were essentially the same as in absolute alcohol. However, isomerization of the acetyl–benzoyl mixed diacyls was very much slower in 95% aqueous alcohol and complete equilibrium was not obtained even after 900 h. In addition, extensive solvolysis to form the monoacyls occurred in this solvent and this solvolysis reaction was much greater for the o-benzamidophenyl acetate than for its isomeride. In anhydrous methanol, the mixed diacyls of the acetyl–benzoyl system isomerized very rapidly so that equilibrium was reached in only 5 h. Again, extensive solvolysis occurred so that after 5 h the mixtures contained about 13% of the monoacyls and after 144 h about 87% of the monoacyls was present. The ratio of the percent o-acetamidophenyl benzoate to o-benzamidophenyl acetate remained constant from 5 to 144 h, however, and was the same (within experimental error limits) as that observed in the absolute alcohol or pyridine solutions. Thus, it was concluded that the isomerization solvent did not affect the final equilibrium composition attained.

Table II. Melting Points of Mixed Diacyl Derivatives of o-Aminophenol

No.	Compd	Mp, °C Found	Mp, °C Lit.
I	o-Acetamidophenyl benzoate	138–140	139–141[a]
II	o-Benzamidophenyl acetate	141–145	138–140[a]
III	o-Acetamidophenyl p-nitrobenzoate	165–167	
IV	o-(p-Nitrobenzamido)phenyl acetate	143–144	
V	o-Acetamidophenyl propionate	72–73	57–75[b]
VI	o-Propionamidophenyl acetate	102–103	85–103[b]

[a] Reference 6a. [b] Reference 3.

The acetyl–propionyl mixed diacyls were unusual in that they were appreciably soluble in water. Surprisingly, no trace of the monoacyls were detected when isomerizations were carried out in this solvent and isomerization proceeded very slowly being only about 90% complete for either isomer after 245 h.

B. Saponification of Mixed Diacyls. Le Rosen and Smith predicted that saponification of either pure mixed diacyl (or mixtures thereof) should result in a mixture of the two possible monoacyls. They reasoned that this should occur since isomerizations in alkaline solution were very rapid, and that the more unstable isomer should saponify faster than its isomeride. In this work, saponifications were carried out with a 20% excess of aqueous NaOH. The mixed diacyls were stirred with the aqueous alkali until complete solution was obtained and for at least 30 min thereafter to ensure complete saponification. The resulting clear solutions were acidified and extracted with chloroform to ensure complete recovery of the monoacyls. The chloroform extracts were then diluted to an appropriate volume and aliquots analyzed by HPLC. No interferences from the acids resulting from saponification were observed although peaks were seen for benzoic and p-nitrobenzoic acid. The results of these saponifications confirmed the predictions of Le Rosen and Smith in that a mixture of the two possible monoacyls was obtained in each case. The relative percentages of o-acetylaminophenol found were 26, 66, and 44% for the acetyl–benzoyl, acetyl–p-nitrobenzoyl, and acetyl–propionyl systems, respectively. No significant difference in these percentages was noted for the two mixed diacyls in each system so these values represent the averaged result. It should be noted that the value of 26% o-acetylaminophenol is appreciably different from the value of 37% reported by Le Rosen and Smith for the acetyl–benzoyl system, and this discrepancy is probably due to the more refined methods of extraction and analysis used here. While no significance is attached to the relative quantities of monoacyls produced by saponification at present, these ratios, taken together with the mixed diacyl ratios in the equilibrium mixture, should prove useful in assessing the relative rates of saponification of the mixed diacyls. For example, in the acetyl–p-nitrobenzoyl system the saponification rates of the two mixed diacyls must be nearly identical since the monoacyl mixture obtained on saponification corresponds exactly to that which would be predicted on this basis from the mixed diacyl equilibrium composition. In the other two systems, the monoacyl derived from the less stable mixed diacyl isomer predominated showing that this isomer saponified appreciably faster than its isomeride.

Finally, since the mixed diacyls of the acetyl–propionyl system were water soluble, it was felt worthwhile to carry out an acid hydrolysis of these compounds. A 1% solution of each isomer was stirred at room temperature for 3 days with 1.6 N HCl and the resulting mixture extracted with chloroform. In each case, the extracts were free of the mixed diacyls and the monoacyl resulting from rearrangement and hydrolysis constituted only 7% of the monoacyl mixtures. Thus, it was evident that isomerization in acid media was slow relative to hydrolysis in marked contrast to the results obtained with hydrolysis in base.

Experimental Section

The synthesis and characterization of compounds used in this work are described below. Melting points are uncorrected and were taken on a Fisher digital melting point analyzer. Infrared spectra were recorded from potassium bromide disks on a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet spectra were recorded using a Bausch and Lomb Model 600 UV–visible spectrophotometer.

The chromatographic analyses were performed using a Waters ALC/GPC 202 liquid chromatograph equipped with a differential ultraviolet detector (254 nm) and a 30 cm × 4 mm (i.d.) μ-Porasil column. Normal hexane was used as the principal developing solvent in all cases and was modified by the addition of small amounts of chloroform and ethanol. In isomerization experiments, the chromatographic conditions were chosen such that the two possible monoacyls were clearly separated. Standard solutions were prepared in chloroform and although this solvent contained about 1% ethanol as a stabilizer, no evidence of isomerization of the mixed diacyls was observed even after several months standing.

Isomerization experiments were carried out by periodically analyzing solutions containing 0.5–2.0% (w/v) of the mixed diacyl. Generally, 1-μl aliquots of the alcohol solutions were injected directly into the chromatograph, since it was found that the results so obtained gave reliable concentration results. However, for pyridine solutions it was necessary to evaporate aliquots to dryness and reconstitute these with chloroform before chromatographing.

A. Preparation of Monoacyl Derivatives of o-Aminophenol. The preparation of these stable derivatives has been adequately described in the earlier literature and need not be repeated in detail here. However, it was discovered early in this work that they were best prepared in high purity by saponification of the homogeneous diacylated derivatives. For example, when equimolar quantities of benzoyl chloride and o-aminophenol (sublimed product, mp 170–171 °C) were reacted in pyridine solution, the resulting product contained 19% of the homogeneous diacyl. It was found that recrystallization of this mixture from various solvents was not an efficient way of purifying the desired monoacyl. On the other hand, saponification of the o-dibenzoylaminophenol gave good yields of the o-benzamidophenol, which was then easily purified by recrystallization.

B. Preparation of Mixed Diacyl Derivatives of o-Aminophenol. Generally, the *N*-acetyl isomers were prepared satisfactorily by acylating o-acetamidophenol with the appropriate acid chloride or anhydride in pyridine followed by recrystallization from nonpolar solvents. The more unstable *O*-acetyl isomers were prepared in glacial acetic acid or in acetone containing 2–10% of pyridine. Use of these reaction solvents gave minimal isomerization and a reasonable rate of reaction. The crude products were obtained by pouring the reaction mixture over ice or by evaporating to dryness as described in detail below.

1. o-Acetoamidophenyl Benzoate. Reaction of o-acetamidophenol in pyridine solution with a 15% excess of benzoyl chloride followed by pouring the solution over cracked ice gave a light tan product melting at 141–143 °C. Analysis by LC showed that the recovered product contained about 2.5% of the rearranged isomer. Recrystallization from benzene with carbon treatment gave white needles melting at 137.5–139 °C in 62% yield. A single liquid chromatographic peak was observed for the recrystallized compound.

2. o-Benzamidophenyl Acetate. Acetylation of o-benzamidophenol with a 10% excess of acetyl chloride in glacial acetic acid gave a 75% yield of crude product melting at 141–145 °C. Recrystallization of this fine white powder yielded white needles, mp 141–145 °C. LC

Table III. Infrared Carbonyl Absorption Bands in Mixed Diacyl Derivatives

Compd[a]	Equil %	Ester, μm	Amide, μm	Δμm[b]
I	83	5.77	5.90	0.13
II	17	5.65	6.00	0.35
III	66	5.69	5.96	0.27
IV	34	5.63	5.98	0.35
V	63	5.65	6.00	0.35
VI	37	5.65	5.98	0.33

[a] See Table II for compound identification. [b] Amide absorption minus ester absorption.

Table IV. Ultraviolet Absorption Maxima of Mixed Diacyls

Compd	Solvent	Absorption maxima λ, nm	Absorption maxima ε × 10⁻³
I	Cyclohexane[a]	234	32.5
II	Hexane[a]	266	12.5
III	Hexane	244	28.8
IV	Hexane	241	19.3
		295	10.8
V	Hexane	240	11.2
VI	Hexane[a]	240	15.5

[a] Because of their low solubility, these solutions were prepared by dilution of chloroform solutions and their absorbance measured against appropriate blank samples diluted similarly.

6. o-Propionylamidophenyl Acetate. The acetylation of o-propionylamidophenol was carried out using a 1200% excess of acetyl chloride in acetone. Pyridine was eliminated from this preparation since its presence seemed to promote the formation of tars. The solvent and excess acetyl chloride were removed under vacuum, leaving a tarry residue which was dissolved in hot benzene and carbon treated. On cooling, tan crystals separated (40% yield) which melted at 100.5–102 °C. A final recrystallization from benzene yielded white needles melting at 101.5–103 °C. LC analysis showed less than 0.5% of unreacted o-propionylamidophenol to be present, and the opposite isomer was not detected.

C. Characterization of Compounds. 1. Melting Point Data. The melting point data for the mixed diacyl compounds prepared in this work are summarized in Table II. The data for the better known stable monoacyls and homogenous diacyls are not recorded here but were in good agreement with the literature values. Good agreement with the literature data for the acetyl–benzoyl mixed diacyls was also obtained, but it is obvious from the wide melting point range recorded that impure products were obtained by earlier workers with the mixed diacyls of the acetyl–propionyl system. The mixed diacyls of the acetyl–p-nitrobenzoyl system with o-aminophenol were prepared for the first time.

2. Infrared Absorbtion Data for Ester and Amide Carbonyl Bands of Mixed Diacyl Derivatives (Table III). It was initially thought that the separation of the infrared ester and amide carbonyl bands would prove to be useful in assigning structures to the mixed diacyl derivatives. Theoretically, one might expect to find a wider separation of these bands in the more unstable of the mixed diacyl isomers owing to the greater differences in charge on the ester and amide carbonyl carbons. It was further thought that the magnitude of these differences might be a measure of the relative stabilities of these isomers. These ideas appear to work for the first two systems but clearly fail in the third and are probably too unsophisticated to have much merit.

Table V. Carbon and Hydrogen Analyses of Mixed Diacyl Derivatives of o-Aminophenol[a]

Registry no.	No.	Compd	Theory % C	Theory % H	Found % C	Found % H
60949-47-5	I	o-Acetamidophenyl benzoate	70.6	5.13	70.5	5.14
60978-39-4	II	o-Benzamidophenyl acetate	70.6	5.13	70.5	5.18
60949-48-6	III	o-Acetamidophenyl p-nitrobenzoate	60.0	4.03	59.9	4.05
60949-49-7	IV	o-(p-Nitrobenzamido)phenyl acetate	60.0	4.03	60.0	4.06
60949-50-0	V	o-Acetamidophenyl propionate	63.8	6.32	63.8	6.36
60978-38-3	VI	o-Propionamidophenyl acetate	63.8	6.32	63.9	6.37

[a] Results of single analyses performed by Atlantic Microlab, Inc., Atlanta, Ga.

analysis showed the recrystallization compound to contain 0.3% of the opposite isomer.

3. o-Acetamidophenyl p-Nitrobenzoate. Reaction of o-acetamidophenol with a 10% excess of p-nitrobenzoyl chloride in pyridine solution followed by precipitation over ice gave a 53% yield of crude product, mp 162–167 °C. Two recrystallizations from benzene gave white needles melting at 165–167 °C. LC analysis showed that 0.7% o-(p-nitrobenzamido)phenyl acetate was present in the recrystallized product.

4. o-(p-Nitrobenzamido)phenyl Acetate. o-(p-Nitrobenzamido)phenol was reacted with acetyl chloride in acetone solution containing 4% pyridine. A large excess (300%) of acetyl chloride was found to be required for good conversion. On pouring this reaction mixture over cracked ice, an 88% yield of crude product was obtained melting at 140–143 °C. Recrystallization from benzene with carbon treatment yielded yellow crystals melting at 143–144 °C. LC analysis of the recrystallized product showed it to contain 0.5% of the rearranged isomer.

5. o-Acetamidophenyl Propionate. o-Acetamidophenol was reacted in acetone solution containing 1% pyridine with propionic anhydride (470% excess). Evaporation of the solvent produced a brown oil which was dissolved in 50% hexane in benzene and carbon treated. An 18% yield of white needles were recovered which melted at 72–73 °C. Analysis by LC showed the product to contain 2.6% of the rearranged isomer. Additional recrystallizations from various hexane–benzene mixtures failed to remove the undesired isomer. Mixture melting points with both o-propionylamidophenol and o-propionylamidophenyl propionate gave large melting point depressions.

3. Ultraviolet Absorbtion Data for Mixed Diacyls. The ultraviolet absorbtion maxima for the mixed diacyls prepared in this work are recorded in Table IV. The only literature data available were for the acetyl–benzoyl compounds and these agreed well with the data obtained in this work. These data may be useful both for characterization and for increasing analysis sensitivity in liquid chromatography where a variable wavelength detector is available. However, sensitivity with a 254-nm fixed wavelength detector was very good and full scale deflection was obtained with about 2–3 μg samples of these compounds.

Registry No.—o-Acetamidophenol, 614-80-2; benzoyl chloride, 98-88-4; o-benzamidophenol, 3743-70-2; acetyl chloride, 75-36-5; p-nitrobenzoyl chloride, 122-04-3; o-(p-nitrobenzamido)phenol, 3743-17-7; propionic anhydride, 123-62-6; o-propionylamidophenol, 6963-37-7.

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Acylanthranils. 4. The Effect of Steric Hindrance on Selectivity in the Reaction of Amines with Acetylanthranil[1]

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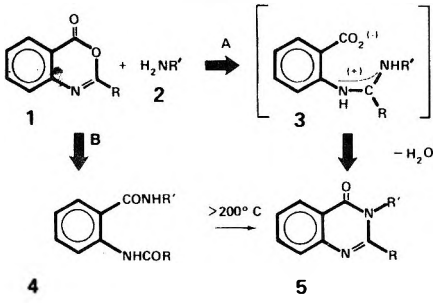
Received March 16, 1976

Acetylanthranil (1) was made to react with a set of 17 amines to give acetamidines, 3, via pathway A, and/or *o*-acetamidobenzamides, 4, via pathway B as shown in Scheme I. Simple primary amines, such as ethylamine and aniline, follow pathway A, whereas secondary amines and those primary amines with substituents on the α-carbon atom, such as *tert*-butylamine or isopropylamine, follow pathway B. The rate of conversion to products 3 and/or 4 varies directly with pK_a, but inversely with the bulk of the amine substituents. These results show that both the steric and electronic contributions are important factors that determine overall reactivity via either pathway, but only the steric factor has a significant effect on selectivity.

In our previous publications[2-4] concerned with the reinvestigation of the reaction of acylanthranils, **1**, with amines, **2**, we reported that the products, ortho-substituted benzamides (**4**) and/or quinazolones (**5**), are not formed sequentially (**5** from **4**) as was assumed by the early investigators, but rather are formed competitively via alternative pathways A and B as illustrated in Scheme I. We showed that the precursors of **5** are in fact novel amidine salt intermediates, **3**, which undergo cyclodehydration in solution even at room temperature. In contrast to this facile conversion, temperatures in excess of 200 °C are required to effect cyclodehydration of **4** to give **5**.

Scheme I



We observed[3,4] that the product distribution obtained with a given amine is markedly dependent upon the substituent R at the 2 position of the benzoxazone, **1**. The selectivity ratio for reaction via pathway A to pathway B, i.e., k_A/k_B = (**3** and/or **5**)/**4**, as well as the rate of conversion to products, decreases with increase in bulk of R, showing that steric hindrance on the part of the acylanthranil is a major factor that determines selectivity. Thus, the selectivity ratio with reference to aniline is >50/1 for acetylanthranil (**1a**, R = CH_3), whereas at the other extreme it is <1/25 for benzoylanthranil (**1b**, R = Ph). We noted that substituents at other positions on the aromatic ring increase or decrease only the overall rate of reaction with the given amine, depending upon their respective electronic contribution to the electrophilic centers at the 2 and 4 positions, but do not alter significantly the selectivity manifested by the parent acylanthranil.[4] Thus, all reported reactions of benzoylanthranils with an amine follow pathway B, whereas all but two reported reactions of acetylanthranils with an amine followed pathway A. The exceptions are (1) the reaction of 7-acetamidoacetylanthranil with 2-aminobutane to give in good yield the corresponding 2,4-diacetamidobenzamide as reported by Bogert,[5] and (2) the reaction of acetylanthranil with anthranilic acid to give in good yield *o*-(*o*-acetamidobenzamido)benzoic acid as reported by us.[3]

We suggested[4] that perhaps both exceptions are due to steric hindrance on the part of the coreactant amine. We now report results obtained with acetylanthranil and a large set of aliphatic amines, which show that steric hindrance on the part of the amine is indeed a major factor that influences reaction selectivity.

Results and Discussion

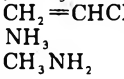
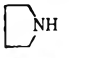
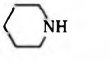
Acetylanthranil (**1a**, R = CH_3) was made to react with the set of amines, **2a–q**, either neat or in a nonpolar solvent. The product mixtures were separated according to the material balance procedure described previously,[3] and usually accounted for more than 95% of the starting materials added in equivalent amounts. The percent acetylanthranil units isolated as **3**, **4**, and **5** were then used to calculate the corresponding selectivity ratio for reaction via pathway A relative to pathway B (i.e., k_A/k_B). The data are collected in Table I and the supporting characterization data are collected in Table II. Unreacted acetylanthranil was either recovered per se (example **d**) or isolated as o-acetamidobenzoic acid, which was produced by reaction with water as part of the postreaction separation procedure (examples **g, i, j, k, p,** and **q**). The reaction conditions list the solvent, temperature, and elapsed time before beginning the separation procedure, which was sometimes longer than the minimum time required for total conversion of **1** to **3** or **5** (examples **a, b, c, e, f, h, l, m,** and **n**).

The data show that the rate of reaction with amines that manifest the same selectivity is markedly dependent upon the pK_a of the amine. Thus, reaction with primary aromatic amines, such as aniline (**2a**) and *p*-toluidine (**2b**), which have pK_a values of about 5, required about 2–3 h for completion, whereas reaction with simple primary aliphatic amines, such as methylamine (**2c**) and ethylamine (**2h**), which have pK_a values of about 11, required only 5–10 min for completion. The reaction rate was significantly slower, however, with primary aliphatic amines with more bulky substituents, such as a neopenthyl group, **2n**, presumably owing to the effect of steric hindrance. Similarly, reaction with secondary aliphatic amines, such as dimethylamine (**2f**) and pyrrolidine (**2p**), is considerably faster than that with *N*-methylaniline (**2o**), which did not interact significantly even after several days in refluxing benzene.

Although the reaction rate is a function of the amine basicity, the reaction selectivity appears to be independent of this parameter. Thus, the set of amines that follow pathway A exclusively (amines **a–e, h, l**) have pK_a values that range from 5 to 11, and the same is true of the set of amines that follow pathway B exclusively (amines **f, k, o, p,** and **q**).

Selectivity appears to be more associated with the combined bulk of the substituents about the nucleophilic center, rather

Table I. Product Distribution in the Reaction of Acetylanthranil (1a) with Amines 2

Amine 2	pK_a,[a] 25 °C	Reaction conditions: Solv[b]	Temp, °C	Time[c]	% 1a units Isolated as: 4	3	5	Selectivity k_A/k_B = (3 + 5)/4
a, $PhNH_2$	4.63	a, b	RT	4 h	0	75	25	>50/1
b, p-CH_3PhNH_2	5.08	a, b	RT	4 h	0	70	25	>50/1
c, $CH_2{=}CHCH_2NH_2$	9.49	c	RT	1 h	0	0	91	>50/1
d, NH_3	9.26	a, b	RT	2 days[f]	0	0	0	>50/1[d]
e, CH_3NH_2	10.7	a	RT	1 h	0	100	32	>50/1
		d	RT	1 h	20	43	32	4/1
f, $(CH_3)_2NH$	10.8	c	0	1 h	100	0	0	>1/25
g, $(CH_3)_3N$	9.9	c	Reflux	1 day	0	0	0	*d*
h, $CH_3CH_2NH_2$	10.8	a	RT	1 h	0	100	0	>50/1[e]
i, $(CH_3)_2CHNH_2$	10.6	a	RT	18 h	8	40	0	5/1[e]
		c	RT	18 h	43	0	0	>1/25[e]
j, 	10.7	a	RT	18 h	9	79	0	9/1[e]
k, $(CH_3)_3CNH_2$	10.7	a	Reflux	4 h	65	0	0	>1/25[e]
		c	RT	1 day	59	0	0	>1/25[e]
l, $CH_3CH_2CH_2NH_2$	10.71	c	0	1 h	0	90	0	>50/1
m, $(CH_3)_2CHCH_2NH_2$	10.5	b	RT	18 h	4	95	0	23/1
n, $(CH_3)_3CCH_2NH_2$	10.2	b	RT	18 h	8	92	0	12/1
o, $PhNHCH_3$	4.84	a	Reflux	4 days	0	0	0	*e*
p, 	11.3	b	RT	4 h	56	0	0	>1/25[e]
q, 	11.1	b	RT	4 h	65	0	0	>1/25[e]

[a] pK_a values taken from D. D. Perrin, "Dissociation Constant of Organic Bases in Aqueous Solutions," Butterworth, London, 1965. [b] a = benzene; b = ether; c = neat; d = pyridine. [c] Interval to reaction termination by initiation of separation procedure. [d] 1a units not isolated as 5 were recovered as unreacted 1a. [e] 1a units not isolated as 4, 3, or 5 isolated as o-acetamidobenzoic acid, owing to reaction with water in postreaction separation. [f] $T_{1/2}$ = 1.3 days.

Table II. Characterization Data for Products as Noted in Table I

Product	Mp, °C	Key IR absorption bands, μ
Acetamidines, 3		
from amine **a**	115–116	3.2–4.4, 6.3
b	119–120	3.2–4.4, 6.3
c	136–137	3.0–4.0, 6.3
h	109–110	3.0–4.4, 6.3
i	167–168	3.4–4.1, 6.3
j	184–185	3.3–4.3, 6.3
l	117–119	3.2–4.3, 6.3
m	150–151	3.2–4.3, 6.3
n	170–171	3.2–4.3, 6.3
2-Methylquinazolones, 5		
from amine **a**	147–148	6.0, 6.3
b	151–152	5.9, 6.3
c	78–79	6.0, 6.3
d	240–241	6.0, 6.2
e	70–71	6.0, 6.2
h	79–80	6.0, 6.2
l	81–82	6.0, 6.3
m	71–72	6.0, 6.3
o-Acetamidobenzamide, 4		
from amine **a**	180–181	3.1, 6.0, 6.1, 6.2, 6.3, 6.5
f	83–86	2.9, 6.0, 6.2, 6.5
l	140–141	3.0, 5.9, 6.2, 6.3, 6.6
j	147–149	3.0, 6.0, 6.2, 6.3, 6.6
k	158–159	3.0, 3.1, 6.0, 6.2, 6.3, 6.6
m	158–159	3.0, 6.0, 6.2, 6.3, 6.5
n	164–165	3.0, 3.2, 6.0, 6.2, 6.3, 6.5
p	90–93	2.9, 6.1, 6.3, 6.6
q	86–88	2.9, 3.1, 6.0, 6.2, 6.6

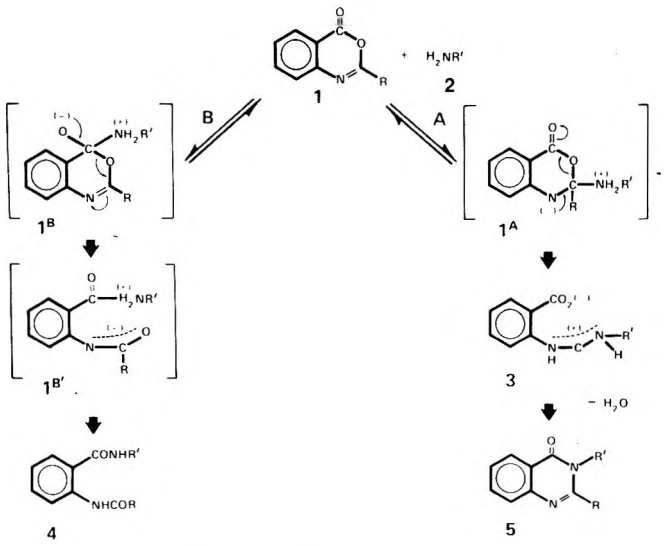
than the resultant electronic contribution to this site. The effect of steric hindrance on selectivity is particularly striking when the observed k_A/k_B values within the sets $H_{(3-n)}N(CH_3)_n$, $H_2NCH_{(3-n)}(CH_3)_n$, and $H_2NCH_2CH_{(3-n)}(CH_3)_n$ are examined as a function of n. Table I shows that crossover in selectivity from pathway A (i.e., k_A/k_B >50/1) to pathway B (i.e., k_A/k_B <1/25) within the first two sets of amines (**d, e, f,** and **g** and **e, h, i,** and **k**) occurs when n = 2 (i.e., with amines **f** and **i**). This is exactly where one would expect the effect of steric hindrance to manifest itself in both sets, according to the well-known results of Brown[6] and others,[7] who developed the now classical theories regarding steric effects in the reaction of amines with electrophilic reagents. The data in Table I also show that within the third set (amines **h, l, m,** and **n**), k_A/k_B decreases from >50/1 for **2h** to 12/1 for **2n**, but does not exhibit the crossover in selectivity noted in sets 1 and 2. This demonstrates that the effect due to the branching in an isopropyl or *tert*-butyl group is substantially reduced when this branched group is separated from the nucleophilic center by only one methylene unit. This is as would be expected if steric hindrance were the important factor that determines selectivity.

The k_A/k_B for cyclohexylamine (**2j**) in benzene (9/1) is somewhat higher than that for isopropylamine (**2i**) in benzene (5/1) and considerably higher than that of isopropylamine neat (<1/25), which is consistent with the expectation that steric hindrance should be less when the rotational freedom of the interfering components on the α-carbon atom is restrained by the ring structure. Such a change of selectivity does not occur, however, when the interfering groups are attached directly to the nucleophilic nitrogen atom instead of the α-carbon atom. Reaction with a secondary amine (**f, p,** and **q**) appears always to follow pathway B exclusively even when the secondary amine is a small heterocyclic compound such as pyrrolidine, **p,** or piperidine, **q.**

The observation that the rate of reaction of an amine with a given acylanthranil is a function of both the electronic and steric factors on the part of the amine whereas the selectivity is determined only by steric differences parallels the observations noted earlier regarding the reactions of acylanthranils with a given amine as described in the introduction. Both sets

of results can be rationalized on the basis that the transition states **1A** and **1B**, produced by addition of the amine to the 2 and 4 positions, respectively, of the acylanthranil, **1**, are in equilibrium with each other as illustrated in Scheme II. Al-

Scheme II



though addition to the more electrophilic center at the 4 position may occur faster than to the less electrophilic center at the 2 position, nothing fruitful occurs until either cyclic transition state **1A** or **1B** rearranges to give the more stable product **4** or **3**, respectively. These are the rate-determining steps to product formation.

It should be easier to transfer negative charge from N to O of **1A** via pathway A than from O to N of **1B** via pathway B, because O is more electronegative than N. Accordingly, pathway A occurs more readily than B, and we obtain the amidine product **3** preferentially. When the formation of **1A** is strongly inhibited or precluded by steric factors, owing to bulky substituents either on the amine or at the 2 position of the acylanthranil, then reaction is limited to the alternative pathway B which occurs more slowly. The overall rate of reaction via pathways A and/or B is of course affected by ring substituents that influence the electrophilicity at the 2 and 4 positions of the acylanthranil and by substituents that influence the nucleophilicity of the amine. These electronic rate considerations are modified in turn by steric factors that interfere with the approach of these mutually attractive centers. The selectivity, however, is determined by the competitive rate-limiting pathways to stable products. In the absence of steric hindrance, this occurs faster via the more electronically favored pathway A, whereas in the presence of steric hindrance it is limited to the less favored pathway B.

This sensitivity to steric hindrance, resulting in a readily detected selectivity in product distribution, makes available a useful "chemical" method to complement existing "physical" methods for detecting and measuring the influence of steric hindrance in the reactions of amines with electrophiles. The isolation of a quinazolone, **5** (or its precursor, **3**), as the major product indicates that the coreactant is a primary amine with no branching on the α-carbon atom, whereas the isolation of a *o*-acetamidobenzamide, **3**, as the major product indicates that the coreactant is either a secondary amine or a primary amine exhibiting steric hindrance.

In view of the foregoing discussion, the results obtained with ammonia (**2d**) are somewhat anomalous, since one would expect reaction to occur rapidly to give **3d** and/or **5d**, owing to the high pK_a and small size of the nucleophile. Although the product was **5d**, as expected, the rate of reaction in benzene and in ether saturated with anhydrous ammonia was so slow that conversion, which was first order with respect to acetylanthranil, was only half complete after 1.3 days. The product was removed periodically by filtration to follow the progress of reaction, and about a third of the starting material was recovered unchanged by evaporating the mother liquor to dryness after separation of the last product fraction at the end of the second day. Obviously more investigation is needed to understand why reaction with this nucleophile in nonpolar solvents is so unusually slow. This is particularly important, since some of the earlier investigators,[8] who used more polar solvents in their investigation, reported that o-acetamidobenzamide (**4d**) is the major product. Perhaps the solvent plays a more important role in determining reactivity with ammonia than with amines in general.

Experimental Section

The general procedure for reaction of acetylanthranil with an amine, the separation of the resultant product mixture into components, and the use of these data to calculate the corresponding reaction selectivity are described in earlier publications.[2-4] The percent acetylanthranil units isolated as the products **3**, **4**, and **5** for each of the amines in this investigation and the corresponding calculated reaction selectivity, k_A/k_B, are collected in Table I. The characterization data for the products listed in Table I are collected in Table II.

Registry No.—**1a**, 525-76-8; **2a**, 62-53-3; **2b**, 106-49-0; **2c**, 107-11-9; **2d**, 7664-41-7; **2e**, 74-89-5; **2f**, 124-40-3; **2g**, 75-50-3; **2h**, 75-04-7; **2i**, 75-31-0; **2j**, 108-91-8; **2k**, 75-64-9; **2l**, 107-10-8; **2m**, 78-81-9; **2n**, 5813-64-9; **2o**, 100-61-8; **2p**, 123-75-1; **2q**, 110-89-4; **3a**, 34264-61-4; **3b**, 58426-41-8; **3c**, 61041-27-6; **3h**, 61047-28-7; **3i**, 61047-29-8; **3j**, 61047-30-1; **3l**, 34242-12-1; **3m**, 34264-52-3; **3n**, 61047-31-2; **4a**, 54364-31-7; **4f**, 30367-86-3; **4i**, 61047-32-3; **4j**, 61047-33-4; **4k**, 61047-34-5; **4m**, 61047-35-6; **4n**, 61047-26-5; **4p**, 42103-90-2; **4q**, 42103-91-3; **5a**, 2385-23-1; **5b**, 22316-59-2; **5c**, 833-32-9; **5d**, 1769-24-0; **5e**, 1769-25-1; **5h**, 50677-59-3; **5l**, 50677-60-6; **5m**, 391-03-7.

Supplementary Material Available. More detailed procedures for reaction of **1** with the amines **2a–q**, and the characterization data of the products (12 pages). Ordering information is given on any current masthead page.

References and Notes

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(2) Part 1: L. A. Errede, *J. Org. Chem.*, **41**, 1763 (1976).
(3) Part 2: L. A. Errede, J. J. McBrady, and H. T. Oien, *J. Org. Chem.*, **41**, 1765 (1976).
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(5) M. T. Bogert, C. G. Amend, and V. J. Chambers, *J. Am. Chem. Soc.*, **32**, 1297 (1910).
(6) H. C. Brown and G. K. Barbaras, *J. Am. Chem. Soc.*, **75**, 6 (1953).
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(8) A. Weddige, *J. Prakt. Chem.*, **36**, 141 (1887).

Carbon-13 Magnetic Resonance Study of Solvent Stabilized Tautomerism in Pyrazoles

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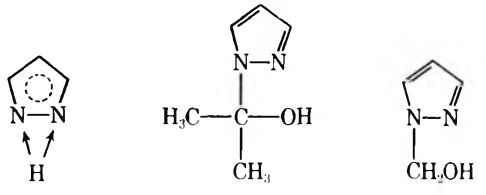
Received May 17, 1976

Using ^{13}C NMR methods, the interactions of pyrazole with an appropriate solvent (HMPT) allow the rate of tautomeric exchange to be reduced, and thereby the coalescence of the tautomeric lines appears at room or higher temperatures. Unlike acetone solutions no addition product was observed in the HMPT solutions. Instead, solvent stabilized tautomeric structures account for the increased activation energies between the alternative forms.

Tautomerism in pyrazoles has been studied by many techniques,[1] with special attention given to the problem with NMR.[2] These NMR experiments at ambient temperature failed to detect the two tautomers N(1)H and N(2)H since the processes were in the fast exchange limit on the NMR time scale for the solvents selected. Two studies[3,4] at lower temperatures have identified tautomeric forms of pyrazole, but in these instances the temperature had to be reduced below −100 °C. We wish to report that it is possible to reduce significantly the rate of tautomeric exchange in pyrazoles with an appropriate solvent and thereby preventing coalescence of the tautomeric lines at room temperature or even higher.

Three polar aprotic solvents with increasing basicity[5] (acetone, Me_2SO, and HMPT; $[(CH_3)_2N]_3PO$) were selected for the study. As reported earlier[3] extra lines were observed in acetone solution for the addition compound (**2**) of acetone with pyrazole (**1**). Furthermore, these lines do not exhibit the



1 **2** **3**

proper temperature dependence expected for rapidly interconverting tautomers. The presence of an additional compound was confirmed as the intensities of these lines depend on the amount of acetone in the mixtures. The structure proposed for **2** has also been corroborated by ^{13}C NMR data obtained for **3** (see Table I).

The solvation effect on the tautomeric exchange rate is demonstrated graphically in Figure 1. For pyrazole dissolved in HMPT the exchange rate is sufficiently slow at ambient temperature that separate signals are found for C-3,5. At their coalescence temperature (47 °C in a 1 M solution) a $\Delta G^{\ddagger}$ value of 15 kcal/mol can be evaluated from the corresponding exchange rate. At low temperature, the acetone/HMPT solution exhibits additional broadening while an intermediate exchange rate with a very broad line is found for the acetone/Me_2SO mixture. Such a broad line is also observed for a Me_2SO solution (1 M) at 6 °C, the temperature that may be reached before freezing the sample; at ambient temperature the NH exchange rate is in the fast exchange limit, as it was already observed by ^{14}N NMR.[6] Only the fast exchange limit is found for acetone solutions at corresponding temperatures. These results reflect the respective basicities of the solvents.

The data obtained for 3-methylpyrazole (**4**) exhibit the same characteristics as those of pyrazole (**1**). An addition complex is observed only when the solutions contain some acetone, and the exchange rate is reduced with increasing solvent basicity. For a 1 M solution in HMPT the signals of C-3, C-5, and CH_3 relative to the two tautomeric forms are well separated at −17 °C (see Figure 2). Both the C-3 and C-5 pairs of signals coalesce at approximately 30 °C and the CH_3 lines at 13 °C. Corresponding $\Delta G^{\ddagger}$ values of 14 kcal/mol are similar to those observed for pyrazole. Integration of the two CH_3 lines obtained without NOE effect by a gated decoupling experiment indicates essentially equal populations for the N(2)H form (about 54%) and the N(1)H form (about 46%). This result is at variance with LCAO–MO calculations,[7] which suggest the predominance of the N(2)H tautomer. It may be that the HMPT solvent interaction is invalidating the previous findings. No quantitative conclusions had been drawn from previous extensive NMR studies[2] of tautomerism in 3-methylpyrazole.

No addition complex was observed for 3,5-dimethylpyrazole (**5**) in acetone. This is consistent with earlier ^{1}H NMR data[3] and is probably due to steric interference. For a 1 M solution of **5** in HMPT, the methyl signals coalesce at 35 °C ($\Delta G^{\ddagger} \sim$ 15 kcal/mol) and the C-3,5 resonances have line widths of about 40 Hz. However, upon further reduction in temperature to −10 °C these signals narrow to 9 Hz.

The chemical shifts of the N(1)H and N(2)H tautomers of the several compounds are summarized in Table I. It is interesting to note that the difference of the chemical shifts of a carbon adjacent to a nitrogen in the two tautomers [$\delta_{N(1)H} - \delta_{N(2)H}$] decreases from 10.5 to 8.5 ppm when this carbon is substituted by a methyl group. In pyrazole and 3,5-dimethylpyrazole C-4 is not affected by the tautomeric process as might be expected from the identical structural relationship of C-4 and the labile proton in both the N(1)H and N(2)H structures. In the 3-methylpyrazole C-4 also exhibits a single line for both tautomeric structures. Again similarity of structural relationships could account for the single line, but the possibility of the tautomeric exchange not being slow enough even at low temperatures to reveal two very closely positioned lines cannot be ruled out.

It was not possible to observe separate tautomeric lines in the ^{1}H NMR spectra of pyrazole in HMPT even at −17 °C, the lowest temperature which could be reached without freezing the solution. This is in contrast with the data on 1,2,4-triazole in HMPT.[8] The absence of ^{1}H NMR lines due to addition products, however, confirms our conclusion that only tautomeric forms need to be considered for pyrazole in HMPT.

In concentrated solutions of pyrazole in an inert solvent, the solute mainly consists of hydrogen bonded pyrazole polymers.[4] Thus, the formation of hydrogen bond complexes between pyrazole and a basic solvent is competitive with this self-association process. The more basic the solvent is, the more the relative amount of complexes increases at the expense of polymerization as shown by IR data[9] and the ^{1}H NMR data in Table II. The downfield shift of the NH line

Table I. ^{13}C NMR Chemical Shifts[a] of Certain Pyrazoles

Compd	Concn, M	Temp, °C	Tautomeric form	C-3	C-4	C-5	3-CH_3	5-CH_3
1	2	−17	N(1)H	138.1_2	103.9_0	127.6_0		
			N(2)H	127.6_0	103.9_0	138.1_2		
2[b]	0.2	−17		139.2_2	(105.4)	126.5_5		
3[c]	1	35		139.9_3	106.3_6	129.7_5		
4	1	−17	N(1)H	$146.C_5$	103.1_7	128.3_4	13.6_8	
			N(2)M	137.1_8	103.1_7	138.5_9	10.5_5	
5	1	−10	N(1)H	146.5_3	102.6_7	138.0_3	13.8_4[d]	10.6_1[d]
			N(2)H	138.03	102.6_7	146.5_3	10.6_1[d]	13.8_4[d]

[a] Chemical shifts are in parts per million with respect to Me_4Si. Solvent is HMPT for **1**, **4**, and **5** and acetone for **2** and **3**. [b] $\delta_{C(CH_3)_2}$ 87.0_7 ppm. [c] δ_{CH_2} 74.7_1 ppm. [d] At −10 °C, these signals are not totally separated.

Table II. ^1H NMR Chemical Shifts[a] of Pyrazole in Some Polar Aprotic Basic Solvents

Solvent	H-4	H-3, H-5	NH
Acetone	6.27	7.61	12.26
Me_2SO	6.26	7.61	12.82
HMPT	6.16	7.48	13.74

[a] The chemical shifts are in parts per million with respect to Me_4Si. Pyrazole concentration 1 M. T = 27 °C.

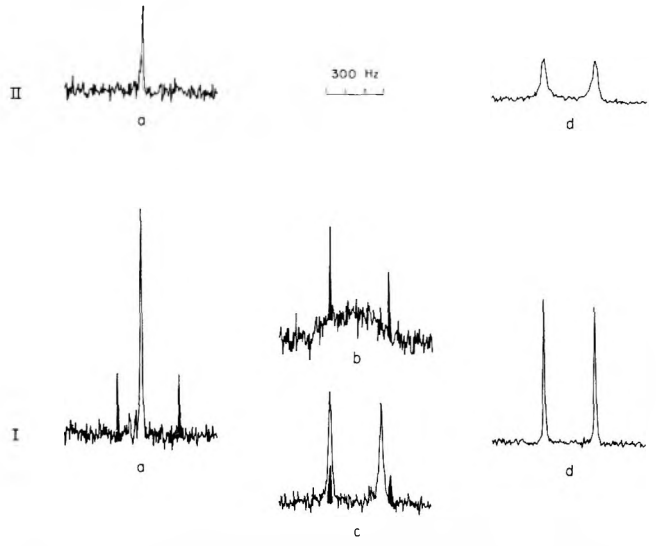


Figure 1. The ^{13}C NMR signals of carbons 3 and 5 of pyrazole in various solvents: Ia, IIa, 1 M in acetone; Ib, 1 M in 1/1 acetone/Me_2SO; Ic, 1 M in 1/1 acetone/HMPT; and Id, IID, 2 M in HMPT. The temperature was 29 °C for IIa and 33 °C for IId; all I spectra were recorded at −17 °C. Addition products with acetone indicated by darkened peaks.

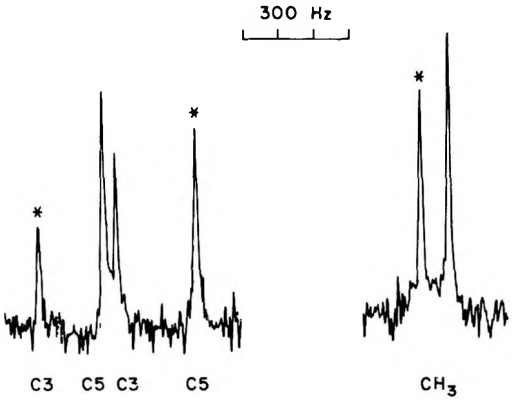


Figure 2. The ^{13}C NMR signals of carbons 3, 5, and methyl group of 3-methylpyrazole, 1 M in HMPT, at −17 °C. Lines from the N(1)H tautomer are indicated with an asterisk.

increases with the basicity of the solvent. In light of these data it is also interesting to compare the $\Delta G^{\ddagger}$ values obtained at 47 °C for pyrazole in HMPT solution (~15 kcal/mol) and in ether/tetrahydrofuran mixture (~11 kcal/mol, evaluated from data in ref 4). As competing solvation processes can be expected to lower the average energy of the solvated pyrazoles in more basic solvent, the increase in $\Delta G^{\ddagger}$ in HMPT is compatible with both the IR and ^1H NMR studies. The solvation process will also change the averaged energy of the activated complex. Unfortunately, little is known about such effects and therefore the above interpretation of the significant effect of solvent upon $\Delta G^{\ddagger}$ must be considered to be tentative. The common practice[10] in ^1H NMR to use Me_2SO to slow down exchange of –OH protons in alcohols and thus observe coupling to adjacent protons is based on this same solvation process: bonding of a labile hydrogen to a polar aprotic basic solvent.

It has been shown that hexamethylphosphoric triamide (HMPT) is a very effective solvent for studying tautomerism by ^{13}C NMR spectroscopy in a more convenient and accessible range of temperatures. However, according to a recent report,[11] HMPT appears to be toxic and must be handled with appropriate precaution. This ability to determine the chemical shifts of the different tautomeric forms allows avoidance of the cumbersome and indirect method of using model compounds to estimate chemical shifts from which tautomeric populations can be calculated,[12] and tautomeric equilibrium constants determined.

Experimental Section

Compounds were obtained from commercial sources except for 1-hydroxymethylpyrazole (**3**), which was synthesized according to published procedure.[13] The samples were dissolved in dry spectroquality solvents. The ^1H NMR spectra were recorded on a Varian HA-100 spectrometer and the ^{13}C spectra on a Varian XL-100-15-FT except for data on **3**, which were obtained on a Varian CFT-20.

Acknowledgment. The authors wish to thank Dr. L. B. Townsend and Dr. R. P. Panzica for highly purified samples of pyrazole and HMPT, and Dr. M. F. Lautié for the synthesis of 1-hydroxymethylpyrazole. This research was supported by the U.S. Public Health Service under Grant RR00574-05 from the National Institutes of Health.

Registry No.—**1**, 288-13-1; **2**, 60803-64-7; **3**, 1120-82-7; **4**, 1453-58-3; **5**, 67-51-6.

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^1H and ^{13}C Nuclear Magnetic Resonance Spectroscopic Study of 6,6-Disubstituted Fulvenium Ions[1]

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Received August 30, 1976

A series of 6,6-disubstituted fulvenes including 6-cyclopropyl-6-methylfulvene (**5**), 6-cyclopropyl-6-phenylfulvene (**6**), 6,6-(2-norbornylidene)fulvene (**7**), and 6,6-admantylidenefulvene (**8**) were prepared by the condensation of cyclopentadiene with the corresponding ketones. Precursor fulvenes were protonated to give the corresponding fulvenium ions under superacidic conditions at low temperatures. Protonation takes place exclusively at the C_2 position of the fulvene ring in accord with the calculated electron density distributions. The effects of substituent at C_6 on charge distributions in the studied fulvenium ions are discussed with regard to their respective ^1H and ^{13}C NMR data.

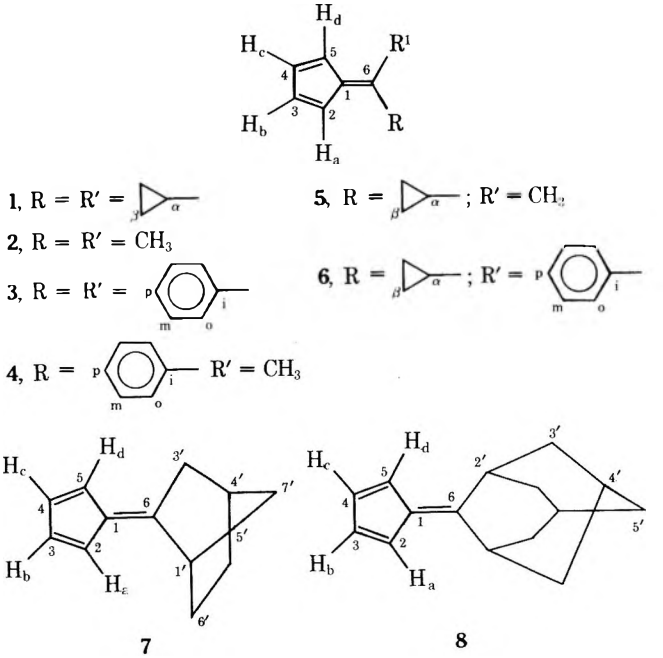
Fulvenes are highly colored compounds with considerable chemical reactivity, isomeric with benzenes, but with properties intermediate between those of aromatic and olefinic systems. Synthesis and properties of fulvenes have been reviewed.[2] For theoretical studies, fulvenes have been of great interest because they represent relatively simple nonalternate hydrocarbons which are readily adaptable to quantum mechanical treatment by either simple valence bond or molecular orbital methods. Thus, for example, the rather large dipole moments found for many 6,6-disubstituted fulvenes have been accounted for by several refinements of HMO type calculations of the parent fulvene.[3-5] Recently more sophisticated calculations were reported on fulvalene ions.[6] These calculations agree on the point that the dipole moment of the fulvenes is a direct consequence of their electronic structure and the moment is directed with its negative pole toward the ring.

Fulvenes undergo a variety of reactions,[2d] but relatively little is known about their electrophilic reactions.[2c] Such reactions, however, are reported on heptafulvenes.[7] In continuation of our studies on the carbocationic intermediates of electrophilic reactions and particularly on the nature of substituent effects adjacent to carbocationic centers, we wish to report the study, based on ^1H and ^{13}C NMR spectroscopic data, of the carbocations obtained upon protonation of 6,6-disubstituted fulvenes in superacidic media.

Results

6,6-Dicyclopropylfulvene (**1**), 6,6-dimethylfulvene (**2**), 6,6-diphenylfulvene (**3**), and 6-methyl-6-phenylfulvene (**4**) were prepared by reported methods.[8] 6-Cyclopropyl-6-methylfulvene (**5**), 6-cyclopropyl-6-phenylfulvene (**6**), 6,6-(2-norbornylidene)fulvene (**7**), and 6,6-adamantylidenefulvene (**8**) were prepared by the condensation of cyclopentadiene with the corresponding ketones in the presence of sodium ethoxide in ethanol.

Protonation of studied fulvenes was carried out in FSO_3H/SO_2ClF or SO_2F_2 at −78 or −120 °C (using an ethanol/liquid nitrogen bath), respectively. Precursors **2**, **5**, and



7 gave only polymeric materials with all-acid systems such as HF/SbF_5, FSO_3H/SbF_5, and HF/BF_3. Precursors **1**, **3**, **4**, **6**, and **8** gave clean solutions of the resulting ions and the ^1H NMR spectrum of the ion obtained from **1** is shown in Figure 1 together with the ^{13}C NMR spectrum of the precursor **7**. The ^1H and ^{13}C NMR spectra of the ion generated from precursor **8** as representative are shown in Figure 2. The ^1H NMR shifts of the ions obtained are tabulated in Table I. The ^{13}C NMR data of the ions as well as their precursors along with the assignments are listed in Tables II and III, respectively.

Discussion

The bonding nature of fulvenes can be qualitatively described in terms of the mesomeric covalent structure **9** and the

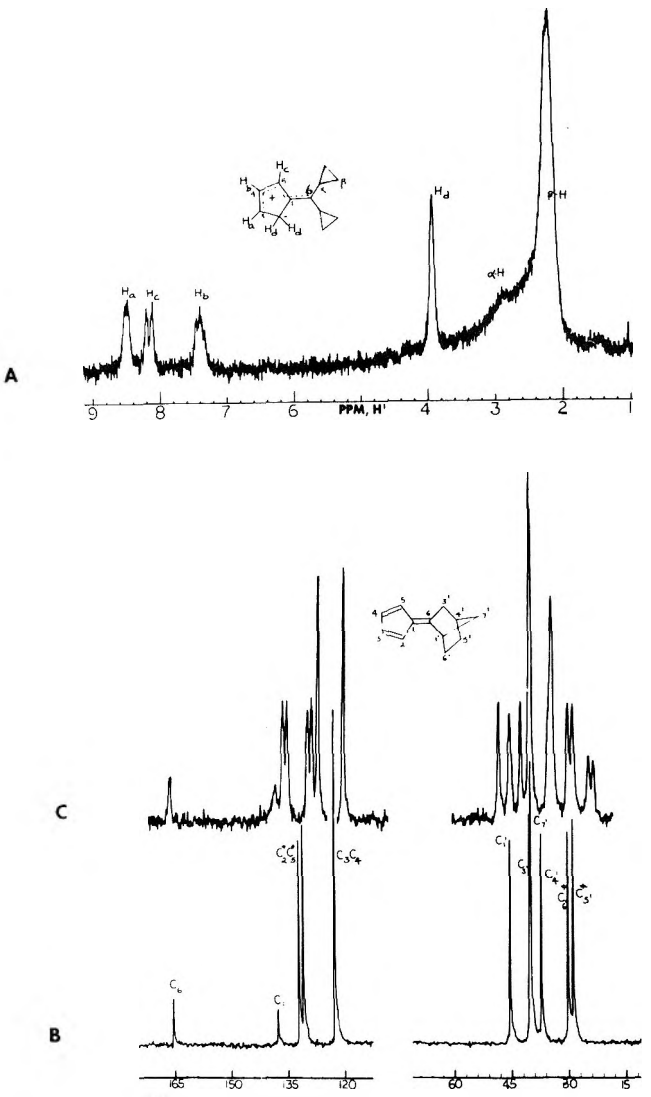
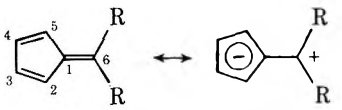


Figure 1. (A) ^{1}H NMR spectrum of ion **16** in FSO_3H/SO_2F_2 at −70 °C. (B, C) ^{13}C NMR spectrum of precursor **7** in $CDCl_3$ at 37 °C: B, proton noise decoupled; C, proton noise coupled.

polar structure **10**. The contribution of the dipolar structure can be assessed from the dipole moments, UV absorptions, and NMR shifts. Further, the contribution of **10** is also de-



9 **10**

pendent on the nature of the substituents on the exocyclic α-carbon atom C_6. The effect of substituents on the tendency of aromatization of the cross-conjugated system can also be studied by varying substituents. It has been reported that fulvenes undergo Diels–Alder reactions, both as dienes and as dienophiles, add halogens, and form peroxides, all characteristic olefinic properties.[2c,d] Fulvenes as cyclic conjugated isomers of benzenoid compounds also undergo substitution reactions. Nucleophilic reagents such as alkyllithiums attack fulvenes at the exocyclic carbon atom C_6 to form alkylcyclopentadienyl compounds. The driving force for this reaction is the gain in resonance energy originating from the transition of the cross-conjugated system to a cyclic Hückeloid 6π-aromatic system.

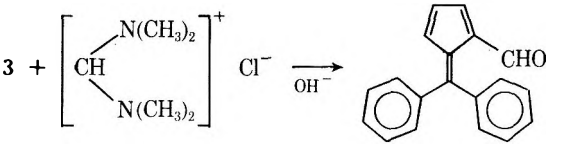
Electrophilic reactions of fulvenes have not yet attracted much attention. However, fulvenes should be as susceptible to electrophilic reactions as other nonbenzenoid cyclic con-

Table I. ^{1}H NMR Data[a] of Fulvenium Ions in SO_2ClF or SO_2F_2 Solutions at −80 or −70 °C

Ions	Shifts
16	8.5 (b, 1 H, H_a), 8.2 (d, 1 H, H_c, $J_{H_cH_b}$ or $J_{H_aH_b}$ = 12 Hz), 7.4 (b, 1 H, H_b), 3.9 (broad singlet, 2 H, H_d), 2.0–3.0 (b, 10 H, Cpr protons)
15	8.8–9.1 (m, 2 H, H_a and H_c), 7.7–8.3 (m, 11 H, aromatic protons), 4.3 (s, 2 H, H_d)
18	8.8–9.1 (b, 2 H, H_a and H_c), 7.7–8.3 (b, 6 H, H_b and aromatic protons), 4.2 (s, 2 H, H_d), 3.2 (s, 3 H, CH_3)
17	9.9 (b, 1 H, H_a), 9.1 (d, 1 H, H_c, $J_{H_cH_b}$ or $J_{H_aH_b}$ = 8 Hz), 7.8 (b, 1 H, H_b), 4.2 (b, 3 H, H_d and proton at 2′), 3.6 (b, 1 H, proton at 2′), 1.9–2.8 (broad multiplet, 12 H, protons at 3′, 4′, and 5′)
19	8.6 (d, 1 H, H_a, $J_{H_aH_b}$ or $J_{H_bH_c}$ = 8 Hz), 8.2 (b, 1 H, H_c), 7.2–7.9 (broad multiplet, 6 H, H_b and aromatic protons), 4.2 (broad singlet, 2 H, H_d), 2.9–3.3 (m, 1 H, CH of Cpr), 1.9–2.5 (m, 4 H, CH_2 of Cpr)

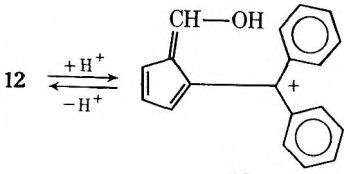
[a] Shifts are in δ values from external capillary Me_4Si.

jugated compounds. **3** is known to undergo formylation with ease and in high yield by treatment with Wilsmeier's complex **11**.[9,10] In accordance with theoretical electron density distri-



11 **12**

bution calculations,[11] the electrophilic reagent attacks at C_2 of the cross-conjugated system. The fulvenaldehyde **12** undergoes facile reversible protonation to give the conjugated acid **13**.[2c] There was only a reference to an otherwise unpub-



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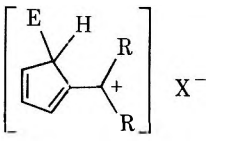
lished Ph.D. Thesis[12] by Hafner[2c] to have achieved protonation (as well as alkylation and nitrosation) of fulvenes **2** and **3** to corresponding σ complexes of type **14** which were stable



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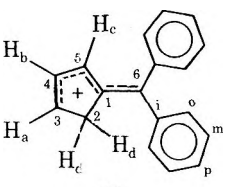
only below −80 °C. For a systematic study of the protonation of fulvenes under stable ion conditions with ^{1}H and ^{13}C NMR spectroscopy, we synthesized a series of 6,6-disubstituted fulvenes and carried out their protonation under superacid conditions at low temperatures.

Fulvene **3** underwent facile protonation in FSO_3H/SO_2ClF at −78 °C at C_2 to give fulvenium ion **15**. The ion is stable up



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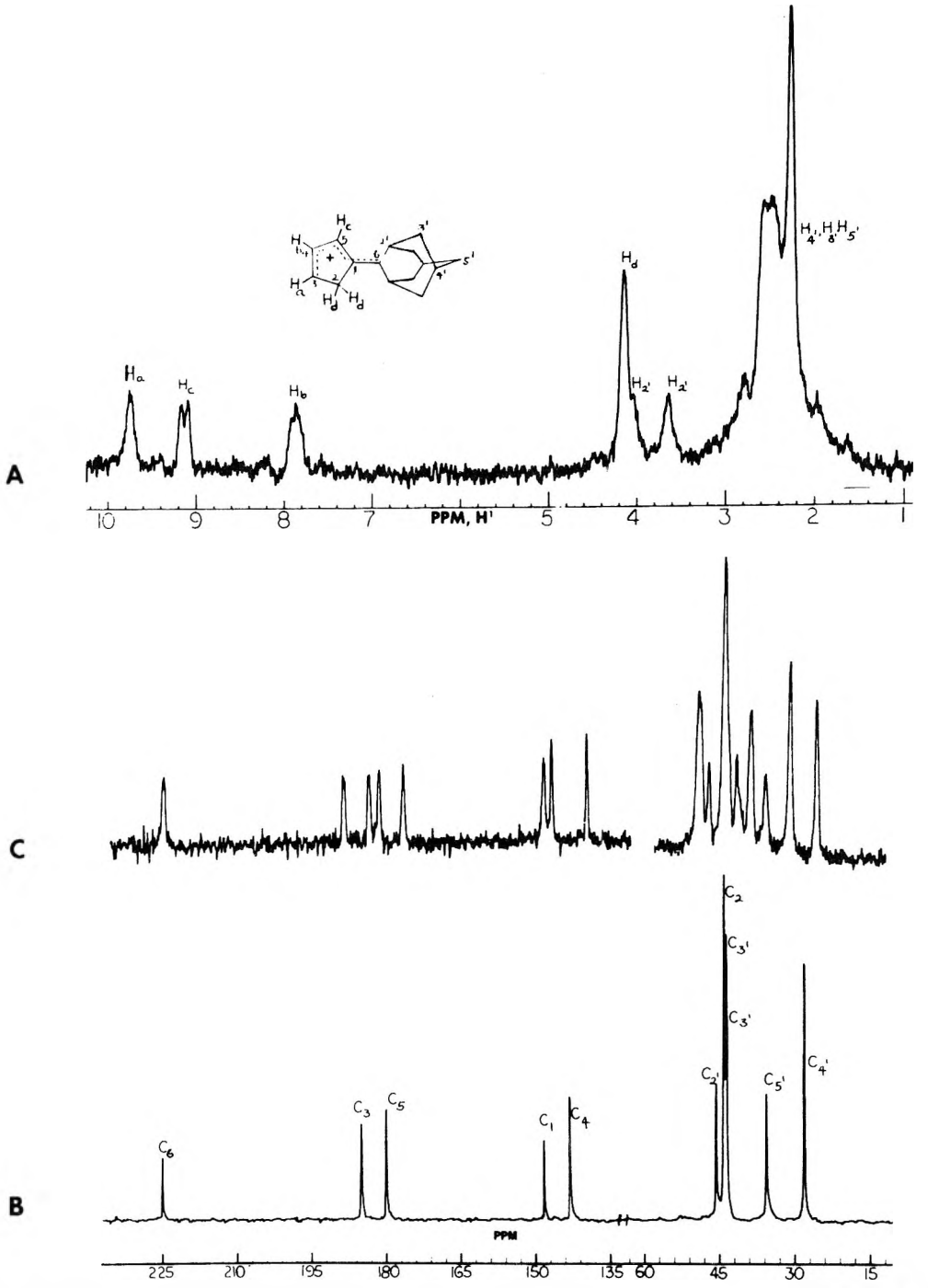

Figure 2. (A) ^1H NMR spectrum of ion **17** in FSO_3H/SO_2ClF at −70 °C. (B, C) ^{13}C NMR spectrum of ion **17** in FSO_3H/SO_2ClF at −70 °C: B, proton noise decoupled; C, proton noise coupled.

to −40 °C. In the ^1H NMR spectrum H_a and H_c protons absorb around δ 8.8–9.1 and H_b absorbs along with the aromatic protons around δ 7.7–8.3, showing a shift pattern characteristic of an extended conjugated allyl cationic system. The H_d protons absorb at δ 4.3. In the ^{13}C NMR spectrum the most deshielded C_6 carbon absorbs at $\delta^{13}C$ 189.9 followed by $\delta^{13}C_3$ 182.5, $\delta^{13}C_5$ 179.2, $\delta^{13}C_1$ 152.1, and $\delta^{13}C_4$ 142.7. This indicates that the charge is highly dispersed along the C_3 to C_6 carbon centers. The para carbons of the phenyl rings are deshielded as compared to the precursor and both the phenyl rings are magnetically equivalent. In the ^{13}C NMR spectrum of the precursor the C_6 carbon is deshielded over the C_1 carbon by 7.9 ppm, which justifies the dipolar nature of the C_1–C_6 bond.

Fulvene **1** was also protonated in FSO_3H/SO_2F_2 at −120 °C to give the C_2 protonated fulvenium ion **16**, which is stable up to −40 °C (in a sealed NMR tube). In the ^1H NMR spectrum of the ion at −70 °C, H_a absorbed at δ 8.5, H_c at δ 8.2 with a coupling of $J_{H_cH_b}$ or $J_{H_aH_b}$ = 12 Hz with the neighboring proton H_b. H_b absorbs at δ 7.4 as a multiplet. The aliphatic methylene proton absorption is at δ 3.9 as a singlet, which is rather shielded when compared to that in ion **15**. The cyclopropyl protons (both α and β) absorb around δ 2.0–3.0. The spectrum is shown in Figure 1. The ^1H shifts clearly indicate the formation of the ion **16** with maximum charge centered

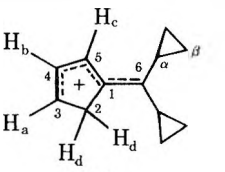

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Table II. ^{13}C NMR Shifts[a] of Fulvenium Ions in FSO_3H/SO_2ClF or SO_2F_2 Solutions at −70 or −80 °C

Ions	C_1	C_2	C_3	C_4	C_5	C_6	Substituents at C_6
17	148.7	44.4	185.5	143.6	180.5	225.3	$C_{2'}$ 45.7, 44.4; $C_{3'}$ 43.8, 43.6; $C_{5'}$ 35.7; $C_{4'}$ 28.2
16	143.0	44.6	165.2	138.6	164.3	224.8	C_α 31.9, 21.7; C_β 32.4, 22.2
19	155.2	42.8	179.2	140.6	175.7	207.1	C_i 132.1; C_p 132.1; C_o 128.8; C_m 128.0; C_α 31.4; C_β 25.2
18	154.5	49.2	186.3	143.8	180.9	196.3	C_i 139.9; C_p 138.6; C_o 133.6; C_n 130.1; CH_3 26.6
15	152.1	47.9	182.5	142.7	179.2	189.1	C_p 140.5; C_i 139.1; C_o 137.9, 136.8; C_m 129.8

[a] Shifts are in parts per million from external capillary Me_4Si.

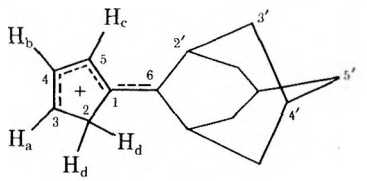
Table III. ^{13}C NMR Shifts[a] of Precursor Fulvenes in $CDCl_3$ at 37 °C

Fulvenes	C_1	C_2	C_3	C_4	C_5	C_6	Subtituents at C_6
8	137.1	131.6	120.5	120.5	131.6	167.3	$C_{2'}$ 41.3; $C_{1'}$ 40.9; $C_{4'}$ 38.4; $C_{3'}$ 29.4
7	135.6	129.9[c]	120.5	120.5	128.8[c]	163.3	$C_{1'}$ 43.9; $C_{3'}$ 38.8; $C_{7'}$ 38.4; $C_{4'}$ 35.7; $C_{6'}$ 28.7[c]; $C_{5'}$ 27.3[c]
1	144.9	131.2	121.7	121.7	131.2	160.4	C_α 16.3; C_β 8.8
6	145.0	130.6[b]	124.5[c]	121.5[c]	128.6[b]	157.0	C_i 138.2; C_p 133.0; C_o 130.6; C_m 128.2; C_α 17.9; C_β 8.0
5	143.9	131.0[c]	121.3[b]	121.0[b]	130.3[c]	155.4	CH_3 15.5; C_α 18.4; C_β 8.4
3	144.9	129.6	125.4	125.4	129.7	152.8	C_i 142.3; C_p 133.4; C_o 133.1; C_m 128.7
2	132.7	131.3	121.3	121.3	131.3	139.3	CH_3 23.4
4	144.6	130.3[b]	124.8	122.2	129.3	150.7	C_i 143.1; C_p 133.0; C_o 132.6; C_m 129.0; CH_3 23.6

[a] Shifts are in parts per million from external capillary Me_4Si. [b,c] Assignment interchangeable.

at C_6. The ^{13}C NMR spectrum also substantiates this conclusion. In the ^{13}C NMR spectrum C_6 absorbs at $\delta^{13}C$ 224.8 followed by $\delta^{13}C_3$ 165.2, $\delta^{13}C_5$ 164.3, $\delta^{13}C_1$ 143.0, and $\delta^{13}C_4$ 138.5. C_6 is substantially deshielded as compared to previously discussed ion **15** even if one takes into account the unusually large neighboring group deshielding effect by the cyclopropyl groups adjacent to a carbocationic center.[14] The C_α and C_β carbons of the two cyclopropyl groups show nonequivalence and are also substantially deshielded compared to the precursor **1**. The corresponding ^{13}C NMR shifts are $\delta^{13}C_\alpha$ 31.9 and 21.7 and $\delta^{13}C_\beta$ 32.4 and 22.4, respectively. The large difference within the C_α and C_β shifts indicates that one of the cyclopropyl groups is delocalizing charge better than the other. In the ^{13}C NMR spectrum of **1** C_α absorbs at $\delta^{13}C$ 16.3 and C_β at $\delta^{13}C$ 8.8. The difference between C_6 and C_1 shifts ($\delta^{13}C_6 - \delta^{13}C_1 = 15.6$) demonstrates the increased dipolar nature of **1** over **3**, which is indeed the case.[8b]

The symmetrical and highly hindered fulvene **8** in FSO_3H/SO_2ClF at −78 °C gave fulvenium ion **17**. The ^1H and



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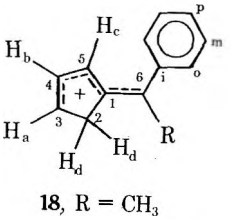
^{13}C NMR spectra of the ion **17** are shown in Figure 2. In the ^1H NMR spectrum H_a absorbs at δ 9.9, H_c at δ 9.1 with a coupling $J_{H_cH_b}$ or $J_{H_aH_b}$ = 8 Hz, and H_b at δ 7.8. The methylene protons absorb at δ 4.2. The shift pattern clearly shows that more positive charge is present in the five-membered ring (along C_3 to C_1) than in the previously discussed ions **15** and **16**. The two bridgehead protons $H_{2'}$ are also substantially deshielded compared with the corresponding shifts of the precursor **8** (absorptions at δ 4.2 and 3.2, respectively). The ^{13}C NMR spectrum shows C_6 absorption at $\delta^{13}C$ 225.3 followed by $\delta^{13}C_3$ 185.5, $\delta^{13}C_5$ 180.5, $\delta^{13}C_1$ 148.7, and $\delta^{13}C_4$ 143.6. The large deshielding of C_6 may also be due to the rigidity of the adamantyl ring skeleton. C_3 and C_5 centers also show considerable charge delocalization as compared to ions **15** and **16**. In the ^{13}C NMR spectrum of the precursor **8**, C_6 is substantially deshielded compared to C_1, the shift difference being $\delta^{13}C_6 - \delta^{13}C_1 = 30.2$, which also demonstrates the rigidity of the adamantane cage system as well as the dipolar nature of the species.

Fulvenes **4** and **6**, being unsymmetrical, can undergo protonation at either C_2 or C_5 to give rise to two different ions. We protonated the two precursors **4** and **6** in FSO_3H/SO_2ClF at −120 °C and obtained only a single ion in each case; we tentatively assign to the ions structures **18** and **19**, respectively.



18, R = CH_3

19, R =

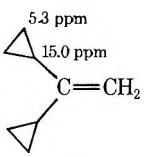
However, our data do not allow us to determine the site of protonation with certainty. The two different ionic species formed by the protonation at C_2 or C_5 can become equivalent if the barrier of rotation along the C_1–C_6 bond becomes low due to charge dispersion. In the ^1H NMR spectrum of the ion **18**, the H_a and H_c protons absorb around δ 8.8–9.1; H_b absorbs along with aromatic protons at δ 8.3. The methylene absorption occurs at δ 4.2 and the methyl absorption at δ 3.2. In the

precursor **4** the methyl group absorbs at δ 1.85. This shows that substantial positive charge is present at C_6. In the ^{13}C NMR spectrum C_6 absorbs at $\delta^{13}C$ 196.3 followed by $\delta^{13}C_3$ 186.3, $\delta^{13}C_5$ 180.9, $\delta^{13}C_1$ 154.5, and $\delta^{13}C_4$ 143.8. The aromatic carbons (ortho and para) are notably deshielded as compared to those of the corresponding shifts in precursor **4**, indicating greater participation of the phenyl ring to share the positive charge. Considerable charge is also dispersed over the C_3–C_5 centers as indicated by their ^{13}C NMR shifts.

Fulvenium ion **19** shows particularly interesting features. In its ^1H NMR spectrum, H_a absorbs at δ 8.6, H_c at δ 8.2, and H_b absorbs along with aromatic protons at δ 7.2–7.9. The methylene absorption (H_d) is at δ 4.2. The α and β protons of the cyclopropyl group are also deshielded compared to the precursor, indicating substantial positive charge in the three-membered ring. In the ^{13}C NMR spectrum C_6 absorbs at $\delta^{13}C$ 207.1, falling in between the C_6 shifts of ions **15** and **16**, indicating a characteristic shift pattern of the effect of cyclopropyl substitution over that of phenyl. A similar shift pattern is observed in many cyclopropyl, phenyl substituted carbinyl cations.[15] The C_3 carbon absorbs at $\delta^{13}C$ 179.2 followed by $\delta^{13}C_5$ 175.7, $\delta^{13}C_1$ 155.2, and $\delta^{13}C_4$ 140.5. These shifts also fall midway between the shifts of ions **15** and **16**. The cyclopropyl carbons (both α and β) are substantially deshielded as compared to precursor **6** shifts, i.e., $\delta^{13}C_\alpha$ 31.40 and $\delta^{13}C_\beta$ 25.2. It is also interesting to note that little change is observed with aromatic carbon shifts over those of the precursor shifts. This further demonstrates the superiority of cyclopropyl over phenyl groups to share the positive charge in these extended conjugated systems.

Comparing the fulvenium ions **15**, **16**, **17**, **18**, and **19**, it is evident that positive charge distribution over the C_3–C_6 centers is considerably altered depending upon the nature of the substituents at C_6. Cyclopropyl groups at C_6 tend to decrease the charge over the C_3–C_5 positions with a subsequent smaller effect by phenyl and methyl groups. In these extended conjugated cationic systems the cyclopropyl group delocalizes charge better than a phenyl group which in turn is much more effective than a methyl group. The same trend was also observed in our previous studies on allylic cation systems.[14] In the highly strained adamantylidene substituent in **17**, the positive charge is highly dispersed over C_3–C_5 centers. Fulvenes **2**, **5**, and **7** did not give identifiable ions upon protonation in any of the superacidic systems, i.e., FSO_3H, FSO_3H + SbF_5, HF/SbF_5, HF, HF + BF_3/SO_2ClF, or SO_2F_2, even at −120 °C. They obviously undergo protonation, but tend to react further with excess, yet unprotonated, precursor to give rise to polymeric products.

The ^{13}C NMR spectral data of neutral fulvene precursors **1**–**8** are tabulated in Table III. The difference in the C_6 and C_1 shifts demonstrates the effect of substituents as well as the dipolar nature of the precursors. The difference in C_6–C_1 shifts from **1** to **8** are 15.6, 6.6, 7.9, 6.0, 11.4, 13.0, 27.7, and 30.2 ppm, respectively. The dipolar nature order can be estimated as **8** > **7** > **1** > **6** > **5** > **3** > **2** > **4**. The ^{13}C NMR spectrum of the precursor **7**, as representative, is shown in Figure 1. In the ^{13}C NMR spectra of fulvenes **4**, **5**, and **6** all the fulvene ring carbons are nonequivalent, which is as expected. In the case of **7** only C_2 and C_5 are nonequivalent, whereas C_3 and C_4 are equivalent. The dipolar nature can also be demonstrated by comparing ^{13}C NMR shifts to that of 1,1-disubstituted ethylenes. For example, when comparing cyclopropyl α and β carbon shifts of fulvene **1** to that of 1,1-dicyclopropylethylene **20**, it is found that α carbon is deshielded by 1.3 ppm and the β carbon by 3.6 ppm. This indicates the increased dipolar nature of **1** over **20**. This effect was also demonstrated to some degree by the ^1H NMR shifts by Linde and co-workers.[8b]



20

Conclusions

Our study on fulvenium ions shows that protonation occurs exclusively at the C_2 position of the fulvene ring in accordance with calculated electron density distributions. The charge dispersion pattern is governed by the nature of the substituents at C_6 position. Data also show that in the fulvenium ions the ability of neighboring substituent groups adjacent to carbenium center in delocalizing positive charge is c-C_3H_5 > Ph > CH_3 in accordance with previous studies.[14,15] The increase in the C_1–C_6 carbon chemical shift difference in the neutral precursors indicate their increased dipolar nature.

Experimental Section

Fulvenes **1**, **2**, **3**, and **4** were prepared by reported methods.[8]

6-Cyclopropyl-6-methylfulvene (5). To a stirred solution of 6.9 g (0.3 mol) of sodium in 75 ml of absolute ethanol under dry nitrogen gas was slowly added a mixture of freshly distilled cyclopentadiene (13.2 g, 0.2 mol) and 16.8 g of cyclopropyl methyl ketone (0.2 mol). After the mixture was stirred for 8 h at room temperature, it was quenched with crushed ice; the product was extracted with methylene chloride, the organic layer washed with water and dried over anhydrous $MgSO_4$, and the solvent evaporated. The yellow liquid obtained was immediately distilled under vacuum using a 15-cm fractionating column. The fraction distilling at 68 °C (2 mm) was collected, 7.2 g (27.2%), air-sensitive yellow liquid (stable at −78 °C for months). The infrared spectrum (neat, cm^{-1}) showed $\delta_{C=C}$ at 1630 (s), 1615 cm^{-1} (m). The UV spectrum (cyclohexane) showed maxima at 284 nm (log ϵ 4.31) and 367.5 (2.59). The mass spectrum showed *m/e* 132 (100, M^+). The ^1H NMR spectrum (60 MHz, $CDCl_3$, from external capillary Me_4Si, 37 °C) showed absorptions at δ 5.6–5.9 (s, b, 4 H, H_a, H_b, H_c, and H_d), 1.9–2.3 (m, 1 H, CH of Cpr), 1.65 (s, 3 H, CH_3), 0.7–0.95 (unsymmetric doublet, 4 H, CH_2 of Cpr).

Anal. Calcd for $C_{10}H_{12}$: C, 90.90; H, 9.09. Found: C, 90.89; H, 9.04.

6-Phenyl-6-cyclopropylfulvene (6). The reaction was carried out as described previously with sodium (4.6 g, 0.20 mol), absolute ethanol (60 ml), freshly distilled cyclopentadiene (6.6 g, 0.1 mol), and phenyl cyclopropyl ketone (14.6 g, 0.1 mol). The mixture was stirred for 10 h and then worked up with methylene chloride. The product was distilled under vacuum and the dark orange-yellow liquid distilling at 111–112 °C (0.65 mm) collected, 8.6 g (43%), air-sensitive liquid. The infrared spectrum (neat) showed $\nu_{C=C}$ 1600 (m), 1610 cm^{-1} (s). The UV spectrum (cyclohexane) showed maxima at 287.5 nm (log ϵ 4.35), 370 (2.60). The mass spectrum showed *m/e* 194 (100, M^+). The ^1H NMR spectrum (60 MHz, $CDCl_3$, from external capillary Me_4Si, 37 °C) showed peaks at δ 7.3–7.7 (b, 5 H, aromatic protons), 7.1 (m, 1 H, H_a or H_d), 6.9 (m, 1 H, H_a or H_d), 6.5 (m, 1 H, H_b or H_c), 6.0 (m, 1 H, H_b or H_c), 4.5–4.9 (m, 1 H, CH of Cpr), and 0.8–1.3 (m, 4 H, CH_2 of Cpr).

Anal. Calcd for $C_{15}H_{14}$: C, 92.78; H, 7.21. Found: C, 92.76; H, 7.24.

6,6-Adamantylidenefulvene (8). To a solution of sodium metal (4.6 g, 0.2 mol) in 75 ml of absolute ethanol under dry nitrogen, 6.6 g (0.1 mol) of freshly distilled cyclopentadiene was added followed by immediate addition of adamantanone (15.0 g, 0.1 mol). Stirring was continued at room temperature for 3 h and thereafter the reaction mixture was very carefully quenched with crushed ice, the product extracted with methylene chloride and dried, and the solvent evaporated. The yellow solid obtained was recrystallized from hot ethanol, 16.0 g (81.8%), mp 91–92 °C. The infrared spectrum (CCl_4) showed $\nu_{C=C}$ 1638 cm^{-1} (s). The UV spectrum (cyclohexane) showed maxima at 273.0 nm (log ϵ 4.34), 281.5 (4.32), and 360.0 (2.52) and a shoulder at 290.5 nm. The mass spectrum showed *m/e* 198 (100, M^+). The ^1H NMR spectrum (60 MHz, $CDCl_3$ from external capillary Me_4Si, 37 °C) showed absorptions at δ 7.93 (s, 4 H, ring protons), 2.67 (2 H, protons at 2′ of adamantane), 1.07–1.57 (b, 12 H, protons of adamantane at 3′, 4′, and 5′).

Anal. Calcd for $C_{15}H_{18}$: C, 90.90; H, 9.09. Found: C, 90.88; H, 8.97.

6,6-(2-Norbornylidene)fulvene (7). To a stirred solution of sodium metal (2.3 g, 0.1 mol) in 40 ml of absolute ethanol under nitrogen, 3.3 g (0.05 mol) of freshly distilled cyclopentadiene was added followed by 5.5 g (0.05 mol) of norcamphor. The stirring was continued for 14 h and the reaction mixture was worked up as described earlier. The product was fractionated under vacuum. The yellow, oily fraction distilling at 80–81 °C (0.5 mm) was collected, 4.2 g (53%), air-sensitive liquid. The infrared spectrum (neat) showed $\nu_{C=C}$ 1656 (s), 1620 cm^{-1} (m). The UV spectrum (cyclohexane) showed maxima at 276.5 nm (log ϵ 4.30), 283.5 (4.28), 365 (2.49), and a shoulder at 295 nm. The mass spectrum showed *m/e* 158 (100, M^+). The ^1H NMR spectrum (60 MHz, $CDCl_3$ from external capillary Me_4Si, 37 °C) showed absorptions at δ 6.8 (s, 4 H, ring protons), 3.7 (b, 1 H, bridgehead proton at 1′), 2.9 (b, 3 H, methylene protons at 3′ and bridgehead proton at 4′), 1.6–2.4 (b, 6 H, methylene protons at 5′, 6′, and 7′).

Anal. Calcd for $C_{12}H_{14}$: C, 91.14; H, 8.86. Found: C, 91.06; H, 8.90.

Preparation of Fulvenium Ions. Freshly distilled FSO_3H was dissolved in about twofold amount of SO_2ClF or SO_2F_2 at dry ice/acetone temperature (ca. −78 °) or ethanol/liquid nitrogen temperature (ca. −120 °C). To this solution was slowly added with vigorous stirring a cooled slurry of the appropriate fulvene precursor in SO_2ClF or SO_2F_2, to give an approximately 10% solution of the ion.

^1H NMR spectra were obtained on a Varian Model A56/60A spectrometer equipped with variable temperature probes and external capillary Me_4Si was used as the reference.

^{13}C NMR spectra were obtained using a Varian Model XL-100 NMR spectrometer equipped with an FT accessory with variable temperature probe as previoulsy described.[16]

The infrared spectra were obtained on a Beckman IR-10 spectrophotometer, the ultraviolet spectra were recorded on a Beckman DB-G spectrophotometer, and the mass spectra on a Du Pont Model 21-094 GC/MS system operating at a filament current of 70 eV.

Acknowledgment. Support of our work by the National Institutes of Health is gratefully acknowledged.

Registry No.—1, 4479-62-3; 2, 2175-91-9; 3, 2175-90-8; 4, 2320-32-3; 5, 61010-59-1; 6, 61010-60-4; 7, 61010-61-5; 8, 16668-82-9; 15, 61010-54-6; 16, 61010-55-7; 17, 61010-56-8; 18, 61010-57-9; 19, 61010-58-0; cyclopentadiene, 542-92-7; cyclopropyl methyl ketone, 765-43-5; phenyl cyclopropyl ketone, 3481-02-5; adamantanone, 700-58-3; norcamphor, 497-38-1.

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(13) In the studied fulvenium ions from **15** to **19** it was not possible to differentiate H_a from H_c or C_3 from C_5 in both ^1H and ^{13}C NMR spectra as H_a lacked any coupling with H_d protons. Hence we have tentatively assigned H_a and C_3 to be more deshielded than H_c and C_5. However, this does not alter any of our conclusions.
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Carbon-13 Nuclear Magnetic Resonance. Steric and Electronic Effects on the α, β, and γ Shifts in Norcarane Derivatives

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Received July 13, 1976

Fourier transform carbon-13 nuclear magnetic resonance spectra were measured for a number of endo- and exo-7-substituted and 7,7-disubstituted norcaranes. The substituent shift parameters were calculated from a series of 7-monosubstituted norcaranes and were used for predicting the shifts of stereoisomers of some 7,7-disubstituted norcaranes. The agreement between the observed and the calculated shifts was satisfactory, proving the validity of this general approach. Interpretation of the observed substituent shifts in terms of steric and electronic effects has shown that (1) the α and β substituent effects as well as the γ gauche and anti effects are dependent on the relative orientation of the substituent on the α carbon, and (2) a long-range γ anti effect produced on the γ carbon nuclei by the exo 7 substituent can be explained more reasonably by the back-lobe interaction mechanism than by the hyperconjugative interaction mechanism. Several $^{13}C-^{19}F$ and $^{13}C-^1H$ coupling constants are also reported and interpreted in terms of the s character of the C–F and C–H bonds, respectively.

The carbon-13 magnetic resonance spectra of a number of molecules containing hetero substituents have been recorded and interpreted in terms of inductive, steric, and bond delocalization effects.[1-8] In the literature, however, there is no systematic investigation on the conformational and substituent factors, which affect carbon-13 shieldings, in cyclopropyl ring systems possessing hetero substituent(s).

Now we have determined the carbon chemical shifts for a series of norcarane derivatives. These compounds were chosen because the norcaryl skeleton provides a relatively rigid and stereochemically defined framework suitable for the investigation of substituent effects. Our aim was to determine steric and substituent shift factors and to investigate their variations due to the orientational changes of a substituent on the norcaryl skeleton. This will make it possible to test quantitatively the validity of the theories and speculations which have been advanced to explain carbon-13 shieldings on an electronic ground.

Experimental Section[9]

Materials. All 7,7-disubstituted norcaranes except 7-chloro- (and -bromo-) 7-methoxycarbonylnorcarane were obtained by the addition of the corresponding halocarbene (or carbenoid) to cyclohexene.[10] 7-Chloro- (and -bromo-) 7-methoxycarbonylnorcarane was prepared

Table I. Carbon-13 Chemical Shifts in Endo and Exo 7-Substituted Norcaranes[a]

Registry no.	Compd	X	C-7	C-1,6	C-2,5	C-3,4	Others
286-08-8	1	Nil	10.6	9.8	24.4	21.8	
				Endo Derivatives			
16646-97-2	**2a**	F	74.7 (−64.1)	11.1 (−1.3)	17.7 (6.7)	22.4 (−0.6)	
18688-22-7	**3a**	Cl	40.0 (−29.4)	12.5 (−2.7)	18.6 (5.8)	21.8 (0.0)	
1121-40-0	**4a**	Br	33.4 (−22.8)	12.3 (−2.5)	20.1 (4.3)	21.6 (0.2)	
2988-67-2	**5a**[b]	OCH_3	60.4 (−49.8)	11.6 (−1.8)	18.3 (6.1)	22.6 (−0.8)	58.0
36744-58-8	**6a**	$COOCH_3$	22.1 (−11.5)	16.6 (−6.8)	18.9 (5.5)	21.5 (0.3)	50.8, 172.1 (C=O)
10503-37-4	**7a**	Ph	22.4 (−11.8)	12.9 (−3.1)	20.4 (4.0)	21.9 (−0.1)	138.6, 128.2 (*o*), 131.3 (*m*), 125.8 (*p*)
14222-39-0	**8a**	CH_3	12.2 (−1.6)	10.4 (−0.6)	18.9 (5.5)	22.9 (−1.1)	8.3
				Exo Derivatives			
16646-98-3	**2b**	F	79.5 (−68.9)	17.0 (−7.2)	21.9 (2.5)	21.7 (0.1)	
18688-22-7	**3b**	Cl	37.9 (−27.3)	21.5 (−11.7)	22.5 (1.9)	21.4 (0.4)	
1121-41-1	**4b**	Br	25.3 (−14.7)	21.6 (−11.8)	22.7 (1.7)	21.1 (0.7)	
3101-24-4	**5b**[b]	OCH_3	66.4 (−55.8)	17.7 (−7.9)	22.7 (1.7)	22.0 (−0.2)	57.4
36744-59-9	**6b**	$COOCH_3$	25.9 (−15.3)	22.1 (−12.3)	23.1 (1.3)	21.3 (0.5)	51.2, 174.7 (C=O)
10503-36-3	**7b**	Ph	28.9 (−18.3)	22.5 (−12.7)	23.8 (0.6)	21.6 (0.2)	144.5, 125.4 (*o*), 128.2 (*m*), 125.0 (*p*)
14135-43-4	**8b**	CH_3	18.0 (−7.4)	18.4 (−8.6)	24.0 (0.4)	22.0 (−0.2)	19.0

[a] The values in parentheses are substituent shifts relative to norcarane (1), expressed in parts per million; a negative sign denotes a downfield shift on substitution. [b] The chemical shifts were obtained from the measurement for an isomeric mixture.

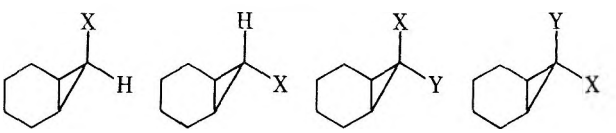
by the carbonation of 7-chloro- (or -bromo-) 7-norcaryllithium with solid carbon dioxide followed by esterification with the conventional procedure.[11] 7-Monosubstituted norcaranes were obtained by the reduction of the corresponding 7-norcaryl halides with tri-*n*-butyltin hydride.[12] Only 7-methoxynorcarane was synthesized according to the previously reported method.[13] Separation of isomers of these compounds was achieved by use either of preparative gas chromatography (GLC) or of thermal decomposition of an isomeric mixture in hot quinoline[14] Stereochemistry of the isomers was determined on the basis of their proton and fluorine magnetic resonance spectra and of the difference in rate of the thermal decomposition in hot quinoline.[14]

Spectra. ^{13}C NMR spectra were recorded on a Varian Associates CFT-20 computer-controlled spectrometer operating at 20 MHz. The Fourier transform (FT) technique was applied.[15] Samples for measurement were prepared as 0.2–0.4 M solutions in chloroform-*d* with tetramethylsilane (Me_4Si) as an internal standard. All chemical shifts were determined from proton noise decoupling (PND) spectra and are expressed in parts per million downfield from Me_4Si. The precision of the computer-measured chemical shifts is within ±0.1 ppm (4K data points in the time-domain spectra for a 200-ppm spectral width) and narrow peaks as close as 0.1 ppm can be resolved. Single frequency off-center decoupled (sfocd) (off-resonance) spectra were used to assign the resonance of carbons in questionable cases. In a few instances, spectra were taken on an isomeric mixture because of the difficulties in separation of the isomers. The resonance lines due to each component in the mixture could be readily identified from their intensities because the components were present in unequal amounts in all cases. The chemical shifts determined for an isomer alone or as an isomeric mixture were practically identical.

Results

In almost all proton noise decoupled (PND) spectra, four signals generally appeared except those due to the carbon(s) contained in the substituent because of the presence of an element of symmetry in the norcaryl system studied. The chemical shifts for the series of 7-substituted and 7,7-disubstituted norcaranes are given in Tables I and II, respectively. The assignment for four signals in the spectrum of norcarane (1) was made as follows: carbon 7 and carbons 1,6 were assigned from the off-resonance experiment because this technique splits the carbon signals according to the number of directly attached hydrogen. The assignment for carbons 2,5 and carbons 3,4 was unambiguously made on the basis of the criterion that substitution with a methyl or a methylene group causes a downfield shift at both the α and β carbons and an upfield shift at the γ carbons.[1] Further confirmation of this assignment was obtained by comparison with the relative chemical shifts of the α and β carbons in decalin.[16] In the case

Scheme I



a b c d

1, X = H
2, X = F
3, X = Cl
4, X = Br
5, X = OCH_3
6, X = $COOCH_3$
7, X = Ph
8, X = CH_3
9, X = F; Y = Cl
10, X = F; Y = Br
11, X = Cl; Y = Br
12, X = Cl; Y = Ph
13, X = Cl; Y = $COOCH_3$
14, X = Br; Y = $COOCH_3$
15, X = Y = Cl
16, X = Y = Br

Table II. Carbon-13 Chemical Shifts in Some 7,7-Disubstituted Norcaranes

Registry no.	Compd	C-7	C-1,6	C-2,5	C-3,4	Others
16646-94-9	**9c**	95.7	22.8	17.5	21.1	
16646-93-8	**9d**	101.7	21.2	20.5	18.4	
19144-91-3	**10c**	85.2	23.7	17.4	21.1	
19144-90-2	**10d**	97.1	22.0	20.3	19.6	
24321-25-3	**11c**	51.8	26.7	19.1	20.5	
24321-26-4	**11d**	58.2	26/9	20.1	20.6	
6434-79-3	**12c**	55.2	21.4	19.3	21.2	145.1, 127.1 (*o*), 128.3 (*m*), 127.1 (*p*)
6508-78-7	**12d**[a]	48.5	24.7	20.7	20.6	138.0, 128.8 (o), 130.9 (*m*), 128.0 (*p*)
37863-38-0	**13c**	56.9	24.6	18.8	21.0	52.9, 179.8 (C=O)
38213-17-1	**14d**	32.2	25.9	19.6	20.7	52.6, 172.7 (C=O)
823-69-8	**15**	67.5	26.2	19.0	20.4	
2415-79-4	**16**	40.4	27.2	20.2	20.7	

[a] See footnote *b*, Table I.

Table III. ^{13}C–^{19}F Coupling Constants in Fluoro Compounds[a]

Compd	$^1J_{CF}$	$^2J_{CF}$	$^3J_{CF}$	$^4J_{CF}$
2a	221.6	10.6	4.8	1.1
2b	221.6	10.6	3.4	0
9c	289.8	11.0	2.8	2.0
9d	282.4	11.3	2.7	0
10c	305.6	10.2	3.1	1.7
10d	295.6	10.5	2.6	0

[a] All coupling constants are in hertz.

Table IV. ^{13}C–^1H Coupling Constants on 7 Carbon in Some 7-Substituted Norcaranes[a] (RX[b])

		J_{CH}	
Compd	X	Endo-X	Exo-X
1	H	154.6	
2	F	196.8	194.5
3	Cl	189.0	186.5
4	Br	187.8	*c*
5	OCH_3	179.5	177.4

[a] See footnote *a*, Table III. [b] R stands for 7-norcaryl group. [c] No value could be obtained owing to overlapping with other signals.

of fluorinated compounds, 7-fluoronorcarane (**2**), 7-chloro-7-fluoronorcarane (**9**), and 7-bromo-7-fluoronorcarane (**10**), the observation of C–F coupling constants and the dependence of their magnitude on the number of intervening bonds made a straightforward assignment possible for all carbon nuclei (Table III). The α carbon, C-7, has the largest J value, followed by the β carbons, C-1,6, and the γ carbons, C-2,5. The δ carbons, C-3,4, have the smallest or zero J value. The assignment presented here clearly demonstrates the great utility of fluorine substitution for the identification of carbon-13 resonances. Sfocd experiments were not performed on these fluoro compounds since several carbon signals were split by fluorine nucleus, giving a complex sfocd spectrum. The assignment for carbon resonances in spectra of nonfluorinated compounds was made by comparison with those of 7-fluoronorcarane. The δ carbons (C-3,4) were readily assigned since they are distant from the 7 substituent(s) enough to be invariant in their chemical shift. In exo 7-substituted norcaranes, however, the assignment for the γ and δ carbons cannot be decisive because their shifts are too close for certainty. For the differentiation of the α carbon (C-7) from the β carbons (C-1,6), their relative intensities could be a good aid in addition to the larger downfield shift on the α carbon caused by the 7 substituent(s). The assignment was further confirmed from the sfocd experiments.

Table III compiles the C–F coupling constants observed for several fluoro compounds. The J_{CF} values on 7-fluoronorcarane (**2**) were in good agreement with those found for the other two fluoronorcaranes with exception of the one-bond coupling constant $^1J_{CF}$, which had a value of 221.6 Hz. An additional polar substituent caused a further increase in the algebraic sense in the $^1J_{CF}$ value (assumed to be of negative sign[17]) and this increase was similar to the one observed in other studies on the series of fluoromethanes.[18,19] The geminal and vicinal coupling constants, $^2J_{CF}$ and $^3J_{CF}$, were slightly different between the endo- and the exo-fluoro isomers. Carbons more than three bonds apart (the δ carbons) can be coupled with the fluorine nucleus when they are close together in space. Thus, a long-range coupling occurred on the endo-fluoro isomers with a value of 1.1–2.0 Hz and on the exo counterparts with a zero value. This variation in $^4J_{CF}$ has an important bearing on the theory of coupling constants between heavy nuclei, because it shows that a through-space interaction contributes significantly to the overall effects.[20]

Table IV lists the direct C–H coupling constants determined from natural-abundance experiments of some 7-substituted norcaranes.

Discussion

The data given in Tables I and II demonstrate that a substituent can have a substantial influence on the chemical shifts for the α (C-7), β (C-1,6), and γ (C-2,5) carbons but very little effect on that for the δ (C-3,4) carbons. Though smaller and subtler changes at the δ carbons may be proved of significance in the future, we will discuss here the α, β, and γ effects alone.

The α and β Effects. Table I shows that in the norcarane systems studied the electronegativity and the anisotropy of the substituents affect the α and β shifts in such a way as can be expected from the previous studies on acyclic[1] and other alicyclic[1,21-23] systems. To be noted is, however, that the magnitudes of the α and β effects are somewhat smaller than those observed in acyclic systems.[1]

Especially significant is the fact that the orientation of the substituent on the norcaryl skeleton has a profound effect on the magnitudes of the α and β shifts as well as of the γ shifts. As is shown in Table I, the shifts caused by the endo substituents are consistently smaller by 2–10 ppm than those by the exo substituents except for chlorine and bromine. It is not possible to decide whether this difference comes from an electronic basis or is caused by slight difference in the mo-

lecular geometry, since the endo substituents may introduce additional steric interaction which could be partially relieved by some distortion of the norcaryl skeleton. However, the difference between the effects for endo and exo orientations of 7 substituents is much larger than that observed in 2-substituted norbornanes.[8] Such a situation can be attributed to the steric elongation of the C_α–C_β bond due to an endo substituent. Elongation of this bond will, according to the theory of Litchman and Grant,[24] produce upfield shifts at the α and β carbons.

In the case of 7,7-disubstituted norcaranes, as given in Table II, an additional polar substituent has a major effect on the chemical shifts for the α, β, and γ carbons in this order but has little effect on the δ carbons. One of the most important features is the fact that the chemical shift for the α carbon is in good agreement with the one calculated from a set of the corresponding substituent parameter compiled in Table I and the chemical shift of the 7 carbon in the parent compound. For example, the observed shift for the α carbon in *exo*-7-bromo-*endo*-7-fluoronorcarane (**10c**) is 85.2 ppm and the calculated value is 89.4 ppm, which is the sum of 64.1 ppm for endo-7-fluorine substitution, 14.7 ppm for exo-7-bromine substitution, and 10.6 ppm for the 7 carbon in norcarane. In all cases except 7-chloro-7-fluoronorcarane, the deviation of the calculated from the observed values falls within the difference between the chemical shifts for the α carbon in each set of stereoisomers. Thus, the chemical shift calculated from the data in Table I allows stereochemical assignment to these related compounds, which otherwise is often very troublesome.

The γ Effects. As shown in Table I, the γ shifts are most easily recognized for overall series of endo 7-substituted norcaranes. In these compounds, the substituent at the 7 carbon is syn to the γ carbons (C-2,5). The effect on the γ carbons is clearly steric in origin and is essentially analogous to that observed in other studies.[6-8,25,26] The magnitude of this γ gauche effect is given in Table I. However, it does not correlate simply with the bulkiness of substituents nor with their electronic property; e.g., chlorine and methoxycarbonyl groups have the effect of the same order of magnitude, in spite of the substantial difference in electronegativity. These results suggest the dependence of the γ gauche effect on the nonbonded distance between the hydrogen attached to the γ carbon and an interacting substituent. This distance, which has been measured using a Dreiding stereomodel, is nicely correlated with the magnitude for the observed γ gauche effect.

On the other hand, the data compiled in the lower half of Table I clearly demonstrate that the signal of the γ carbon nucleus anti to a polar substituent generally appears at a significantly higher field than that of the parent compound. The γ carbons (C-2,5) in exo 7-substituted norcaranes are invariably shielded by the exo substituents. It is evident that this effect cannot be explained in terms of sterically nonbonded interactions discussed above. The upfield shift of this type has also been observed in the studies on several other compounds.[8,27,28] To our best knowledge, two mechanisms have been proposed to explain the γ anti effect. The first mechanism[8,27] involves back-lobe interactions of the bonding orbitals on the γ carbon with those on the α carbon used to bind a polar substituent, by analogy with the model used to explain long-range spin–spin coupling through a "W" arrangement of bonds.[29] The other is hyperconjugative interactions of free-electron pairs on a substituent with the C_α–C_β bond accompanied by a subsequent alternation of the electron density at the γ anti carbon. The latter mechanism was recently suggested by Eliel et al.[28] for the apparently unique role which the second-row heteroatoms (e.g., N, O, and F elements) do play but the third-row elements (e.g., Cl and S elements) do not in the γ anti effect. At a glance of the data in Table I, it can be noted that almost all substituents have a profound effect on the chemical shifts for the γ anti carbons. The magnitude of the upfield shift due to chlorine or bromine is nearly identical with that due to the methoxy group, and even other groups (i.e., methoxycarbonyl and phenyl groups) have nonnegligible effects. The order of the γ anti effect in magnitude appears to correlate roughly with the electronic nature of the substituents and this correlation has also been found in norbornane derivatives.[8] Consideration of such situations led us to prefer the back-lobe interaction mechanism for explaining the γ anti effect, although we do not have tools available to unravel the physical basis for this. The contrast between our data and those obtained by Eliel and his coworkers,[28] which apparently lack the γ shielding due to antiperiplanar third-row heteroatoms, seems to be due to the slight difference in rigidity of molecular framework. The results obtained here would provide a further opportunity to examine the mechanistic interpretation of the γ anti effect.

^{13}C–^{19}F and ^{13}C–^{1}H Coupling Constants. Table III demonstrates that the one-bond coupling constants $^1J_{CF}$ are markedly affected by additional substitution and that $^1J_{CF}$ and the long-range couplings $^4J_{CF}$ are dependent on the relative orientation of the C–F bond on the norcaryl skeleton. Previously, it was suggested that the largest $^1J_{CF}$ value occurs for the most strongly deshielded fluorine nucleus and there is a tendency for $^1J_{CF}$ (assumed to be of negative sign[17]) to decrease, i.e., to become more positive, with increasing ^{19}F shielding.[18] This is not necessarily the case. Endo fluorinated compounds have larger $^1J_{CF}$ values than exo counterparts, whereas in their ^{19}F NMR spectra[30] the endo-fluorine nucleus is invariably more strongly shielded than the exo one. This trend is analogous to that found for the direct C–H couplings (Table IV) but the relative signs are opposite. It seems that the major factor contributing to $^1J_{CF}$ includes the s character of the carbon orbital in the C–F bond; the $^1J_{CF}$ value decreases in magnitude with increase of the s character. In the case of vicinal couplings $^3J_{CF}$, the carbons at the position cis to fluorine have larger coupling constants than the ones trans to fluorine. An apparently similar trend can be noted with the vicinal H–H[31] or H–F[32] coupling in the cyclopropyl ring systems. Of more importance is that the long-range coupling of carbon nuclei separated by four bonds with fluorine occurs in endo fluorinated compounds. This is closely related with their proximity in space, which indicates the contribution of through-space interactions to this effect.

As shown in Table IV, the magnitudes of the direct C–H coupling constants are dependent upon the nature of 7 substituents and are in good agreement with those reported for other monosubstituted cyclopropanes.[33] The magnitudes, furthermore, depend slightly on the relative orientation of the C–H bond with respect to the cyclopropyl ring, though the difference is relatively small. It is well known that the coupling constant J_{CH} correlates with the s character of carbon in the C–H bond of interest: the equation $J_{CH} = a(\%\,s) - b$ generally applies though the values of a and b vary with the author.[34] If the approximate relationship $J_{CF} = (5.70)(\%\,s) - 18.4$[35] is used to estimate the s characters of the 7-carbon atoms in these compounds, they fall in the range of 30.4–37.8%, which corresponds to the hybridization state of $sp^{2.3}$–$sp^{1.7}$. These values may be regarded as satisfactory.

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Electrochemical Oxidation of Tropanes

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Received August 30, 1976

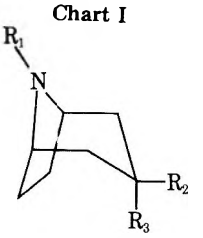
Tropane and nortropane were selected as examples of the tropane alkaloids for study of their anodic reactions. The tertiary amine, tropane, undergoes anodically induced dealkylation, and, like nortropane, does not show further cleavage of carbon–nitrogen bonds, presumably because of the presence of bridgehead carbon atoms α to nitrogen. Instead, reactions that involve formation of carbon–nitrogen and of nitrogen–nitrogen bonds are observed. These reactions involve reaction of the solvent, acetonitrile, with electrochemically generated intermediates. Evidence is presented to support a proposed reaction scheme that involves electrochemical reaction of the amine and of hydroxide ion.

The electrochemical oxidation of saturated aliphatic amines in wet acetonitrile proceeds through the aminium cation radical which typically loses a proton from an α carbon atom to form an intermediate that ultimately undergoes hydrolytic cleavage between the nitrogen atom and the adjacent carbon atom.[1,2] Thus a symmetrically substituted tertiary straight chain alkylamine forms the secondary amine and the aldehyde corresponding to the cleaved alkyl group. The process can be successively repeated to form a primary amine, ammonia, and nitrogen. By contrast, anodic oxidation of aromatic or olefinic amines may lead to formation of relatively stable intermediates owing to delocalization of the unpaired electron. In some cases, radical intermediates with appreciable lifetimes are observed; in others, products from coupling and polymerization are found.[3–6]

Complex amines of both aliphatic and aromatic character are formed in plants and animals. Those of plant origin fall in the general classification of alkaloids. The physiological function of alkaloids is often obscure, but it is generally accepted that chemical and enzymatic redox reactions occur. Electrochemistry provides a tool with which to study redox reactions of biogenic compounds outside living systems.[7–11]

The tropane alkaloids are nonaromatic bicyclic amines. The parent compounds of the series are nortropane (I) (8-azabicyclo[3.2.1]octane) and tropane (II) (8-methyl-8-azabicyclo[3.2.1]octane). Many compounds of this class exist; some, such as atropine, scopolamine, and cocaine, are very well known. Our attention has been attracted to them because of their pharmacological importance. Compounds studied in the work are identified in Chart I and Table I.

Chart I



Experimental Section

Apparatus. Electrolyses were performed with conventional potentiostats. Hydrogen–nitrogen gas coulometers or electronic integrators were used for current integration.[12] Cyclic voltammograms were obtained at a platinum button anode on a PAR Model 173 potentiostat equipped with a H-P model 300A function generator and an X-Y recorder.

Table I. Tropane Derivatives Cited in This Work

	Compd	R_1	R_2	R_3
I	Nortropane	H	H	H
II	Tropane	Me	H	H
III	Tropacocaine	Me	H	OCOPh
V	Atropine	Me	±-OCOCHPhCH$_2$OH	H
VI	3-Tropinone	Me	=O	H
VII	*N*-Formylnortropane	CHO	H	H
VIII	8,8′-Binortropane	$C_7H_{12}N$	H	H
IX	(*N*-Nortropanyl)nortropane carboxamide	$C_7H_{12}NCO$	H	H
X	*N*-Cyanomethylnortropane	CH_2CN	H	H

Various two-compartment H cells were used. The compartments were fitted with ground glass joints which permitted filling under an atmosphere of inert gas. Total solution volume ranged from 20 to 200 ml. Cylindrical perforated platinum sheet anodes and mercury pool cathodes were used. Asbestos fiber tipped reference electrodes consisting of a silver wire immersed in 0.1 M $AgClO_4$ in MeCN made contact with the anode solution by way of a fiber-tipped salt bridge which was filled with the anode supporting electrolyte solution. For electrolyses in benzonitrile, the reference electrode was a silver wire in contact with a 0.1 M $LiClO_4$ solution saturated with $AgClO_4$ in benzonitrile. It was used with the type of salt bridge described above. NMR spectra were obtained on 60-, 90-, or 270-MHz spectrometers. Mass spectra were obtained on a AEI MS902 instrument operated in high or low resolution mode as needed.

Electrolysis Procedures. Supporting electrolyte and solvent were mixed and degassed in a reservoir which provided for transfer to the cell without contact with the atmosphere. All oxidations were carried out at the voltammetric peak potentials observed in the respective solvents. Preelectrolyses were run at +0.75 V prior to the injection of reactant with a syringe. Nortropane was placed in the anode compartment as nortropanium perchlorate along with an excess of powdered NaOH prior to the addition of solvent and supporting electrolyte. Neutralization was allowed to occur before oxidations were begun. No preelectrolyses were possible when this procedure was used. A fivefold molar excess of water with respect to the amine concentration was added to the anode compartment before all electrolyses.

Reagents. The solvents, MeCN, PhCN, and benzene, and the supporting electrolytes, $NaClO_4$ and $LiClO_4$, were purified by established procedures.[13-15] Tropane (II) and tropacocaine (III), received as the hydrochlorides, and atropine (V) (Aldrich Chemical Co.) were used as received. 3-Tropinone (VI) (City Chemical Co.) was sublimed before use.

Nortropane (I). Compound I was prepared by the chemical[16] and electrochemical demethylation of II. That prepared chemically was freed of tertiary amine contaminants by the Hinsburg method[17] and converted to the perchlorate salt which was recrystallized from MeCN–Et_2O. The neutral compound has the following properties: bp 96–97 °C (104 mm) [lit.[18] 161 °C (760 mm)]; NMR ($CDCl_3$) 3.46 (m, 2 CH), 1.74–2.05 (s, 1, NH, shifts with concentration[19]), and 1.2–1.9 ppm (m, 10); mass spectrum (70 eV) *m/e* (rel intensity) 111 (60), 110 (5.3), 96 (4.2) 83 (69.5), 82 (87.4), 69 (23.2), 68 (100), 67 (12.6), 56 (14.7), 55 (12.1), 54 (13.7).[20]

Tropane (II). Compound II was prepared by the Huang-Minlon modification[21,22] of the Wolff–Kishner reduction of VI: bp 98–99 °C (107 mm) [lit.[18] 167 °C (760 mm)]; NMR ($CDCl_3$) 2.2 (s, 3, NCH_3), 3.1 (m, 2, CH), and 1.2–2.1 ppm (m, 10); mass spectrum (70 eV) *m/e* (rel intensity) 125 (23.2), 110 (2.6), 97 (58.9), 96 (84.2), 83 (35.8), 82 (100), 68 (18.9), 67 (12.6), 55 (29.5), 42 (75.8) (lit.[23-25] derivatives); mass spectrum (75 eV, high resolution) 125.1214 (calcd for $C_8H_{15}N$, 125.1204).

***N*-Formylnortropane (VII).** Compound VII was prepared by the formylation of I[26] and by the electrochemical oxidation of II in moist MeCN–$NaClO_4$ and moist MeCN–$NaClO_4$–NaOH and I in moist MeCN–$NaClO_4$–NaOH (Table III). Derivative VII exhibited the following properties: bp 95 °C (2 mm); IR (thin film) 1650 (amide I), 2748 (CH stretch), and 1381 cm^{-1} (CH in-plane deformation); NMR ($CDCl_3$) 8.11 (s, 1, CHO), 4.59 (m, 1, CH), 4.02 (m, 1, CH), and 1.4–2.2 ppm (m, 10); mass spectrum (70 eV) *m/e* (rel intensity) 139 (7.4), 111 (27.4), 110 (12.6), 97 (4.2), 96 (10.5), 95 (28.4), 83 (52.6), 82 (65.3), 69 (21.1), 68 (100), 67 (17.9), 56 (15.8), 55 (23.2), 53 (9.5).

8,8′-Binortropane (VIII). Compound VIII was prepared by the electrochemical oxidation of I in PhCN–$LiClO_4$–NaOH. Attempted preparations by oxidation of I with Ag_2O[27,28] and $KMnO_4$–acetone[29] at 0 °C failed. Derivative VIII has the following properties: NMR (C_6D_6) 3.31 (m, 4, CH), 1.7–2.3 (m, 8, CH_2CH_2), and 1,2–1.6 ppm (m, 12, $CH_2CH_2CH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 220 (100), 192 (10.5), 191 (21), 178 (11.6), 177 (75.6), 165 (6.3), 164 (14.7), 163 (16.8), 151 (25.3), 138 (25.3), 137 (41.1), 125 (27.4), 110 (100), 95 (23.2), 83 (44.2), 82 (62.1), 80 (42.1), 69 (30.5), 68 (88.4), 67 (43.2), 55 (58.9), 54 (33.7); mass spectrum (75 eV, high resolution) 220.1948 (calcd for $C_{14}H_{24}N_2$, 220.1939).

(*N*-Nortropanyl)nortropanecarboxamide (IX). Compound IX was prepared by the electrochemical oxidation of I in moist MeCN–$NaClO_4$–NaOH: mp 115.0–115.5 °C; IR (thin film) 1619 cm^{-1} (amide I); NMR (CCl_4) 4.07 (m, 4, CH) and 1.2–2.2 ppm (m, 20); mass spectrum *m/e* (rel intensity) 248 (63.2), 220 (9.5), 219 (12.6), 205 (16.8), 193 (3.2), 192 (4.2), 191 (2.1), 139 (17.9), 138 (100), 111 (6.3), 110 (22.1), 96 (18.9), 95 (100), 83 (13.7), 82 (4.2), 69 (5.3), 68 (14.7), 67 (23.2), 55 (20); mass spectrum (75 eV, high resolution) 248.1873 (calcd for $C_{15}H_{24}N_2O$, 248.1888).

***N*-Cyanomethylnortropane (X).** Compound X was synthesized from I by the procedure for cyanomethylation of amines:[26] NMR (in CCl_4) 3.69 (s, 2, CH_2), 3.38–4.2 (m, 2, CH), 1.44–2.78 (m, 10, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 150 (38.2), 122 (26.5), 121 (44.1), 108 (47.1) 107 (100), 83 (38.2), 82 (41.2), 55 (47.1); IR (thin film) 2250 cm^{-1} (weak, nitrile).

Mass spectrometry was the major tool used in the identification of tropane derivatives. The bicyclic ring system undergoes characteristic cleavage under electron impact.[24-26] In addition to the parent ion peaks, most of the tropane derivative revealed peaks with *m/e* ratios of 111–110, 96–95, 83, 82, 68, and 55.

Product Analyses. Summarized results are collected in Table III.

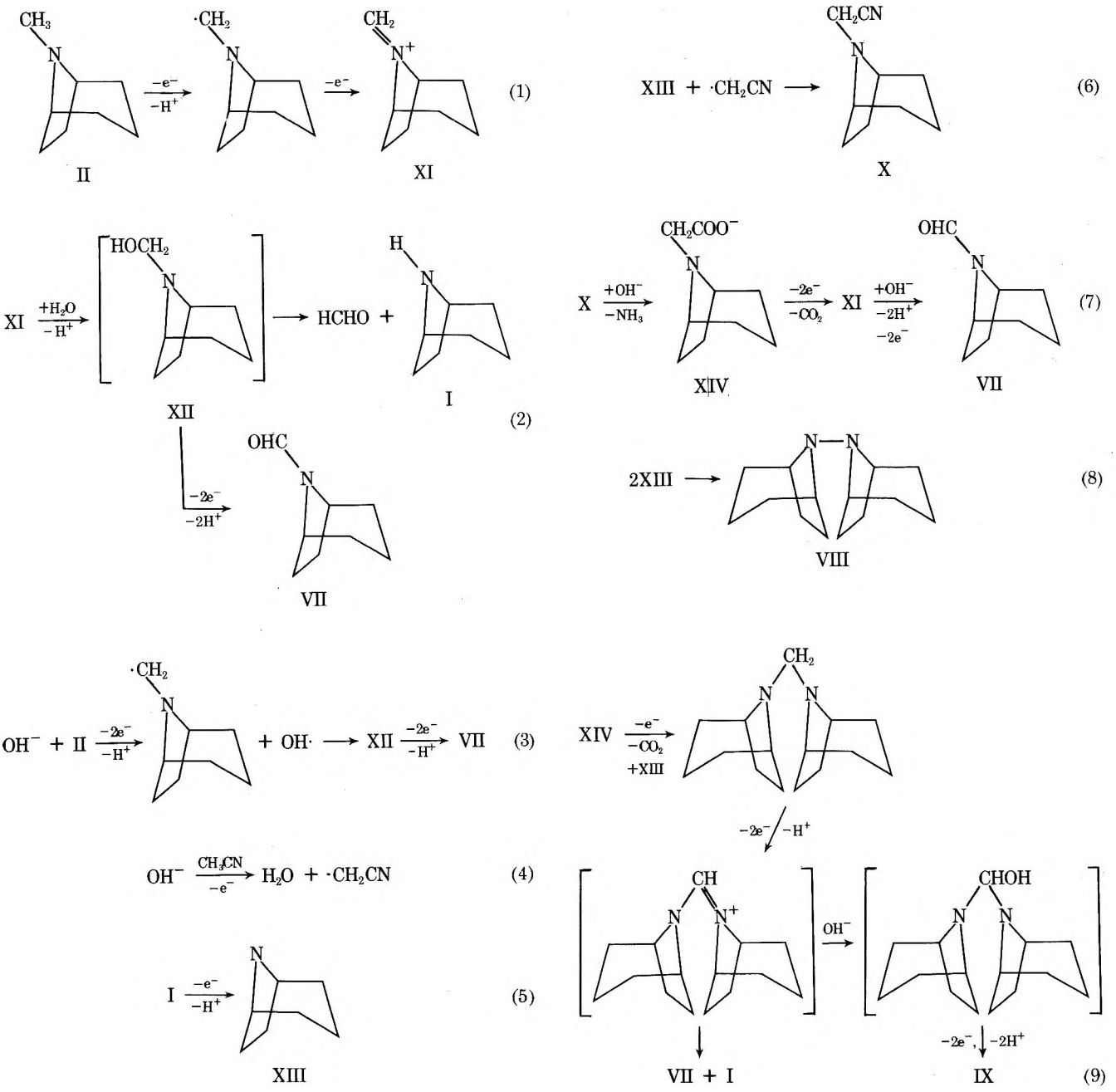
Tropane Oxidation. All basic material in the anolyte was protonated by the addition of 60% $HClO_4$ prior to solvent evaporation. The free bases were extracted into benzene or ether from a basic aqueous solution of these perchlorate salts. Reactants and products were separated and isolated by variable temperature gas chromatography on a 6 ft × 0.25 in. column of 17.5% Dowfax 9N9, 2.5% NaOH on Chromosorb W. Quantitative analyses were based on integration of gas chromatographic peak areas.

Nortropane Oxidation. In MeCN the anolyte was filtered, evaporated to dryness, and extracted into benzene. In PhCN the anolyte was acidified with concentrated $HClO_4$ or HCl and evaporated to dryness under vacuum at 70 °C. The residue was dissolved in MeCN, neutralized, filtered, concentrated, and extracted into benzene. Reactants and products were separated and isolated by variable temperature gas chromatography on a 3 ft × 0.25 in. column of 10% SE-30 on Chromosorb W.

Results and Discussion

The voltammetric peak potentials (Table II) observed for the tropane alkaloids follow the general trends expected for aliphatic amines.[1] Tertiary amines are oxidized in the range of 0.5–0.8 V and secondary amines are oxidized at more anodic potentials of 0.9–1.2 V vs. $Ag/AgClO_4$ (0.1 M). As would be expected for an amide, *N*-formylnortropane reacts at much more anodic potentials.[30]

Reactions of Tropane (II). The pathway followed in the electrochemical oxidation of tropane corresponds to that observed for the oxidation of other tertiary aliphatic amines. Tropane reacts at the potential of its voltammetric peak to give 14.4 mol % of nortropane (I) and 4.2 mol % of *N*-formylnortropane (VII), with 64% recovery of starting material



(average of five runs). Oxidation of tropane in the presence of NaOH increases the yield of VII to 88%.

The previously reported sequence of reactions[1,2] (eq 1, 2) can account for the formation of I. Loss of an electron, a proton, and a second electron produces the ionic intermediate XI. This adds water to give XII which may be cleaved to formaldehyde and nortropane. A finite stability of XII would allow oxidation to the amide VII. Ring cleavage does not occur, presumably because the steric restrictions imposed by the bicyclic ring system do not allow formation of an intermediate endocyclic iminium ion.

Previously reported electrochemical oxidations of amines to amides have involved elemental oxygen,[1] making it unnecessary to postulate an intermediate amino alcohol such as XII. The situation is apparently different in this case. *N*-Formylnortropane (VII) is formed in solutions from which elemental oxygen has been excluded. Water is present; however, we have specifically determined that a 70 mM solution of water in MeCN–0.1 M $NaClO_4$ is not appreciably electrolyzed at +1.0 V. When the experiment was repeated at 0.75 V, the electrolysis current again substantially increased only when II was subsequently added. A small but significant quantity of amide (VII) was then formed.

The presence of NaOH in the electrolysis medium greatly increases the yield of VII. Since hydroxide ion apparently undergoes a one-electron oxidation near +0.75 V in MeCN,[31] the increased yield of VII may be due to participation of a hydroxyl radical in the oxidation of II (eq 3) or to proton scavenging by hydroxide. The amide yield in the presence of hydroxide is very much larger than has been observed in the oxidation of other amines, even when oxygen has been deliberately added. Similarly, chemical oxidations of *N*-methylamines to form amides occur in lower[29,32-38] yields.

Reactions of Nortropane (I). The major product of the oxidation of nortropane at +1.0 V in the presence of NaOH is *N*-formylnortropane (VII). Binortropane (VIII) and the urea (IX) are minor products, as shown in Table III. As the total electrolysis time is increased, the amount of VII and IX increases while that of VIII decreases. Semiquantitative analyses of the products in an exhaustive oxidation at a less positive potential, 0.9 V, showed increased yields of the hydrazine (VIII). Presumably the oxidation potential of VIII is slightly more positive than that of I. Such a large oxidation potential for a hydrazine may be expected in cases in which

Table II. Voltammetric Peak Potentials[a]

Compd	Sweep rate, mV/s	$+E_p$
Nortropane	650	1.00
Tropane	238	0.72
Tropine	632	0.72
Atropine	590	0.67
3-Tropinone	647	0.94
Tropacocaine	666	0.70
N-Formylnortropane	400	1.83

[a] $Ag/AgClO_4$ (0.1 M)–MeCN reference electrode.

Table III. Product Analyses[a]

Compd	Amount taken, mmol	Electrolysis time, h	Apparent *n*, F/mol	Analysis results (mol %)
I	0.2464[c]	11.5	0.93	I (45.7), VII (15.3) VIII (1.7), IX (0.7)
I	0.2401[c]	19.9	1.09	I (31.9), VII (23.8) VIII (1.5), IX (1.2)
I	0.2427[c]	42.7	2.24	I (24.2), VII (42.5) VIII (1.10), IX (4.6)
I	0.2381[c]	57.3	3.46	I (35.7), VII (36.2) VIII (5.8), IX (5.8)
II	0.375[f]	5.2	0.79	I (13.6), II (57.6) VII (5.3)
II	0.1875[c,d]	18.5	2.07	VII (87.6)
I	0.2346[c,e]	27.8	0.97	VIII (58.1)
X	0.9596[c]	4.5	0.89	VII (24.8), X (74)

[a] Solvent MeCN–$NaClO_4$, reaction potential +1.00 V, except as noted. [b] Based upon starting material and including charge consumed by hydroxide ion. [c] Solid NaOH present during reaction. [d] Oxidation run at +0.65 V. [e] Oxidation at +1.05 V in PhCN–$LiClO_4$–NaOH. [f] Oxidation at +0.75 V.

ring strain restricts flattening of the tetrahedral geometry about nitrogen upon oxidation and steric interaction inhibits the formation of a 0° dihedral angle between the nitrogen lone pair orbital axes.[39]

The formation of *N*-formylnortropane by oxidation of nortropane was unexpected since it involves forming rather than breaking a carbon–nitrogen bond. The only sources of carbon atoms in this system are the solvent and carbon dioxide from the atmosphere. The latter is excluded, owing to the formation of very slightly soluble carbamates;[40,41] accordingly, we conclude that the solvent is involved.

Involvement of nitrile solvents in anodic reactions has often been observed;[42] however, these reactions have usually involved attack by an electrochemically generated positive ion on the nitrile nitrogen, followed by hydrolysis to an amide. The present example evidently does not follow that path, since the carbon–nitrogen bond formed involves the amine nitrogen.

Hydroxide ion has been shown to be oxidized at platinum and gold in Me_2SO–$NaClO_4$[31,43] and MeCN–Et_4NClO_4.[31] Although bulk electrolysis products eluded isolation and identification, the initial product of the diffusion-controlled oxidation at approximately +0.7 V vs. Ag/0.1 M $AgClO_4$ in MeCN was thought to be adsorbed or solvated hydroxyl radicals.

We suggest that in the system used in this work, these radicals decay by hydrogen atom abstraction from the solvent to form cyanomethyl radicals which can react with the electrochemically generated intermediate XIII to form the nitrile X as indicated in eq 4–6. The observed products are thought to be formed by hydrolysis of the nitrile to give the carboxylic acid salt which is oxidized to give the carbinol XV. This compound would be expected to lose water to form VII (eq 7).

To get further information about this, the nitrile X was synthesized. When it is electrolyzed under the conditions of this work, it forms VII, as indicated in Table III. When the nitrile is allowed to stand in the reaction mixture without electrolysis for a period of time comparable to that of an electrolytic run, only part of it is recovered. Hydrolysis of the nitrile under basic conditions is plausible.

In the proposed reaction scheme, the hydrazine VIII is formed by dimerization of radical XII (eq 8). When the reaction is carried out in PhCN–$LiClO_4$–NaOH, the hydrazine, formed in 58 mol % yield, is the major product. This is a very unusual result for anodic reactions of aliphatic amines. Presumably it occurs because the ordinarily reactive positions α to the amine nitrogen are inactivated by the bridgehead structure and because the solvent lacks hydrogen α to the nitrile, which would allow it to undergo reactions analogous to eq 4.

The urea IX may be formed as a result of reaction of intermediate XIII with the one-electron Kolbe product from XIV. This is shown in eq 9.

Acknowledgment. The authors wish to acknowledge financial support from the National Institutes of Health through Grant NS 10528.

Registry No.—I, 280-05-7; II, 529-17-9; III, 537-26-8; V, 51-55-8; VI, 532-24-1; VII, 56771-95-0; VIII, 56847-10-0; IX, 61064-10-6; X, 4903-43-9; tropine, 120-29-6.

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Dual Reactivity of 3,3-Dimethoxycyclopropene

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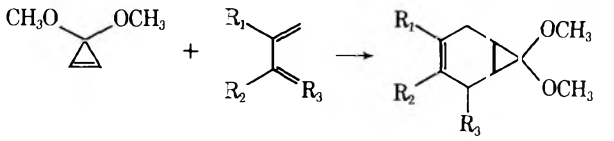
Received August 5, 1976

Charge transfer complex studies indicate that 3,3-dimethoxycyclopropene (I) is an electron-deficient olefin. Initial studies of its chemical reactivity were consistent with this conclusion. Diels–Alder reactions with electron-rich dienes (II) gave high yields of the postulated 7,7-dimethoxy-3-norcarenes (III) under mild conditions. Secondary amines (IV) reacted with I to give cyclopropylamines (V) and/or β-alanine derivatives (VI). Both products could arise from nucleophilic attack of the amine on the cyclopropene system. However, an alternative mechanism is also proposed. The reactions of I with tetracyclone (VII) and hexafluoroacetone (VIII) are best explained by nucleophilic attack of I on the carbonyl carbon of these compounds. The reaction with VII proceeds with cleavage of the cyclopropene ring and subsequent ring closure to a 2-furanone derivative (IXb). In the case of VIII, the adduct is a bicyclic oxetane (X). An improved synthesis of I is also reported. Also, cyclization of 1-bromo-3-chloro-2,2-ethylenedioxypropane (XII) to yield 3,3-ethylenedioxycyclopropene (XIII) along with 3,3-ethylenedioxycyclopropane (XIV) as a by-product is reported.

The synthesis of 3,3-dimethoxycyclopropene (I) in pure form was first accomplished in 1968.[2] Preliminary studies of its chemical reactivity indicated it to be a highly reactive species possessing a somewhat electron-deficient double bond. A study of charge transfer (CT) complexation using the NMR method now adds support to this conclusion. It was found that both styrene and divinyl ether, two electron-rich olefins, gave CT complexes with I. The equilibrium constants were 9.3×10^{-2} l. mol^{-1} for the styrene complex and 0.5×10^{-2} in the case of divinyl ether.

Diels–Alder Reactions of I. Diels–Alder reactions of I with electron-rich dienes (II) was therefore considered a favorable route to the unusual 7,7-dimethoxy-3-norcarenes. When I was mixed with an excess of IIa, IIb, or IIc and the solution allowed



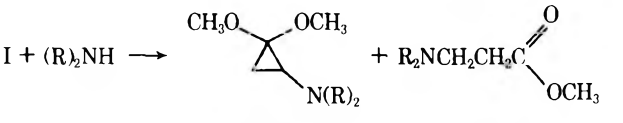
I IIa-d IIIa-d

R_1, R_2, R_3 = (a) H, H, H; (b) H, CH_3H; (c) CH_3, CH_3H; (d) H, H, OCH_3

to stand at room temperature for several days, the expected adducts were formed in high yield. Because of the symmetry of these systems, only one isomer was possible in each case. Pure samples were obtained by preparative gas chromatography (GC). Spectroscopy and elemental analysis (see Experimental Section) confirmed the predicted structures of IIIa–c. IIIa was hydrogenated to yield methyl cyclohexanecarboxylate.

When I and IId (threefold excess of diene) were mixed without solvent, high conversion to the adduct was observed. Analysis of the product after distillation (by GC) showed four components in the approximate ratio of 5:9:20:66. Isolation of the major component by preparative GC gave a product whose NMR, IR, and elemental analysis were completely consistent with the expected adduct, IIId. The second and third minor components were shown to consist largely of methyl benzoate. The first minor component was not identified (See supplementary material for further experimental details.)

Reactions of I with Secondary Amines. When I was added to excess diethylamine (IVa) and the mixture stored at room temperature for several days, the major product formed (60% by preparative GC) was 1,1-dimethoxy-2-diethylaminocyclopropane (Va). The NMR, IR, and mass spectra and elemental analysis gave data consistent with Va.

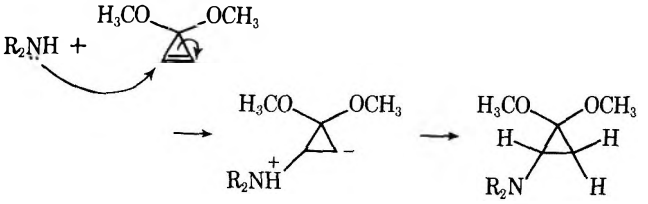


IVa-c Va-c VIa-c

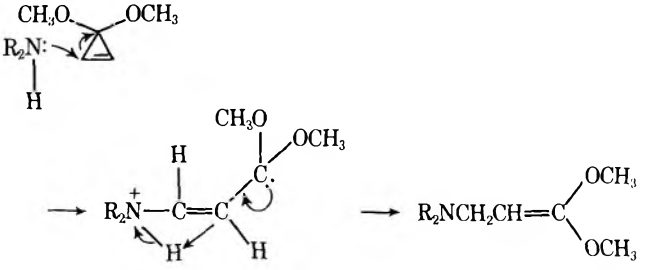
R = (a) C_2H_5; (b) C_3H_7; (c) C_6H_5

Addition of I to IVb gave a considerably more complex product. Analysis by GC indicated that two major components comprised about 85% of the mixture and that these components were present in a ratio of 40:60. Pure samples of each were then obtained by preparative GC.

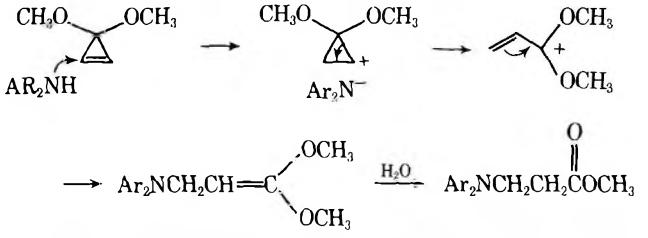
The first component was identified by spectroscopy as 1,1-dimethoxy-2-di-*n*-propylaminocyclopropene (Vb), the expected product. The second component was identified by spectroscopy as *N,N*-di-*n*-propyl-β-alanine methyl ester (VIb). Use of diphenylamine (IVc) in the reaction with I led predominantly to *N,N*-diphenyl-β-alanine methyl ester (VIc). Analysis of the crude reaction product by NMR revealed the absence of cyclopropyl protons; indicating only ring-opened product. Purification by silica gel chromatography yielded VIc in 65% recovery. NMR, IR, mass spectral, and elemental analyses were consistent with this structure. Mechanistically, the simple addition reaction may be considered as a nucleo-



philic attack at C-1 by the electron pair on nitrogen with production of negative charge at C-2, followed by proton transfer to complete the addition. Alternatively, 1,3 cleavage could occur followed by reorganization of the electron system and protonation at C-1 to give the ketene acetal. Hydrolysis



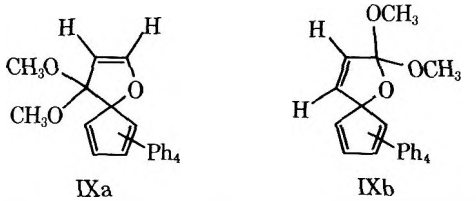
of the ketene acetal would then give the alanine esters observed. However, an alternative mechanism which may account for the increased degree of ring opening of I with acidity of the amine could involve initial proton attack followed by ring opening and amide addition to complete the process:



The order of reactivity here is consistent with the acidity constants for the amines (Ar_2NH, $pK_a = 23$; $EtNH_2$, $pK_a = 33$).

Reaction of I with Ketones. Reaction of I with tetracyclone (VII) might have been expected to give the Diels–Alder adduct. Such a reaction might serve as a convenient synthesis of substituted cycloheptatrienes through 1,4 cycloaddition and loss of carbon monoxide. However, NMR analysis of the product of this reaction was inconsistent with all of the expected structures and elemental analysis was consistent with a 1:1 adduct without the loss of carbon monoxide. Also, the IR spectrum was free of carbonyl absorption. Treating a sample of this adduct with aqueous acetone and a trace of acid resulted in the loss of methoxy signals in the NMR and the appearance of an intense carbonyl peak at 1780 cm^{-1} in the IR spectrum. The NMR spectrum also showed a widely separated AB quartet with a coupling constant, J_{AB}, of 5.5 Hz.

These observations are consistent with a structure in which a ring-opened cyclopropene has added across the carbonyl of VII. Two modes of addition appear possible, to give either IXa or IXb. Acid-catalyzed hydrolysis of these compounds should

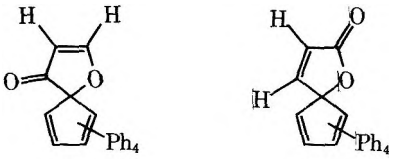


IXa IXb

give derivatives of a 3(2*H*)-furanone (IXc) and a 2(5*H*)-furanone (IXd), respectively. Spectral data for the unsubstituted furanones, available from the literature, are tabulated in Table I and compared with the data obtained for the hydrolysis product. On the basis of these comparisons, structure IXb was assigned to the adduct.

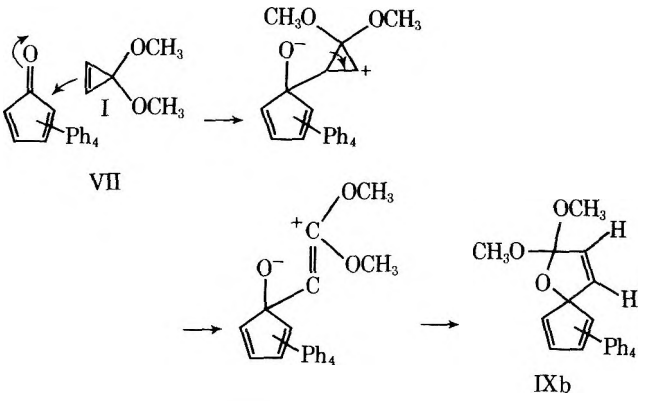
Table I. NMR Spectral Data for Certain Unsubstituted Furanones

Compd	IR, cm^{-1}	Chemical shift, δ A protons	B protons	J_{AB}, Hz
3(2*H*)-Furanone (IXc)[3]	1706	5.07	8.23	2.5
2(5*H*)-Furanone (IXd)[3]	1775, 1745[4]	7.63[5]	6.15	5.2
Hydrolyzed adduct	1780	7.45	6.10	5.5



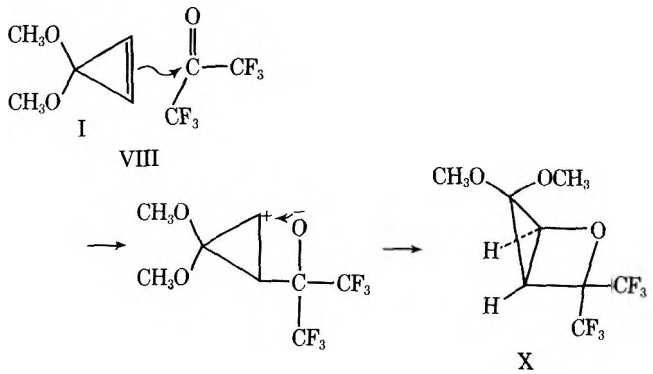
IXc IXd

Since VII has an electron-deficient carbonyl group, the mechanism can be viewed as nucleophilic attack by the olefin on that carbonyl carbon, followed by 1,3-bond cleavage and cyclization.



VII IXb

Hexafluoroacetone (VIII) is electrophilic in nature and two modes of addition to I could be postulated. The first is analogous to the reaction with VII, involving ring opening of the cyclopropene. Alternatively, the product could retain the three-membered ring by closure at C-2 to give the bicyclic system, 3,3-bis(trifluoromethyl)-5,5-dimethoxy-2-oxabicyclo[2.1.0]pentane (X).



I VIII X

When I and excess VIII were mixed and allowed to stand for 3 days at room temperature there was smooth and complete conversion to a single compound which was readily purified by use of a silica gel 60 column (EM Reagents, 70–230 mesh).

^1H and ^{19}F NMR, IR, mass spectral, and elemental analysis are consistent with the assignment of structure X to this compound. In contrast to IXb, X was resistant to hydrolysis.

Table II. Mass Spectral Fragments from 3,3-Ethylenedioxycyclopropane

m/e	Rel intensity	Mol formula	Fragment lost
100	74	$C_5H_8O_2^+$	Molecular ion
56	62	$C_3H_4O^+$	C_2H_4O
44	48	$C_2H_4O^+$	C_3H_4O
99	100	$C_5H_7O_2^+$	H
55	92	$C_3H_3O^+$	C_2H_5O
43	90	$C_2H_3O^+$	C_3H_5O
40	42	$C_3H_4^+$	$C_2H_4O_2$

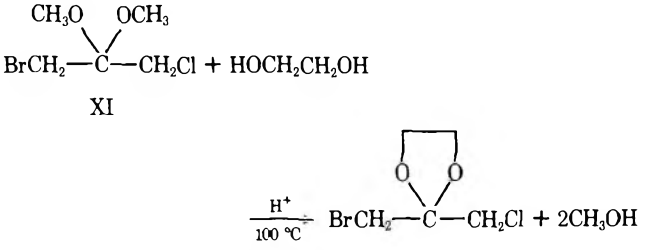
After 17 h in refluxing aqueous dioxane containing a trace of acid, X was recovered unchanged.

Improved Synthesis of I. Cyclization of 1-bromo-3-chloro-3,3-dimethoxypropane (XI) with potassium amide in liquid ammonia was accomplished[2] by addition to the potassium amide solution. Yields were reported to be 30–50%; however, in this work, this procedure gave inconsistent yields of 0–50% with 10–15% being the most frequent results.

Significant improvement was realized by reversing the order of addition of reactants in the cyclization process. Yields in the range of 40–58% were consistently obtained. This modification also results in a safer process which permitted scaling up to five times the original 0.1 M quantities.

The apparatus used was similar to that of Schlatter,[6] which consisted of two flasks arranged side by side with appropriate connecting tubes and provisions for pressurizing one of the flasks. The potassium amide was prepared in the usual fashion and then transferred by means of nitrogen pressure to the other flask which contained XI in excess ammonia. A relatively short reaction time at the temperature of refluxing ammonia was required to complete the cyclization and excess amide was destroyed with ammonium chloride. Isolation of the product then followed the established process.

Preparation of 1-Bromo-3-chloro-2,2-ethylenedioxypropane (XII). Successful preparation of XII was achieved

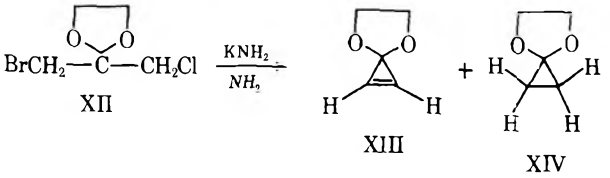


XI

XII

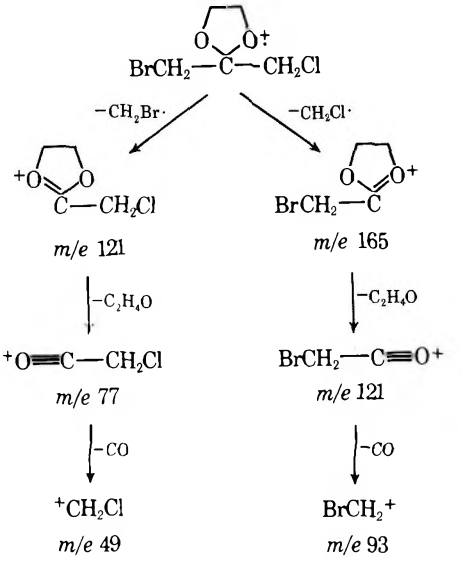
in essentially quantitative yield by acid-catalyzed exchange of ethylene glycol on XI. The NMR, IR, and elemental analysis are consistent with the proposed structure. The mass spectrum shows no parent peak, which is characteristic of ethylene ketals.[7] The base peak at m/e 121 shows an unusual isotopic abundance ratio of 1.65:1 since it can arise from two sources, one with bromine and one with chlorine. The ions are at m/e 49 and 93 and correspond to CH_2Cl^+ and CH_2Br^+, respectively, but the expected metastable peaks are not observed to confirm that they arise from the oxonium ion species as indicated in Scheme I.

Synthesis of 3,3-Ethylenedioxycyclopropene (XIII). Cyclization of XII was accomplished via the original procedure,[2] to yield XIII, identified by spectroscopy. However, an



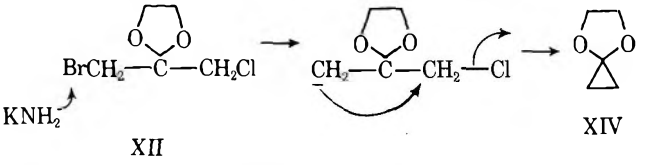
XII XIII XIV

Scheme I. Mass Spectral Fragmentation Pattern for 1-Bromo-3-chloro-2,2-ethylenedioxypropane (XII)



unexpected product, 4,7-dioxaspiro[2.4]heptane (XIV), was obtained as the major component in this cyclization, the ratio of XIII:XIV being 20:80.

Formation of XIV is difficult to rationalize. The preparation of the potassium amide was carefully conducted to ensure that no unreacted metal remained. Thus, when the bromochloro ketal was added, the reaction medium should not have been a reducing system; thus, it is unlikely that the cyclopropene derivative is being hydrogenated. Likewise, a dehalogenation reaction involving the free metal is not possible. Baucom[8] obtained a similarly unexpected product which retained all four methylene protons from the reaction of XI with lithium hydride in the presence of VII. The reaction scheme postulated to account for that product could apply in this case although the amide displacement on bromine does not have compelling precedence. Both the mass and IR spectra of XIV



XII XIV

exhibited some unexpected characteristics. The mass spectrum showed an abundant molecular ion at m/e 100 which had 74% of the intensity of the base peak at m/e 99. This is not a usual characteristic of ethylene ketals.[7] Each of these ions, then, apparently experiences a similar fragmentation pattern as indicated by Table II.

The appearance of ions at m/e 44 and 43 by loss of C_3H_4O from the molecular ion and the base peak ion, respectively, suggests rupture of the dioxolane ring and extrusion of the elements of cyclopropane. Such involvement of the dioxolane ring is unusual and reflects the structural peculiarity of this spiro ketal.[7] Support for this process is found in the metastable peaks produced. The transition m/e 99 to 55 by loss of C_2H_4O is a common reaction of ethylene ketals and gives an observable metastable peak at 30.6. A metastable peak at 18.7 is only slightly less intense and corresponds to the transition m/e 99 to 43 by loss of C_3H_4O.

A characteristic feature of the IR spectra of dioxolane derivatives is a group of four or five peaks between 1000 and 1200 cm^{-1}. This pattern is prominent in the spectrum of XII with peaks at 1030, 1095, 1130, and 1140 cm^{-1}. The spectrum of the cyclization product, however, does not have this characteristic pattern. In the region of interest there are only two strong peaks at 1030 and 1185 cm^{-1}. Apparently the molecular vi-

brations responsible for absorptions at these frequencies are constrained by the small ring attached as a spiro derivative to the dioxolane ring.

Experimental Section

General Methods. All temperatures are reported uncorrected. Melting points were determined in open capillary tubes using a Thomas-Hoover melting point apparatus. All pressures are expressed in millimeters of mercury. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga., or PCR, Inc., Gainesville, Fla. Proton nuclear magnetic resonance (NMR) spectra were obtained on a Varian A-60 spectrometer. The chemical shift data are reported relative to the internal reference tetramethylsilane using the parameter δ. Unless otherwise noted the solvent was deuteriochloroform. Mass spectral data were obtained from a Hitachi Perkin-Elmer RMU mass spectrometer using an ionization voltage of 70 eV. Infrared (IR) spectra were recorded with either a Beckman IR8 infrared spectrophotometer or a Perkin-Elmer 137 sodium chloride spectrophotometer. The data are reported in units of reciprocal centimeters (cm^{-1}).

Gas chromatography (GC) was conducted on a Hewlett-Packard 700 laboratory chromatograph or on an Aerograph Hy-Fi Model 600-D. Refractive indices were measured on a Bausch and Lomb ABBE-3L refractometer. Dimethoxycyclopropene was prepared either by the previously published procedure[2] or by the improved procedure reported in this paper. All other chemical reactants were purified according to standard practices.

Preparation of 3,4-Dimethyl-7,7-dimethoxy-3-norcarene (IIIc). A mixture of 0.8 g (8 mmol) of I and 1.0 g (12 mmol) of IIc was charged to a 5-ml round-bottomed flask and stored at room temperature for 4 weeks. At the end of this time the excess diene was evaporated in a stream of nitrogen and NMR analysis of the residue indicated almost quantitative conversion to the expected adduct (IIIc). Analysis by gas chromatography on a 12-ft column of Carbowax 30 at 150 °C indicated that the mixture consisted of 90–95% of the major component. A pure sample was obtained by preparative GC under the same conditions.

The NMR spectrum showed the following absorptions: δ 3.38 (s, 3, OCH_3), 3.28 (s, 3, OCH_3), 2.10 (m, 4, ring CH_2), 1.58 (s, 6, CH_3), and a multiplet centered at 1.30 (m, 2, bridgehead H).

The IR spectrum (neat) gave absorbances at 2900 (s), 1445 (s), 1410 (m), 1385 (w), 1325 (m), 1270 (s), 1230 (m), 1205 (m), 1125 (s), 1080 (s), 1020 (w), 980 (w), 935 (m), 895 (w), and 815 cm^{-1} (w).

Mass spectral analysis gave an abundant molecular ion at *m/e* 182 (63% of base peak) and other fragments at *m/e* 167, 135, 108, 107 (base peak), 105, 94, 93, 91, and 59. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.43; H, 9.95. Found: C, 72.54; H, 9.72.

For preparation, properties, spectral data, and analysis of structures IIIa, IIIb, and IIId, see supplementary material.

Preparation of 1,1-Dimethoxy-2-diethylaminocyclopropane (Va). A mixture of 1.5 g (15 mmol) of I and 25 ml of IVa was stored at room temperature for 3 weeks. Excess amine was evaporated in a stream of nitrogen and the residue was distilled bulb to bulb at 1 mm pressure. Analysis by GC indicated one major and two minor components. The major component constituted about 60% of the mixture and was isolated by preparative GC (8-ft column of 10% Carbowax at 160 °C).

The NMR spectrum of the major component (Va) gave absorbances at δ 3.42 (s, 3, OCH_3), 3.32 (s, 3, OCH_3), 2.89–2.51 (q, 4, $-CH_2H$), 2.14–1.90 (m, 1, ring CH), 1.18–0.94 (t, 6, CH_3), and 1.05–0.75 (m, 2, ring CH_3).

The IR spectrum (neat) showed peaks at 2960 (s), 2840 (m), 2205 (w), 1750 (w), 1625 (w), 1450 (s), 1390 (m), 1370 (m), 1280 (s), 1220 (s), 1170 (s), 1095 (s), 1065 (s), 1045 (s), 1015 (m), 990 (m), 920 (m), 895 (m), 875 (m), and 765 cm^{-1} (s).

Mass spectral analysis showed a trace of the parent peak and a peak at P − 1 for loss of hydrogen. The base peak occurred at *m/e* 158 corresponding to the loss of methyl radical. Other fragments were observed at *m/e* 142, 126, 116, 101, 98, 84, and 56. The peak at *m/e* 56 is prominent (64% of base peak) but it is difficult to rationalize.

Anal. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.09. Found: C, 62.15; H, 11.00; N, 7.89.

Preparation of 1,1-Dimethoxy-2-di-*n*-propylaminocyclopropane (Vb) and *N,N*-Di-*n*-dipropyl-β-alanine Methyl Ester (VIb). Freshly distilled IVb (22 ml) and 1.0 g (10 mmol) of I were mixed and the solution was stored at room temperature for 3 weeks. Distillation under reduced pressure gave one fraction [bp 50 °C (0.5 mm), 1.5 g] whose NMR spectrum indicated some of the expected cyclopropylamine. GC (8-ft Carbowax, 190 °C) showed two major components in the approximate ratio of 40:60 in the order of elution time. These two components were isolated by preparative GC.

The first component (0.6 g) (Vb) gave an IR spectrum almost superimposable on that of Va. The NMR spectrum showed absorbances at δ 3.45 (s, 3, OCH_3), 3.35 (s, 3, CH_3), 2.85–2.40 (m, 7, $-CH_2N$), 2.22–1.90 (d of s, 1, ring CH), 1.80–1.19 (m, 4, CCH_2C), and 1.10–0.65 (m, 8, CH_3 and ring CH_2).

The second component (0.9 g) (VIb) gave an NMR spectrum showing absorptions at δ 3.65 (s, 3, CH_3), 2.97–2.62 (m, 3, $-CH_2C{=}O$), 2.56–2.17 (m, 6, $-CH_2N$), 1.78–1.17 (m, 4, CCH_2C), and 1.07–0.66 (m, 6, CCH_3).

The IR spectrum gave absorbances at 2940 (s), 2875 (w), 2800 (m), 1750 (s), 1460 (m), 1440 (m), 1250 (m), 1205 (s), 1080 (w), and 1060 cm^{-1} (w).

Mass spectral analysis showed a molecular ion at *m/e* 187 (13% of base peak); the base peak was observed at *m/e* 158 (loss of ethyl radical). Another abundant fragment was recorded at *m/e* 114 (65% of base peak) and arises from the loss of a methyl acetate radical. Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.13: H, 11.30; N, 7.48. Found: C, 64.25; H, 11.37; N, 7.39.

Preparation of *N,N*-Diphenyl-β-alanine Methyl Ester (VIc). To a 25-ml round-bottomed flask was added 1.0 g (10 mmol) of I, 1.8 g (11 mmol) of IVc (recrystallized from pentane), and 10 ml of methylene chloride which had been passed through a column of alumina. The solution was stored at room temperature for 4 weeks and then added dropwise to pentane to precipitate unreacted IVc. When all material was found to be soluble at 0 °C, the solvents were removed and the residue was analyzed by NMR. Adduct formation was indicated by two nonequivalent methoxy groups. A new compound giving a sharp singlet at δ 3.18 was also noted.

About half of this sample was placed on a silica gel column with pentane to attempt chromatographic separation of the mixture. A vigorous exothermic reaction occurred immediately. Development of the column gave 1.0 g of material which appeared to be largely a single compound. A second chromatography on silica gel gave this material in pure form (VIc).

The NMR analysis gave absorbances at δ 7.32–6.65 (m, 10, aromatic H), 4.15–3.80 (m, 2, $-CH_2N$), 3.51 (5, 3, OCH_3), and 2.75–2.38 (m, 2, $-CH_2C{=}O$).

In the IR there were absorbances at 3040 (m), 2960 (m), 1750 (s), 1600 (s), 1500 (s), 1465 (m), 1440 (m), 1365 (s), 1315 (s), 1280 to 1165 (three or four broad bands), 1100 (m), 1065 (s), 1035 (m), 995 (m), 895 (w), and 695 cm^{-1} (s).

The mass spectrum showed only two major peaks, an abundant (40% of base peak) molecular ion at *m/e* 255 and the base peak at *m/e* 182. The next most abundant fragment was *m/e* 77 (16% of the base peak). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.26; H, 6.71; N, 5.49. Found: C, 75.33; H, 6.76; N, 5.42.

Solvent separation techniques were applied to that portion of the original reaction mixture which was not chromatographed. First, it was dissolved in pentane and cooled in dry ice. No selective precipitation was achieved. The solvent was then evaporated and the material was dissolved in methanol. This solution was divided into two portions. One portion was allowed to slowly evaporate but no crystallization occurred. The oil which remained was found to be the same product as from the chromatography experiment (VIc).

The second half of the methanolic solution was treated with a few drops of water which caused an oil to separate. This oil was separated and dried under vacuum at room temperature. The NMR spectrum showed the expected absorptions for VIc. In addition there was a multiplet at δ 1.9–2.3, a singlet at δ 3.18, and increased absorptions in the aromatic region.

The IR (neat) of this sample gave absorbances at 3390 (w), 3030 (w), 2940 (m), 1740 (m), 1665 (w), 1590 (s), 1495 (s), 1460 (w), 1440 (w), 1360 (m), 1305 (m), 1265 (w), 1225 (s), 1190 (w), 1150 (m), 1125 (w), 1085 (m), 1060 (s) 990 (w), 950 (w), 915 (w), 870 (w), 750 (s), 740 (shoulder), and 695 cm^{-1} (s).

Further attempts to obtain this compound in pure state were unsuccessful as all manipulations resulted in conversion of the material to VIc.

Reaction of I with VII. To a solution of 0.5 g (5 mmol) of I in 25 ml of freshly distilled THF was added to a THF solution of 1.0 g (5 mmol) of VII. This mixture was heated to reflux and held for 8 h with no observed color change. GC analysis of a sample indicated decomposition of I and no reaction of the diene. Additional I (0.6 g) was added and the mixture was stored at room temperature. After 2 weeks the color had faded from the solution. Solvent was evaporated from the reaction mixture and methanol was added to the tan residue. A white solid separated which was recrystallized from acetone to yield 0.3 g (12.5%) of pure material, mp 213.5–215.0 °C.

The NMR spectrum (str. IXb) showed absorbances at δ 7.44–6.68 (m, 20, aromatic H), 6.35–5.96 (AB, 2, vinylic H), and 2.95 (s, 6, OCH_3).

The IR spectrum showed weak absorbances at 3100, 3070, 3050, 2990, 2960, and 2860 cm^{-1}. Other peaks were observed at 1630 (w), 1600 (w), 1495 (m), 1447 (m), 1345 (m), 1265 (m), 1240 (m), 1190 (m), 1160 (m), 1130 (s), 1105 (w), 1070 (s), 1045 (s), 1000 (s), 870 (m), 820 (m), 780 (m), 765 (m), 735 (m), and 700 cm^{-1} (s).

Mass spectral analysis gave a molecular ion at *m/e* 434 which was also the base peak. Other major fragments were observed for P − 15 and P − 28. Anal. Calcd for $C_{34}H_{28}O_3$: C, 84.27; H, 5.82. Found: C, 84.11; H, 5.79.

Preparation of 3,3-Bis(trifluoromethyl)-5,5-dimethoxy-2-oxabicyclo[2.1.0]pentane (X). Approximately 5 ml of VIII was condensed into a Fisher-Porter pressure bottle by cooling the bottle in a dry ice–2-propanol bath and also using a dry ice cooled condenser over it. To this was added 1 ml of I. The pressure bottle was then sealed and allowed to warm to room temperature. After 3 days, the excess VIII was allowed to evaporate and the residue was analyzed by NMR. The spectrum was very simple and showed a poorly resolved multiplet at δ 5.66 (one proton), a broad singlet at δ 4.86 (one proton), and sharp singlets at δ 3.81 and 3.50 (three protons each). There was also evidence for a small amount of impurity near δ 3.35, but this was easily removed by dissolving the sample in pentane and passing it through a column of silica gel.

The ^{19}F NMR spectrum revealed that the compound had two different trifluoromethyl groups which were coupled with each other. Additional coupling, probably to one or more protons, was indicated but no further information about the structure could be obtained from this spectrum.

The IR spectrum showed absorbances at 3150 (w), 2970 (m), 2865 (w), 2855 (w), 1725 (w), 1670 (s), 1465 (m), 1410 (m), 1358 (m), 1325 (s), 1290 (s), 1225 (s), 1115 (s), 1055 (s), 1008 (m), 962 (s), 945 (s), 828 (m), 775 (m), 746 (w), 736 (w), and 715 cm^{-1} (s).

The mass spectrum showed a small peak at *m/e* 266 for the molecular ion. The base peak occurred at *m/e* 197, corresponding to loss of trifluoromethyl radical. Other abundant fragments (greater than 20% of base peak) were observed at *m/e* 235 (loss of methoxy radical) and 69 (CF_3^+ ion). Anal. Calcd for $C_8H_8F_6O_3$: C, 36.10; H, 3.30. Found: C, 36.13; H, 3.02.

Improved Synthesis of I. An apparatus resembling that of Schlatter[6] was used. It consisted of two three-necked flasks arranged side by side. Each was equipped with a mechanical stirrer and an adequate dry ice cooled condenser which was protected from the atmosphere by a drying tube filled with soda lime. One 500-ml flask had a Hershberg stirrer of chromel wire and its third opening was fitted with a two-holed rubber stopper. One hole was for a nitrogen inlet tube which extended to just within the neck of the flask. The other hole contained a bent tube which reached to the very bottom. The other 1000-ml flask was also equipped with a two-holed rubber stopper. One hole was for a short section of tubing which reached just inside the neck of the flask and was connected to the longer tube of the first flask by a short section of rubber tubing. The second hole was for a nitrogen inlet. A Teflon stirrer was used in the second flask. Ammonia was collected in the first flask and potassium amide was prepared from 11.2 g (0.29 mol) of potassium metal as previously described.[2] The second flask was charged with 21.7 g (0.1 mol) of XI and about 400 ml of ammonia.

Transfer of the amide solution was made by closing the nitrogen line to the second flask, opening the line between the two flasks, and partially blocking the vent from the first flask with one finger. The stirring of the reaction mixture caused the flask to be filled when the addition was only two-thirds complete, so some ammonia was allowed to evaporate. As a result, the total addition time was 1.5 h. The color of the reaction mixture was bright yellow until near the end when it became dark green.

Stirring was continued for 4 h longer and then excess amide was destroyed by adding ammonium chloride. A marked color change from green to brown occurred when 4.5 g (0.08 mol) had been added. Ammonia was then allowed to evaporate under vigorous stirring and ethyl ether was added as replacement solvent. After 400 ml had been added, the mixture was stirred until the temperature rose to −25 °C. The solution was then filtered and the equipment and solid by-products were rinsed well with ether. The solid weighed 25.0 g (theory, 26.0 g) and gave an aqueous solution of pH 7 or 8 in which very little organic material was apparent.

Following overnight storage in the dry ice chest, the ether was distilled from the filtered solution under 80 mm pressure until the temperature of the flask rose to 0 °C. Receivers were then changed and the pressure was slowly reduced to 0.5 mm. Product was distilled until the pot temperature rose to 25 °C. The yield was 12.5 g of a 38% solution of dimethyoxycyclopropene in ether. This represents a yield of 4.9 g (49%) of pure product. Redistillation of the ether solvent at atmospheric pressure yielded an additional 0.9 g for a total recovery of 58%. Residue from the main product distillation weighed only 1.6 g and did not contain any unreacted starting material.

When scaled up to five times this size, the amide was prepared in a 2-l. flask and the reaction was conducted in a 3-l. flask. The yield from 108.5 g (0.5 mol) of bromochloro ketal was 32.4 g (65%) of pure dimethoxycyclopropene.

Preparation of 1-Bromo-3-chloro-2,2-ethylenedioxypropane (XII). A mixture of 21.7 g (0.1 mol) of XI and 7.6 g (0.12 mol) of ethylene glycol was placed in a 100-ml round-bottomed flask along with 2 drops of concentrated H_2SO_4 and heated on the steam bath for 6 h. Analysis of an aliquot indicated quantitative conversion to the ethylene ketal.

The crude product was dissolved in pentane and washed with water. After drying with Na_2SO_4, the solvent was removed on a rotary evaporator to yield 17.0 g (79%) of ketal. Distillation under reduced pressure [bp 70 °C (1.2 mm)] gave analyticaly pure material, mp 10 °C, $n^{26}D$ 1.5020.

The NMR spectrum showed a four-proton singlet at δ 4.05 and two two-proton singlets at δ 3.62 and 3.47. IR absorbances were observed at 2980 (s), 2905 (s), 1477 (s), 1422 (s), 1200–1020 (group of four strong bands), 1000 (s), 950 (s), 805 (m), 750 (s), and 660 cm^{-1} (m).

The mass spectral analysis showed no parent peak. Fragments were observed at *m/e* 165 (1:1), 121 (1.65:1) (base peak), 93 (1:1), 77 (3:1), and 49 (3:1). (The numbers in parentheses are the ratios of the indicated peak to the P + 2 peak.) Anal. Calcd for $C_5H_8O_2BrCl$: C, 27.87; H, 2.74; Br, 37.09; Cl, 16.45. Found: C, 28.01; H, 3.71; Br, 36.80; Cl, 16.32.

Cyclization of XII. This cyclization was accomplished by the published procedure[2] for synthesis of I from XI, yield 1.3 g (13%) as an 80% solution in ether. The NMR spectrum showed three singlets at δ 7.72, 4.01, and 0.90. When a sample was treated with D_2O, the signal at δ 7.72 disappeared and left the other two in equal intensities. Hydrolysis of the entire reaction mixture was then effected by stirring for 3 h with 17 ml of H_2O. Preparative GC on a 12-ft column of Carbowax 30 at 150 °C gave a pure sample of 4,7-dioxaspiro[2.4]heptane (XIV).

The IR spectrum gave absorbances at 3110 (w), 3030 (m), 2990 (m), 2910 (s), 1490 (m), 1460 (s), 1405 (w), 1335 (s), 1185 (s), 1030 (s), 1000 (s), 945 (w), 930 (w), 850 (m), 765 (w), and 755 cm^{-1} (w).

Mass spectral analysis showed a molecular ion at *m/e* 100, which was 74% as intense as the base peak (*m/e* 99). Other fragments were observed at *m/e* 56, 55, 44, 43, and 40. Anal. Calcd for $C_5H_8O_2$: C, 59.98; H, 8.05. Found: C, 59.85; H, 8.13.

Charge Transfer Complex Studies. I was purified by redistillation under reduced pressure [bp 36 °C (33 mm)]. The donor reagents styrene (St) and divinyl ether (DVE), as well as all solvents, were distilled just prior to use.

A stock solution (0.25 M) of I was used and Me_4Si was used as internal standard. One milliliter of the stock solution was transferred by pipet to each of a series of labeled 5-ml volumetric flasks. The concentration of acceptor was thus held constant for each series of solution. A varying quantity of donor was added to each flask from a buret and then each solution was diluted to volume with the solvent being used for that study. After dilution, each solution was mixed thoroughly and an aliquot was transferred to the appropriately labeled NMR tube.

The NMR spectra for each series were obtained without the intervention of other samples which might affect the instrument response. No special precautions were taken to maintain a constant temperature, but 5 min was allowed for each solution to equilibrate at the ambient operating temperature of the spectrometer (about 38 °C). Because of the large concentration difference between donor and acceptor, only the NMR signals for Me_4Si and the cyclopropene protons were recorded. The chemical shift of the acceptor protons (δ^A_{obsd}) was measured as cycles per second downfield from Me_4Si. Data and observations for the study using styrene as donor are shown in Table IV and those for the divinyl ether case are given in Table V.

The equilibrium constant for complex formation and the shift of acceptor protons in the pure complex were calculated by use of the Hanna–Ashbaugh equation:[9]

$$\frac{1}{\Delta^A_{obsd}} = \frac{1}{Q\Delta^A_{AD}}\frac{1}{C_D} + \frac{1}{\Delta^A_{AD}} \quad (1)$$

where $\Delta^A_{obsd} = \delta^A_{obsd} - \delta^A_{O'}$ is the difference between the shift of the acceptor protons in complexing media and the shift of the acceptor

Table III. NMR Determination of the Equilibrium Constants of Charge Transfer Complexes

Complex	Solvent	Temp, °C	Δ^{A}_{AD}, Hz	K, l. M^{-1}
DVE-DMCP	Hexane	38	125.0	0.005
DVE-MA[10]	$CDCl_3$	24	33.5	0.036
St-DMCP	CCl_4	38	37.0	0.093
St-MA[10]	CCl_4	38	125.0	0.216

in uncomplexed form; $\Delta^{D}_{AD} = \delta^{A}_{AD} - \delta^{A}_{O}$ is the difference in the shift of the acceptor protons in pure complex; C_D is the concentration of the donor (which must always be much greater than the acceptor concentration in order that the quotient $\gamma_{AD}/\gamma_A\gamma_D$ remains constant over the range of solutions studied and thus $Q = K$, the equilibrium constant of complexation).

In these experiments the acceptor concentration was kept constant at 0.05 mol $l.^{-1}$, while the donor concentration was increased from 0.4 to 8.8 mol $l.^{-1}$. By plotting $1/\Delta^{A}_{obsd}$ as a function of $1/C_D$ a straight line was obtained in both cases. The slope of the line and its intersection with the ordinate permit a first approximation of the equilibrium constant of complexation and of the shift of acceptor protons in the pure complex. For a more exact determination of K and Δ^{A}_{AD}, the method of least squares was applied to eq 1, and the results obtained are shown in Table III. The data from the DVE study were subjected to a computer program for evaluation by the least-squares method. The results corroborated those obtained by a simple calculation, and further a correlation coefficient of 0.9995 was indicated. The corresponding values for maleic anhydride complexes are shown for comparison. The electron affinity of I thus appears to be considerably less than that of maleic anhydride. [See supplementary material (Tables IV and V) for additional experimental data.]

Acknowledgments. We gratefully acknowledge the support of this work in the form of financial support to one of us (R.M.A.) by the Glidden Organic Chemical Division of the SCM Corp. and by the donors of the Petroleum Research Fund, administered by the American Chemical Society. We also gratefully acknowledge the many contributions by Dr. Richard L. Veazey during the course of this work.

Registry No.—I, 23529-83-1; IIa, 106-99-0; IIb, 78-79-5; IIc, 513-81-5; IId, 3036-66-6; IIIa, 60934-91-0; IIIb, 60934-92-1; IIIc, 60934-93-2; IIId, 60934-94-3; IVa, 109-89-7; IVb, 142-84-7; IVc, 122-39-4; Va, 60934-95-4; Vb, 60934-96-5; VIb, 27453-35-6; VIc, 52850-21-2; VII, 479-33-4; VIII, 684-16-2; IXb, 60934-97-6; X, 60934-98-7; XI, 22089-54-9; XII, 60934-99-8; XIV, 18552-96-0; St, 100-42-5; DVE, 109-93-3; DVE:DMCP, 60935-00-4; St:DMCP, 60935-01-5; ethylene glycol, 107-21-1; methyl cyclohexanecarboxylate, 4630-82-4.

Supplementary Material Available. Preparation, properties, and spectral data of IIIa, IIIb, and IIId and Tables IV and V (7 pages). Ordering information is given on any current masthead page.

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Reaction of Cyclopropenone Ketals with Alcohols[1]

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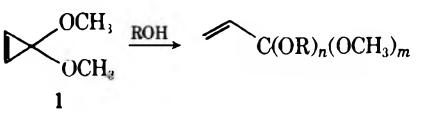
Received August 5, 1976

3,3-Dimethoxycyclopropene (**1**), synthesized as previously described, undergoes a ring-opening reaction under mild conditions, with a variety of alcohols to give the corresponding monoalkyl dimethyl orthoacrylates. These results are consistent with a mechanism which involves initial protonation of **1** followed by solvolysis of the intermediate allyl oxonium cation. Less mild conditions result in exchange reactions between the alcohol and the methoxy groups of **1** giving the dialkyl methyl orthoacrylates and the trialkyl orthoacrylates. By a procedure similar to that used for **1**, 1,5-dioxaspiro[5.2]oct-7-ene (**5**), 1,5-dioxa-3,3-dimethylspiro[5.2]oct-7-ene (**6**) and 4,8,12,15-tetraoxatrispiro[2.2.2.2.2.2]pentadeca-1,10-diene (**7**) were prepared. These cyclic 3,3-dialkoxycyclopropenes were found to undergo reaction with alcohols in a manner similar to **1**. In addition, **5** was found to undergo an apparent thermal dimerization to yield the cyclobutane, dispiro[tricyclo[3.1.0.0^{2,4}]hexane-3,2′-(1′,3′-dioxane)-6,2″-(1″,3″-dioxane)] (**8**). The proposed structures were confirmed by NMR, IR, mass spectral, and elemental analyses.

In an attempt to prepare 1,1,2-trimethoxycyclopropane,[3a] a by-product in the preparation of 3,3-dimethoxycyclopropene (**1**),[3b] anhydrous methanol was reacted with **1**. Instead of the expected trimethoxycyclopropane, methyl orthoacrylate was obtained as the only product. To the best of our knowledge orthoacrylate esters have not been reported previously. We were interested in assessing the versatility of this reaction as a general synthetic route in substituted orthoacrylates.



1

$n = 1, m = 2$, R = CH_3 **2**
$n = 1, m = 2$, R = C_2H_5 **3**
$n = 2, m = 1$, R = C_2H_5 **3a**
$n = 3, m = 0$, R = C_2H_5 **3b**
$n = 1, m = 2$, R = $CH_3CH_2CH_2$ **4**
$n = 1, m = 2$, R = $(CH_3)_2CH$ **4a**
$n = 1, m = 2$, R = $(CH_3)_3C$ **4b**

Results and Discussion

Reaction with Alcohols. Optimum yields (73%) of methyl orthoacrylate (**2**) were obtained by treating **1** with anhydrous methanol at 0 °C for about 3 h. Higher temperatures, longer reaction times, and/or exposure to moisture gave rise to methyl β-methoxypropionate as a by-product. **2** prepared by this procedure had properties and spectra identical with those previously reported by Baucom.[4]

When **1** was treated with anhydrous ethanol under the same conditions as with methanol, ethyl dimethyl orthoacrylate (**3**) was obtained.

Should **3** or any mixed orthoacrylate not be isolated as soon as the reaction is complete, further exchange reactions are possible. For example, when **2** was allowed to react with ethanol at room temperature for several days, all three substituted orthoacrylates, **3**, **3a**, and **3b**, were obtained.

The reaction of 1-propanol with **1** also yielded the monosubstituted product, **4**. Anhydrous conditions must be employed or β-alkoxypropionate esters are obtained.

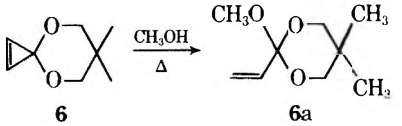
When **1** is treated with 2-propanol, the monosubstituted isopropyl dimethyl orthoacrylate (**4a**) is formed. A longer reaction time at 0 °C for 5 h was necessary.

tert-Butyl alcohol reacted even more slowly with **1**. The reaction required about 22 h at 23 °C before cyclopropenyl hydrogens were no longer detectable in the NMR spectrum of the product mixture. The product, *tert*-butyl dimethyl orthoacrylate (**4b**), is unstable at temperature much above room temperature but could be purified by distillation under vacuum at room temperature or below.

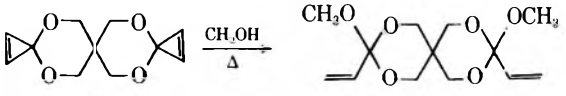
Reactivity of Cyclopropenone Cyclic Ketals with Alcohols. Since cyclic ketals are known to be more stable than their acyclic analogues,[5] we hoped that the cyclopropenone analogues would also be more thermally stable than **1**. The desired cyclic ketals were prepared by first reacting 1-bromo-3-chloro-3,3-dimethoxypropane with the appropriate diol in the presence of a catalytic amount of sulfuric acid. The cyclic 2-bromomethyl-2-chloromethyl-1,3-dioxanes were obtained in yields up to 90%.

Cyclopropene ring formation was accomplished with potassium amide in liquid ammonia by employing the procedure reported by Albert and Butler.[6]

In a similar manner compounds **6** and **7** reacted with refluxing methanol to yield orthoacrylates (**6a**, **7a**) in 59 and 55% yields, respectively.

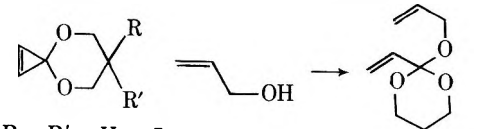


6 **6a**



7 **7a**

The addition of allyl alcohols to **5** and **6** should result in the formation of cyclopolymerizable diene monomers.[8] The dienes were prepared by reacting a 1:1 molar ratio of either **5** or **6** with

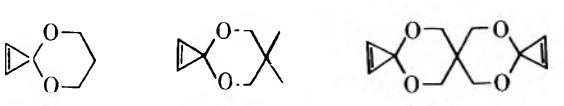


R = R' = H **5**
R = R' = CH_3 **6**

10
11

allyl alcohol in methylene chloride. The reaction required several days at room temperature to go to completion. The dimer, **8**, was obtained as a side product when **5** was the reactant.

Spectral Analysis. The nuclear magnetic resonance spectra (NMR) of the cyclopropenyl ketals show characteristic cyclopropenyl hydrogen absorptions as a singlet around δ 7.8–7.9.[9] The vinyl protons of the orthoacrylates appear as complex ABC multiplets between δ 5.1 and 5.8. Cyclic orthoacrylates show complex absorbances due to the complex

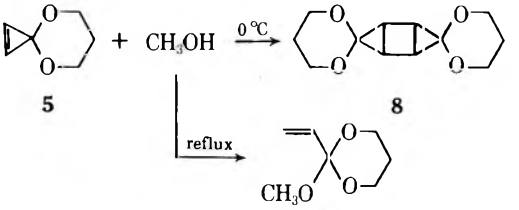


5 **6** **7**

couplings of the ring protons. Further NMR studies are being carried out in this department on these compounds. In this manner 1,5-dioxaspiro[5.2]oct-7-ene (**5**), 1,5-dioxa-3,3-dimethylspiro[5.2]oct-7-ene (**6**), and 4,8,12,15-tetraoxatrispiro[2.2.2.2.2.2]pentadeca-1,10-diene (**7**) were prepared.

Albert and Butler prepared the ethylene ketal 1,4-dioxaspiro[4.2]hept-6-ene but were unable to separate it from side products.[7]

When **5** was treated with methanol under the same conditions as employed for **1**, a quantitative yield of the dimer, dispiro[tricyclo[3.1.0.0^{2,4}]hexane-3,2′-(1′,3′-dioxane)-6,2″-(1″,3″-dioxane)] (**8**) was obtained. None of the expected



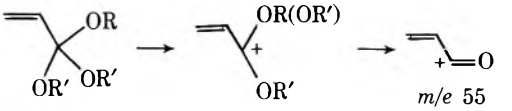
5 **8**

9

orthoacrylate, **9**, was detected. However, under reflux conditions a moderate yield of **9** (65%) was obtained along with 9% of **8**. No further reaction with methanol occurs as it does with the orthoacrylates of **1**. In separate experiments it was found that neither the dimer of **1** nor **8** reacts with hot methanol.

The infrared spectra of the orthoacrylates exhibit very weak and sometimes no peaks around 1625 cm^{-1} for the vinyl protons.[10] This was attributed to a combination of both steric and electron-withdrawing effects of the ortho ester group.[11]

Predominant peaks in the mass spectra of orthoacrylates are those due to the loss of alkoxy groups. The resulting allyl oxonium ions usually give rise to the vinyl carbonyl ion as the base peak at *m/e* 55. Only the trimethyl derivative, **2**, shows



m/e 55

a parent ion and then only at 0.02% of the base peak. The ion fragmentation patterns are similar to those of other ortho esters.[12] The dimer, **8**, shows a prominent parent ion as well as a P − 1 ion. The stabilities of these ions can be attributed to their electronic isomeric structures.[12]

Experimental Section

All temperatures are reported uncorrected in °C. All pressures are expressed in millimeters of mercury. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Proton nuclear magnetic resonance (NMR) spectra were obtained on a Varian A-60A spectrometer. The chemical shift data are reported relative to an internal reference tetramethylsilane using the parameter δ. The solvent used was deuteriochloroform. Mass spectral data were obtained from a Hitachi Perkin-Elmer RMU mass spectrometer using an ionization voltage of 70 eV unless otherwise stated. Infrared spectra were recorded with a Beckman IR8 infrared spectrophotometer. The IR8 scan is linear with respect to wavenumber and data are reported in units of reciprocal centimeters (cm^{-1}). Gas chromatography (GC) was conducted on a Hewlett-Packard 700 laboratory chromatograph. The column used was stainless steel, 12 ft × 0.5 in. o.d. The solid support was Chromosorb G* (60–80 mesh); the liquid phase was loaded 30% w/w Carbowax*. Injection port and column temperatures were 120–140 °C; detector temperature was 150 °C. All solvents and chemicals used as reactants were commercial grade and were used as received unless otherwise noted. The alcohols used were dried carefully by standard procedures immediately prior to use.

Preparation of 1. The procedure developed by Albert and Butler was used without revision.[6,7]

Reaction of 1 with Anhydrous Methanol. A clean, dry, 50-ml round-bottom flask was equipped with a stirring bar and rubber septum, and dried by passing nitrogen through it for 45 min. This flask was then charged with 25.0 ml of anhydrous methanol, and the system was cooled to 0 °C in an ice bath. Then 2.11 g (2.11×10^{-2} mol) of **1** was injected with a small syringe into the stirring methanol. The system was stirred for approximately 3 h and the ice bath was allowed to warm to room temperature. At the end of 3 h, GC analysis showed methanol and a single product peak. The product was recovered by distillation of the methanol and vacuum distillation (25 °C, 1.0 mm) of the methyl orthoacrylate (**2**). A total of 2.04 g (73.2% yield) of product was recovered.

The NMR spectrum showed peaks at δ 3.23 (9 H, s) and 5.53 (3 H, m). The IR spectrum exhibited absorbances at 2960 (s), 1625 (w), 1440 (m), 1411 (m), 1240 (m), 1180 (s), 1080 (s), 1040 (s), 994 (m), and 948 cm^{-1} (m). Mass spectral analysis revealed major ion peaks at *m/e* (rel intensity) 132 (0.02), 131 (0.04), 117 (8.2), 105 (30.2), 102 (9.2), 101 (100), 59 (23.4), 55 (97.4), 45 (21.3), 27 (42.1); metastable ion (reaction), 29.9 (101 → 55). Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.17. Found: C, 54.55; H, 9.25.

Reaction of 1 with Other Alcohols. **1** was treated with anhydrous ethanol by a procedure analogous to that reported for the reaction with methanol. Dimethyl ethyl orthoacrylate (**3**) was recovered by vacuum distillation of the ethanol at 25 °C (25 mm); **3** distilled at 35 °C (0.025 mm), yield 29.5%.

The reaction of **1** with anhydrous 1-propanol was accomplished by the same procedure. The product, dimethyl propyl orthoacrylate (**4**), was recovered by vacuum distillation of propanol at 25 °C (25 mm); **4** distilled at 45 °C (0.75 mm) and was further purified by GC.

The reaction of **1** with anhydrous 2-propanol was accomplished by the same procedure except that a reaction time of 5 h was necessary before the NMR absorbances of the vinyl protons were no longer detectable. A single product, dimethyl isopropyl orthoacrylate (**4a**), was recovered after vacuum distillation of 2-propanol at approximately 25 °C (25 mm), followed by preparative GC.

The reaction of **1** with *tert*-butyl alcohol was accomplished by the same procedure except that a reaction time of about 22 h at room temperature (23 °C) was necessary for complete reaction. The product, dimethyl *tert*-butyl orthoacrylate (**4b**), was recovered from the remaining, decomposed **1** by vacuum distillation at 20 °C (0.5 mm), yield 3.69 g (68%).

Exchange Reaction between 2 and Ethanol. A clean, dry, 25-ml round-bottom flask was equipped with a stirring bar and rubber septum, and dried by passing nitrogen through it for 35 min. Into the vessel were injected 10.0 ml of anhydrous ethanol and 1.44 g (1.09×10^{-2} mol) of **2**. After 4 days at room temperature with stirring, the ethanol was vacuum distilled at 25 °C (25 mm). The product mixture was analyzed by GC. Temperatures and column parameters were as follows: oven, 95 °C; detector, 190 °C; injection port, 170 °C; 0.25 in. o.d. × 8 ft loaded 10% w/w Carbowax on Chromosorb P*. Four fractions were collected and analyzed. The first fraction (F1) constituted 11.8% of the product mixture and was identified by retention time as **2**. The second fraction (F2) constituted 20.6% of the product mixture and was identified by NMR, IR, and mass spectral analysis to be **3**. The third fraction (F3) was identified as diethyl methyl orthoacrylate (**3a**) which constituted 25.9% of the product mixture. The fourth fraction (F4) was identified as ethyl orthoacrylate (**3b**). It constituted 31.7% of the product mixture.

Preparation of 2-Bromomethyl-2-chloromethyl-1,3-dioxane. A mixture of 108.7 g (0.5000 mol) 1-bromo-3-chloro-2,2-dimethoxypropane and 38.0 g (0.5000 mol) of 1,3-propanediol was heated to about 95 °C in the presence of 4 drops of sulfuric acid. The mixture was maintained at 95 °C for 2 h while methanol distilled. The temperature of the reaction mixture was then increased to 130 °C and maintained there for 2 h to ensure complete reaction. The product was crystallized from ether/pentane to yield 57.8 g of a white, crystalline solid product. The combined filtrates were concentrated to a light yellow oil. An NMR analysis of this oil revealed that it was mostly the starting ketal. To it was added 20.0 g (0.263 mol) of 1,3-propanediol, and the mixture was heated to 110–130 °C for 8 h. After cooling, the yellow-brown oil was crystallized from ether/pentane to yield an additional 23.0 g of product. The combined yield of the product was 80.8 g (77.5%). The product was recrystallized from ether/pentane to give white crystals which melted at 59–60 °C. The NMR spectrum showed peaks at δ 1.78 (2 H, p, J = 5.6 Hz), 3.70 (2 H, s), 3.81 (2 H, s), and 3.96 (4 H, t, J = 5.6 Hz). The IR spectrum (KBr) showed absorbances at 2997 (m), 2887 (m), 2807 (m), 1478 (m), 1469 (m), 1425 (s), 1246 (s), 1207 (s), 1096 (s), 1017 (s), 930 (m), 851 (m), 738 (m), and 674 cm^{-1} (m). The mass spectrum showed major ions at *m/e* (rel intensity) 181 (46.2), 179 (47.7), 153 (7.7), 151 (7.7), 137 (35.4), 135 (100.0), 123 (38.5), 121 (41.5), 109 (6.2), 107 (16.9), 95 (9.2), 93 (9.2), 79 (23.1), 77 (69.2), 59 (13.8), 51 (7.7), 49 (20.0), 43 (9.2), 42 (23.1), 41 (26.2), 39 (12.3), 29 (13.8), and 27 (24.6). Anal. Calcd for $C_6H_{10}O_2ClBr$: C, 31.40; H, 4.40; Cl, 15.45; Br, 34.82. Found: C, 31.53; H, 4.40; Cl, 15.32; Br, 35.00.

Preparation of 2-Bromomethyl-2-chloromethyl-5,5-dimethyl-1,3-dioxane. This compound was prepared in 86% yield according to the procedure described for 2-bromomethyl-2-chloromethyl-1,3-dioxane. The compound distilled as a colorless liquid, bp 98 °C (0.04 mm).

Preparation of 2,4,8,10-Tetraoxaspiro[5.5]-3,9-di(bromomethyl)-3,9-di(chloromethyl)undecane. This compound was prepared in 92% yield by the same procedure as reported for 2-bromomethyl-2-chloromethyl-1,3-dioxane. Pentaerythritol was the starting alcohol. The compound is a white solid, mp 157.5–158.5 °C.

Preparation of 5. This compound was prepared in 73.8% yield from 2-bromomethyl-2-chloromethyl-1,3-dioxane according to the procedure described by Albert and Butler.[6,7] The product distilled at 35–40 °C (0.3–0.4 mm) as a colorless liquid. The NMR spectrum showed peaks at δ 1.81 (2 H, p, J = 5.6 Hz), 3.97 (4 H, t, J = 5.6 Hz), and 7.83 (2 H, s). The IR spectrum (neat) showed absorbances at 3138 (m), 3108 (s), 2980 (s), 2868 (s), 1598 (s), 1483 (m), 1458 (m), 1428 (m), 1364 (m), 1297 (s), 1272 (s), 1242 (s), 1150 (s), 1082 (s), 1023 (s), 923 (s), 900 (s), 856 (m), and 728 cm^{-1} (m). The mass spectrum showed major ion fragments at *m/e* (rel intensity) 112 (19.2), 111 (3.8), 86 (9.6), 82 (7.6), 55 (40.4), 54 (100.0), 53 (13.5), 42 (13.5), 41 (11.5), 32 (13.5), 29 (11.5), 28 (55.8), and 26 (32.7). Metastable ion (reactions) occur at 110.01 (112 → 111) and 66.74 (112 → 86). Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.10; H, 7.19.

Preparation of 6. The preparation of this compound was accomplished in 70% yield by using the procedure described by Albert and Butler,[6,7] bp 40–55 °C (0.015 mm) (colorless liquid).

Preparation of 7. This compound was prepared in 95% yield from 2,4,8,10-tetraoxaspiro[5.5]-3,9-di(bromomethyl)-3,9-di(chloromethyl)undecane according to the procedure reported by Albert and Butler.[6,7] The product is a white solid which explodes above 130 °C. The compound was recrystallized from a mixture of ethyl acetate and hexane.

Reaction of 5 with Methanol at 0 °C. The procedure described for the reaction of **1** and methanol was repeated with **5**. A white precipitate immediately began to form, and at the conclusion of the 3-h reaction time a 95% yield of a white solid, mp 158–160 °C, was obtained. The compound was identified as the dimer, **8**, based upon spectral examination. The NMR spectrum showed absorbances at δ 1.86 (4 H, p, J = 5.6 Hz), 1.91 (4 H, s), 3.94 (4 H, t, J = 5.6 Hz), and 4.03 (4 H, t, J = 5.6 Hz). The IR spectrum (KBr) showed peaks at 3058 (m), 2990 (s), 2970 (m), 2933 (m), 2859 (w), 1472 (m), 1461 (w), 1397 (s), 1376 (s), 1285 (m), 1248 (s), 1197 (s), 1154 (s), 1101 (s), 1074 (s), 996 (m), 944 (m), 908 (m), and 871 cm^{-1} (s). The mass spectrum showed major ion fragments at *m/e* (rel intensity) 224 (10.9), 223 (5.5), 195 (25.5), 194 (5.5), 167 (9.1), 166 (49.1), 165 (9.1), 153 (26.4), 152 (90.1), 139 (12.7), 138 (36.2), 137 (14.5), 126 (12.7), 112 (18.2), 96 (18.2), 95 (10.9), 94 (54.5), 82 (20.0), 54 (20.0), 52 (54.5), 42 (54.5), and 41 (63.6). Metastable ion peaks appear (reaction) at 169.8 (224 → 195), 114.7 (166 → 138), and 87.8 (138 → 110). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.38; H, 7.11.

Reaction of 5 with Refluxing Methanol. To 20 ml of refluxing freshly distilled anhydrous methanol was added 2.16 g (0.0193 mol) of **5**. The solution was gently refluxed for 4 h, cooled, and analyzed by NMR spectroscopy. The NMR showed that cyclopropenyl hydrogens were absent. The methanol was distilled at room temperature and reduced pressure to yield a light straw colored oil. Distillation at 38–44 °C (0.04 mm) yielded 1.80 g (64.7%) of the cyclic orthoacrylate (**9**) and 0.19 g (8.8%) of the dimer, **8**. The NMR spectrum of the adduct showed absorbances at δ 1.24–2.56 (2 H, m), 3.23 (3 H, s), 3.57–4.47 (4 H, m), and 5.20–5.81 (3 H, m). The IR spectrum (neat) showed peaks at 2989 (m), 2903 (w), 2848 (w), 1416 (m), 1257 (m), 1247 (m), 1149 (w), 1117 (s), 1078 (s), 1054 (s), and 967 cm^{-1} (m). The mass spectrum showed major ion fragments at *m/e* (rel intensity) 113 (3.7), 99 (5.5), 89 (15.7), 87 (5.5), 73 (14.8), 72 (88.8), 71 (24.1), 59 (14.8), 57 (13.0), 55 (100.0), 45 (92,5), 44 (7.4), 43 (5.5), 42 (14.8), 41 (13.0), 32 (16.7), 31 (24.1), 29 (18.5), and 27 (24.1). Anal. Calcd for $C_7H_{12}O_3$: C, 63.51; H, 8.29. Found: C, 63.34; H, 8.26.

Reaction of 6 with Methanol. The procedure described for the reaction of **5** with refluxing anhydrous methanol was followed for **6**. A 59% yield of a colorless liquid which distilled at 30 °C (0.01 mm) was obtained as the only product (**6a**).

Reaction of 7 with Methanol. The procedure described for the reaction of **5** with refluxing anhydrous methanol was repeated with

7. Distillation at 120 °C (0.03 mm) gave a 54.7% yield of a colorless liquid which solidified upon standing. The compound was further purified by sublimation at 90 °C (0.03 mm) to give **7a**, a white solid, mp 53–54 °C.

Reaction of 1-Dimer[3b] or 8 with Refluxing Anhydrous Methanol. Approximately 0.5 g of the appropriate dimer was placed in 50 ml of methanol, and the solution was heated to reflux for 30 min. Upon cooling, the respective dimer crystallized and was identified by comparing its melting point and NMR spectrum to those of the authentic compound. No other products were detected.

Reaction of 5 with Allyl Alcohol. To a clean, dry, 25-ml round-bottom flask flushed with dry nitrogen and capped with a rubber septum were added 2.11 g (0.0188 mol) of **5** and 5 ml of dry methylene chloride by means of a syringe. After the contents of the flask were stirred to ensure solution, 1.17 g (0.0200 mol) of anhydrous allyl alcohol was added in one portion by means of a syringe. The sample was stirred and allowed to stand at room temperature for 7 days, at which time an NMR spectrum of the solution showed no cyclopropenyl hydrogens present. The sample was diluted with 25 ml of ether, and 0.74 g (35.0% yield) of a white solid was recovered. This compound was identified as the dimer, **8**, by comparing its melting point, IR, and NMR spectra to that of the authentic compound. The ether–methylene chloride solution was concentrated to about 1 ml in volume by distillation at room temperature and reduced pressure. High vacuum distillation yielded 0.91 g (28% yield) of a colorless liquid which boiled at 38–42 °C (0.1 mm). This compound was identified as the allyl alcohol adduct, **10**, on the basis of IR, NMR, and mass spectral analysis. The NMR spectrum gave peaks at δ 1.15–2.28 (2 H, m), 3.28–4.05 (6 H, m), and 4.53–5.74 (6 H, m). The IR spectrum (neat) gave absorbances at 3108 (m), 3093 (m), 2971 (s), 2936 (s), 2892 (s), 1647 (m), 1468 (m), 1407 (s), 1367 (m), 1292 (m), 1238 (s), 1117 (s), 1063 (s), 1027 (s), 969 (m), 922 (m), and 856 cm^{-1} (w). The mass spectrum gave major ion fragments at *m/e* (rel abundance) 143 (1.2), 129 (1.2), 114 (3.8), 113 (42.2), 100 (1.9), 87 (2.5), 86 (5.0), 85 (6.3), 73 (6.9), 71 (2.3), 69 (2.3), 58 (12.0), 57 (39.0), 56 (10.7), 55 (100.0), 43 (5.0), 42 (6.3), 41 (40.8), 39 (15.7), 31 (18.9), 29 (13.8), 28 (25.2), and 27 (28.3). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.34; H, 8.26.

Reaction of 6 with Allyl Alcohol. This compound was treated with allyl alcohol by employing the same procedure as reported for **5** and allyl alcohol. No dimeric product was obtained upon the addition of ether. After the ether and methylene chloride were removed at reduced pressure and room temperature, several milliliters of a light straw colored oil remained. Distillation at 38 °C (0.04 mm) gave a 40% yield of a colorless liquid which was identified as the allyl alcohol adduct, **11**, by analysis of its spectra.

Acknowledgments. This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society, for which we are grateful. One of us (P.L.L.) also received financial support from the National Science Foundation Undergraduate Research Participation Program, summer 1973.

Registry No.—**1**, 60935-33-3; **2**, 60935-34-4; **3**, 60935-35-5; **3a**, 60935-36-6; **3b**, 42216-96-6; **4**, 60967-61-5; **4a**, 60935-37-7; **4b**, 60935-20-8; **5**, 60935-21-9; **6**, 60935-22-0; **6a**, 60935-23-1; **7**, 60935-24-2; **7a**, 60935-25-3; **8**, 60935-26-4; **9**, 60935-27-5; **10**, 60935-28-6; **11**, 60935-29-7; methanol, 67-56-1; ethanol, 64-17-5; propanol, 71-23-8; 2-propanol, 67-63-0; *tert*-butyl alcohol, 75-65-0; 2-bromomethyl-2-chloromethyl-1,3-dioxane, 60935-30-0; 1-bromo-3-chloro-2,2-dimethoxypropane, 22089-54-9; 1,3-propanediol, 504-63-2; 2-bromomethyl-2-chloromethyl-5,5-dimethyl-1,3-dioxane, 60935-31-1; 2,4,8,10-tetraoxaspiro[5.5]-3,9-di(bromomethyl)-3,9-di(chloromethyl)undecane, 60935-32-2; pentaerythritol, 115-77-5; allyl alcohol, 107-18-6; 2,2-dimethyl-1,3-propanediol, 126-30-7.

Supplementary Material Available. Mass spectra of orthoacrylates and additional NMR and mass spectral data (8 pages). Ordering information is given on any current masthead page.

References and Notes

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(2) To whom correspondence should be addressed.
(3) (a) Unreported results, G. B. Butler and R. L. Veazey; (b) K. B. Baucom and G. B. Butler, *J. Org. Chem.*, **37**, 1730 (1972).
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Direct Oxidation of Tertiary Allylic Alcohols. A Simple and Effective Method for Alkylative Carbonyl Transposition[1]

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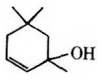
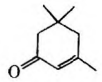
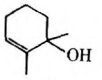
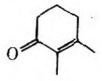
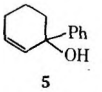
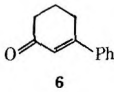
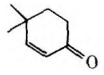
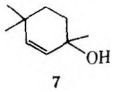
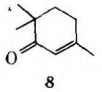
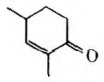
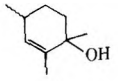
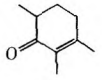
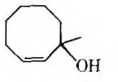
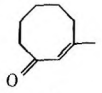
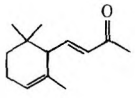
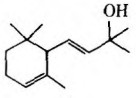
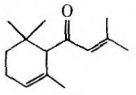
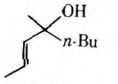
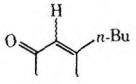
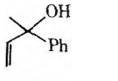
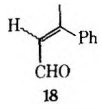
Received July 6, 1976

The oxidation of cyclic tertiary allylic alcohols, generated by the 1,2 addition of organometallic reagents to α,β-unsaturated cyclic ketones, with pyridinium chlorochromate (PCC) affords transposed 3-alkyl α,β-unsaturated ketones in excellent yield. Acyclic tertiary allylic alcohols also undergo this rearrangement in fair to good yields. Tertiary allylic alcohols generated by the addition of vinylmagnesium bromide to saturated ketones can be oxidized to the corresponding α,β-unsaturated aldehydes in good to excellent yield with PCC.

The ability to transpose a functional group efficiently from one carbon to another, as in 1,3-carbonyl transposition of α,β-unsaturated ketones, offers a wide degree of latitude in synthetic design of many naturally occurring compounds. In recent years a number of synthetic methods and reagents have become available for effecting this type of functional exchange. Among the methods commonly employed are included allylic interconversion of oxygen with selenoxide,[2] sulfoxide,[3] and amine oxides[4] via 2,3-sigmatropic rearrangements and the Wharton epoxy ketone rearrangement.[5] The formation and subsequent rearrangement of isoxazoles[6] has also been used to accomplish this exchange of functionality. In general, however, these methods suffer from inferior yields and/or multistep manipulation of delicate intermediates.

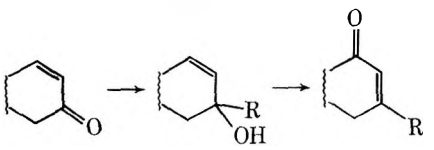
In a variation on this theme, Trost[7] has recently developed a procedure by which tertiary allylic alcohols, generated by the 1,2 addition of an organometallic reagent to an α,β-unsaturated ketone, are converted in several steps to new,

Table I. Intramolecular Alkylative-1,3-Carbonyl Transposition

Starting enone[k]	Alkyllithium Reagent	Allylic Alcohol[l]	Yield,[a] %	Transposed enone[m]	Yield[b]
	MeLi	 1	96	 2	94
	MeLi	 3	90	 4	93
	PhLi	 5	91	 6	90
	MeLi	 7	95	 8	98
	MeLi	 9	81	 10	84
	MeLi	 11	93	 12	88
	MeLi	 13	96	 14	31[c,d]
	*n*-BuLi	 15	90	 16	50[c,e]
	PhLi	 17	85	 18	51[c,f,g,h,i] 50[f,i,j]

[a] Crude yield. [b] Isolated yield, not optimized. [c] Yield determined by vapor phase chromatography. [d] 3 equiv of PCC and 16 h reaction time used. [e] ~4:3 mixture of *E* and *Z* isomers, respectively. [f] Yield based on recovered starting material. [g] A 35% yield of acetophenone also isolated. [h] ~4:1 mixture of *E* and *Z* isomers, respectively. [i] 3 equiv of PCC used. [j] Solid anhydrous sodium acetate added to buffer the reaction medium. [k] Registry no. are, respectively, 4694-17-1, 1121-18-2, 930-68-7, 1073-13-8, 40122-96-1, 1728-25-2, 127-41-3, 625-33-2, 78-94-4. [l] Registry no. are, respectively, 37779-25-2, 51036-24-9, 60174-90-5, 60934-84-1, 53846-74-5 (*cis*-**9**), 53846-76-7 (*trans*-**9**), 51783-32-5, 60934-85-2, 60934-86-3, 6051-52-1. [m] Registry no. are, respectively, 78-59-1, 1122-2-9, 10345-87-6, 23438-77-9, 20030-29-9, 60934-87-4, 31089-97-1, 60934-88-5, 21866-70-6 (*E*-**18**), 21878-52-4 (*Z*-**18**).

Scheme I

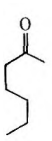
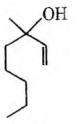
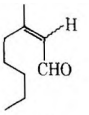
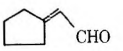
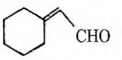
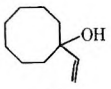
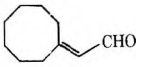
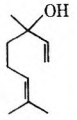
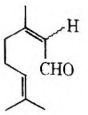


transposed β-alkyl conjugated ketones (Scheme I). This exchange of functionality has also been achieved by acid-catalyzed[8] rearrangement of the allylic alcohol followed by hydrolysis and oxidation. However, the direct oxidation of tertiary allylic alcohols has received only scant attention. In the steroids, various tertiary allylic alcohols upon oxidation yield either transposed α,β-unsaturated ketones and/or epoxy ketones depending on the stereochemistry of the initial hydroxy group.[9a-c] In simpler systems it has been demonstrated that Jones oxidation of substituted tertiary allylic alcohols affords the transposed unsaturated ketones in poor to moderate yield.[9d-h]

In recent years, a number of mild oxidizing reagents, compatible with a variety of acid-sensitive functional groups, have become available[10] and in this present investigation, the results of a study dealing with the scope and limitations of the oxidation of tertiary allylic alcohols with pyridinium chlorochromate[11] are reported. The overall result of the reaction sequence, as outlined in Scheme I, is an efficient method for alkylative carbonyl transposition which offers a number of advantages including mildness of reaction conditions and ease of operation.

It has been found that oxidation of cyclic allylic tertiary alcohols with 2 equiv of pyridinium chlorochromate in dichloromethane affords the transposed α,β-unsaturated ketones in good to excellent isolated yields (see Table I). For example, oxidation of 1-methylcyclooct-2-en-1-ol gave 3-methylcyclooct-2-en-1-one in 88% yield, uncontaminated with its more stable β,γ isomer. Use of the Jones reagent[12] as the oxidant, with this compound, gave a mixture of α,β- and β,γ-enones (4:3, respectively) in 48% yield. Acyclic allylic

Table II. Intermolecular Alkylative 1,3-Carbonyl Transposition

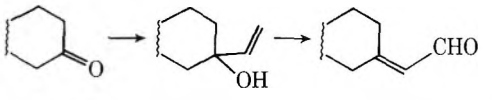
Ketone[g]	Allylic alcohol[h]	Yield,[a] %	α,β-Unsaturated aldehyde[i]	Yield,[b] %	Recovered starting material, %	Other products (%)
	 19	86	 20	90[a,c]	20	2-Heptanone (7)
	 21	71	 22	89[a]	25	Cyclopentanone (5)
	 23	86	 24	83[d]	29	Cyclohexanone (7)
	 25	85	 26	73[d]	24	Cyclooctanone (15)
				54[d,f]	0	Cyclooctanone (20)
	 27		 28	86[c,d,e]	50	6-Methylhept-5-en-2-one (3)
				78[a,c,f]	≤2	6-Methylhept-5-en-2-one (2)

[a] Isolated yield. [b] Based on recovered starting material. [c] ~2:1 mixture of *E* and *Z* isomers, respectively. [d] Yield determined by vapor phase chromatography. [e] Solid anhydrous sodium acetate added to buffer the reaction medium. [f] 3.5 equiv of PCC and 48 h reaction time used. [g] Registry no. are, respectively, 110-43-0, 120-92-3,108-94-1, 502-49-8. [h] Registry no. are, respectively, 24089-00-7, 3859-35-6, 1940-19-8, 6244-48-0, 78-70-6. [i] Registry no. are, respectively, 60934-89-6 (*E*-20), 60934-90-9 (*Z*-20), 5623-82-5, 1713-63-9, 7071-24-1, 5392-40-5.

tertiary alcohols also afforded transposed α,β-unsaturated ketones, albeit in lower yield and contaminated with unusual side products. For example, oxidation of 2-phenylbut-3-en-2-ol afforded a 35% yield of acetophenone in addition to the transposed aldehyde. Two allylic alcohols examined, 2-(1′-cyclohexenyl)propan-2-ol and 4-(2′,6′,6′-trimethylcyclohex-1-enyl)-2-methylbut-3-en-2-ol, failed to give useful yields of transposed products.

An obvious extention of this reaction sequence, the oxidation of tertiary allylic alcohols generated by the condensation of saturated ketones with vinylmagnesium bromide,[13] has also been examined. The net effect of the process, as outlined in Scheme II, is a simple and effective method for the formation

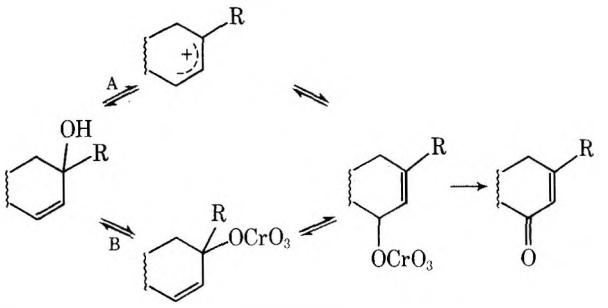
Scheme II



of α,β-unsaturated aldehydes.[14] The results of this study are reported in Table II and reveal that α,β-unsaturated aldehydes were obtained in good yield, based upon recovered starting material. Extended reaction times and increased oxidant levels had unpredictable effects. Thus, oxidation of linalool with 3.5 equiv of pyridinium chlorochromate (in place of the standard 2 equiv) for 48 h led to a 78% isolated yield of citral (>96% pure), whereas oxidation of 1-vinylcyclooctan-1-ol under similar conditions gave the α,β-unsaturated aldehyde in lower yield than found under less forcing conditions.

While it is premature to speculate on the detailed mechanism of this oxidation, conceptually at least, there are two pathways which may be operating (Scheme III). Owing to the acidic nature of pyridinium chlorochromate,[15] it is possible that there may be a prior solvolysis of the tertiary alcohol to an allylic carbonium ion which subsequently collapses with a chromate ion at the lesser substituted termini to generate

Scheme III



an isomeric chromate ester which undergoes oxidation, as in path A. Alternatively, tertiary chromate ester formation may precede rearrangement (either stepwise or concerted), as in path B. Presently, this latter pathway appears to be in operation for the following reasons: (1) the use of buffered conditions had no effect on the oxidation; (2) attempted oxidation of 2-cyclopropylpropan-2-ol, a system known to undergo carbonium ion rearrangements,[16] afforded, at most, trace amounts (≤2%) of the transposed aldehyde, the major product being 5-chloro-2-methylpent-2-ene (~40%) in addition to recovered starting material, even after extended periods of reaction; (3) finally, the transposition–oxidation reaction was effected equally well using the basic Collins[17] reagent. In fact, using 1,4,4-trimethylcyclohex-2-en-1-ol as a standard substrate, the relative effectiveness of the Jones,[9] Collins,[17] and Corey[11] oxidizing reagents were examined and it was found that the yields of the transposed α,β-unsaturated ketones were 76, 94, and 97%, respectively.

Thus, the readily available pyridinium chlorochromate[18] can effect oxidation of tertiary allylic alcohols to the corresponding transposed α,β-unsaturated carbonyl compounds in good to excellent yields, making the overall reaction process a useful synthetic method for alkylative 1,3-carbonyl transposition.

Experimental Section

Unless otherwise noted, the following general conditions were used in all reactions. Infrared spectra were recorded using either a Perkin-Elmer 137 Infracord or 710 grating spectrometer. NMR spectra were obtained with a Varian T-60 or Perkin-Elmer R24B spectrometer with tetramethylsilane as an internal standard. Ultraviolet spectra were obtained on a Perkin-Elmer 202 spectrometer. Mass spectral analysis and exact mass determinations were obtained from the Analytical Laboratory, College of Chemistry, University of California, Berkeley, Calif. Unless otherwise noted, all reactions run in nonaqueous media were maintained under an atmosphere of purified nitrogen. Diethyl ether and tetrahydrofuran were purified by distillation from sodium benzophenone. Mallinckrodt reagent grade dichloromethane was used without further purification. The formation of isophorone is representative of the procedure followed.

1,5,5-Trimethylcyclohex-2-en-1-ol (1).[5] To a stirred solution of 5,5-dimethylcyclohex-2-en-1-one[19] (2.0 g, 16.1 mmol) in 20 ml of anhydrous ether at −78 °C was added, dropwise, an ethereal solution of methyllithium (11 ml of a 1.56 M ethereal solution). The resulting solution was allowed to warm to room temperature, stirred for 2.0 h, and quenched by the dropwise addition of 10 ml of water. The phases were separated and the aqueous layer extracted with two 10-ml portions of ether. The combined organic layers were washed with two 20-ml portions of water and dried over anhydrous $MgSO_4$. The solvent was removed at reduced pressure to afford 2.15 g (96%) of a clear, colorless oil, judged by VPC[20] to be 97% pure. The alcohol was not purified further but used directly in the next step.

Isophorone (2). To a magnetically stirred slurry of pyridinium chlorochromate (4.30 g, 20.0 mmol) in 30 ml of dichloromethane, there was added in one portion a solution of **1** (1.40 g, 10.0 mmol) in 10 ml of dichloromethane at room temperature. The resulting dark red-black mixture was allowed to stir for 2.0 h at room temperature, and was diluted with an equal volume of ether. The ethereal solution was decanted from the black resinous polymer, which in turn was washed with three 20-ml portions of ether. The combined ethereal phases were washed successively with two 100-ml portions of 5% aqueous NaOH, 100 ml of 5% aqueous HCl, and two 50-ml portions of saturated aqueous $NaHCO_3$, and dried over anhydrous $MgSO_4$. The solvent was removed at reduced pressure and the residue bulb to bulb distilled to afford 1.33 g (96%) of isophorone (≥97% pure), spectrally identical with an authentic sample.

Registry No.—**29**, 930-39-2; cyclopropyl methyl ketone, 765-43-5.

Supplementary Material Available. Detailed experimental and spectroscopic data (IR, NMR, UV, mass spectrum) for compounds **3**, **7**, **9**, **13**, **14**, **15**, and **20** (11 pages). Ordering information is given on any current masthead page.

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Structure Effects in the Oxidation of Alkenes by Solutions of Thallic Salts[1]

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Received March 31, 1976

The determination of polar, steric, and resonance effects in the oxidation of alkenes by solutions of thallic salts was carried out using the linear free energy relationship for the chosen set of $RCH{=}CH_2$, $R_1R_2C{=}CH_2$, and the internal alkenes; it was found that polar effects were the most important for the oxidation of $RCH{=}CH_2$ and $R_1R_2C{=}CH_2$ alkenes in this case. Both steric and resonance effects are important in the oxidation of internal alkenes. An aqueous medium is advantageous for the preparation of the carbonyl compounds from alkenes with electron-releasing substituents. The structure effects on the selectivity of the oxidation are discussed.

The oxidation of alkenes by thallic salts has been intensively studied from the point of view of the preparative organic chemistry,[2-7] as well as from theoretical aspects.[8-16] A more complete quantitative comparison of the influence of the individual parameters on the course of oxidation has been lacking so far.

The present investigation has been carried out to provide further information on the mechanism and the effect of structure on the rates of oxidation of alkenes by thallic salts, and on the distribution of products of the oxidation.

The kinetic behavior of the lower alkenes (C_2 to C_4) during their reaction with thallic salts along with the distribution of the oxidation products are described in the fundamental studies of Henry.[8] In aqueous medium, two characteristic products are formed by the oxidation of alkenes, viz. a carbonyl compound (an aldehyde or ketone) and vicinal diol. The

formation of these products, as well as their kinetics, has been explained by a generally adopted mechanism, whose principal features are shown in eq A and B:

$$Tl^{3+} + CH_2{=}CHR + H_2O \xrightarrow[k_{II}]{\text{slow}} H^+ + [TlCH_2CH(OH)R]^{2+} \quad (A)$$

$$[TlCH_2CH(OH)R]^{2+} \xrightarrow{\text{fast}} \begin{cases} \xrightarrow{} CH_3COR + Tl^+ + H^+ \\ \xrightarrow{H_2O} CH_2(OH)CH(OH)R + Tl^+ + H^+ \end{cases} \quad (B)$$

The oxidation rates for alkenes are in accordance with the kinetic equation of the second order:

$$-d[\text{alkene}]/dt = -d[Tl^{3+}]/dt = k_{II}[Tl^{3+}][\text{alkene}] \quad (1)$$

The step determining the reaction rate is the formation of the intermediate hydroxythallation adduct according to eq A. The assumption that the formation of the intermediate adduct occurs as one step of the reaction is substantiated by the fact that the adduct could be isolated under favorable conditions.[2,3,17] In addition, a spectral proof of the formation of the hydroxythallation adduct during the oxidation of alkenes in aqueous medium has also been presented.[12]

Experimental Section

Materials. The oxidation solution of thallium(III) sulfate was prepared as described previously.[18] The concentration of thallium(III) was determined by two independent methods which yielded consistent results, namely (a) titration of iodine released by the reaction of Tl^{3+} with KI with a standard solution of $Na_2S_2O_3$,[19] and (b) by uv spectrophotometry.[20]

2-Methyl-1-butene, 1-hexene, 1-heptene, 1-octene, 4-methyl-1-pentene, 3-methyl-1-butene, 1-nonene, 1-decene, 2-methyl-1-pentene, and 2-ethyl-1-hexene (all of a chromatographic purity minimum 99.8%) were prepared by pyrolysis of the acetate prepared by the acetylation of a corresponding alcohol according to a modified method.[21] 2-Methyl-2-pentene, *trans*-4-methyl-2-pentene, and *cis*-4-methyl-2-pentene were obtained by isomerization of 4-methyl-1-pentene in the presence of $PdCl_2$ as a catalyst[22] and with the subsequent rectification of the mixture of isomeric methylpentenes. 2,4,4-Trimethyl-2-pentene and 2,4,4-trimethyl-1-pentene were prepared according to our previous work.[18] 1-Undecene, 1-dodecene, 1-tridecene, 1-tetradecene, 1-pentadecene, and 1-hexadecene (all of a chromatographic purity minimum 99.6%) were obtained by the redistillation of alkenes, supplied by the Research Institute of Crude Oil and Hydrocarbon Gases, Bratislava, and α-methylstyrene by the redistillation of the crude product supplied by Slovnaft, Bratislava (chromatographic purity minimum 99.9%).

The other chemicals used were commercial products of a reagent grade purity (Lachema, Brno).

Standards for GC–MS. Vicinal diols were prepared by the oxidation of corresponding alkenes with catalytic amounts of OsO_4 in anhydrous *tert*-butyl alcohol.[23]

2-Pentanone, 3-hexanone, 2-hexanone, 2-methylbutanal, 2-ethylhexanal, and 2-octanone were prepared by the oxidation of the appropriate alcohols with $Na_2Cr_2O_7$.[23]

2-Methyl-3-pentanone was prepared by pyrolysis of the mixture of barium isobutyrate and barium propionate and with the subsequent rectification of the crude product.

Analysis of the Oxidation Products. For the identification of the oxidation products and determination of their distribution, alkenes were oxidized using a relatively high initial concentration of thallium(III) sulfate. The standard reaction conditions were as follows: 150 ml of $Tl_2(SO_4)_3$ ($[Tl^{3+}]$ 0.370 mol/l.), 10 ml of alkene, $[H_2SO_4]$ = 1.254 mol/l., T = 20 °C. The procedure was described in the our previous work.[18]

The glycols obtained were determined by the periodate method.[24] The GC–MS analysis was used for the determination of the other organic products.

GC. The products of oxidation were analyzed by a Fractovap 2300 (Carlo Erba, Milan) with a flame ionization detector. The column, length 2.5 m and diameter 2 mm, contained 10% polyethylene glycol adipate on Chromatone NAW DMCS. The working conditions follow: temperature of the injector 175 °C, temperature of the column 120 °C; the flow rates of N_2, H_2, and air were 35, 85, and 75 ml/min.

MS. The device was a MAT 111 GNOM (Varian). The chromatograph was equipped with a packing column (length 1 m, diameter 3 mm), isothermal at 105 °C, flow rate of He 13 ml/min, energy of electrons 80 eV, intensity 270 mA, temperature of the ion source 200 °C. The identity was found by comparison of the measured spectra with the authentic ones.

Kinetic Measurements. The kinetics of oxidation of alkenes by the aqueous solution of thallium(III) sulfate was followed by uv spectrophotometrically in the wavelength range of 200–240 nm by measuring the decrease of absorbance caused by the decrease of concentration of the Tl^{3+} ions. The kinetic measurements were carried out using concentrations appropriate to the spectral technique, i.e., with the concentration of Tl^{3+} ions 2.5×10^{-5} to 2.0×10^{-4} mol/l. and that of the alkene 2.5×10^{-4} to 2.0×10^{-3} mol/l. The concentration of sulfuric acid was 0.05 mol/l. (μ = 0.15 M) in all cases. The rates of reaction with half-lives less than 30 s were determined by applying the stopped-flow method on a spectrophotometer (Durrum-Gibson D-110), while the rates of slower reactions were measured in a spectrophotometer (VSU-2-P, Zeiss, Jena). The reaction temperature of 25 °C was kept at a chosen level within the limit of ±0.1 °C.

Results and Discussion

The results have been analyzed to provide a quantitative evaluation of the contributions of polar, steric, and resonance effects to the free energy of activation.

By using the principle of additivity we can consider in the first approximation the steric (S) and polar (P) effects to be different functions of structure, originating from independent quantities. (However, the resonance effects are not independent of the steric effects.[25]) Then, the full "polar–steric" Taft equation may be written using a common standard (in the case of alkenes CH_3):

$$\log (k/k_0) = \rho^*\Sigma\sigma^* + \delta\Sigma E_s \quad (2)$$

Some reactions may be correlated with the solely polar portion of the equation. The validity of these considerations was ascertained on the model whose reaction center is represented by the C=C bond.

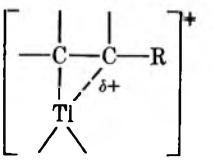
The kinetics of the hydroxythallation were followed in accordance with our earlier work.[26] These reactions exhibited second-order kinetics corresponding to the rate law defined by eq 1. The alkene was always in sufficient excess over Tl^{3+} so that the observed kinetics were pseudo-first-order (eq 3).

$$-d \ln [Tl^{3+}]/dt = k_{obsd} = k_{II}[\text{alkene}] \quad (3)$$

The values of k_{II} are listed in Table I.

The linear free energy–polar energy relationship is depicted in Figure 1 in the form of a plot of log k_{II} (for $RCH{=}CH_2$) vs. Taft σ^* for R.[27] There is fulfilled the condition of constant mechanism, i.e., the transition state geometry is (approximately) unchanged; only the distribution of charge during the reaction is changed.[28]

The slope for the dependence of log k_{II} vs. σ^* has a value of $\rho^* = -3.00 \pm 0.05$, which indicates that in the transition state of the reaction, the positive charge is highly localized at the carbon atom (approaching thus in its nature the carbonium ion), to which the substituent R is attached:



A similar correlation has been found for the oxidation of alkenols by thallium(III) perchlorate in aqueous medium,[12] with $\rho^* = -3.2$. The concept concerning the nature of the transition state occurring during the oxidation of thallic ions is, in addition, supported by the character of analogous reaction be-

Table I. Values of the Rate Constants of the Second Order for Oxidation of Alkenes by Thallium(III) Sulfate in Aqueous Sulfuric Acid at 25 °C

Registry no.	No.	Alkene	k_{II}, l. mol^{-1} s^{-1}
	1	Ethylene[a]	0.335 ± 0.002
	2	Propylene[a]	9.423 ± 0.067
	3	1-Butene[a]	18.80 ± 0.132
109-67-1	4	1-Pentene	20.85 ± 0.146
592-41-6	5	1-Hexene	25.72 ± 0.180
592-76-7	6	1-Heptene	14.91 ± 0.104
111-66-0	7	1-Octene	8.40 ± 0.059
107-18-6	8	Allylalcohol	0.25 ± 0.002
691-37-2	9	4-Methyl-1-pentene	19.80 ± 0.139
563-45-1	10	3-Methyl-1-butene	35.01 ± 0.245
124-11-8	11	1-Nonene	2.30 ± 0.016
872-05-9	12	1-Decene	2.51 ± 0.018
821-95-4	13	1-Undecene	3.42 ± 0.024
112-41-4	14	1-Dodecene	1.50 ± 0.011
2437-56-1	15	1-Tridecene	0.214 ± 0.002
1120-36-1	16	1-Tetradecene	0.390 ± 0.003
13360-61-7	17	1-Pentadecene	0.491 ± 0.003
629-73-2	18	1-Hexadecene	0.230 ± 0.002
627-40-7	19	Methyl allyl ether	0.260 ± 0.002
927-73-1	20	4-Chloro-1-butene	0.660 ± 0.005
100-42-5	21	Styrene	1.160 ± 0.008
625-27-4	22	2-Methyl-2-pentene	49.60 ± 0.35
674-76-0	23	*trans*-4-Methyl-2-pentene	81.90 ± 0.57
691-38-3	24	*cis*-4-Methyl-2-pentene	23.80 ± 0.17
107-40-4	25	2,4,4-Trimethyl-2-pentene	2.14 ± 0.01
763-29-1	26	2-Methyl-1-pentene	27.80 ± 0.19
107-39-1	27	2,4,4-Trimethyl-1-pentene	13.00 ± 0.09
1632-16-2	28	2-Ethyl-1-hexene	22.03 ± 0.56
98-83-9	29	α-Methylstyrene	1.79 ± 0.01

[a] Values were calculated from the data in ref 8.

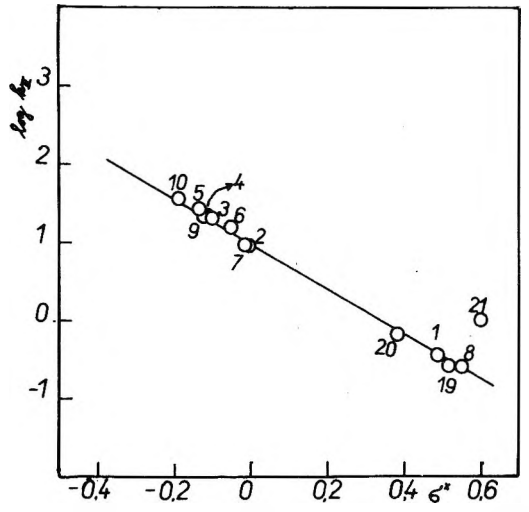


Figure 1. Verification of the Taft equation for the oxidation of $RCH{=}CH_2$ alkenes by thallium(III) sulfate at 25 °C: R = 0.999, S = 99.80%, a = 2.41.

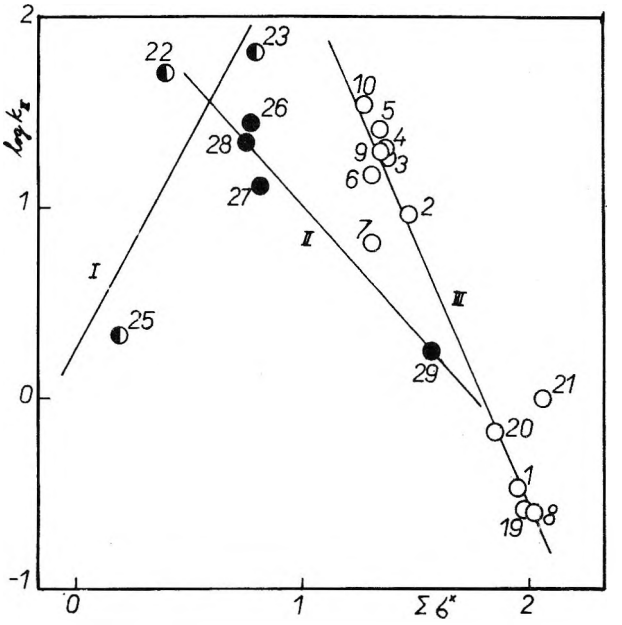


Figure 2. LFE–PE relationship of the oxidation of $R_1R_2C{=}CR_3R_4$ alkenes by thallium(III) sulfate at 25 °C: I, oxidation of internal alkenes, ◐; II, oxidation of $R_1R_2C{=}CH_2$ alkenes, ●; III, oxidation of $RCH{=}CH_2$ alkenes, ○.

tween mercuric ions (Hg^{2+} is isoelectronic with Tl^{3+}) and alkenes in water, resulting in stable hydroxymercuration adducts. For this reaction, Halpern and Tinker[29] found a correlation between reactivity of alkene and its structure (ρ^* = −3.3), which again is in accordance with the idea of the transition state with a character approaching that of the carbonium ion. A completely free (open) carbonium ion, however, can be ruled out for the hydroxymercuration, as the cis–trans isomerization of internal olefins, such as that of *cis*- or *trans*-butene[30] or *cis*-stilbene,[31] has not been observed during that reaction.[32]

In order to evaluate quantitatively the structure effects in the case of internal alkenes, it was necessary to introduce the hypothesis of the additivity polar and steric effects (Table II).

The measure of the validity of the additivity principle of polar effects is illustrated in Figure 2.

Palm[33] showed that for the quantitative evaluation of steric effects it is necessary to introduce other variables, resonance

Table II. Principle of Additivity for $R_1R_2C{=}CR_3R_4$ Alkenes

No.	Substituent R_1	R_2	R_3	R_4	$\Sigma\sigma^{*a}$	$\Sigma E_s{}^b$
1	H	H	H	H	1.960	4.96
2	CH_3	H	H	H	1.470	3.72
3	C_2H_5	H	H	H	1.370	3.65
4	n-C_3H_7	H	H	H	1.355	3.36
5	n-C_4H_9	H	H	H	1.340	3.33
6	n-C_5H_{11}	H	H	H	1.310	3.32
7	n-C_6H_{13}	H	H	H	1.310	3.31
8	CH_2OH	H	H	H	2.025	5.18
9	i-C_4H_9	H	H	H	1.345	2.79
10	i-C_3H_7	H	H	H	1.280	3.25
19	CH_3OCH_2	H	H	H	1.990	3.53
20	$Cl(CH_2)_2$	H	H	H	1.855	2.82
21	C_6H_5	H	H	H	2.070	4.96[b]
22	CH_3	CH_3	H	C_2H_5	0.390	1.17
23	CH_3	H	H	i-C_3H_7	0.790	2.01
25	CH_3	CH_3	H	t-C_4H_9	0.190	−0.30
26	n-C_3H_7	CH_3	H	H	0.765	2.12
27	neo-C_5H_{11}	CH_3	H	H	0.815	0.74
28	n-C_4H_9	C_2H_5	H	H	0.750	2.02
29	C_6H_5	CH_3	H	H	1.580	−0.07[c]

[a] Values were calculated from the data in ref 27. [b] Values were calculated from the data in ref 25. [c] Value was calculated from the data in ref 34.

Table III. Regression Analysis

Eq	$\log k_{11} = \rho^*\Sigma\sigma^* + b$				$\log k_{11} = \delta\Sigma E_s + c$				$\log k_{11} = \delta\Sigma E_s{}^\circ + d$			
	ρ^*	b	S, %	R	δ	c	S, %	R	δ	d	S, %	R
$RCH{=}CH_2$	−2.91 ± 0.08	6.35	95.45	0.977	−0.92 ± 0.06	6.66	84.46	0.919	−0.78 ± 0.10	5.62	77.26	0.879
Internal alkenes[a]			64.32	0.802			94.67	0.973			98.01	0.990
$R_1R_2C{=}CH_2$[a]			95.45	0.977			86.12	0.928			81.72	0.904

[a] There are not enough compounds to attempt a correlation slope.

effects and the nonclassical bonding interactions, which can be included as a contribution of the C–C as well as the C–H hyperconjugation to E_s. In this way, one gets the new "right steric constant" $E_s{}^\circ$:

$$E_s{}^\circ = E_s + 0.33(n_H - 3) + 0.13n_C \quad (4)$$

Results of these relationships are in Table III. From Table III it is obvious that oxidation of $RCH{=}CH_2$ alkenes by thallium(III) sulfate in aqueous medium may be correlated with solely the polar Taft equation. In addition, from here it can be seen that steric and resonance effects are the most important factors in the oxidation of internal alkenes. The relatively considerable importance of the resonance effects in this case explains the observed isomerization of the oxidation of 2,4,4-trimethyl-2-pentene.[18]

The combined linear free energy–polar energy and steric energy relationship is best expressed, for the oxidation of $R_1R_2C{=}CR_3R_4$ alkenes, by the modified eq 2. Using a multiple linear regression analysis it is found that the rates of oxidation are satisfactorily fitted by eq 5:

$$\log k_{II} = -(2.75 \pm 0.37)\Sigma\sigma^* + (0.97 \pm 0.41)\Sigma E_s + (3.24 \pm 0.94) \quad (5)$$

The correlation coefficient is 0.946; the scope of validity 89.49%. Representation of this relationship is in Figure 3.

A similar conclusion has been found for the bromination of mono-, di-, tri-, and tetrasubstituted olefins.[36]

The second stage of reaction which, according to the interpretation that we have adopted, corresponds to the dethallation step and formation of the final oxidation products (eq B), was examined from point of view of selectivity. For these substrates the proposed dethallation step, following the interpretations of Henry[8] and other previous workers, can be represented as

$$[RCH(OH)CH_2Tl]^{2+} \rightarrow \left[R{-}\underset{\displaystyle O\,|\,H}{\overset{\displaystyle H}{\overset{|}{C}}}{-}CH_2 \ldots Tl^+ \right]^{2+} \xrightarrow[S_Ni]{H^- \text{ shift}} RCOCH_3 + Tl^+ + H^+ \quad (C)$$

$$\left[R{-}\underset{\displaystyle O\,|\,H}{\overset{\displaystyle H}{\overset{|}{C}}}{-}CH_2 \ldots Tl^+ \right]^{2+} \xrightarrow[S_N2]{+H_2O} RCH(OH)CH_2OH + Tl^+ + H^+$$

There is the case when a compound satisfying the structural assumption for a given empirical relationship undergoes two concurrent reactions of the same order (to the intermediate hydroxythallation adduct). Then, according to absolute rate theory,[35] the ratio of the amounts of both products X_c/X_g is independent of time and equal to the ratio of the two kinetic constants k_c/k_g.

$$\log (X_c/X_g) = \log (k_c/k_g) = (\rho_c{}^* - \rho_g{}^*)\sigma^* + \log (k_c{}^0/k_g{}^0) \quad (6)$$

For the oxidation of $RCH{=}CH_2$ and $R_1R_2C{=}CH_2$ the dependence of the yield of the carbonyl (X_c) and glycol (X_g) on the substituent R was investigated (Table IV, Figure 4).

A quantitative estimation (Table III) suggested that the effect of the substitution is exclusively polar. The slope in

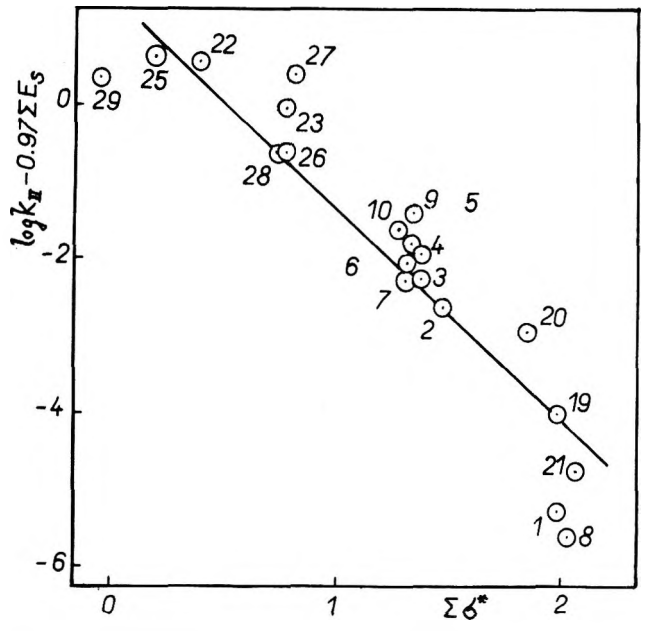


Figure 3. Reactivity of $R_1R_2C{=}CR_3R_4$ alkenes in the oxidation by thallium(III) sulfate in aqueous medium as a function of polar and steric effects at 25 °C.

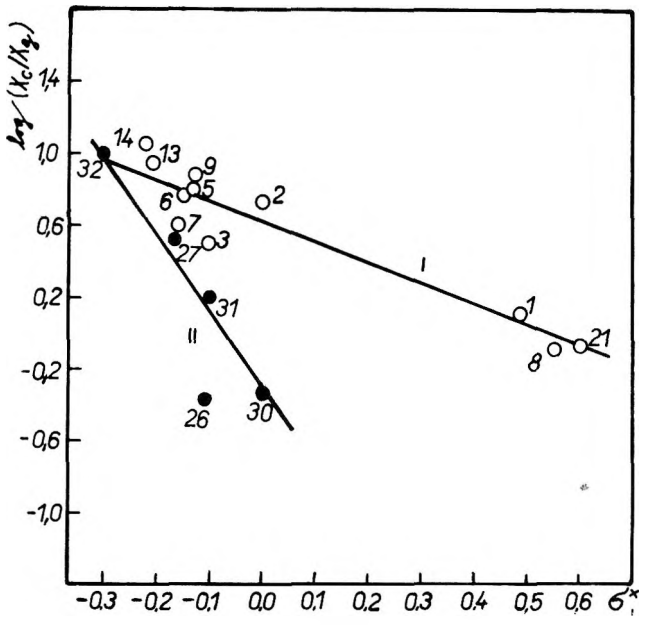


Figure 4. Dependence of selectivity on the structure of alkenes for their oxidation by thallium(III) sulfate at 20 °C:[37] I, oxidation of $RCH{=}CH_2$ alkenes, $(\rho_c^* - \rho_g^*) = -1.20 \pm 0.15$, $\log (k_c^0/k_g^0) = 1.05$, $R = 0.950$, $S = 90.25\%$; II, oxidation of $R_1R_2C{=}CH_2$ alkenes, $(\rho_c^* - \rho_g^*) = -4.39 \pm 0.09$, $\log (k_c^0/k_g^0) = 3.52$, $R = 0.996$, $S = 99.20\%$.

Figure 4 (*I*), equal to -1.20 ± 0.15, has relatively a lower value, and is in agreement with the assumption of the S_N2 mechanism of the formation of vicinal glycol (eq C). The individual values of ρ_c^* and ρ_g^* cannot be determined, however, although it can be assumed with certainty that $|\rho_c^*| > |\rho_g^*|$ and hence $\rho_c^* < 0$. The assumption according to which ρ_g^* would be positive is quite acceptable. The effect on the migration aptitude of H^-, giving carbonyl product, is increased with electron-releasing substituents.

In the case of $R_1R_2C{=}CH_2$ alkenes it was considered necessary to stick to series with one constant substituent (CH_3). The correlation for these alkenes (Figure 4, II) has a considerable negative slope (-4.39 ± 0.09). The high absolute value of ρ^* is in agreement with the substitution directly in the C=C bond. There is the possibility that the R_1 and R_2 groups rearrange simultaneously with splitting off of the C–Tl bond and are completely rearranged by the time the Tl is detached.

Table IV. Structure Effects on the Distribution of Products of the Oxidation of $RCH{=}CH_2$ and $R_1R_2C{=}CH_2$ Alkenes by Thallium(III) Sulfate at 20 °C

$RCH{=}CH_2$	Mol fraction		$\Delta\Delta G^{\ddagger} = -2.303RT$
	Carbonyl[f]	Glycol	$\log (X_c/X_g)$, kcal[b]
H[a]	0.565	0.435	−0.15 ± 0.01
CH_3[a]	0.840	0.160	−0.98 ± 0.03
C_2H_5[a]	0.760	0.240	−0.67 ± 0.02
n-C_4H_9	0.865	0.135	−1.07 ± 0.06
i-C_4H_9	0.882	0.118	−1.17 ± 0.07
n-C_5H_{11}	0.853	0.147	−1.03 ± 0.04
n-C_6H_{13}	0.795	0.205	−0.79 ± 0.02
n-C_9H_{19}	0.901	0.099	−1.28 ± 0.04
n-$C_{10}H_{21}$	0.920	0.080	−1.42 ± 0.06
C_6H_5	0.461[c]	0.539	0.09 ± 0.01
CH_2OH	0.448[d]	0.552	0.12 ± 0.01
$R(CH_3)C{=}CH_2$			
CH_3[a,g]	0.455	0.545	0.46 ± 0.02
C_2H_5[h]	0.607	0.393	−0.25 ± 0.01
n-C_3H_7	0.274	0.610	0.47 ± 0.02
t-C_4H_9[i]	0.905	0.095	−1.31 ± 0.07
neo-C_5H_{11}[e]	0.244	0.073	−0.70 ± 0.04

[a] Values from ref 8. [b] $\Delta\Delta G^{\ddagger} = \Delta G_c^{\ddagger} - \Delta G_g^{\ddagger}$. [c] Phenylacetaldehyde. [d] Hydroxyacetone. [e] Others are the aldolization products. [f] Ketone ($RCH{=}CH_2$), ketones and aldehyde together ($R_1R_2C{=}CH_2$). [g] Registry no., 115-11-7. [h] Registry no., 563-46-2. [i] Registry no., 594-56-9.

Registry No.—Thallium(III) sulfate, 16222-66-5.

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(32) From Figure 1 it can see that point 21 (oxidation of styrene) is off the line. This can be explained by the fact that there is a resonance effect present. In the graph (Figure 1) values for the alkenes 11–18 are not plotted. The substituents on these alkenes are too great already so that they may cause rotation (mobile substituents) and hence hinder the admission of the thallic ion to the reaction center—this is against the principle of the conservation of rigidity.[28] In this way we have explained the relative low values of rate constants in comparison with the other RCH=CH_2 alkenes.
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(37) Number of alkenes see Table I. The other ones are **30** (isobutene), **31** (2-methyl-1-butene), **32** (2,3,3-trimethyl-1-butene).
(38) The following symbols are used: LFER, linear free energy relationships; PE, polar energy; SE, steric energy; σ^*, electrostatic and electronic effect of substituent (with respect to CH_3); ρ^*, parameter characteristic the sensibility of reaction to polar effects; E_s, steric parameter of substituent with respect to CH_3 (Taft); E_s^0, "right steric parameter" (Palm); δ, parameter characteristic the sensibility of reaction to steric effects; n_H, number of C–H bonds in α position with respect to substituent; n_C, number of C–C bonds in α position with respect to substituent; R, regression coefficient; $S = 100R^2$, the number of experimental results (%) that can be brought objectively into context with the linear regression relation.

Cationic Polymerizations by Aromatic Initiating Systems. 1. A Model for Initiation and Termination Using the *p*-$CH_3C_6H_4CH_2Cl/Et_3Al$ System

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Received July 2, 1976

The interaction between *p*-$CH_3C_6H_4CH_2Cl$ and Et_3Al (or Et_2AlCl) has been investigated using CH_2Cl_2 solvent in the range from −50 to −80 °C. The reaction yields three products: *p*-$CH_3C_6H_4CH_2Et$, *p*-$CH_3C_6H_4CH_2H$, and oligomeric polybenzyls. The first two arise upon ethylation and hydridation of the *p*-$CH_3C_6H_4{}^+CH_2$ cation by the Et_3AlCl^- counteranion while the third one is the result of self-polybenzylation. The relative amounts of termination products and polybenzyls can be controlled by temperature and reagent stoichiometry (Al/Cl ratio). Surprisingly, fastest *p*-$CH_3C_6H_4CH_2Cl$ disappearance was observed at low Al/Cl ratios. Kinetic studies indicate that ethylation and hydridation occur readily with Et_3Al, i.e., via the *p*-$CH_3C_6H_4{}^+CH_2$ Et_3AlCl^- pair, while the in situ formation of Et_2AlCl leads to the *p*-$CH_3C_6H_4{}^+CH_2$ $Et_2AlCl_2^-$ pair which in turn gives rise mainly to polybenzyls. The understanding of the mechanism of ethylation and hydridation in the *p*-$CH_3C_6H_4CH_2Cl/Et_3Al$ reaction is important as a model of initiation followed by immediate termination of cationic polymerizations by benzyl halide/alkylaluminum initiator systems.

During our fundamental studies on the mechanism of cationic olefin polymerizations it appeared of interest to investigate the mechanism of initiation by the use of aromatic cations, in particular to study the initiation of isobutylene polymerization by the $CH_3C_6H_4{}^+CH_2$ cation and thus to introduce a UV-active *p*-methylbenzyl head group into a polyisobutylene chain. Quantitative analysis of UV-active aromatic head groups promised to provide increased insight into the mechanistic details of initiation and chain breaking.

We have shown that isobutylene polymerization can be initiated readily by the use of a variety of tertiary alkyl and allyl halides in conjunction with alkylaluminum compounds,[1,2] presumably by direct alkylation of the olefin:

$$RX + Et_2AlX \rightarrow R^+Et_2AlX_2^- \text{ (or } R^+//Et_2AlX_2^-)$$

$$R^+Et_2AlX_2^- + C{=}C \rightarrow R{-}C{-}C^+\ Et_2AlX_2^-$$

$$R{-}C{-}C^+ + nC{=}C \rightarrow R{+}C{-}C{+}_nC{-}C^+$$

R = tertiary alkyl or allyl, X = halide

This paper concerns the interaction between the benzyl halide (initiator) and alkylaluminum (coinitiator) in the absence of olefin and the effect of experimental variables on the reaction. Subsequent papers of this series will deal with further model studies and polymerizations.

Because benzyl chloride in the presence of Friedel–Crafts acids readily undergoes self-benzylation and rapidly leads to polybenzyls,[6] an undesirable side reaction for our study, we used the *p*-methyl substituted derivate, *p*-methylbenzyl chloride, to afford at least some protection against para self-benzylation and to increase the reaction rate.

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Results and Discussion

A. Interaction between *p*-Methylbenzyl Chloride and Triethylaluminum. The reaction between alkyl chlorides and alkylaluminums may be viewed as a model for initiation followed by immediate termination in carbenium ion polymerization ("polymerization without propagation").[1,2] In particular, the first step is the generation of a carbenium ion R^+

$$RCl + R_3'Al \rightarrow R^+ + R_3'AlCl^-$$

which in the absence of monomer is rapidly followed by the collapse of the cation–counterion pair by alkylation

$$R^+ + R_3'AlCl^- \rightarrow R{-}R' + R_2'AlCl$$

or by hydridation if a β hydrogen with respect to aluminum is available:[2-4]

$$R^+ + Et_3AlCl^- \rightarrow RH + CH_2{=}CH_2 + Et_2AlCl$$

With aromatic carbenium ion sources, specifically with *p*-methylbenzyl chloride and triethylaluminum, the following reactions are expected to occur:

$$CH_3C_6H_4CH_2Cl + Et_3Al \rightleftharpoons CH_3C_6H_4\overset{+}{C}H_2 + Et_3AlCl^- \quad (1)$$

$$CH_3C_6H_4\overset{+}{C}H_2 + Et_3AlCl^- \rightarrow CH_3C_6H_4CH_2Et + Et_2AlCl \quad (2)$$

$$CH_3C_6H_4\overset{+}{C}H_2 + Et_3AlCl^- \rightarrow CH_3C_6H_4CH_2H + CH_2{=}CH_2 + Et_2AlCl \quad (3)$$

Table I. The Effect of Reaction Conditions on p-Methylpropylbenzene and p-Xylene Formation[a]

$[p\text{-}CH_3C_6H_4CH_2Cl]$, M	[Alkylaluminum] / $[p\text{-}CH_3C_6H_4CH_2Cl]$	Temp, °C	$\frac{[p\text{-}CH_3C_6H_4CH_2Et] + [p\text{-}CH_3C_6H_6CH_2H]}{[p\text{-}CH_3C_6H_4CH_2Cl]_0} \times 100$[b]	$\frac{[p\text{-}CH_3C_6H_4CH_3Et]}{[p\text{-}CH_3C_6H_4CH_2H]}$[b]
	Et_3Al			
0.012	1	−50	13	3.4
0.012	1	−50	12	3.5
0.020	1	−65	17	2
0.020	1	−80	20	1.7
0.020	2	−80	35[c]	1.8
0.020	5	−80	63	1.6
0.020	10	−80	78	1.6
0.020	20	−80	90	1.8
0.0075	16	−80	75[d]	1.8
	Et_2AlCl			
0.020	5	−80	5	
0.020	10	−80	7	2.5
0.020	20	−80	10	1.9

[a] Solvent CH_2Cl_2. [b] After total p-$CH_3C_6H_4CH_2Cl$ consumption. [c] At 93% p-$CH_3C_6H_4CH_2Cl$ consumption. [d] At 72% p-$CH_3C_6H_4CH_2Cl$ consumption.

We have studied the interaction between p-$CH_3C_6H_4CH_2Cl$ and Et_3Al at Et_3Al/p-$CH_3C_6H_4CH_2Cl$ (Al/Cl) ratios ≥1 using CH_2Cl_2 solvent in the range from −50 to −80 °C. The Al/Cl ratio was changed by changing the concentration of the Et_3Al; the concentration of p-$CH_3C_6H_4CH_2Cl$ was kept constant. A few experiments with Et_2AlCl have also been carried out. Table I shows representative data. High Al/Cl ratios and low temperatures were used to minimize side reactions leading to undesirable products.

Confirming our analysis above, evidence for the presence of p-methylpropylbenzene and p-xylene has been found. Quantitative material balance determinations, however, have indicated that in addition to these two expected "termination products", other resinous materials, probably polybenzyls, have also been formed, the structure(s) of which have not been analyzed in detail. The terminology "termination products" refers to termination by ethylation and hydridation of cationic polymerization by the Et_3AlCl^- counteranion.

The yield of p-$CH_3C_6H_4CH_2Et$ and p-$CH_3C_6H_4CH_2H$ is strongly affected by the initial molar ratio of Et_3Al/p-$CH_3C_6H_4CH_2Cl$ (Al/Cl ratio). The ratio p-$CH_3C_6H_4CH_2Et/p$-$CH_3C_6H_4CH_2H$ (column 5 in Table I) reflects the relative rates of ethylation and hydridation and is affected by the temperature, i.e., it increases from 1.7 to 3.4 by raising the temperature from −80 to −50 °C. Similarly to these results, ethylation was found to be 2.3 times faster than hydridation when α-phenethyl chloride was reacted with Et_3Al using EtCl solvent at −65 °C.[5] The relative rates of ethylation vs. hydridation are probably governed by steric factors, i.e., the four-membered transition state leading to ethylation is more compressed than the six-membered one leading to hydridation.[2]

Column 4 in Table I shows the overall yield of ethylation and hydridation. Highest yields (80–90%) are obtained at Al/Cl ratios of 10–20 whereas the yields drop with decreasing Al/Cl ratios. In addition to these well-defined termination products a yellow-brown, resinous, brittle material, conceivably a mixture of oligobenzyls or polybenzyls, is formed, the structure and composition of which have not been studied. Such polybenzyls are expected to form upon mixing p-$CH_3C_6H_4CH_2Cl$ with Friedel–Crafts acids.[6] Thus in the polymerization of isobutylene using the benzyl halide/Et_3Al initiator system, the initiator consumption by Friedel–Crafts alkylation would be reduced at higher Al/Cl ratios.

A few experiments have also been carried out with Et_2AlCl. The yield of p-$CH_3C_6H_4CH_2Et$ plus p-$CH_3C_6H_4CH_2H$ (termination products) obtained with this relatively strong Lewis acid was much lower (<10%) and that of polybenzyls much higher even at high Al/Cl ratios than with the weaker Et_3Al (cf. Table I). This observation is probably due to the different nucleophilicities of the counterions: polybenzylation is more likely to occur in the presence of the less nucleophilic $Et_2AlCl_2^-$ than with the more nucleophilic Et_3AlCl^-. The lifetime of the benzyl cation is longer when it is associated with $Et_2AlCl_2^-$ and thus polyalkylation is favored; in contrast, the lifetime of the carbocation is shorter and ethylation or hydridation is favored over that of polybenzylation in the presence of the more nucleophilic Et_3AlCl^-. Differences in the tightness of these ion pairs has already been invoked by Kennedy and Rengachary[2] to explain rapid termination by Et_3AlCl^- of isobutylene polymerizations.

Finally, another important observation was the absence of p-$CH_3C_6H_4CH_2OCH_3$ among the reaction products. Since all experiments were quenched by the addition of methanol, we expected the formation of this ether; however, we did not find any evidence for the presence of p-$CH_3C_6H_4CH_2OCH_3$ among the reaction products. The mechanism discussed in the next section helps to rationalize this observation.

B. Kinetic Studies. Kinetic experiments have been carried out to study the effect of the Al/Cl ratio and temperature on the p-$CH_3C_6H_4CH_2Cl + Et_3Al$ reaction. Figure 1 summarizes our data obtained at Al/Cl = 1, 2, and 20 at −80 °C by plotting the rate of disappearance of p-$CH_3C_6H_4CH_2Cl$ and the rates of appearance of the products of ethylation and hydridation, respectively.

Surprisingly, the rate of p-$CH_3C_6H_4CH_2Cl$ disappearance is fastest at the lowest Et_3Al concentration, i.e., at Al/Cl = 1, and decreases by increasing the Al/Cl ratio from 1 to 5. Above Al/Cl ≈ 5 the rates remain essentially constant within what is considered to be experimental error. Other data (not shown) indicate that p-$CH_3C_6H_4CH_2Cl$ consumption is faster at −65 °C and that the yield of termination products is lower than at −80 °C.

The p-$CH_3C_6H_4CH_2Et/p$-$CH_3C_6H_4CH_2H$, i.e., the termination product ratio, seems to remain constant throughout the reaction; however, the amount of these products formed is a function of the Al/Cl ratio, and highest ethylation plus hydridation (~90%) occurs at highest (20) Al/Cl values. This

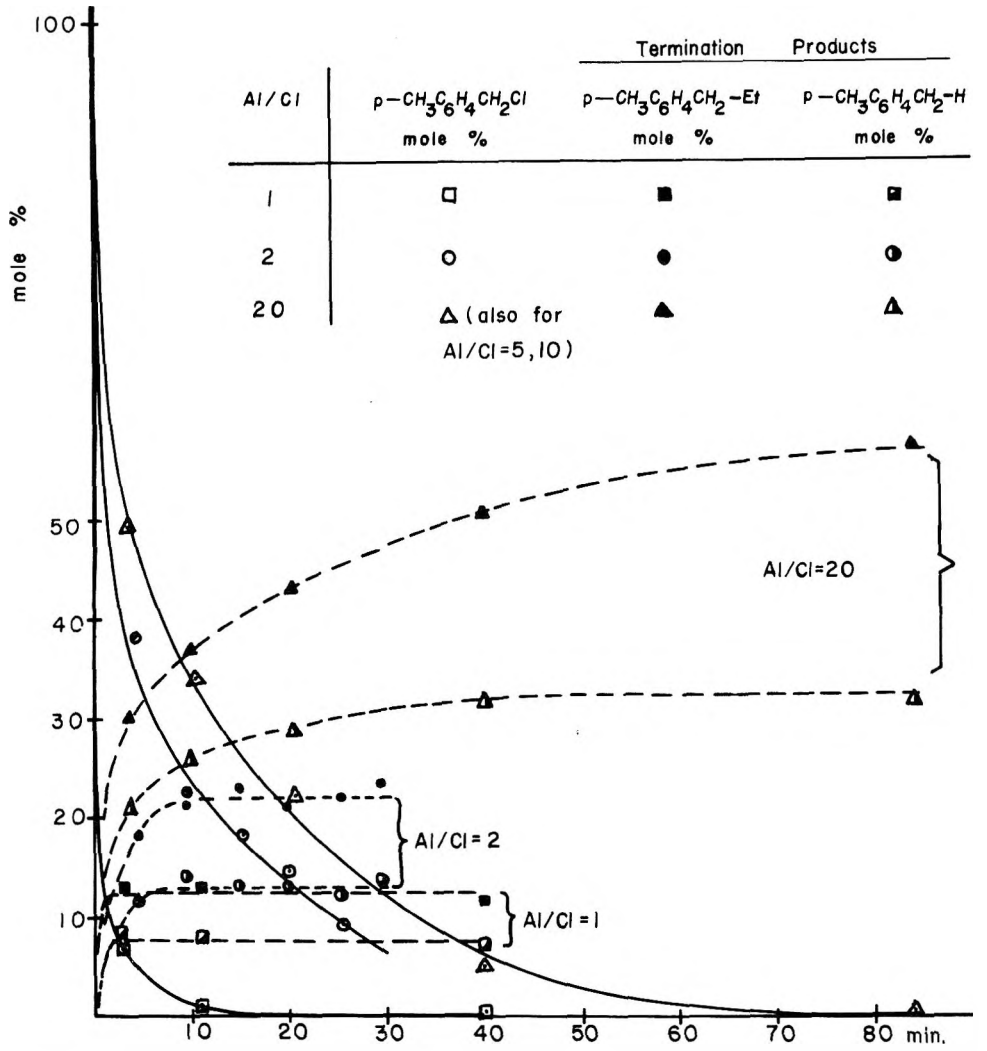

Figure 1. Effect of the Al/Cl ratio on the rate of p-$CH_3C_6H_4CH_2Cl$ disappearance and the rate of formation of p-$CH_3C_6H_4CH_2Et$ and p-$CH_3C_6H_4CH_2H$ ([p-$CH_3C_6H_4CH_2Cl$] 0.02 M, −80 °C).

statement is illustrated by Figure 2, which shows the sum of termination products (in mol % of p-$CH_3C_6H_4CH_2Cl$) and the termination products/polybenzyls ratio as a function of Al/Cl. The termination products/polybenzyls mole ratio was calculated from the analytically directly available sum of p-$CH_3C_6H_4CH_2Et$ and p-$CH_3C_6H_4CH_2H$ and the molar amount of polybenzyl that was obtained by assuming that besides the two termination products only polybenzyls formed.

On closer examination of our results it became increasingly apparent that the kinetics governing this reaction are more complex, partly because at least two of the by-products, i.e., Et_2AlCl and $CH_3C_6H_4CH_2$-$C_6H_3(CH_3)CH_2Cl$, are much more reactive than the original reagents and partly because the nature and polarity of the reagents change during the reaction thus leading to unpredictable/uncontrollable changes in rates and solvation. While the extent of our data is far from sufficient for a complete kinetic analysis, indeed such an analysis is quite outside the scope of these studies, they still allow the drawing of some conservative conclusions valuable for the understanding of the mechanism of these reactions and, by inference, for the mechanism of cationic polymerization initiated by benzyl cations.

The key to the understanding of these at first glance unexpected observations described in this and the previous section is to rationalize why the rate of disappearance of p-$CH_3C_6H_4CH_2Cl$ decreases with increasing Et_3Al concentration at constant initial p-$CH_3C_6H_4CH_2Cl$ concentration. A possible explanation is provided by the following set of equations:

$$CH_3C_6H_4CH_2Cl + Et_3Al \overset{K}{\rightleftharpoons} [CH_3C_6H_4\overset{+}{C}H_2\ Et_3AlCl^-]$$

$$[CH_3C_6H_4\overset{+}{C}H_2\ Et_3AlCl^-] \longrightarrow CH_3C_6H_4CH_2Et + Et_2AlCl$$

$$[CH_3C_6H_4\overset{+}{C}H_2\ Et_3AlCl^-] \longrightarrow CH_3C_6H_4CH_2H + CH_2{=}CH_2 + Et_2AlCl$$

$$[CH_3C_6H_4\overset{+}{C}H_2\ Et_3AlCl^-] \xrightarrow{n\text{-}CH_3C_6H_4CH_2Cl} CH_3C_6H_4CH_2C_6H_3(CH_3)CH_2Cl + Et_2AlCl + C_2H_6$$

(and similar polybenzyls)

$$CH_3C_6H_4CH_2Cl + Et_2AlCl \overset{K'}{\rightleftharpoons} [CH_3C_6H_4\overset{+}{C}H_2\ Et_2AlCl_2^-] \longrightarrow \text{mainly polybenzyls (cf. Table I)}$$

According to this mechanism the two reactants rapidly form an ion pair. In line with similar carbenium ion systems the equilibrium constant K which governs the concentration of the ion pair is probably quite low. This ion pair is formed from a large reservoir of $CH_3C_6H_4CH_2Cl$-Et_3Al molecular complex. A similar problem has already been treated in greater depth in conjunction with the t-BuCl-Me_3Al system.[1] The ion pair can either collapse to the two termination products or ring-benzylate the unreacted p-$CH_3C_6H_4CH_2Cl$ to give a mixture of polybenzyls. All these reactions, i.e., ethylation, hydridation, and polybenzylation, give rise to Et_2AlCl. This species,

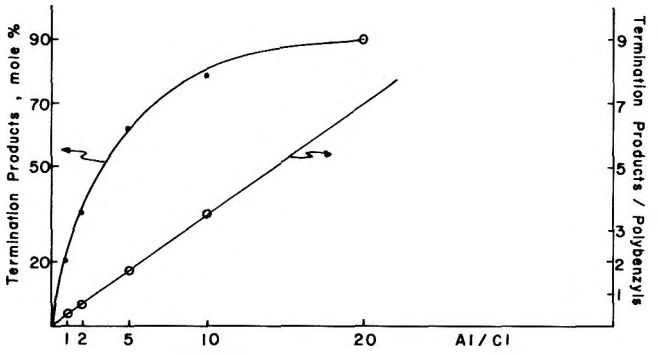

Figure 2. Termination products as a function of Al/Cl.

being a stronger Lewis acid than Et_3Al, will much more rapidly react with unconverted p-$CH_3C_6H_4CH_2Cl$ to produce polybenzyls than Et_3Al. Indeed, it is well known that Et_2AlCl rapidly converts benzyl halides to polybenzyls[6,7] and our own experiments also indicate that Et_2AlCl consumes p-$CH_3C_6H_4CH_2Cl$ much more rapidly than Et_3Al and gives almost exclusively polybenzyls (cf. Table I). In the reaction under investigation Et_3Al and Et_2AlCl compete for p-$CH_3C_6H_4CH_2Cl$; while the p-$CH_3C_6H_4{}^+CH_2$ Et_3AlCl^- ion pair rapidly collapses either by ethylation or hydridation, the p-$CH_3C_6H_4{}^+CH_2$ $Et_2AlCl_2{}^-$ pair is longer lived and produces mainly polybenzyls.

By increasing the concentration of Et_3Al relative to that of p-$CH_3C_6H_4CH_2Cl$, i.e., increasing the Al/Cl ratio, the rate of p-$CH_3C_6H_4CH_2Cl$ disappearance decreases (cf. Figure 1), most likely because the concentration of unreacted p-$CH_3C_6H_4CH_2Cl$ (and consequently the rate of polybenzyl formation) decreases. In other words, at high Al/Cl ratios the concentration of the ion pair increases while that of the free p-$CH_3C_6H_4CH_2Cl$ decreases, which results in reduced polybenzylation rates. Apparently at Al/Cl = 1.0 sufficient p-$CH_3C_6H_4CH_2Cl$ remains for rapid polybenzylation while at Al/Cl > 5 unconsumed p-$CH_3C_6H_4CH_2Cl$ is converted to the p-$CH_3C_6H_5{}^+CH_2$ cation thus reducing the rate of polybenzylation. Indeed, at Al/Cl = 20 hardly any polybenzyl is formed.

The fact that in the Al/Cl range from 1.0 to 5.0 polybenzyl formation predominates suggests that polybenzylation is extremely rapid and it is able to compete with ethylation and/or hydridation, rapid first-order reactions involving the collapse of an ion pair. In the system under investigation the ion pair may be highly solvated p-$CH_3C_6H_4{}^+CH_2//et_3AlCl^-$ and the carbenium ion may be preferentially solvated by the reagent p-$CH_3C_6H_4CH_2Cl$ rather than the CH_2Cl_2 solvent.

The fact that p-$CH_3C_6H_4CH_2OCH_3$ has not been found among the reaction products after quenching with methanol is explained by the very small equilibrium concentration of the carbenium ion pair p-$CH_3C_6H_4{}^+CH_2$ Et_3AlCl^-.

We can compare the reults obtained with the t-BuCl/Me_3Al/CH_3Cl system[1] and those of the present study with p-$CH_3C_6H_4CH_2Cl/Et_3Al/CH_2Cl_2$. The t-BuCl + Me_3Al reaction gave only the one expected termination product, t-BuMe (neopentane); however, in the present case, in addition to the expected two termination products, polybenzyls have also been obtained. The formation of polybenzyls indicates the great facility of alkylations in these systems. Since aromatic compounds lead to undesirable, complex ring alkylations, their use should be minimized in the study of the mechanism of cationic polymerization.

The overall activation energy of the p-$CH_3C_6H_4CH_2Cl$ + Et_3Al reaction was determined by carrying out a series of experiments at −49, −64, and −80 °C (p-$CH_3C_6H_4CH_2Cl$ 0.01 M, CH_2Cl_2 solvent) at Al/Cl = 20 to minimize polybenzyl

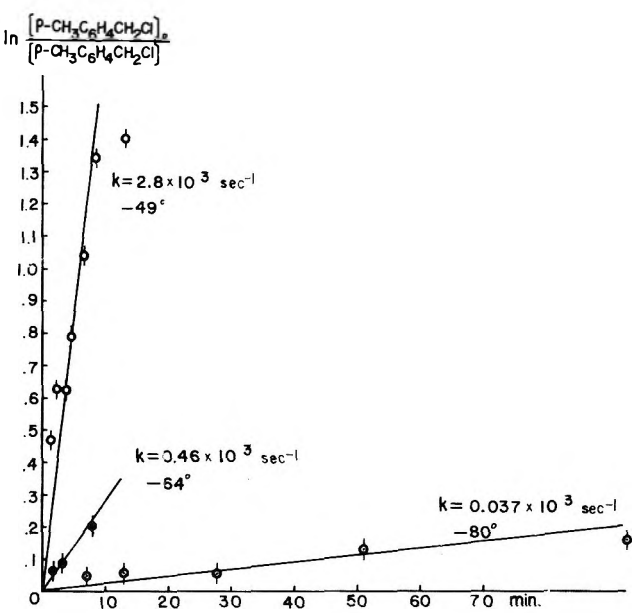

Figure 3. First-order plot of the p-$CH_3C_6H_4CH_2Cl$ + Et_3Al reaction ([p-$CH_3C_6H_4CH_2Cl$] 0.01 M).

formation. The accuracy of the data was not sufficient to determine unambiguously the order of the reaction with respect to p-$CH_3C_6H_4CH_2Cl$. However, assuming that the rate of p-$CH_3C_6H_4CH_2Cl$ disappearance is first order we have determined the reaction rate constants (Figure 3) and constructed the Arrhenius plot from these data. According to these results $k = 2.8 \times 10^{-3}$, 0.46×10^{-3}, and 0.037×10^{-3} at −49, −64, and −80 °C, respectively, and the overall activation energy of the reaction $\Delta E = 12 \pm 1$ kcal/mol. This value is very similar to those obtained for the *tert*-butyl halide + Me_3Al reactions using polar solvents (10 ± 1 kcal/mol) (5).

Experimental Section

Alkylaluminium compounds (Ethyl Co.), p-methylbenzyl chloride (Aldrich), and n-nonane (Chemical Samples Co.) were commercially available. These materials were distilled in the absence of oxygen and moisture. Distilled Et_2ClAl was stored over sodium chloride to prevent the accumulation of $EtAlCl_2$. Methylene chloride (Matheson) was refluxed over Et_3Al and freshly distilled before use. All experiments and material handlings were performed in a stainless steel enclosure under N_2 atmosphere (<50 ppm moisture), using Pyrex glassware with septum caps. The glassware was dried at 140 °C for 24 h and cooled under nitrogen.

A representative experiment (line 10 in Table I) was carried out as follows. To 10 ml of CH_2Cl_2 was added 1.23 ml of Et_3Al (0.8 M Et_3Al). Of this solution 5 ml was poured into a round-bottom flask. The flask was tightly capped with a septum cap and cooled to −80 °C. A solution containing 0.57 ml of p-$CH_3C_6H_4CH_2Cl$ and 10 ml of CH_2Cl_2 was prepared in a test tube and further diluted tenfold (0.04 M p-$CH_3C_6H_4CH_2Cl$). The test tube was capped and cooled to −80 °C. After temperature equilibrium 4.5 ml of this solution at −80 °C (5 ml at room temperature) was rapidly added by a prechilled pipet to the 5 ml of 0.8 M solution Et_3Al and the round-bottom flask capped again and shaken. Subsequently, 1-ml aliquots of the mixture were withdrawn at suitable intervals by means of a prechilled syringe and poured into test tubes containing 0.5 ml of prechilled CH_3OH. Then 1 ml of 0.082% p-methylethylbenzene in CH_2Cl_2 was added as an internal standard to the quenched solution. n-Nonane was the internal standard in the three experiments illustrated in Figure 3. The aluminum oxide residues were separated from the organic phase by adding aqueous sodium–potassium tartrate at 0 °C.

After extraction, the organic layers were analyzed using a Hewlett-Packard 5750 research chromatograph with a flame detector. The column used (12 ft × 0.125 in.) contained 10% SE-30 Silicone gum as a liquid phase and helium was the carrier gas. The reaction products were identified by peak enhancement using authentic samples. Conditions when p-$CH_3C_6H_4CH_2CH_3$ was the standard: injection port 230 °C, oven 130 °C; retention times (in s) 150 (p-$CH_3C_6H_4CH_3$),

210 (p-$CH_3C_6H_4CH_2CH_3$), 320 (p-$CH_3C_6H_4CH_2CH_2CH_3$), 420 (p-$CH_3C_6H_4CH_2Cl$). Using n-nonane as a standard: injection port 230 °C, oven 110 °C for 4 min, raised to 148 °C at 30 °C/min and held at limit; retention times (in s) 190 (p-$CH_3C_6H_4CH_3$), 215 (n-nonane), 390 (p-$CH_3C_6H_4CH_2CH_2CH_3$), 450 (p-$CH_3C_6H_4CH_2Cl$).

The accuracy of the determination of p-$CH_3C_6M_4CH_2Cl$ concentration was estimated to be ±5%.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also wish to thank Professor M. Litt for his valuable comments.

Registry No.—p-$CH_3C_6H_4CH_2Cl$, 104-825; Et_3Al, 97-93-8; Et_2AlCl, 96-10-6; p-methylpropylbenzene, 1074-55-1; p-xylene, 106-42-3.

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Neopentylallyllithium. 5. Stereochemistry of Nonrearrangement Reactions with Epoxides

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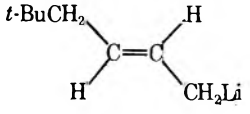
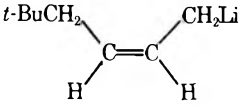
Received August 4, 1976

Reactions of neopentylallyllithium (NpALi), the 1:1 addition product of *tert*-butyllithium and 1,3-butadiene, with cyclohexene oxide and *cis*- and *trans*-2,3-epoxybutane are reported. In aliphatic hydrocarbon solvent each reaction is shown to consist predominantly of "normal," i.e., nonrearranged, addition of the allylic system to the epoxide. The products are shown to be those arising from trans ring opening of the epoxide.

In previous papers in the series, we have examined some of the spectra[1,2] and reactions[3,4] of neopentylallyllithium I (NpALi), the 1:1 addition product of *tert*-butyllithium and 1,3-butadiene. NpALi exists as a "partially delocalized" species in hydrocarbon solvents,[1,5-7] but the evidence presently available speaks against the existence of a dynamic allyl equilibrium of the classical type.[8] Thus, cis and trans isomers of NpALi (Ia and Ib) are directly observable in the ^1H NMR



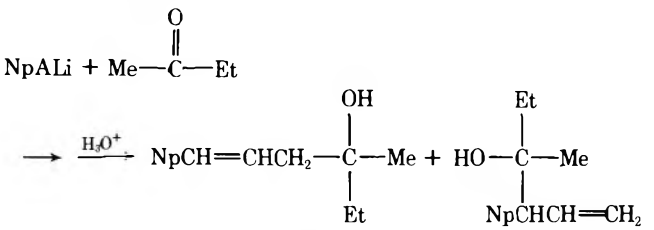
Ia



Ib

spectrum and do not appear to interconvert in the absence of Lewis bases such as THF. In the absence of such agents, NpALi may be considered as a nondynamic mixture of Ia and Ib, probably in the form of mixed dimers and tetramers[1] in which there is some delocalization of charge from the α to the γ carbon atom. The extent of this delocalization is increased by the addition of THF and other Lewis bases[2] and by the replacement of lithium with sodium and potassium.[9]

The reactions of NpALi in hydrocarbon solvents differ from those in ether solvents and from the corresponding allylmagnesium compounds[10] in that they usually yield lesser amounts of "rearranged" products. As one example, we have reported that NaALi reacts with 2-butanone to yield 52%



IIa (trans)
IIb (cis)

IIc

rearranged product IIc in pentane[3] and 78% in THF[4] as compared to 70% and 96% of the same product from bis(neopentylallyl)magnesium in pentane and diethyl ether solvents, respectively.[11]

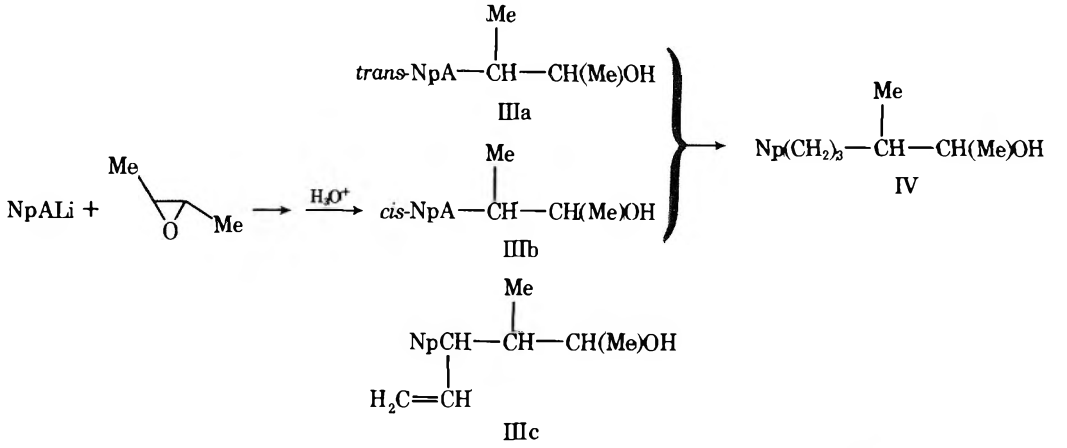
We now report on the reactions of NpALi in THF and pentane with another class of reagents, namely epoxides. Allyl metal compounds are known to add to epoxides to yield secondary carbinol salts, and such reactions have been the subject of numerous papers. Recently, Courtois and Miginiac have reviewed this reaction for zinc, cadmium, lithium, sodium, magnesium, and aluminum allylic compounds.[12] However, the present work represents the first report on the reaction of epoxides with an allylic lithium species in hydrocarbon solvent and is the first to establish the stereochemistry of the nonrearrangement process leading to products analogous to IIa and IIb.

Results and Discussion

Reaction of NpALi with 2,3-Epoxybutanes. NpALi prepared in pentane as described before[3] consists of a mixture of trans and cis isomers in 3:1 ratio. Upon reaction with *trans*-2,3-epoxybutane (and subsequent hydrolysis), NpALi yields a mixture of three compounds identified as IIIa-c (eq 1). The relative amounts of the products are shown in Table I; absolute yields totaled approximately 90% (internal standard GC). The identity of the three compounds IIIa-c was established by a combination of IR, ^1H NMR, MS, and elemental analyses (see Experimental Section for details).

Likewise, *cis*-2,3-epoxybutane yields compounds IIIa′-c′ as shown in Table I. However, the GC retention times of the products from the cis and trans epoxides were observed to be different. This observation was not unanticipated, since the two epoxides were expected to give different diastereomeric alcohols which would probably be separated by GC.

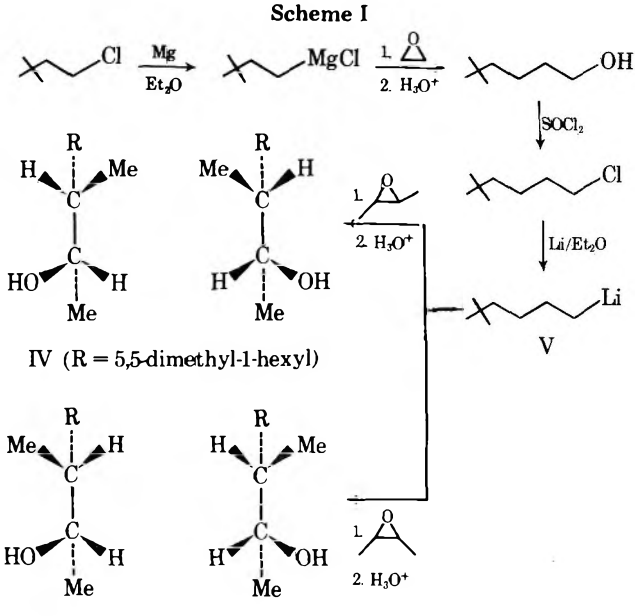
The identification of IIIa,b and IIIa′,b′ as the "nonrearranged" diastereomeric alcohols resulting from trans addition of NpALi to the corresponding epoxides was accomplished



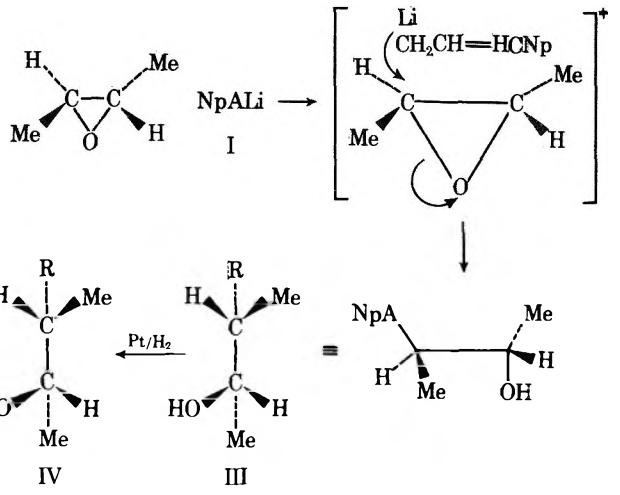
by a method originally employed by Felkin and co-workers.[13] IIIa and IIIb were collected by preparative GC and hydrogenated with platinum black catalyst to IV, shown by GC to be a single compound. Subsequently, IV was shown to be 2-(*R,S*)-hydroxy-3-(*R,S*)-8,8-trimethylnonane by the alternate synthetic route shown in Scheme I. In a similar manner, IV′ from the cis epoxide was shown to be 2-(*R,S*)-hydroxy-3-(*S,R*)-8,8-trimethylnonane.

The critical step in the alternate route to IV and IV′ shown in Scheme I involves the addition of 5,5-dimethyl-1-hexyllithium (V) to *cis*- and *trans*-2,3-epoxybutanes. We assume this reaction to be a trans addition process on the basis of the work of Malenovskii and co-workers.[13] In their work, *n*-propyllithium and *n*-butyllithium were shown to add to epoxides in a trans process. We assume that the saturated lithium alkyl V is analogous to the reagents used by Malenovskii et al., thus establishing the reaction of I with both epoxides to be a trans addition process as well (Scheme II). An S_E2 process such as that shown in Scheme II would account for the present observations. However, we have no evidence to exclude a prior dissociation of the lithium compound I to form an allylic anion which then attacks the epoxide in a trans addition process. Indirect evidence in favor of such an ionic mechanism may be inferred from the fact that the same products are observed in THF, a solvent in which the predominant organometallic species are ion pairs.[2,9] As expected, the product corresponding to allylic rearrangement (IIIc) is enhanced in THF, but it is still the minor product. This is in sharp contrast to reports of similar reactions of allylic Grignard reagents

Scheme I



Scheme II



wherein the rearranged product is usually formed in yields greater than 80%.[13] It should also be noted that the relative yield of the cis olefinic addition product (IIIb or IIIb′) is substantially increased upon the addition of THF solvent to the reacting system. We have previously noted that this effect occurs in all reactions of NpALi in THF vs. hydrocarbon solvents[4] and parallels an observed increase in the relative concentration of the *cis*-NpALi species as observed by ^1H NMR.[2] That the cis anion is more stable than the trans form is corroborated by recent work on the analogous sodium compound[9] in which the cis/trans ratio is even higher than that for the lithium allyl.

Reaction of NpALi with Cyclohexene Oxide. This reaction yields three products which have been identified as VIa–c. Again, the major products are IVa and VIb, the products which correspond to normal, i.e., nonrearranged, addition (Table I). The ^1H NMR spectra of compound VIa, the major

Table I. Product Yields from NpALi–Epoxide Reactions in Pentane and THF[a]

Epoxide	Solvent: Pentane	Solvent: THF
trans-2,3-Epoxybutane	IIIa (80); IIIb (11); IIIc (9)	IIIa (34); IIIb (39); IIIc (27)
cis-2,3-Epoxybutane	IIIa′ (68); IIIb′ (13); IIIc′ (18)	IIIa′ (29); IIIb′ (32); IIIc′ (39)
Cyclohexene oxide	VIa (65); VIb (15); VIc (20)	VIa (30); VIb (41) VIc (29)

[a] Roman numerals refer to structures on text; figures in parentheses refer to relative yields of isomeric alcohols as determined by GLC.

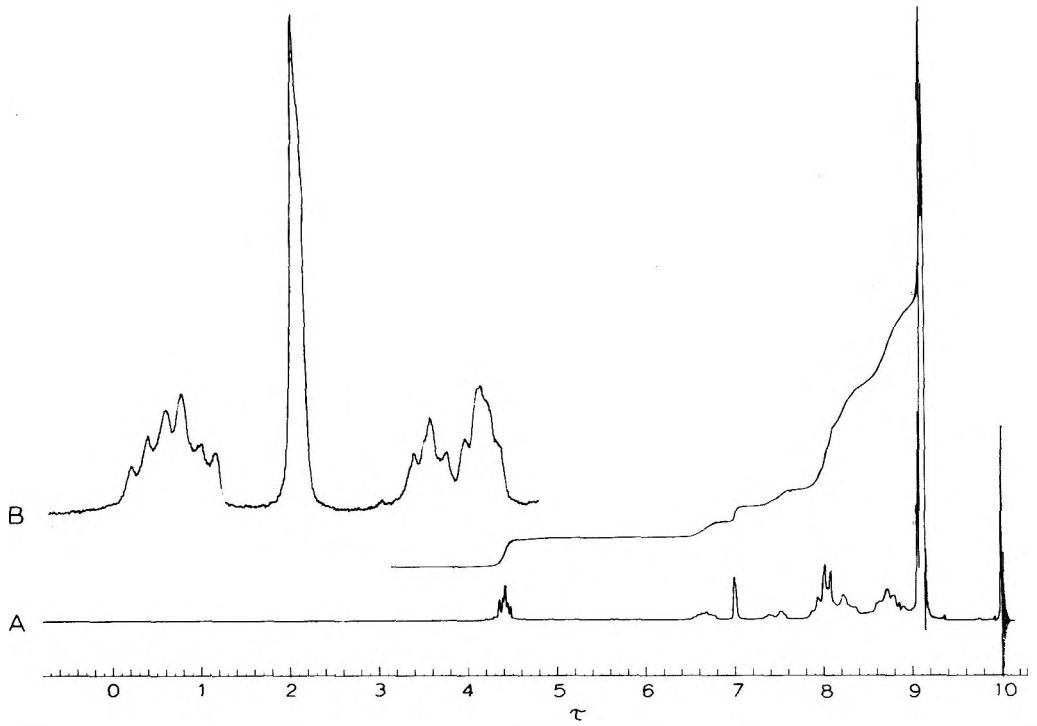
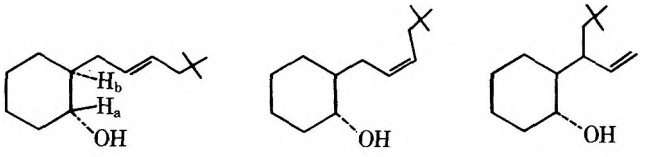


Figure 1. ^{1}H NMR spectrum (100 MHz) of VIa, the principal product from 3-neopentylallyllithium and cyclohexene oxide. Trace B offset 500 Hz and expanded × 10.

product, are shown in Figure 1. Most significant is the coupling pattern at τ 6.7 of the proton H_a, geminal to the hydroxyl



VIa VIb VIc

group. The pattern is that to be expected from an axially disposed proton with an axially disposed H_b in a position vicinal to H_a. A similar pattern was observed for the corresponding proton H_a in VIc. The spectra are not consistent with other structures in which the hydroxyl and NpA groups are in axial–equatorial or equatorial–equatorial orientations with regard to one another. Unless one rejects the chair conformation of the cyclohexane ring,[14] then one is forced to conclude that structures VIa and VIc predominate, and that both "normal" and "rearrangement" addition processes occur in a trans fashion.

The data in Table I also show the effect of THF solvent on the product distributions of addition of NpALi to cyclohexene oxide. The effect is the same as that observed with the acyclic epoxides; namely, that the percentage of rearranged product increases slightly, but less so than the yield of the cis olefinic product (VIb). The latter reflects the increased concentration of the cis allylic lithium compound (NpALi) in THF,[2] where at 0 °C it is present in 35% excess over the trans species. The identity of the three alcohols obtained in THF and pentane solvents shows that in both cases the trans addition process prevails.

Conclusion

Neopentylallyllithium has been shown to react with *cis*- and *trans*-2,3-epoxybutane and with cyclohexene oxide in a trans addition process. Unlike the corresponding Grignard reagents, NpALi yields a predominance of the "normal", i.e., "nonrearranged", addition products. That both types of processes occur in a trans fashion, both for the Grignard and lithium allyls and in a variety of solvents, is evidence for the strong preference of this mechanism over other alternatives.

Experimental Section

^{1}H NMR and IR spectra were recorded on JEOL PS-100 and Perkin-Elmer 237 spectrometers, respectively, with tetramethylsilane as the internal ^{1}H NMR reference. Analyses were performed by C. F. Geiger, Ontario, Calif. Gas chromatography was performed on a Varian Model 1800 with thermal conductivity and flame ionization detectors.

Neopentylallyllithium was prepared as described previously[1-4] using rigorously dried solvents and inert gas atmospheres. *trans*-2,3-Epoxybutane and 1-chloro-3,3-dimethylbutane were used as received from Chemical Samples Co., Columbus, Ohio. A mixture of *trans*- and *cis*-2,3-epoxybutane was obtained from the same source and separated by preparative gas–liquid chromatography using a 6 ft × 0.25 in. EDO-1 (Supelco, Bellefonte, Pa.) glass column at 25 °C and 30 ml/min helium flow. The epoxides collected were shown to be >99% chromatographically pure. Cyclohexene oxide was used as obtained from MCB, Cincinnati, Ohio.

Reaction of NpALi with *trans*-2,3-Epoxybutane in *n*-Pentane. To a stirred solution of 1 M NaALi (44 mmol) in *n*-pentane under argon, 3.3 g (46 mmol) of *trans*-2,3-epoxybutane was added while cooling the flask with dry ice. After stirring overnight at ca. 25 °C, the mixture was quenched with water and acidified, and the organic layer spearated and dried over magnesium sulfate. The majority of the solvent was evaporated and the mixture analyzed by GLC (13 ft × 0.25 in. FFAF at 70 °C, 29 ml He/min). Three peaks other than solvent were observed, IIIa–c (diastereomers of IIIc not resolved). Each was collected by preparative GLC and analyzed by various spectral methods. IIIa: IR (neat) 3350 (b, OH$^-$), 3010 (w, =CH), 1650 (w, C=C), 965 cm^{-1} (trans CH=CH); ^{1}H NMR ($CDCl_3$) τ 4.62 (m, 2 H, CH=CH), 6.31 (m, 1 H, CHOH), 7.83 (m, 2 H, =CHC**H**$_2$CH), 8.15 (d, 2 H, J = 6 Hz, *t*-BuC**H**$_2$CH=), 8.37 (s, 1 H, OH), 8.47 [m, 1 H, C**H**$_2$C**H**(CH$_3$)], 8.87 (d, 3 H, J = 6 Hz, C**H**$_3$CHOH), 9.13 (d, 3 H, C**H**$_3$CHCH$_2$), 9.15 (s, 9 H, *t*-Bu); MS (70 eV) *m/e* 184 (parent ion), 166 (M − H_2O). IIIb: IR (neat) 3350 (b, OH), 3010 (w, =CH) 1620 (w, C=C), 760 cm^{-1} (cis CH=CH); ^{1}H NMR ($CDCl_3$) τ 4.53 (m, 2 H, CH=CH), 6.29 (m, 1 H, CHOH), 7.89 (m 2 H, =CHC**H**$_2$CH), 8.08 (d, 2 H, J = 6 Hz, *t*-BuC**H**$_2$CH=), 8.3 [m, 1 H, C**H**$_2$C**H**(CH$_3$)], 8.56 (s, 1 H, OH), 8.88 (d, 3 H, J = 6.5 Hz, C**H**$_3$CHOH), 9.18 (d, 3 H, J = 6 Hz, C**H**$_3$CHCH$_2$), 9.18 (s, 9 H, *t*-Bu); MS (70 eV) *m/e* 184 (parent ion), 166 (M − H_2O). IIIc: IR (neat) 3350 (b, OH), 3030 (s, =CH), 1620 (w, C=C), 995, 900 cm^{-1} (m, CH=C**H**$_2$); ^{1}H NMR ($CDCl_3$) τ 4.4 (m, 1

H), 5.12 (m, 2 H) ($CH{=}CH_2$), 6.32 (m, 1 H, CHOH), 7.92 (d, 2 H, *t*-BuCH_2CH), 9.13 (s, 9 H, *t*-Bu), other peaks too overlapping to be resolved; MS (80 eV) *m/e* 184 (parent ion), 166 ($M - H_2O$).

Anal. Calcd for $C_{12}H_{24}O$: C, 78.20, H, 13.12. Found (mixture of IIIa and IIIb): C, 78.29, H, 13.13. Found (IIIc): C, 77.73; H, 12.68.

Reaction of NpALi with *cis*-2,3-Epoxybutane in *n*-Pentane. The procedure used was similar to that for the trans epoxide. GLC separation yielded four isomeric olefinic alcohols, IIIa′-c′ (two diastereomers of IIIc′). IIIa′: IR (neat) 3330 (b, OH) 3005 (w, =CH), 1620 (w, C=C), 965 cm^{-1} (m, trans CH=CH); ^1H NMR ($CDCl_3$) τ 4.62 (m, 2 H, CH=CH), 6.38 (m, 1 H, CHOH), 7.25 (s, 1 H, OH), 7.86 (m, 2 H, $=CHCH_2CH$), 8.14 (d, 2 H, J = 6 Hz, *t*-Bu$CH_2CH{=}$), 8.46 [m, 1 H, $CH_2CH(CH_3)$], 8.90 (d, 3 H, J = 6.5 Hz, CH_3CHOH), 9.16 (s, 9 H, *t*-Bu), 9.20 (d, 3 H, CH_3CHCH_2); MS (70 eV) *m/e* 184 (parent ion), 166 ($M - H_2O$). IIIb′: IR (neat) 3330 (b, OH) 3040 (w, =CH) 1650 (w, C=C), 763 cm^{-1} (w, cis CH=CH); ^1H NMR (neat) τ 4.56 (m, 2 H, CH=CH), 6.32 (m, 1 H, CHOH), 6.27 (s, 1 H, OH), 7.83 (m, 2 H, $=CHCH_2CH$), 8.05 (d, 2 H, J = 6 Hz, *t*-Bu$CH_2CH{=}$), 8.49 [m, 1 H, $CH_2CH(CH_3)$], 8.90 (d, 3 H, J = 6 Hz, CH_3CHOH), 9.09 (s, 9 H, *t*-Bu), 9.15 (d, 3 H, CH_3CHCH_2); MS (70 eV) *m/e* 184 (parent ion), 166 ($M - H_2O$). IIIc′: IR (neat) 3350 (b, OH), 3040 (s, =CH), 1625 (w, $CH{=}CH_2$), 995, 910 cm^{-1} (s, $CH{=}CH_2$); ^1H NMR ($CDCl_3$) τ 4.50 (m, 1 H), 5.06 (m. 2 H) ($CH{=}CH_2$), 6.28 (s, 1 H, OH), 6.52 (m, 1 H, CHOH), 7.27 (*m*, 1 H, $CHCH{=}CH_2$), 8.68 (*m*, 3 H, *t*-BuCH_2 and CH_3CH), 8.82 (d, 3 H, CH_3CH, J = 6 Hz), 9.06 (s, 9 H, *t*-Bu), 9.32 (d, 3 H, CH_3CHOH, J = 6 Hz).

Anal. Calcd for $C_{12}H_{24}O$: C, 78.20 H, 13.12. Found (mixture of IIIa′ and IIIb′): C, 78.01, H, 13.02. Found (mixture of diastereomers of IIIc′): C, 77.96, H, 13.21.

Hydrogenation of IIIa,b and IIIa′,b′. A mixture of IIIa and IIIb (8:1 ratio), collected by preparative GLC (FFAP column, 70 °C), was hydrogenated in cyclohexane solvent using a rocking bomb apparatus with platinum oxide catalyst. The resulting product contained only one GLC peak (IV), which was subsequently collected for analysis. IV: ^1H NMR ($CDCl_3$) no olefin peaks, τ 6.32 (m, 1 H, CHOH), 7.70 (s, 1 H, OH), 8.78 (b, H, CH_2), 8.87 (d, 3 H, CH_3CHOH, J = 6 Hz), 9.11 (d, 3 H, CH_3CHCH_2, J = 6 Hz), 9.17 (s, 9 H, *t*-Bu). IV′ was similarly prepared by hydrogenation of a mixture of IIIa′ and IIIb′ (5:1 ratio). IV′: ^1H NMR ($CDCl_3$) no olefin peaks, 6.38 (*m*, 1 H, CHOH), 8.11 (s, 1 H, OH), 8.92 (d, 3 H, CH_3CHOH, J = 6 Hz), 9.16 (s and overlapping doublet, 12 H, *t*-Bu and CH_3CHCH_2).

Alternate Route to IV and IV′. Preparation of 5,5-Dimethyl-1-hexanol. To 11 g (0.46 mol) of magnesium turnings covered with dry ether under argon, 10 ml of a 50% solution of 1-chloro-3,3-dimethylbutane in ether was added to initiate the reaction. After initiation, the remaining chloride solution (total amount 0.41 mol) was added dropwise over a period of 2 h. The reaction mixture was stirred at room temperature for an additional 2 h. Ethylene oxide was bubbled into the solution until all visible signs of the very exothermic reaction had disappeared. After hydrolysis and acidification, the ether layer was separated and dried with anhydrous magnesium sulfate. GLC (FFAP column, 70 °C) showed only one product which was verified by IR and ^1H NMR as 5,5-dimethyl-1-hexanol: IR (neat) 3270 (s, b, OH), 1460 (*m*) (CH_2), 1385 (w), 1360 (*m*) *t*-Bu, 1050 cm^{-1} (*m*, b, OH); ^1H NMR ($CDCl_3$) τ 6.32 (t, 2 H, CH_2OH, J = 7.5 Hz), 7.30 (s, 1 H, OH), 8.3–8.8 (m, 6 H, CH_2), 9.10 (s, 9 H, *t*-Bu).

Preparation of 1-Chloro-5,5-dimethylhexane. 5,5-Dimethyl-1-hexanol (10 g, 0.077 mol) obtained by preparative GLC was reacted with $SOCl_2$ after the manner of Whitmore.[17] The alcohol was dissolved in 6.3 g (0.08 mol) of dry pyridine and treated with 10.7 g (0.09 mol) of $SOCl_2$ at −5 °C. The reaction mixture was warmed to 104 °C over a 4-h period and held at that temperature for an additional 2 h. The mixture was extracted with dilute HCl and then with bicarbonate solution. The organic layer was distilled, yielding a product of ca. 85% purity by GLC (bp 160–180 °C). The desired product (4.8 g) was obtained by preparative GLC (20 ft FFAP column, 140 °C, 110 ml He/min): IR (neat) no OH peak, 1460 (*m*, CH_2), 1395 (w), 1370 (*m*, *t*-Bu), 725 cm^{-1} (m, b, CCl); ^1H NMR ($CDCl_3$) τ 6.48 (t, 2 H, CH_2Cl, J = 6.7 Hz), 8.23 (t, 2 H, CH_2CH_2Cl, J = 6 Hz), 8.35–8.95 (m, 4 H, CH_2), 9.10 (s, 9 H, *t*-Bu).

Preparation of 5,5-Dimethylhexyllithium (V). To 0.6 g (0.086 mol) of lithium sand in ether under argon was added dropwise 0.031 mol of 1-chloro-5,5-dimethylhexane as a 10% solution in ether. After initiation with approximately 10% of the solution, the remainder was added over a period of 2 h, and then refluxed for 2 h more. The reaction mixture was filtered in a helium-filled drybox yielding 55 ml of 0.090 M RLi by the Gilman titration.[18]

Reaction of 5,5-Dimethylhexyllithium (V) with *cis*- and *trans*-2,3-Epoxybutane. The solution of the lithium alkyl V was halved in the drybox and reacted individually with the trans (5.5 mmol) and the cis epoxide (3.4 mmol). GLC of the reaction mixture from the trans epoxide and V showed a single peak with retention time identical with that of IV prepared by hydrogenation of IIIa and IIIb within. A mixture of IV prepared by the two methods showed only a single GLC peak. Likewise, GLC of the product from the cis epoxide and V yielded a peak with identical retention time with that of IV′ prepared from IIIa′ and IIIb′ and not identical with IV. GLC conditions: 6 ft × 0.125 in. FFAP, 96 °C, 63 ml He/min. Retention times: IV, 23.7 min; IV′, 25.3 min.

Reaction of NpALi with Cyclohexene Oxide. To 40 ml of a 0.14 M solution of NpALi in *n*-pentane was added 4.0 g of cyclohexene oxide while keeping the solution in a dry ice–acetone bath. The reaction mixture was allowed to warm to room temperature and at that temperature was stirred for 1 h. Following hydrolysis the organic layer was separated and dried with anhydrous $MgSO_4$. The pentane, evaporated in a stream of nitrogen, yielded approximately 5 g of crude product. GLC on a 10 ft × 0.25 in. SE-30 column at 100 °C showed three products subsequently shown to be VIa–c in the ratio 65:15:20. IVa and VIb were collected together since they were poorly resolved. Anal. Calcd for $C_{14}H_{26}O$: C, 80.00; H, 12.38. Found: C, 80.19; H, 12.42. ^1H NMR ($CDCl_3$) τ 4.42 (m, 2 H, CH=CH), 6.66 (m, 1 H, CHOH), 7.00 (s, 1 H, OH), 7.48 (m, 1 H, $CHCH_2CH{=}$), 7.8–8.4 (m, 7 H), 8.5–8.9 (*m*, 5 H), 9.08, 9.11 (s, 9 H, cis and trans *t*-Bu). Likewise VIc was collected by GLC. Anal. Calcd for $C_{14}H_{26}O$: C, 80.00; H, 12.38. Found: C, 79.81; H, 12.12. ^1H NMR ($CDCl_3$) τ 4.36 (1 H), 5.08 (2 H) ($CH{=}CH_2$), 6.68 (1 H, CHOH), 7.40 (m, 1 H), 8.18 (s, 1 H, OH), 8.0–8.2 (m, 2 H), 8.2–8.5 (m, 3 H), 8.5–9.0 (m, 6 H), 9.14 (s, 9 H, *t*-Bu). Analysis of axial CHOH multiplet for VIa with ca. 20% VIb (X portion of A_2BX): $J_{AX} = J_{axial\text{-}axial}$ = 9.0 Hz; $J_{BX} = J_{axial\text{-}equatorial}$ = 2.4 Hz.

Reactions of NpALi in THF. In each case dry THF was added to the *n*-pentane solution in large excess over of lithium species, and the solution allowed to equilibrate for a few minutes at 0 °C before reagent was added. Workup was the same as with *n*-pentane solvent.

Acknowledgment. The support of The Robert A. Welch Foundation in the form of Grant B-105 is gratefully acknowledged.

Registry No.—Ia, 39056-16-1; Ib, 39056-17-2; IIIa, 60967-62-6; IIIa′, 60967-63-7; IIIb, 60967-64-8; IIIb′, 60967-65-9; IIIc, 60967-66-0; IV, 60967-67-1; IV′, 60967-68-2; V, 60967-69-3; VIa, 60967-70-6; VIb, 61009-14-1; VIc, 60996-33-0; *trans*-2,3-epoxybutane, 21490-63-1; *cis*-2,3-epoxybutane, 1758-33-4; 1-chloro-3,3-dimethylbutane, 2855-08-5; ethylene oxide, 75-21-8; 5,5-dimethyl-1-hexanol, 2768-18-5; 1-chloro-5,5-dimethylhexane, 60996-32-9; cyclohexene oxide, 286-20-4.

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On the Mechanism of the Pyrolytic Elimination Reaction of Acetates[1]

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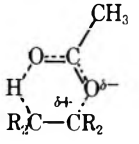
Received July 1, 1976

The mechanism generally accepted for the pyrolysis of acetates to alkenes is a one-step gas-phase reaction with a cyclic transition state. The isomer ratios observed in the alkene products are generally inconsistent with the mechanism, but are consistent with a surface-catalyzed reaction. While true gas-phase reactions appear to have been observed in kinetic experiments, we believe that the experimental conditions employed in most cases where isomer ratios in the products have been reported, which are the conditions commonly used for preparative work, result in a surface-catalyzed reaction.

The pyrolysis of a carboxylic ester to yield an alkene and a carboxylic acid has been known for more than 100 years. Other esters, such as xanthates, undergo a similar reaction. These pyrolyses have been of interest for synthetic purposes, and also from a mechanistic point of view. Extensive review articles have been published concerning them.[2,3]

The most common method of pyrolyzing an ester is referred to as the *gas-phase* method. In this method, the ester is added dropwise to a heated glass tube (200–600 °C) and the products and unreacted ester are swept through the tube by a steady stream of an inert gas. The heated tube is often filled with helices or glass wool. While this procedure is the most common one, various modifications are also used. If the ester is a high-boiling compound, the ester may be pyrolyzed in the liquid phase by simply heating below its boiling point.[2] A number of variations of the methods described above are used. For example, a liquid phase pyrolysis can be carried out on a low-boiling ester using a sealed ampule.[4] Gas phase pyrolyses are also conducted in static reactors.

The generally accepted mechanism for these pyrolyses has one step, with a cyclic transition state as shown.[2,3]



Assuming this transition state to be correct, the correlation of reaction rates with Hammett substituent constants[3,5] indicates that there is a significant amount of charge separation in the breaking of the C–O bond, and none in breaking of the C–H bond. The reaction is generally believed to be concerted, because products that might be produced by a carbonium ion mechanism are not usually found. Thus, free carbonium ions of the kind generated during a solvolysis reaction do not occur here. Since the elimination is predominantly cis and a free carbonium ion intermediate is not formed, it has been assumed that the transition state is cyclic.[2,3]

Sixma[6] found that at lower temperatures the pyrolysis of esters showed first-order kinetics only when the surfaces of the reactor were deactivated. Sixma's product isomer ratios are in good agreement with other data from pyrolyses run over undeactivated surfaces, which seems to indicate that the amount of reaction caused by active surfaces is small compared with the amount of normal reaction.

Smith and co-workers[5,7] have also found that first-order kinetics and no change in rate with change in the surface/volume ratios were obtained only when the surface of their stainless steel reactor was deactivated. They do not indicate that they believe the mechanism of the reaction occurring under those conditions to be completely different from that observed by other workers, who did not deactivate their surfaces, so apparently it is believed that the amount of reaction caused by active surfaces is normally small.

Original Objectives. When this research project was undertaken, it seemed well established that the gas-phase mechanism was in all cases the predominant reaction pathway. It has been known for a long time that more trans alkene than cis alkene is formed when a secondary alcohol is pyrolyzed. As shown in the representative examples in Table I, the experimental cis/trans ratios agree to within experimental error with the ratios predicted by the equation $k_{rel} = \exp(-\Delta H/RT)$, where k_{rel} = cis/trans ratio and $\Delta H° = H°_{cis} - H°_{trans}$, and $H°$ = the heat of formation of the compound. If the gas-phase mechanism were correct, this relationship is consistent with a transition state which looks either like the alkene produced or like the eclipsed ester, because there are approximately the same eclipsed interactions present in the eclipsed ester as there are in the alkene.

It has been proposed[2] that the transition state has a geometry like the staggered, ground-state ester. We do not believe that such a transition state is consistent with the cis/trans ratios in Table I—especially the small cis/trans ratio found for 2,2-dimethyl-3-hexene.

If the gas-phase mechanism were correct, we should be able to use a relationship similar to that found useful in prediction of the cis/trans ratio to predict the 1-alkene/2-alkene ratios found when esters of the type $CH_3CR_1(OCOCH_3)CHR_2R_3$ are pyrolyzed.

The number of experimental enthalpy differences available for alkenes are too few to test the prediction of isomer ratios by this method. Fortunately, experimental enthalpies are not the only ones available. In recent years molecular mechanics calculations have been developed and refined for use in calculating such quantities.[11] These calculations have found use in structural and thermodynamic studies. More recently there calculations have been applied to the study of chemical reactions.[12]

Table II compares some experimental 1-alkene/2-alkene ratios obtained by pyrolysis, corrected for statistical effects (k_1^H/k_2^H) with the corresponding energy differences. As one can readily see, there is no correlation between k_1^H/k_2^H and the relative stabilities of the alkenes. The data were cast in the form

$$RT \ln (k_1^H/k_2^H) = \Delta G_{sub} + C\Delta E$$

where ΔG_{sub} accounts for differences in the relative stability of the alkenes due to changes in the amount of substitution in going from the 1-alkene to the 2-alkene, and C is a proportionality constant to take into account that the transition state is not exactly like the alkene in geometry. A least-squares analysis gave a value of C that was small and negative. The correlation coefficient for this value of C was low. This means that if there was in fact a relationship between the relative energies of the alkenes and the isomer ratios, there is a small tendency for the less stable isomer to be preferred. As expected, an analysis of the data assuming that the geometry of

Table I. The Cis/Trans Ratios of Some Pyrolysis Products

Compd	Exptl[a] cis/trans	Calcd[b] cis/trans
2-Butene	0.54[8]	0.47
2-Pentene	0.67[9]	0.52
2-Hexene	0.49[9]	(0.75) 0.67
3-Hexene	0.47[9]	(0.29) 0.51
2,2-Dimethyl-3-hexene	0.08[9]	0.04

[a] Obtained by direct measurement on pyrolysis products. [b] Calculated from the heats of formation (ref 10).

the transition state is like that of the eclipsed ester gave no better results.

Proposed Mechanism. The data in Table II cannot be explained by the generally accepted mechanism. An alternative mechanism which will account for these facts involves a three-step surface reaction. The steps are as follows. (1) In a rapid equilibrium step the compound is adsorbed with the ester group on the surface. (2) In a second step the ester C–O bond is broken to form a carbonium ion. This carbonium ion is stabilized by the surface, and in so far as possible, the ion adopts a conformation which allows maximum contact between the surface and the ion. In the pyrolysis of at least some esters, this step appears to be reversible. (3) In the rate-determining step, the carbonium ion loses a β hydrogen to form the alkene. These steps may be more or less concerted, and the degree of concertedness may vary with the compound.

Discussion

There is a large amount of data in the literature on the pyrolysis of esters. Any reaction mechanism proposed for the reaction must be consistent with *all* of these data. Tables III–VII are samples of the data available. The observations about the pyrolysis of esters which are consistent with the gas phase mechanism are as follows. (1) As shown in Table V, the loss of a cis β hydrogen is much preferred to the loss of a trans β hydrogen. (2) Rearrangement products are rare. (3) When both the cis and the trans alkene can be formed by the loss of a cis β hydrogen, the cis/trans ratio is about what would be expected on the basis of the relative stabilities of the alkenes. (4) The deuterium isotope effect, shown in Table VII, shows that the β hydrogen is lost in the slow step of the reaction. (5) The more acidic the acid produced, or the more stable the carbonium ion that would result from alkyl–oxygen cleavage, the faster the reaction.[20] The change in rate shown in Table VI and in ref 20 with increased ability of the acid or hydrocarbon portion of the ester to stabilize a charge has been rationalized[3] as being consistent with the gas-phase mechanism by saying that there is increased charge separation in going from the ester to the transition state.

In addition to the five observations which can be accounted for by the gas-phase mechanism, there are four additional "anomalies" that a reaction mechanism should be able to account for. They are: (6) How are the rearrangement products in Table IV formed? The esters prolyzed in Table IV are different from most esters in that if a carbonium ion forms on the carbon bonded to the ester, it will be stabilized by neighboring group participation, or it is an ion hypothesized to be nonclassical. The gas-phase mechanism does not explain why the presence of neighboring group participation causes rearrangement products to be formed. (7) In the pyrolysis of 3-methyl-2-pentyl[5] acetate the cis/trans ratio is 2/1, while a ratio of 1/1 would be anticipated. If only cis eliminations occur, then *cis*-3-methyl-2-pentene is formed from *threo*-3-methyl-2-pentyl acetate and *trans*-3-methyl-2-pentene is formed from *erythro*-3-methyl-2-pentyl acetate. This means that the 1-alkene/2-alkene ratio for the threo isomer is half that of the erythro isomer. Why is the 1-alkene/2-alkene ratio for two compounds as similar as *erythro*- and *threo*-3-methyl-2-pentyl acetate so different, when there is in general so little difference between the k_1^H/k_2^H ratios of the quite different compounds in Table II?

(8) The pyrolysis of *trans*-1,2-dimethylcyclopentyl acetate gives almost no exocyclic alkene, while the pyrolysis of *cis*-1,2-dimethylcyclopentyl acetate gives 20–30% exocyclic alkene.[8] Since the trans acetate has ½ the number of cis β ring hydrogens as the cis acetate, one would expect about 50% more of the exocyclic alkene in the pyrolysis of the trans acetate, not 90–100% less.

(9) Why is the k_1^H/k_2^H ratio for the compounds in Table II so similar—except for 4,4-dimethyl-2-pentyl acetate?

Ion Pair Mechanism. The mechanism described in the introduction is not the only mechanism that has been proposed for the pyrolysis of esters. The ion pair mechanism, shown schematically below, was proposed to account for the

$$R{-}OAc \rightleftharpoons [R^+\bar{O}Ac] \longrightarrow \text{alkene + acid}$$

$$\downarrow$$

$$[{}^*R^+\bar{O}Ac] \longrightarrow \text{rearranged alkene + acid}$$

where $[R^+\bar{O}Ac]$ is the gas phase ion pair intermediate formed by heterolytic cleavage of the ester C–O bond.

$[{}^*R^+\bar{O}Ac]$ is the ion pair after rearrangement

charge effects discussed in observation 5 above, and the rearrangement products shown in Table IV.[4,6,25]

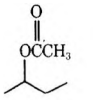
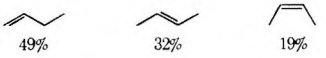
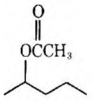
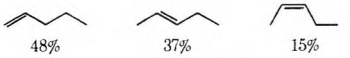
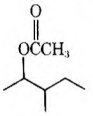
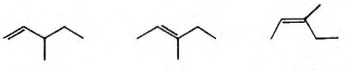
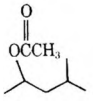
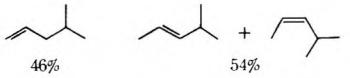
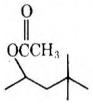
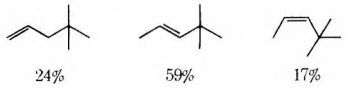
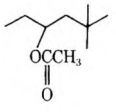
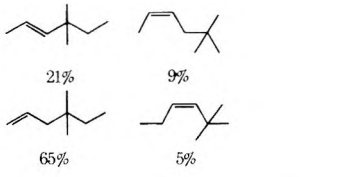
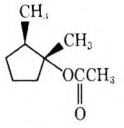
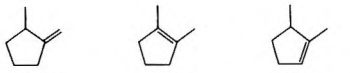
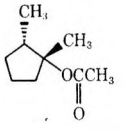
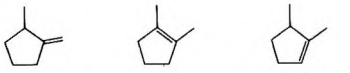
Our objections to this mechanism are: (1) It is no better at

Table II. Isomer Ratio Compared with Energy Differences

Registry no.	Alcohol (as acetate)	Exptl 1-alkene/2-alkene ratio	k_1^H/k_2^H[a]	$RT \ln (k_1^H/k_2^H)$ T = 450 °C	ΔE,[b] kcal/mol	Ref[c]
	2-Butanol	0.94	0.62	−0.43	0.24	6
626-38-0	2-Pentanol	0.92	0.61	−0.70	0.80	
34860-03-2	3-Methyl-2-pentanol	2.0	0.68	−0.55	1.30	
	4-Methyl-2-pentanol	0.85	0.57	−0.81	0.85	14
60388-83-2	4,4-Dimethyl-2-pentanol	0.31	0.21	−2.2	0.80	
	2-Methyl-2-butanol	1.6	0.53	−0.90	0.20	14
34859-98-2	2-Methyl-2-pentanol	2.1	0.69	−0.52	0.52	
34856-44-5	2,4-Dimethyl-2-pentanol	1.6	0.54	−0.90	1.60	
27540-75-6	2,4,4-Trimethyl-2-pentanol	2.85[d]	0.85	−0.15	4.15	

[a] 1-Alkene/2-alkene ratio, adjusted to account for the relative numbers of β hydrogens. [b] Energy of the 2-alkene minus the energy of the 1-alkene, calculated using the force field in ref 13. For the kind of number being calculated here, average errors of the order of 0.4 kcal/mol may be expected. [c] If no reference is given, the results are from the present work. [d] The products isomerized rapidly.

Table III. Pyrolysis Products of Some Esters

Ester	Products and yields	Note
	 49% 32% 19%	*a*
	 48% 37% 15%	*b*
	 70% 10% 20%	*c*
	 46% + 54%	*d*
	 24% 59% 17%	*b*
	 21% 9% 65% 5%	*e*
	 20-30% 40-50% 25-30%	*f*
	 1-4% 5-10% 89-95%	*f*

[a] Reference 6. [b] This work. [c] Reference 6. The percentages actually reported in ref 6 are 3-methyl-1-pentene, 70%; *cis*-3-methyl-2-pentene; 10%; and *trans*-3-methyl-2-pentene; 20%. We have reversed the percentages for the cis and trans isomers because in the early 1960's the American Petroleum Institute reversed the designation of the isomers. We believe that the old designations were used in ref 6. [d] Reference 14. [e] Reference 9. [f] Reference 8.

explaining observations 7–9 than the generally accepted mechanism is. (2) One would expect many esters to rearrange, not just esters in which the carbonium ion is stabilized by neighboring group participation. (3) The ion pair mechanism does not readily explain why the loss of a cis β hydrogen is much preferred to the loss of a trans β hydrogen. (4) The term ion pair intermediate means that an energy barrier separates the ion pair from the ester and the alkene. There is no reason to believe that an energy barrier would separate the ion pair from the ester. The gas-phase cleavage of a bond is generally taken to be a monatonic function with energy increasing with increased distance between the atoms forming the bond.

Explanation of Experimental Observations by Proposed Mechanism. The number preceding each explanation (below) refers to the correspondingly numbered observation above.

(1) The almost exclusive loss of cis β hydrogens is explained by the fact that it is the surface or the acid counterion lying on the surface that pulls off the hydrogens. The ester is adsorbed on the surface with the ester group down. Only hydrogens cis to the ester will be in contact with the surface.

(2) Carbonium ions in solution readily rearrange. One might

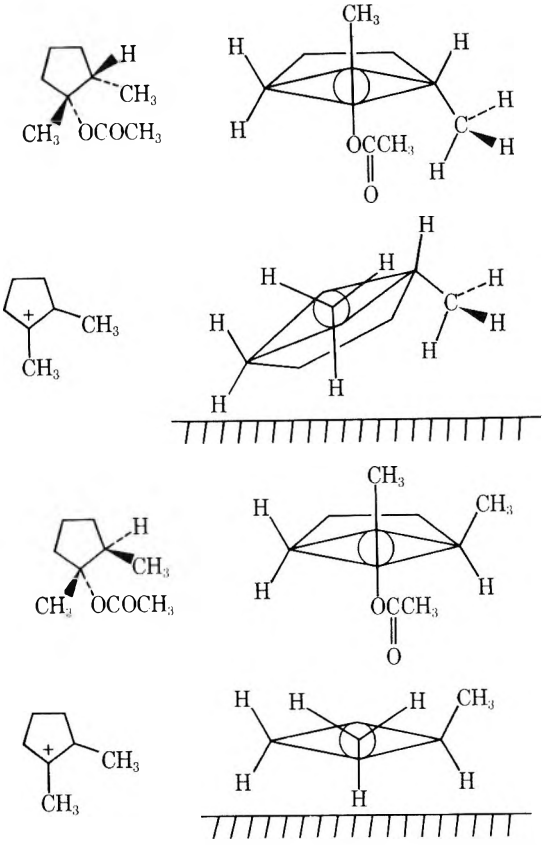


Figure 1. 1,2-Dimethylcyclopentane carbonium ions adsorbed on a surface.

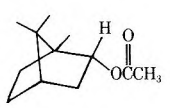
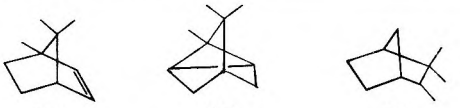
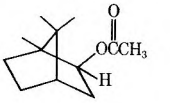
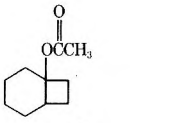
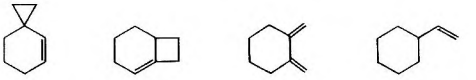
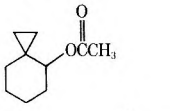
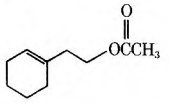
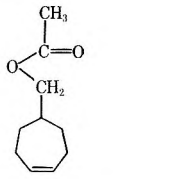
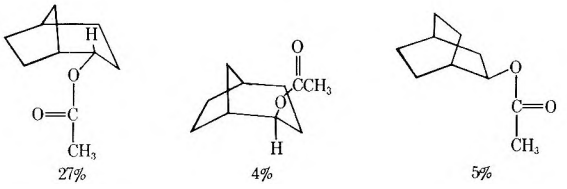
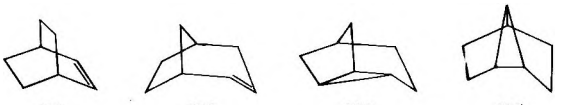
expect that the carbonium ion intermediate here should also readily rearrange. However, a carbonium ion stabilized by interactions with a solid surface is in a quite different environment than the same ion in solution. A solvent is highly mobile and it can stabilize the ion no matter how the charge moves during the course of a rearrangement. An ion on a surface is stabilized by an immobile "active" site and/or by the similarly immobile acid counterion. If the charge on such an ion were to move it would become a "free" and therefore unstabilized ion. This means that an ion on a surface, compared with the same ion in solution, would be very reluctant to rearrange.

(3) Trans alkenes are formed in preference to cis alkenes because it is energetically favored for the ester and carbonium ion to have as close a contact with the surface as possible.[26] Closest contact is possible only if the molecule is in a planar conformation—that is to say, the molecule must have either an anti-coplanar or an eclipsed coplanar conformation. The eclipsed conformation leads to the cis alkene, while the anti conformation leads to the trans alkene. Since the anti conformation is lower in energy than the eclipsed conformation, more of the ester will be absorbed in the anti than in the eclipsed conformation.

(4) We believe that the loss of the β hydrogen is the rate-determining step of the reaction, so the proposed mechanism is consistent with with deuterium isotope effects shown in Table VII.

(5) Our mechanism is consistent with the data in Table VI and related facts,[20] which show that the more acidic the parent acid of the ester, and/or the more stable a carbonium ion formed, the faster the reaction rate. Since the total activation energy is the sum of the energy required to form the carbonium ion plus the activation energy for the removal of the β hydrogen, the more stable the carbonium ion is, the faster the overall reaction will be (other things being equal).

Table IV. Pyrolysis of Some Esters That Give Rearrangement Products

Ester	Products and yields	Temp, °C	Ref
	 61% 23% 14%	345	15
	20% 32% 48%	345	15
	 80% 7% 0% 12%	240	16
	9% 50% 21% 19%	480	16
	95% 4% 0% 1%	320	16
	26% 0% 0% 74%	330	16
	14% 0% 0% 85%	440	16
 350 °C	 27% 4% 5%	350	4
	 7% 32% 10% 15%		

(6) The rearrangement products in Table IV are produced from carbonium ions that are stabilized by neighboring group participation or by the formation of a 2-norbornyl or cyclopropylcarbinyl cation. Despite the exceptionally rapid skeletal rearrangements of the 2-norbornyl and cyclopropylcarbinyl cations in solution, the origin of the nonclassical carbonium hypothesis, the interactions of the ions with the surface have slowed the rate of skeletal rearrangement sufficiently that even at the elevated temperatures at which the pyrolyses are run, a distinctly nonequilibrium distribution of products is obtained.

Thus we can conclude that the carbonium ion stabilization by the surface is highly effective in reducing the rate of rearrangement, but not 100% so. Only ions with a high propensity for rearrangement manage to do so.

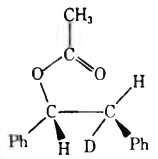
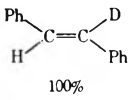
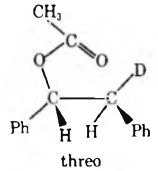
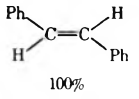
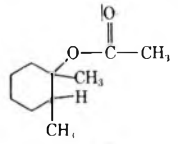
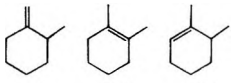
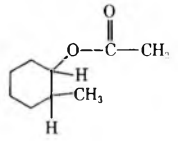
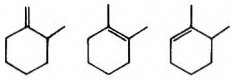
(7) As explained above, the cis/trans ratio in the pyrolysis of 3-methyl-2-pentyl acetate is the result of the 1-alkene/2-alkene ratio of the *threo*-3-methyl-2-pentyl acetate being half that of *erythro*-3-methyl-2-pentyl acetate. This difference is readily explained if one examines the two possible conformations each ester can adopt when it is absorbed on the surface. In conformation A both the erythro and threo isomers have the 3-methyl and the 3-ethyl on the surface; the 3-hydrogen is held off the surface. Conformation A leads to 1-alkene only because the 3 hydrogen is not on the surface. Conformation B of the threo isomer has the 3 ethyl and 3 hydrogen on the surface; the 3 methyl is held off the surface. Conformation B of the erythro isomer has the 3 methyl and 3 hydrogen on the surface; the 3 ethyl is held off the surface. Since it is energetically more favorable to have the larger 3 ethyl on the surface than to have the 3 methyl on the surface, conformation B of the erythro is less stable than conformation B of the threo isomer, and the A/B ratio of the threo will be lower as a result. Since conformation B leads to both 1-alkene and 2-alkene, the lower A/B ratio of the threo isomer means its 1-alkene/2-alkene ratio will be lower, in agreement with what is observed.

(8) Table III shows that the pyrolysis of *trans*-1,2-dimethylcyclopentyl acetate gives almost no exocyclic alkene, while the pyrolysis of *cis*-1,2-dimethylcyclopentyl acetate gives 30–35% exocyclic alkene. As shown in Figure 1, when the methyl groups are cis, the carbonium ion has the 1-methyl on the surface and as a result one of its hydrogens can be removed by the surface to form the exocyclic alkene. When the methyls are trans, the 2-methyl is on the surface. This causes the 1-methyl to be held off the surface and as a result the surface is unable to remove a methyl hydrogen and form the exocyclic alkene.

(9) The generally small differences in the k_1^H/k_2^H ratios in Table II are the result of the fact that generally both the 1-alkene and the 2-alkene can be formed from both of the two planar conformations of the carbonium ion. As a result, any differences in the energies of the two planar conformations will not affect the k_1^H/k_2^H ratio. Usually the change in steric interactions in going from the carbonium ion to an alkene adsorbed on the surface is small so the change in geometry in going from carbonium ion to alkene generally has no effect on the ratios either.

Esters with *tert*-butyl groups γ to the ester (i.e., 4,4-dimethyl-2-pentyl acetate and 5,5-dimethyl-3-hexyl acetate)

Table V. Preference for Elimination of Cis β Hydrogen

Ester	Products	Ref
 erythro	 100%	17
 threo	 100%	17
	 46% 28% 26%	8
	 45% 0% 55%	8

are exceptions to the general rule, that the change in the steric energy is small in going from carbonium ion to alkene. In the planar ion there is a very severe steric interaction between the α hydrogen and a γ *tert*-butyl group. When a double bond forms between the ester carbon and a γ *tert*-butyl group (e.g., when $(CH_3)_3CCH{=}CHR$ rather than $(CH_3)_3CCH_2CH{=}CHR$ is formed) the angle between the ester carbon and the γ *tert*-butyl group changes from approximately tetrahedral (109.5°) to trigonal (120°). The increase in the bond angle reduces the severity of the interaction between the α hydrogen and the γ *tert*-butyl group. This is the cause of the seemingly anomolous k_1^H/k_2^H ratio for the pyrolysis of 4,4-dimethyl-2-pentyl acetate, and the reason that the 2-alkene/3-alkene ratio in the pyrolysis of 5,5-dimethyl-3-hexyl acetate is so much less than 1/1. Note that the severity of the interaction between the α hydrogen and the γ *tert*-butyl group is caused by the requirement that the ion be planar. As shown in Table II, the steric energy difference in 4,4-dimethyl-1-pentene and 4,4-dimethyl-2-pentene *after* they have left the surface and are able to adopt the most favorable geometries is no different from similar alkenes in Table II.

True Gas Phase Ester Pyrolysis. We believe that the only conditions which have been demonstrated to give a true gas-phase reaction are those used by Smith[5,7] and by Maccoll.[27] They have shown that when a stainless steel reactor is deactivated by carbonizing the surfaces, and air is excluded from the apparatus, there is not change in rate with change in the surface/volume ratio. Only small amounts of air reactivated the carbonized surface, so we assume that workers who carbonized the surfaces of their apparatus, but did not discuss excluding air from the apparatus, were in fact observing a surface reaction.

Recently Taylor[28] observed that some of the esters he pyrolyzed were undergoing a surface reaction, despite the fact the reactions were first order and that he believed that the remainder of the esters pyrolyzed were true gas-phase reactions. Since the conditions used in his study were almost identical with those used by Smith[5,7] and co-workers (where they observed no change in rate with change in the surface to volume ratio), it is unclear what conditions are necessary to ensure that the reaction takes place in the gas phase. It is possible that these conditions vary from one ester to another.

Table VI. Relative Rates of Pyrolysis of Acetates

Ester	Rel rate	Ref
$C_2H_5OCOCH_3$	1.0	18
i-$C_3H_7OCOCH_3$	19.0	18
t-$C_4H_9OCOCH_3$	1170.0	19

Table VII. Deuterium Isotope Effects

Ester	K_H/K_D	Temp, °C	Note
Ethyl-*1,1,2,2-d*$_4$ acetate	2.0	500	*a*
Ethyl-*1,1,2,2,2-d*$_5$ acetate	2.1	400	*b*
dl-erythro-2-Butyl acetate	1.7	400	*c*
1-Methylcyclohexyl-*2,2,6,6-d*$_4$ acetate	1.9	400	*d*

[a] Reference 22. [b] Reference 23. [c] Reference 21. [d] Reference 24.

It appears that glass might be so active as to be impossible to deactivate. Thies and Shick[4] were able to deactivate their glass apparatus to the extent that the rate decreased by a factor of 100, but they were able to obtain an unrearranged product only when the pyrolysis was conducted in the liquid phase and at a much higher temperature. Sixma[6] obtained first-order kinetics when the glass apparatus was coated with silicone oil. We believe that Sixma was still observing a surface reaction. As discussed above, the 1-alkene/2-alkene ratio observed by Sixma[6] in the pyrolysis of 3-methyl-2-pentyl acetate is consistent with the surface mechanism but not with the cyclic mechanism, and first-order kinetics are not inconsistent with a surface reaction.

The ability of surfaces to catalyze the pyrolysis of esters is probably related to the separation of charge that occurs in going to the transition state. It is unclear to us why, in a transition state located in between an ester and an alkene, the carbon bonded to the ester should show increased positive charge and not a decrease in the positive charge, but it is clear that charge separation requires energy, especially in the gas phase. A polar surface, like glass, would be expected to stabilize the charge separation, and thus decrease the activation energy for the reaction. A carbonized surface is nonpolar and therefore inactive, but after such a surface has reacted with air it becomes polar and catalytically active.

Reactions Similar to Carboxylic Ester Pyrolyses. There are a variety of other thermolytic reactions which also produce alkenes. Among these are the pyrolyses of xanthates, alkyl halides, and vinyl ethers. Each of these reactions is believed to have a unimolecular gas-phsse reaction pathway, and each is considered to be so similar to ester pyrolyses that they have been included with the latter in the same review articles.[2,3] We have not looked in detail at any of these reactions, but, like carboxylic ester pyrolyses, it is known that under some conditions surfaces influence these reactions.[3] Surface catalysis in these reactions is generally believed to result from the surface being a source of free radicals. In the light of the foregoing discussion, surface catalysis by a nonradical mechanism—namely stabilization of charge separation in the transition state—could be important.

Experimental Section

Starting Acetates. All of the alcohols used were purchased except for 2,4,4-dimethyl-2-pentanol, which was prepared using the mercuric acetate oxidation of Brown.[29]

A mixture of the alcohol, acetic anhydride, and pyridine in a 3:5:1 ratio was placed in a flask fitted with a reflux condenser and a drying tube. After the flask was heated on a steam bath overnight, the reaction mixture was washed successively with approximately five times its volume of each of the following solutions: (1) saturated NaCl-$NaHCO_3$ solution, (2) 10% HCl in saturated NaCl solution, and (3) saturated NaCl-$NaHCO_3$ solution. The ester was then dried over molecular sieves for several days and an IR was taken to confirm the conversion of the alcohol to ester.

Pyrolysis Procedure. The ester was dropped onto an electrically heated column packed with Pyrex helecies at a rate of about 1-2 drops every 5 s. The column was heated to 450 ± 5 °C and the column was flushed with N_2 at a rate estimated to be 0.5 ml/s. The receiver at the bottom of the column was kept in a dry ice-acetone bath.

Analysis of the Pyrolysis Products. The pyrolysis products were analyzed on a Varian Aerograph Model 700 (commonly known as an Autoprep) equipped with a thermal conductivity detector. To separate the isomers, a 15 or 30 ft × 0.25 in. i.d. column packed with a saturated $AgNO_3$-ethylene glycol solution on Chromosorb W (40-60 mesh) was used. The ratio of absorbent to $AgNO_3$ solution was 2:1. The column temperature was about 35 °C. A flow rate of approximately 60 ml/min of He was generally used. The column decomposed rapidly (1 week) when left at room temperature, and was kept in a freezer when not in use.

The peaks were identified by simultaneous injection into the VPC of a mixture of the pyrolysis product mixture and a sample of the olefin in question. To determine the relative amounts of the isomeric olefins in the mixture, the VPC trace of the product mixture was Xeroxed and the peaks were cut and weighed.

Registry No.—1-Pentene, 109-67-1; *trans*-2-pentene, 646-04-8; *cis*-2-pentene, 627-20-3; 3-methyl-1-pentene, 760-20-3; *trans*-3-methyl-2-pentene, 616-12-6; *cis*-3-methyl-2-pentene, 922-62-3; 4,4-dimethyl-1-pentene, 762-62-9; *trans*-4,4-dimethyl-2-pentene, 690-08-4; *cis*-4,4-dimethyl-2-pentene, 762-63-0; 2-methyl-1-pentene, 763-29-1; 2-methyl-2-pentene, 625-27-4; 2,4-dimethyl-1-pentene, 2213-32-3; 2,4-dimethyl-2-pentene, 625-65-0; 2,4,4-trimethyl-1-pentene, 107-39-1; 2,4,4-trimethyl-2-pentene, 107-40-4.

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Carbamate Analogues of Oligonucleotides

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Received August 6, 1976

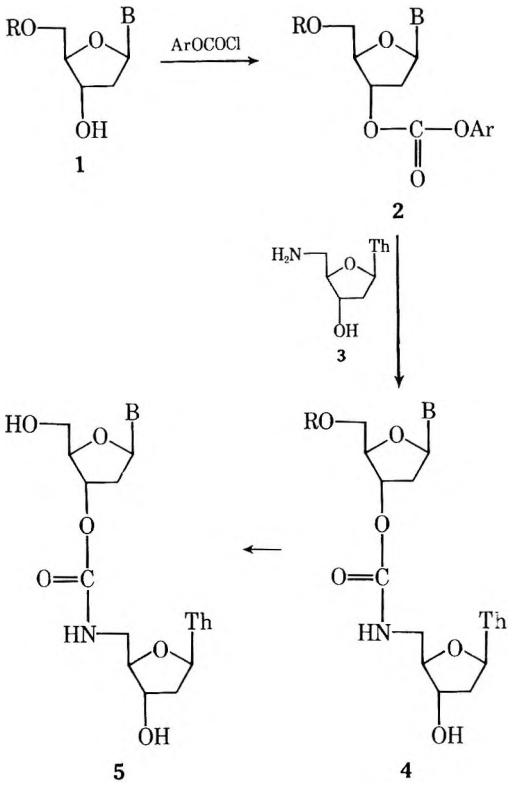
Some dinucleoside phosphate and trinucleoside diphosphate analogues that possess internucleoside carbamate bonds (-OCONH-) are described. These compounds are prepared in good yields under mild conditions by reaction of a nucleoside 3′-*O*-*p*-nitrophenyl carbonate intermediate with a 5′-aminonucleoside. The internucleoside carbamate linkage is stable and does not hydrolyze in acidic or basic solution or in solutions containing snake venom or spleen phosphodiesterase.

We describe in this paper the synthesis and chemical properties of oligonucleotide analogues containing 3′-5′ carbamate linkges between nucleoside units.[1] These compounds were prepared as models to explore the synthesis and stability of oligonucleotides with such linkages. Our interest in this class of compounds was stimulated by the prospect that the stepwise chemical synthesis of such analogues might be readily achieved and that these unique analogues might have important biochemical properties such as template activity, resistance to enzyme-catalyzed degradation, interferon induction, or phosphodiesterase inhibition. The carbamate linked analogues were particularly interesting since Baker and co-workers, working with isolated enzyme systems, found evidence for the simulation of phosphate by the *O*-carbamate in a derivative of 6-mercaptopurine.[2] However, these same workers were unable to detect such simulation with several other nucleoside carbamates.[3] Various oligonucleotide analogues containing such linkages as phosphonate,[4] thiophosphate,[5] phosphoramidate,[6] carboxymethyl,[7] and carbonate[8,9] have been reported in the literature and several of these have been found to have interesting biochemical activity.

The general synthetic approach for the formation of the carbamate linkage was modeled after the active ester method of polypeptide synthesis and Baker's method of nucleoside

carbamate synthesis.[3] Appropriately protected deoxynucleosides were converted into the 3′-*O*-*p*-nitrophenyl carbonate derivatives by the method of Letsinger and Ogilvie.[10] It was found that if dioxane was used as the solvent, instead of pyridine, this reaction proceeded at a much faster rate and that the 3′-*O*-carbonates (**2**) could be obtained in better than 80% yields by precipitation from hexane. Further purification was generally not required. The 3′-*O*-*p*-nitrophenyl carbonates (**2a** and **2b**) reacted smoothly with 5′-amino-5′-deoxythymidine[11] (**3**) in pyridine at room temperature to yield the protected dinucleoside carbamates **4a** and **4b**. A blocking

Scheme I



1a, **2a**, and **4a**, R = trityl; B = thymine
1b, **2b**, and **4b**, R = monomethoxytrityl; B = *N*-benzoylcytosine
5a, B = thymine
5b, B = cytosine

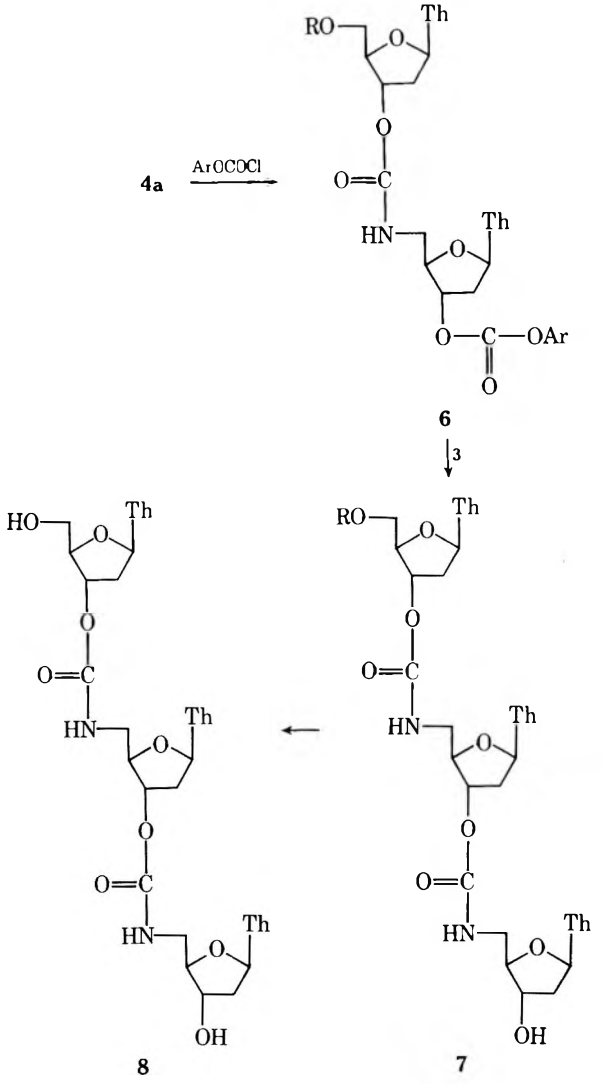
group at the 3′ position of the aminonucleoside is not required to achieve a selective reaction to form the 3′–5′ linkage. Isolated yields of better than 70% of crystalline product **4a** were typical. Reaction of the 3′-*O*-phenyl carbonate of **2a** with **3** was very sluggish under these conditions, and acceptable yields were obtained only upon prolonged reaction in *N*,*N*-dimethylformamide at 50 °C.[12]

In agreement with expectations, the internucleoside carbamate linkages were very stable to hydrolytic conditions. The 5′-*O*-trityl group was selectively removed from **4a** by treatment with aqueous acetic acid at 100 °C without detectable degradation of the carbamate linkage, and the product (**5a**) was isolated in over 80% yield. Elemental and spectroscopic analyses confirmed the structure of the product. Compound **5a** was found to be stable at room temperature in 0.1 M NaOH or in 0.1 M HCl solutions for periods of at least 24 h. When treated with snake venom phosphodiesterase or spleen phosphodiesterase under conditions where complete hydrolysis of thymidylyl-(3′-5′)-thymidine rapidly occurred, compound **5a** was found to be completely resistant to degradation. Heating **5a** in 2 M NaOH at 100 °C for 2 h resulted in partial hydrolysis of the carbamate linkage. Thymidine and **3** were identified by paper chromatography as the hydrolysis products.

The preparation of compound **4b** demonstrates the utility of this synthetic sequence for the preparation of a dinucleoside carbamate which requires a protecting group on the base. The *N*-benzoyl and monomethoxytrityl protecting groups were removed by the usual treatment first with ammonium hydroxide and then with acetic acid to yield **5b**. Spectroscopic analysis of the product showed the expected shift of λ_{max} to higher wavelength on going from a neutral to an acidic solution. This is characteristic of cytosine derivatives.

To test this synthetic procedure in the preparation of oligonucleotide analogues containing more than two nucleoside units, compounds **7** and **8** were prepared. Treatment of compound **4a** with a tenfold excess of *p*-nitrophenyl chloroformate in dioxane–pyridine (8:1) for 30 min gave a quantitative yield of the 3′-*O*-*p*-nitrophenyl carbonate derivative (**6**). Attempts

Scheme II



R = trityl; Ar = *p*-nitrophenyl

to prepare this derivative in pyridine had resulted in slow reactions and poor yields owing to the decomposition of the carbonate in this solvent. Compound **6** reacted rapidly (less than 1 h) with the aminonucleoside to give compound **7** in a 61% isolated yield. This compound was purified by recrystallization from tetrahydrofuran, and the elemental analysis and spectroscopic data were consistent with the assigned structure. The blocking group was selectively removed from

7 by treatment with acetic acid and the trinucleoside dicarbamate, 8, was isolated in 70% yield after purification by preparative thin layer chromatography.

This work demonstrates that carbamate analogues of oligonucleotides can be synthesized in good yields under mild conditions with short reaction times. The carbamate linkage has been shown to be one of the most stable linkages that has been developed for oligonucleotide analogues. Further analysis of these model compounds as enzyme substrates is in progress.

Experimental Section

Infrared spectra were recorded on Perkin-Elmer Model 621 or 137 spectrophotometers and ultraviolet spectra were recorded on a Cary 14 spectrophotometer. Melting points were determined with a Fisher-Johns apparatus and are not corrected. Elemental analyses were made by Galbraith Laboratories, Knoxville, Tenn.

Reagent grade pyridine and 2,6-lutidine were each distilled from *p*-toluenesulfonyl chloride, redistilled from calcium hydride, and stored over Linde 4A molecular sieves. Reagent grade 1,4-dioxane was distilled from lithium aluminum hydride and stored over molecular sieves. Reagent grade triethylamine was distilled from *p*-toluenesulfonyl chloride and redistilled from calcium hydride. *p*-Nitrophenyl chloroformate was purified by sublimation at reduced pressure.

For analytical TLC, Eastman 6060 silica gel plates were used. Preparative TLC was done using plates with a 1-mm silica layer obtained from Quantum Industries (PQ1F). Nucleosides and their derivatives were located under UV light. In addition, trityl containing materials were detected by spraying the chromatogram with 10% $HClO_4$ and drying under a stream of hot air, and compounds containing the *p*-nitrophenyl carbonate moiety were detected by exposing the chromatogram to ammonia fumes. Column chromatography was performed using 60–200 mesh chromatographic grade silica gel from Sargent-Welch Co. Paper chromatography was carried out on Whatman 3MM paper using the descending technique with a solvent system of isopropyl alcohol–concentrated ammonium hydroxide–water (7:1:2 v/v/v).

Reactions were generally run in septum-sealed flasks or test tubes with stirring provided by a Teflon-coated magnet. Solvents were removed under reduced pressure with a bath temperature less than 35 °C. Phosphodiesterase catalyzed rections were carried out by the procedures previously described.[6] Hydrolytic analyses were monitored by paper chromatography.

5′-*O*-Tritylthymidylyl-(3′-5′ carbamoyl)-5′-amino-5′-deoxythymidine (4a). *p*-Nitrophenyl 5′-tritylthymidine 3′-carbonate[10] (1.00 g, 1.54 mmol) was added to 5′-amino-5′-deoxythymidine[11] (0.37 g, 1.54 mmol) in 30 ml of pyridine. The solution turned yellow immediately owing to the formation of the *p*-nitrophenoxide anion, and after 30 min triethylamine (0.16 g, 1.5 mmol) was added. TLC analysis (ethyl acetate) showed that the reaction was complete after 1 h. The reaction mixture was stirred overnight without further change in the TLC analysis. Then 60 ml of ethyl acetate was added, the solution was concentrated under reduced pressure, and 100 ml of ether–ethyl acetate (1:1) was added. The resulting precipitate was isolated by filtration and dried under vacuum at 50 °C. The yield was 0.83 g (71%) of compound **4a** which was homogeneous on TLC with ethyl acetate (R_f 0.07) and with acetone (R_f 0.35). This compound was recrystallized from methanol–tetrahydrofuran: mp 230–232 °C; λ_{max} 262 nm (ϵ 2.4 $\times 10^4$ in dioxane); λ_{min} 242 nm.

Anal. Calcd for $C_{40}H_{41}N_5O_{10}$: C, 63.90; H, 5.50; N, 9.31. Found: C, 64.00; H, 5.76; N, 9.21.

Thymidylyl-(3′-5′-carbamoyl)-5′-amino-5′-deoxythymidine (5a). Compound **4a** (3.77 mg, 0.05 mmol) was dissolved in 3 ml of acetic acid–water (4:1 v/v) and heated on the steam bath for 40 min. The solvent was then evaporated under reduced pressure and the last traces of acid were removed by coevaporation with ethanol. The resulting solid residue was dissolved in solvent grade tetrahydrofuran and compound **5a** was isolated in an 83% yield after the addition of hexane: mp 219–221 °C; λ_{max} 262 nm (ϵ 2.0 $\times 10^4$ in dioxane), λ_{min} 234 nm; homogeneous on paper chromatography (R_f 0.52) and on TLC in tetrahydrofuran (R_f 0.39).

Anal. Calcd for $C_{21}H_{27}N_5O_{10}\cdot\frac{1}{2}H_2O$: C, 48.64; H, 5.44; N, 13.50. Found: C, 48.74; H, 5.52; N, 13.27.

Preparation of 4a from Phenyl 5′-*O*-Tritylthymidine 3′-Carbonate.[12] Phenyl 5′-*O*-tritylthymidine 3′-carbonate[13] (88 mg, 0.15 mmol) and 5′-amino-5′-deoxythymidine (35 mg, 0.15 mmol) were dissolved in 10 ml of *N*,*N*-dimethylformamide. Reaction progress, which was monitored by TLC, was very slow at room temperature so the reaction was placed in a bath at 50 °C. After 36 h the product was isolated (81 mg, 72%) as described above. This material was identical with compound **4a**, prepared from the *p*-nitrophenyl carbonate derivative, on TLC analysis, melting point, and infrared analysis.

***p*-Nitrophenyl 5′-*O*-Monomethoxytrityl-*N*-benzoyl-2′-deoxycytidine 3′-Carbonate (2b).** 5′-*O*-Monomethoxytrityl-*N*-benzoyl-2′-deoxycytidine[14] (69.9 mg, 0.12 mmol) was dried by the evaporation of two 4-ml portions of dioxane under reduced pressure. The resulting solid was dissolved in 4 ml of dioxane. The solution was cooled to 10 °C, treated with 2,6-lutidine (0.1 ml, 0.9 mmol) and *p*-nitrophenyl chloroformate (35.7 mg, 0.18 mmol), and stirred at room temperature for 2 h. A second portion of the chloroformate (24 mg, 0.12 mmol) was then added and stirring was continued for 18 h. Chloroform (50 ml) was added to the reaction mixture and this solution was washed with two 50-ml portions of an aqueous solution buffered at pH 5, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue was dissolved in a minimum of tetrahydrofuran, and this solution was added to an excess of hexane. The precipitate which formed was isolated by filtration and dried to give 79 mg (86%) of the *p*-nitrophenyl carbonate **2b**, which on TLC analysis in ethyl acetate (R_f 0.62) was shown to contain both the monomethoxytrityl and the *p*-nitrophenoxy groups by the appropriate tests. This compound was used in the preparation of **4b** without further purification.

5′-*O*-Monomethoxytrityl-*N*-benzoyldeoxycytidylyl-(3′-5′-carbamoyl)-5′-amino-5′-deoxythymidine (4b). Compound **2b** (78 mg, 0.10 mmol) and 5′-amino-5′-deoxythymidine (38 mg, 0.16 mmol) were dissolved in 5 ml of pyridine at 0 °C. TLC analysis showed that the reaction had gone to completion in 30 min. After the solvent was removed under reduced pressure, the residue was dissolved in tetrahydrofuran–ethyl acetate (1:1 v/v) and washed with two portions of salt water. The organic layer was dried over sodium sulfate, concentrated under reduced pressure, and applied to a silica gel column (2.5 $\times$ 40 cm). The column was first eluted with ethyl acetate and then the product was obtained by elution with tetrahydrofuran. Compound **4b** was isolated as a dihydrate by precipitation from hexane in a 47% yield (41 mg): mp 147–154 °C; UV max (CH_3OH) 261 nm (ϵ 3.1 $\times 10^4$) and 303 (9.8 $\times 10^3$); homogeneous on TLC in ethyl acetate–tetrahydrofuran (1:1 v/v, R_f 0.23).

Anal. Calcd for $C_{47}H_{46}N_6O_{11}\cdot 2H_2O$: C, 62.51; H, 5.35; N, 9.31. Found: C, 62.02; H, 5.37; N, 9.51.

For removal of the blocking groups, 6 mg of **4b** was dissolved in 0.25 ml of pyridine and 0.25 ml of concentrated ammonium hydroxide was added. After standing overnight at room temperature, this solution was concentrated under a stream of nitrogen and the resulting residue was dissolved in 0.25 ml of acetic acid. The solution was heated on the steam bath for 15 min and again concentrated under a stream of nitrogen. The residue was chromatographed on paper and the only nucleoside product, **5b** (R_f 0.49), was eluted from the paper and analyzed by UV spectroscopy: λ_{max} 266 nm (H_2O, pH 7), and λ_{max} 271 (H_2O, pH 1). The product was homogeneous on TLC in methanol (R_f 0.58).

***p*-Nitrophenyl 5′-*O*-Tritylthymidylyl-(3′-5′-carbamoyl)-5′-amino-5′-deoxythymidine 3′-Carbonate (6).** The protected dinucleoside carbamate, **4a** (520 mg, 0.70 mmol), was dried by the evaporation of two 10-ml portions of pyridine, dissolved in a mixture of 0.5 ml of pyridine and 4 ml of dioxane, and treated with *p*-nitrophenyl chloroformate (1.40 g, 7.0 mmol) at 0 °C. Then the reaction mixture was removed from the ice bath, and after 30 min at room temperature, TLC analysis showed no unreacted dinucleoside. Anhydrous ethanol (2 ml) was added to the reaction mixture and solvents were evaporated under reduced pressure. The residue was dissolved in ethanol and concentrated to a gum to remove pyridine. After dissolving the residue in tetrahydrofuran–ethyl acetate (1:1 v/v) and washing with two portions of aqueous pH 5 buffered solution, the organic layer was dried over sodium sulfate, concentrated, and added to a 20-fold volume of hexane. The resulting precipitate was collected by filtration and dried under reduced pressure: yield 0.80 g, mp 148–155 °C, TLC analysis in acetone–benzene (1:1, R_f 0.11) showed only one major component which gave positive tests for the trityl and the *p*-nitrophenyl groups.

5′-*O*-Tritylthymidylyl-(3′-5′-carbamoyl)-5′-amino-5′-deoxythymidylyl-(3′-5′-carbamoyl)-5′-amino-5′-deoxythymidine (7). Compound 6 (15.3 mg, 0.016 mmol) and 5′-amino-5′-deoxythymidine (7.8 mg, 0.032 mmol) were dissolved in 1 ml of pyridine. After 1 h, TLC analysis showed that the reaction had gone to completion and the solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran–ethyl acetate and the solution was washed with a saturated sodium bicarbonate solution. The organic layer was dried over sodium sulfate and concentrated. Compound 7

was isolated as a precipitate from hexane and dried to give 10.2 mg (61%) of material which was homogeneous on TLC in ethyl acetate–tetrahydrofuran (1:1, R_f 0.22) and in tetrahydrofuran (R_f 0.54). This material was purified for analysis by recrystallization from tetrahydrofuran and isolated as a bis solvate: mp 168–170 °C (loss of solvent at 152–155 °C); λ_{max} (CH_3OH) 267 nm (ϵ 2.8 × 10^4), λ_{min} 234 nm.

Anal. Calcd for $C_{51}H_{54}N_8O_{15}\cdot 2C_4H_8O$: C, 60.91; H, 6.06; N, 9.63. Found: C, 60.75; H, 6.07; N, 9.34.

The trityl blocking group was removed from compound **7** (30 mg) by the usual treatment with hot 80% acetic acid. After preparative TLC on a 1 mm thick silica plate with dioxane, compound **8** was isolated in a 70% yield: R_f 0.51 in tetrahydrofuran; λ_{max} 267 nm; paper chromatography R_f 0.38.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—**1b,** 60920-99-2; **2a** (Ar = *p*-nitrophenyl), 10270-35-6; **2a** (Ar = phenyl), 34311-55-2; **2b** (Ar = *p*-nitrophenyl), 60921-00-8; **3,** 25152-20-9; **4a,** 54666-95-4; **4b,** 60921-01-9; **5a,** 54667-52-6; **5b,** 60921-02-0; **6,** 60921-03-1; **7,** 60921-04-2; **8,** 60921-05-3; *p*-nitrophenyl chloroformate, 7693-46-1.

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(12) Compound **4a** has been reported to have been prepared from **2a** (Ar = phenyl) previously; see ref 1a.
(13) This compound, **2a** (Ar = phenyl), was prepared by the method of Letsinger and Ogilvie (ref 10) in a 90% yield and is considerably more stable than the *p*-nitrophenyl carbonate, **2a** (Ar = *p*-nitrophenyl): mp 96–100 °C, homogeneous on TLC in ethyl ether (R_f 0.34) and ethyl acetate (R_f 0.50); NMR and IR consistent with structure.
(14) H. Schaller, G. Weinmann, B. Lerch, and H. G. Khorana, *J. Am. Chem. Soc.*, **85,** 3821 (1963).

Simple Models of Nucleic Acid Interactions. 2. Aminoacyl Derivatives of "Bridged" Nucleosides: Synthesis of 2′(3′)-*O*-L-Phenylalanyl- and 2′(3′)-*O*-L-Leucyl-1,2-di(adenosin-N^6-yl)ethane[1]

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Received August 23, 1976

The synthesis of the title compounds XIIa and XIIb is described. 2′,3′-*O*-Isopropylidene-1,2-di(adenosin-N^6-yl)ethane (I) on reaction with 4-methoxytrityl chloride in pyridine gave dityrityl derivative III accompanied by trityl compound IV. The formation of IV was suppressed by blocking of the remaining cis-diol group in I with 2′,3′-*O*-dimethylaminomethylene function (intermediate VII). Acetylation of I gave the corresponding tetraacetyl derivative II, whereas III and IV afforded di- and monoacetyl derivatives V and VI, respectively. Condensation of III with ZPheOH or ZLeuOH using dicyclohexylcarbodiimide in pyridine led to the phenylalanyl or leucyl derivative VIIIa and VIIIb. Deblocking of VIIIa and VIIIb with 80% acetic acid afforded intermediates Xa and Xb which after treatment with 90% trifluoroacetic acid or Dowex 50 (H^+) gave the *N*-benzyloxycarbonylaminoacyl derivatives XIa and XIb as the mixtures of 2′ and 3′ isomers. Hydrogenolysis of XIa and XIb using PdO–$BaSO_4$ in cold 80% acetic acid as catalyst led to the phenylalanyl and leucyl derivatives XIIa and XIIb. Equilibration of 2′ ⇆ 3′ isomers of compounds XIa and XIb is also described.

According to the current views[2] protein biosynthesis takes place in two distinct steps: (a) formation of aminoacyl transfer ribonucleic acids (AA-tRNA) catalyzed by aminoacyl–tRNA synthetases and (b) formation of the peptide bond between peptidyl and aminoacyl tRNA which is catalyzed by ribosomes. The process (a) involves activation of an amino acid (AA) by reaction with adenosine 5′-triphosphate (ATP) to give aminoacyl adenylate (AA-AMP) and inorganic pyrophosphate (PP, Scheme I, eq 1) followed by a transfer of aminoacyl residue of AA-AMP to the 2′ or 3′ hydroxy group of tRNA's terminal adenosine unit[3a] (Scheme I, eq 2). An alternate concerted mechanism has also been proposed where ATP, AA, and tRNA react simultaneously (Scheme II) to afford AA-tRNA, AMP, and PP.[3a] Although a considerable body of information has been gathered on the substrate requirements of the process,[3a,b] the mutual orientation (topochemistry) of AA-AMP and tRNA in the last step of the transformation (Scheme I, eq 2) remains an intriguing problem of molecular biology.

Scheme I

$$\text{AA} + \text{ATP} \rightleftarrows \text{AA-AMP} + \text{PP} \quad (1)$$

$$\text{AA-AMP} + \text{tRNA} \rightleftarrows \text{AA-tRNA} + \text{AMP} \quad (2)$$

Scheme II

$$\text{AA} + \text{ATP} + \text{tRNA} \rightleftarrows \text{AA-tRNA} + \text{AMP} + \text{PP}$$

It is conceivable that in the process of AA-tRNA formation the adenosine moiety of AA-AMP and that of the 3′ terminal of tRNA are stacked. Thus, a space-filling (CPK) model can be constructed for such a situation (adenine–adenine stacking) in which the aminoacyl residue of AA-AMP would be in a suitable position to attack the 2′ or 3′ hydroxy group of the adenosine terminal unit of tRNA (Figure 1).

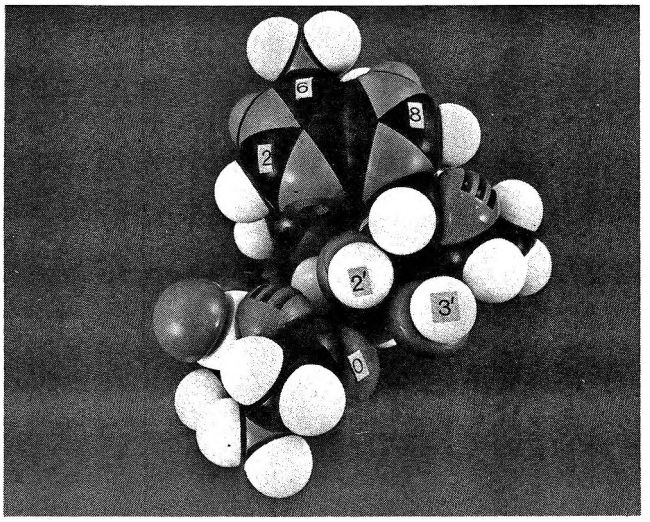


Figure 1. Possible CPK model of transfer of an aminoacyl (glycyl) residue from AA-AMP to tRNA. For simplicity only terminal adenosine of tRNA is shown. Conformations of both adenine residues and $C_{4'}$–$C_{5'}$ are arbitrary anti-g,g. Note the stacking of adenine rings and the closeness of glycyl carbonyl group (O) to the 2′ and 3′ hydroxy groups of terminal adenosine. Adenine moiety of adenosine is on top of that of AA-AMP. Also note the possibility of bridging the N-6 positions of both bases. Numbering is in accord with the current nomenclature of purine ribonucleosides.

It was, therefore, of interest to study simple adenosine derivatives which would combine the structural features of aminoacyl adenylates, AMP, and AA-tRNA, including the stacking of the adenine residues (transition state analogues). A "bridged" nucleoside in which two adenosine units were covalently joined through an aliphatic chain of the N-6 positions to ensure base stacking and containing an amino acid residue could, therefore, be useful. The synthesis and stacking properties of some N^6–N^6 bridged adenosine nucleosides have been the subject of a previous report.[1a] In this communication we describe the introduction of one amino acid residue into a bridged adenine nucleoside leading to compounds XIIa and XIIb.

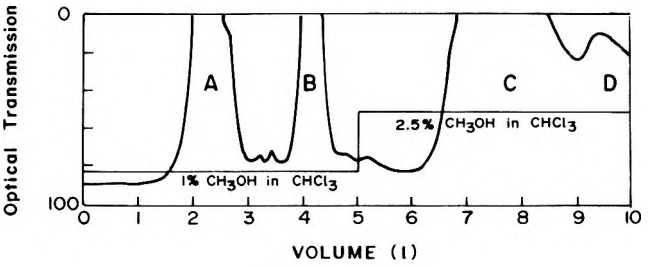


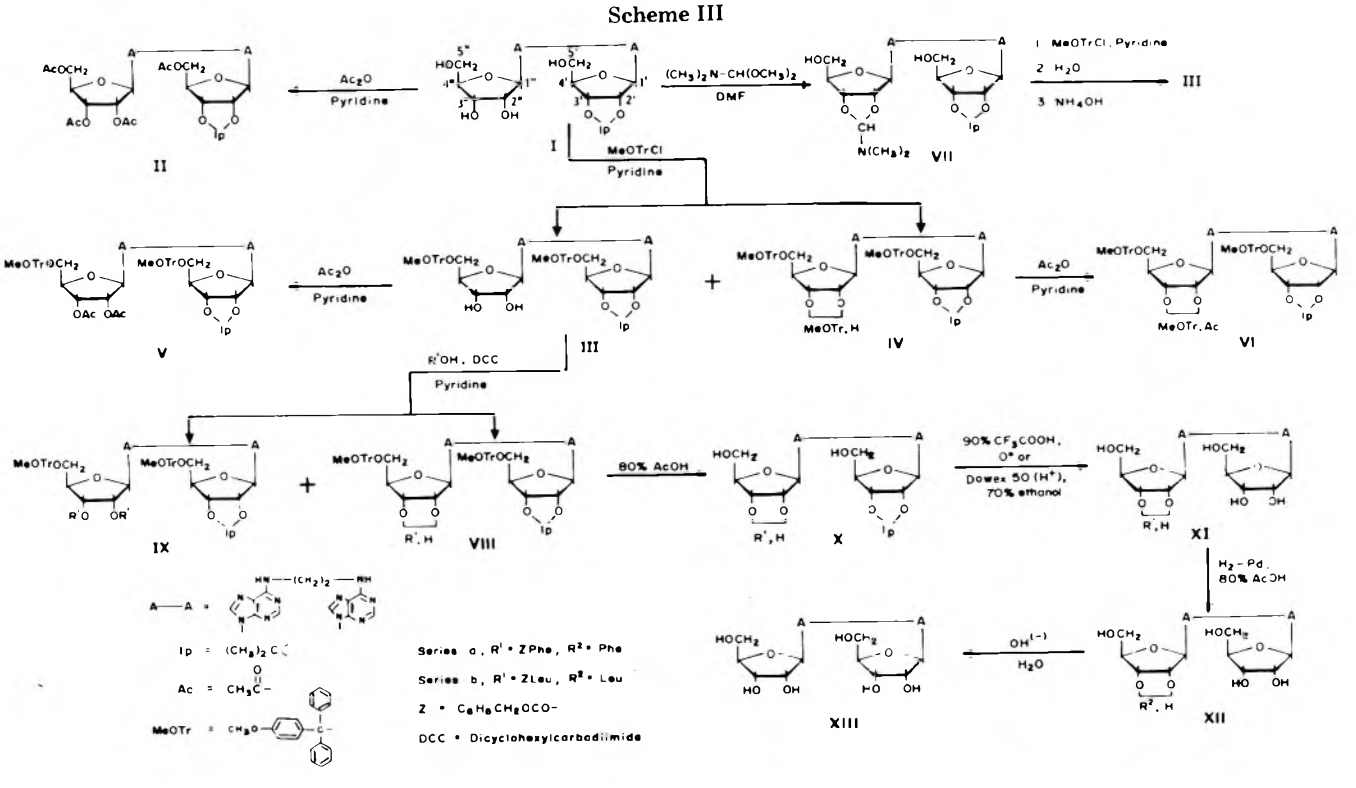
Figure 2. Chromatography of the products from the reaction of 4-methoxytrityl chloride with compound I in pyridine on 45 × 5 cm silica gel column (see Experimental Section). Identification of peaks: A, 4-methoxytriphenylcarbinol; B, tritrityl derivative IV; C, ditrityl derivative III; D, monotrityl derivative(s). Tops of the main peaks were off scale.

The selective substitution of one ribofuranose residue in a bridged nucleoside by an amino acid requires a specific strategy not dissimilar from that employed in the synthesis of oligonucleotides.[4] However, the considerable lability of an aminoacyl ester group at the 2′ or 3′ position of a ribonucleoside severely restricts the choice of appropriate protecting groups for the successful course of the synthesis.

The 2′,3′-*O*-isopropylidene-1,2-di(adenosin-N^6-yl)ethane (I) provided a convenient starting material in the present approach. The latter, which was prepared in 70% yield by an improved coupling procedure[1a] from 6-chloro-9-(β-D-2,3-*O*-isopropylideneribofuranosyl)purine with N^6-(2-aminoethyl)adenosine, has both ribofuranose residues (vicinal glycol groups) functionally differentiated. In addition, the 2′,3′-*O*-isopropylidene group can be easily removed with trifluoroacetic acid[5] using conditions under which the aminoacyl ester bond is essentially stable.[6]

Compound I was tritylated using 2 equiv of 4-methoxytrityl chloride in pyridine to give two major products, the desired ditrityl derivative III (55%) and tritrityl derivative IV (12%), which were isolated by column chromatography (Figure 2). The formation of IV could be suppressed with a stoichiometric amount of 4-methoxytrityl chloride (2 mol) but the reaction mixture contained a considerable amount of monotrityl derivatives as indicated by TLC (Scheme III).

Scheme III



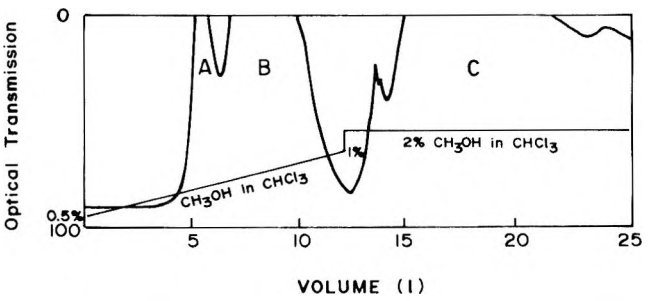


Figure 3. Chromatography of the products from the condensation of ZLeuOH with compound III using DCC in pyridine on 50 × 5 cm silica gel column (see Experimental Section). Identification of peaks: A, dileucyl derivative IXb; B, monoleucyl derivative VIIIb; C, starting material III. Tops of the main peaks were off scale.

The structures of III and IV followed from UV and NMR spectra. Thus, the UV spectra (the longer wavelength absorption bands) were very similar to the parent nucleoside XIII which indicated the absence of N-tritylation.[7] NMR spectra of III and IV (integration of aromatic protons) were in agreement with the presence of two and three trityl groups, respectively. Interestingly, the aromatic methoxy groups were distinctly different in III whereas in compound IV only a single signal for all three methoxy groups was observed. It is recognized that the conformation of ribofuranose and 2′,3′-*O*-isopropylideneribofuranose moieties is different.[8] This difference may be reflected in magnetic nonequivalency of the two methoxy groups. It is, however, more difficult to explain the presence of only one signal for the methoxy group in the tritrityl derivative IV. One can argue that introduction of a second trityl group into the ribofuranose moiety of III may lead to a conformational change similar to that caused by 2′,3′-*O*-isopropylidene group. However, a simple comparison of $J_{1',2'}$ for 2′,5′- and 3′,5′-di-*O*-trityluridine (7.5 and 5 Hz, respectively)[9] with that of 2′,3′-*O*-isopropylideneuridine (2.4 Hz)[8a] is not compatible with such an argument.[10] It appears then that more subtle conformational changes resulting in the different shielding of 4-methoxytrityl groups in III and IV are operational.

The structures of III and IV were further confirmed by oxidation with periodate (only III is oxidized) and by acetylation studies. Acetylation of I using acetic anhydride in pyridine gave only the tetraacetyl derivative II whose UV spectrum was very similar to that of XIII. Thus, the exocyclic (N-6) imino groups are not acetylated under the conditions used. An NMR spectrum of II showed the acetoxy methyl groups as two singlets which integrated for 3 and 9 protons, respectively. As expected, acetylation of III and IV led to the formation of di- and monoacetyl derivatives V and VI whose UV and NMR spectra were in accord with the proposed structures and with the absence of any N-tritylation or N-acetylation. The methoxy group in the NMR spectrum of V showed as two singlets (cf. compound III) whereas the acetoxy signals (methyl) appeared as a lone singlet. On the other hand, all three methoxy groups in VI were nonequivalent which is in sharp contrast to the findings for compound IV. It was possible to separate 2′- and 3′-*O*-acetyl isomers of compound VI by preparative TLC. The acetoxy (methyl) signal in the faster moving (presumably 3′-*O*-acetyl isomer) was slightly more shielded than that of the 2′ isomer. The fact that both isomers were identified is consistent with the possibility that compound IV (starting material for VI) is also a mixture of isomeric 2′ and 3′ tritylated derivatives.

Undesired 2′(3′)-*O*-tritylation could be suppressed if compound I first was reacted with dimethylformamide dimethyl acetal in dimethylformamide (DMF).[11] The resultant 2′,3′-*O*-isopropylidene-2″,3″-*O*-dimethylaminomethylene derivative VII, obtained as a syrup, was then tritylated as above to give III in 85% yield after hydrolysis of the 2″,3″-*O*-dimethylaminomethylene group in NH_4OH (Scheme III).

Protected compound III with a free vicinal glycol grouping was condensed with *N*-benzyloxycarbonyl-L-phenylalanine (ZPheOH) or *N*-benzyloxycarbonyl-L-leucine (ZLeuOH) using dicyclohexylcarbodiimide (DCC) in pyridine.[12] The resultant mixture, consisting of the starting material III, monoaminoacyl derivative VIIIa or VIIIb, and diaminoacyl compound IXa or IXb, was separated by preparative TLC (series a) or column chromatography (series b, Figure 3). The products were characterized by their UV and NMR spectra. The integrated NMR signals in VIIIa and VIIIb were in accord with the presence of only one aminoacyl residue (Phe or Leu) in the molecule. As in compound III, the methoxy groups in both VIIIa and VIIIb showed as two well-separated singlets. The attempted condensation of tritrityl derivative IV with ZPheOH using DCC in pyridine was not successful, presumably owing to the steric hindrance of the 2′ or 3′ hydroxy groups by a neighboring bulky 4-methoxytrityl function. By contrast, acetylation of IV was achieved without difficulty (cf. compound VI).

The removal of 4-methoxytrityl and isopropylidene groups was performed separately. Thus, for reasons which are not apparent the complete deprotection of VIIIa in a single step using 90% trifluoroacetic acid afforded XIa in a low yield after extensive purification by TLC. Therefore, the 4-methoxytrityl group was selectively removed in 80% acetic acid to give the isopropylidene derivatives Xa and Xb which were purified by preparative TLC. Compounds Xa and Xb were then treated with 90% trifluoroacetic acid for 20 min at 0 °C to give the corresponding *N*-benzyloxycarbonyl derivatives XIa and XIb in 83 and 85% overall yield, respectively. Alternatively, the isopropylidene group of Xa and Xb could be removed by treatment with Dowex 50 (H^+) in 70% ethanol for 1 h at room temperature. The latter procedure is very mild and accordingly should find a wider application in nucleic acid chemistry.

The structures XIa and XIb were confirmed by spectral (UV and NMR) data. Although two sets of $H_{1'}$ signals corresponding to two ribofuranose moieties are clearly discernible in the NMR spectra of XIa and XIb, it was impossible to determine the ratio of 2′ and 3′ aminoacyl isomers, primarily because of insufficient resolution of signals. However, direct evidence for the presence of both isomers was provided by TLC in solvent S_6 where compounds XIa and XIb moved as two distinct spots in the ratio of 7:3; the faster moving component was more abundant. It seemed conceivable that in both cases the 2′ and 3′ aminoacyl isomers were resolved. Thus, the ratio 7:3 corresponded as well to the isomeric composition of related 2′(3′)-*O*-(*N*-benzyloxycarbonyl)aminoacyl ribonucleosides.[13] In addition, the prevalence of the faster moving component indicated that it was probably the 3′ isomer.[14] In a micropreparative (μmol scale) experiment the separated bands of both isomers were equilibrated at room temperature in solvent S_5. A 7:3 mixture of isomers was again obtained from both bands and in both cases (XIa and XIb) after TLC in solvent S_6.

In the final step, the *N*-benzyloxycarbonyl group of XIa and XIb was removed by hydrogenolysis using PdO–$BaSO_4$ as catalyst in 80% acetic acid at 0 °C for 2 h in the usual fashion.[12] The resultant phenylalanyl and leucyl derivatives XIIa and XIIb, obtained in 81 and 85% yield, respectively, were characterized by TLC, paper chromatography, electrophoresis, and UV spectra. In addition, alkaline hydrolysis afforded the parent nucleoside XIII and amino acid (PheOH or LeuOH) in a manner similar to other 2′(3′)-*O*-aminoacyl nucleosides.[12]

The biological testing of XIIa and XIIb along with that of some precursors will be reported elsewhere.

Experimental Section

General Procedures. See ref 1a. Samples for analysis were dried at room temperature for 15–20 h at 10^{-2} mm over P_2O_5 and paraffin oil. Descending paper chromatography was performed on Whatman No. 1 paper in the following solvents: S_1, 2-propanol–concentrated NH_4OH–water (7:1:2), and S_2, 1-butanol–acetic acid–water (5:2:3). Thin layer chromatography (TLC) including preparative TLC was conducted as described[1a] in solvents: S_3, chloroform–methanol (95:5); S_4, chloroform–methanol (9:1); S_5, chloroform–methanol (4:1); and S_6, chloroform–methanol–acetic acid (8:1:1). For paper electrophoresis 0.02 M $Na_2B_4O_7$ (pH 9.0) and 1 M acetic acid were used as buffers at 40 V/cm and 1–2 h. NMR spectra were determined using a Varian A-60A instrument. Tetramethylsilane was used as an internal reference in $CDCl_3$ whereas in CD_3SOCD_3 the internal reference was sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS). Detection of cis-diol groups was performed on TLC plates by spraying with 0.5% aqueous $NaIO_4$ and, after several minutes, with 0.5% benzidine in acetic acid–ethanol (1:4) mixture. A positive reaction showed a white spot on a dark blue background.[15] Because benzidine is carcinogenic the use of a hood for the spraying operation is imperative. 4-Methoxytrityl groups were detected by spraying with 10% $HClO_4$.[16]

Column Chromatography. The short column chromatographic technique[17] was modified as follows. Silica gel GF 254 (type 60, for TLC, Merck, Darmstadt, Germany) and glass columns (Glenco Scientific, Inc., Houston, Texas, 60 × 5 cm) were used. Silica gel was mixed in a blender with chloroform or dichloromethane (3.5 ml/l g) and the slurry was poured into the column with the tap open. A slight pressure of nitrogen was then applied until the descendant liquid caught up with the silica gel surface; 100 g of silica gel settles to ca. 200 ml. The solution of the mixture to be separated was allowed to soak into the column without applying any pressure, the space above the silica gel was filled with the solvent, and FMI laboratory pump Model RPP (Fluid Metering, Inc., Oyster Bay, N.Y.) was attached. The use of an adjustable plunger (Glenco Scientific Co., Houston, Texas) eliminates the dead volume above the silica gel which is of particular importance when a gradient elution technique is employed. It is imperative to remove all air from the solvents used by evacuation (aspirator). All air bubbles from the whole system should be removed prior to the elution by opening the vent in the top screw of the column. The chromatography was monitored continuously by UV absorption (transmission) at 260 nm using LKB Uvicord II (LKB, Bromma, Sweden) and the fractions were collected using a linear fraction collector LKB Ultrorac. The flow rate was maintained at 3 ml/min. The ratio of the mixtures of compounds to silica gel was 1/40 (w/w) for easy separations (as judged from TLC) and 1/100 for difficult ones.

Starting Materials and Reagents. Pyridine (reagent grade) was distilled twice (from *p*-toluenesulfonyl chloride and KOH) and it was stored over Linde molecular sieves, 4A. Trifluoroacetic acid was distilled before use. 4-Methoxytrityl chloride (MeOTrCl), dimethylformamide dimethyl acetal, and dicyclohexylcarbodiimide (DCC) were products of Aldrich Chemical Co., Milwaukee, Wis. *N*-Benzyloxycarbonyl-L-phenylalanine (ZPheOH) was purchased from Sigma Chemical Co., St. Louis, Mo., and *N*-benzyloxycarbonyl-L-leucine (ZLeuOH) was the product of Tridom Fluka Chemical Co., Hauppauge, N.Y.

2′,3′-*O*-Isopropylidene-1,2-di(adenosin-*N*^{6}-yl)ethane (I). The previously described[1a] procedure was modified as follows. The solution of 6-chloro-2′,3′-*O*-isopropylidene(9-β-D-ribofuranosyl)purine (6.2 g, 20 mmol), N^6-(2-aminoethyl)adenosine[18] (6.55 g, 20 mmol), and triethylamine (14.05 ml, 100 mmol) in DMF (100 ml) was stirred for 4 days at room temperature. Crystalline triethylamine hydrochloride was filtered off and the filtrate was evaporated at 0.04 mm and room temperature. The residue was dissolved in 50% aqueous ethanol (100 ml) and the solution was passed through a Dowex 1 (X2, 200–400 mesh) column (150 ml, HCO_3^- form). The column was eluted with the same solvent (1.7 l.). Evaporation of the eluate afforded a white solid (12 g) which was washed twice with acetone (50 and 20 ml). The resultant solid was dissolved in 50% aqueous pyridine (80 ml) and the solution was passed through a Dowex 50 (X2, 100–200 mesh) column (350 ml, pyridinium form) and the column was eluted with the same solvent (2 l.). Evaporation of the eluate gave a white solid which was washed with acetone–ether to afford 8.4 g (70%) of I, mp 154–156 °C, lit.[1a] 154–155 °C, homogeneous on TLC (S_5) and paper electrophoresis ($Na_2B_4O_7$); UV and NMR spectra were identical with those of an authentic sample.[1a]

5′,5″-*O*-Di(4-methoxy)trityl-2′,3′-*O*-isopropylidene-1,2-di(adenosin-*N*^{6}-yl)ethane (III) and 2″(3″),5′,5″-*O*-tri(4-methoxy)trityl-2′,3′-*O*-isopropylidene-1,2-di(adenosin-*N*^{6}-yl)ethane (IV). A. Direct Tritylation of I. A solution of compound I (6.0 g, 10 mmol) and 4-methoxytrityl chloride (12.36 g, 40 mmol) in pyridine (50 ml) was stirred for 10 h at room temperature. The reaction mixture was then added dropwise into cold water (1 l.) with stirring, and the precipitate was collected by filtration, washed with water, and dried at 0.04 mm at room temperature. The crude product was dissolved in a minimum amount of chloroform and the solution was added dropwise into an excess of petroleum ether. The resultant solid was collected by filtration and further purified by column chromatography on 400 g of silica gel (Figure 2). Peak B afforded after evaporation compound IV (1.7 g, 12%), homogeneous on TLC (S_3), UV max (ethanol) 274 nm (ε 34 800), min 249 (24 200); NMR ($CDCl_3$) δ 8.43 and 8.17 (2 s, 2, H_8), 7.82 and 7.66 (2 s, 2, H_2, the signal at 7.66 is partially overlapped with phenyl), 7.59–6.70 (m, 42, 4-methoxytrityl), 6.07 (broad s, 2, $H_{1'}$), 3.56 (s, 9, CH_3O), 1.62 and 1.42 (2 s, 6, CH_3 of isopropylidene).

Anal. Calcd for $C_{85}H_{80}N_{10}O_{11}$: C, 72.01; H, 5.69; N, 9.88. Found: C, 71.76; H, 5.77; N, 9.60.

Evaporation of peak C afforded ditrityl derivative III (6.3 g, 55%): homogeneous on TLC (S_3); UV max (ethanol) 274 nm (ε 33 500), min 248 (20 200); NMR ($CDCl_3$) δ 8.18 and 8.10 (2 s, 2, H_8), 7.97 and 7.55 (2 s, 2, the signal at 7.55 is partially overlapped with phenyl), 7.55–6.70 (m, 28, 4-methoxytrityl), 6.30 and 6.08 (2 broad s, 2, $H_{1'}$), 3.64 and 3.49 (2 s, 6, CH_3O), 1.65 and 1.46 (2 s, 6, CH_3 of isopropylidene).

Anal. Calcd for $C_{65}H_{64}N_{10}O_{10}$: C, 68.16; H, 5.63; N, 12.23. Found: C, 68.31; H, 5.69; N, 12.00.

B. Tritylation via Intermediate VII. Compound I (6.0 g, 10 mmol) was dried by evaporation with DMF at 0.05 mm and room temperature, the residue was dissolved in DMF (50 ml), dimethylformamide dimethyl acetal (13.4 ml, 100 mmol) was added, and the solution was kept for 17 h at room temperature. Evaporation at 0.05 mm and room temperature afforded a syrup VII which was coevaporated with DMF (50 ml) and dried at 0.05 mm and room temperature overnight. The residue was dissolved in pyridine (50 ml), 4-methoxytrityl chloride (18.5 g, 60 mmol) was added, and the solution was stirred at room temperature for 20 h. The reaction mixture was then poured on ice (ca. 700 g) and extracted with chloroform (3 × 400 ml) and the combined organic layers were dried ($MgSO_4$). Evaporation afforded a syrup which was coevaporated with ethanol (500 ml) and dissolved in a mixture of dioxane (100 ml) and concentrated NH_4OH (10 ml). The solution was kept overnight at room temperature and then it was evaporated. The residue was partitioned between chloroform and water, and the organic layer was dried ($MgSO_4$) and evaporated to give III as a TLC (S_3) homogeneous foam. Purification by column chromatography (see method A and Figure 2) afforded 9.7 g (85%) of III, UV and NMR identical with those of the sample obtained by method A.

Aminoacylation of Ditrityl Derivative III. A. Preparation of Phenylalanyl Derivatives VIIIa and IXa. A mixture of compound III (0.8 g, 0.7 mmol) and ZPheOH (0.22 g, 0.77 mmol) was dried by evaporation with pyridine (20 ml) at 0.05 mm and room temperature. The residue was dissolved in cold pyridine (7 ml) and the cooled solution of DCC (0.16 g, 0.77 mmol) in pyridine (3 ml) was added. The reaction mixture was stirred for 1 h at 0 °C and 24 h at room temperature. A piece of ice was then added, and dicyclohexylurea was filtered off and washed with pyridine (5 ml). The filtrate was evaporated at 0.05 mm and room temperature to a syrup which was lyophilized from dioxane (50 ml). The resultant white solid was partitioned between chloroform and saturated aqueous $NaHCO_3$, and the combined organic layers were washed with water (2 × 100 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed on 4 mm thick loose layer of silica gel (35 × 15 cm) in solvent S_3. The three major UV absorbing bands were obtained which were eluted with the same solvent and the eluates evaporated. The fastest band afforded diaminoacyl derivative IXa: 36 mg (3%); TLC (S_3) homogeneous; UV max (ethanol) 274 nm (ε 34 900), min 248 (22 100); NMR ($CDCl_3$) δ 8.26 and 8.16 (2 s, 2, H_8), 7.80 and 7.63 (2 s, 2, H_2), 7.40–6.86 (m, 48, 4-methoxytrityl − phenyl), 6.18–6.07 (poorly resolved m, 2, $H_{1'}$), 4.96 (s, 4, CH_2 of benzyloxycarbonyl), 3.71 and 3.61 (2 s, partially overlapped, 6, CH_3O), 1.63 and 1.40 (2 s, 6, CH_3 of isopropylidene).

Anal. Calcd for $C_{99}H_{94}N_{12}O_{16}\cdot 3H_2O$: C, 67.29; H, 5.99; N, 9.51. Found: C, 67.14; H, 5.93; N, 9.34.

The next (slower) band afforded compound VIIIa: 0.28 g (28%); TLC (S_3) homogeneous; UV max (ethanol) 274 nm (ε 34 300), min 248 (21 200); NMR ($CDCl_3$) δ 8.10 and 8.05 (2 s, 2, H_8), 7.65 and 7.48 (2 s partially overlapped with phenyl, 2, H_2), 7.20–6.71 (m, 38, 4-methoxytrityl + phenyl), 6.00 and 5.90 (2 d, 2, $H_{1'}$), 5.01 (s, 2, CH_2 of benzyloxycarbonyl), 3.55 and 3.50 (2 s, 6, CH_3O), 1.62 and 1.41 (2 s, 6, CH_3 of isopropylidene).

Anal. Calcd for $C_{82}H_{79}N_{11}O_{13}$: C, 69.04; H, 5.58; N, 10.80. Found: C, 68.90; H, 5.56; N, 10.79.

The third (slowest) band afforded after evaporation 0.35 g (43%) of starting material III.

B. Preparation of Leucyl Derivatives VIIIb and IXb. Method A was followed except that a 8.4-mmol (9.6 g) of III scale and ZLeuOH instead of ZPheOH were used. After the workup the crude product was purified by column chromatography on 550 g of silica gel (Figure 3). Peak A afforded diaminoacyl derivative IXb: 1 g (7%); TLC (S_3) homogeneous; UV max (ethanol) 274 nm (ϵ 34 300), min 248 (21 500); NMR ($CDCl_3$) δ 8.28 and 8.17 (2 s, 2, H_8), 7.98 and 7.81 (2 s partially overlapped with phenyl, 2, H_2), 7.69–6.68 (m, 38, 4-methoxytrityl + phenyl), 6.31 and 6.08 (2 d, 2, $H_{1'}$), 5.04 (s, 4, CH_2 of benzyloxycarbonyl), 3.63 and 3.53 (2 s, 6, CH_3O), 1.64 and 1.42 (the former signal is overlapped with CH_2 of Leu, 2 s, 6, CH_3), 0.92 (m, 12, CH_3 of ZLeu).

Anal. Calcd for $C_{93}H_{98}N_{12}O_{16}$: C, 68.11; H, 6.02; N, 10.25. Found: C, 67.83; H, 6.16; N, 10.27.

Peak B afforded compound VIIIb: 5.54 g (50%); TLC (S_3) homogeneous; UV max (ethanol) 273 nm (ϵ 34 500), min 247 (20,900); NMR ($CDCl_3$) δ 8.30 and 8.23 (2 s partially overlapped, 2, H_8), 7.80 and 7.64 (2 s partially overlapped with phenyl, 2, H_2), 7.39–6.68 (m, 33, 4-methoxytrityl + phenyl), 6.13 and 6.03 (2 d, 2, $H_{1'}$), 5.18 (s, 2, CH_2 of benzyloxycarbonyl), 3.67 (s, 6, CH_3O), 1.69 and 1.46 (overlapped with CH_2 of Leu, 2 s, 6, CH_3), 1.03 (m, 6, CH_3 of ZLeu).

Anal. Calcd for $C_{79}H_{81}N_{11}O_{13}$: C, 68.13; H, 5.86; N, 11.06. Found: C, 67.91; H, 5.95; N, 11.01.

Peak C afforded after evaporation 2.85 g (31%) of the starting material III.

2′(3′)-*O*-(*N*-Benzyloxycarbonyl)-L-phenylalanyl-1,2-di(adenosin-*N*^{6}-yl)ethane (XIa). A. Using 80% CH_3COOH and 90% CF_3COOH. A solution of compound VIIIa (0.28 g, 0.2 mmol) in 80% acetic acid (20 ml) was kept at room temperature for 6 h; the detritylation was complete as judged from TLC (S_4). The reaction mixture was evaporated at 0.04 mm, the residue was coevaporated with ethanol, and crude Xa was chromatographed on 4 mm thick loose silica gel layer 35 × 15 cm in solvent S_4. The major UV absorbing band of Xa was eluted with the solvent, the eluate was evaporated, and the residue dissolved in cold 90% CF_3COOH (3 ml). The solution was stirred for 20 min at 0 °C and then evaporated at 0.04 mm. The resultant syrup was stirred with Dowex 1 (acetate form, 20 ml) in 70% ethanol (40 ml) for 30 min at room temperature. The resin was filtered off, and washed with 70% ethanol and the filtrate was evaporated. The crude XIa was chromatographed on 4 mm thick loose layer of silica gel in solvent S_4. The major UV absorbing band was worked up as above to give phenylalanyl derivative XIa, 0.14 g (82%), homogeneous on TLC in S_4, in solvent S_6 two spots were obtained (vide supra): UV max (ethanol) 273 nm (ϵ 32 800), min 223 (5000);[19] NMR (CD_3SOCD_3) δ 8.38 and 8.28 (2 s partially overlapped, 4, H_8 and H_2), 7.35 (s, 10, phenyl), 6.03 and 5.93 (2 s, 2, $H_{1'}$), 5.07 (s, 2, CH_2 of benzyloxycarbonyl).

Anal. Calcd for $C_{39}H_{43}N_{11}O_{11}\cdot H_2O$: C, 54.47; H, 5.28; N, 17.92. Found: C, 54.54; H, 5.47; N, 17.69.

B. Using 80% CH_3COOH and Dowex 50 (H^+). Intermediate Xa (0.13 g, 0.15 mmol) obtained by method A (deblocking in 80% CH_3COOH) was stirred in 70% ethanol with Dowex 50 (H^+, 3 ml) for 1 h at room temperature. The resin was filtered off and washed with 50% pyridine (60 ml), the filtrate was evaporated, and the residue lyophilized from dioxane (30 ml). The crude product was chromatographed on one 4 mm thick 15 × 35 cm loose layer of silica gel in solvent S_4. The major UV absorbing band was eluted with the same solvent and the eluate evaporated to give XIa (0.07 g, 80%), homogeneous on TLC (S_4) and identical (UV, NMR) with the sample obtained by method A.

2′(3′)-*O*-(*N*-Benzyloxycarbonyl)-L-leucyl-1,2-di(adenosin-*N*^{6}-yl)ethane (XIb). Method A for preparation of compound XIa was followed on a 1-mmol scale via intermediate Xb to give 0.68 g (85%) of XIb: TLC (S_4) homogeneous; in solvent S_6 two spots were observed (vide supra); UV max (ethanol) 274 nm (ϵ 32 200), min 222 (5000);[19] NMR (CD_3SOCD_3) δ 8.47 and 8.36 (2 s partially overlapped, 4, H_8 and H_2), 7.4 (s, 5, phenyl), 6.04 and 5.95 (2 s, 2, $H_{1'}$), 5.14 (s, 2, CH_2 of benzyloxycarbonyl), 1.67 (m, 2, CH_2 of Leu), 0.97 and 0.90 (2 s partially overlapped, CH_3 of ZLeu).

Anal. Calcd for $C_{36}H_{45}N_{11}O_{11}\cdot 1\frac{1}{4}H_2O$: C, 52.06; H, 5.79; N, 18.55. Found: 52.26; H, 5.96; N, 18.22.

Using method B compound XIb was prepared in 81% yield.

2′(3′)-*O*-L-Phenylalanyl-1,2-di(adenosin-*N*^{6}-yl)ethane (XIIa). A slow stream of hydrogen was bubbled through a solution of compound XIa (10–20 μmol) in 80% acetic acid (2 ml) containing 5% PdO–$BaSO_4$ (20–30 mg) at 0 °C with stirring for 2 h. The catalyst was filtered off through a thin Celite bed and it was washed with cold 80% acetic acid (4 ml). The volume of the clear filtrate was adjusted to 10 ml (volumetric flask), the aliquots were pipetted for UV spectra, TLC, paper chromatography, and electrophoresis, and the bulk was lyophilized. UV (0.01 N HCl) corresponded to that of the parent nucleoside XIII: max 263 nm, min 232, shoulder ca. 276. TLC (S_4) showed the complete absence of the starting material XIa; compound XIIa was homogeneous (R_f 0.65) on paper chromatography in S_2 and electrophoresis in 1 M acetic acid (mobility 1.93 of PheOH). It was nynhydrin positive and in S_1 it was hydrolyzed to nucleoside XIII and PheOH. Yield (determined spectrophotometrically at 263 nm using ϵ_{263} 26 300)[1a] was 81%.

2′(3′)-*O*-L-Leucyl-1,2-di(adenosin-*N*^{6}-yl)ethane (XIIb) was prepared and characterized as stated above for compound XIIa, yield 85%, R_f 0.70 (S_2), electrophoretic mobility in 1 M acetic acid 2.2 of PheOH. In solvent S_1 compound XIIb was hydrolyzed to nucleoside XIII and LeuOH.

Acetyl Derivatives II, V, and VI. Compounds I, III, and IV were acetylated as follows. The solution of the compound (0.5 mmol) in a mixture of pyridine (2 ml) and acetic anhydride (1 ml) was kept overnight at room temperature. The reaction mixture was evaporated at 0.05 mm and room temperature, the residue was dissolved in dioxane (10 ml), and the solution was lyophilized to a white solid which was further purified by precipitation from chloroform solution using petroleum ether. After drying at 0.04 mm and room temperature an essentially quantitative yield of the corresponding acetyl derivative was obtained.

Tetraacetyl Derivative II. Homogeneous on TLC (S_3); UV max (ethanol) 270 nm (ϵ 32 300), min 229 (5100);[19] NMR ($CDCl_3$) δ 8.29 (s, 2, H_8), 7.85 and 7.77 (2 s, 2, H_2), 6.02 (m, 2, $H_{1'}$), 3.96 (broad s, 4, dimethylene bridge), 2.1 (3 s partially overlapped, 9) and 1.96 (s, 3, CH_3 of acetyl), 1.62 and 1.44 (2 s, 6, CH_3 of isopropylidene).

Anal. Calcd for $C_{33}H_{40}N_{10}O_{12}\cdot 3H_2O$: C, 48.17; H, 5.51; N, 17.02. Found: C, 48.34; H, 5.14; N, 17.02.

Diacetyl Derivative V. Homogeneous on TLC (S_3); UV max (ethanol) 274 nm (ϵ 34 200), min 248 (21 800); NMR ($CDCl_3$) δ 8.16 and 7.79 (2 s, 4, $H_8 + H_2$), 7.17–6.7 (m, 28, 4-methoxytrityl), 6.12 and 5.98 (2 m, 2, $H_{1'}$), 3.62 and 3.58 (2 s, 6, CH_3O), 2.02 (s, 6, CH_3 of acetyl), 1.62 and 1.40 (2 s, 6, CH_3 of isopropylidene).

Anal. Calcd for $C_{69}H_{68}N_{10}O_{12}$: C, 66.45; H, 5.66; N, 11.23. Found: C, 66.73; H, 5.63; N, 10.94.

Monoacetyl Derivative VI. Two partially overlapped spots on TLC (S_3)—2′ and 3′ isomers; UV max (ethanol) 274 nm (ϵ 34 900), min 248 (24 600). The isomers were separated on a loose layer of silica gel in solvent S_3. The faster moving compound (presumably 3′-*O*-acetyl derivative) was obtained in 60% yield: NMR ($CDCl_3$) δ 8.25 and 8.00 (2 s, 2, H_8), 7.64 and 7.54 (2 s, 2, H_2), 7.15–6.7 (m, 42, 4-methoxytrityl), 5.97 (s, 2, $H_{1'}$), 3.67, 3.64, and 3.62 (3 s partially overlapped, 9, CH_3O), 2.05 (s, 3, CH_3 of acetyl), 1.60 and 1.40 (2 s, 6, CH_3 of isopropylidene). The slower moving component (presumably 2′-*O*-acetyl derivative) was obtained in 40% yield: NMR ($CDCl_3$) δ 1.92 (s, 3, CH_3 of acetyl), the rest of the signals were identical with those of the faster moving isomer.

Anal. (mixture of isomers). Calcd for $C_{87}H_{82}N_{10}O_{12}$: C, 71.54; H, 5.73; N, 9.57. Found: C, 71.46; H, 5.97; N, 9.76.

Equilibration of 2′ and 3′ Isomers of Phenylalanyl and Leucyl Derivative XIa and XIb. Compound XIa (2 mg, 2.5 μmol) was chromatographed on a precoated silica gel aluminum foil (10 × 5 cm) in solvent S_6. Two well-separated UV absorbing bands were eluted with solvent S_5 and the eluates were evaporated. UV spectra of both bands in 0.01 N HCl were identical (max 263, shoulder 276 nm) and corresponded to nucleoside XIII. The ratio of faster/slower moving component as determined from UV was 7/3. Both bands were dissolved in solvent S_5 and the solution was kept at room temperature overnight. Subsequent TLC in S_6 showed the presence of both isomer in each sample in the same ratio as above.

The same result was obtained with leucyl derivative XIb.

Acknowledgment. The authors are indebted to Dr. H. L. Chung and Mr. D. Marks for measuring the UV and NMR spectra.

Registry No.—I, 60996-27-2; II, 60967-39-7; III, 60967-40-0; IV 3′-*O*-MeOTr isomer, 60967-41-1; IV 2′-*O*-MeOTr isomer, 60996-28-3; V, 60967-42-2; VI 3′-*O*-acetyl isomer, 60967-43-3; VI 2′-*O*-acetyl isomer, 60996-29-4; VII, 60967-44-4; VIIIa 3′-*O*-ZPhe isomer, 60996-30-7; VIIIa 2′-*O*-ZPhe isomer, 60996-31-8; VIIIb 3′-*O*-ZLeu isomer, 60967-45-5; VIIIb 2′-*O*-ZLeu isomer, 60967-46-6; IXa, 60967-47-7; IXb, 60967-48-8; Xa 3′-*O*-ZPhe isomer, 60967-49-9; Xa, 2′-*O*-ZPhe isomer, 60967-50-2; Xb 3′-*O*-ZLeu isomer, 60967-51-3; Xb

2′-*O*-ZLeu isomer, 60967-52-3; XIa 3′-*O*-ZPhe isomer, 60967-53-5; XIa 2′-*O*-ZPhe isomer, 60967-54-6; XIb 3′-*O*-ZLeu isomer, 60967-55-7; XIb 2′-*O*-ZLeu isomer, 60967-56-8; XIIa 3′-*O*-Phe isomer, 60967-57-9; XIIa 2′-*O*-Phe isomer, 60967-58-0; XIIb 3′-*O*-Leu isomer, 60967-59-1; XIIb 2′-*O*-Leu isomer, 60967-60-4; XIII, 60687-64-1; 4-methoxytrityl chloride, 14470-28-1; dimethylformamide dimethyl acetal, 4637-24-5; ZPheOH, 1161-13-3; ZLeuOH, 2018-66-8.

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Nucleosides. 104. Synthesis of 4-Amino-5-(D-ribofuranosyl)pyrimidine *C*-Nucleosides from 2-(2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetonitrile[1]

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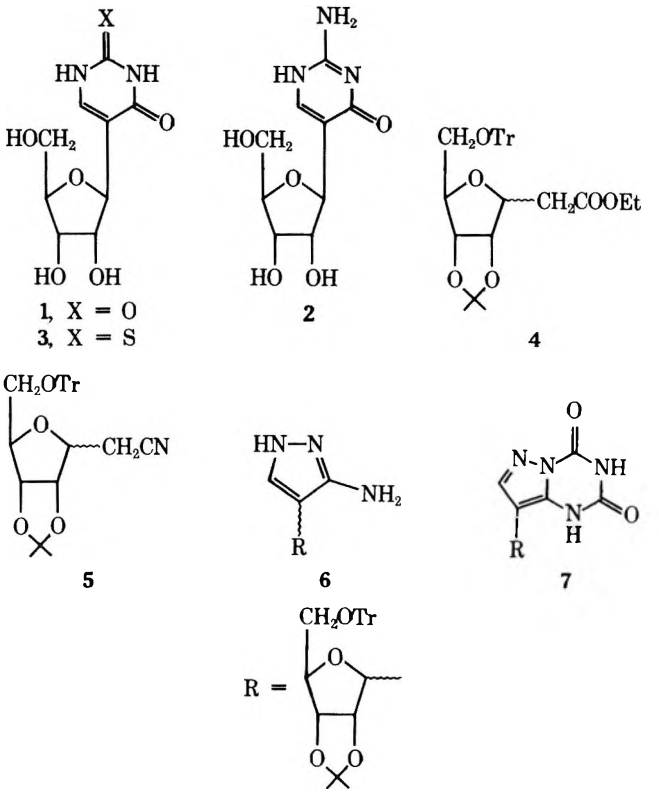
Received June 24, 1976

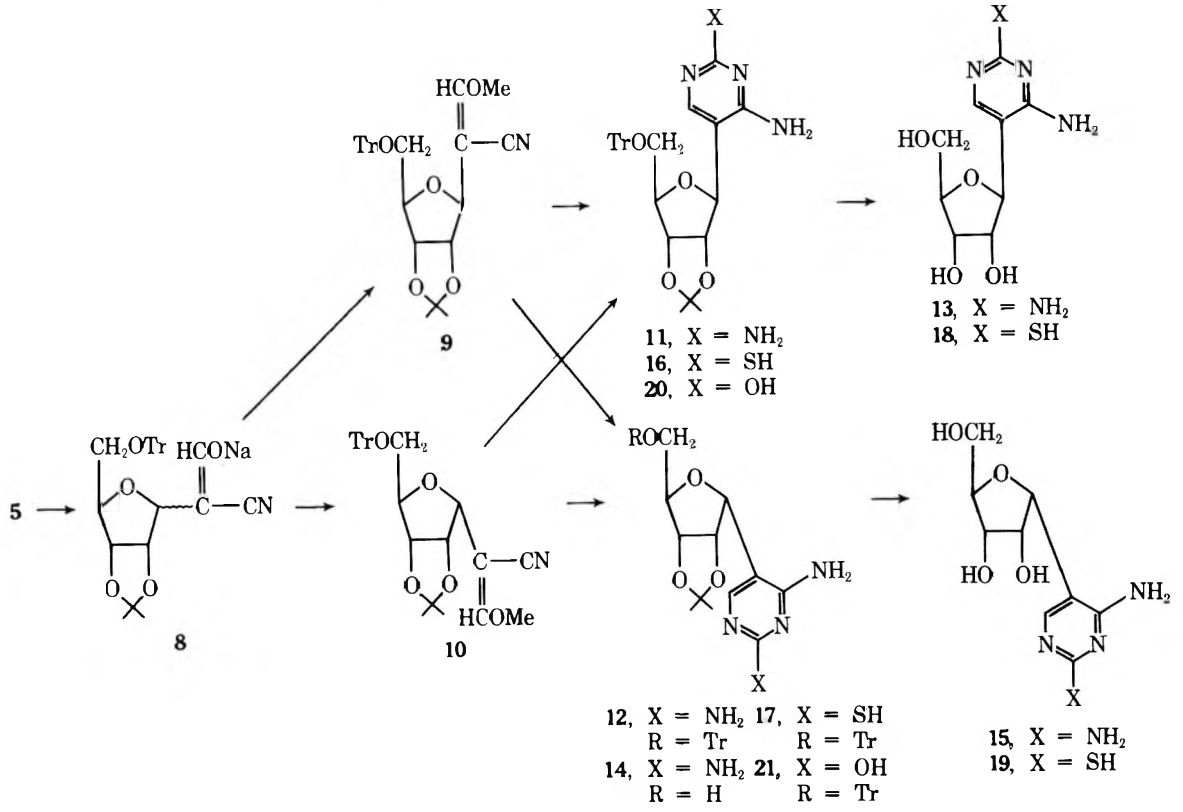
2,4-Diamino-5-(β-D-ribofuranosyl)pyrimidine and 5-(β-D-ribofuranosyl)-2-thiocytosine (2-thiopseudocytidine) were synthesized along with their α isomers in four steps from 2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)-acetonitrile.

As a part of our program in search of anticancer agents, we have recently developed[2] a novel method for general synthesis of pseudouridine (**1**) and its analogues, e.g., pseudoisocytidine (**2**) and 2-thiopseudouridine (**3**), from a common intermediate, ethyl 2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetate (**4**). Pseudoisocytidine (**2**) was found[3] to be as active chemotherapeutically as the naturally occurring antibiotic 5-azacytidine,[4] against various mouse leukemias, and more importantly, **2** was effective against arabinofuranosylcytosine (ara-C)-resistant mouse leukemia cell lines.[3] Further biochemical and preclinical toxicological studies are currently underway with **2** in our institute in preparation for clinical trials.

In our previous communication,[5] we have briefly described the use of 2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetonitrile (**5**) for the synthesis of 3-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)-4-thio-6-oxopyrazolo[1,5-*a*]-1,3,5-triazine (**7**) via the 3-aminopyrazole derivative (**6**).

In this report we describe the synthesis of pyrimidine C-5 nucleosides bearing a 4-amino function from the versatile intermediate **5** which was prepared previously by Ohrui et al.[6] Formylation of **5** with ethyl formate and sodium hydride in a mixture of ether and ethanol gave crude sodium enolate **8** which, without further purification, was treated with methyl iodide in dimethylformamide. Two products (**9** and **10**) in a ratio of ~4:1 were detected on a thin layer chromatogram and separated by silica gel column chromatography. ^1H NMR analyses showed that these products were the β (**9**) and α (**10**)





isomers[7,8] of 2-ribosyl-3-methoxyacrylonitrile. The compound with lower H-1 chemical shift was tentatively assigned to the α structure (**10**).[8] The separation and structural assignment, however, are not important from the practical viewpoint, since *either* isomer gave the same isomeric mixture of the protected 5-ribosyl-2,4-diaminopyrimidines (**11** and **12**) upon treatment with guanidine in the presence of sodium ethoxide. Both nucleosides **11** and **12** were isolated in pure form after separation on a silica gel column.

The assignment of the ribosyl configuration of **11** and **12** is based on ^{1}H NMR studies. The difference in chemical shifts of the two methyl signals of the isopropylidene group ($\Delta\delta$ 21 Hz) for **11** (which eluted from the column first) is larger than that for **12** ($\Delta\delta$ 19.5 Hz)[5] and H-1′ of **11** (δ 4.56) resonated in higher field than that of **12** (δ 5.19). These data indicate[2,5,8] that **11** and **12** are the β and α nucleoside, respectively.

When the protected β nucleoside **11** was treated with methanolic hydrogen chloride at room temperature, the free nucleoside **13** crystallized from the solution as its hydrochloride. Under the same conditions, however, the α isomer **12** did not give the corresponding free nucleoside **15,** but afforded the isopropylidene derivative **14.** In order to obtain **15,** more stringent conditions were required. The ^{1}H NMR spectra of **13** and **13** possessed quite common characteristics of those of the corresponding pairs of pseudouridine[9] and pseudoisocytidine.[2] The chemical shift for H-1′ of **13** (δ 4.63) is higher than that of **15** (δ 5.05), which establishes the configuration at C-1′ as β and α, respectively. The chemical shift of H-6 for the β isomer **13** (δ 7.77) is lower than that for the α isomer **15** (δ 7.75). This difference ($\Delta\delta$ 2 Hz), though small, is consistent with previous $\Delta\delta$ observations[2,9] for H-6 with other α,β pairs of related *C*-nucleosides. Isomerization (**13** $\rightleftarrows$ **15**) was not observed during the deblocking experiments. These data further confirm the assignment of configuration to protected nucleosides **11** and **12.**

The versatility of intermediates **9** and **10** was further demonstrated by the synthesis of 5-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)-2-thiocytosines (**16** and **17**). Cyclization of **9** with excess thiourea gave an isomeric mixture of **16** and **17** in good yield. Compound **10** also afforded the same mixture. Each isomer was separated by fractional crystallization from hot methanol. The β isomer **16** is more soluble in this solvent than the α nucleoside **17.** The assignment of the ribosyl configuration of these derivatives was based on ^{1}H NMR data of these and the corresponding unprotected nucleosides **18** and **19** as previously described for the diamino nucleosides **13** and **15.**

The protected 5-ribofuranosylcytosine derivatives (pseudocytidines **20** and **21**) were also prepared by cyclization of **9** with urea. Each isomer was isolated in pure state after fractional crystallization from methanol. ^{1}H NMR spectral as well as analytical data were consistent with the structure of protected pseudocytidines **20** and **21.** Treatment of **20** or **21** with methanolic hydrogen chloride at room temperature for 30 min, however, produced an intractable mixture which, according to its UV spectrum, was characteristic of a 5-substituted cytosine and showed at least four signals in the δ 4.8–5.1 region indicating that isomerization of the ribosyl configuration as well as of the ring size (furanosyl to pyranosyl) had occurred. Even at milder conditions (e.g., 10% methanolic hydrogen chloride at room temperature for 10 min) considerable coloration and some isomerization were observed. A yellow solid which could be obtained from the mixture was shown to contain ~20% impurities as judged by ^{1}H NMR.

Pseudocytidine (5-β-D-ribofuranosylcytosine) was obtained previously by David and Lubineau[10] in 4% overall yield and was purified by chromatography on Dowex 50 (H^+) using 0.1 M sulfuric acid as the eluent. Using similar conditions,[10] we were unable to elute pseudocytidine from the Dowex 50 column even using higher acid concentrations of eluent. The synthesis of pseudocytidine by alternate approaches is now being undertaken in our laboratory.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a JEOL PFT-100 spectrometer, and Me_4Si was the internal standard for organic solvents and $Me_3Si(CH_2)_3SO_3Na$ (external) for D_2O. TLC was performed on microscope slides coated with silica gel GF_{254} (Merck), and column chromatography on silica gel G or silica gel 60

Table I. ^{1}H NMR Parameters of 4-Amino-5-(D-ribofuranosyl)pyrimidines and Related Compounds

Registry no.	Compd	Chemical shifts, δ								
		H-1′	H-2′	H-3′	H-4′	H-5′	H-6	Isopropyl CH_3		Solvent
61008-78-4	**9**	4.81			4.05	3.28[a]		1.31	1.52	$CDCl_3$
61008-79-5	**10**	5.29	4.88	4.62	4.31	3.27[b]		1.31	1.60	$CDCl_3$
60949-51-1	**11**	4.56		4.98	4.14	3.49	7.85	1.37	1.58	$CDCl_3$
60949-52-2	**12**	5.19[c]	4.66	4.85	4.35[d]	3.2–3.3	7.77	1.29	1.50	$CDCl_3$
60949-53-3	**13**	4.63	4.12		4.32	3.82	7.77			D_2O
60949-54-4	**14**	4.92		5.12	4.42	3.72[e]	7.75			D_2O
60949-55-5	**15**	5.05[f]	4.31	4.49	4.10	3.82[g]	7.75	1.36	1.46	Me_2SO-d_6
60949-56-6	**16**	4.67	4.67	4.67	4.12	3.17[h]	7.50	1.28	1.51	Me_2SO-d_6
60949-57-7	**17**	4.79	4.79	4.61	4.25	3.08	7.35	1.20	1.31	Me_2SO-d_6
60978-37-2	**18**	4.15			4.80	3.81	7.88			D_2O
60949-58-8	**19**	5.10	4.26	4.45	4.08	3.75[i]	7.86			D_2O
60949-59-9	**20**	5.34	5.40	5.10	3.90	2.80	7.35	1.13	1.29	Me_2SO-d_6
60949-60-2	**21**	5.44	5.31	4.78	4.15	3.00	7.55	1.28	1.32	Me_2SO-d_6

[a] Octet, $J_{5',5''} \sim 10.4$, $J_{4',5'} \sim J_{4',5''} \sim 3.6$ Hz. [b] Doublet, $J_{4',5'} \sim 5.3$ Hz. [c] Doublet, $J_{1',2'} \sim 3.4$ Hz. [d] Triplet, $J_{3',4'} \sim J_{4',5'} \sim 4.3$ Hz. [e] Doublet, $J_{4',5'} \sim 5.8$ Hz. [f] Quartet, $J_{1',2'} \sim 3.3$, $J_{1',6} \sim 0.9$ Hz. [g] Octet, $J_{5',5''} \sim 13$, $J_{4',5'} \sim 5.0$, $J_{4',5''} \sim 3.8$ Hz. [h] Doublet, $J_{4',5'} \sim 5.8$ Hz. [i] Octet, $J_{5',5''} \sim 12.5$, $J_{4',5'} \sim 5.2$, $J_{4',5''} \sim 2.8$ Hz.

(70–230 mesh, ASTM, Merck). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich.

2-Formyl-2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetonitrile Sodium Enolate (8). To a suspension of sodium hydride (15 g, 50% in mineral oil) in absolute ether (150 ml, distilled over $LiAlH_4$) was added 4 ml of absolute ethanol followed immediately by dropwise addition of a mixture of compound **5**[11] (91 g, 0.2 mol), ethyl formate (70 ml, distilled over K_2CO_3), and absolute ethanol (4 ml) in dry ether (150 ml). The mixture was stirred overnight at room temperature, and the solvent was evaporated in vacuo below 30 °C. Crude **8** (105 g) was obtained as a brown syrup which was not purified but directly used in the next step.

3-Methoxy-2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acrylonitrile (9 and 10). The crude **8** (105 g) was dissolved in DMF (200 ml, dried over 4 Å molecular sieves). Methyl iodide (56 g, 0.4 mol) was added dropwise to the solution over a period of 1 h. The mixture was stirred for 5 h at room temperature and then poured into a mixture of ice and water (2 l.). The supernatant was removed by decantation and the residual syrup was dissolved in ether (1 l.), washed with water, dried over sodium sulfate, and evaporated to a brown syrup. TLC (benzene–ethyl acetate, 9:1) of the syrup showed that it contained three components [R_f 0.7 (starting material), 0.6 (major), and 0.55]. The lower two components were separated by silica gel 60 (1 kg) column chromatography using benzene–ethyl acetate (19:1) as the eluent. The less polar compound **9** (45 g, 43%) was obtained as a syrup (see Table I for ^{1}H NMR data).

The minor component **10** (5.0 g, 5%) was obtained as white crystals after crystallization from methanol, mp 164–165 °C.

Anal. Calcd for $C_{31}H_{31}NO_5$: C, 74.83; H, 6.27; N, 2.81. Found for **9**: C, 75.03; H, 6.23; N, 2.66. Found for **10**: C, 74.86; H, 6.50; N, 2.77.

2,4-Diamino-5-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)pyrimidine (11 and 12). A mixture of **9** (21.5 g, 0.043 mol) and guanidine hydrochloride (7.5 g, 0.071 mol) in ethanolic sodium ethoxide (200 ml, 0.75 N) was refluxed for 15 h. The mixture was concentrated to ~100 ml in vacuo and neutralized with 1 N HCl. A brown precipitate was dissolved in ether (~200 ml), washed with water, dried over sodium sulfate, and evaporated to a brown semisolid. TLC (benzene–methanol, 4:1) showed that the brown solid contained two major components (R_f 0.65 and 0.60). The mixture was chromatographed over a column of silica gel G60 (1 kg) using chloroform–methanol (20:1) as the eluent. The first compound eluted (6.1 g, corresponding to R_f 0.65 on TLC) was obtained as a powder and assigned structure **11** by ^{1}H NMR analyses (see Table I).

Compound **12** was eluted as the second fraction (3.9 g) as a white powder.

Anal. Calcd for $C_{31}H_{32}N_4O_4$: C, 70.97; H, 6.15, N, 10.68. Found for **11**: C, 70.77, H, 6.19; N, 10.40. Found for **12**: C, 70.72; H, 6.35; N, 10.41.

2,4-Diamino-5-(β-D-ribofuranosyl)pyrimidine Hydrochloride (13). Compound **11** (1.26 g, 2.4 mmol) was dissolved in 10% methanolic hydrogen chloride (12 ml) and the solution was stirred for 1 h at room temperature. Compound **13** precipitated as colorless crystals which were filtered and washed with ether: 0.60 g (90%), mp 215–216 °C dec; UV λ_{max} (pH 1) 270 nm (ε 5080), λ_{max} (pH 7) 280 (5530), λ_{max} (pH 14) 286 (7090), 235 (13 050).

Anal. Calcd for $C_9H_{14}N_4O_4$·HCl: C, 38.78; H, 5.43; N, 20.10; Cl, 12.72. Found: C, 38.60; H, 5.38; N, 20.05; Cl, 12.85.

2,4-Diamino-5-(2,3-*O*-isopropylidene-α-D-ribofuranosyl)pyrimidine Hydrochloride (14). A mixture of **12** (0.97 g, 18 mmol) and 12 ml of methanolic hydrogen chloride (10%) was stirred for 1 h, during which time colorless crystals precipitated. The mixture was evaporated to dryness below 30 °c in vacuo and the residue was coevaporated several times with ether. Recrystallization of the residue from acetone–methanol afforded 450 mg (80%) of **14**: mp 231–233 °C dec; UV λ_{max} (pH 1–7) 270 nm, λ_{max} (pH 13) 285, 235 nm (sh).

Anal. Calcd for $C_{12}H_{18}N_4O_4$·HCl: C, 45.21; H, 6.00; N, 17.57, Cl, 11.12. Found: C, 45.14; H, 5.97; N, 17.48; Cl, 11.39.

2,4-Diamino-5-(α-D-ribofuranosyl)pyrimidine Hydrochloride (15). Compound **12** (350 mg, 11 mmol) was dissolved in 8 ml of methanolic hydrogen chloride (saturated at 0 °C). The solution was left at room temperature for 15 h. The solvent was removed by evaporation and the residue was coevaporated several times with ether when a white solid was obtained. The residue was triturated with acetone and filtered. Compound **15** (300 mg, 98%) was obtained as white crystals: mp 185–188 °C dec; UV λ_{max} (pH 1) 270 nm (ε 4710), λ_{max} (pH 7) 280 (4910), λ_{max} (pH 14) 286 (6750), 234 (11 050).

Anal. Calcd for $C_9H_{14}N_4O_4$·HCl: C, 38.78; H, 5.43; N, 20.10; Cl, 12.72. Found: C, 38.55; H, 5.59; N, 20.04; Cl, 13.00.

5-(2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranosyl)-2-thiocytosine (16 and 17). A mixture of **9** (20.8 g, 0.042 mol) and thiourea (7.6 g, 0.1 mol) in ethanolic sodium ethoxide (200 ml, 1 N) was refluxed for 35 h. The mixture was concentrated under vacuum to ~100 ml, cooled to room temperature, and neutralized with 1 N HCl. The white precipitates were collected by filtration and recrystallized from methanol. The first crop (12.0 g, 53%) was rich in the α isomer **17**. After two recrystallizations of the first crop, pure **17** (3.5 g, 15%) was obtained as colorless needles, mp 214–215 °C.

The combined mother liquors were evaporated and the residue was recrystallized three times from methanol. The pure β isomer (6.1 g, 26%) was obtained as white crystals, mp 208–210 °C.

Anal. Calcd for $C_{31}H_{31}N_3SO_4$: C, 68.76; H, 5.73; N, 7.76; S, 5.92. Found for **16**: C, 68.81; H, 5.81; N, 7.80; S, 5.91. Found for **17**: C, 68.40; H, 5.73; N, 7.43; S, 5.76.

5-(D-Ribofuranosyl)-2-thiocytosine Hydrochloride (18 and 19). A mixture of **12** (1.0 g, 1.8 mmol) and 10% methanolic hydrogen chloride (10 ml) was stirred at room temperature for 1 h. The solvent was removed in vacuo at room temperature. The residue was triturated several times with ether. The β nucleoside **18** was obtained as a white powder, 0 47 g (98%): λ_{max} (pH 1) 280 nm (ε 20 700), 227 (9100), λ_{max} (pH 7) 274 (20 100), 245 (14 900), λ_{max} (pH 14) 269 (15 500), 287 (sh) (9000), 227 (15 900).

In the same manner 0.36 g (94%) after recrystallization from ethanol of the α isomer **19** was obtained from 0.8 g of **17**: mp 196–198 °C dec; UV λ_{max} (pH 1) 280 nm (ε 21 300), 227 nm (9600), λ_{max} (pH 7) 274 (22 100), 243 (16 200), λ_{max} (pH 14) 267 (15 360), 287 (sh) (8300), 224 (16 520).

Anal. Calcd for $C_9H_{13}N_3O_4S$·HCl·0.5CH_3OH: C, 36.60; H, 5.17; N,

13.47; S, 10.28; Cl, 11.37. Found for **18**: C, 36.91; H, 5.30; N, 13.32; S, 10.67; Cl, 11.37. Found for **19**: C, 36.96; H, 5.33; N, 13.43; S, 10.63, Cl, 11.58.

The ^{1}H NMR spectra (Me_2SO-d_6) of the analytical samples showed that both of them contained a small amount of methanol.

5-(2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranosyl)cytosine (20 and 21). A mixture of **9** (16.6 g, 0.033 mol) and urea (6.0 g, 0.1 mol) in ethanolic sodium ethoxide (200 ml, 0.7 N) was refluxed for 24 h. The mixture was concentrated to ~100 ml in vacuo and, after cooling, the concentrated solution was neutralized with 1 N HCl to give a white precipitate (7.2 g, 41%). One crystallization of the precipitate from methanol afforded crystals rich in **21**. Two more recrystallizations of the crystals gave the pure α isomer **21** (2.2 g, 12%) as colorless needles, mp 234–235 °C.

The mother liquors of crystallization were combined and evaporated to dryness. The residue was recrystallized from methanol. The pure β isomer **20** (1.8 g, 10%) was obtained as needles, mp 222–224 °C.

Anal. Calcd for $C_{31}H_{31}N_3O_5$: C, 70.86; H, 5.90; N, 8.00. Found for **20**: C, 70.67; H, 5.93; N, 7.95. Found for **21**: C, 71.03; H, 6.01; N, 8.17.

Registry No.—**5** β isomer, 56703-40-3; **5** α isomer, 56779-60-3; **8** β isomer, 61008-80-8; **8** α isomer, 61008-81-9; guanidine hydrochloride, 50-01-1; thiourea, 62-56-6; urea, 57-13-6.

References and Notes

(1) This investigation was supported in part by funds from the National Cancer Institute, DHEW (Grants CA-08748, −18856, and −17085).
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(8) Though no systematic studies have been done to assure the configurational assignment at glycosyl center of *C*-glycosyl derivatives, an extensive literature survey with more than a score of isomeric pairs of *C*-glycosyl derivatives including *C*-nucleosides showed that H-1′ signal always appears at lower field when it is cis than trans to H-2′.
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(11) Compound **5** has been prepared as previously described[6] but was not purified by chromatography. The by-product triphenylphosphine oxide was removed by precipitation three times from ether.

A General Method for the Synthesis of 2′-Azido-2′-deoxy- and 2′-Amino-2′-deoxyribofuranosyl Purines

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Received July 13, 1976

A new general method for the preparation of 2′-azido-2′-deoxy- and 2′-amino-2′-deoxyribofuranosyl purines is described. Treatment of 2′-azido-2′-deoxyuridine (**3**) with hydrazine hydrate and subsequent treatment of the products with benzaldehyde in boiling water affords 2-azido-2-deoxyribose (**4**), which is derivatized by standard methods to the 1,3,5-triacetate (**7**). Condensation of **7** with N^6-octanoyladenine and subsequent deacylation affords a mixture of α and β anomers of 2′-azido-2′-deoxyadenosine (**8a** and **8b**) which is separable on Dowex 1 × 2 (OH^-). Replacement of N^6-octanoyladenine by N^2-palmitoylguanine affords a mixture of products from which 7- and 9-(2-azido-2-deoxy-β-D-ribofuranosyl)guanine (**11b** and **10b**) are isolable by fractional crystallisation. The α anomers (**11a** and **10a**) also appear to be formed, but have not yet been isolated. Reduction of **8a, 8b, 10b,** and **11b** with triphenylphosphine and ammonia affords the corresponding 2′-amino-2′-deoxy nucleosides **9a, 9b, 12b,** and **13b** in good yield.

V. Ph. 25 April 1978

Analogues of the common ribonucleosides containing an azido or amino group at the 2′ position have valuable potential for investigation of chemical or biochemical problems in which the 2′ moiety is involved. Since the azido group is readily reducible to the amino group, the synthesis of 2′-azido-2′-deoxy nucleosides constitutes a primary aim.

2′-Azido-2′-deoxyuridine[1] and -cytidine[2] have already been described along with their nucleotides and polynucleotides derived by phosphorylation and enzymatic polymerization.[2-4] These compounds show promise for studying the control of synthesis of DNA,[5] among other properties.[6] Reduction of the azido group affords the corresponding 2′-amino-2′-deoxy compounds[1,2,3a] in which further derivatization at the amino group allows a possible source of antibiotics[7] and affinity labels.[8]

The synthesis of the corresponding purine nucleosides has been fraught with difficulty. 9-(2-Azido-2-deoxy-β-D-ribofuranosyl)adenine was recently obtained in low yield[9] by reaction of 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine with azide ion, and subsequent inversion of the configuration at C-3′. Since, however, the ring opening favors attack at the 3′ position over the 2′ position in a ratio of 10:1, this is not a promising synthetic method for the 2′-azido nucleosides. 9-(2-Amino-2-deoxy-β-D-ribofuranosyl)-6-dimethylaminopurine was obtained by Baker et al.,[10] following a 14-step synthesis from an aminated D-altrose derivative as "a noncrystalline substance of somewhat doubtful purity". The α and β anomers of 2′-amino-2′-deoxyadenosine have been obtained via a lengthy synthesis starting from 2-glucosamine.[11] The corresponding guanine nucleosides have not been reported, to our knowledge, although it has been suggested that a strain of Aerobacter produces a 2-amino-2-deoxypentofuranosyl guanine nucleoside which may be 2′-amino-2′-deoxyguanosine.[12]

Although 2′-chloro-2′-deoxyuridine and -cytidine tend to form cyclonucleosides with loss of hydrogen chloride under hydrolytic conditions,[13] experience with the corresponding 2′-azido-2′-deoxy nucleosides indicates that these are comparatively stable.[14] Since 2′-azido-2′-deoxyuridine is relatively easily obtained from uridine,[1] we were led to investigate the possibility of detaching the sugar moiety from this nucleoside, and using it to form a derivative suitable for purine nucleoside

synthesis by one of the standard methods. We here describe the success of this approach in affording not only the adenosine nucleosides in better yield than previously obtainable, but also the guanosine nucleosides.

Results and Discussion

The synthetic method is indicated in Scheme I. The method of Verheyden et al.[1] was adapted to afford 2′-azido-2′-deoxyuridine in 50% yield in a "one-pot" reaction. Uridine (1) was treated with diphenyl carbonate in hexamethylphosphoramide at 140 °C with a little sodium bicarbonate as catalyst, and, on cessation of effervescence, lithium azide was added. The phenol liberated during O^2,2′-cyclouridine (2) formation serves as a proton source, aiding ring opening to give the desired product (3), and addition of benzoic acid as catalyst[1] was found unnecessary. The workup seemed cleaner than that experienced when benzoic acid was added, and 3 was obtained as a yellow gum which crystallized spontaneously at room temperature. A sample which had been decolorized by passage over Dowex 1 (OH^-) and allowed to crystallize melted over a range of 139–147 °C, with incipient decomposition. Since the preparation of the compound is also carried out in this temperature range, temperature and yield seem likely to be closely interdependent. It is probably significant that uracil was found to be a major by-product of this reaction.

Upon stirring 3 with 15% hydrazine hydrate at 65 °C for 1 h,[15] the ultraviolet absorption of the starting material disappeared. Evaporation of the solution in vacuo gave a pale orange gum, which was dissolved in water and heated with excess benzaldehyde at 100 °C. Upon cooling, benzaldehyde azine[16] and other insoluble condensation products crystallized out, leaving an aqueous solution containing 2-azido-2-deoxy-D-ribose (4), which was isolated as a pale yellow gum by chromatography on silica gel. The sugar was chromatographically homogeneous, as indicated by aniline phosphate spray,[17] and showed a strong azide stretching frequency in the infrared spectrum (all azido compounds reported here showed a strong infrared absorption in the range 2100–2140 cm^{-1}). A film of the gum showed no appreciable carbonyl stretch, however, indicating absence of the open-chain form.

The NMR spectrum of 4 in D_2O showed a strong resemblance to that reported for D-ribose by Lemieux and Stevens,[18] showing four doublets of total intensity one at δ 5.53, 5.28, 4.97, and 4.96, of relative intensity ca. 1:1:2:6, and with splittings of 4.0, 2.5, 7.5, and 2.0 Hz, respectively. We tentatively assign the signals at δ 4.97 and 4.96 to $H_1{}^\beta$ and $H_1{}^\alpha$ of the pyranose form and those at δ 5.28 and 5.53 to $H_1{}^\beta$ and $H_1{}^\alpha$ of the furanose form, respectively. Double-resonance studies support this assignment and are entirely consistent with the results of Lemieux and Stevens.[18] The total integral for these signals was one-fifth of that for the remaining protons in the molecule.

Conversion of 4 to its 1-*O*-methyl glycoside (5) took place rather slowly under standard conditions,[19] to afford a mixture of the α and β anomers in 67% yield after chromatography on silica gel, which also allowed unconsumed starting material to be reisolated. The anomers ran with the same R_f value on TLC, and were detected by spraying with aniline phosphate and incubating for an extended period at 100 °C. NMR in Me_2SO showed $H_1{}^\alpha$ at δ 4.97, $J^\alpha{}_{1,2}$ = 4.5 Hz, and $H_1{}^\beta$ as a singlet at δ 4.69, in a ratio 15:85, the total intensity corresponding to one proton. The methoxyl signal was also split giving sharp singlets at δ 3.31 and 3.24, total intensity three. These figures are similar to those given for methyl D-ribofuranoside in the same solvent.[20] The occurrence of a triplet at δ 4.68, strongly coupled to $H_{5a,b}$ at δ 3.48 and exchanging with deuteriomethanol, indicates that a primary hydroxyl group is present at C-5 and thus that the ribofuranose form is present.

Conversion of 5 to the diacetate 6 was performed using pyridine and acetic anhydride, to give a single product as indicated by TLC, consisting of the anomer mixture in the same proportions as 5.

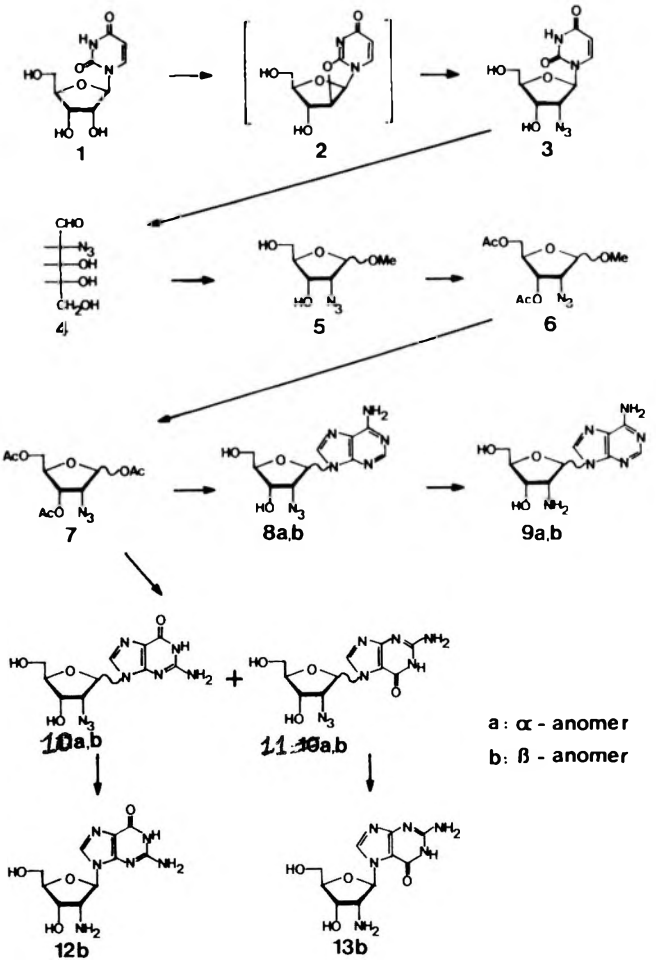
Treatment of 6 with concentrated sulfuric acid in acetic acid–acetic anhydride[19] afforded the triacetate 7 in high yield. It was found preferable to make the conversion 5 → 7 in two stages, as described, rather than in one direct stage,[19] since the direct method afforded a number of products as indicated by TLC, whereas the conversion as described gave only 7 as an anomeric mixture (α:β, 40:60) in which replacement of the methoxyl group in 6 by acetate was shown by NMR to have proceeded quantitatively.

No attempt was made to separate the α and β anomers of 5, 6, and 7, although the anomers of 5 should be separable by chromatography on Dowex-1 (OH^-).[21] The reason for this omission is that the anomer ratio changes during the conversion 6 → 7 rendering an earlier separation preparatively superfluous, and also indicating that the replacement of methoxyl by acetate in this system affords an equilibrium mixture of anomers as expected, rather than one generated by simple S_N2 displacement.

Decoupling experiments indicated differences in the chemical shifts of the H-2 in the α and β anomers of 5, 6, and 7. Some variation in the chemical shift of H-2 in α and β anomers in, for instance, the methyl *O*-methyl-D-xylofuranosides has been noted previously.[22]

7 was condensed with N^6-octanoyladenine in 1,2-dichloroethane using stannic chloride as catalyst, as described by Furukawa and Honjo.[23] Initially the quantities used were those described as optimum by these authors, namely sugar

Scheme I



derivative:acylated base:stannic chloride in the ratio 4:5:5, but it was subsequently found that a small further addition of stannic chloride (0.25 mol/mol **7**) was required to drive the reaction to completion. Following deacylation with sodium methoxide in methanol, the mixture obtained was separated on a Dowex 1 × 4 (OH^-) column according to the method of Dekker,[24] to give the α and β anomers of 2′-azido-2′-deoxyadenosine (**8a** and **8b**) in a ratio of 1:2, and a total yield of 60–65%. No other nucleoside products were obtained. **8b** was not affected by sodium methoxide under the conditions employed during deacylation. **8b** was found to be identical in all respects with an authentic sample[9] kindly supplied by Drs. H. Wiedner and R. Mengel, University of Konstanz, Germany.

Since no acylated group is present at the 2 position of the sugar derivative, Baker's rule[25] does not apply in this instance, and a mixture of the α and β anomers of the resultant nucleosides is to be expected. However, the proportions obtained were found to be critically dependent on the quantity of stannic chloride added to the reaction, and the time at reflux temperature. Thus, in another run in which no further stannic chloride was added to drive the reaction to completion, the overall yield was only 32%, but the ratio of **8a:8b** was 1:6.

When N^6-octanoyladenosine is replaced by N^2-palmitoylguanine[23,26] in the above condensation, a complex mixture is formed, condensation taking place rapidly compared with the adenine reaction. This is noteworthy, since Furukawa and Honjo,[23] using N^2-acetylguanine and tetraacetyl-β-D-ribofuranose, obtained no product under the same conditions, indicating that the solubility of the guanine derivative is the critical factor. Before deacylation, the mixture of crude products was passed over silica gel to separate unreacted N^2-palmitoylguanine, since this simplifies product separation. Deacylation was carried out with methoxide, and the products were applied to Dowex 1 × 4 (OH^-) as described above and eluted with 0.4 M triethylammonium bicarbonate solution. As anticipated, the products were a mixture of the 9 and 7 isomers of α- and β-2′-azido-2′-deoxyguanosine (**10a, 10b, 11a, 11b**). By knowing the ultraviolet characteristics of the 7 and 9 isomers of the β anomers (**10b** and **11b**), and assuming that those of the corresponding α anomers are identical, a total yield, based on **7**, of 56.5% was calculated. Fractional crystallization allowed the isolation of **10b** and **11b** (21 and 15%, respectively, based on **7**). Examination of the mother liquors by NMR showed the presence of four H-8 resonances and four H-1′ resonances, of which two are practically coincident. Two of the H-8 resonances and the H-1′ resonances could be assigned to **10b** and **11b** which had not crystallized out. The other resonances, tentatively assumed to be those of **10a** and **11a**, were "paired" by comparing their integrated intensities. The identification of **10b** and **11b** as the β anomers relies on (a) these having the two highest field resonances of the four H-1′ signals (as a general rule,[27] the proton at H-1′ trans to H-2′ appears at higher field); (b) analogy with the signals of the corresponding ribo compounds, reported by Imai et al.;[28] (c) CD data (see below).

Integration of the NMR signals allowed the distribution of products from this condensation to be determined as **10a:10b:11a:11b** = 7:51:12:30, giving a ratio of 58:42 for the distribution of 9-guanyl to 7-guanyl isomers, in good agreement with a value of 55:45 calculated from UV data and employing extinction coefficients determined for pure **10b** and **11b**.

Although very high yields of pyrimidine nucleosides have been obtained[29] on condensation of silylated pyrimidines with sugar acetates using Friedel–Crafts catalysts in 1,2-dichloroethane, the yields reported when silylated purines were employed are more modest,[30] and do not appear significantly better than those reported here. For this reason, we have not investigated the reaction using silylated bases. Reactions using aluminum chloride[15,26] in chlorobenzene or xylene afforded poor yields, with the α anomer predominating, and numerous side products.

8a, 8b, 10b, and **11b** were reduced on treatment with triphenylphosphine[31] in a mixture of equal volumes of dry pyridine and ammonia-saturated methanol, to afford the corresponding 2′-amino-2′-deoxy nucleosides **9a, 9b, 12b,** and **13b** in high yield. The data obtained for **9a** and **9b** concur with those previously published[11] for these compounds. Much difficulty was experienced in trying to obtain an analytical sample of **12b,** and despite apparent chromatographic and electrophoretic homogeneity in all systems tested and good purity as evidenced by the NMR spectrum, the elemental analysis repeatedly gave a high value for carbon, and the extinction coefficient was slightly low. Attempted recrystallization from aqueous solvents repeatedly gave rise to gels. Compound **13b** initially formed a gel, but crystallized satisfactorily from water, after long storage.

No formation of complexes in borate buffer at pH 10 could be detected in the 2′-azido nucleosides here reported, thus indicating that all contain the furanose, rather than the pyranose, form of the ribose. Small mobilities shown by the guanosine derivatives **10b** and **11b** are presumably due to the acidic pK_a of guanine, which lies at 9.6. All the 2′-amino nucleosides showed small mobilities in this buffer, which were, however, markedly less than those for the corresponding ribonucleosides. As expected, all the 2′-amino nucleosides had significantly higher mobilities at pH 3.5 than their ribofuranosyl counterparts, the differences observed between the adenine and guanine compounds again being consistent with the pK_a's of the bases.

In the circular dichroism spectra of the nucleosides, the β anomers of the adenosine compounds **8b** and **9b** have negative Cotton effects in the region of 260 nm, while those of the α anomers **8a** and **9a** have positive effects in agreement with the empirically determined rule.[32] The amplitudes of the spectra near 260 nm are higher for the α anomers than for the β anomers.

The 9-guanyl nucleosides **10b** and **12b** present marked contrasts in their CD spectra, and since the interpretation of the spectra of guanosine compounds is complicated, our conclusions are tentative. The spectrum of 2′-azido-2′-deoxyguanosine (**10b**) is markedly different from that of guanosine and resembles more that of 2′,3′,5′-triacetylguanosine or 2′,3′-*O*-isopropylideneguanosine, or certain 8-substituted guanosine derivatives.[33,34] However, the reduction product, 2′-amino-2′-deoxyguanosine (**12b**), possesses a CD spectrum almost superimposable with that of guanosine. The CD spectrum of **11b** strongly resembles that published for 7-β-D-ribofuranosylguanine,[33] and we take this similarity to indicate β configuration. However, the reduction product, **13b,** exhibits a similar spectrum above 250 nm, but sign inversion in the band at 220 nm.

The synthetic method described here affords products **8a, 8b, 9a,** and **9b** in yields of 3.2, 7.0, 2.6, and 6.8%, respectively, based on uridine as starting material, and represents a notable improvement, both in yield and synthetic length, over the syntheses previously described for **8b, 9a,** and **9b.** All chemicals required are either readily available or, in the case of the acylated bases, can be simply synthesized. The synthesis thus provides a general method for 2′-azido- and 2′-amino-2′-deoxyribosyl nucleosides, since any base which can be employed in standard nucleoside condensations could be used. Furthermore, it seems likely that such a synthetic method could be employed for other 2′ substituents where the uridine derivative is simply synthesized, provided that the 2′ substituent is reasonably stable to acid and base hydrolysis.

The azido nucleosides described here are convenient intermediates for the preparation of the corresponding nu-

cleotides. Thus, **8b** may be phosphorylated chemically in high yield,[14] and converted to the 5′-diphosphate or -triphosphate by standard methods.[35] Treatment with triphenylphosphine and ammonia then affords the 5′-diphosphate or -triphosphate of **9b** in high yield, thus circumventing any complications arising from reaction of a 2′-amino group with phosphorylating or condensing agents.

The 5′-triphosphate of **9b** has previously been obtained by enzymatic phosphorylation of the nucleoside,[36] a procedure in which great care must be taken to avoid ribonucleotides contaminating the products. The 5′-diphosphates of **8b** and **9b** are substrates for polynucleotide phosphorylase from *Micrococcus luteus* in the presence of Mn^{2+} thus forming poly(2′-azido-2′-deoxyadenylic acid) and poly(2′-amino-2′-deoxyadenylic acid). (Results not shown.) The corresponding homopolymers containing uracil and cytosine as base moieties have been described previously.[2,3]

2′-Azido and 2′-amino nucleosides and nucleotides have recently found useful application as enzyme inhibitors[37] and affinity labels.[8] Moreover, a 2′-amino group should afford a valuable attachment point for immobilizing nucleotides for use in affinity chromatography. We are currently investigating some of these applications.

Experimental Section

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 137 spectrometer, UV spectra on a Shimadzu Model UV 200 and Zeiss PMQ II spectrometer, NMR spectra on a Bruker Physik HFX 60 spectrometer, and CD spectra on a Cary 61 spectrometer. Chemical shifts are reported in δ units, parts per million downfield from internal tetramethylsilane.

Thin layer chromatography was performed on Merck Kieselgel 60 F 254 0.2 mm layer thickness, in solvent systems A [methanol–chloroform, 2:8 (v/v)] or B [ethanol–1 M ammonium acetate, 7:3 (v/v)] or as specified. Preparative layer chromatography was performed on 60 F 254 plates of 2 mm thickness from the same supplier. For column chromatography on silica gel, Merck Kieselgel 60 (0.063–0.2 mm) was used. Dowex 1 × 2 and 1 × 4 were obtained in their chloride forms from Serva Feinbiochemica, treated with a large excess of 2 N aqueous hydroxide, and washed to neutrality.

Electrophoresis was performed in the buffers as stated, using 30 V/cm for 90 min.

Paper chromatography was carried out using Schleicher and Schüll 2043 b (washed) paper, in solvent system B or as stated.

Elemental analyses were performed by Mikroanalytisches Labor Beller, Göttingen.

***N*⁶-Octanoyladenine** and ***N*²-palmitoylguanine** were prepared essentially as described by Furukawa and Honjo.[23]

2′-Azido-2′-deoxyuridine (3) was prepared by a modification of the procedure given by Verheyden et al.[1] Uridine (10 g, 41 mmol) and diphenyl carbonate (12 g, 56 mmol) in hexamethylphosphoramide (80 ml) were heated on an oil bath at 140 °C with stirring, and sodium bicarbonate (0.24 g, 2.8 mmol) added. When effervescence had ceased (ca. 30 min), lithium azide (8 g, 163 mmol) was added to the solution which was heated for a further 2 h, after which TLC in system A showed that the intermediate O^2,2′-cyclouridine had almost disappeared, and the required compound was the major product. Workup was performed as described in ref 1. The product was obtained as a yellow gum, homogeneous on TLC in system A and acetone–ethyl acetate, 1:1 (v/v), yield 5.49 g (20.5 mmol, 50%). This material was used for further preparations without further purification. On standing at room temperature, the gum crystallized spontaneously. No solvent giving satisfactory recrystallization has yet been found.

A quantity of 2′-azido-2′-deoxyuridine was applied to Dowex 1 × 4 (OH^-),[24] and the column washed with water, 50% methanol, and finally with 0.1 M triethylammonium bicarbonate, which eluted the required material. Evaporation gave the product as a stiff, clear gum, crystallizing on scraping to give white needles, mp 139–147 °C with darkening and decomposition which became very rapid above 180 °C. Anal. Calcd for $C_9H_{11}N_5O_5$: C, 40.15; H, 4.12; N, 26.02. Found: C, 40.51; H, 3.80; N, 26.15. IR (film of gum) 2120 cm^{-1}. NMR (Me_2SO-d_6) identical with that reported in ref 1.

2-Azido-2-deoxyribose (4). 2′-Azido-2′-deoxyuridine (2.54 g, 9.5 mmol) was dissolved in 15% hydrazine hydrate solution (250 ml, 0.77 mol hydrazine) and heated with stirring on an oil bath at 65 °C for 1 h. At the end of this time TLC in system A indicated complete disappearance of starting material. The solution was evaporated in vacuo to give an orange gum, which was dissolved in water (100 ml). Benzaldehyde (10 ml, 100 mmol) was added, and the mixture heated for 8 min on a boiling water bath, with constant agitation. The solution was cooled rapidly to below room temperature and filtered to remove a sticky precipitate, mainly benzaldehyde azine. The filtrate was extracted with ether (3 × 100 ml) and the aqueous solution evaporated; the gum dissolved in the minimum quantity of methanol and applied to a silica gel column (2.3 × 32 cm) which had been prepared in chloroform. The column was eluted with 100-ml fractions of chloroform (200 ml), 5% methanol–chloroform (700 ml), and 10% methanol–chloroform (600 ml). The required product was eluted in fractions 9–13, and was detected by examining a sample of each fraction by TLC in system A, spraying the plates with aniline phosphate solution[17] (1-butanol, 17 ml; H_2O, 6 ml; aniline, 0.36 ml; 85% phosphoric acid, 0.28 ml) and heating in a drying oven at 110 °C for 10 min. 2-Azido-2-deoxyribose is revealed as a red-brown spot, R_f 0.5. The product-containing fractions were combined and evaporated to give a clear gum (1.05 g, 6 mmol, 64%) which did not crystallize. Anal Calcd for $C_5H_9N_3O_4$: C, 34.29; H, 5.18; N, 23.99. Found: C, 34.45; H, 5.07; N, 23.60. IR (liquid film) 3270 (–OH), 2100 cm^{-1} ($-N_3$).

NMR (D_2O) δ 3.37–4.50 (5 H, complex pattern of H-2, H-3, H-4, and $H_{a,b}$-5 of furanose and pyranose forms (see discussion), 4.96 (0.2 H, $J_{1,2}$ = 2 Hz), 4.97 (0.6 H, $J_{1,2}$ = 7.5 Hz), 5.28 (0.1 H, $J_{1,2}$ = 2.5 Hz), 5.53 (0.1 H, $J_{1,2}$ = 4 Hz) (H-1 α and β anomers of pyranose and β and α anomers of furanose, respectively).

Methyl 2-Azido-2-deoxyriboside (5). 2-Azido-2-deoxyribose (1.02 g, 5.8 mmol) was dissolved in dry methanol (15 ml) and cooled to 0 °C. Concentrated sulfuric acid (0.075 ml) was added, and the reaction mixture stored in a refrigerator at 3–5 °C for 5 days. The course of reaction was followed by TLC in system A. Product is revealed as a gray-brown spot, R_f 0.7, by spraying with aniline phosphate solution (see above) and incubating at 110 °C for a prolonged period, the spot only reaching full intensity after incubation overnight. After 5 days pyridine (2 ml) was added, and the mixture evaporated to dryness, dissolved in the minimum quantity of methanol, and applied to a silica gel column (1.7 × 24 cm) made up in chloroform. The column was eluted with chloroform (300 ml) and 3% methanol–chloroform (700 ml), collecting 50-ml fractions. Fractions 10–17 contained material which gave a single spot on TLC as detailed above. The product-containing fractions were combined and evaporated to give a clear gum which did not crystallize (0.74 g, 3.9 mmol, 67%). Anal. Calcd for $C_6H_{11}N_3O_4$: C, 38.09; H, 5.86; N, 22.21. Found: C, 38.11; H, 6.01; N, 22.24. IR (liquid film) 3300 (–OH), 2910 ($-CH_3$), 2110 cm^{-1} ($-N_3$). NMR (Me_2SO-d_6) δ 3.24; 3.31 (3 H, two singlets, methoxy signals of β and α anomers, respectively), 3.33–4.0 (4 H, complex multiplet, $H_{a,b}$-5 centered at δ 3.48, H-4, H-2), 4.21 (1 H, q, H-3, $J_{2,3} = J_{3,4}$ = 5.5 Hz), 4.68 (1 H, t, OH-5), 4.69 (0.85 H, s, H-1 of β anomer), 4.97 (0.15 H, d, $J_{1,2}$ = 4.5 Hz, H-1 of α anomer), 5.60 (1 H, d, OH-3).

Methyl 3,5-Di-*O*-acetyl-2-azido-2-deoxyriboside (6). Methyl 2-azido-2-deoxyriboside (0.666 g, 3.5 mmol) was dissolved in pyridine (10 ml) and acetic anhydride (4 ml, 42 mmol) added. After standing overnight at room temperature the solvents were evaporated, and the residue dissolved in chloroform (80 ml) and washed with water (3 × 20 ml). The chloroform phase was separated, dried with anhydrous magnesium sulfate, filtered, and evaporated to give the product as a clear gum (0.893 g, 3.3 mmol, 93%) giving a single spot, R_f 0.91, on TLC in ethyl acetate–diethyl ether (1:1 v/v) and development with aniline phosphate spray. Anal. Calcd for $C_{10}H_{15}N_3O_6$: C, 43.96; H, 5.53; N, 15.38. Found: C, 44.11; H, 5.38; N, 15.36. IR (liquid film) 2890 ($-CH_3$), 2100 ($-N_3$), 1740 cm^{-1} (carbonyl). NMR ($CDCl_3$) δ 2.06 (3 H, s), 2.15 (3 H, s), 3.35, 3.47 (3 H, two singlets, methoxy signals of β and α anomers respectively), 3.57–4.5 (4 H, complex pattern, H-4 centered at δ 4.25, H-2, $H_{a,b}$-5), 4.83 (0.85 H, s, H-1 of β anomer), 5.08 (0.15 H, d, $J_{1,2}$ = 4.5 Hz, H-1 of α anomer), 5.26 (1 H, t, H-3, $J_{2,3} = J_{3,4}$ = 5.5 Hz).

1,3,5-Tri-*O*-acetyl-2-azido-2-deoxyribose (7). Methyl 3,5-di-*O*-acetyl-2-azido-2-deoxyriboside (0.87 g, 3.2 mmol) was dissolved in glacial acetic acid (4.5 ml) and acetic anhydride (1.2 ml, 12.7 mmol) and cooled to 0 °C. Concentrated sulfuric acid (0.23 ml) was added slowly with vigorous stirring. When addition was complete the solution was allowed to warm to room temperature, and left for 22 h, during which time a dark red color developed. Ice (6.25 g) was then added to the mixture, which was extracted with chloroform (4 × 13 ml). The combined chloroform phases were washed with saturated sodium bicarbonate solution (2 × 25 ml) and water (25 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to give the product as a clear gum (0.889 g, 2.95 mmol, 93%) having similar R_f (0.89) to the starting material on TLC in ethyl acetate–diethyl ether (1:1 v/v) but in which NMR revealed complete loss of the methoxy

signal. Anal. Calcd for $C_{11}H_{15}N_3O_7$: C, 43.86; H, 5.02; N, 13.95. Found: C, 44.17; H, 4.91; N, 13.82. IR (liquid film) 2920 (-CH_3), 2110 (-N_3), 1745 cm^{-1} (carbonyl). NMR ($CDCl_3$) δ 2.10 (4.1 H, s), 2.20 (4.9 H, s), 3.6–4.5 (4 H, complex pattern, H-4 centered at δ 4.30, H-2, $H_{a,b}$-5), 5.27 (1 H, m, H-3), 6.09 (0.6 H, s, H-1 of β anomer), 6.43 (0.4 H, d, $J_{1,2}$ = 4.5 Hz, H-1 of α-anomer).

9-(2-Azido-2-deoxyribofuranosyl)adenine (8a and 8b) (α and β Anomers). 1,3,5-Tri-*O*-acetyl-2-azido-2-deoxyribose (515 mg, 1.71 mmol) was dissolved in 1,2-dichloroethane (40 ml) and N^6-octanoyladenine (590 mg, 2.1 mmol) added. The mixture was heated to reflux temperature, and stannic chloride (588 mg, 2.1 mmol, 0.27 ml) added. After 6 h under reflux, a further 0.07 ml (0.5 mmol) of stannic chloride was added. After 9 h all solid material had dissolved, and the mixture had become dark in color. TLC in solvent system A showed a large spot running at the solvent front, and unconsumed octanoyladenine (R_f 0.74). The solution was evaporated, and the residue dissolved in 2 N sodium methoxide (8 ml) and methanol (28 ml). After 10 h at 37 °C, deacylation was complete, TLC in system A showing essentially only the α and β anomers of the product (R_f 0.42 and 0.55). The solvent was evaporated and the residue dissolved in 10% methanol/water and applied to a column (2.1 × 30 cm) of Dowex 1 × 4 (OH^-), which was washed with 30% methanol–water, and the products eluted with 50% methanol–water. The α anomer is eluted first. Separation was incomplete and further passage over Dowex 1 × 4 (OH^-) was necessary, affording finally the α anomer (4350 A_{260} units, 17%) and the β anomer (9700 A_{260} units, 38%) as well as a small unseparated fraction (1050 A_{260} units, 4%, mostly α anomer). Total yield, 15 100 A_{260} units, 59%. 9-(2-Azido-2-deoxy-β-D-ribofuranosyl)adenine (**8b**) was obtained crystalline (190 mg, 0.65 mmol) on evaporation of the solution, but may be recrystallized from water: mp 217–220 °C dec, lit.[9] 205 °C; λ_{max} (H_2O) 259.5 nm (ϵ 14 900), λ_{max} (pH 1) 257 nm (ϵ 14 500); NMR (Me_2SO-d_6) identical with that in ref 9; CD λ_{max} (H_2O) 262 nm ([θ] −3530), $\lambda_{crossover}$ 240 nm.

9-(2-Azido-2-deoxy-α-D-ribofuranosyl)adenine (8a) was obtained as a clear gum which crystallized slowly from acetone (82 mg, 0.28 mmol), mp 171–173 °C dec. Anal. Calcd for $C_{10}H_{12}N_8O_3$ (292.3): C, 41.10; H, 4.14; N, 38.34. Found: C, 41.44; H, 4.31; N, 38.02. IR (KBr) 3300–3050 (OH, NH_2), 2120 (N_3) 1690, 1640, 1600 cm^{-1} (NH, purine); λ_{max} (H_2O) 259.5 nm (ϵ 14 900), λ_{max} (pH 1) 257.5 nm (ϵ 14 400); CD λ_{max} (H_2O) 259 nm ([θ] +1900), $\lambda_{crossover}$ 224 nm; NMR (Me_2SO-d_6) 3.59 (2 H, d, $H_{a,b}$-5′) 4.12 (1 H, m, H-4′), 4.56 (2 H, m, H-2′ and H-3′), 4.95 (1 H, t, OH-5′) 6.24 (1 H, d, OH-3′), 6.39 (1 H, d, $J_{1',2'}$ = 5 Hz, H-1′) 7.28 (2 H, s, -NH_2), 8.13, 8.24 (2 H, s, H-2 and H-8).

Electrophoretic mobilities in 0.1 M borate, pH 10: **8b**, 0.6 cm; **8a**, 0.5 cm; adenosine, 7.6 cm. R_f values on paper in solvent system B: **8b**, 0.73; **8a**, 0.76; adenosine, 0.66.

9-(2-Amino-2-deoxy-β-D-ribofuranosyl)adenine (9b). 9-(2-Azido-2-deoxy-β-D-ribofuranosyl)adenine (37.9 mg, 0.13 mmol) was dissolved in dry pyridine (0.9 ml) and 50% saturated methanolic ammonia (0.9 ml) and triphenylphosphine (92 mg, 0.35 mmol) added. After standing overnight at room temperature, TLC in system B indicated almost quantitative conversion of the starting material (R_f 0.83) to a product, R_f 0.57. The solution was evaporated and the residue partitioned between benzene and water. The aqueous layer was separated, the benzene layer washed with water, and the combined aqueous solutions evaporated, redissolved in water, and applied to a column of Dowex 1 × 4 (OH^-) (1.2 × 16 cm). The required product (1800 A_{260}, 96%) was obtained on elution with water. The aqueous solution was evaporated and the residue crystallized from dry acetonitrile to give white crystals (27.3 mg, 0.11 mmol): mp 199–201 °C (lit.[11] 194–196 °C); CD λ_{max} (H_2O) 270 nm ([θ] −3460), 234 nm ([θ] +1590), $\lambda_{crossover}$ 248, 223 nm. The material was chromatographically and electrophoretically identical with an authentic sample.

9-(2-Amino-2-deoxy-α-D-ribofuranosyl)adenine (9a). 9-(2-Azido-2-deoxy-α-D-ribofuranosyl)adenine (81.4 mg, 0.28 mmol) was dissolved in dry pyridine (2 ml) and 50% saturated methanolic ammonia (2 ml) and triphenylphosphine (196 mg, 0.75 mmol) added. After standing overnight the starting material (R_f 0.75 on TLC in system B) had been converted almost quantitatively to a new spot (R_f 0.5). The solution was evaporated and the residue triturated with benzene–ether (1:1, 50 ml in three portions), and then taken up in water and passed over Dowex 1 × 2 (OH^-) (1.6 × 17 cm). Elution with water gave a homogeneous product (3540 A_{260}, 84%) which was crystallized from ethanol–water to give white crystals (60 mg, 0.22 mmol): mp 148–149 °C (lit.[11] 149–151 °C); CD λ_{max} (H_2O) 257 ([θ] +6650), 220 nm ([θ] +9900).

7-(2-Azido-2-deoxy-β-D-ribofuranosyl)guanine (11b), 9-(2-Azido-2-deoxy-β-D-ribofuranosyl)guanine (12b), and Their α Anomers 10a and 11a. 1,3,5-Tri-*O*-acetyl-2-azido-2-deoxyribose (689 mg, 2.29 mmol) was dissolved in 1,2-dichloroethane (50 ml) and N^2-palmitoylguanine (1.11 g, 2.86 mmol) added. The mixture was heated to reflux temperature, and stannic chloride (0.34 ml, 2.8 mmol) added. After 90 min heating under reflux the solid material had all been consumed, and TLC in solvent system A showed two spots running almost at the solvent front (R_f 0.94 and 0.89) and palmitoylguanine (R_f 0.67, streaking). The solution was cooled to room temperature and evaporated, and the resulting dark gum dissolved in chloroform and applied to a silica gel column (2.2 × 36 cm) which had been prepared in chloroform. The column was washed with chloroform (400 ml) and eluted with 3% methanol–chloroform (600 ml). Fractions containing material which ran faster than palmitoylguanine in solvent system A were combined and evaporated to give a light brown gum (1.32 g), which was dissolved in 2 N sodium methoxide (10 ml) and methanol (40 ml) and maintained overnight at 37 °C, after which deacylation was found to be complete (TLC system A). The solution was evaporated and the residue suspended in water and applied to a column of Dowex 1 × 2 (OH^-) (2.2 × 36 cm), which was washed thoroughly with water, and then with 0.1 M triethylammonium bicarbonate solution (to remove strongly adsorbed inorganic salts), and the products then eluted as a single peak with 0.4 M triethylammonium bicarbonate. The peak contained 12 310 A_{253} units and 8620 $A_{285.5}$ units, indicating the formation of ca. 0.57 mmol of the 7-(2-azido-2-deoxyribofuranosyl)guanine isomers and ca. 0.71 mmol of the 9-(2-azido-2-deoxyribofuranosyl)guanine isomers (this necessarily assumes that the α and β anomers of each species possess the same λ_{max} (H_2O) and extinction coefficients). The total yield for the condensation was 1.29 mmol of nucleoside (56.5%). The solution was evaporated to dryness, traces of triethylamine being removed by addition and reevaporation of methanol, and the residue was dissolved in boiling water (ca. 250 ml). On cooling to room temperature, a crystalline precipitate formed. This was collected and recrystallized once from boiling water to give 7-(2-azido-2-deoxy-β-D-ribofuranosyl)guanine (**11b**, 102.3 mg, 0.33 mmol, 14.6% based on sugar triacetate) as white crystals, darkening above 238 °C, no melting point <300 °C. Anal. Calcd for $C_{10}H_{12}N_8O_4$ (308.3): C, 38.96; H, 3.92; N, 36.35. Found: C, 38.91; H, 3.92; N, 36.39. IR (KBr) 3350–3100 (OH, NH_2) 2850, 2650 (NH), 2120 (N_3), 1670, 1620, 1560, 1460 cm^{-1} (NH, CO, purine); λ_{max} (H_2O) 285.5 nm (ϵ 7600), 240 (sh) (6600), 216 (20 100); λ_{max} (pH 1) 250 nm (ϵ 9400), 270 (sh) (6700); λ_{max} (pH 13) 282 nm (ϵ 6400), 240 (sh) (7600). CD λ_{max} (H_2O) 287 nm ([θ] +2460), 249 ([θ] −720), 218 ([θ] +12 670), $\lambda_{crossover}$ 256, 240 nm. NMR (Me_2SO-d_6) δ 3.63 (2 H, m, $H_{a,b}$-5′), 3.92 (1 H, m, H-4′), 4.13–4.53 (2 H, m, H-2′ and H-3′), 5.07 (1 H, t, OH-5′), 5.90 (1 H, d, OH-3′), 6.15 (1 H, d, $J_{1',2'}$ = 5.0 Hz, H-1′), 6.22 (2 H, s, -NH_2), 8.32 (1 H, s, H-8).

On reduction of the volume of the mother liquor to about half and storage at room temperature, a further precipitate was formed and on investigation found to be virtually pure 9-(2-azido-2-deoxy-β-ribofuranosyl)guanine (**10b**) obtained as white crystals (149.3 mg, 0.48 mmol, 21% based on sugar triacetate), mp 206 °C dec. Anal. Calcd for $C_{10}H_{12}N_8O_4$ (308.3): C, 38.96; H, 3.92; N, 36.35. Found: C, 38.84; H, 4.18; N, 36.31. IR (KBr) 3400–3150 (OH, NH_2), 2900, 2700 (NH), 2120 (N_3), 1710, 1690, 1630, 1600, 1530, 1480 cm^{-1} (NH, CO, purine); λ_{max} (H_2O) 253 nm (ϵ 13 700), 270 (sh) (9800); λ_{max} (pH 1) 257.5 nm (ϵ 12 000), 280 (sh) (7900); λ_{max} (pH 13) 258–268 (ϵ 11 600). CD λ_{max} (H_2O) 267 nm ([θ] +1610), 215 ([θ] +10 020). NMR (Me_2SO-d_6) δ 3.58 (2 H, m, $H_{a,b}$-5′), 3.91 (1 H, m, H-4′), 4.32–4.58 (2 H, m, H-2′ and H-3′), 5.05 (1 H, t, OH-5′), 5.81 (1 H, d, $J_{1',2'}$ = 5.5 Hz, H-1′), 5.97 (1 H, d, OH-3′), 6.48 (2 H, s, -NH_2), 7.94 ([H, s, H-8).

Electrophoretic mobilities in 0.1 M borate, pH 10: **11b**, 4.2 cm; **10b**, 5.8 cm; guanosine, 11.6 cm. R_f values on paper in solvent system B: **11b**, 0.60; **10b**, 0.71; guanosine, 0.60.

Evaporation of the mother liquor and examination of the residue by NMR (Me_2SO-d_6) shows H-8 signals at δ 7.86, 7.94, 8.08, and 8.32 in ratio 25:45:40:16, a doublet at δ 5.81, $J_{1',2'}$ = 5.5 Hz, a broadened doublet, probably two almost coincident superimposed doublets, $J_{1',2'} \simeq 5$ Hz, at δ 6.17, and a further doublet at δ 6.56 ($J_{1',2'}$ = 4.5 Hz), the extra signals presumably being due to **11a** (at 8.08 and 6.56) and **10a** (at 7.86 and 6.17). The distribution of the products of condensation is thus **11a**, 12%; **11b**, 30%; **10a**, 7%; **10b**, 51%, and the ratio of 7 isomers:9 isomers is 42:58 (cf. result from UV estimation, 45:55).

9-(2-Amino-2-deoxy-β-D-ribofuranosyl)guanine (12b). 9-(2-Azido-2-deoxy-β-D-ribofuranosyl)guanine (30.0 mg, 0.097 mmol) was dissolved in dry pyridine (1 ml) and 50% saturated methanolic ammonia (1 ml) in a 10-ml flask and triphenylphosphine (91 mg, 0.35 mmol) added. The solution was stirred overnight at room temperature, transferred quantitatively to a larger flask with aqueous methanol, and evaporated. The residue was triturated with diethyl ether–benzene (1:1 v/v; three portions, totaling 25 ml) and the remaining solid product dissolved in 25 ml of H_2O and extracted with 2 × 10 ml of benzene. Evaporation of the aqueous solution afforded

a white, microcrystalline material (21.1 mg, 0.075 mmol, 77%) giving a single spot on TLC in system B, R_f 0.38 (starting material, R_f 0.76), mp 221–223 °C dec. Anal. Calcd for $C_{10}H_{14}N_6O_4$ (282.3): C, 42.55; H, 5.00; N, 29.78. Found: C, 43.26; H, 5.27; N, 29.44. IR (KBr) 3400–3050 (OH, NH_2) 2890, 2710 (NH), 1720, 1690, 1630, 1600, 1540, 1530, 1480 cm^{-1} (NH, CO, purine); λ_{max} (H_2O) 252 nm (ϵ 13 200), 270 (sh) (9400); λ_{max} (pH 1) 256 nm (ϵ 12 500), 280 (sh) (8200); λ_{max} (pH 13) 256–266 nm (ϵ 11 500). CD λ_{max} (H_2O) 253 nm ([θ] −1710), 217 ([θ] +8960), $\lambda_{crossover}$ 235 nm. NMR (Me_2SO-d_6) δ 3.28 (2 H, s, $-NH_2$-2′), 3.40–4.05 (5 H, m, H-2′, H-3′, H-4′, $H_{a,b}$-5), 5.00 (1 H, broad s, OH-5′), 5.46 (1 H, d, $J_{1',2'}$ = 8 Hz, H-1′), 6.40 (2 H, s, $-NH_2$), 7.84 (1 H, s, H-8).

Electrophoretic mobility in 0.1 M borate, pH 10: **12b,** 6.7 cm; guanosine, 11.7 cm. In 0.05 M ammonium formate, pH 3.5: **12b,** 14.6 cm; guanosine, 4.6 cm. R_f value on paper in solvent system B: **12b,** 0.54; guanosine, 0.60.

7-(2-Amino-2-deoxy-β-D-ribofuranosyl)guanosine (13b). 7-(2-Azido-2-deoxy-β-D-ribofuranosyl)guanine (50 mg, 0.16 mmol) was dissolved in dry pyridine (2 ml) and 50% saturated methanolic ammonia (2 ml) in a 10-ml flask, and triphenylphosphine (138 mg, 0.53 mmol) added. After stirring overnight at room temperature the solution was transferred to a larger flask with methanol–water and evaporated, and the residue shaken with 3 × 10 ml water; the filtered aqueous solutions were combined and extracted with 3 × 10 ml of benzene, and then evaporated to give 36.4 mg (0.13 mmol, 79.5%) of residue, which was pure by TLC. The residue was dissolved in hot water to form a stiff gel on cooling, which slowly decomposed depositing white microcrystals of product (25.6 mg, 0.091 mmol, 56%) which decomposed slowly above 250 °C and rapidly above 265 °C, but showed no melting point <300 °C. TLC in system B gave a single spot, R_f 0.35, streaking. Anal. Calcd for $C_{10}H_{14}N_6O_4$ (282.3): C, 42.55; H, 5.00; N, 29.78. Found: C, 42.54; H, 5.14; N, 29.77. IR (KBr) 3400–3100 (OH, NH_2), 2880, 2650 (NH), 1660, 1560, 1470 cm^{-1} (NH, CO, purine); λ_{max} (H_2O) 286.5 nm (ϵ 7700), 240 (sh) (6700), 215.5 (19 100); λ_{max} (pH 1) 250 nm (ϵ 8500), 270 (sh) (7200); λ_{max} (pH 13) 282.5 nm (ϵ 7900), 240 (sh) (7900). CD λ_{max} (H_2O) 283 nm ([θ] +1800), 220 ([θ] −8710), $\lambda_{crossover}$ 260 nm. NMR (Me_2SO-d_6) 3.30 (3 H, broad s, $-NH_2'$ + HO?) 3.42–4.07 (5 H, m, H-2′, H-3′, H-4′, $H_{a,b}$-5′), 4.94 (1 H, broad s, OH-5′?), 5.73 (1 H, d, $J_{1',2'}$ = 7.5 Hz, H-1′), 6.17 (2 H, s, $-NH_2$), 8.17 (1 H, s, H-8).

Electrophoretic mobility in 0.1 M borate, pH 10: **3b,** 6.1 cm; guanosine, 11.7 cm. In 0.05 M ammonium formate, pH 3.5: **13b,** 16.2 cm; guanosine, 4.6 cm. R_f values on paper in solvent system B: **13b,** 0.49; guanosine, 0.60.

Acknowledgments. We thank Drs. V. W. Armstrong and H. Wiedner for helpful discussions, Mr. B. Seeger for measuring NMR spectra, and Mrs. P. Pauls and Mrs. G. Daenecke for excellent technical assistance. This work was supported by the Deutsche Forschungsgemeinschaft.

Registry No.—**1,** 58-96-8; **3,** 26929-65-7; **4a** pyranose form, 60921-16-6; **4a** furanose form, 60921-17-7; **4b** pyranose form, 60921-18-8; **4b** furanose form, 60921-19-9; **5a,** 60921-20-2; **5b,** 60921-21-3; **6a,** 60921-22-4; **6b,** 60921-23-5; **7a,** 60921-24-6; **7b,** 60921-25-7; **8a,** 60921-26-8; **8b,** 58699-61-9; **9a,** 10407-64-4; **9b,** 10414-81-0; **10a,** 60921-27-9; **10b,** 60921-28-0; **11a,** 60921-29-1; **11b,** 60921-30-4; **12b,** 60966-26-9; **13b,** 60921-31-5; N^6-octanoyladenine, 52854-12-3; N^2-palmitoylguanine, 21047-87-0.

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Synthesis of Blood-Group Substances. 6. Synthesis of *O*-α-L-Fucopyranosyl-(1→2)-*O*-β-D-galactopyranosyl-(1→4)-*O*-[α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-α-D-glucopyranose, the Postulated Lewis d Antigenic Determinant[1]

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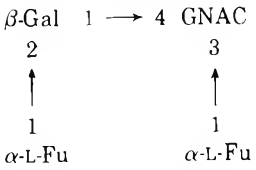
Received June 10, 1976

The chemical synthesis of the title tetrasaccharide is reported. It involves condensation of benzyl 2-acetamido-3-*O*-allyl-6-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**8**) with 3,4,6-tri-*O*-benzyl-1,2-*O*-(*tert*-butoxyethylidene)-α-D-galactopyranose (**11**). After O-deacetylation of **12**, the obtained compound **13** was glycosylated by 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide (**22**) using the bromide ion catalyzed reaction. The allyl ether of **23** was cleaved and the resulting trisaccharide **24** condensed again with **22**. The title tetrasaccharide was obtained in crystalline form after catalytic hydrogenolysis of **27**.

Practical syntheses of complex oligosaccharides containing a variety of linkages has represented one of greatest challenges in carbohydrate chemistry. The fascinating oligosaccharidic structures of blood-group substances, as proposed by Kabat,[2] present an attractive target to the synthetic chemists. With the success achieved by Lemieux and Driguez[3] in the synthesis of the terminal trisaccharide units of the human B and Lewis a blood-group antigenic determinants, the onslaught is now launched and other groups[4,5] have taken up the challenge. Our interest in type II blood-group determinants arose after we described[6] a practical synthesis of *N*-acetyllactosamine. The H specific trisaccharide (type II) has recently been obtained by us[5] and, using a similar strategy, we report here the synthesis of a more complex tetrasaccharide. Potapov[7] has discovered an antibody which reacts only with Lewis (a^-b^-) red cells of secretors. The structure of the corresponding antigen, named Lewis d by him and Y by Hakomori,[8] was postulated[9] to be

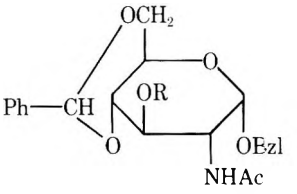


An oligosaccharide containing this complex structure as a terminal nonreducing group has been isolated from blood-group glycoproteins.[10] Despite its similarity to the Lewis b active tetrasaccharide, it was inactive as a Lewis b inhibitor.[11] This tetrasaccharide has been incorporated into the composite structure proposed for the carbohydrate chains in a HLeb substance.[12] As far as we are aware, it has not yet been possible to identify and isolate the title tetrasaccharide and therefore the synthesis of this compound is of interest for immunological studies.[20]

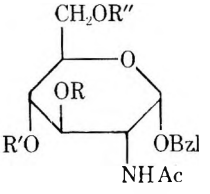
Results and Discussion

We have shown[6,13] that benzyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside is an attractive aglycon for the high-yield synthesis of various disaccharides of the type (α or β) × 1→4 *N*-acetylglucosamine.

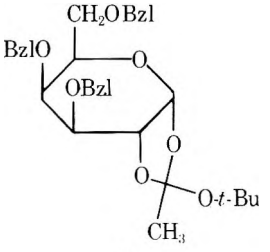
A key compound for the synthesis of the title tetrasaccharide (**28**) was benzyl 2-acetamido-3-*O*-allyl-6-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**8**). Benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[14] was quantitatively converted into its 3-*O*-allyl derivative (**1**) and, after hydrolysis (60% acetic acid), to benzyl 2-acetamido-3-*O*-allyl-2-deoxy-α-D-glucopyranoside (**2**). When **2** was treated with *N*-benzoylimidazole in dioxane under reflux, a selective benzoylation took place and benzyl 2-acetamido-3-*O*-allyl-6-*O*-benzoyl-2-deoxy-α-D-glucopyranoside (**4**) was obtained in 89% yield. The expected compound **8** was then obtained through a sequence already used[15] for the synthesis of benzyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside: after temporary protection of the C-4 hydroxyl group with tetrahydropyranyl ether, the primary position was easily benzylated; acid hydrolysis finally gave benzyl 2-acetamido-3-*O*-allyl-6-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**8**), whose ^1H NMR spectrum is in full agreement with the structure. The total yield from **2** to **8** was ca. 70%, each intermediate being obtained in pure form and excellent yield after one crystallization. Alternatively, **8** may be obtained after selective benzylation of benzyl 2-acetamido-3-*O*-allyl-2-deoxy-α-D-glucopyranoside (**2**). It was obtained in 37% yield after chromatographic separation from benzyl 2-acetamido-3-*O*-allyl-4,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**10**).



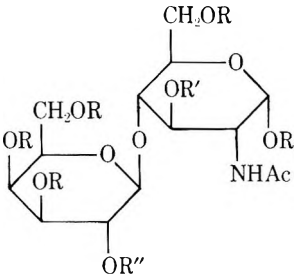
1, R = A



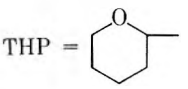
2, R = A; R′ = R″ = H
3, R = A; R′ = R″ = Ac
4, R = A; R′ = H; R″ = Bz
5, R = A; R′ = THP; R″ = Bz
6, R = A; R′ = THP; R″ = OH
7, R = A; R′ = THP; R″ = Bzl
8, R = A; R′ = H; R″ = Bzl
9, R = A; R′ = Ac; R″ = Bzl
10, R = A; R′ = R″ = Bzl



11

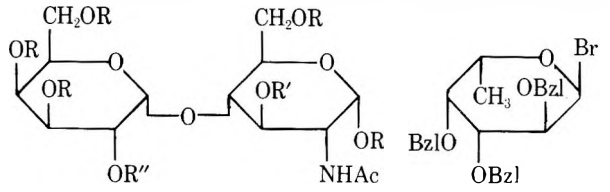


A = $CH_2CH{=}CH_2$
Bz = C_6H_5CO
Bz = $C_6H_5CH_2$

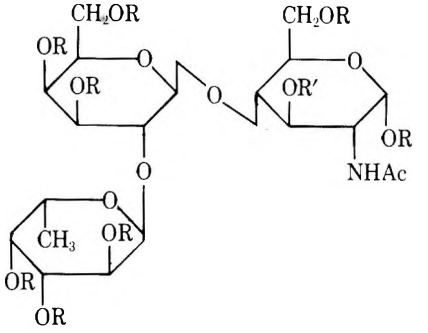


12, R = Bzl; R′ = A; R″ = Ac
13, R = Bzl; R′ = A; R″ = H
14, R = Bzl; R′ = R″ = H
15, R = Bzl; R′ = R″ = Ac
16, R = R′ = R″ = H

Condensation of aglycon 8 with the ortho ester 11[5] (reflux in chlorobenzene in the presence of 2,6-dimethylpyridinium perchlorate[16]) gave a mixture of the two disaccharides 12 and 18. After a chromatographic separation of the starting material 8 from the disaccharidic fractions, 12 was obtained directly by crystallization in 38% yield. The mother liquors were O-deacetylated (sodium methoxide in methanol) to give the α anomer 17 in crystalline form. The formation of a 1,2-cis glycoside, with preservation of the acetate on C-2, during a glycosylation with a benzylated ortho ester has already been observed and discussed during the synthesis of a closely related disaccharide.[5] After O-deacetylation, 12 was converted into crystalline benzyl 2-acetamido-3-*O*-allyl-6-*O*-benzyl-4-*O*-(3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-2-deoxy-α-D-glucopyranoside (13). This derivative of lactosamine is properly protected to reach our objective, the two fucopyranosyl residues being introduced successively. Its structure was confirmed by conversion into known *N*-acetyllactosamine[6] after O-deallylation (potassium *tert*-butoxide in dimethyl sulfoxide) and catalytic hydrogenolysis. The structure of 18 was similarly confirmed by transformation into known[5] reducing disaccharide 21.



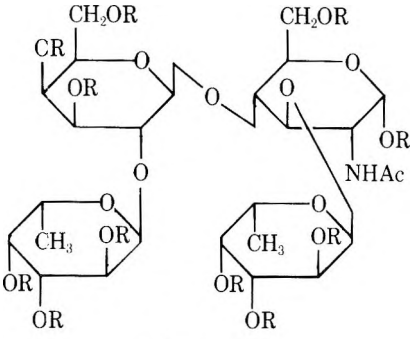
17, R = Bzl; R′ = A; R″ = H
18, R = Bzl; R′ = A; R″ = Ac
19, R = Bzl; R′ = R″ = H
20, R = Bzl; R′ = R″ = Ac
21, R = R′ = R″ = H



22

23, R = Bzl; R′ = A
24, R = Bzl; R′ = H
25, R = Bzl; R′ = Ac
26, R = R′ = H (α,β)

The bromide ion catalyzed reaction[17] has proven to be an excellent way to obtain an α-L-fucoside.[3,5,13,17,19] Condensation of aglycon 13, with 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide[18] (22), in 1,2-dichloroethane–*N*,*N*-dimethylformamide in the presence of tetraethylammonium bromide, diisopropylethylamine, and molecular sieves 4 Å gave the protected trisaccharide 23 in excellent yield (91%). The configuration of the newly established glycosidic linkage was demonstrated by ^{1}H NMR. The doublet at δ 5.68 (J = 3.5 Hz) was assigned to the anomeric proton of the L-fucopyranosyl residue, in a cis equatorial–axial relationship to the vicinal proton. After acid hydrolysis, trisaccharide 23 was selectively cleaved to disaccharide 13 and 2,3,4-tri-*O*-benzyl-α-L-fucopyranose.[18] After O-deallylation, 23 was converted into an amorphous alcohol 24. The structure of 24 was established by ^{1}H NMR spectroscopy and by catalytic hydrogenolysis to give the known[5] trisaccharide 26. A new condensation of 24 with 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide using the bromide ion catalyzed reaction[17] gave the fully benzylated tetrasaccharide 27 in good yield (80%). The doublet at δ 5.23 (J = 3 Hz) was assigned to the anomeric proton of the newly established glycosidic linkage, showing a cis equatorial–axial relationship to the vicinal proton. Alternatively the tetrasaccharide 27 was obtained (74%) after condensation of the diol 14 with 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide. A by-product of this reaction was the trisaccharide 24. After catalytic hydrogenolysis in glacial acetic acid and purification of the residue by chromatography on a charcoal–Celite column, the title tetrasaccharide was obtained in crystalline form. ^{1}H NMR spectroscopy and mutarotation strongly suggest the α configuration at the reducing center.



27, R = Bzl
28, R = H

Experimental Section

General Methods. Melting points were determined with capillary tubes on a Büchi apparatus and were not corrected. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. IR spectra were recorded with a Jouan-Jasco IRA-1 infrared spectrometer. Nuclear magnetic resonance spectra were obtained in chloroform-*d* solution (Me_4Si as internal standard) or deuterium oxide (Me_4Si as external standard) with a Perkin-Elmer R-32 spectrometer. The indexes respectively refer to: primary, galactose; secondary, fucose bound to galactose; tertiary, fucose bound to glucosamine. Gas–liquid chromatography (GLC) of the per-*O*-(trimethylsilyl) derivatives was performed with a Girdel 3000 apparatus, provided with a flame ionization detector, using a 3.40-m Pyrex column (4% OV-17 on Gas-Chrom Q, 80–100 mesh), programmed for a rise of 10 °C/min from 150 to 300 °C; t_R is given relative to that of hexakis-*O*-(trimethylsilyl)-*myo*-inositol. Purity of products was determined by thin layer chromatography (TLC) on silica gel 60 F 254 (E. Merck). Components were located by spraying with 50% sulfuric acid in ethanol and heating. Column chromatography was performed on silica gel Merck 60, powder 0.063–0.200 mm, which was used without pretreatment. Elemental analyses were obtained from the Service Central de Microanalyse du Centre National de la Recherche Scientifique (Thiais, France).

Benzyl 2-Acetamido-3-*O*-allyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (1). A solution of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (15 g, 37.5 mmol) in *N*,*N*-dimethylformamide (250 ml) was stirred at room temperature for 20 min with barium oxide (25 g), barium hydroxide octahydrate (7.5 g), and allyl bromide (6.25 ml). The resulting crystalline mass was dissolved by heating and barium oxide was precipitated by addition of pyridine (200 ml). After filtration, the organic phase was evaporated, the last traces of barium oxide being eliminated after dissolution of the residue in the minimum amount of pyridine and filtration. After evaporation of the organic phase, the residue was crystallized from methanol–pyridine–water, giving 15.85 g (95%) of benzyl 2-acetamido-3-*O*-allyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (1): mp 255–256 °C; $[\alpha]^{20}D$ + 125° (c 1.0, C_5H_5N); ν_{max} (Nujol) 3340 (NH), 1660, 1570 cm^{-1} (CONH).

Anal. Calcd for $C_{25}H_{29}NO_6$ (439.49): C, 68.62; H, 6.65; N, 3.19. Found: C, 68.74; H, 6.66; N, 3.13.

Benzyl 2-Acetamido-3-*O*-allyl-2-deoxy-α-D-glucopyranoside (2). A suspension of 1 (10 g, 22.7 mmol) in 60% acetic acid (600 ml) was heated at 100 °C for 1 h, then cooled. Following evaporation of the solution the residue was coevaporated several times with water then with toluene and crystallized from 2-propanol, giving 7.36 g (91%) of 2: mp 177–178 °C; $[\alpha]^{20}D$ + 164° (c 1.0, MeOH); ν_{max} (Nujol) 3420 (OH), 3340 (NH), 1645, 1560 cm^{-1} (CONH).

Anal. Calcd for $C_{18}H_{25}NO_6$ (351.39): C, 61.52; M, 7.17; N, 3.99. Found: C, 61.67; H, 7.16; N, 3.57.

Benzyl 2-Acetamido-4,6-di-*O*-acetyl-3-*O*-allyl-2-deoxy-α-D-glucopyranoside (3). A solution of **2** (250 mg, 0.71 mmol) in a mixture of pyridine (5 ml) and acetic anhydride (1 ml) was stirred for 3 h at room temperature. Following evaporation of the solution the residue was coevaporated with toluene and crystallized twice from 2-propanol, giving 285 mg (92%) of **3**: mp 159–160 °C; $[\alpha]^{20}D$ +120° (*c* 1.0, MeOH); ν_{max} (Nujol) 3360 (NH), 1750 (OAc), 1660, 1560 cm^{-1} (CONH); ^1H NMR ($CDCl_3$) δ 1.90 (s, 3, NHAc), 2.04, 2.06 (2 s, 6, OAc), 7.30 (s, 5, aromatic).

Anal. Calcd for $C_{22}H_{29}NO_8$ (435.46): C, 60.68; H, 6.71; N, 3.22. Found: C, 60.75; H, 6.70; N, 3.07.

Benzyl 2-Acetamido-3-*O*-allyl-6-*O*-benzoyl-2-deoxy-α-D-glucopyranoside (4). A solution of benzoyl chloride (4.8 g, 34.2 mmol) in dichloromethane (50 ml) was added to a solution of imidazole (4.66 g, 68.53 mmol) in dichloromethane (110 ml). After 15 min at 5 °C, imidazole hydrochloride was removed by filtration. The resulting filtrate was added to a solution of **2** (10 g, 28.5 mmol) in dioxane (200 ml). The mixture was heated under reflux for 36 h and then evaporated to dryness. The residue was dissolved in chloroform (500 ml) and the organic phase washed successively with dilute aqueous sodium bicarbonate and water, dried (Na_2SO_4), and evaporated. The residue was crystallized from ethyl acetate, giving 11.37 g (89%) of benzyl 2-acetamido-3-*O*-allyl-6-*O*-benzoyl-2-deoxy-α-D-glucopyranoside (**4**): mp 161–162 °C; $[\alpha]^{20}D$ +91° (*c* 1.0, $CHCl_3$): ν_{max} (Nujol) 3540 (OH), 3350 (NH), 1720 (OBz), 1645, 1560 (CONH), 708 cm^{-1} (aromatic).

Anal. Calcd for $C_{25}H_{29}NO_7$ (455.49): C, 65.92; H, 6.42; N, 3.08. Found: C, 66.01; H, 6.42; N, 3.22.

This compound was fully resistant to tritylation (trityl chloride in pyridine for 3 days at 100 °C).

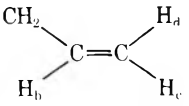
Benzyl 2-Acetamido-3-*O*-allyl-6-*O*-benzoyl-2-deoxy-4-*O*-tetrahydropyranyl-α-D-glucopyranoside (5). A solution of **4** (3 g, 6.59 mmol), 3,4-dihydro-2*H*-pyran (1.5 ml, 16.5 mmol), and *p*-toluenesulfonic acid monohydrate (45 mg) in dioxane (25 ml) was stirred at room temperature for 1 h, then diluted with chloroform (150 ml). The reaction mixture was washed successively with dilute aqueous sodium bicarbonate and water, dried (Na_2SO_4), and evaporated. The residue was crystallized from ether–hexane, giving 3.35 g (93%) of benzyl 2-acetamido-3-*O*-allyl-6-*O*-benzoyl-2-deoxy-4-*O*-tetrahydropyranyl-α-D-glucopyranoside (**5**): mp 119–120 °C; $[\alpha]^{20}D$ +91° (*c* 1.0, $CHCl_3$) (mixture of diastereoisomers); ν_{max} (Nujol) 3350 (NH), 1730 (OBz), 1650, 1550 (CONH), 705 cm^{-1} (aromatic).

Anal. Calcd for $C_{30}H_{37}NO_8$ (539.60): C, 66.71; H, 6.91; N, 2.60. Found: C, 66.83; H, 6.90; N, 2.73.

Benzyl 2-Acetamido-3-*O*-allyl-6-*O*-benzyl-2-deoxy-4-*O*-tetrahydropyranyl-α-D-glucopyranoside (7). A 2 M methanolic solution of sodium methoxide (2 ml) was added to a solution of **5** (3.55 g, 6.21 mmol) in methanol (20 ml) and stirred at room temperature for 1 h, then diluted with chloroform (500 ml). The reaction mixture was washed with water, dried (Na_2SO_4), and evaporated. The residue was crystallized from ether, giving 2.65 g (95%) of benzyl 2-acetamido-3-*O*-allyl-2-deoxy-4-*O*-tetrahydropyranyl-α-D-glucopyranoside (**6**) (mixture of diastereoisomers): ν_{max} (Nujol) 3560 (OH), 3350 (NH), 1650, 1555 (CONH), 720 cm^{-1} (aromatic). A solution of **6** (2.5 g, 5.74 mmol) in *N,N*-dimethylformamide (40 ml) was stirred for 5 h at room temperature with barium oxide (4 g), barium hydroxide octahydrate (1.3 g), and benzyl bromide (1.5 ml, 11.5 mmol). After dilution with chloroform (180 ml), the salts were removed by filtration and the filtrate was evaporated to dryness. To eliminate benzyl bromide, the residue was dissolved in a mixture of pyridine (20 ml) and dioxane (35 ml) and cooled overnight to 0 °C. The resulting precipitate was collected by filtration and the filtrate was evaporated to dryness. The residue was crystallized from ether–hexane, giving 2.57 g (85%) of benzyl 2-acetamido-3-*O*-allyl-6-*O*-benzyl-2-deoxy-4-*O*-tetrahydropyranyl-α-D-glucopyranoside (**7**): mp 118–119 °C; $[\alpha]^{20}D$ + 103° (*c* 1.0, $CHCl_3$) (mixture of diastereoisomers); ν_{max} (Nujol) 3340 (NH), 1650, 1550 (CONH), 725 cm^{-1} (aromatic).

Anal. Calcd for $C_{30}H_{39}NO_7$ (525.62): C, 68.55; H, 7.48; N, 2.67. Found: C, 68.68; H, 7.49; N, 2.64.

Benzyl 2-Acetamido-3-*O*-allyl-6-*O*-benzyl-2-deoxy-α-D-glucopyranoside (8). **6** (2.5 g, 5.74 mmol) was benzylated as described above. The residue was dissolved in 60% acetic acid (50 ml) and heated for 10 min on a boiling water bath. Following evaporation to dryness the residue was coevaporated with water, then with toluene, and crystallized from ethyl acetate–ether, giving 1.96 g (80%) of benzyl 2-acetamido-3-*O*-allyl-6-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**8**): mp 149–150 °C; $[\alpha]^{20}D$ +103° (c 1.0, $CHCl_3$); ν_{max} (Nujol) 3500 (OH), 3340 (NH), 1640, 1555 (CONH), 740, 690 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 1.94 (s, 3, NHAc), 2.90 (OH), 4.48, 4.78 (2 d, AB system, J = 12 Hz, CH_2Ar), 4.62 (s, 2, CH_2Ar), 4.92 (d, 1, $J_{1,2}$ = 4 Hz, H-1), 5.17 (m, 1, $J_{c,d}$ = 2 Hz, H_c), 5.27 (m, 1, H_d), 5.66 (d, 1, $J_{NH,2}$ = 9 Hz, NH), 5.93 (m, 1, $J_{b,c}$ = 10 Hz, $J_{b,d}$ = 17 Hz, H_b), 7.37 (s, 10, aromatic). Allyl group:



Anal. Calcd for $C_{25}H_{31}NO_6$ (441.51): C, 68.00; H, 7.08; N, 3.17. Found: C, 68.20; H, 7.16; N, 3.37.

This compound was fully resistant to tritylation (trityl chloride in pyridine for 96 h at 100 °C). **8** (8.65 g, 19.6 mmol) was subsequently prepared from **2** (10 g, 28.5 mmol) without isolating the intermediates **4, 5, 6,** and **7** (yield 69%).

Benzyl 2-Acetamido-4-*O*-acetyl-3-*O*-allyl-6-*O*-benzyl-2-deoxy-α-D-glucopyranoside (9). **8** (0.2 g, 0.45 mmol) was acetylated (pyridine–acetic anhydride), giving 212 mg (97%) of **9** after crystallization from ethyl acetate–ether: mp 149–150 °C; $[\alpha]^{20}D$ +119° (c 1.0, $CHCl_3$); ν_{max} (Nujol) 3360 (NH), 1750 (OAc), 1650, 1550 (CONH), 730, 690 cm^{-1} (aromatic).

Anal. Calcd for $C_{27}H_{33}NO_7$ (483.54): C, 67.06; H, 6.88; N, 2.90. Found: C, 67.00; H, 6.82; N, 3.08.

Selective Benzylation of Benzyl 2-Acetamido-3-*O*-allyl-2-deoxy-α-D-glucopyranoside. A solution of **2** (5 g, 14.2 mmol) in *N,N*-dimethylformamide (50 ml) was stirred for 4 h at room temperature with barium oxide (5 g), barium hydroxide octahydrate (1.2 g), and benzyl bromide (2.4 ml, 18.4 mmol). After dilution with chloroform (400 ml), the organic phase was washed successively with 60% aqueous acetic acid, saturated aqueous sodium bicarbonate, and water, dried ($CaCl_2$), and evaporated to dryness. The residue was chromatographed on a column (100 g) using chloroform–acetone (9:1 v/v) which separated benzyl 2-acetamido-3-*O*-allyl-4,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**10,** 3.18 g, 42%), mp 137.5–138.5 °C (ethyl acetate–hexane), and benzyl 2-acetamido-3-*O*-allyl-6-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**8**), crystallized from ethyl acetate–ether (2.32 g, 37%), mp 148–149.5 °C, identical with the compound previously prepared.

Benzyl 2-Acetamido-3-*O*-allyl-4,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (10). A solution of **2** (1.15 g, 3.27 mmol) in *N,N*-dimethylformamide (25 ml) was stirred for 24 h at room temperature with barium oxide (1.3 g), barium hydroxide octahydrate (450 mg), and benzyl bromide (1.5 ml, 11.5 mmol). Following the treatment described above, a residue was obtained which was crystallized from ether, giving 1.49 g (81%) of benzyl 2-acetamido-3-*O*-allyl-4,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**10**): mp 137.5–138.5 °C; $[\alpha]^{20}D$ + 102° (*c* 1.0, $CHCl_3$); ν_{max} (Nujol) 3350 (NH), 1655, 1560 (CONH), 725, 690 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 1.96 (s, 3, NHAc), 4.95 (d, 1, $J_{1,2}$ = 4.5 Hz, H-1), 5.60 (d, 1, $J_{NH,2}$ = 9 Hz, NH), 5.90 (m, 1, $J_{b,c}$ = 10, $J_{b,d}$ = 17 Hz, H_b), 7.30, 7.37 (2 s, 15, aromatic).

Anal. Calcd for $C_{32}H_{37}NO_6$ (531.62): C, 72.29; H, 7.02; N, 2.63. Found: C, 72.00; H, 6.96; N, 2.63.

Benzyl 2-Acetamido-4-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-3-*O*-allyl-6-*O*-benzyl-2-deoxy-α-D-glucopyranoside (12). A solution of freshly prepared 3,4,6-tri-*O*-benzyl-1,2-*O*-(*tert*-butoxyethylidene)-α-D-galactopyranose (**11,** 3.29 g, 6 mmol) and **8** (1.766 g, 4 mmol) in chlorobenzene (30 ml) was heated at 140 °C under a dry atmosphere of nitrogen. After 15 ml of solvent had been distilled off, a 0.2 M solution of 2,6-dimethylpyridinium perchlorate in 1,2-dichloroethane (1.5 ml) was added and the solvent was continuously distilled off for 1 h at 140 °C, the volume of the reaction mixture being held constant (15 ml) by the dropwise addition of chlorobenzene. After cooling, the reaction mixture was diluted with chloroform (150 ml), washed successively with saturated aqueous sodium bicarbonate and water, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on a column (135 g) using chloroform–acetone (11.5:1 v/v), giving first a disaccharide fraction, then starting material **8** (529 mg, 30% after crystallization from ethyl acetate–ether).

The disaccharide fraction was crystallized from chloroform–ether, giving 1.361 g (38% based on **8**) of **12**: mp 136–137 °C; $[\alpha]^{20}D$ +66.5° (c 1.0, $CHCl_3$); ν_{max} (Nujol) 3375 (NH), 1750 (OAc), 1650, 1540 (CONH), 720 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 1.92, 1.93 (2 s, 6, Ac), 4.45 (d, 1, $J_{1',2'}$ = 8.5 Hz, H-1'), 4.95 (d, 1, $J_{1,2}$ = 4.5 Hz, H-1), 5.58 (d, 1, $J_{NH,2}$ = 9 Hz, NH), 7.30, 7.34 (2 s, 25, aromatic).

Anal. Calcd for $C_{54}H_{61}NO_{12}$ (916.08): C, 70.80; H, 6.71; N, 1.52. Found: C, 70.97; H, 6.64; N, 1.65.

Benzyl 2-Acetamido-3-*O*-allyl-6-*O*-benzyl-4-*O*-(3,4,6-tri-

O-benzyl-α-D-galactopyranosyl)-2-deoxy-α-D-glucopyranoside (17). The mother liquors from the crystallization of **12** were evaporated to dryness. The residue was O-deacetylated (sodium methoxide in methanol), giving, after crystallization from ether, 438 mg (16% based on **8**) of **17**: mp 136–137 °C; $[\alpha]^{20}D$ + 91° (c 1.0, $CHCl_3$); ν_{max} (Nujol) 3440 (OH, shoulder), 3390 (NH), 1660, 1535 (CONH), 730, 690 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 1.92 (s, 3, Ac), 2.95 (d, 1, $J_{OH,2'}$ = 9 Hz, OH), 4.88 (d, 1, $J_{1,2}$ = 4 Hz, H-1), 5.35 (d, 1, $J_{1',2'}$ = 4 Hz, H-1'), 5.63 (d, 1, $J_{NH,2}$ = 9 Hz, NH), 5.94 (m, 1, H_b), 7.32, 7.38 (2 s, 25, aromatic).

Anal. Calcd for $C_{52}H_{59}NO_{11}$ (874.11): C, 71.45; H, 6.80; N, 1.60. Found: C, 71.59; H, 6.72; N, 1.79.

Benzyl 2-Acetamido-4-O-(2-O-acetyl-3,4,6-tri-O-benzyl-α-D-galactopyranosyl)-3-O-allyl-6-O-benzyl-2-deoxy-α-D-glucopyranoside (18). Compound **17** (100 mg, 0.11 mmol) was acetylated (pyridine–acetic anhydride). After treatment, the residue was purified chromatographically on a column (2 g) using chloroform–ether (1:1, v/v), giving 96 mg (92%) of **18** as a colorless glass: $[\alpha]^{20}D$ +93.5° (c 1.0, $CHCl_3$); ν_{max} (film) 3320 (NH), 1745 (OAc), 1650, 1540 (CONH), 740, 685 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 1.93 (s, 3, NHAc), 2.05 (s, 3, OAc), 4.93 (d, 1, $J_{1,2}$ = 4.5 Hz, H-1), 5.60 (m, 2, NH and H-1', $J_{NH,2}$ = 9, $J_{1',2'}$ = 3.5 Hz).

Anal. Calcd for $C_{54}H_{61}NO_{12}$ (916.08): C, 70.80; H, 6.71; N, 1.52. Found: C, 70.90; H, 6.85; N, 1.57.

Benzyl 2-Acetamido-6-O-benzyl-4-O-(3,4,6-tri-O-benzyl-α-D-galactopyranosyl)-2-deoxy-α-D-glucopyranoside (19). A solution of **17** (960 mg, 1.1 mmol) and potassium *tert*-butoxide (740 mg) in dimethyl sulfoxide was stirred and heated at 100 °C in a current of nitrogen for 2 h. After cooling the reaction mixture was poured into iced water (100 ml) and the mixture was extracted with chloroform (90 ml). The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness. The colored oily residue was stirred in acetone–water (20 ml, 9:1 v/v) with yellow mercuric oxide (500 mg). A solution of mercuric chloride (450 mg) in acetone–water (5 ml, 9:1 v/v) was added dropwise for 5 min. The reaction mixture was then filtered and evaporated to dryness. The residue was dissolved in chloroform and the solution washed successively with 10% aqueous potassium iodide and water, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed twice on a column (45 g) using chloroform–methanol (24:1, v/v), giving 697 mg (76%) of **19** as a colorless glass: $[\alpha]^{20}D$ + 90° (c 1.0, $CHCl_3$); ν_{max} (film) 3350 (broad, NH and OH), 1650, 1545 (CONH), 690 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 1.93 (s, 3, Ac), 5.00 (d, 1, $J_{1,2}$ = 4 Hz, H-1), 5.21 (d, 1, $J_{1',2'}$ = 3.5 Hz, H-1'), 5.90 (d, 1, $J_{NH,2}$ = 9 Hz, NH), 7.32, 7.35 (2 s, 25, aromatic).

Anal. Calcd for $C_{49}H_{55}NO_{11}$ (833.97): C, 70.57; H, 6.64; N, 1.68. Found: C, 70.38; H, 6.65; N, 1.68.

Benzyl 2-Acetamido-3-O-acetyl-4-O-(2-O-acetyl-3,4,6-tri-O-benzyl-α-D-galactopyranosyl)-6-O-benzyl-2-deoxy-α-D-glucopyranoside (20). Acetylation of **19** (251 mg, 0.3 mmol) with acetic anhydride and pyridine gave 240 mg (86%) of **20** as a colorless glass: $[\alpha]^{20}D$ + 103° (c 1.1, $CHCl_3$); ν_{max} (film) 1750 (OAc), 1680, 1510 (CONH), 685 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 1.87 (s, 3, NHAc), 2.03 (s, 6, OAc), 4.92 (d, 1, $J_{1,2}$ = 4 Hz, H-1), 5.51 (d, 1, $J_{1',2'}$ = 4.5 Hz, H-1'), 5.66 (d, 1, $J_{NH,2}$ = 10 Hz, NH), 7.30–7.37 (m, 25, aromatic).

Anal. Calcd for $C_{53}H_{59}NO_{13}$ (918.05): C, 69.34; H, 6.48; N, 1.52. Found: C, 69.55; H, 6.24; N, 1.36.

2-Acetamido-2-deoxy-4-O-(α-D-galactopyranosyl)-α-D-glucopyranose (21). A solution of **19** (346 mg, 0.41 mmol) in acetic acid (13 ml) was hydrogenolyzed with Pd/C (10%) for 24 h. The reaction mixture was filtered and evaporated to dryness. Crystallization of the residue from 2-propanol–methanol gave 125 mg (79%) of **21**: mp 193–195 °C; $[\alpha]^{20}D$ + 147° (2 min) → + 131° (3 h) (c 0.50, water–methanol, 9:1 v/v) [lit.[5] mp 196–198 °C; $[\alpha]^{20}D$ + 151° (2 min) → + 132° (5 h) (c 0.40, water–methanol, 9:1 v/v)]; mmp 193–195.5 °C.

Benzyl 2-Acetamido-3-O-allyl-6-O-benzyl-4-O-(3,4,6-tri-O-benzyl-β-D-galactopyranosyl)-2-deoxy-α-D-glucopyranoside (13). A molar solution of sodium methoxide in methanol (1 ml) was added to a solution of **12** (500 mg, 0.55 mmol) in methanol (10 ml) and the mixture was stirred for 12 h at room temperature. After evaporation to dryness, the residue was dissolved in chloroform (50 ml), and the organic phase was washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue was crystallized from ether, giving 451 mg (95%) of **13**: mp 122–123 °C; $[\alpha]^{20}D$ +72.5° (c 1.0, $CHCl_3$); ν_{max} (Nujol) 3330, 3280 (OH, NH), 1645, 1560 (CONH), 725, 690 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 1.93 (s, 3, Ac), 4.92 (d, 1, $J_{1,2}$ = 4 Hz, H-1), 5.57 (d, 1, $J_{NH,2}$ = 9 Hz, NH).

Anal. Calcd for $C_{52}H_{59}NO_{11}$ (874.11): C, 71.45; H, 6.80; N, 1.60. Found: C, 71.33; H, 6.84; N, 1.62.

Benzyl 2-Acetamido-6-O-benzyl-4-O-(3,4,6-tri-O-benzyl-β-D-galactopyranosyl)-2-deoxy-α-D-glucopyranoside (14). Compound **13** (1.22 g, 1.4 mmol) was transformed into **14** as described above for the synthesis of **19**. The residue was chromatographed twice on a column (100 g) using ethyl acetate, giving 908 mg (78%) of **14** as a colorless, glassy mass: $[\alpha]^{20}D$ +61° (c 1.0, $CHCl_3$); ν_{max} (film) 3360 (OH, NH), 1650, 1540 (CONH), 690 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 1.95 (s, 3, Ac), 2.94 (broad s, 1, OH'), 3.35 (dd, 1, $J_{2',3'}$ = 9, $J_{3',4'}$ = 3 Hz, H-3'), 4.30 (d, 1, $J_{1',2'}$ = 9 Hz, H-1'), 5.03 (d, 1, $J_{1,2}$ = 4 Hz, H-1), 5.71 (d, 1, $J_{NH,2}$ = 9 Hz, NH), 7.31–7.38 (m, 25, aromatic).

Anal. Calcd for $C_{49}H_{55}NO_{11}$ (833.97): C, 70.57; H, 6.64; N, 1.68. Found: C, 70.61; H, 6.51; N, 1.76.

Benzyl 2-Acetamido-3-O-acetyl-4-O-(2-O-acetyl-3,4,6-tri-O-benzyl-β-D-galactopyranosyl)-6-O-benzyl-2-deoxy-α-D-glucopyranoside (15). Acetylation of **14** (100 mg, 0.12 mmol) with acetic anhydride in pyridine gave a crude compound. Purification on a column (5 g) using chloroform–ether (7:3 v/v) gave 103 mg (93%) of **15** as a glassy mass: $[\alpha]^{20}D$ +74° (c 1.1, $CHCl_3$); ν_{max} (film) 3360 (NH), 1755 (OAc), 1675, 1520 (CONH), 740, 690 cm^{-1} (aromatic); ^1H NMR δ 1.87 (s, 3, NHAc), 1.91, 1.92 (2 s, 6, OAc), 4.47 (d, 1, $J_{1',2'}$ = 9 Hz, H-1'), 4.90 (d, 1, $J_{1,2}$ = 4 Hz, H-1), 5.76 (d, 1, $J_{NH,2}$ = 9 Hz, NH), 7.34 (s, 25, aromatic).

Anal. Calcd for $C_{53}H_{59}NO_{13}$ (918.05): C, 69.34; H, 6.48; N, 1.52. Found: c, 69.23; H, 6.63; N, 1.60.

2-Acetamido-2-deoxy-4-O-(β-D-galactopyranosyl)-α-D-glucopyranose (*N*-Acetyllactosamine) (16). A solution of **14** (100 mg, 0.12 mmol) in acetic acid (10 ml) was hydrogenolyzed with Pd/C (10%, 100 mg) for 60 h. The reaction mixture was filtered and evaporated to dryness. Crystallization of the residue (41 mg) from 2-propanol–methanol gave 36 mg (82%) of **16**: mp 169–170 °C; $[\alpha]^{20}D$ +48° (2 min) → + 29° (3 h) (c 0.45, water–methanol, 9:1 v/v) [lit.[6] mp 170–171 °C; $[\alpha]^{20}D$ + 50° → + 28.5° (12 h) (c 0.6, water–methanol, 9:1 v/v)].

Benzyl 2-Acetamido-3-O-allyl-6-O-benzyl-4-O-[2-O-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-3,4,6-tri-O-benzyl-β-D-galactopyranosyl]-2-deoxy-α-D-glucopyranoside (23). Compound **13** (1.748 g, 2 mmol) was dissolved in *N*,*N*-dimethylformamide (3 ml) which contained tetraethylammonium bromide (2.10 g, 10 mmol) and molecular sieves 4 Å (1 g). A solution of freshly prepared 2,3,4-tri-O-benzyl-α-L-fucopyranosyl bromide (2.49 g, 5 mmol) in 1,2-dichloroethane (12 ml) and diisopropylethylamine (1.5 ml, 5.25 mmol) was added and the mixture was stirred under dry nitrogen at room temperature for 3 days. After addition of methanol (10 ml), the mixture was stirred for 4 h, the solids were removed by filtration, and the filtrate, after dilution with chloroform (100 ml), was washed twice with water, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed twice on a column (220 g), using chloroform–ether (7:3 v/v), giving 2.36 g (91% based on **13**) of **23** as a colorless glass: $[\alpha]^{20}D$ −0.5° (c 1.0, $CHCl_3$); ν_{max} (film) 3330 (NH), 1550, 1545 (CONH), 690 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 1.10 (d, 3, J = 7 Hz, CH_3), 1.96 (s, 3, Ac), 5.04 (d, 1, $J_{1,2}$ = 4 Hz, H-1), 5.58 (d, 1, $J_{NH,2}$ = 9 Hz, NH), 5.68 (d, 1, $J_{1'',2''}$ = 3.5 Hz, H-1''), 7.17–7.33 (m, 30, aromatic).

Anal. Calcd for $C_{79}H_{87}NO_{15}$ (1290.56): C, 73.52; H, 6.79; N, 1.08. Found: C, 73.36; H, 6.83; N, 1.13.

The trisaccharide **23** (60 mg) was hydrolyzed for 3.5 h at 100 °C in a mixture of 80% aqueous acetic acid (4 ml) and 1 M hydrochloric acid (1 ml). After cooling, the reaction mixture was poured into iced water and extracted with chloroform (30 ml). The organic phase was washed successively with 5% aqueous sodium bicarbonate and water, dried ($MgSO_4$), and evaporated to dryness. The residue (57 mg) was chromatographed on a column (6 g) using chloroform–acetone (11:1 v/v), giving two compounds: 3,4,6-tri-O-benzyl-α-L-fucopyranose (15 mg, 75%), crystallized from ethyl acetate–ether–hexane, mp 102–103 °C (lit.[18] 102–103 °C); compound **13** (31 mg, 76%), crystallized from ether–hexane, mp 121–123 °C.

Benzyl 2-Acetamido-6-O-benzyl-4-O-[2-O-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-3,4,6-tri-O-benzyl-β-D-galactopyranosyl]-2-deoxy-α-D-glucopyranoside (24). The allyl group of compound **23** (2.102 g, 1.63 mmol) was removed as described above for the preparation of **19**. The residue was chromatographed on a column (150 g) using chloroform–ether (7:3 v/v), giving 1.693 g (83%) of **24** as a colorless glass: $[\alpha]^{20}D$ +1.5° (c 1.2, $CHCl_3$); ν_{max} (film) 3480 (OH), 3340 (NH), 1660, 1550 (CONH), 690 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 1.10 (d, 3, J = 7 Hz, CH_3), 5.08 (d, 1, $J_{1,2}$ = 3.5 Hz, H-1), 5.66 (d, 1, $J_{NH,2}$ = 9 Hz, NH), 5.73 (d, 1, $J_{1'',2''}$ = 4 Hz, H-1''), 7.25–7.33 (m, 40, aromatic).

Anal. Calcd for $C_{76}H_{83}NO_{15}$ (1250.49): C, 72.99; H, 6.69; N, 1.12; O, 19.12. Found: C, 72.88; H, 6.76; N, 1.04; O, 19.12.

Acetate **25** (pyridine–acetic anhydride): glass; $[\alpha]^{20}D$ +2° (c 1.0, $CHCl_3$); ν_{max} (film) 3460 (NH), 1750 (OAc), 1685, 1530 (CONH), 685 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 1.15 (d, 3, J = 7 Hz, CH_3), 4.97

(d, 1, $J_{1,2}$ = 4 Hz, H-1), 5.64 (d, 1, $J_{1'',2''}$ = 4 Hz, H-1''), 5.74 (d, 1, $J_{NH,2}$ = 9.5 Hz, NH), 7.23–7.33 (m, 40, aromatic).

Anal. Calcd for $C_{78}H_{85}NO_{16}$ (1292.53): C, 72.49; H, 6.63; N, 1.08. Found: C, 72.35; H, 6.65; N, 0.93.

***O*-α-L-Fucopyranosyl-(1 → 2)-*O*-β-D-galactopyranosyl-(1 →4)-2-acetamido-2-deoxy-D-glucopyranose (26).** A solution of **24** (20 mg, 1.6×10^{-2} mmol) in acetic acid (1 ml) was hydrogenolyzed with Pd/C (10%, 20 mg) for 72 h. The reaction mixture was filtered and evaporated to dryness, giving **26**, identical with an authentic sample.[5] After sodium borohydride reduction and trimethylsilylation, the compound was homogeneous by GLC, t_R 2.90.

Benzyl 2-Acetamido-6-*O*-benzyl-3-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-4-*O*-[2-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl]-2-deoxy-α-D-glucopyranoside (27). A. From Compound 24. 24 (1.41 g, 1.127 mmol) was dissolved in *N,N*-dimethylformamide (2 ml) which contained tetraethylammonium bromide (1.05 g, 5 mmol) and molecular sieves 4 Å (1 g). A solution of freshly prepared 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide (1.24 g, 2.5 mmol) in 1,2-dichloroethane (8 ml) and diisopropylethylamine (0.35 ml, 2.62 mmol) was added and the mixture was stirred under dry nitrogen at room temperature for 3 days. The reaction mixture was worked up as described above for the synthesis of **23**. The residue was chromatographed twice on a column (200 g), using chloroform–acetone (32:1 v/v), giving 1.503 g (80% based on **24**) of **27** as a colorless glass: $[\alpha]^{20}D$ −31.5° (*c* 1.0, $CHCl_3$); ν_{max} (film) 3320 (NH), 1660, 1540 (CONH), 740, 695 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 1.14 (d, *J* = 7 Hz, CH_3), 1.80 (s, 3, Ac), 4.97 (d, 1, $J_{1,2}$ = 4 Hz, H-1), 5.23 (d, 1, $J_{1''',2'''}$ = 3 Hz, H-1'''), 5.72 (d, 1, $J_{NH,2}$ = 9 Hz, NH), 5.74 (d, 1, $J_{1'',2''}$ = 4 Hz, H-1''), 7.25–7.33 (m, 55, aromatic).

Anal. Calcd for $C_{103}H_{111}NO_{19}$ (1667.01): C, 74.21; H, 6.71; N, 0.84. Found: C, 74.01; H, 6.78; N, 0.94.

B. From Compound 14. 14 (930 mg, 1.12 mmol) was dissolved in *N,N*-dimethylformamide (2 ml) which contained tetraethylammonium bromide (2.10 g, 10 mmol) and molecular sieves 4 Å (1 g). A solution of freshly prepared 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide (2.49 g, 5 mmol) in 1,2-dichloroethane (8 ml) and diisopropylethylamine (0.7 ml, 5.24 mmol) was added and the mixture was stirred under dry nitrogen at room tempeature for 3 days. The same treatment as above gave 1.383 g (74% based on **14**) of **27** as a colorless glass, identical with the compound prepared from **24**. A compound that migrated more slowly was isolated in pure form and identified as **24** (192 mg, 14%).

The tetrasaccharide **27** (84 mg, 5×10^{-2} mmol) was hydrolyzed as described for the acid hydrolysis of **23**. The residue was chromatographed on a column (10 g) using chloroform–ether (7:3 v/v), giving two compounds: 2,3,4-tri-*O*-benzyl-α-L-fucopyranose (36 mg, 83%), crystallized from ether–hexane, mp 102–103 °C; compound **14** (35 mg, 84%), $[\alpha]^{20}D$ + 62° (c 1.0, $CHCl_3$).

***O*-α-L-Fucopyranosyl-(1→2)-*O*-β-D-galactopyranosyl-(1 →4)-*O*-[α-L-fucopyranosyl-(1→3)]-2-acetamido-2-deoxy-α-D-glucopyranose (28).** A solution of **27** (2.638 g, 1.58 mmol) in acetic acid (50 ml) was hydrogenolyzed with Pd/C (10%) (2.5 g) for 8 days. The reaction mixture was filtered and evaporated to dryness. The residue (997 mg) was purified on a charcoal–Celite column (18 × 220 mm, 30 g of 1:1 mixture). Fractions eluted with water–ethanol (19:1 v/v, 2 l.) and water–ethanol (4:1 v/v, 1 l.) were pooled and evaporated to dryness, giving 813 mg (76%) of tetrasaccharide **28**. This compound was pure on paper chromatography (Whatman no. 1) using ethyl acetate–pyridine–water (10:4:3 v/v/v) and showed $R_{lactose}$ 0.41 (aniline phthalate reagent).

A fraction was crystallized from methanol–ethanol, giving **28**: mp 214–216 °C dec; $[\alpha]^{20}D$ −113° (3 min) → −124.5° (18 h) (c 0.5, water–methanol, 9:1 v/v); ^1H NMR (D_2O) δ 1.30 (d, 6, *J* = 7 Hz, CH_3), 2.10 (s, 3, Ac), 4.55 (d, 1, $J_{1',2'}$ = 7.5 Hz, H-1'), 5.15 (d, 2, $J_{1,2}$ = 3, $J_{1''',2'''}$ = 3 Hz, H-1 and H-1'''), 5.34 (d, 1, $J_{1'',2''}$ = 3 Hz, H-1'').

Anal. Calcd for $C_{26}H_{45}NO_{19}$ (675.63): C, 46.22; H, 6.71; N, 2.07; O, 44.99. Found: C, 46.33; H, 6.87; N, 2.16; O, 45.01.

Registry No.—**1**, 60920-72-1; **2**, 60920-73-2; **3**, 60920-74-3; **4**, 60920-75-4; (4*R*)-**5**, 60920-76-5; (4*S*)-**5**, 60920-77-6; (4*R*)-**6**, 60920-78-7; (4*S*)-**6**, 60920-79-8; (4*R*)-**7**, 60920-80-1; (4*S*)-**7**, 60920-81-2; **8**, 60920-82-3; **9**, 60920-83-4; **10**, 60920-84-5; **11**, 60920-85-6; **12**, 60920-86-7; **13**, 60920-87-8; **14**, 60920-88-9; **15**, 60920-89-0; **17**, 60920-90-3; **18**, 60920-91-4; **19**, 60920-92-5; **20**, 60920-93-6; **21**, 60966-24-7; **23**, 60920-94-7; **24**, 60920-95-8; **25**, 60920-96-9; **27**, 60920-97-0; **28**, 60966-25-8; benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside, 13343-63-0; allyl bromide, 106-95-6; benzoyl chloride, 98-88-4; 3,4-dihydro-2*H*-pyran, 110-87-2; benzyl bromide, 100-39-0; 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide, 33639-77-9; 2,3,4-tri-*O*-benzyl-α-L-fucopyranose, 33639-75-7.

References and Notes

(1) (a) Synthesis of Blood-Group Substances. 6. For part 5, see J.-P. Cartron, C. Mulet, J. Badet, J.-C. Jacquinet, and P. Sinaÿ, *FEBS Lett.*, **67**, 143 (1976). (b) This work was supported by Centre National de la Recherche Scientifique, Caisse Régionale d'Assurance Maladie du Centre, and Délégation Générale à la Recherche Scientifique et Technique (ASCO, agreement no. 74 7 0973).

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(20) After this manuscript has been submitted for publication, Dr. Henry A. Graham (Ortho Diagnostics, Raritan, N.J.) completed inhibition studies with this tetrasaccharide. It does not inhibit haemagglutination with a goat anti-Le dH serum, supporting the idea that this structure is not the Le d antigenic determinant, as previously postulated.[9]

Electron Impact Induced Fragmentation of Cholesterol and Related C-5 Unsaturated Steroids[1]

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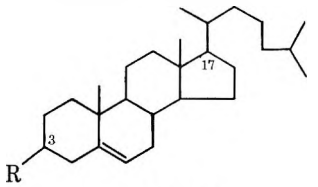
Received July 16, 1976

Comparison of the mass spectra of cholest-5-ene and various C-5 unsaturated 3β-hydroxy sterols indicates that the fragmentations leading to the characteristic $(M - 85)^+$ and $(M - 111)^+$ ions in these sterols are triggered solely by the double bond. With the aid of 11 deuterium labeled analogues all diagnostic cleavages of this biologically important class of compounds have now been identified. Both $(M - 85)^+$ and $(M - 111)^+$ ions of cholesterol are due to very complex fragmentations involving the loss of ring A and part of ring B by cleavages of the 1–10, 5–10 and 5–6 or 7–8 bonds, respectively, with a hydrogen transfer mainly from C-6 in the $(M - 85)^+$ ion. Fragmentations of such complexity can be revealed only with the aid of isotope labeling. The mechanisms of these fragmentations and the syntheses of the deuterium labeled compounds are discussed.

Mass spectroscopy, particularly in combination with gas chromatography, has proved to be a powerful and commonly used tool in the identification and structure elucidation of sterols.[2] Detailed knowledge of the fragmentation triggering behavior of the common functional groups on the steroid skeleton is essential, however, for reliable structure assignments by this technique.

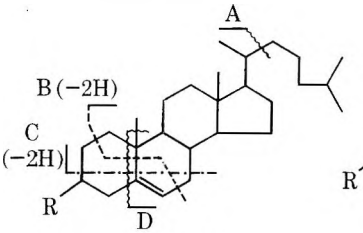
In view of our interest in the electron impact induced behavior of the unsubstituted steroid skeletons[3] and side chain unsaturated steroids[4] we decided to examine the fragmentation of cholesterol (I), which is the most common sterol lipid in tissues of fauna and a frequently used model compound for C-5 unsaturated 3β-hydroxy sterol homologues. Reports on the mass spectrum of cholesterol both as a natural product or as a material for testing instrumental performance span the history of organic mass spectroscopy. The high-mass range of its spectrum (see Figure 1) exhibits a number of diagnostically important peaks besides the common steroid fragments resulting from the loss of a methyl radical and/or water from the molecular ion. On the basis of comparative studies various interpretations have been proposed for the formation of these ions, but there has been no report on any isotope labeling study for the rigorous establishment of the cracking patterns and the mechanisms which lead to these ions.



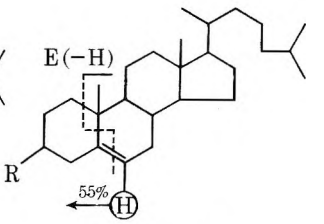
I, R = OH
II, R = H
III, R = OD

Some of the diagnostic peaks in Figure 1 are due to common steroid skeletal cleavages and have been correctly identified earlier. Such fragmentations are, for example, the loss of the C-17 side chain[5–8] (*m/e* 273), the loss of ring D with the side chain and an extra hydrogen[6–8] (*m/e* 231), and their respective dehydration products (*m/e* 255 and 213).

The prominent peaks at *m/e* 301 and 275 are more characteristic for cholesterol. At least four different cleavages have been proposed for the formation of the *m/e* 301 ion as shown on IV. The loss of C_6H_{13} from the side chain (cleavage A) was first proposed by Ryhage and Stenhagen,[6] then later by Wulfson et al.[7] and Zaretskii et al.[9] In 1967 Knights[8] suggested cracking patterns B and C without any mechanistic explanation. In 1968 the Spitellers[10] proposed cleavage C with a very reasonable mechanism to explain the loss of 85 mass units from androst-5-ene-3β,17β-diol. This was not correlated with the $M^+ - 85$ (*m/e* 301) cleavage in cholesterol, although these fragmentations are analogous. Recently, Mujtaba Naqvi[11] proposed pattern D, without any supporting evidence, mechanistic considerations, or evaluation against the earlier proposals. Our initial deuterium labeling efforts in trying to select the correct cleavage pattern indicated that, in fact, none of these proposals are valid, and in 1970 we reported[1] that the actual cleavage is E, as shown on V. The complexity of this a priori unexpected cleavage led us to examine its mechanism in more detail. While this manuscript was in preparation, Budzikiewicz and Ockels[12] confirmed this cleavage in an independent, detailed study of the fragmentation of androst-5-en-3β-ol with the aid of extensive deuterium labeling evidence. They, however, did not provide mechanistic explanation for any of the fragmentations.

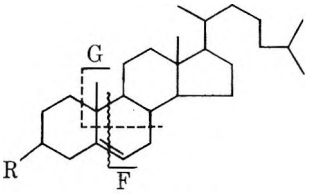


IV (*m/e* 301)



V (*m/e* 301)

The fragmentation patterns proposed to explain the genesis of the $(M - 111)^+$ ion are depicted in VI. Cleavage F was originally suggested by Friedland et al.[5] in 1959. They pointed out that "shifting of the double bond probably precedes the cleavage of the C_5–C_6 bond because a double bond would not be expected to cleave in preference to a single bond". In 1967, cleavage G was proposed independently by Knights[8] and by Zaretskii et al.[9] There was no further mechanistic explanation, isotope labeling, or other supporting evidence provided for this mode of cleavage. Our results confirmed[1] that cleavage



VI (*m/e* 275)

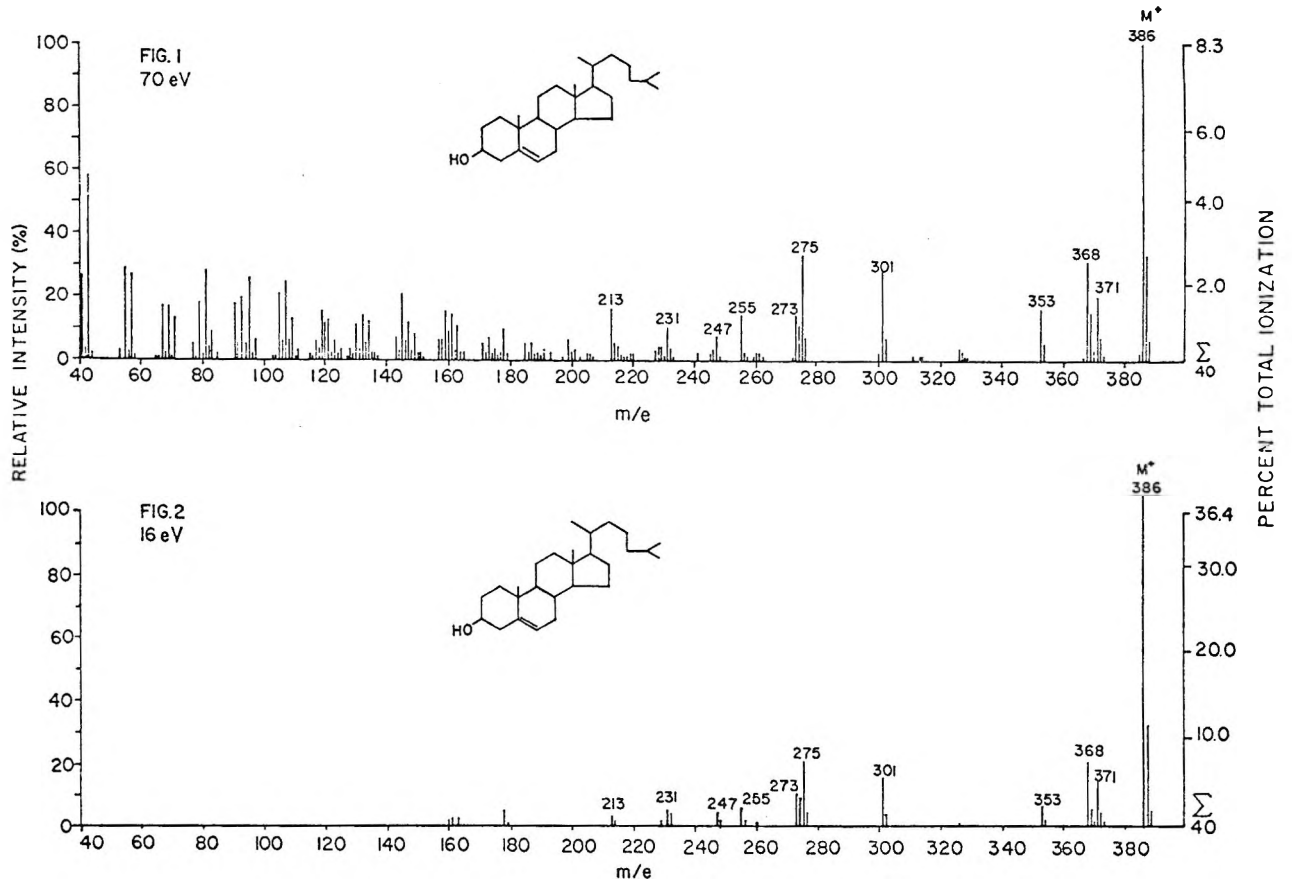
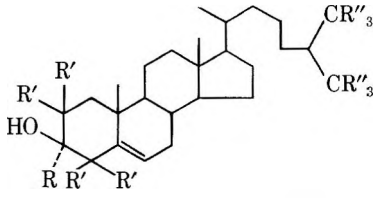


Figure 1. Mass spectrum of cholesterol (I), measured at 70 eV.
Figure 2. Mass spectrum of cholesterol (I), measured at 16 eV.

G is the correct one and this is now fully supported by the results of Budzikiewicz and Ockels in androst-5-en-3β-ol.[12]

To establish the exact cleavage patterns and to shed light on the mechanism of these fragmentations it was necessary to examine the mass spectra of various deuterium labeled analogues, which revealed some of the most complicated fragmentations encountered so far in the steroid field. The syntheses of these deuterated compounds and their spectral analyses are described in the following sections.

Syntheses of Labeled Compounds. During the course of this work the mass spectra of 11 site specifically deuterated analogues have been analyzed with labels at the following positions: C-1, 2, 3, 4, 6, 7, 8, 9, 19, 26, 27, and -OH. Of these, the preparations of *3*α-d_1[13] (VII), *2,2,4,4*-d_4[13] (VIII), and *26,27*-d_6[14] cholesterols (IX) have been reported previously. Cholesterol-*O*-*d* (III) was readily accessible by recrystallization of cholesterol from methanol-*O*-*d*.



VII, R = D; R′ = R″ = H
VIII, R = R″ = H; R′ = D
IX, R = R′ = H; R″ = D

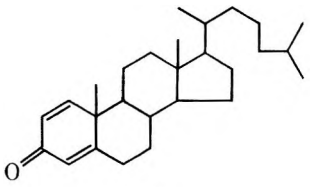
At C-1 both α and β positions had to be labeled to distinguish between the loss of this methylene group and a possible stereospecific deuterium transfer from either of these sites. Separate stereospecific labeling of the positions by homogeneous and heterogeneous catalytic deuterations of the C-1 double bond in cholesta-1,4-dien-3-one (X) proved to be the easier and ultimately more beneficial route than the preparation of cholesterol-*1,1*-d_2.

The stereochemical course of homogeneous catalytic saturation of the C-1 double bond has been established to proceed primarily (83–86%) from the α side in the tritiations of cholesta-1,4-dien-3-one[15] (X) and 17β-hydroxyandrosta-1,4-dien-3-one,[16] and in the deuteration of androsta-1,4-diene-3,17-dione.[17]

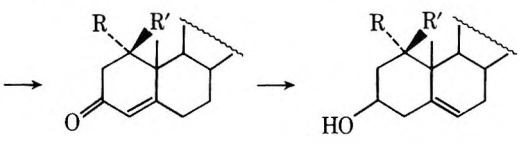
By analogy, cholest-4-en-3-one-*1*α-d_1 (XI) was prepared by the deuteration of X with Wilkinson's catalyst in benzene, followed by alkaline exchange of the C-2 deuterium. Conversely, in the presence of 5% palladium on charcoal catalyst this sequence provided the *1*β-d_1 analogue (XII) predominantly. The stereochemistry of the deuterium in XII was established by the over 80% retention of the label upon its reoxidation to cholesta-1,4-dien-3-one-*1*-d_1 with 2,3-dichloro-5,6-dicyanobenzoquinone, a step which is known to remove specifically the 1α and 2β axial hydrogens,[18] and by the characteristic C1–βD bond stretching[19] at 2180 cm^{-1} in the IR spectrum of XIV. These results are in agreement with the reported[20] 3:1 preference for β side tritiation of the C-1 double bond in the presence of palladium on charcoal in 17β-hydroxyandrosta-1,4-dien-3-one.[21]

The resulting d_1-cholestenones XI and XII on deconjugation and reduction with sodium borohydride yielded *1*α-d_1 (XIII) and *1*β-d_1 (XIV) cholesterols, respectively. These deuterio epimers showed a marked difference in the deuterium transfers from C-1 in association with the loss of water in their mass spectra (see Table I). This observation parallels the mechanism of the electron impact induced dehydration of 5α-cholestan-3β-ol[22] (vide infra), and provides supporting evidence for the stereochemical assignment of the deuteriums in XIII and XIV.

The ketone at the C-6 position in 3β-hydroxy-5α-choles-

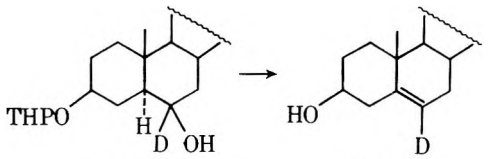


X

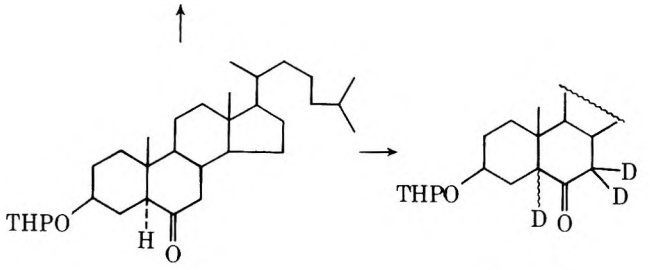


XI, R = D; R′ = H
XII, R = H; R′ = D
XIII, R = D; R′ = H
XIV, R = H; R′ = D

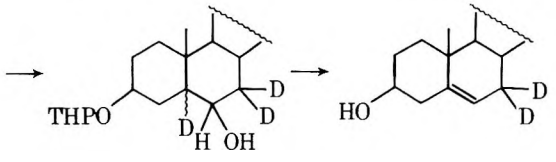
tan-6-one tetrahydropyranyl ether (XV) facilitated the deuteration of both C-6 and C-7 positions. Reduction of the carbonyl group with lithium aluminum deuteride, followed by dehydration of the resulting alcohol (XVI), and hydrolysis of the tetrahydropyranyl ether, gave cholesterol-6-d_1 (XVII) in 96% isotopic purity. This reaction sequence yielded cholesterol-7,7-d_2 (XX) when it was carried out on ketone XVIII in which the C-5 and C-7 hydrogens were exchanged with deuterium before reduction with lithium aluminum hydride.



XVI XVII

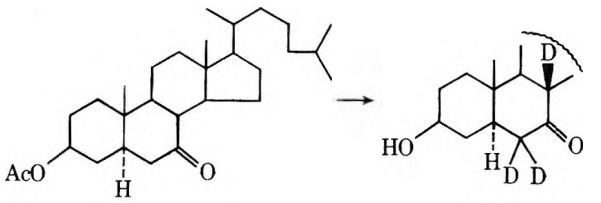


XV XVIII

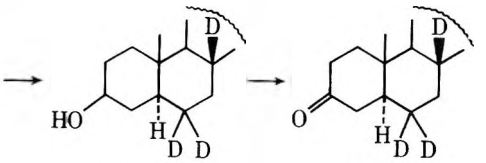


XIX XX

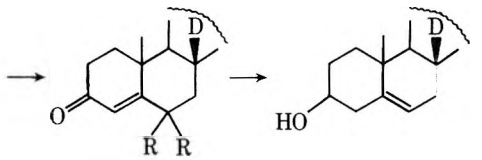
Deuteration of the 8β position was accomplished by base-catalyzed exchange of the C-6 and C-8 hydrogens in 3β-acetoxy-5α-cholestan-7-one (XXI). Owing to the slow exchange rate of the 8β hydrogen[23] this reaction required 3 days of heating to obtain sufficient isotopic purity. Reduction of the carbonyl function at C-7 in XXII was achieved without any deuterium loss by sodium borohydride treatment of its tosylhydrazone derivative.[3a,24] Oxidation of the hydroxyl function in XXIII gave cholestan-3-one-6,6,8β-d_3 (XXIV) which was converted into cholest-4-en-3-one-6,6,8β-d_3 (XXV) by bromination with pyridinium bromide perbromide,[25] followed by dehydrobromination of the 2α-bromo intermediate with lithium chloride in dry dimethylformamide.[26] Base-catalyzed back exchange of the deuteriums from C-6 yielded cholest-4-en-3-one-8β-d_1 (XXVI), which upon deconjugation and reduction with sodium borohydride gave cholesterol-8β-d_1 (XXVII) in 95% isotopic purity.



XXI XXII

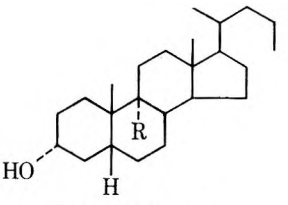


XXIII XXIV

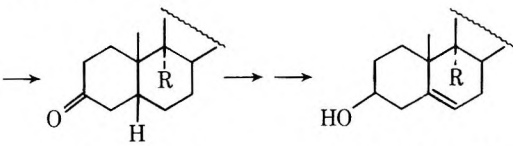


XXV, R = D
XXVI, R = H
XXVII

The preparation of a 9α-deuterated analogue was carried out in the cholane series, starting with 5β-cholan-3α-ol-9α-d_1 (XXIX) prepared by Klein and Djerassi.[27] Introduction of the C-5 double bond in both labeled (XXIX) and unlabeled (XXVIII) 5β-cholan-3α-ols was effected on their 3-keto derivatives (XXX and XXXI) by the usual bromination, dehydrobromination, deconjugation, and reduction sequence yielding chol-5-en-3β-ol-9α-d_1 (XXXIII) and the unlabeled reference compound XXXII, respectively.

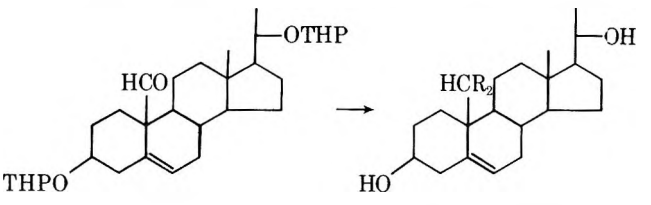


XXVIII, R = H
XXIX, R = D



XXX, R = H
XXXI, R = D
XXXII, R = H
XXXIII, R = D

Reduction of the aldehyde function in pregn-5-ene-3β,20β-diol-19-al ditetrahydropyranyl ether (XXXIV), which was available to us from other studies, provided an attractive route to a C-19 labeled analogue. Replacement of the carbonyl oxygen by two deuteriums in XXXIV, a conversion which is known to be difficult by conventional chemical means,[28] could be achieved easily by electrochemical reduction in strongly acidic medium.[29] The resulting pregn-5-ene-3β,20β-diol-19,19-d_2 (XXXVI) exhibited 94% isotopic purity, and was a



XXXIV
XXXV, R = H
XXXVI, R = D

Scheme I

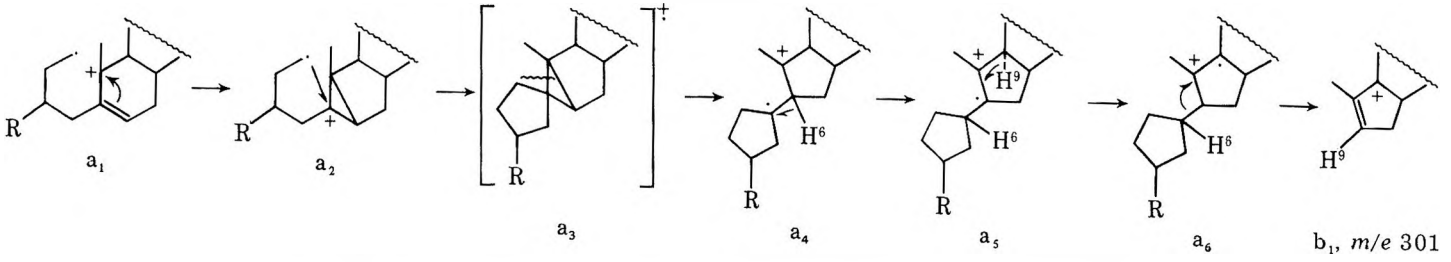


Table I. Shifts[a] of the Peaks in the Mass Spectra of Deuterium Labeled Compounds

Registry no.	Compd	*m/e* (%)										
		M^+	$(M - CH_3)^+$	$(M - H_2O)^+$	$[M - (CH_3, H_2O)]^+$	Ion b	Ion c	$(M -$ side chain$)^+$	$[M -$ (side chain, $H_2O)]^+$	Ion f	$[M -$ (ring D, H)$]^+$	$[M -$ (ring D, H, $H_2O)]^+$
	Cholesterols											
57-88-5	d_0 (I)	386	371	368	353	301	275	273	255	247	231	213
60816-12-8	*-O-d* (III)	387	372	368	353	301	275	274	255	247	232	213
60816-13-9	*1α-*d_1 (XIII)	387	372	369	354	301	275	274	256	247	232	214
60816-14-0	*1β-*d_1 (XIV)	387	372	369 (71) 368 (29)	354 (74) 353 (26)	301	275	274	256 (81) 255 (19)	247	232	214 (83) 213 (17)
7604-91-3	*2,2,4,4-*d_4 (VIII)	390	375	372	357	301	275	277	259	247	235	217
51467-57-3	*3α-*d_1 (VII)	387	372	369	354	301	275	274	256	247	232	214
16374-87-1	*6-*d_1 (XVII)	387	372	369 (75) 368 (25)	354 (90) 353 (10)	301 (55) 302 (45)	275	274	256 (75) 255 (25)	247	232	214 (80) 213 (20)
60816-15-1	*7,7-*d_2 (XX)	388	373	370	355	303	275	275	257	247[b]	233 (~90)	215 (~90)
60816-16-2	*8β-*d_1 (XXVII)	387	372	369 (94) 368 (6)	354 (80) 353 (20)	302	276	274	256 (83) 255 (17)	247 (55) 248 (45)	232 (~95)	214 (80) 213 (20)
60816-17-3	*26,27-*d_6 (IX)	392	377	374	359	307	281	273	255	253	231	213
5255-15-2	Chol-5-en-3β-ol (XXXII)	344	329	326	311	259	233	273	255	205	231	213
60816-18-4	*9α-*d_1 (XXXIII)	345	330	327 (75) 326 (25)	312 (83) 311 (17)	260 (93) 259 (7)	234	274	256 (84) 255 (16)	206 (56) 205 (44)	232 (92) 231 (8)	214 (67) 213 (33)
901-57-5	Pregn-5-ene-3β,20β-diol (XXXV)	318	303	300	285	233	207	273	255		231	213
20810-63-3	*19,19-*d_2 (XXXVI)	320	303 (58) 305 (42)	302 (96) 301 (4)	287 (30) 285 (70) 286[c]	235	209	275	257[b]		233[b]	215[b]

[a] Shift values are corrected for isotopic impurity as well as for ^{13}C contributions and are reliable to ±5% unless otherwise indicated. [b] Mainly at the indicated value but exact calculations were not possible owing to the low intensity of these peaks and overlap by other fragment ions. [c] A few percent of the *m/e* 285 peak was shifted to 286. The exact shift value for this peak was not calculated owing to the complexity of this group of peaks, and the uncertainty as to which of the two hydroxyl fractions is responsible for deuterium transfer from C-19.

legitimate C-19 labeled model compound for the $(M - 85)^+$ and $(M - 111)^+$ ions since these fragments were present in the mass spectra of both labeled (XXXVI) and unlabeled (XXXV) compounds.[30]

Discussion of Mass Spectral Results. The 70- and 16-eV spectra of cholesterol are reproduced in Figures 1 and 2. The shift values of the diagnostic peaks in the mass spectra of the deuterium labeled analogues are summarized in Table I.

As apparent from Figures 1 and 2, the diagnostic $(M - 85)^+$ and $(M - 111)^+$ peaks (*m/e* 301 and 275) are prominent at both high and low ionizing voltages. High-resolution analysis of these ions revealed that their elemental compositions are $C_{22}H_{37}$ and $C_{20}H_{35}$, respectively. This finding eliminates cleavage A (see IV) for the *m/e* 301 ion since the hydroxyl group is lost in both fragments. Furthermore, comparison of the mass spectra of various side chain analogues of cholesterol (see, for example, compounds IX, XXXII, and XXXV in Table I) shows that the C-17 side chain (if present) remains fully intact in both $(M - 85)^+$ and $(M - 111)^+$ ions.

Two other observations are important concerning the nature of these fragmentations. One is the presence of both *m/e* 301 and 275 peaks in the spectrum of cholest-5-ene (II),[31] in about the same relative intensity as in the spectrum of cholesterol. These peaks are absent in the spectra of the saturated analogues, 5α and 5β-cholestanes,[3c] indicating that *the cleavages leading to these ions are triggered solely by the C-5 double bond.* The other observation is that the relative significance of the $(M - 85)^+$ and $(M - 111)^+$ peaks is not decreased in the absence of the C-17 side chain (*m/e* 189 and 163 in the spectrum of androst-5-en-3β-ol[12]). This shows that the 13–17 bond, which is very cleavage prone in the presence of a C-17 side chain[3a] and is known to influence fragmentations at remote sites,[3c] remains intact during the formation of these ions.

The *m/e* 301 Ion. According to the labeling results shown in Table I, this ion lost all deuteriums at C-1, 2, 3, and 4, and retained them completely at C-7, 8, 19, 26, and 27. These results are incompatible with all four cleavages (A–D on IV) proposed earlier and are indicative of a complex cracking pattern which involve scissions of the 1–10, 5–10, and 5–6 bonds with a hydrogen transfer from the charge retaining side as shown in V. To complicate matters even further, this hydrogen transfer involves several sites, the most important (55%) being C-6. This is a priori the least expected site since it involves a vinylic hydrogen on a carbon which formally also has to cleave its double bond to C-5. An additional 7% transfer was observed from the 9α position, leaving 38% unaccounted for. This may come from one or more of the hitherto unlabeled positions, C-14 being a very likely one.

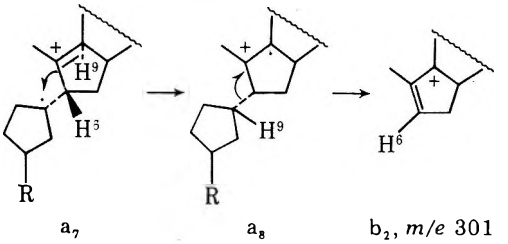
On mechanistic grounds this cleavage poses some problems. Formally, it involves the ruptures of two carbon–carbon bonds of C-10, and double bond as well as single bond of C-5, in addition to the unexpected hydrogen transfer from C-6. A fragmentation of such complexity can be considered as prima facie evidence for the participation of extensive skeletal rearrangements.[32] A possible mechanistic explanation for the major fragmentation pathway which involves the transfer of the C-6 hydrogen is depicted by Scheme I.

The sequence $a_1 \rightarrow a_4$ in Scheme I is apparently common for the formation of both $(M - 85)^+$ and $(M - 111)^+$ ions (vide infra). In essence, the transformation of a_1 into a_3 involves a shift of the 1–10 bond to the carbonium ion at C-5 and bond formation between the isolated radical and ionic sites (C-6 and C-10). This transformation can be synchronous[33] or stepwise as shown in Scheme I. Spirostane skeletons with three- and five-membered rings, similar to molecular ion a_3, are well-known photolysis products of conjugated steroidal dienones and trienes.[34]

The final steps in Scheme I, involving scissions of the 5–10 and 5–6 bonds with a concomitant hydrogen transfer from the charge retaining side ($a_3 \rightarrow b_1$), is a typical fragmentation of cyclopropyl hydrocarbons.[35] Opening of the most substituted bond in a_3 (5–10 bond) and a 1,2 hydrogen shift from the doubly activated C-6 position to C-5 in ion radical a_4 lead to an ionized olefin a_5. Such ionized olefins are well-documented intermediates in the fragmentation of steroidal hydrocarbons.[36] The loss of the cyclopentyl radical in a_5 is analogous to the loss of vinylic alkyl substituents from cyclic olefins,[35-37] and is probably preceded by a 1:3 hydrogen shift from the activated 9α position to facilitate the homolysis of the 5–6 bond.

The minor part of this fragmentation, involving the 7% hydrogen transfer from the 9α position, may proceed also via molecular ion a_4. Steps $a_1 \rightarrow a_4$ can lead to two stereoisomers at C-6, both of which can yield a_5 with equal facility. In the stereoisomer of a_4 with the cyclopentyl group on the α side (a_7) hydrogen transfer to C-5 may occur also from the activated 9α position. This route yields fragment ion b_2, via an ionized olefin a_8 (Scheme II). These are essentially identical with ions

Scheme II

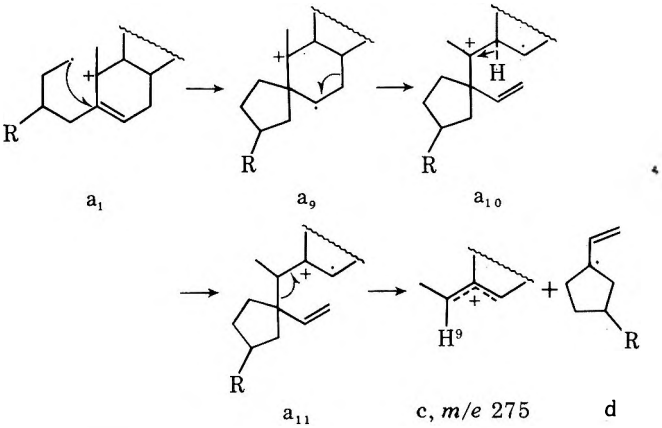


a_7 a_8 b_2, *m/e* 301

a_6 and b_1 in Scheme I, the difference being only the origin of the hydrogens at C-5 and C-6. The eightfold preference for the longer fragmentation sequence $a_4 \rightarrow b_1$, as compared to $a_7 \rightarrow b_2$, is probably due to the relative facility of the hydrogen transfers involved. Judging from Dreiding models, the minimum internuclear distance between the 9α hydrogen and the carbon radical is less in a_5 (2.8 Å) than in a_7 (3.2 Å). Actually, both of these distances are quite large compared to the <1.8 Å internuclear distance criterion for bond formation between hydrogens and carbonyl oxygens in the McLafferty rearrangement,[38] but analogous internuclear distance requirements for carbon–hydrogen bond formation have not been established as yet.

The *m/e* 275 Ion. The labeling results in Table I indicate that the $C_7H_{11}O$ fragment expelled in forming this ion encompasses C-1 to C-7, without any detectable hydrogen transfer. These findings are in complete agreement with cleavage G (see VI) and they invalidate cleavage F. A possible mechanism for this fragmentation is shown in Scheme III.

Scheme III



a_1 a_9 a_{10} a_{11} c, *m/e* 275 d

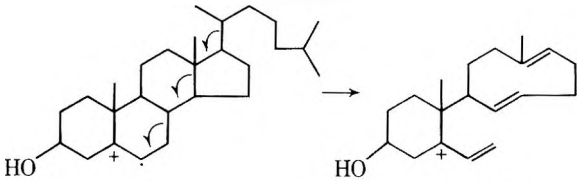
Bond formation between C-1 and C-5 in molecular ion a_1 relieves the C-1 primary radical while forming an isolated

secondary radical in a_9. This radical can either form a bond with C-10 (see a_3), or can trigger the cleavage of the 7–8 bond, forming an olefin a_{10} with a new isolated radical at C-8. Migration of the doubly activated 9α hydrogen to the adjacent carbonium ion gives an ionized diene a_{11} in which homolysis of the 5–10 bond yields the allylic ion c (*m/e* 275) and a conjugated radical d.

The origin of the *m/e* 301 and 275 fragments from the molecular ion has been confirmed by the observed intense metastable peaks corresponding to these transitions in the pure metastable spectrum of cholesterol, using the method of Jennings.[39] Weak metastable peaks corresponding to the formation of these fragments from the $(M - H_2O)^+$ peak were also detected.

The *m/e* 273 and 255 Ions. The labeling results (Table I) substantiate earlier proposals[5-8] that these ions are due to the losses of the C-17 side chain (*m/e* 273) and the combination of the side chain and a molecule of water (*m/e* 255). These are common steroid fragmentations, although they are relatively insignificant in the spectra of 5α- and 5β-cholestanes,[3a,c] or 5α-cholestan-3β-ol.[22] The considerable intensity of these ions in Figure 1 indicates that, by analogy to Djerassi's proposal[31] for cholest-5-ene (II), the side chain loss in cholesterol is enhanced by the C-5 double bond as shown in Scheme IV.

Scheme IV

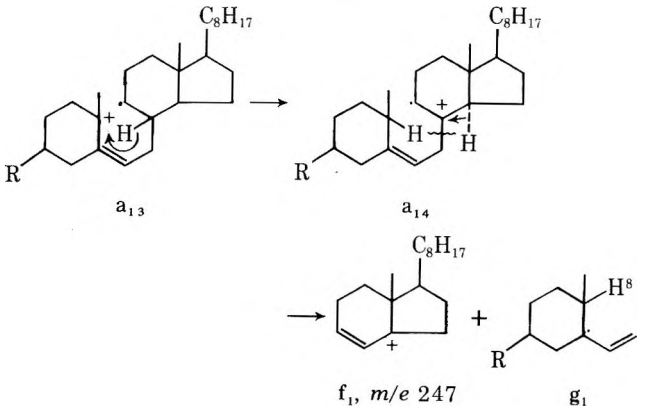


a_{12} e, *m/e* 273

The *m/e* 247 Ion. Friedland et al.[5] attributed this ion to the loss of rings A and B plus an extra hydrogen by cleavage of the 7–8 and 9–10 bonds. This proposal has been generally accepted and is confirmed now by our labeling results, which also establish that the sources of the extra hydrogen are the 8β (55%) and 9α (44%) positions. It is noteworthy that once again the hydrogen transfer sites are carbon atoms which undergo skeletal bond cleavage as well.

Apparently, two different cleavages are participating in the formation of this ion. One cleavage may be initiated by the rupture of the allylic 9–10 bond, forming molecular ion a_{13} which can undergo facile hydrogen shift from the activated 8β position to C-10 in a six membered transition state. By analogy to the fragmentation of other ionized olefin intermediates,[36] a 1,2 shift of the 14α hydrogen to C-8, followed by fission of the 7–8 bond leads to ion f_1 (*m/e* 247) and radical g_1, both of which are allylically stabilized (Scheme V).

Scheme V

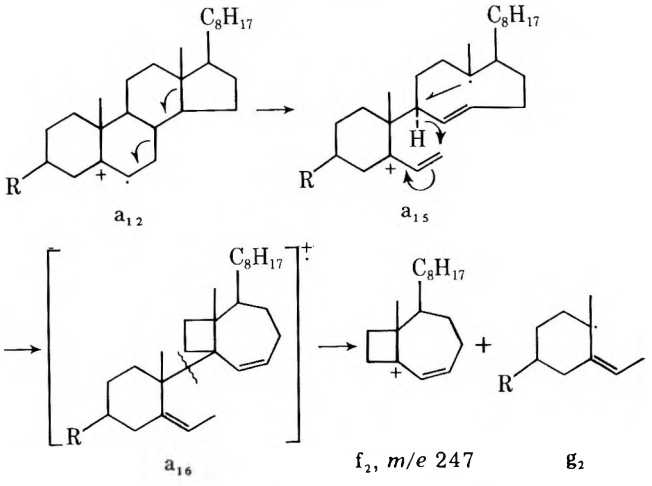


a_{13} a_{14}

f_1, *m/e* 247 g_1

The second cleavage, which involves the loss of the 9α hydrogen, may start with the simultaneous rupture of both 7–8 and 13–14 bonds as shown in Scheme VI. In this case, however, instead of losing the C-17 side chain as in $a_{12} \rightarrow$ e, vide supra, hydrogen transfer occurs through a six-membered transition state from the allylic 9α position to C-7. This step may be further assisted by bond formation between the isolated C-13 radical and C-9 yielding a_{16}. Cleavage of the doubly allylic 9–10 bond then leads to ion f_2 (*m/e* 247) and radical g_2.

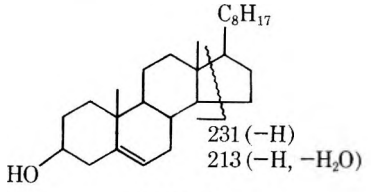
Scheme VI



a_{12} a_{15}

a_{16} f_2, *m/e* 247 g_2

The *m/e* 231 and 213 Ions. The *m/e* 231 ion and its dehydration product (*m/e* 213) are generated by the loss of ring D with the side chain and an extra hydrogen (see XXXVII), which is a characteristic fragmentation of C-17 side chain bearing steroids.[3a,40] Consequently, these ions are of negligible intensity in the spectrum of androst-5-en-3β-ol.[12] Detailed study of this cleavage in the hydrocarbon series revealed that the origin of the extra hydrogen is random, involving the 7, 8β, 9α, 12, 14α, and 18 positions, the 14α position being the major contributor.[3a] The present labeling results (Table I) are in agreement with these earlier reports.



XXXVII

The Loss of Water and Methyl Radical. The labeling results in Table I shed light also on the complexity of the mechanism of electron impact induced loss of water in the genesis of the *m/e* 368 $(M - H_2O)^+$, 353 $[M - (CH_3, H_2O)]^+$, 255 $[M - (\text{side chain}, H_2O)]^+$, and 213 $[M - (\text{ring D}, H_2O)]^+$ ions. Karliner, Budzikiewicz, and Djerassi reported[22] that 5α-cholestan-3β-ol lost 28% deuterium from the 1β position and 11% from the 5α position in the $[M - (CH_3, H_2O)]^+$ fragment while all labels were retained at the 1α, 2, 3α, and 4 positions. The remaining 61% hydrogen transfer was unaccounted for. By contrast, the corresponding 3α-hydroxy compound lost mainly the 5α label (73%) and only small amounts from the 1α (4.5%) and, possibly, from the 1β (2.5%) positions.

In cholesterol the stereospecific loss of 26–29% deuterium from the 1β position and the lack of any other transfer from positions 1–4 resemble closely those reported for 5α-cholestan-3β-ol. It is evident, however, from our results that in the presence of a C-5 double bond the major transfer sites include remote positions also, such as the 6 (10–25%), 8β (6–20%), 9α (17–25%), and probably the C-19 positions. The sum of these transfers in cholesterol accounts for about 89% and over 73% of the hydrogen losses in the $(M - H_2O)^+$ and $[M - (CH_3,$

$H_2O)]^+$ ions, respectively. Similar transfers were also apparent in the *m/e* 255 and 213 ions.

Extensive hydrogen transfer (80%) from the distant 9α position during the dehydration of a C-3 hydroxyl group has been reported with 5β-cholan-3α-ol by Klein and Djerassi.[27] There was no transfer from this site in the corresponding 3β hydroxy epimer. These observations were readily explainable by the spatial relationship between the hydroxyl group and the potential hydrogen transfer sites in the intact molecules.[41] In the 5β series with ring A in the boat conformation only the 3α hydroxyl group is in the proper spatial arrangement for hydrogen transfer from the 9α position. In cholesterol, however, there is no possibility for the 3β-hydroxyl group to approach the 6, 8β, and 9α positions and, therefore, skeletal cleavages must precede the hydrogen transfers from these sites.

The complete retention of the deuterated C-26 and C-27 terminal methyl groups in IX and the 58% loss of the labeled C-19 methyl function in XXXVI provide supporting evidence for the earlier reports that the 18 and 19 angular methyl groups are the exclusive source of the expelled methyl radicals in the $(M - CH_3)^+$ process in androstane[3b] and pregnane.[3a]

In conclusion, the characteristic $(M - 85)^+$ and $(M - 111)^+$ fragmentations of 3β-hydroxy Δ^5-steroids are triggered by the C-5 double bond and are present in the spectra of compounds lacking any strong fragmentation triggering functions in ring A or other parts of the molecule. Consequently, the corresponding fragment ions are detected in the spectra of Δ^5-steroids with or without a hydroxy or keto group at C-3, but are absent or very weak when an acetoxy,[8,42] silyloxy,[8,13] or double bond[6,42] function is present at C-3. These fragmentations are also hindered by the presence of alkyl substituents at C-4. In these compounds the molecular ions which are analogous to a_1 undergo a different rearrangement which involves migration of the hydroxyl group to C-6.[43]

Experimental Section

The mass spectra were measured on Varian MAT CH-7 and CH-4 (equipped with an EFO-4B ion source) and AEI MS-902 mass spectrometers at 70 eV ionizing voltage unless otherwise stated. The high-resolution measurements were carried out on the AEI MS-902 mass spectrometer at a resolution of 10 000 (10% valley) and ±5 ppm accuracy. The IR spectra were recorded on a Perkin-Elmer Model 237 Infracord spectrometer. The NMR spectra were measured on a Varian HA-100 spectrometer using tetramethylsilane as internal reference. The melting points are uncorrected.

Isotope composition of labeled compounds follows.

Cholesterol-1α-d_1 (XIII): d_0 3%, d_1 87%, d_2 10%. Cholesterol-1β-d_1 (XIV): d_0 23%, d_1 76%, d_2 1%. Cholesterol-2,2,4,4-d_4[13] (VIII): d_1 4% d_2 15%, d_3 42%, d_4 39%. Cholesterol-3α-d_1[13] (VII): d_0 2%, d_1 98%. Cholesterol-6-d_1 (XVII): d_0 4%, d_1 96%. Cholesterol-7,7-d_2 (XX): d_0 5%, d_1 55%, d_2 38%, d_3 2%. Cholesterol-8β-d_1 (XXVII): d_0 3%, d_1 95%, d_2 2%. Chol-5-en-3β-ol-9α-d_1 (XXXIII): d_0 11%, d_1 86%, d_2 3%. Pregn-5-ene-3β,20β-diol-19,19-d_2 (XXXVI): d_1 6%, d_2 94%. Cholesterol-26,27-d_6[14] (IX): d_2 1%, d_3 5%, d_4 8%, d_5 23%, d_6 63%. Cholesterol-*O*-*d* (III): d_0 16%, d_1 84%.

Acknowledgments. We wish to thank Professor C. Djerassi of Stanford University for the generous supply of labeled and unlabeled 5β-cholan-3α-ol samples (XXVIII and XXIX), and Dr. A. F. Hofmann of Mayo Clinic for a sample of cholesterol-26,27-d_6 (IX).

Registry No.— X, 566-91-6; XI, 60816-19-5; XII, 60816-20-8; XV, 58704-09-9; XVI, 60816-21-9; XVIII, 60816-22-0; XIX, 60816-23-1; XXI, 6038-71-7; XXII, 60816-24-2; XXII tosylhydrazone, 60816-25-3; XXIV, 60816-26-4; XXIV 2-bromo, 60816-27-5; XXV, 60816-28-6; XXVI, 60816-29-7; XXVIII, 5352-77-2; XXIX, 42921-50-6; XXXI, 60816-30-0; XXXIV, 60816-31-1; cholest-4-en-3-one-1,2-d_2, 60816-32-2; cholesta-1,4-dien-3-one-1-d_1, 60816-33-3; cholesterol THP ether-6-d_1, 60840-36-0; *p*-toluenesulfonhydrazide, 1576-35-8; pyridinium bromide perbromide, 39416-48-3; chol-4-en-3-one-9α-d_1, 60816-34-4.

Supplementary Material Available. Experimental part for the preparation of deuterium labeled compounds (4 pages). Ordering information is given on any current masthead page.

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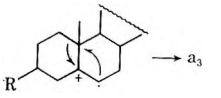

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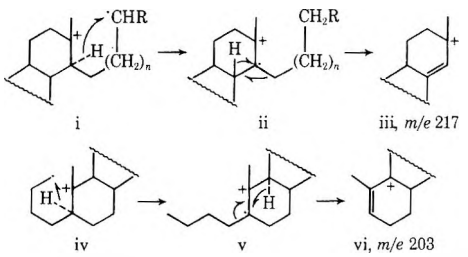

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The Effect of the Trimethylsilylmethyl Substituent on Ketene Cycloadditions

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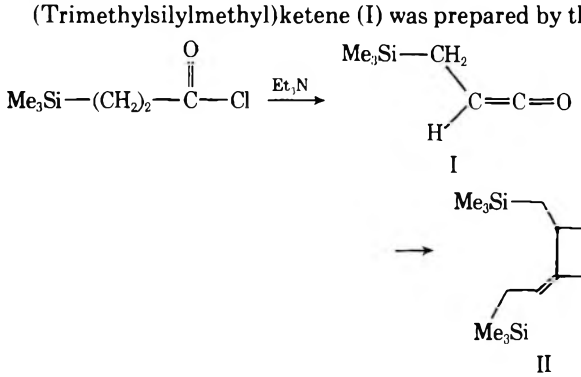
Received July 6, 1976

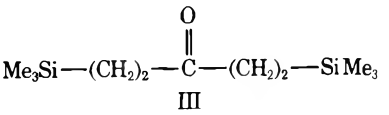
(Trimethylsilylmethyl)ketene is prepared by the dehydrochlorination of β-trimethylsilylpropionyl chloride. The 2-oxetanone dimer of the ketene is readily converted to 1,5-bis(trimethylsilyl)-3-pentanone. The ketene readily undergoes in situ cycloaddition to cyclopentadiene to yield only the *endo*-trimethylsilylmethylcyclobutanone and cycloaddition to ethyl vinyl ether yields only the trans cyclobutanone. Vinyltrimethylsilane would not undergo cycloaddition with a variety of ketenes. However, allyltrimethylsilane readily underwent cycloaddition with methylchloro- and dichloroketenes. An interpretation of these results is offered.

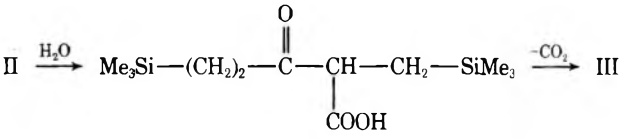
The effect of the trimethylsilyl substituent on the properties and chemistry of trimethylsilylketene is truly remarkable. This aldoketene is very stable, does not dimerize upon heating, and can be stored for long periods of time.[1,2] Numerous efforts to effect cycloaddition of trimethylsilylketene with a variety of unsaturated compounds have been mostly unsuccessful; the only cycloaddition which has been reported was with dimethyl and diethyl acetal of ketene under rather vigorous conditions for a ketene cycloaddition.[3] Also, condensation of trimethylsilylketene with benzaldehyde gave *cis*- and *trans*-trimethylsilylstyrene which presumably involved cycloaddition to form the 2-oxetanone which underwent decarboxylation to yield the olefins.[4] We have recently reported on the preparation and cycloaddition of trimethylsilylbromoketene and this ketene appears to be more reactive in cycloaddition reactions than trimethylsilylketene, although only cycloadducts with an imine and carbodiimide have been prepared.[5]

In this report we describe the effect of the trimethylsilylmethyl substituent on the properties and chemistry of (trimethylsilylmethyl)ketene and also describe the effect of the trimethylsilyl substituent and the trimethylsilylmethyl substituent on the reactivity of the olefin in ketene cycloaddition reactions.

(Trimethylsilylmethyl)ketene (I) was prepared by the triethylamine dehydrochlorination of β-trimethylsilylpropionyl chloride in hexane as evidenced by a band in the infrared at 2123 cm.$^{-1}$ The ketene was not isolable but underwent dimerization to yield the expected dimer, II. This dimer was accompanied by an unexpected product, 1,5-bis(trimethylsilyl)-3-pentanone (III). The formation of III was quite





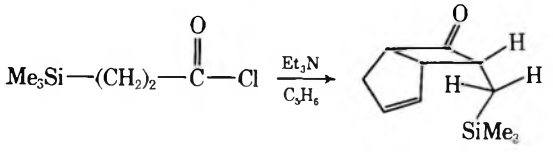


puzzling; however, it was established that this ketone was formed from the 2-oxetanone dimer. The dimer was hygroscopic and would slowly react with atmospheric moisture yielding the keto acid which decarboxylated to the ketone. Normal drying tube precautions were not sufficient to keep II from being hydrolyzed.

The β-trimethylsilylpropionyl chloride was prepared from vinyltrimethylsilane by the addition of hydrogen bromide in the presence of benzoyl peroxide, Grignard formation, carbonation, hydrolysis, and acid halide formation with thionyl chloride. In some original preparations, II and III were also accompanied by 1,4-bis(trimethylsilyl)butane. This was the result of a coupling reaction in the Grignard step and this coupled product codistilling with β-trimethylsilylpropionyl chloride. Careful distillation of the β-trimethylsilylpropionic acid eliminated this problem.

An alternate route to I would be the zinc dehalogenation of α-halo-β-trimethylsilylpropionyl chloride. Attempts to α-halogenate β-trimethylsilylpropionyl chloride were unsuccessful owing to cleavage of the carbon–silicon linkage.

The in situ cycloaddition of cyclopentadiene and (trimethylsilylmethyl)ketene occurred in 65% yield. The cyclobutanone structure was assigned on the basis of the infrared

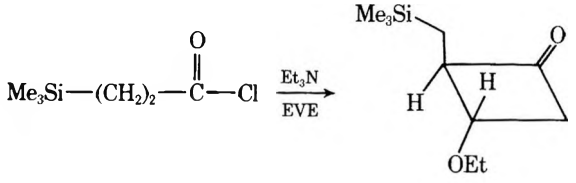


IV

band at 1785 cm^{-1} and also on NMR evidence. The vinyl protons appear as a multiplet and doublet. However, by decoupling the methylene protons in the cyclopentenyl ring, the olefinic protons clear up to a sharp double-doublet pattern.

Two isomeric cyclobutanone structures are possible depending on whether the trimethylsilylmethyl substituent is endo or exo. Only one isomer is formed from the reaction of trimethylsilylmethylketene with cyclopentadiene. The methylene protons adjacent to the trimethylsilylmethyl substituent appeared as an eight-line pattern in the NMR. This indicates that the methylene protons are diastereotopic. Each methylene proton from this isomer appears as a doublet doublet, this accounting for the eight lines. It has been well established that in [2 + 2] concerted ketene olefin cycloadditions the large substituent on the ketene occurs in the endo position owing to less steric hindrance in the transition state. If there is a large difference in the size of the substituents on the ketene, only that isomer is formed where the largest substituent is endo. Consequently, it is suggested that the *endo*-trimethylsilylmethyl substituted isomer is the one found in this cycloaddition.

The in situ cycloaddition of ethyl vinyl ether and trimethylsilylmethylketene yielded the expected cyclobutanone in good yield. The methylene protons adjacent to the trimeth-

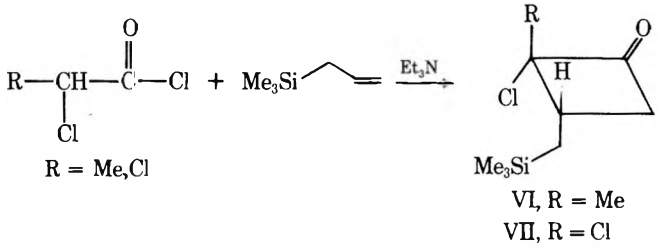


V

ylsilylmethyl substituent appeared as a doublet. In this case the methylene protons are not diastereotopic and it is likely that the only isomer which been found in this cycloaddition is the trans isomer.

The in situ cycloaddition of dichloro-, methylchloro-, and dimethylketenes with vinyltrimethylsilane were unsuccessful. Dimethylketene yielded only the dimer, methylchloroketene produced the vinyl ester, and the dichloroketene yielded only polymer. Apparently, the π electrons of the vinyl group interact with the empty d orbitals of the silicon atom resulting in a decreased nucleophilicity of the olefin. It is well known that the reactivity of olefins in ketene cycloaddition reactions strongly parallels the nucleophilicity of the olefin. Vinyltrichlorosilane and vinyltriethoxysilane have also been subjected to ketene cycloadditions and VPC and infrared data suggested only trace amounts of the cycloadducts. These vinylsilanes were also subjected to cycloaddition with diphenylketene with no success.

The in situ cycloaddition of dichloro- and methylchloroketenes with allyltrimethylsilane resulted in the expected cyclobutanones in 50–60% yield. Only the β-trimethylsilylmethylcyclobutanones were found in each case as evidenced by the NMR data. The chemical shift of the methylene protons of the cyclobutanone ring occur near δ 3.0, indicating that this downfield shift is due to being adjacent to the carbonyl group. Two isomers are possible in the cycloaddition of

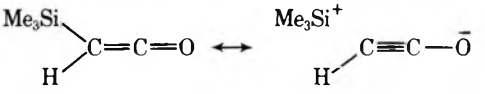


VI, R = Me
VII, R = Cl

methylchloroketene and allyltrimethylsilane. The ratio is 6:1 as evidenced by the integration of the two methyl singlets and it is believed that isomer predominates which has the methyl group cis to the trimethylsilylmethyl substituent (upfield chemical shift).

The vinyltrimethylsilane is unreactive in a ketene cycloaddition because of the electron-withdrawing effect of the trimethylsilyl substituent. The trimethylsilylmethyl substituent appears to be electron donating and thus activating based on the ease of cycloaddition of allyltrimethylsilane. This is consistent with reports in the literature on the electronic effects of these two silyl substituents.[7] However, the effect of the trimethylsilylmethyl substituent on ketene reactivity is not very pronounced. The chemistry of this aldoketene is about what would be expected from an aldoketene with a large substituent such as the trimethylsilylmethyl group assuming no electronic effects.

The spearhead of ketene reactions, both nucleophilic addition and cycloaddition, is the electrophilicity of the sp-hybridized carbon. Since the trimethylsilyl substituent is usually an electron-withdrawing substituent, the lack of reactivity of trimethylsilylketene seems inconsistent with these facts. Although we have suggested above that the trimethylsilyl substituent is electron withdrawing in the case of vinyltrimethylsilane, we now offer that this substituent is electron donating in this particular environment in trimethylsilylketene. This effect can be ascribed to hyperconjugation as illustrated below.



Experimental Section

^{1}H NMR spectra were recorded on a Jeolco PS-100 nuclear magnetic resonance spectrometer employing chloroform as the solvent and as the internal standard. VPC was performed on an F & M Scientific Model 700 gas chromatograph with a 10 ft × 0.25 in. column packed with 10% SE-30 on an acid-washed Chromosorb W (80/100). The infrared spectra were recorded on a Beckman 320 spectrometer.

Hexane was distilled from sodium prior to use. β-Trimethylsilylpropionic acid was prepared from vinyltrimethylsilane and converted to the acid chloride by a standard procedure.[8,9]

3-Trimethylsilylmethyl-4-(2-trimethylsilyl)ethylidene-2-oxetanone (II). To a solution of 0.2 mol of triethylamine in 150 ml of dry hexane was added dropwise 0.1 mol of β-trimethylsilylpropionyl chloride in 20 ml of hexane under a dry nitrogen atmosphere at room temperature over a 0.5-h period.[10] At the completion of the addition, the reaction mixture was refluxed for about 2 h. The ketene was very short lived as evidenced by the disappearance of the band in the infrared at 2123 cm^{-1}. The solvent was evaporated on a rotatory evaporator, residual salt removed by filtration, and vacuum distillation afforded the dimer at 71–73 °C (0.05 mm) (85%): IR 1850 and 1710 cm^{-1}; NMR, δ 0.1 (s, 9 H), 0.18 (s, 9 H), 1.40 (d, 2 H), 1.42 (d, 2 H), 3.80 (t, 1 H), and 4.54 (t, 1 H); mass spectrum parent peak at *m/e* 256 (theory 256).

Anal. Calcd for $C_{12}H_{24}O_2Si_2$: C, 56.25; H, 9.37. Found: C, 56.20; H, 9.41.

1,5-Bis(trimethylsilyl)-3-pentanone (III). This disilylated ketone was also isolated from the dimerization reaction mixture unless the reaction was run under a dry nitrogen atmosphere and strict precautions were taken to keep atmospheric moisture from the system. All of the 2-oxetanone dimer could be converted to this ketone

by the addition of water to the dimer. This ketone distilled at 55–56 °C (0.05 mm): IR 1720 cm^{-1}; NMR δ 0.10 (s, 18 H), 0.70 (t, 4 H), 2.26 (t, 4 H); mass spectrum parent peak at *m/e* 230 (theory 230).

1,4-Bis(trimethylsilyl)butane. This disilylated compound was isolated from the reaction mixture described above unless the β-trimethylsilylpropionic acid was carefully distilled. 1,4-Bis(trimethylsilyl)butane is a product from a Grignard coupling reaction in the preparation of the acid and vacuum distills at 36–38 °C (0.05 mm): NMR δ −0.10 (s, 18 H), 0.48 (m, 4 H), and 1.18 (m, 4 H).

Anal. Calcd for $C_{10}H_{26}Si_2$: C, 59.41; H, 12.87. Found: C, 59.67; H, 13.05.

General Procedure for Cycloadditions. To a solution of 0.2 mol of triethylamine and 0.2 mol of olefin in 150 ml of dry hexane at room temperature was added 0.1 mol of acid halide in 20 ml of hexane dropwise over a 0.5-h period.[10] After the addition was complete, the reaction mixture was stirred and refluxed for 2 h. The reaction was monitored by VPC analysis, and upon completion of the reaction, the salt was removed by filtration and the solvent by rotary evaporation. The residue was vacuum distilled.

***endo*-7-Trimethylsilylmethylbicyclo[3.2.0]hept-2-en-6-one (IV).** This cycloadduct of (trimethylsilylmethyl)ketene and cyclopentadiene was obtained at 65 °C (0.05 mm) (65%): IR 1800 and 1610 cm^{-1}; NMR δ 0.20 (s, 9 H), 0.84 (8 lines, 2 H), 2.64 (m, 2 H), 3.80 (m, 3 H), and 5.98 (dm, 2 H); mass spectrum parent peak at *m/e* 194 (theory 194).

Anal. Calcd for $C_{11}H_{18}OSi$: C, 68.04; H, 9.28. Found: C, 67.96; H, 9.52.

***trans*-3-Ethoxy-2-trimethylsilylmethylcyclobutanone (V).** This cycloadduct of (trimethylsilylmethyl)ketene and ethyl vinyl ether was distilled at 40–42 °C (0.05 mm) (60%): IR 1780 cm^{-1}; NMR δ 0.10 (s, 9 H), 0.88 (d, 2 H), 1.22 (t, 3 H), 2.94–3.90 (m, 5 H), and 4.27 (m, 1 H); mass spectrum parent peak at *m/e* 200 (theory 200).

Anal. Calcd for $C_{10}H_{20}O_2Si$: C, 60.00; H, 10.00. Found: C, 59.51; H, 10.82.

2-Chloro-2-methyl-3-trimethylsilylmethylcyclobutanone (VI). The cycloadduct of methylchloroketene and allyltrimethylsilane distilled at 68–70 °C (0.025 mm) (62%): IR 1780 cm^{-1}; NMR (both isomers) δ 0.24 (s, 9 H), 1.04 (8 lines, 2 H), 1.68 and 1.80 (two singlets, ratio 6:1, 3 H), 2.84 (m, 2 H), and 3.40 (m, 1 H).

Anal. Calcd for $C_9H_{17}ClOSi$: C, 52.81; H, 8.31. Found: C, 52.39; H, 8.26.

2,2-Dichloro-3-trimethylsilylmethylcyclobutanone (VII). This cycloadduct of dichloroketene and allyltrimethylsilane was vacuum distilled at 65–66 °C (0.025 mm) (54%): IR 1785 cm^{-1}; NMR δ 0.12 (s, 9 H), 1.20 (8 lines, 2 H), 2.98 (m, 2 H), and 3.40 (m, 1 H).

Anal. Calcd for $C_8H_{14}Cl_2OSi$: C, 42.67; H, 6.22. Found: C, 42.89; H, 6.11.

Acknowledgments. The authors wish to express appreciation to the Robert A. Welch Foundation and the North Texas State University Faculty Research Fund for support of this investigation.

Registry No.—I, 61063-48-7; II, 61063-49-8; III, 18053-95-7; IV, 61063-50-1; V, 61063-51-2; *cis*-VI, 61063-52-3; *trans*-VI, 61063-53-4; VII, 61063-54-5; β-trimethylsilylpropionyl chloride 18187-31-0; 1,4-bis(trimethylsilyl)butane, 18001-81-5; cyclopentadiene, 542-92-7; ethyl vinyl ether, 106-98-9; methylchloroketene, 13363-86-5; allyltrimethylsilane, 762-72-1; dichloroketene, 4591-28-0.

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(10) The use of a stoichiometric amount of triethylamine resulted in the same distribution of products but a lower yield.

Synthesis of 4,5-Dihydroxy-1,3,6,8-tetramethylphenanthrene[1]

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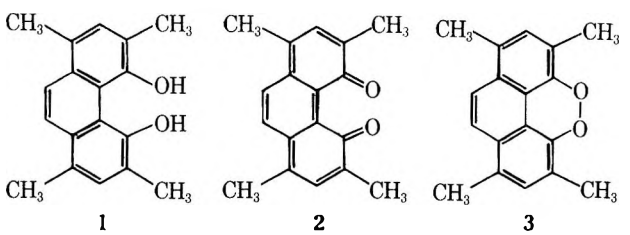
Received July 12, 1976

Bromination of 4,6-dimethyl-3-hydroxybenzoic acid (**4**) yielded exclusively 2-bromo-4,6-dimethyl-3-hydroxybenzoic acid (**5**), which was methylated to yield methyl 2-bromo-4,6-dimethyl-3-methoxybenzoate (**6**). Ullman coupling of **6** afforded dimethyl 6,6′-dimethoxy-3,3′,5,5′-tetramethyldiphenate (**7**). Reduction of **7** with $LiAlH_4$ yielded 2,2′-di(hydroxymethyl)-6,6′-dimethoxy-3,3′,5,5′-tetramethylbiphenyl (**8**), which was converted into 2,2′-di(chloromethyl)-6,6′-dimethoxy-3,3′,5,5′-tetramethylbiphenyl (**9**) via the dimesylate of **8**. A new phenanthrene synthesis which involved treatment of **9** with sodamide in ammonia afforded 4,5-dimethoxy-1,3,6,8-tetramethylphenanthrene (**11**) in almost quantitative yield. Demethylation of **11** by heating with pyridine hydrochloride or with anhydrous sodium sulfide yielded 4,5-dihydroxy-1,3,6,8-tetramethylphenanthrene (**1**), which could not be oxidized to a monomeric quinone.

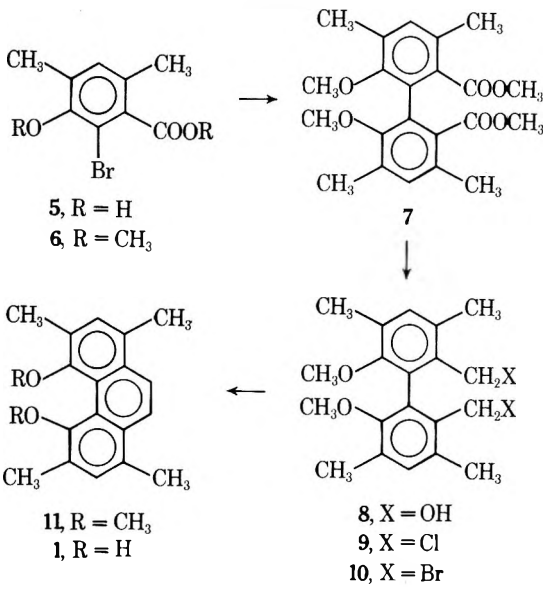
The main objective of this work was to synthesize 4,5-dihydroxy-1,3,6,8-tetramethylphenanthrene (**1**), to see if it could be oxidized to the corresponding quinone, **2**, whose stability with respect to the tautomeric cyclic peroxide, **3**, would be of interest. It was hoped that the methyl groups would decrease the nuclear oxidation encountered in a previous attempt to synthesize 4,5-phenanthrenequinone from 4,5-dihydroxyphenanthrene.[3]



1 **2** **3**

The synthesis of **1** was carried out as outlined in Scheme I. 4,6-Dimethyl-3-hydroxybenzoic acid (**4**), prepared as described[4] except that diethyl acetylenedicarboxylate, made by an improved procedure, was used in place of dimethyl acetylenedicarboxylate, was brominated cleanly to 2-bromo-4,6-dimethyl-3-hydroxybenzoic acid (**5**). This structure is supported by analysis and the fact that acid-catalyzed esterification failed. Hence a highly hindered acid, namely **5**, was at hand.

Scheme I



Methylation of the dipotassium salt of **5** with methyl iodide produced methyl 2-bromo-4,6-dimethyl-3-methoxybenzoate (**6**), which on coupling via the Ullmann reaction afforded dimethyl 6,6′-dimethoxy-3,3′,5,5′-tetramethyldiphenate (**7**). The yields in this coupling reaction were quite erratic (0–75%) as the age and type of copper used evidently affect the course of the reaction (see Experimental Section for details). One side reaction involved reduction of the bromine as in some experiments appreciable quantities of methyl 2,4-dimethyl-5-methoxybenzoate[4] were obtained. Attempts to improve the coupling reaction by utilizing the anhydride[5] in place of **7** were unpromising because of the difficulty of forming the anhydride. Reduction of **7** to **8** and conversion of **8** to **9** via the dimesylate proceeded well.

A new phenanthrene synthesis was developed to convert **9** to **11**. The use of sodamide in liquid ammonia afforded **11** in high yield, although, if a Teflon-coated magnetic stirrer was used in place of a steel stirrer, no appreciable amounts of **11** were obtained. This new phenanthrene synthesis is patterned after the intermolecular coupling of benzyl chloride to stilbene[6] and represents an improved version of the phenanthrene synthesis[7] which involves coupling of a 2,2′-di(bromomethyl)biphenyl to a 9,10-dihydrophenanthrene followed by aromatization.[8] Attempts to utilize the dibromide, **10**, in liquid ammonia as above failed to yield **11**. When the dibromo compound was treated with phenyllithium,[7] only a small yield of 9,10-dihydro-9,10-dimethyl-1,3,6,8-tetramethylphenanthrene was obtained.

The demethylation of **11** to **1** was readily effected by heating at reflux with anhydrous sodium sulfide[9] in *N*-methylpyrrolidone (NMP) or with pyridine hydrochloride[10] at 200–210 °C.

All attempts to oxidize **1** to **2** (or **3**) failed. In many cases (e.g., heating with *o*-chloranil) evidence was obtained that oxidation had occurred but all attempts at isolation of **2** or **3** resulted in the formation of polymeric materials. With most oxidants pronounced color changes occurred. The electrochemical oxidation of **1** and 2,7-dihydroxyphenanthrene were studied briefly using conventional voltammetric techniques.[11] A carbon-paste working electrode, platinum auxiliary electrode, and saturated calomel reference electrode (SCE) were used in the usual manner.[12]

A cyclic voltammogram of 2,7-dihydroxyphenanthrene in aqueous 0.1 M NaOH includes a well-defined oxidation wave with a half-peak potential of +0.10 V vs. SCE. After this initial oxidation, there appears a new, reversible redox couple centered at −0.03 V. It is most likely that the initial oxidation corresponds to formation of a quinone, which undergoes hydroxylation to form the new redox couple. The addition of nucleophiles to quinones to form electroactive products has been well characterized.[13]

A voltammogram of **1** is quite different, with the observation of a single oxidation peak, with the half-peak potential equal to +0.03 V vs. SCE. On the second voltammetric scan, the peak current for this wave is greatly reduced (by about 73%), indicating deposition of electroinactive material on the electrode surface. It is unlikely that this material is intact quinone, since in that case a desorptive reduction should have been observed on the negative-going scan.

One would conclude that although the oxidation of the 2,7-dihydroxy compound is complicated by an addition reaction, it is otherwise well behaved. In contrast, the oxidation of **1** appears to form a highly unstable product which reacts to form an insoluble, nonreducible film on the electrode. The nature of this film is unknown, but its properties are not what one would expect for **2**.

Experimental Section[14]

Diethyl Acetylenedicarboxylate.[15] To a stirred mixture of 120 g of the potassium acid salt of acetylenedicarboxylic acid, 200 ml of ethanol, and 200 ml of benzene in a 1-l. three-neck flask fitted with a dropping funnel, stirrer, and a 1.5 ft × 1 in. packed column topped with a phase-separating head, was added slowly 100 g of concentrated H_2SO_4. The mixture was refluxed for 24 h during which the lower layer in the head was removed (100 ml in all). After a conventional workup 120 g (90%) of colorless diethyl acetylenedicarboxylate, bp 140–142 °C (15 mm), was obtained.

2-Bromo-4,6-dimethyl-3-hydroxybenzoic Acid* (5). In the best of many experiments, 18 g of bromine was added at room temperature to a solution of 18.0 g of **4** in 75 ml of acetic acid. After 20 h the solvent was removed and the reaction product was taken into $(CH_2Cl)_2$ (30 ml), methanol (12 ml), and 1.25 ml of H_2SO_4. After refluxing for 20 h the reaction product was separated into acidic and neutral fractions. From the acid fraction 22.0 g (88%) of **5**, mp 155–156 °C, was obtained. Recrystallization from benzene gave the analytical sample: mp 155.5–157.0 °C; *m/e* 244, 246.[16] When the bromination was carried out at 45–50 °C the yield of **5**, mp 154–155 °C, was 85%.

Methyl 2-Bromo-4,6-dimethyl-3-methoxybenzoate* (6). In the best of many experiments, 40.0 g of **5** was dissolved in 40 ml of water containing 23 g of KOH. The water was removed on a rotary evaporator and the solid salt was stirred for 14 h with 80 ml of DMF and 55 ml of methyl iodide with slight refluxing of methyl iodide. After removal of the DMF under vacuum an ether–benzene solution of the products was extracted with a little aqueous NaOH to remove acidic material. Distillation then yielded 43.3 g (97%) of **6**, bp 169–170 °C (3 mm), as a colorless oil: *m/e* 272, 274; NMR ($CDCl_3$) δ 2.18 (s, 3, $ArCH_3$), 2.27 (s, 3, $ArCH_3$), 3.65 (s, 3, OCH_3), 3.74 (s, 3, OCH_3), 6.95 (s, 1, ArH).

Dimethyl 6,6′-Dimethoxy-3,3′,5,5′-tetramethyldiphenate* (7). Attempts to run the Ullmann coupling reaction with **6** gave results which were difficult to reproduce. In the best of many runs a stirred mixture of 3.50 g of **6**, 3.0 g of copper powder (Venus F-44, American Bronze Powder Co., from a freshly opened can), and 15 ml of freshly distilled DMF was held at reflux for 6 h. After the usual workup crystallization of the reaction mixture products from petroleum ether afforded 2.0 g (83%) of **7**: mp 122–123 °C; *m/e* 386; NMR δ 2.32 (s, 12, $ArCH_3$), 3.45 (s, 6, OCH_3), 3.55 (s, 6, OCH_3), 7. (s, 2, ArH) (Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.4; H, 6.8. Found: C, 68.8; H, 7.0). However, in other similar runs with Venus F-44 copper and other copper (some activated by various treatments) yields varied from 0 to 75%. The most frequent by-product was methyl 2,4-dimethyl-5-methoxybenzoate, a reduction product.

2,2′-Di(hydroxymethyl)-6,6′-dimethoxy-3,3′,5,5′-tetramethylbiphenyl* (8). Reduction of **7** with $LiAlH_4$ in ether afforded **8**, mp 168–169 °C, *m/e* 330, in almost quantitative yields in small (0.5 g) and relatively large (10 g) runs.

2,2′-Di(chloromethyl)-6,6′-dimethoxy-3,3′,5,5′-tetramethylbiphenyl* (9). In a typical reaction a solution of 3.00 g of **8** and 4.2 ml of triethylamine in 45 ml of benzene was treated with 1.8 ml of methanesulfonyl chloride for 3 h at room temperature. After the benzene layer had been washed with water, about 0.3 g of Aliquat-

336,[17] 45 ml of saturated KCl solution, and some solid KCl were added. After stirring for 24 h at room temperature the benzene solution was passed through a short column of alumina (to remove the Aliquat-336). After the usual workup there was obtained 3.0 g (90%) of **9**:[18] mp 175–176 °C; *m/e* 366, 368; NMR δ 2.33 and 2.46 (s, 6 each, $ArCH_3$), 3.47 (s, 6, OCH_3), 4.34 (s, 4, CH_2Cl), 7.1 (s, 2, ArH).

2,2′-Di(bromomethyl)-6,6′-dimethoxy-3,3′,5,5′-tetramethylbiphenyl* (10). In reactions involving KBr similar to the above preparation of **9**, about 80% yields of **10**, mp 145–146 °C, *m/e* 454, 456, 458, after recrystallization of the distilled product from benzene–petroleum ether were obtained.

4,5-Dimethoxy-1,3,6,8-tetramethylphenanthrene[4] (11). In the best of many experiments sodium amide was prepared from 2 g of sodium in 100 ml of liquid NH_3.[19] This mixture (stirred with an iron stirrer) was cooled to about −70 to −65 °C by an external dry ice bath and then 150 ml of toluene followed (after cooling) by 5.8 g of **9** were added. After 2 h at −70 to −65 °C the cooling bath was removed and the reaction mixture was left under reflux (dry ice condenser) overnight. After the usual workup (initial treatment of the reaction mixture with 20 g of solid NH_4Cl) the crude product showed only one spot on TLC. Crystallization from ethanol afforded 4.45 g (95%) of **11**, mp 129–130 °C (lit.[4] mp 130–131 °C).

9,10-Dihydro-9,10-dimethoxy-1,3,6,8-tetramethylphenanthrene (12). A solution of 1.70 g of **10** in 10 ml of ether was added to the C_6H_5Li prepared from 0.2 g of Li and 1.75 g of C_6H_5Br in ether. After 2 h at reflux the reaction products were chromatographed over silica gel to yield a small amount of **12**, mp 101–102 °C *m/e* calcd 296.1776, found[16] 296.1782.

4,5-Dihydroxy-1,3,6,8-tetramethylphenanthrene (1). In the best of several attempts at demethylation of **11**, a solution of 1.0 g of **11** and 4.0 g of Na_2S[9] (dried at room temperature to constant weight in a desiccator over P_2O_5) in 10 ml of pure NMP[20] was held at reflux for 3.5 h. The reaction mixture was poured into water and the product isolated as usual to give a slightly yellow solid in 91% yield (in other attempts on heating with $C_5H_5N{\cdot}HCl$[10] high yields of similar product having darker colors were obtained). Various samples of this material melted in the 240–249 °C range. The analytical sample [mp 246.5–248.0 °C; *m/e* 266; NMR (Me_2SO-d_6) δ 2.40 (s, 6, $ArCH_3$, C_3, C_6), 2.59 (s, 6, $ArCH_3$, C_1, C_8), 7.43 (s, 2, ArH), 7.70 (s, 2, ArH)] was obtained by recrystallization from ethanol. The diol, **1**, was converted into the corresponding diacetate:* mp 224–225 °C; IR (KBr) 1750, 1760, cm^{-1}; NMR δ 2.23 (s, 6, $ArCH_3$), 2.30 (s, 6, $ArCH_3$), 2.65 (s, 6, CH_3CO_2), 7.26 (s, 2, ArH), 7.71 (s, 2, ArH).

Registry No.—**1**, 60935-38-8; **1** diacetate, 60935-46-8; **4**, 50790-68-6; **5**, 60935-39-9; **6**, 60935-40-2; **7**, 60935-41-3; **8**, 60935-42-4; **9**, 60935-43-5; **10**, 60935-44-6; **11**, 50790-66-4; **12**, 60935-45-7.

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(2) Postdoctoral Research Associate.
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(14) All melting points and boiling points are uncorrected. IR spectra were recorded using a Perkin-Eimer Infracord using NaCl disks (neat liquids) or KBr pellets. NMR spectra were recorded on a Varian A-60 instrument and are reported as δ units (Me_4Si, 0) in $CDCl_3$ unless otherwise noted. The phrase "worked up in the usual way" means that an ether–benzene solution of the products was washed with dilute acid and/or base, with saturated NaCl solution. The ether–benzene solution was then filtered through a cone of $MgSO_4$ and the solvent was removed on a rotary evaporator. All compounds marked with an asterisk gave elemental analytical data consistent (±0.3%) with the theoretical values, which were submitted for review. Analyses were by M-H-W Laboratories, Garden City, Mich.
(15) The present procedure represents an improvement over that described in "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 329.
(16) Mass spectra were determined on an Associated Electrical Industries, Ltd., instrument by Mr. R. Weisenburger.
(17) Aliquat 336 is methyltricaprylammonium chloride, obtainable from the McKerson Corp., Minneapolis, Minn.
(18) The analytical sample was kindly prepared by Dr. R. Kannan.
(19) The technique and apparatus are described in M. S. Newman, "An Advanced Organic Laboratory Course", Macmillan, New York, N.Y., 1972, p 145.
(20) We thank the General Aniline and Film Corp. for a generous gift of NMP.

Synthesis and Properties of the Vicinal Trans Dihydrodiols of Anthracene, Phenanthrene, and Benzo[*a*]anthracene

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Received August 6, 1976

The vicinal, trans, non-K-region dihydrodiols of anthracene, phenanthrene, and benzo[*a*]anthracene have been synthesized by a common approach involving bromination, dehydrobromination, and hydrolysis of the appropriate tetrahydrodiesters of the parent aromatic hydrocarbons. Utilization of tetrahydrodiacetate derivatives proved important for successful preparation of dihydrodiols in angular benzo rings, whereas tetrahydrodibenzoates served as appropriate precursors in all other cases. The NMR spectra of the dihydrodiols and dihydrodioldiesters are discussed. Of the dihydrodiols, only 3,4-dihydroxy-3,4-dihydrobenzo[*a*]anthracene (**9k**) could be metabolically activated to species highly mutagenic to bacteria, although 8,9-dihydroxy-8,9-dihydrobenzo[*a*]anthracene and 10,11-dihydroxy-10,11-dihydrobenzo[*a*]anthracene could be activated to weakly mutagenic species. The much greater biological activity of metabolically activated **9k** is in accord with the enhanced reactivity predicted by PMO calculations for the benzylic positions of many intermediate diol epoxides in which the oxirane ring occupies a bay region.

Vicinal, trans dihydrodiols, both at K-region and non-K-region (**1**, Scheme I) positions, are common metabolites of polycyclic aromatic hydrocarbons in mammals.[1] Their formation consists of initial oxidation of the hydrocarbons to arene oxides[2] which are then hydrated by the enzyme epoxide hydrase to trans dihydrodiols that are often optically active.[3] Recently, substantial interest has developed in dihydrodiols since they can be metabolically activated to diol epoxides[4] (**2**,

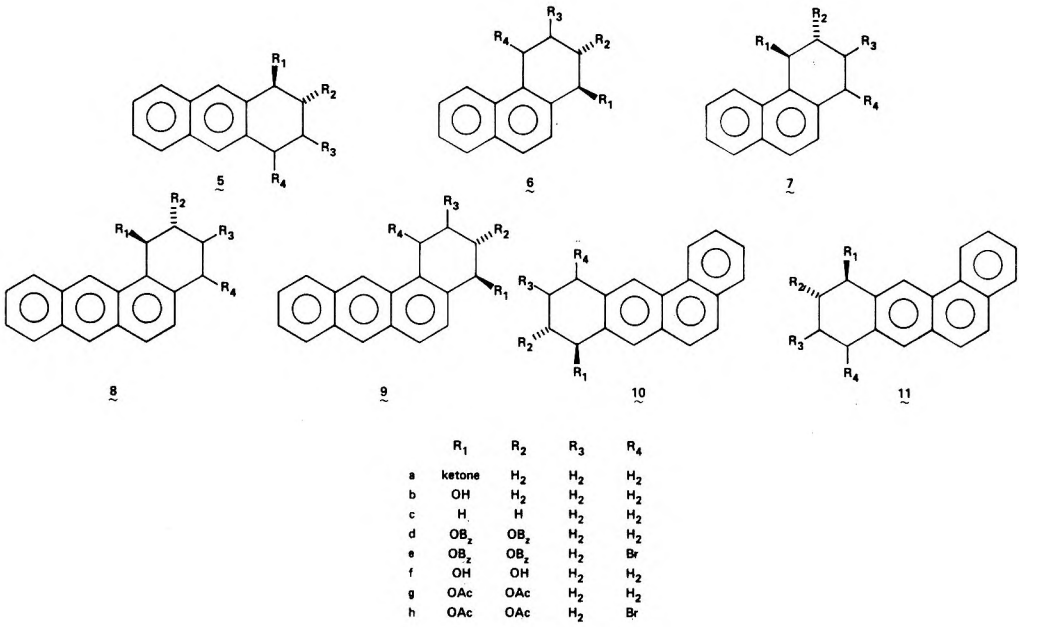


Figure 1.

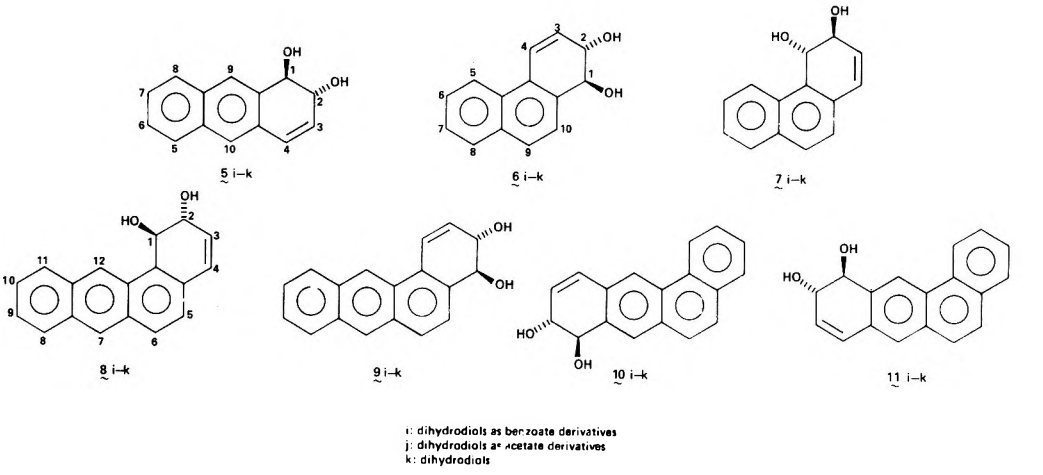
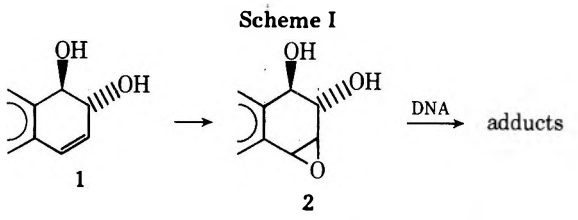
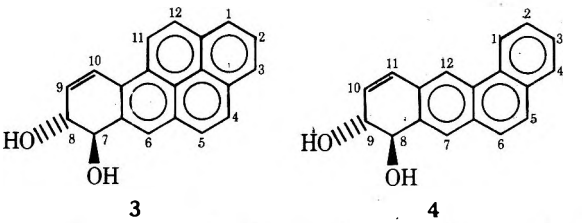


Figure 2.

Scheme I



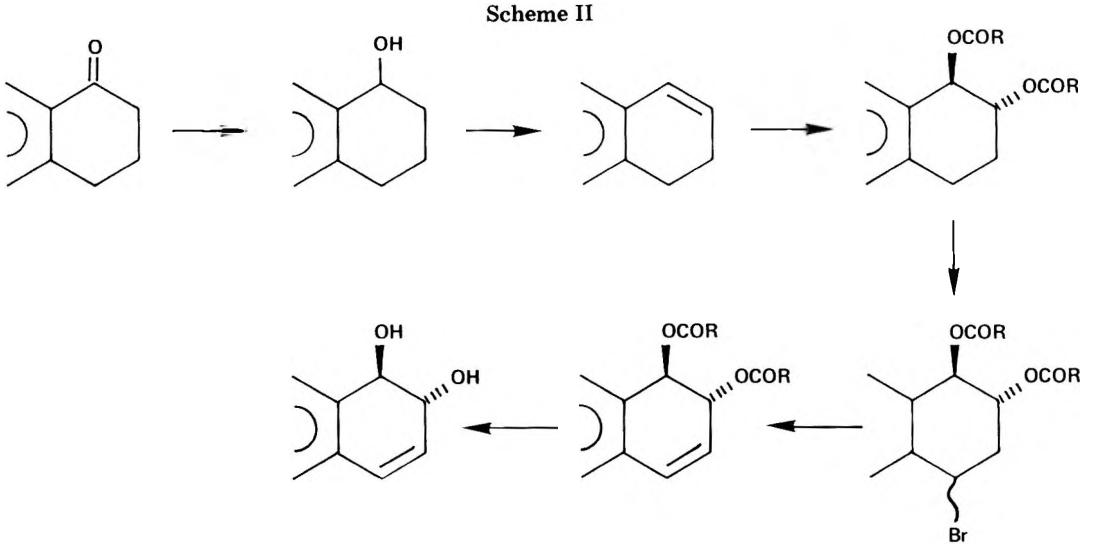


Scheme I). Stereoisomeric diol epoxides of *trans*-7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene (**3**),[4a,5] for example, appear to account for much of the covalent binding of benzo[*a*]pyrene (BP) to the DNA of mouse skin in vivo[6] and are highly mutagenic toward bacterial[7a–e] and mammalian cells.[4b,7a–d,f] In addition, **3** is a potent transforming agent toward cultured mammalian cells which possess drug metabolizing activity.[8] These results, taken together with the facts that BP 7,8-oxide[9] and BP 7,8-dihydrodiol (**3**)[10] are potent carcinogens on mouse skin, strongly indicate that BP 7,8-diol-9,10-epoxides may be the long sought ultimate carcinogenic forms of the ubiquitous environmental carcinogen BP.

At present, relatively little information is available as to which positional isomers of dihydrodiols from a given hydrocarbon can be metabolically activated to diol epoxides with high biological activity. Although BP 7,8-dihydrodiol (**3**) can be activated to potent mutagens, BP 4,5-, 9,10-, and 11,12-dihydrodiols are weak or inactive as mutagens after metabolic activation.[11] For benzo[*a*]anthracene (BA), the 8,9-dihydrodiol (**4**) could be activated to mutagens whereas the 5,6- (K-region) dihydrodiol could not.[7e] The present study describes the synthesis of vicinal, trans dihydrodiols of anthracene, phenanthrene, and benzo[*a*]anthracene at non-K-region positions (Figure 2) to enable the examination of their carcinogenicity and metabolic activation to mutagens. The procedure is general and can be applied to a wide range of unsubstituted hydrocarbons. Synthetic K-region dihydrodiols are available through existing methods (cf. ref 12).

Previously, trans dihydrodiols were prepared by metal hydride reduction of the corresponding *o*-quinones.[13] However, recent application of the approach to the non-K-region trans dihydrodiols of anthracene and phenanthrene resulted in very low yields of the desired products.[14] More recently, *cis*- and *trans*-7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene have

Scheme II



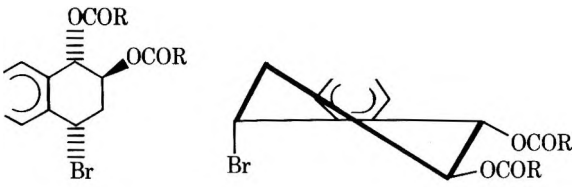
been prepared by an alternate approach involving bromination, dehydrobromination, and hydrolysis of vicinal tetrahydrodiesters of aromatic hydrocarbons.[5b,15] The present study establishes the generality of the latter approach, as well as modifications that are occasionally required.

Results and Discussion

The synthetic sequence utilized for the preparation of the dihydrodiols is outlined in Scheme II. The ketonic starting materials (**5a–11a**, Figure 1) are available by succinylation of smaller aromatic hydrocarbons, reduction of the resulting keto acids to aryl butyric acids, and cyclization. Their conversion to the desired dihydroaromatic hydrocarbons, previously described for **5c–7c**, could be routinely achieved by reduction of the ketones to alcohols with $NaBH_4$ in methanol and dehydration of the alcohols with catalytic quantities of HCl in glacial HOAc.[16] The alkenes could be isolated in good yield (80–90%), but in some cases they appear to be air sensitive in solution. 3,4-Dihydrobenzo[*a*]anthracene (**8c**) appeared to be especially labile during purification attempts and was used without purification.

Synthesis of Dihydrodiols from Dihydroaromatics. The dihydroaromatic compounds, **5c–11c**, were converted to trans tetrahydro diesters via the Prévost reaction, with either silver benzoate (**5d, 7d–11d**) or silver acetate (**6g**) and iodine in benzene.[17] Yields ranged from 32 to 76% for the reactions with silver benzoate whereas the trans diacetate **6g** was obtained in 51% yield. An attempt to prepare diacetate **9g** by the Prévost reaction, however, was not successful. Thus, the trans diacetates **7g, 8g,** and **9g** were prepared by the sequence dibenzoate → diol → diacetate (the reason for preparing dibenzoates in some cases and diacetates in others will be described later). The dibenzoates were hydrolyzed with NaOH in methanolic THF and the resulting diols were acetylated with Ac_2O/pyridine. Good overall conversions of the dibenzoates to the diacetates were achieved in that fashion (73–82%).

Bromination of the trans diesters was effected with *N*-bromosuccinimide (NBS) in CCl_4 at temperatures below 70 °C. The yields of bromo diesters were high in most cases, but mixtures of stereoisomers usually resulted. The crude reaction products were obtained as oils, but purification was readily achieved by the addition of ether, which precipitates the major isomer. In those cases (**5e, 6h, 9h, 10e, 11e**) where the nuclear magnetic resonance (NMR) spectrum permitted an assignment of structure (see Experimental Section for NMR data), the major isomer possessed the relative stereochemistry shown in **12**, where the benzylic ester and the bromine atom are cis. As indicated, the predominant conformation of **12** is that in



12

which the bromine atom is quasi-axial. This observation is in accord with previous results obtained in the bromination of analogous bromohydrin esters with NBS.[16a] Only for the bromination product of **7g** and **8g** were NMR data inadequate to permit an unequivocal structure assignment. In these cases, the benzylic ester moieties (groups R_1) in **7** and **8** occupy "bay region" positions,[18] and steric interactions force them to be quasi-axial, with consequent effects upon the conformation of the molecules and their NMR spectra.[14]

All bromo diesters were thermally dehydrobrominated in boiling toluene or xylene to which $NaHCO_3$ had been added to neutralize HBr. The water formed was continually removed as an azeotrope. Yields varied from 25 to 65%. The use of bromodibenzoates in some series (**5, 10, 11**) and bromodiacetates in others (**6, 7, 8, 9**) requires comment. It appears that bromodibenzoates are reliable substrates for thermal elimination of HBr when the ring being modified has no "bay region" positions. Thus, dehydrobromination in systems **5, 10,** and **11** proceeds in over 80% yield. However, attempts to effect the analogous conversions, **6e → 6i** and **7e → 7i**, in the phenanthrene series were unsuccessful. Thus, **6i** could not be isolated after pyrolysis of **6e**, and a very low yield of **7i** was obtained from **7e**. Respectable yields of the desired dihydrodiol diesters **6j** and **7j** were obtained, however, on thermal dehydrohalogenation of the analogous bromodiacetates. Although the basis for the observed difference in behavior is not known, there is evidence that the desired dihydrodiol dibenzoates were formed from **6e** and **7e**, but aromatized under the reaction conditions by further elimination of benzoic acid since fully aromatic products were isolated.

An alternative procedure for the elimination of HBr proved effective for the preparation of dihydrodiol diacetates **7j** and **8j**. In these cases, treatment of the bromo diesters with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in anhydrous THF at 0 °C afforded high yields of the desired products. This alternative is especially valuable in the case of **8j**, where the yield obtained thermally is low (25%). Reaction of the crude bromo diester mixture, rather than the pure isomer, also resulted in higher yields of the dihydrodiol diesters (based upon tetrahydrodiester) in the syntheses of **5i** and **7j** by the DBN route.

Table I. NMR Spectra of Dihydrodiol Diesters[a]

Registry no.	Compd	Carbinol ester hydrogens		Vinyl hydrogens		Acetyl hydrogens	Aromatic hydrogens
		Benzylic	Nonbenzylic	Benzylic	Nonbenzylic		
60967-83-1	*trans*-1,2-Dibenxoyloxy-1,2-dihydroanthracene (**5i**)	H_1 6.78	H_2 6.07 ($J_{1,2}$ = 7.0; $J_{2,3}$ = 3.7; $J_{3,4}$ = 9.8; $J_{2,4}$ = 1.2)	H_4 6.89	H_3 6.20		7.27–8.18
60890-34-8	*trans*-1,2-Diacetoxy-1,2-dihydrophenanthrene (**6j**)	H_1 6.29	H_2 5.61 ($J_{1,2}$ = 5.6; $J_{2,3}$ = 4.2; $J_{3,4}$ = 10.0)	H_4[b]	H_3 6.22	2.11, 2.04	7.43–8.23 (6 H, H_4[b])
61009-15-2	*trans*-3,4-Diacetoxy-3,4-dihydrophenanthrene (**7j**)	H_4 6.80	H_3 5.40 ($J_{3,4}$ = 1.6; $J_{2,3}$ = 5.4; $J_{1,2}$ = 9.6)	H_1 6.88	H_2 6.05	2.02, 1.98	7.27–8.09
60967-84-2	*trans*-1,2-Diacetoxy-1,2-dihydrobenzo[*a*]anthracene (**8j**)	H_1 6.95	H_2 5.47 ($J_{1,2}$ = 1.8; $J_{2,3}$ = 5.5; $J_{3,4}$ = 9.5; $J_{1,3}$ = 0.8)	H_4 6.87	H_3 6.31	1.99, 1.94	7.24–8.10 (6 H) 8.40, 8.50 (H_7, H_{12})
60967-85-3	*trans*-3,4-Diacetoxy-3,4-dihydrobenzo[*a*]anthracene (**9j**)	H_4 6.37	H_3 5.69 ($J_{3,4}$ = 6.1; $J_{2,3}$ = 4.3; $J_{1,2}$ = 10.4; $J_{1,3}$ = 1.1)	H_1[b]	H_2 6.28	2.10, 2.02	7.2–8.2 (6 H, H[b]) 8.64, 8.34 (H_7, H_{12})
60967-86-4	*trans*-8,9-Dibenzoyloxy-8,9-dihydrobenzo[*a*]anthracene (**10i**)	H_8 6.85	H_9 6.14 ($J_{8,9}$ = 7.0; $J_{9,10}$ = 3.6; $J_{10,11}$ = 9.3; $J_{9,11}$ = 1.2)	H_{11} 6.95	H_{10} 6.24		7.2–8.2 (16 H) 8.45 (H_{12}), 8.65 (H_1)
60967-87-5	*trans*-10,11-Dibenzoyloxy-10,11-dihydrobenzo[*a*]anthracene (**11i**)	H_{11} 6.84	H_{10} 6.07 ($J_{10,11}$ = 6.2; $J_{9,10}$ = 4.0; $J_{8,9}$ = 9.8; $J_{8,10}$ = 1.0)	H_8 6.91	H_9 6.26		7.2–8.2 (16 H) 8.56 (H_1), 8.71 (H_{12})

[a] NMR spectra were recorded in $CDCl_3$, with Me_4Si as internal standard. For 5i, 6j, and 7j spectra were recorded at 220 MHz; for 8j, 9j, 10i, and 11i, spectra were recorded at 100 MHz. [b] The resonance of the indicated bay region hydrogens occurs within the aromatic absorption envelope owing to edge deshielding by the proximate aromatic ring.

Table II. NMR Spectra of Dihydrodiols[a]

Registry no.	Compd	Carbinol hydrogens		Vinyl hydrogens		Aromatic hydrogens
		Benzylic	Nonbenzylic	Benzylic	Nonbenzylic	
4841-37-6	*trans*-1,2-Dihydroxy-1,2-dihydroanthracene (**5k**)	H_1 4.83	H_2 4.42 ($J_{1,2}$ = 10.0; $J_{2,3}$ = 2.2; $J_{3,4}$ = 9.7; $J_{2,4}$ = 2.2; $J_{1,Ar}$ = 1.3[c])	H_4 6.60	H_3 6.02	7.3–8.1
60917-41-1	*trans*-1,2-Dihydroxy-1,2-dihydrophenanthrene (**6k**)	H_1 4.91	H_2 4.50 ($J_{1,2}$ = 11.4; $J_{2,3}$ = 2.3; $J_{3,4}$ = 10.4; $J_{2,4}$ = 2.3)	H_4 7.25	H_3 6.21	7.4–8.3
569-20-0	*trans*-3,4-Dihydroxy-3,4-dihydrophenanthrene (**7k**)	H_4 5.37	H_3 4.36 ($J_{3,4}$ = 2.0; $J_{2,3}$ = 5.4; $J_{1,2}$ = 9.6; $J_{2,4}$ = 10.)	H_1 6.69	H_2 6.22	7.3–8.4
60967-88-6	*trans*-1,2-Dihydroxy-1,2-dihydrobenzo[*a*]anthracene (**8k**)	H_1 5.56	H_2 4.45 ($J_{1,2}$ = 1.7; $J_{2,3}$ = 5.4; $J_{3,4}$ = 9.5; $J_{1,3}$ = 0.8)	H_4 6.73	H_3 6.30	7.27–8.30 (6 H); 8.48, 8.93 (H_7, H_{12})
60967-89-7	*trans*-3,4-Dihydroxy-3,4-dihydrobenzo[*a*]anthracene (**9k**)	H_4 4.96	H_3 4.56 ($J_{3,4}$ = 11.5; $J_{2,3}$ = 2.3; $J_{1,2}$ = 10.1; $J_{1,3}$ = 2.3)	H_1[b]	H_2 6.28	7.30–8.30 (6 H, H_1[b]); 8.86, 8.52 (H_7, H_{12})
34501-24-1	*trans*-8,9-Dihydroxy-8,9-dihydrobenzo[*a*]anthracene (**10k**)	H_8 4.90	H_9 4.50 ($J_{8,9}$ = 10.0; $J_{9,10}$ = 2.0; $J_{10,11}$ = 10.0; $J_{9,11}$ = 2.4)	H_{11} 6.75	H_{10} 6.10	7.55–8.20 (6 H); 8.52 (H_{12}); 8.80 (H_1)
60967-90-0	*trans*-10,11-Dihydroxy-10,11-dihydrobenzo[*a*]anthracene (**11k**)	H_{11} 4.75	H_{10} 4.50 ($J_{10,11}$ = 10.4; $J_{9,10}$ = 2.2; $J_{8,9}$ = 10.0; $J_{8,10}$ = 2.4)	H_8 6.63	H_9 6.06	7.5–8.0 (6 H); 8.77 (H_1); 8.95 (H_{12})

[a] Spectra were recorded in acetone-d_6, with Me_4Si as internal standard. All spectra were recorded at 100 MHz except for that of 8k, which was recorded at 220 MHz. [b] The resonance of the indicated bay region hydrogens occurs within the aromatic absorption envelope. [c] Due to sharp signals for H_3, $J_{1,Ar}$ probably represents coupling to H_9 which suggests that H_1 is predominantly axial.

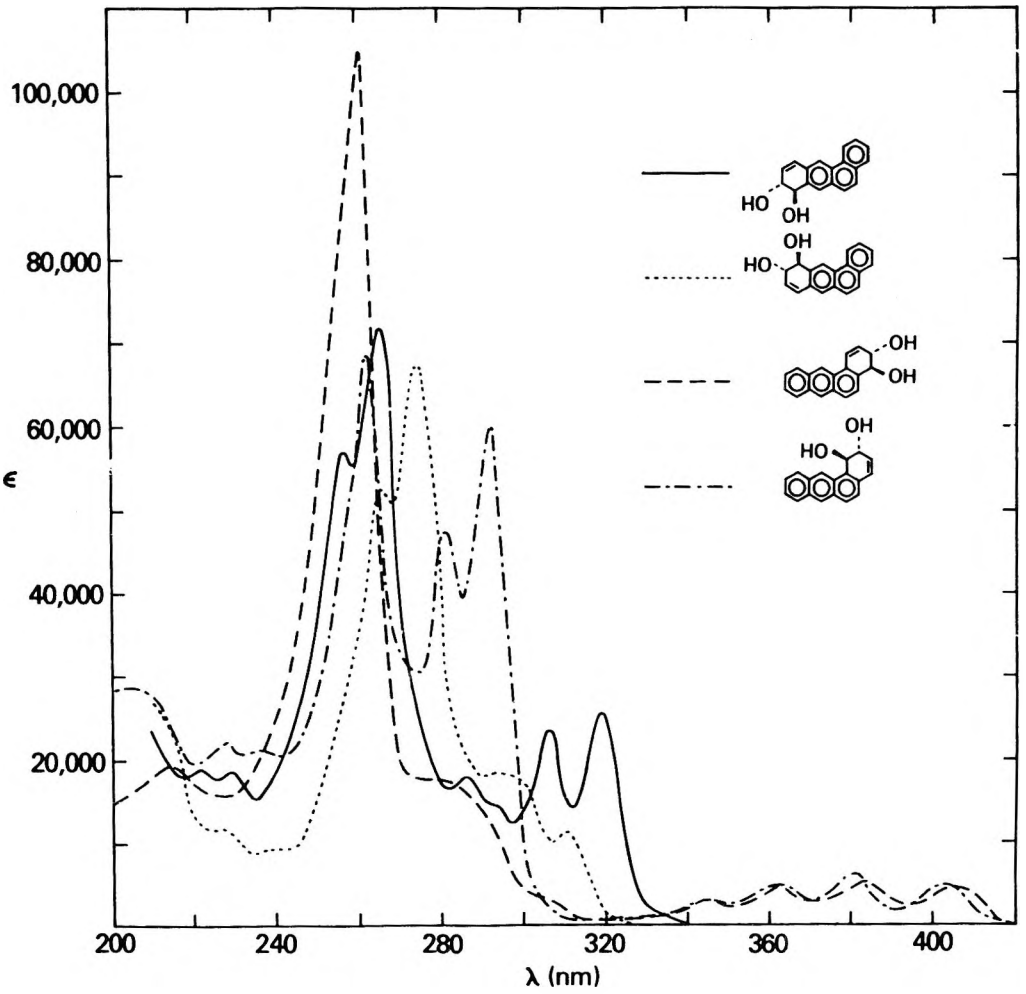


Figure 3. Ultraviolet spectra (in absolute EtOH) of the vicinal, trans, non-K-region dihydrodiols of benzo[*a*]anthracene. Selected maxima and extinction coefficients are cited in the Experimental Section. For comparison, the K-region isomer, *trans*-5,6-dihydroxy-5,6-dihydrobenzo[*a*]anthracene, had the following spectrum in absolute EtOH (λ_{max}, ϵ_{max}): 216 (33 100); 247 (32 200); 258 (39 800); 266 (41 800); 298 (16 400); 309 (14 800); 336 (700).

The conditions required for hydrolysis of the dihydrodiol diesters to dihydrodiols depended upon whether benzoates or acetates were hydrolyzed. Thus, conversion of the dihydrodiol diacetates **6j**, **7j**, **8j**, and **9j** to the corresponding dihydrodiols was readily achieved with dry ammonia in methanol. Hydrolysis of the dibenzoates was achieved with sodium methoxide in THF/MeOH. Yields of the dihydrodiols ranged from 54 to 89%.

Spectral Properties of the Dihydrodiols and Dihydrodiol Diesters. The NMR spectra of the dihydrodiol diesters and dihydrodiols are recorded in Tables I and II. Noteworthy are the substantial downfield shifts expected for protons in bay regions of the dihydrodiols and their diesters (H_4 in **6j**, **6k** and **7j**, **7k**; H_1 in **8j**, **8k** and **9j**, **9k**). Further, the coupling constants between the carbinol hydrogens in the bay region dihydrodiols (J_{diol}) and dihydrodiol diesters (J_{ester}) are very low when they are in bay regions (J_{diol} = 1.8 ± 0.2; J_{ester} = 1.7 ± 0.1 Hz). The values for the bay region substituted compounds are those expected for a predominant quasi-diaxial relationship of the diol and diester functionalities. Further evidence for the quasi-axial conformation of the benzylic hydroxyl groups in the bay region diols is the observed $J_{2,4}$ = 1.0 Hz for **7k** and $J_{1,3}$ = 0.8 Hz for **8k**. This conformation-dependent W coupling was not observed in the other cases. The large values of J_{diol} (10.7 ± 0.8 Hz) for the non-bay region dihydrodiols indicate that the vicinal hydroxyl groups are predominantly quasi-diequatorial. The decrease of this coupling constant in the dihydrodiol diesters (J_{ester} = 6.4 ± 0.8 Hz) is consistent with a conformational change toward a diaxial relationship of these substituents and is in accord with previous observations.[14]

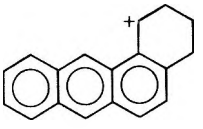
The ultraviolet spectra of the four synthetic non-K-region *trans*-benzo[*a*]anthracene dihydrodiols are shown in Figure 3. The UV spectrum of **10k** agrees with that reported by Sims for BA 8,9-dihydrodiol isolated from metabolism studies.[19] Dihydrodiols substituted in the angular ring of BA (**8k** and **9k**) are yellow and exhibit long-wavelength absorptions in the visible region (~345–405 nm) that are lacking in **10k** and **11k**. In **8k** and **9k**, the double bonds of the dihydrodiols are conjugated with an anthracene nucleus whereas in **10k** and **11k**, they are conjugated with a phananthrene nucleus. The larger bathochromic shifts of the relatively weak p bands (ϵ ~4000–7000) observed for these vinyl anthracene derivatives are consistent with the larger shifts generally observed upon conjugation with the linearly annelated aromatic hydrocarbons (acenes) as contrasted with the shifts observed for conjugation with the angularly annelated aromatic hydrocarbons (phenes).[20]

Mutagenesis of Metabolically Activated Dihydrodiols. Neither the dihydrodiols synthesized in this work nor *trans*-1,2-dihydroxy-1,2-dihydronaphthalene nor the K-region trans dihydrodiols of phenanthrene or BA were mutagenic toward the histidine-dependent bacterial strain TA 100 without metabolic activation.[21] However, three of these dihydrodiols, the non-K-region dihydrodiols **9k**, **10k**, and **11k** of BA, can be activated to mutagenic metabolites.[22] Significantly, the activity within the group of dihydrodiols which could be activated varies greatly. The metabolites of the BA 8,9- and

10,11-dihydrodiols are only weakly mutagenic, in contrast to the metabolites of the BA 3,4-dihydrodiol which are *ten times* as mutagenic as the metabolites obtained from benzo[a]anthracene.

The results of the testing of this complete series of dihydrodiols from several aromatic hydrocarbons allow structure–activity relationships to be assessed. First, it is important that the vicinal diol occupy a non-K region since the K-region dihydrodiols could not be activated. This is likely a consequence of the fact that all unsaturation in the K-region dihydrodiols is fully aromatic, whereas the non-K-region dihydrodiols possess a nonaromatic double bond in the substituted ring. Secondly, the structure of the highly mutagenic (after activation) BA 3,4-dihydrodiol is related to that of BP 7,8-dihydrodiol (**3**) in that both contain double bonds in "bay regions" of the hydrocarbons. In the latter case, the 9,10-epoxides of **3** are known to be formed metabolically[4b,c] and are potent mutagens.[4b,7] By analogy, the 1,2-epoxides of BA 3,4-dihydrodiol are probably the mutagenic metabolites formed from **9k.** Yet, the inability to activate the phenanthrene 1,2-dihydrodiol (**6k**) suggests that the presence of a bay region double bond in the substrate is insufficient to result in the formation of potent mutagens.

The high mutagenicity of the activated BA 3,4-dihydrodiol (**9k**) and BP 7,8-dihydrodiol (**3**) compared to the weak or absent mutagenicity of metabolites from the other dihydrodiols tested can be understood when it is recognized that C_1 of the 1,2-epoxide of BA 3,4-dihydrodiol and C_{10} of the 9,10-epoxide of BP 7,8-dihydrodiol are expected to be especially reactive positions. Thus, perturbational molecular orbital (PMO) calculations[23] indicate that carbonium ions **13** and **14,** with π systems identical with those which would be



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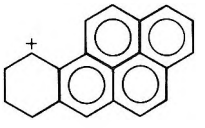

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formed by heterolytic cleavage of the oxirane C–O bonds at C_1 and C_{10}, respectively, are considerably more stabilized by delocalization relative to their neutral precursors than are the carbonium ions analogous to those which would be formed from the diol epoxides of the other dihydrodiols examined. The calculations indicate that bay region carbonium ions are often especially stabilized by delocalization relative to their neutral precursors. The greater stability of these carbonium ions should result in an enhanced S_N1 component of reaction of the precursor diol epoxides and also should permit more binding to relatively weak nucleophilic sites such as those found in DNA and other macromolecules. The synthesis of the diol epoxides of the BA non-K-region dihydrodiols is in progress.

Since submission of this manuscript, the BA dihydrodiols **9k, 10k,** and **11k** have been converted into the three diastereomeric pairs of diol epoxides by introduction of the oxirane ring (cf. ref 5a) at the double bond of each dihydrodiol.[29] These pairs of diastereomers differ in that the oxirane ring is either cis or trans to the benzylic hydroxyl group. As had been previously shown for the diol epoxides of **3,**[5a] the cis isomers of the BA diol epoxides are substantially more reactive toward *p*-nitrothiophenolate in *tert*-butyl alcohol when compared to the corresponding trans isomers, presumably owing to anchimeric assistance to opening of the oxirane ring by the proximate benzylic hydroxyl group. Furthermore, the diol epoxides of **9k,** in which the oxirane ring forms part of a "bay region", are the most reactive as expected from the PMO calculations.[30] As anticipated from the metabolic activation studies on the BA dihydrodiols,[22] the pair of diol epoxides from **9k** are much more mutagenic than are the pairs from **10k** and **11k.**[31]

Experimental Section

Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Proton magnetic resonance spectra were recorded on Varian A-60, HA-100, and 220-MHz spectrometers. Unless noted otherwise, $CDCl_3$ was used as solvent. Coupling constants (J) are recorded in hertz and chemical shifts in parts per million (δ) with tetramethylsilane as internal standard. Melting points are uncorrected. The designations α and β are used to indicate relative stereochemistry.

***trans*-1,2-Dibenzoyloxy-1,2,3,4-tetrahydroanthracene (5d).** Silver benzoate (8.60 g, 0.0376 mol) and iodine (4.45 g, 0.0175 mol) were added to dry benzene (70 ml). The mixture was stirred under N_2 until the red color disappeared. 1,2-Dihydroanthracene (3.0 g, 0.0167 mol)[24] was added and the mixture was stirred at 25 °C for 15 min, then was refluxed for 2.5 h. The reaction mixture was gravity filtered hot, and the filtrate was evaporated to leave a viscous orange oil that was crystallized from $CHCl_3$/petroleum ether to yield a light yellow solid (5.32 g, 76%). Recrystallization from ethanol gave **5d** as a white solid: mp 124–125.5 °C; ^{1}H NMR (60 MHz) δ7.2–8.2 (16 H, m), 6.70 (H_1, d), 5.49–5.77 (H_2), 3.03–3.40 (2 H), 2.13–2.60 (2 H), $J_{1,2}$ = 6 Hz.

4β-Bromo-1β,2α-dibenzoyloxy-1,2,3,4-tetrahydroanthracene (5e). A mixture of CCl_4 (50 ml), *N*-bromosuccinimide (NBS, 116 mg, 0.652 mmol), **5d** (250 mg, 0.592 mmol), and α,α'-azoisobutyronitrile (AIBN, 5 mg) was maintained at ca. 65 °C with a heat lamp for 15 min while a stream of N_2 was passed through the solution. The mixture was cooled and filtered, and the CCl_4 was removed under reduced pressure to leave a yellow, oily residue that crystallized upon addition of ether/hexane (130 mg, 44%). Recrystallization from benzene/hexane gave the bromo diester **5e** as a white solid: mp 137–138 °C; ^{1}H NMR (100 MHz) δ 7.25–8.25 (16 H), 6.85 (H_1), 6.18 (H_2), 5.88 (H_4), 3.05 ($H_{3\beta}$), 2.71 ($H_{3\alpha}$) ($J_{1,2}$ = 8.0, $J_{2,3\alpha}$ = 10.1, $J_{2,3\beta}$ = 3.8, $J_{3\alpha,3\beta}$ = 14.5, $J_{3\alpha,4}$ = $J_{3\beta,4}$ = 4.6, $J_{1,x}$ = 1.0 Hz).

Anal. Calcd for $C_{28}H_{21}O_4Br$: C, 67.07; H, 4.22. Found: C, 66.70; H, 4.36.

***trans*-1,2-Dibenzoyloxy-1,2-dihydroanthracene (5i).** To a stirred mixture of boiling xylene (20 ml) and anhydrous $NaHCO_3$ (250 mg) was added bromodibenzoate **5e** (65 mg, 0.129 mmol). The mixture was heated, under Ar, for 15 min, with continuous removal of water. The mixture was cooled and filtered, and the xylene was removed under reduced pressure to leave a white solid that was recrystallized from ether to give **5i** (24 mg, 44%): mp 169–171 °C; ^{1}H NMR (see Table I). Anal. Calcd for $C_{28}H_{20}O_4$: C, 79.98; H, 4.79. Found: C, 79.71; H, 4.99.

A better conversion to **5i** (46%, based upon tetrahydrodibenzoate **5d**) was obtained if the crude bromination product of **5d** was subjected to the above reaction conditions.

***trans*-1,2-Dihydroxy-1,2-dihydroanthracene (5k).** In the manner described for **10k,** dibenzoate **5i** (27 mg) was converted to dihydrodiol **5k.** Recrystallization of the crude product from EtOAc gave **5k** (11 mg, 61%) as colorless needles, ^{1}H NMR (see Table II).

***trans*-1,2-Diacetoxy-1,2,3,4-tetrahydrophenanthrene (6g).** Benzene (150 ml), 3,4-dihydrophenanthrene (4.05 g, 0.0225 mol),[16a] and silver acetate (8.03 g, 0.0481 mol) were mixed under N_2. Iodine (5.99 g, 0.0236 mol) was added in portions over a 15-min period. After the red color disappeared, the reaction mixture was refluxed for 3 h, then was gravity filtered hot. The benzene was removed under reduced pressure, leaving an oily residue that was column chromatographed on Florisil using 5:95 EtOAc/hexane as developing solvent to give **6g** as a white solid (3.45 g, 51%): mp 118–119 °C; ^{1}H NMR (60 MHz) δ 7.16–8.10 (6 H), 6.20 (H_1, d), 5.07–5.40 (H_2), 2.97–3.36 (2 H), 1.80–2.40 (2 H), 2.06 (3 H, s), 1.94 (3 H, s), $J_{1,2}$ = 6.0 Hz.

4β-Bromo-1β,2α-diacetoxy-1,2,3,4-tetrahydrophenanthrene (6h). The reaction of **6g** (3.83 g), NBS (2.52 g), and AIBN (5 mg) in CCl_4 (150 ml) was effected as described for **5e.** Workup gave the product as a darkened aerosol from which bromodiacetate **6h** was obtained as an off-white solid (3.40 g, 70%) by the addition of ether. Recrystallization from ether afforded **6h** as a white solid: mp 134–138 °C; ^{1}H NMR (220 MHz) δ7.16–8.30 (6 H), 6.49 (H_1), 6.04 (H_4), 5.94 (H_2), 2.83 ($H_{3\beta}$), 2.49 ($H_{3\alpha}$), 2.21 (3 H, s), 2.11 (3 H, s), $J_{1,2}$ = 8.5, $J_{2,3\beta}$ = 4.0, $J_{2,3\alpha}$ = 12.6, $J_{3\beta,4}$ = 3.4, $J_{3\alpha,4}$ = 3.6, $J_{3\alpha,3\beta}$ = 14.0 Hz. Anal. Calcd for $C_{18}H_{17}O_4Br$: C, 57.31; H, 4.54. Found: C, 57.08; H, 4.70.

***trans*-1,2-Diacetoxy-1,2-dihydrophenanthrene (6j).** The reaction of bromodiacetate **6h** (2.71 g) in xylene (250 ml) containing $NaHCO_3$ (13.5 g) was effected as described for **5i.** Workup gave a yellow oil that crystallized from ether (0 °C) to yield 0.69 g of **6j.** Preparative layer chromatography of the mother liquors (alumina,

1:9 EtOAc/hexane) afforded an additional 0.37 g of **6j** [total yield 1.06 g (50%)]. Recrystallization from ether/hexane gave **6j** as a white solid: mp 104–105 °C; ^{1}H NMR (see Table I). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.73; H, 5.40.

***trans*-1,2-Dihydroxy-1,2-dihydrophenanthrene (6k).** Dihydrodiol diacetate **6j** (50 mg) was dissolved in anhydrous MeOH (30 ml) and anhydrous NH_3 was bubbled through the solution for 15 min. The reaction vessel was capped and the reaction mixture was stirred at 25 °C for 2 h. The methanol was removed under reduced pressure, leaving a white solid that was dissolved in CH_2Cl_2 and water. The CH_2Cl_2 layer was extracted with water, dried (anhydrous Na_2SO_4), filtered, and concentrated, to give dihydrodiol **6k** as a white solid (32 mg, 89%): mp 164–165 °C; homogeneous by TLC (alumina, EtOAc as developing solvent); ^{1}H NMR (see Table II).

***trans*-3,4-Dibenzoyloxy-1,2,3,4-tetrahydrophenanthrene (7d).** The reaction of 1,2-dihydrophenanthrene (4.54 g),[16a] silver benzoate (13.01 g), and iodine (6.73 g) in benzene (200 ml) was effected as described for **5d.** Column chromatography of the crude product on Florisil using EtOAc/hexane (15:85) as developing solvent afforded slightly impure **7d,** which gave 3.4 g (32%) of white solid of mp 127–128 °C after recrystallization from ether/hexane: ^{1}H NMR (60 MHz) δ 7.0–8.1 (6 H), 6.97 (H_4), 5.76 (H_3, m), 2.9–3.4 (2 H), 2.2–2.6 (2 H), $J_{3,4}$ = 3.2 Hz.

***trans*-3,4-Diacetoxy-1,2,3,4-tetrahydrophenanthrene (7g).** Dibenzoate **7d** (0.62 g) was dissolved in THF (35 ml) and MeOH (65 ml). To this solution was added 1 N NaOH (12 ml). A white solid separated after a few minutes. The mixture was stirred for 3 h at 25 °C. THF and MeOH were removed under reduced pressure to leave a white solid that was washed with water, isolated by suction filtration, and washed several times with cold water. The diol, **7f,** thus obtained (292 mg, 93%) was added to a mixture of Ac_2O (13 ml) and pyridine (3 ml). The solution was stirred at 25 °C for 12 h. Ethyl acetate (40 ml) was added to the solution and the EtOAc phase was extracted with H_2O (3 × 50 ml), dilute HCl (2 × 50 ml), saturated $NaHCO_3$ (50 ml), and H_2O (2 × 50 ml). The EtOAc layer was dried (anhydrous Na_2SO_4), filtered, and concentrated to leave a light yellow solid which was triturated twice with hexane. The resulting white tetrahydrodiacetate **7g** (329 mg, 81%) had mp 171–173 °C; ^{1}H NMR (60 MHz) δ 7.1–8.0 (6 H), 6.53 (H_4), 5.33 (H_3, m), 2.8–3.2 (2 H), 2.1–2.4 (2 H), 2.03 (3, s), 1.97 (3 H, s), $J_{3,4}$ = 3.2 Hz.

1-Bromo-3α,4β-diacetoxy-1,2,3,4-tetrahydrophenanthrene (7h). The reaction of tetrahydrodiol diester **7g** (230 mg), NBS (151 mg), and AIBN (5 mg) in CCl_4 (70 ml) was effected as described for **5e.** Workup gave a clear, oily residue which crystallized upon the addition of ether, yielding isomer I of **7h** (160 mg): ^{1}H NMR (60 MHz) δ 7.4–9.0 (6 H), 6.67 (H_4), 5.66 (H_1), 5.36 (H_3), 2.5–3.0 (2 H), 2.02 (6 H, br s), $J_{3,4} \sim J_{2,3} \sim J_{2',3} \sim 3$, $J_{1,2} \sim 5.5$, $J_{1,2} \sim 2.5$ Hz. Crystallization of the mother liquors from ether yielded a second solid (90 mg), that was recrystallized from ether to give isomer II of **7h:** mp 159–161 °C; ^{1}H NMR (100 MHz) δ 7.4–8.0 (6 H), (H_4), 5.45–5.70 (H_1, H_3), 2.65–2.85 (2 H), 2.07 (3 H, s), 1.98 (3 H, s). Anal. Calcd for $C_{18}H_{17}O_4Br$: C, 57.31; H, 4.54. Found: C, 57.30; H, 4.66.

***trans*-3,4-Diacetoxy-3,4-dihydrophenanthrene (7j).** The reaction of bromodiacetate **7h** (123 mg, isomer I) in xylene (70 ml) containing $NaHCO_3$ (2 g) was effected as described for **5i,** except that a 6-min heating period was used. Workup gave the product as an oil, which afforded crystalline **7j** (57 mg, 59%) of mp 166–167 °C after crystallization from EtOAc/hexane and recrystallization from benzene/hexane: ^{1}H NMR (see Table I). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.83; H, 5.49.

A much better conversion was achieved by reacting the crude bromodiacetate mixture **7h,** from 309 mg of tetrahydrodiacetate **7g,** in anhydrous THF (8 ml) at 0 °C, under N_2, with DBN (80 drops). The reaction mixture was maintained at 0 °C for 18 h. Ethyl acetate (50 ml) was added to the reaction mixture and the EtOAc phase was extracted with H_2O (2 × 40 ml), 0.1 N HCl (2 × 40 ml), dilute $NaHCO_3$ (1 × 40 ml), and H_2O (40 ml). The EtOAc phase was dried (anhydrous Na_2SO_4), filtered, and concentrated, leaving a yellow oil that was column chromatographed on Florisil with EtOAc/hexane (1:8) to give **7j** as a white solid (175 mg, 56% based on tetrahydrodiacetate **7g**).

***trans*-3,4-Dihydroxy-3,4-dihydrophenanthrene (7k).** Hydrolysis of dihydrodiol diacetate **7j** (40 mg) was effected as described for the preparation of **6k,** except that a reaction time of 18 h was employed and the crude product was dissolved in EtOAc rather than CH_2Cl_2. Crystallization of the crude product from EtOAc gave **7k** as a white solid (5 mg). Additional pure **7k** (16 mg) was obtained by column chromatography of the mother liquor on Florisil, using EtOAc/hexane (1:1) as developing solvent (total yield 72%). The product was chromatographically pure by TLC [silica gel. EtOAc/hexane (1:1)], ^{1}H NMR (see Table II).

1-Hydroxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene (8b). Ketone **8a** (6.0 g)[25] was dissolved in methanol (500 ml) and $NaBH_4$ (3.0 g) was added in portions. After 1 h, the MeOH was removed under reduced pressure and the residue was dissolved in EtOAc (250 ml) and H_2O (100 ml). The EtOAc phase was extracted with H_2O (3 × 100 ml), dried (anhydrous Na_2SO_4), filtered, and concentrated. The residue was crystallized from EtOAc/hexane, which gave **8b** as a light yellow solid (5.2 g, 86%).

***trans*-1,2-Dibenzoyloxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene (8d).** Alcohol **8b** (2.63 g) was added to a solution of HCl (4 drops) in glacial HOAc (200 ml). Nitrogen was bubbled through the solution and an atmosphere of N_2 was maintained throughout the reaction, as well as during the workup. The solution was heated at 55 °C for 3 h, then it was added to ice (150 g). The aqueous phase was extracted with benzene (200 ml). The benzene layer was extracted with H_2O (200 ml) and concentrated under reduced pressure. The resultant yellow solid, primarily 3,4-dihydrobenzo[*a*]anthracene (**8c**), was used in the subsequent step without further purification.

The reaction of 3,4-dihydrobenzo[*a*]anthracene (**8c,** crude reaction product vide supra), silver benzoate (5.46 g), and iodine (2.82 g) in benzene (150 ml) was effected as described for **5d.** The crude product was chromatographed on Florisil, using EtOAc/hexane (1:9) as developing solvent. Slightly impure **8d** (2.78 g) was obtained. It was recrystallized from MeOH to give tetrahydrodibenzoate (3.22 g, 64% based on alcohol **8b**) of mp 162–163 °C; ^{1}H NMR (60 MHz) δ 8.57, 8.27 (H_7, H_{12}, s), 5.87 (H_2), 6.75–8.15 (17 H), 2.2–3.5 (4 H).

***trans*-1,2-Diacetoxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene (8g).** Dibenzoate **8d** (2.84 g) was dissolved in THF (200 ml) and methanol (200 ml) and 1 N NaOH (24 ml) were added. The reaction mixture was stirred for 2 h, MeOH and THF were removed under reduced pressure, water was added, and the aqueous phase was extracted with EtOAc. The EtOAc phase was washed with H_2O, dried (anhydrous Na_2SO_4), filtered, and concentrated. The residue, primarily diol **8f,** was used without purification.

Diol **8f** (vide supra) was dissolved in Ac_2O (25 ml) and pyridine (5 ml). The acetylation was effected as described for the preparation of **7g.** The crude product was treated with EtOAc/hexane to give tetrahydrodiacetate **8g** as a white solid (1.71 g, 82% based on dibenzoate **8d**) of mp 175–176 °C; ^{1}H NMR (60 MHz) δ 8.35 (2 H, br s), 7.1–8.2 (6 H), 6.70 (H_1), 5.41 (H_2), 2.8–3.2 (2 H), 1.9–2.4 (2 H), 2.03 (3 H, s), 1.97 (3 H, s), $J_{1,2} \sim 3$ Hz.

4-Bromo-1α,2β-diacetoxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene (8h). The reaction of **8g** (0.50 g), NBS (281 mg), and AIBN (5 mg) in CCl_4 (75 ml) was effected as described for **5e.** Addition of ether to the crude product yielded isomer I (334 mg) of **8h,** which was recrystallized from EtOAc/hexane to give isomer I of mp 163–164 °C; ^{1}H NMR (100 MHz) δ 8.45, 8.38 (H_7, H_{12}, s), 7.4–8.2 (6 H), 6.82 (H_1), 5.67 (H_4), 5.43 (H_2), 2.93–3.12 (1 H), 2.61–2.91 (1 H), 2.01 (6 H, br s), $J_{1,2}$ = 2.9, $J_{3,4}$ = 1.8, $J_{3',4}$ = 5.4, $J_{2,3} \sim J_{2,3} \sim 3.0$ Hz. Anal. Calcd for $C_{22}H_{19}O_4Br$: C, 61.84; H, 4.48. Found: C, 62.12; H, 4.67.

Crystallization of the mother liquors from EtOAc/hexane afforded isomer II (119 mg) of **8h** as a solid of mp 150–154 °C; ^{1}H NMR (100 MHz) δ 8.36 (2 H, br s), 7.3–8.2 (6 H), 6.77 (H_1), 5.43–5.70 (H_2, H_4), 2.70–2.90 (2 H), 2.06 (3 H, s), 1.98 (3 H, s), $J_{1,2}$ = 4.1 Hz.

***trans*-1,2-Diacetoxy-1,2-dihydrobenzo[*a*]anthracene (8j).** The reaction of bromodiacetate isomer I of **8h** (251 mg) in xylene (100 ml) containing $NaHCO_3$ (4 g) was effected as described for **5i,** except that a reaction time of 5 min was adequate. The crude reaction product, after workup, was column chromatographed on Florisil, using EtOAc/hexane (1:9) as developing solvent. The second compound to elute from the column was dihydrodiol diacetate **8j** (51 mg, 25%), which upon recrystallization from EtOAc had mp 182–183 °C; ^{1}H NMR (see Table I). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.26; H, 5.34.

Similar treatment of bromodiacetate isomer II of **8h** afforded a very low yield of **8j,** as judged by the NMR spectrum of the crude reaction product.

Both bromodiacetate isomers of **8h,** on the other hand, could be efficiently converted to dihydrodiol diacetate **8j** upon treatment with DBN in THF at 0 °C. Thus, isomer I of **8h** (50 mg), when reacted with DBN (15 drops) in THF (3 ml, 0 °C) as described for **7j,** yielded a crude reaction product composed almost entirely of **8j,** as judged by NMR. Treatment of the crude product with EtOAc led to the isolation of **8j** (21 mg, 51%). Similarly, isomer II of **8h** (30 mg), when reacted with DBN (15 drops) in THF (4 ml, 0 °C) as described for **7j,** yielded, upon workup, a crude reaction product whose NMR spectrum indicated it to be composed almost entirely of **8j.** The reaction mixture was not processed further. It is likely that best conversions to **8j** would be achieved by reacting the crude bromination product of tetrahydro diester **8g** with DBN in THF.

***trans*-1,2-Dihydroxy-1,2-dihydrobenzo[*a*]anthracene (8k).** Hydrolysis of dihydrodiol diacetate **8j** (49 mg) in MeOH (150 ml), THF (20 ml), and ammonia was effected as described for the preparation of **6k**, except that a reaction time of 24 h was used. Workup, as described previously, gave the product as a light yellow solid. Recrystallization of the solid from EtOAc/hexane afforded 20 mg (54%) of **8k**, mp 167–168 °C. The dihydrodiol diacetate, **8k**, was pure by TLC [silica gel, hexane/EtOAc (1:1), R_f ~0.4]: ^{1}H NMR (see Table II); UV spectrum (see Figure 2) λ_{max} (ϵ): 228 (22 323), 237 (21 325), 262 (69 238), 281 (47 731), 345 (2904), 361 (4809), 381 (6533), 403 (4809).

1,2-Dihydrobenzo[*a*]anthracene (9c). Ketone **9a** (6.0 g)[26] and $NaBH_4$ (9.0 g) were reacted in MeOH (500 ml), as described for the preparation of **8b**. The alcohol (**9b**) thus obtained was converted, without purification, to **9c**. Thus, the crude alcohol (**9b**) was dissolved in a solution of glacial HOAc (150 ml) and concentrated HCl (6 drops) and the mixture was heated at 90 °C for 1.5 h. The reaction mixture was cooled (25 °C), and H_2O (50 ml) was added. The product, **9c**, precipitated and was collected by filtration. Residual HOAc was removed by dissolving **9c** in CH_2Cl_2 and extracting with aqueous $NaHCO_3$. The product was obtained as a light yellow solid (5.0 g, 90% based on ketone **9a**) which, after recrystallization from EtOAc/hexane, had mp 176–178 °C; ^{1}H NMR (60 MHz) δ 8.48, 8.27 (H_7, H_{12}, s), 7.0–8.1 (6 H, m), 6.55 (H_4), 6.07 (H_3), 3.0–3.5 (2 H), 2.1–2.7 (2 H), $J_{2,3}$ = 3.8, $J_{2,4}$ = 1.9, $J_{3,4}$ = 9.7 Hz.

***trans*-3,4-Dibenzoyloxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene (9d).** The reaction of 1,2-dihydrobenzo[*a*]anthracene (**9c**, 5.0 g), silver benzoate (11.31 g), and iodine (5.85 g) in benzene (150 ml) was effected as described for **5d**. Crystallization of the crude product from acetone gave **9d** as a light yellow solid (5.51 g, 54%). Recrystallization gave **9d** as a light yellow solid (5.51 g, 54%). Recrystallization gave **9d** as a white solid: mp 187–188 °C; ^{1}H NMR (60 MHz) δ 8.57, 8.37 (H_7, H_{12}, s), 7.15–8.20 (16 H), 6.70 (H_4), 5.5–5.9 (H_3), 3.4–3.7 (2 H), 2.3–2.8 (2 H), $J_{3,4}$ = 6.0 Hz.

***trans*-3,4-Diacetoxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene (9g).** The conversion of dibenzoate **9d** (3.5 g) to diol **9f** in THF (200 ml), MeOH (100 ml), and 0.1 N NaOH (74.2 ml) was effected as described for the preparation of **7f**. The white, solid diol thus obtained (1.90 g, 97%) was used without characterization. Acetylation of **9f** (1.90 g) in Ac_2O (20 ml) and pyridine (3 ml) was effected as described for the preparation of **7g**, except that a 24-h reaction time was required. Workup, as described previously, gave the crude product as a solid, which was recrystallized from EtOAc/hexane to give diacetate **9g** as a clear solid (2.11 g, 84%) of mp 145–146 °C; ^{1}H NMR (60 MHz) δ 8.52, 8.37 (H_7, H_{12}, s), 7.1–8.2 (6 H), 6.22 (H_4), 5.15–5.50 (H_3), 3.2–3.6 (2 H), 2.0–2.6 (2 H), 2.14 (2 H, s), 2.03 (3 H, s), $J_{3,4}$ ~ 5.5 Hz.

1β-Bromo-3α,4β-diacetoxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene (9h). The reaction of tetrahydrodiacetate **9g** (1.83 g), NBS (1.03 g), and AIBN (5 mg) in CCl_4 (250 ml) was effected as described for **5e**. Crystallization of the crude product from ether (0 °C) gave **9h** (1.76 g, 78%) as a light yellow solid, which after recrystallization from CH_2Cl_2/hexane had mp 143–144 °C; ^{1}H NMR (100 MHz) δ 8.64, 8.35 (H_7, H_{12}, s), 7.06–8.20 (6 H, m), 6.47 (H_4), 6.11 (H_1), 5.96 (H_3), 2.89 ($H_{2\beta}$), 2.50 ($H_{2\alpha}$), 2.19 (3 H, s), 2.09 (3 H, s), $J_{1,2\beta}$ = 2.9, $J_{1,2\alpha}$ = 3.9, $J_{2\alpha,2\beta}$ = 14.3, $J_{2\alpha,3}$ = 12.3, $J_{2\beta,3}$ = 4.3, $J_{3,4}$ = 8.6 Hz. Anal. Calcd for $C_{22}H_{19}O_4Br$: C, 61.84; H, 4.48. Found: C, 62.23; H, 4.73.

***trans*-3,4-Diacetoxy-3,4-dihydrobenzo[*a*]anthracene (9j).** The reaction of bromodiacetate **9h** (145 mg) in xylene (70 ml) containing $NaHCO_3$ (2.0 g) was effected as described for **5i**, except that a reaction time of 10 min was employed. The crude product was chromatographed on Florisil with EtOAc/hexane (1:9). The second compound off the column was **9k** (39 mg, 33%), a yellow solid of mp 151–154 °C after recrystallization from EtOAc/hexane: ^{1}H NMR (see Table I). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.32; H, 5.54.

***trans*-3,4-Dihydroxy-3,4-dihydrobenzo[*a*]anthracene (9k).** Hydrolysis of dihydrodiol diacetate **9j** (39 mg) in MeOH (50 ml) and NH_3 was effected as described for **6k**. The crude product was triturated with CH_2Cl_2/EtOAc to give **9k** as a yellow solid (22 mg, 73%) of mp 215–217 °C. The product was pure by TLC (1:1 EtOAc/hexane, R_f ~0.4): ^{1}H NMR (see Table I); UV (see Figure 2) λ_{max} (ϵ) 261 (104 950), 280 (17 327), 345 (2970), 363 (4554), 383 (5149), 405 (4257).

***trans*-8,9-Dibenzoyloxy-8,9,10,11-tetrahydrobenzo[*a*]anthracene (10d).** To a mixture of 10,11-dihydrobenzo[*a*]anthracene (8.96 g)[16b,27] and silver benzoate (19.6 g) in benzene (500 ml) was added powdered iodine (10.9 g). The mixture was stirred for 10 min, then refluxed for 2 h. Workup was effected as described for **5d**. Recrystallization of the crude product from benzene/hexane (1:2) gave tetrahydrodibenzoate **10d** (13.8 g, 75%) as colorless needles: mp 153–154 °C; ^{1}H NMR (60 MHz) δ 8.60 (H_1, m), 8.46 (H_{12}, s), 7.20–8.25 (16 H), 6.75 (H_8, d), 5.70 (H_9, m), 3.37 (2 H, m), 2.2–2.8 (2 H, m), $J_{8,9}$ = 6.0 Hz.

11β-Bromo-8β,9α-dibenzoyloxy-8,9,10,11-tetrahydrobenzo[*a*]anthracene (10e). The reaction of **10d** (6.1 g), NBS (2.54 g), and AIBN (5 mg) in CCl_4 (500 ml) was effected as described for **5e**, except that a heating period of 50 min was used. Treatment of the crude product with ether resulted in the crystallization of **10e**. Recrystallization from CH_2Cl_2/hexane (4:6) gave **10e** (5 g, 70%) as colorless needles: mp 137–138 °C; ^{1}H NMR (100 MHz) δ 8.84 (H_{12}, s), 8.69 (H_1, m), 7.20–8.28 (16 H), 6.89 (H_8), 6.16 (H_9), 5.98 (H_{11}), 3.06 ($H_{10\beta}$), 2.74 ($H_{10\alpha}$), $J_{8,9}$ = 8.0, $J_{9,10\beta}$ = 4.0, $J_{9,10\alpha}$ = 10.0, $J_{10\alpha,11}$ = 4.4, $J_{10\beta,11}$ = 4.0, $J_{10\alpha,10\beta}$ = 14.5 Hz. Calcd for $C_{32}H_{23}O_4Br$: C, 69.70; H, 4.20. Found: C, 69.98; H, 4.26.

***trans*-8,9-Dibenzoyloxy-8,9-dihydrobenzo[*a*]anthracene (10i).** The reaction of bromodibenzoate **10e** (3.3 g) in xylene (80 ml) containing $NaHCO_3$ (10.0 g) was effected as described for **5i**, except that a reaction time of 30 min was employed. Recrystallization of the crude product from CH_2Cl_2/hexane (1:1) gave **10i** (1.84 g, 65%) as colorless needles: mp 167–168 °C; ^{1}HNMR (see Table I). Anal. Calcd for $C_{32}H_{22}O_4$: C, 81.68; H, 4.71. Found: C, 81.76; H, 4.92.

***trans*-8,9-Dihydroxy-8,9-dihydrobenzo[*a*]anthracene (10k).** Dibenzoate **10i** (1.5 g) was dissolved in deaerated THF (30 ml) and MeOH (30 ml), under argon. Freshly prepared $NaOCH_3$ (2.5 g) was added and the solution was stirred for 15 min. Ethyl acetate (200 ml) was added and the mixture was washed with H_2O (three times). The water layer was extracted with EtOAc (2 × 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Recrystallization of the crude product from acetone gave **10k** (580 g, 70%) as colorless prisms: mp 168–170 °C dec; ^{1}H NMR (see Table II); UV (see Figure 2) λ_{max} (ϵ) 229 (18 130), 256 (56 700), 265 (71 950), 236 (17 830), 306 (23 240), 319 (25 640).

8,9-Dihydrobenzo[*a*]anthracene (11c). Ketone **11a** (12.0 g)[28] and $NaBH_4$ (10.0 g) were reacted in methanol (900 ml), as described for the preparation of **8b**. Recrystallization of the crude product from EtOH gave alcohol **11b** (10.8 g, 89%) as colorless prisms: mp 119–120 °C; ^{1}H NMR (60 MHz) δ 8.66 (H_{12}, s), 8.50 (H_1, m), 7.40–7.90 (6 H), 4.90 (O–H), 2.85 (2 H, m), 1.6–2.2 (5 H, m).

Alcohol **11b** (10.0 g) was dissolved in a solution of HOAc (250 ml) and concentrated HCl (2 drops), and the mixture was heated at 100 °C, under argon, for 2 h. The reaction mixture was cooled (10 °C) and H_2O (150 ml) was added. The product **11c** precipitated and was collected by filtration. It was washed thoroughly with water and was dried (P_2O_5) under reduced pressure. Recrystallization from EtOH gave **11c** (8.8 g, 95%) as colorless needles: mp 99–100 °C; ^{1}H NMR (60 MHz) δ 8.55 (H_1, m), 8.20 (H_{12}, s), 7.35–7.90 (6 H), 6.70 (H_{11}), 6.07 (H_{10}), 2.91 (2 H, m), 2.36 (2 H, m), $J_{9,10}$ = 4, $J_{10,11}$ = 9.5 Hz.

***trans*-10,11-Dibenzoyloxy-8,9,10,11-tetrahydrobenzo[*a*]anthracene (11d).** The reaction of **11c** (10 g), silver benzoate (22 g), and iodine (12.1 g) in benzene (500 ml) was effected as described for **10d**. Addition of EtOH to the crude reaction product led to the formation of a solid that was recrystallized from CH_2Cl_2/EtOH (4:1) to give **11d** (15.4 g, 75%) as colorless needles: mp 173–174 °C; ^{1}H NMR (60 MHz) δ 8.65 (H_{12}, s), 8.50 (H_1, m), 7.20–8.25 (16 H), 6.80 (H_{11}), 5.71 (H_{10}, m), 3.25 (2 H, m), 2.18–2.80 (2 H), $J_{10,11}$ = 5.5 Hz.

8β-Bromo-10α,11β-dibenzoyloxy-8,9,10,11-tetrahydrobenzo[*a*]anthracene (11e). The reaction of **11d** (7.6 g), NBS (3.16 g), and AIBN (5 mg) in CCl_4 (500 ml) was effected as described for **5e**, except that a heating period of 50 min was used. Treatment of the crude product with ether caused the precipitation of a solid which was recrystallized from CH_2/hexane (4:6) to give **11e** (5.8 g, 6) as colorless prisms: mp 137–138 °C; ^{1}H NMR (100 MHz) δ 8.64 (H_{12}, s), 8.49 (H_1, m), 7.20–8.27 (16 H), 6.90 (H_{11}), 6.13 (H_{10}), 5.85 (H_8), 3.05 ($H_{9\beta}$), 2.53 ($H_{9\alpha}$), $J_{8,9\beta}$ = 4.7, $J_{8,9\alpha}$ = 4.7, $J_{9\alpha,9\beta}$ = 14.5, $J_{9\beta,10}$ = 3.7, $J_{9\alpha,10}$ = 9.4, $J_{10,11}$ = 7.6 Hz. Anal. Calcd for $C_{32}H_{23}O_4Br$: C, 69.70; H, 4.20. Found: C, 69.95; H, 4.11.

***trans*-10,11-Dibenzoyloxy-10,11-dihydrobenzo[*a*]anthracene (11i).** The reaction of bromodibenzoate **11e** (1.1 g) in xylene (80 ml) containing $NaHCO_3$ (5.0 g) was effected as described for **5i**, except that a reaction time of 30 min was used. Recrystallization of the crude product from CH_2Cl_2/hexane (1:20) gave **11i** (0.660 g, 62%) as colorless prisms: mp 170–171 °C; ^{1}H NMR (see Table I). Anal. Calcd for $C_{32}H_{22}O_4$: C, 81.68; H, 4.71. Found: C, 81.72; H, 4.93.

***trans*-10,11-Dihydroxy-10,11-dihydrobenzo[*a*]anthracene (11k).** The hydrolysis of dihydrodiol dibenzoate **11i** (300 mg) was effected as described for the preparation of **10k**. The crude product was recrystallized from EtOAc to give **11k** (109 mg, 65%) as colorless needles: mp 196–200 °C dec; ^{1}H NMR (see Table II); UV (see Figure 2) λ_{max} (ϵ) 227 (11 580), 265 (52 315), 274 (67 280), 294 (18 440), 210 (11 235).

Registry No.—**5d**, 60967-91-1; **5e** ($R_4 = \beta$), 60967-92-2; **6g**, 60967-93-3; **6h** ($R_4 = \beta$), 60967-94-4; **7d**, 60967-95-5; **7f**, 60967-96-6; **7g**, 60967-97-7; **7h** ($R_4 = \alpha$), 60967-98-8; **7h** ($R_4 = \beta$), 60967-99-9; **8b**, 60968-00-5; **8c**, 60968-01-6; **8d**, 60968-02-7; **8f**, 60968-03-8; **8g**, 60968-04-9; **8h** ($R_4 = \alpha$), 60968-05-0; **8h** ($R_4 = \beta$), 60968-06-1; **9a**, 38393-90-7; **9b**, 60968-07-2; **9c**, 60968-08-3; **9d**, 60968-09-4; **9f**, 60968-10-7; **9g**, 60968-11-8; **9h** ($R_4 = \beta$), 60968-12-9; **10d**, 60968-13-0; **10e** ($R_4 = \beta$), 60968-14-1; **11a**, 60968-15-2; **11b**, 60968-16-3; **11c**, 60968-17-4; **11d**, 60968-18-5; **11e** ($R_4 = \beta$), 60968-19-6; silver benzoate, 532-31-0; 1,2-dihydroanthracene, 58746-82-0; *N*-bromosuccinimide, 128-08-5; silver acetate, 563-63-3; 3,4-dihydrophenanthrene, 38399-10-9; 1,2-dihydrophenanthrene, 56179-83-0; ethyl acetate, 141-78-6; 10,11-dihydrobenzo[*a*]anthracene, 34501-50-3.

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Aporphines. 19.[1a] Mass Spectrometry of Nitrobenzylisoquinolines. Influence of Positional Isomerism on Fragmentation and Evidence for an Ionically Induced Intramolecular Migration Process[1b]

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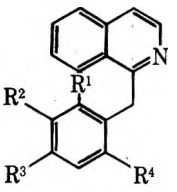
Received May 31, 1976

The mass spectra of a series of nitro-substituted benzylisoquinolines were examined under both electron impact and chemical ionization conditions. A number of fragmentation processes have been observed which can be utilized for structural assignments to positional isomers. Isotopic labeling was used to confirm the mechanism of specific fragmentations. The procedures for synthesis of the title compounds are included.

The importance of 1-(2-nitrobenzyl)isoquinolines as key intermediates in the synthesis of aporphine alkaloids and other biologically active molecules has been well documented in the recent literature.[2] The Reissert[3] alkylation method via 2-benzoyl-1,2-dihydroisoquinaldonitriles is used to advantage for the synthesis of many benzylisoquinolines and 1-(2-nitrobenzyl)isoquinolines.[4] Thus, aporphine alkaloids can be conveniently prepared by the reduction of the isoquinolinium salts of 1-(o-nitrobenzyl)isoquinolines and Pschorr cyclization.[5,6]

As part of a program aimed at the preparation and biological testing of a variety of new aporphine derivatives, we have synthesized a series of benzylisoquinolines, **1a–h**. This report on the mass spectrometric properties—both under electron impact and chemical ionization conditions—has been prompted, in part, by the relative paucity of mass spectral



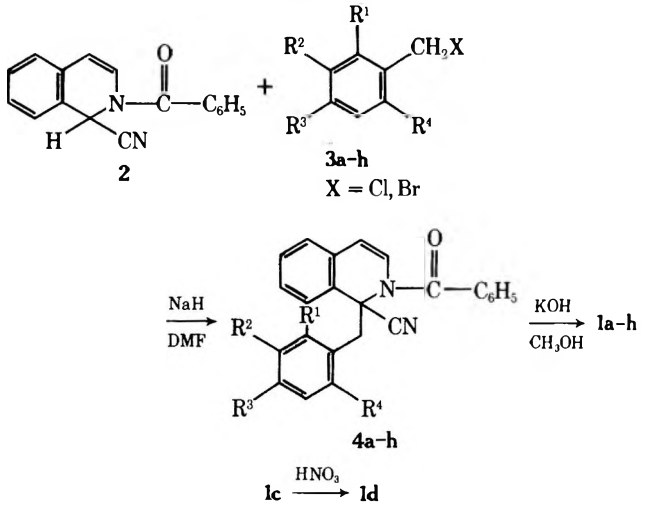
1

	R^1	R^2	R^3	R^4
a	NO_2	H	H	H
b	H	H	NO_2	H
c	H	H	OCH_3	H
d	H	NO_2	OCH_3	H
e	H	NO_2	OCD_3	H
f	NO_2	OCH_3	H	H
g	NO_2	H	OCH_3	H
h	NO_2	H	H	OCH_3

data on compounds of the benzylisoquinoline class. This is in sharp contrast to the partially saturated benzyl- and bisbenzyl-1,2,3,4-tetrahydroisoquinolines, for which a comparative abundance of mass spectrometric information has come to our attention.[7] Furthermore, it was hoped that some analogies might be drawn between the anticipated cleavage of the 1,1′ bond during mass spectral fragmentation and a stereochemically influenced exocyclic carbon–carbon cleavage observed during the reduction of the corresponding isoquinolinium salts.[8] The mass spectrometric investigations of the benzylisoquinolines have brought to light a number of considerations which can be applied to the structural determination of positional isomers of nitrobenzylisoquinolines.

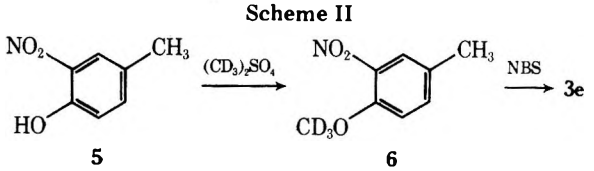
Compounds **1a–h** were prepared via alkylation of 2-benzoyl-1,2-dihydroisoquinaldonitrile (**2**) with the appropriate benzyl halide **3**.[9] The resulting Reissert adducts **4**, which were isolated and characterized in some cases, yielded on hydrolysis the corresponding 1-substituted isoquinoline. In addition, the benzylisoquinoline derivative **1d** was also obtained in 70% yield by nitration of **1c** with concentrated nitric acid (Scheme I). Introduction of the deuteriomethoxy group in **1e** was ac-

Scheme I



complished by the methylation of **5** with dimethyl-d_6 sulfate. The nitroanisole **6** was brominated to the aryl halide **3e** which furnished **1e** according to the procedure described in Scheme II.

Scheme II

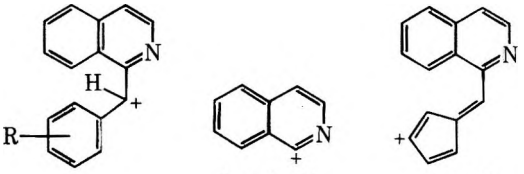


Results and Discussion

Electron Impact Ionization. On examining the electron-impact spectra of the benzylisoquinolines **1a–h** in Figures 1–3 the common features in the fragmentation of these compounds should be considered.

(a) The spectra of compounds containing a 2-nitro substituent exhibit relatively weak molecular ion and $[M - 1]^+$ peaks. This may be attributed, in part, to steric interaction between the NO_2 group and the adjacent methylene group, and is further reflected in the formation of abundant $[M - NO_2]\cdot^+$ ions in the spectra of **1a, 1f, 1g,** and **1h.** The strain introduced from the presence of an ortho substituent on the benzyl ring is also exemplified by the favorable elimination of the 6-methoxy group in compound **1h** to yield the ion at *m/e* 263 $[M - OCH_3]^+$.

(b) Loss of a hydrogen radical from the molecular ion is common to the mass spectra of compounds **1a–h** and presumably involves one of the benzylic hydrogens to produce the resonance stabilized ion a.



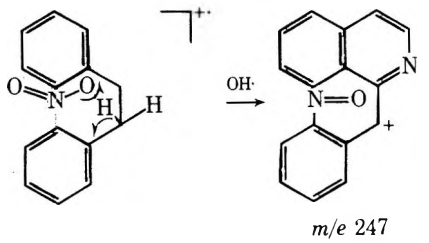
a b, *m/e* 128 c, *m/e* 204

(c) Cleavage of the benzylic–isoquinoline bond, a prominent process in the mass spectra of benzyltetrahydroisoquinolines,[10-12] occurs only to a minor extent in the spectra of the benzylisoquinolines **1a–h.** However, even though of low relative intensity, the presence of a peak at *m/e* 128, corresponding to the isoquinolinyl cation b, is structurally significant as it indicates the presence of that functionality in the molecule. The ions complementary to *m/e* 128 are of moderate abundance in the mass spectra of some of the compounds as noted from the peaks at *m/e* 121 and 166 in the spectra of **1c** and **1g,** respectively. The contrasting behavior of the 1,2,3,4-tetrahydroisoquinolines as opposed to the benzylisoquinoline system has also been noted in a recent publication dealing with the mass spectral behavior of tetrahydroeschscholamidine salts.[13] Similarly, the peak arising from cleavage of the benzylic bond in the spectrum of papaverine *N*-oxide is also of relatively minor intensity.[14]

(d) An ion of *m/e* 204 whose formation involves loss of the benzene ring substituents plus a ring carbon is common to the mass spectra of **1a–h** and a plausible structure for it is depicted by c.

In addition to the variation in the $M\cdot^+$ ion intensity a major qualitative difference in the fragmentation of the two monosubstituted nitro derivatives **1a** and **1b** involves the occurrence of an $[M - OH]^+$ ion (*m/e* 247) in the spectrum of **1a** as compared to the absence of one in the spectrum of the 4-nitro derivative, **1b.** We suggest that the proximity of an oxygen atom of the 2-nitro group and the benzylic hydrogens in **1a** facilitates expulsion of an OH· radical as shown in Scheme III.

Scheme III



m/e 247

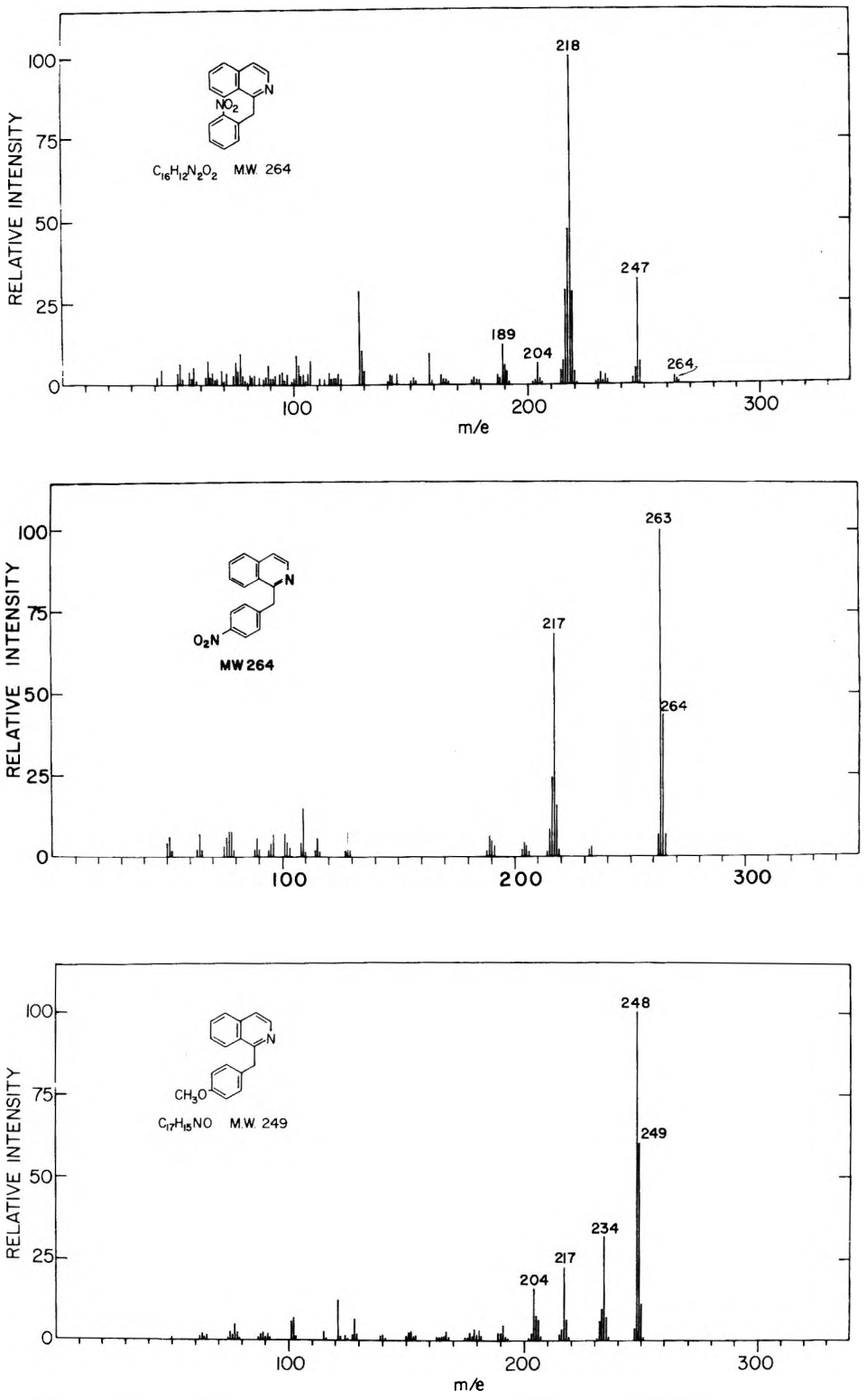


Figure 1. Mass spectra of 1-(2-nitrobenzyl)isoquinoline (**1a**, top spectrum), 1-(4-nitrobenzyl)isoquinoline (**1b**, center), and 1-(4-methoxynitrobenzyl)isoquinoline (**1c**, bottom spectrum).

In the fragmentation of the 4-methoxy derivative **1c** no unique features are apparent. The principal peaks—in addition to ion c (*m/e* 204)—are formed by losses of H· (*m/e* 248), CH_3· (*m/e* 234), and CH_3O· and H· (*m/e* 217) (Figure 1).

The spectrum of 1-(4-methoxy-3-nitrobenzyl)isoquinoline (**1d**) contains fragment ions which are common to the spectra of most of the other isomers, and consequently was examined in greater detail by preparation of the deuterated analogue, 1-(4-methoxy-d_3-3-nitrobenzyl)isoquinoline (**1e**). The mass spectra of **1d** and **1e** are partially summarized in Table I. Analogous to the monosubstituted benzylisoquinolines **1a–c** the principal fragmentations involve the benzylic hydrogen and the nitro and methoxy substituents. On the basis of metastable transitions and isotopic labeling data (Table I), the sequence and mode of formation of the principal fragment ions in the spectrum of **1d** are shown in Scheme IV. The evidence from metastables supports the formation of $[M - OH]^+$ (*m/e* 277) via a two-step process (*m/e* 294 → 293 → 277). In general, the same mechanisms seem applicable to the formation of ions of the same mass in the spectra of the isomers

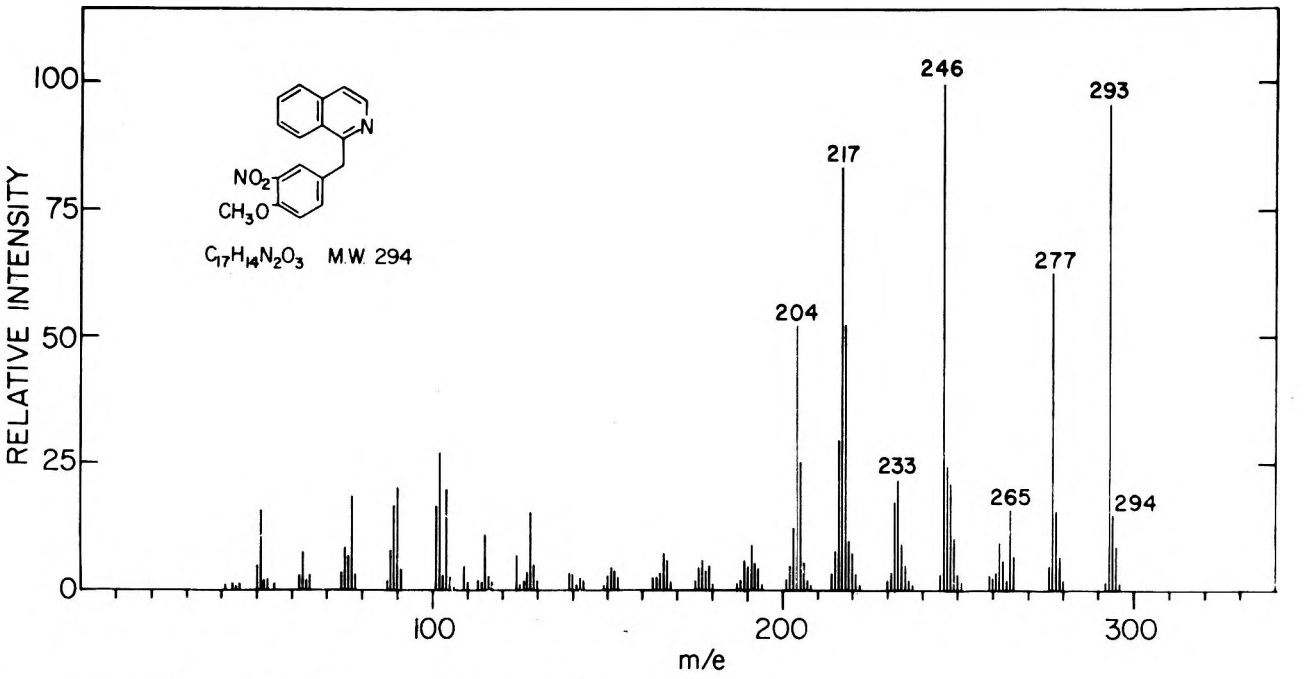


Figure 2. Mass spectrum of 1-(4-methoxy-3-nitrobenzyl)isoquinoline (**1d**).

Scheme IV

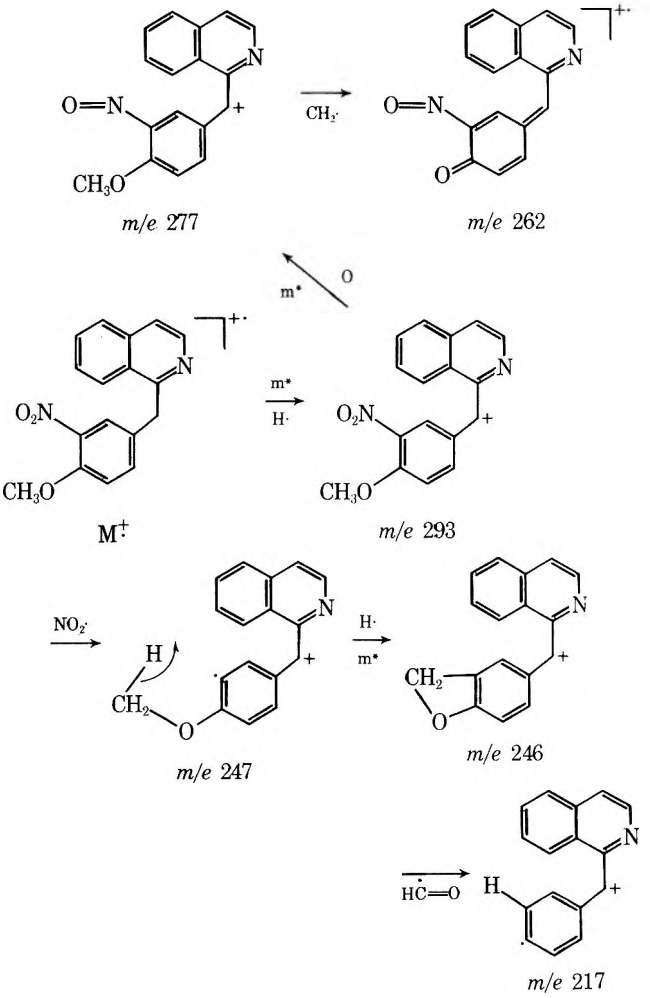
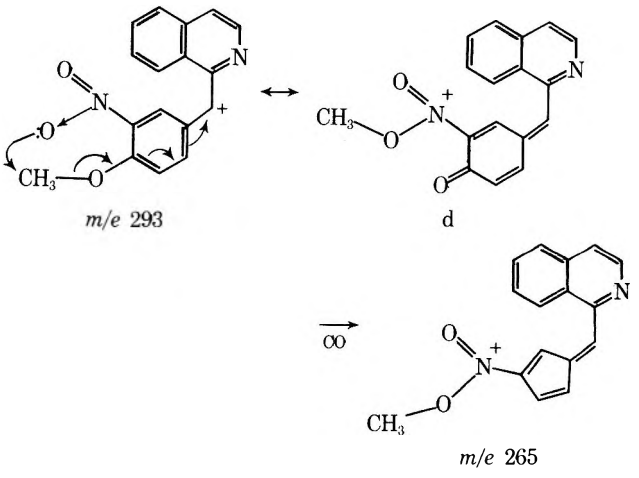


Table I. Mass Shifts of Principal Ions in the Spectra of 1d and 1e

1d	1e	ΔM
294	297	3
293	296	3
277	280	3
265	268	3
262	262	0
246	248	2
233	233	0
217	218	1
204	204	0

I), and is formed by elimination of CO from $[M - H]^+$ (Scheme V). Intramolecular migration of the *O*-methyl group

Scheme V



is a requirement for this process and can be induced by interaction with the vicinal nitro group as shown in Scheme V. The postulated alkyl group migration is consistent with previously proposed mechanisms involving intramolecular group transfers in systems containing heteroatoms and/or aromatic ring systems.[15,16] The resulting quinone-type intermediate

1f, 1g, and **1h.**

Of particular mechanistic interest is the occurrence of an ion at *m/e* 265 in the spectrum of **1d.** This ion contains the 4-methoxy group as indicated by the 3-amu shift in the spectrum of the deuterated methoxy derivative, **1e** (see Table

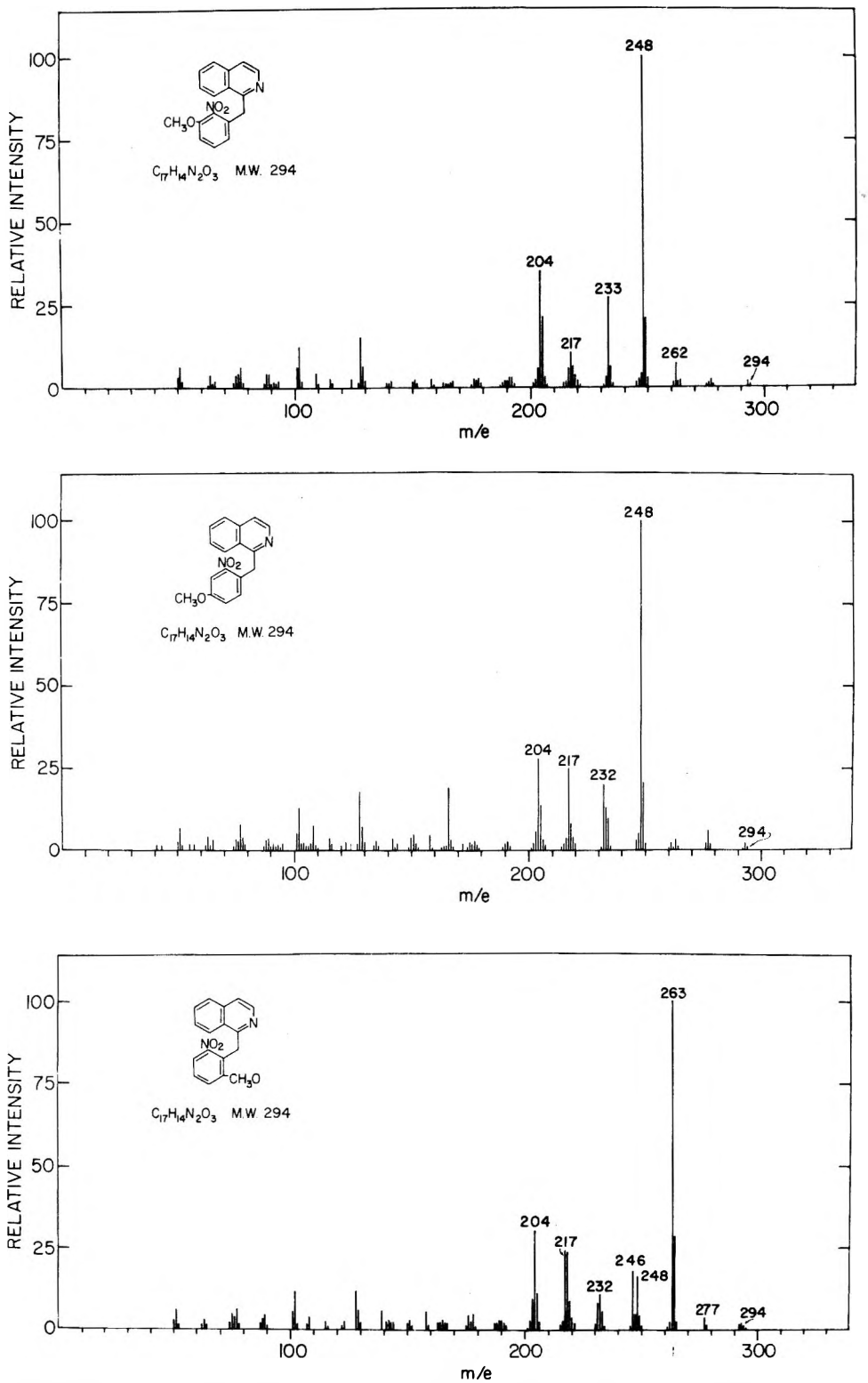
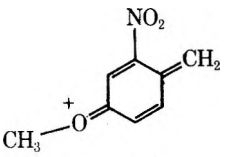


Figure 3. Mass spectra of 1-(3-methoxy-2-nitrobenzyl)isoquinoline (**1f**, top spectrum), 1-(4-methoxy-2-nitrobenzyl)isoquinoline (**1g**, center), and 1-(6-methoxy-2-nitrobenzyl)isoquinoline (**1h**, bottom spectrum).

d is favorably disposed to the elimination of CO, a characteristic process in the spectra of such compounds.[17]

As stated earlier, in the spectra of derivatives containing an ortho nitro group (**1f**, **1g**) or a 2-nitro and 6-methoxy group as in **1h**, the $M\cdot^+$ ion and the $[M-1]^+$ ion intensities are relatively low. In comparing the spectra of **1f** and **1g**, major differences are noted in the peaks at *m/e* 166, 232, and 233. The relatively higher abundance of the *m/e* 166 ion in the spectrum of **1g** in contrast to that of **1f** may be rationalized by the ability of the *p*-methoxy isomer **1g** to contribute the additional

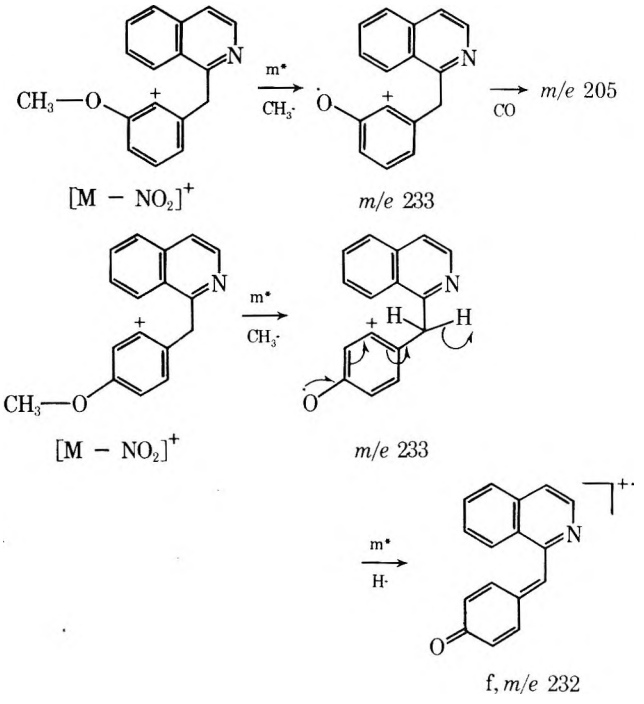


e, *m/e* 166

quinone-type resonance structure e to the stabilization of this fragment ion, following cleavage of the benzyl–isoquinoline linkage. A similar rationale may be applied to explain the

further breakdown of *m/e* 233 to *m/e* 232 in the spectrum of **1g** as opposed to that of **1f** in which only an abundant *m/e* 233 ion is observed. Following loss of the *O*-methyl group further loss of an α-benzyl hydrogen in **1g** is more favorable than **1f** because of the resulting benzoquinone-type ion f. In contrast, the spectrum of **1f** exhibits the competing fragmentation of *m/e* 233 to *m/e* 205 by loss of CO (Scheme VI).

Scheme VI



Chemical Ionization Studies. As noted above, the presence of a substituent in the ortho position of the benzyl ring results in molecular ion peaks of negligible intensity in the EI mass spectra of such compounds. In fact, the facile loss of a hydrogen from $M^{\cdot+}$ introduces an additional complication which hinders identification of the molecular ion peak with the highest degree of confidence. We thus examined the CI[18] mass spectra of these compounds, an approach also used by Fales et al.[19] in their mass spectral studies of related alkaloids containing the aporphine system.

The chemical ionization mass spectra of the benzylisoquinolines **1a–d** and **1f–h** obtained in methane reagent gas are summarized in Table II. As expected, the intensity of the molecular adduct ion peaks is greatly enhanced and, in most cases, these ions dominate the spectra of the respective compounds. It is significant that elimination of HNO_2 and/or CH_3OH from $[M + H]^+$ are the principal fragmentation processes encountered in these mass spectra, and these occur only in cases where the nitro and methoxy groups are present in the ortho position of the benzyl ring (**1a, 1f, 1g,** and **1h**). We suggest that release of the steric strain may be the driving force of this fragmentation process, consistent with the electron impact induced fragmentation.

In summary, the data presented suggest that fragmentation in the mass spectra of benzylisoquinolines is strongly dependent on positional substitution of functional groups. The presence of an ortho substituent on the benzene seems to introduce considerable steric strain and results in molecular ion peaks of very low relative intensity. Conversely, interaction between adjacent nitro and methoxy groups also results in the production of characteristic fragment ions due to intramolecular rearrangement. Thus, these processes can be used for structural characterization of substituted nitrobenzylisoquinolines by mass spectrometry.

Table II. Methane Chemical Ionization Mass Spectra of Benzylisoquinoline Derivatives

	1a	1b	1c	1d	1f	1g	1h
$[M + H]^{+a}$	80[b]	100	100	100	59	100	100
$M^{\cdot+}$	4	2	5	9		2	
$[MH - H_2O]^+$	33	3		10	5	5	3
$[MH - CH_3OH]^+$							29
$[MH - HNO_2]^+$	100	4			100	34	17

[a] Indicates type of ion. [b] Numbers refer to percent relative abundance of indicated ions.

Experimental Section

Melting points were determined on a Thomas-Hoover (Unimelt) apparatus and are uncorrected. All microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. The analytical values for deuterated compounds were obtained by the Pregl method. NMR spectra were recorded on a Varian T-60 spectrometer with Me_4Si as the internal standard. Mass spectra were obtained with a Nuclide 12-90-G mass spectrometer. The ionizing voltage was 70 eV, accelerating voltage 4.5 kV, and the ion source temperature 225 °C.

2-Benzoyl-1,2-dihydroisoquinaldonitrile (2). This compound was prepared by a modified procedure[8] of Weinstock and Boekelheide,[20] mp 125–126 °C (67%) (lit.[20] mp 125–126 °C).

1-(2-Nitrobenzyl)isoquinoline (1a). The preparation of this compound has been described.[5a]

2-Benzoyl-1-(4-nitrobenzyl)-1,2-dihydroisoquinaldonitrile (4b). The Reissert compound **2** (2.99 g, 11.4 mmol) was alkylated in 40 ml of DMF with 4-nitrobenzyl chloride (2.06 g, 12 mmol) in the presence of NaH (0.6 g, 12.5 mmol, 50% mineral oil suspension) according to the procedure of Uff et al.,[9] and yielded 0.12 g (6%) of **1b** and 0.9 g (20%) of **4b** as off-white needles, mp 200–202 °C. (The compound was previously obtained as an oil, which was hydrolyzed directly to **1b**.)[21] Recrystallization from ethanol gave an analytical sample: mp 203–204 °C; NMR ($CDCl_3$) δ 3.70 (q, J = 30 Hz, 2), 5.60 (d, J = 8 Hz, 1), 6.40 (d, J = 8 Hz, 1) 6.95–7.80 (m, 11), 7.95 (d, J = 8 Hz, 2).

Anal. Calcd for $C_{24}H_{17}N_3O_3$: C, 72.90; H, 4.33; N, 10.63. Found: C, 73.08; H, 4.33; N, 10.67.

1-(4-Nitrobenzyl)isoquinoline (1b). A mixture of 2.0 g (5 mmol) of **4b** in 50 ml of dry CH_3OH and 1.5 g (27 mmol) of finely powdered KOH was stirred at 45 °C for 6 min. After the addition of 100 ml of crushed ice the suspension was extracted with benzene (3 × 50 ml). The organic phase was washed with brine (2 × 30 ml) and 10% HCl (4 × 30 ml). The acid layers were combined and made basic with solid KOH under stirring and cooling in ice. The off-white precipitate was collected, washed neutral with water, and dried to give 1.02 g (76%) of **1b**, mp 96–99 °C. Recrystallization from ether gave mp 99–100 °C (lit.[21] 108–109 °C).

1-(4-Methoxybenzyl)isoquinoline (1c). Following the described procedure 17.3 (66 mmol) of **2** was reacted with equimolar amounts of 4-methoxybenzyl chloride (**3c**) and NaH in 250 ml of dry DMF. Hydrolysis of the oily intermediate **4c** with KOH in CH_3OH was carried out as described for **1h** to give a 69% yield of **1c**, mp 68–69 °C. The product was recrystallized from benzene–petroleum ether, mp 69–70 °C (lit.[21] 68.5–69.5 °C).

α-Bromo-4-methoxy-3-nitrotoluene (3d). In a manner analogous to the preparation of **3e**, 4-methoxy-3-nitrotoluene (10.0 g, 60 mmol), prepared from 4-methyl-2-nitrophenol with dimethyl sulfate, was brominated to yield 9.7 g (65%) of **3d**, mp 102–104 °C. An analytical sample was prepared from benzene–ligroin, mp 103–105 °C.

Anal. Calcd for $C_8H_8BrNO_3$: C, 39.04; H, 3.28; N, 5.69. Found: C, 39.31; H, 3.31; N, 6.01.

1-(4-Methoxy-3-nitrobenzyl)isoquinoline (1d). A. By Reissert Alkylation and Hydrolysis. The procedure employed was identical with that used in the preparation of **1h**. Thus, from 5.2 g (20 mmol) of **2** and equimolar amounts of **3d** and NaH in 80 ml of dry DMF the intermediate **4d** was obtained as an oil. Hydrolysis in 200 ml of dry CH_3OH with 7.5 g of KOH gave 2.64 g (50%) of **1d**, as faint yellow crystals, mp 117–118 °C.

B. By Nitration of 1-(4-Methoxybenzyl)isoquinoline (1c). To 24 ml of nitric acid (70%) was added in small portions, with stirring and cooling in ice, 3.0 g (12 mmol) of **1c**. The yellow solution was stirred at 0 °C for 6 h and at room temperature for 18 h. The mixture was poured onto 100 ml of crushed ice and neutralized with concentrated NH_4OH and the beige precipitate was washed neutral with

water. Trituration with $CHCl_3$ and drying gave 3.5 g (81%) of **1d** as the nitrate salt, mp 137 °C dec. A small sample was recrystallized twice from ethanol to give white needles, mp 142 °C dec.

Anal. Calcd for $C_{17}H_{14}N_2O_3 \cdot HNO_3$: C, 57.14; H, 4.23; N, 11.76. Found: C, 57.26; H, 4.43; N, 11.81.

The free base was liberated from the nitrate in 91% yield by suspending the salt in 20% NaOH at 40 °C. After stirring for 1 h the mixture was extracted with $CHCl_3$. The organic phase was washed neutral with water and dried over Na_2SO_4. Removal of the solvent left faint yellow crystals, mp 116–118 °C. An analytical sample was obtained from ethanol: mp 118–119 °C; NMR ($CDCl_3$) δ 3.73 (s, 3), 4.50 (s, 2), 6.83 (d, J = 8 Hz, 1), 7.20–8.20 (m, 7), 5.40 (d, J = 5 Hz, 1).

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.80; N, 9.52. Found: C, 69.39; H, 4.87; N. 9.57.

The NMR and IR spectra of the isoquinoline derivative **1d**, obtained by both methods, were identical. An admixture of the compounds had mp 118–119 °C.

4-Methoxy-d_3-3-nitrotoluene (6). Methylation of **5** (5.26 g, 34 mmol) with dimethyl-d_6 sulfate (10.0 g, 76 mmol, Merck) was carried out at 70–80 °C and pH 8 as described for **3d** to yield 4.83 g (86%) of crude **6**. Distillation [bp 102–104 °C (0.3 mm)] gave an analytical sample: NMR ($CDCl_3$) δ 2.33 (s, 3), 6.95 (d, J = 9 Hz, 1), 7.23 (d, J = 0 Hz, 1), 7.56 (d, J = 2 Hz, 1); mass spectrum (70 eV) m/e 170 ($M^{\cdot+}$, 55%).

Anal. Calcd for $C_8H_6D_3NO_3$: C, 56.46; H, D, 7.10; N, 8.23. Found: C, 56.23; H, D, 7.39; N, 7.95.

α-Bromo-4-methoxy-d_3-3-nitrotoluene (3e). A mixture of 1.85 g (10.9 mmol) of freshly distilled **6**, 1.94 g (10.9 mmol) of recrystallized N-bromosuccinimide, and 50 mg of benzoyl peroxide in 17 ml of dry CCl_4 was refluxed for 3 h under illumination. Without cooling the mixture was filtered, and the mother liquor was concentrated in vacuo to give 1.66 g (61%) of **3e** as a slightly yellow crystalline solid: mp 103–105 °C; NMR ($CDCl_3$) δ 4.46 (s, 2), 7.06 (d, J = 8 Hz, 1), 7.60 (dd, J = 10, 6 Hz, 1), 7.83 (d, J = 2 Hz, 1).

Anal. Calcd for $C_8H_5D_3BrNO_3$: C, 38.57; H, D, 4.45; N, 5.62. Found: C, 38.75; H, D, 4.67; N, 5.77.

1-(4-Methoxy-d_3-3-nitrobenzyl)isoquinoline (1e). Alkylation of **2** (1.35 g, 5.4 nmol) with equimolar amounts of **3e** (1.41 g) and NaH (0.26 g, 50% mineral oil suspension) in 30 ml of dry DMF was carried out as described for the synthesis of **1h**. Hydrolysis in 70 ml of dry methanol with 2.5 g of finely powdered potassium hydroxide yielded 0.63 g (39%) of **1e** as an almost white crystalline solid, mp 118–119 °C. Recrystallization from ethanol gave an analytical sample: mp 119 °C; NMR ($CDCl_3$) δ 4.53 (s, 2), 6.86 (d, J = 8 Hz, 1), 7.20–8.20 (m, 7), 8.43 (d, J = 5 Hz, 1).

Anal. Calcd for $C_{17}H_{11}D_3N_2O_3$: C, 68.67; H, D, 5.76; N, 9.42. Found: C, 68.55; H, D, 5.93; N, 9.57.

1-(3-Methoxy-2-nitrobenzyl)isoquinoline (1f). This compound was prepared as described in the literature.[5g]

1-(4-Methoxy-2-nitrobenzyl)isoquinoline (1g). The synthesis of this compound was carried out as described.[6]

α-Bromo-2-methoxy-6-nitrotoluene (3h). In a similar manner as in the preparation of **1e** the bromination of 2-methyl-3-nitroanisole (20 g, 60 mmol, Aldrich) gave 14.7 g (99%) of **3h**, mp 68–72 °C. Recrystallization from benzene–petroleum ether yielded 12.8 g (87%) of **3h**, mp 75–76 °C.

Anal. Calcd for $C_8H_8BrNO_3$: C, 39.04; H, 3.28; N, 5.69. Found: C, 39.14; H, 3.30; N, 5.58.

1-(2-Methoxy-6-nitrobenzyl)isoquinoline (1h). To a solution of 10.4 g (40 mmol) of **2** and 8.8 g (40 mmol) of **3h** in 160 ml of dry dimethylformamide was added under vigorous stirring and cooling (−20 °C) 1.92 g (40 mmol) of sodium hydride (50% mineral oil suspension) in a nitrogen atmosphere. Stirring was continued for 2 h at −20 °C and 18 h at room temperature. The brown mixture was diluted with 500 ml of chloroform, filtered, washed with water (3 × 100 ml), and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure left an oil which was immediately dissolved in 400 ml of dry methanol. Powdered potassium hydroxide (15 g) was added to the solution and after reflux for 5 min under vigorous stirring the mixture was poured onto 1000 ml of crushed ice. The resulting suspension was extracted with ethyl acetate (3 × 150 ml), the combined organic layers were washed neutral and dried, and the solvent was removed in vacuo to give after cooling in ice 5.0 g (42%) of **1h** as off-white crystals, mp 130–132 °C. Recrystallization from acetonitrile gave an analytical sample: mp 133–134 °C; NMR ($CDCl_3$) δ 3.73 (s, 3), 5.08 (s, 2), 7.0–7.9 (m, 6), 8.18–8.50 (m, 3).

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.80; N, 9.52. Found: C, 69.46; H, 4.77; N, 9.63.

Acknowledgment. We wish to acknowledge the State of New Jersey, Department of Health, Division of Narcotic and Drug Abuse, the American Foundation for Pharmaceutical Education, the Law Enforcement Assistance Administration, and the National Institutes of Health (GM-22787) for financial support.

Registry No.—**1a,** 17750-45-7; **1b,** 21965-90-2; **1c,** 10172-49-3; **1d,** 60967-81-9; **1d** HNO_3, 61010-32-0; **1e,** 61010-33-1; **1f,** 53055-08-6; **1g,** 57559-54-3; **1h,** 60967-82-0; **2,** 844-25-7; **3b** (X = Cl), 100-14-1; **3c** (X = Cl), 824-94-2; **3d** (X = Br), 61010-34-2; **3e** (X = Br), 61010-35-3; **3h** (X = Br), 19689-86-2; **4b,** 61010-36-4; **4c,** 61010-37-5; **4d,** 61010-38-6; **5,** 119-33-5; **6,** 61010-39-7; 4-methoxy-3-nitrotoluene, 119-10-8; nitric acid, 7697-37-2; dimethyl-d_6 sulfate, 15199-43-6; N-bromosuccinimide, 128-08-5; 2-methyl-3-nitroanisole, 4837-88-1.

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Notes

Aporphines. 20.[1] Chemically Induced Fragmentation of Nitrobenzylisoquinolinium Salts

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Received August 16, 1976

The importance of 1-(2-nitrobenzyl)isoquinolines and their quaternary salts as key intermediates in the synthesis of aporphine alkaloids has been well documented in the recent literature.[2] Aporphine alkaloids can thus be conveniently prepared by the reduction of the isoquinolinium salts of 1-(*o*-nitrobenzyl)isoquinolinium salts and subsequent Pschorr cyclization.[3,4] In the course of the synthesis of such aporphines for biological evaluation, we have observed C-1 to C-α bond fission when certain 1-(2-nitrobenzyl)isoquinolinium salts (i.e., **1a**) were treated with excess potassium borohydride in refluxing ethanol.[5] In the limited number of 2-nitrobenzylisoquinolinium salts examined in these earlier experiments, we concluded that cleavage occurs when the nitro group is coplanar with the benzene ring and is able to stabilize the transition state for the nitrotoluene anion (i.e., **1a** and **1g**).[4,5] However, when the nitro group is sterically hindered and forced out of the plane of the benzene ring as in the case of **1e** and **1f** only reduction to the tetrahydrobenzylisoquinoline derivative takes place.[5] In an extension of these earlier studies several positional isomers of nitrobenzylisoquinolinium salts **1** were synthesized or were available in our laboratory and subjected to conditions known to lead to fragmentation. The quaternary salts **1** were prepared by refluxing the appropriate nitrobenzylisoquinoline[1] with either methyl iodide or 1-iodopropane and were then subjected to borohydride reduction as described in the Experimental Section.

Results and Discussion

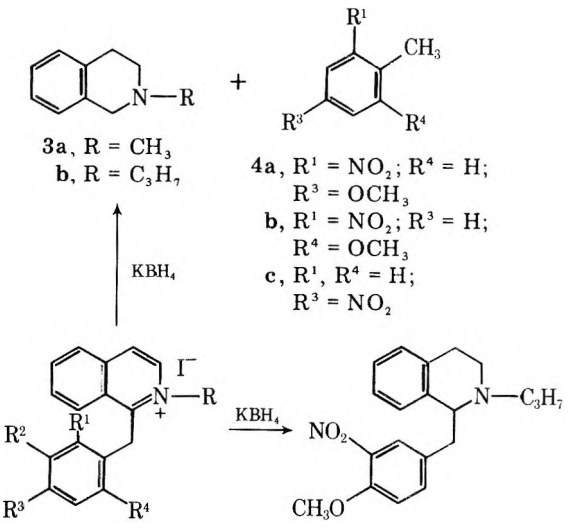
Refluxing **1a–c,g,h** in aqueous ethanol with an excess of the reducing agent leads to the isolation of the cleavage products *N*-propyl- and *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**3a** and **b**) and the nitrotoluenes **4a–c** (Scheme I). Thus, as previously proposed,[5] in the absence of steric constraints the incipient negative charge of the benzyl anion is transmitted through the conjugated system to the nitro group, leading to scission of the carbon–carbon bond.

A similar case can be presented for the observed fragmentation of 1-(4-nitrobenzyl)isoquinoline methiodide (**1b**) to *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**3a**) and 4-nitrotoluene (**4c**). Although the nitro group resides in the para position of the benzyl function, the substituent is still capable of accepting the electron pair.

In sharp contrast to these fragmentations is the reduction of 1-(4-methoxy-3-nitrobenzyl)isoquinoline propiodide (**1d**) to the corresponding benzyltetrahydroisoquinoline (**5**). Despite reaction conditions favoring cleavage, no scission of the exocyclic linkage was observed. The transition state cannot be stabilized by resonance, since the nitro group in the meta position is incapable of accepting the negative charge.

The failure to cleave under fragmentation conditions was in fact used to establish the structure of the product obtained from the reaction of 1-(4-methoxybenzyl)isoquinoline with nitric acid.[1] These results lend further support to the mechanism proposed[5] for such a carbon–carbon cleavage under these conditions. It is of interest to note that in the cleavage with KBH_4 as in the nitrobenzylisoquinolinium salts, the steric effects are reflected in electronic (resonance) phenomona as a function of the planarity of the nitro group and the benzene ring. However, in the case of the ionically induced MS fragmentations observed for the nitrobenzylisoquinolines discussed in the previous paper,[1] the steric effects in such fragmentations are reflected primarily in the case of elimination of the NO_2 or OCH_3 group.

Scheme I



1a, R = CH_3; R^1 = NO_2; R^2 = R^3 = R^4 = H **5**
b, R = CH_3; R^1 = R^2 = R^4 = H; R^3 = NO_2
c, R = C_3H_7; R^1 = NO_2; R^2, R^4 = H; R^3 = OCH_3
d, R = C_3H_7; R^1 = R^4 = H; R^2 = NO_2; R^3 = OCH_3
e, R = CH_3; R^1 = NO_2; R^2 = R^3 = OCH_3; R^4 = H
f, R = CH_3; R^1 = NO_2; R^2 = OCH_3; R^3 = R^4 = H
g, R = CH_3; R^1 = NO_2; R^2 = R^4 = H; R^3 = OCH_3
h, R = C_3H_7; R^1 = NO_2; R^2 = R^3 = H; R^4 = OCH_3

Experimental Section

Melting points were determined on a Thomas-Hoover (Unimelt) apparatus and are uncorrected. All microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. NMR spectra were recorded on a Varian T-60 spectrometer with Me_4Si as the internal standard.

1-(4-Nitrobenzyl)isoquinoline Methiodide (1b) A mixture of 1-(4-nitrobenzyl)isoquinoline[1] (0.12 g, 0.45 mmol) in 5 ml of methyl iodide was allowed to reflux for 4 h. After cooling in ice, the yellow crystals were collected, washed with ether, and dried to give 0.17 g (93%) of **1b**, mp 222–224 °C dec. The analytical sample was recrystallized from methanol. Anal. Calcd for $C_{17}H_{15}IN_2O_2$: C, 50.26; H, 3.72; N, 6.90. Found: C, 50.10; H, 3.87; N, 6.98.

1-(4-Methoxy-2-nitrobenzyl)isoquinoline Propiodide (1c). The preparation of this compound has been reported elsewhere.[4]

1-(4-Methoxy-3-nitrobenzyl)isoquinoline Propiodide (1d). A mixture of 1-(4-methoxy-3-nitrobenzyl)isoquinoline[1] (1.3 g, 4.4 mmol) in 15 ml of 1-iodopropane was allowed to reflux for 48 h. The yellow crystals were collected, washed with ether, and dried to give 1.73 g (85%) of **1d**, mp 217–218 °C dec. Recrystallization from methanol did not change the melting point. Anal. Calcd for $C_{20}H_{21}IN_2O_5$: C, 51.73; H, 4.56; N, 6.07. Found: C, 51.45; H, 4.56; N, 5.97.

In a similar manner as described for **1d** above, **1-(2-methoxy-6-nitrobenzyl)isoquinoline propiodide (1h)** was prepared, mp 214

† Abstracted in part from the thesis of W.P.D. submitted in partial fulfilment of the Ph.D. degree, Northeastern University, June 1976.

°C dec. Anal. Calcd for $C_{20}H_{21}IN_2O_3$: c, 51.74; H, 4.56; N, 6.03. Found: C, 51.66; H, 4.66; N, 6.03.

Potassium Borohydride Reductions. General Procedure. A stirred suspension of the quaternary salt (3 mmol) in a mixture of ethanol (24 ml) and water (11 ml) was heated to reflux. Potassium borohydride (36 mmol) was added in small aliquots over a period of 30 min. Refluxing was continued for 4.5 h and the mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, water (50 ml) was added to the residue, and extraction with ether (3 × 40 ml) followed. The combined organic layers were successively washed with 10% HCl (2 × 25 ml), water (25 ml), 10% NaOH (2 × 25 ml), and water (2 × 25 ml). After drying over Na_2SO_4 the solvent was removed in vacuo to give the toluene derivative (reduction and fragmentation). The combined acid layers were made basic by addition of solid potassium hydroxide under stirring and cooling in ice. Extraction with ether (2 × 25 ml) followed. The organic phases were washed with water and dried and the solvent was removed to yield the N-substituted 1,2,3,4-tetrahydroisoquinoline derivative (reduction and fragmentation), or the substituted 1-benzyl-1,2,3,4-tetrahydroisoquinoline (reduction only).

A. Reduction of 1-(4-Methoxy-2-nitrobenzyl)isoquinoline Propiodide (1c). Under identical conditions as described above 1.4 g (3 mmol) of **1c** was reduced to give 0.35 g (69%) of 4-methoxy-2-nitrotoluene (**4a**) and 0.46 g (87%) of 2-propyl-1,2,3,4-tetrahydroisoquinoline (**3b**) as an oil.

The hydrochloride of **3b** was formed and recrystallized from methanol–ether, mp 242 °C (lit.[6] mp 242 °C).

B. Reduction of 1-(2-Methoxy-6-nitrobenzyl)isoquinoline Propiodide (1h). Similarly reduced with 2.0 g (37 mmol) of potassium borohydride was 1.3 g (2.8 mmol) of **1h** to give 0.37 g (79%) of 2-methyl-3-nitroanisole (**4b**), mp 46–49 °C (lit.[7] mp 52 °C), and 0.41 g (84%) of **3b**, which was identified as described above.

C. Reduction of 1-(4-Methoxy-3-nitrobenzyl)isoquinoline Propiodide (1d). Only one product, 1-(4-methoxy-3-nitro)-2-propyl-1,2,3,4-tetrahydroisoquinoline (**5**), was obtained from the reduction of **1d** (2.8 mmol) with 2.0 g (37 mmol) of potassium borohydride. The reaction yielded 0.75 g (79%) of **5** as an oil.

A hydriodide of **5** was prepared, mp 184–185 °C. Recrystallization from absolute ethanol gave an analytical sample, mp 184 °C.

Anal. Calcd for $C_{20}H_{25}IN_2O_3$: C, 51.28; H, 5.38; N, 5.98. Found: C, 51.20; H, 5.45; N, 5.84.

D. Reduction of 1-(4-Nitrobenzyl)isoquinoline Methiodide (1b). Reaction of **1b** (1.3 g, 3.2 mmol) with 2.44 g (45 mmol) of potassium borohydride afforded 0.16 g (36%) of 4-nitrotoluene (**4c**), mp 49–51 °C (lit.[8] mp 54°C), and 0.4 g (85%) of 2-methyl-1,2,3,4-tetrahydroisoquinoline (**3a**), picrate mp 152–153 °C dec (lit.[5] mp 156 °C dec).

Acknowledgments. We wish to acknowledge the financial support of the state of New Jersey, Department of Health, Division of Narcotic and Drug Abuse Control, and the American Foundation for Pharmaceutical Education for the 1975–1976 Gustaves A. Pfeiffer Memorial Research Fellowship to J.L.N.

Registry No.—**1b,** 60967-77-3; **1c,** 57559-56-5; **1d,** 60967-78-4; **1h,** 60967-79-5; **3a** picrate, 15032-31-2; **3b,** 57928-05-9; **3b** HCl, 57464-74-1; **4a,** 17484-36-5; **4b,** 4837-88-1; **4c,** 99-99-0; **5,** 60967-80-8; **5** HI, 60996-52-3; 1-(4-nitrobenzyl)isoquinoline, 21965-90-2; methyl iodide, 74-88-4; 1-(4-methoxy-3-nitrobenzyl)isoquinoline, 60967-81-9; 1-(2-methoxy-6-nitrobenzyl)isoquinoline, 60967-82-0; iodopropane, 107-08-4.

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Hydrogen Abstraction from Substituted Phenylacetonitriles[1]

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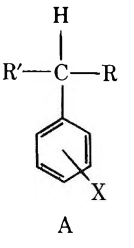
Received August 10, 1976

In the course of the development of linear free energy relationships, certain reaction types have required the introduction of new substituent parameters. Hammett's σ^- [3] and Brown's σ^+ [4] values recognize the possible extra stabilization shown by certain functional groups when charge is formed in direct conjugation with the ring. Reactions leading to the formation of benzylic radicals have long been correlated with σ^+ parameters.[5] It also seems likely that benzylic hydrogen abstraction by "nucleophilic radicals" may ultimately yield optimum correlation with σ^-.[6] The generally accepted view is that this would be indicative of charge separation in the transition state of the rate-determining step.[7]

Although there is substantially less documentation, it has been observed that some ring substituents show an enhanced ability to favor certain radical reactions. The copolymerization of substituted styrenes with maleic anhydride, for example, is generally favored by electron-donating groups in the former.[8] The *p*-CN compound, however, exhibits a reactivity which seems far greater than expected. This substituent may also behave anomalously in other systems. Pryor, Davis, and Gleaton have noted that both benzonitrile and nitrobenzene show enhanced reactivity in the para position during radical methylation.[9] This was attributed to an "extra resonance effect". Along these lines, a particularly striking result is the recent observation of Kaba and Ingold that tricyanomethyl radical is an extremely stable species.[10] This must be at least partially attributable to resonance effects and is somewhat surprising as most of the "persistent" carbon radicals studied by Ingold's group show much greater steric congestion at the radical site.[11]

Recently, one of us put forward an empirical approach for the evaluation of Hammett ρ values for benzylic hydrogen



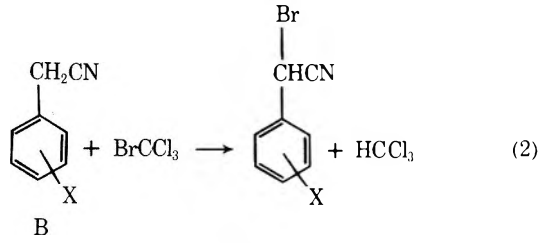
A

abstraction from ring-substituted–α-substituted toluenes, A, by the trichloromethyl radical.[12] The essence of the argument is that for any single series of compounds, the sensitivity toward change of ring substituent would be a function of both the electronic and steric parameters associated with groups directly bonded to the reaction site. This may be expressed by eq 1, where the steric and electronic substituent parameters utilized refer to those for R and R′. Further studies with un-

tested systems have led to experimental ρ values in excellent agreement with their predicted counterparts.[12,13]

$$\rho = -0.606(\sum \sigma_p^+) + 0.195(\sum E_s) - 1.063 \quad (1)$$

It was felt that the above approach might be utilized to assess the importance and extent of radical stabilizing ability of the cyano group. With this in mind, a series of substituted phenylacetonitriles, B, was prepared and reacted photolytically with bromotrichloromethane at 70 °C (eq 2). The sub-



(2)

stituted phenylacetonitriles utilized were either purchased or prepared from the corresponding benzyl chlorides by refluxing in aqueous sodium cyanide solution.[14]

Product studies on unsubstituted phenylacetonitrile showed the major product to be the α-brominated compound. Some dibromination also seemed to occur (ca. 12%). Much more surprising was the isolation of relatively large amounts (ca. 23%) of 2,3-diphenylsuccinonitrile. This compound has been prepared by the action of copper powder or sodium iodide on α-bromophenylacetonitrile.[15] Such agents were absent during the present studies, however, and the simplest explanation for the formation of 2,3-diphenylsuccinonitrile is that it arises by coupling of two α-cyanobenzyl radicals. Little, if any, bibenzyl has been observed in the corresponding reaction of toluene. The α-cyano group appears to impart an added stability to the benzylic radical.

Relative rates of reaction were determined as follows. A substituted phenylacetonitrile and the parent compound were made to compete directly for the trichloromethyl radical. Small amounts of chlorobenzene or *o*-dichlorobenzene were present to function as unreactive internal standard and the reaction course was monitored by GLC. All kinetic runs were carried out in replicate under a nitrogen atmosphere at reduced pressure. Reaction times varied from 91 to 144 h. Total reactivity of the phenylacetonitriles was from 33.7 to 89.9%. The case of *p*-methylphenylacetonitrile caused an additional problem because of the presence of two nonequivalent benzylic positions. It was found that this compound underwent reaction at the methylene group to an extent of 85.4 ± 0.7%. Relative rates of reaction are given in Table I.

Optimum correlation within the framework of the Hammett equation was with σ^+ parameters. This is not surprising. Almost all hydrogen abstractions using bromotrichloromethane have shown this effect.[5] An experimental ρ value of −0.55 ± 0.02 was obtained. The correlation constant of −0.994 was associated with this value. This result is graphically shown in Figure 1.

A problem arose in calculating the predicted ρ value from eq 1. The Taft steric parameter E_s for the cyano group had apparently not been determined. Qualitatively it was felt that a relatively small linear substituent should have rather modest steric demands. Support for this view can be obtained from the study of group conformational free energy differences in monosubstituted cyclohexanes.[16] On a semiquantitative scale this term for the cyano group is almost negligible. The conformational preference for the cyano group to occupy an equatorial site is even less than that of small single atoms such as fluorine. With this as a guide, a rather large range of possible E_s values was considered between the extremes of cyano

Table I. Relative Rates of Hydrogen Abstraction from Substituted Phenylacetonitriles by Trichloromethyl Radical at 70 °C

Registry no.	Substituent	σ^+	Rel rate	No. of runs
4693-91-8	*p*-OCH_3	−0.778	2.82 ± 0.05	5
35675-44-6	*p*-CH_3[a]	−0.311	1.33 ± 0.05	6
3288-99-1	*p*-$C(CH_3)_3$	−0.256	1.26 ± 0.08	7
140-29-4	H	0.000	1.00	
140-53-4	*p*-Cl	0.114	0.81 ± 0.02	7
501-00-8	*m*-F	0.352	0.64 ± 0.01	6
1529-41-5	*m*-Cl	0.399	0.60 ± 0.03	5
2338-76-3	*m*-CF_3	0.520	0.52 ± 0.02	7

[a] Corrected for reaction at the methylene position only.

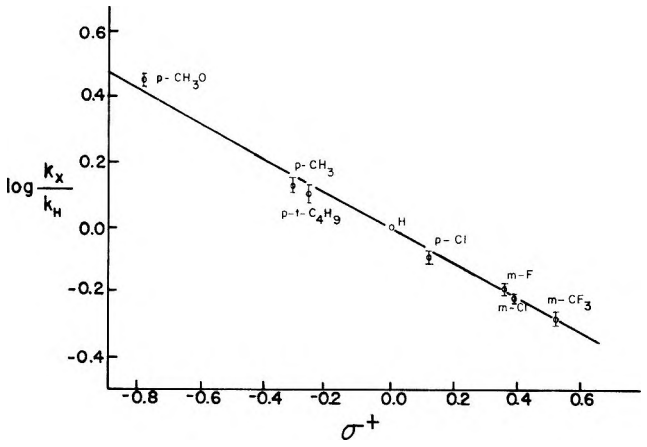


Figure 1. Logarithms of relative rates of reaction vs. σ^+ parameters.

equivalent to hydrogen (1.24) and cyano intermediate between hydrogen and methyl (0.62). Utilization of these values in eq 1 (along with an E_s value of 1.24 for hydrogen and the standard electronic parameters[17]) led to calculated ρ values in the range of −0.98 to −1.10.

It is felt that the lack of agreement between the experimental and theoretical ρ values is explicable by those special radical stabilizing effects of the cyano group invoked by earlier workers. Before terminating this discussion, however, it should be mentioned that a cyano group bonded directly to the site of a benzylic hydrogen apparently need not always exhibit enhanced resonance stabilization.

Friedrich, Friedrich, Andrews, and Keefer have described the reaction between *N*-bromosuccinimide and a series of α-substituted toluenes.[18] No particular rate enhancement was observed for the cyano group relative to the other nine substituents examined. The data defined a good linear relationship with σ^+,[18] or with an expanded four-parameter equation which included steric parameters.[19] It is felt, however, that there may be no incongruity between these findings and those reported above.

The enhanced stabilizing effect of the cyano group in hydrogen abstraction reactions should only be observed in extremely endothermic processes wherein the transition state shows pronounced radical character. If different abstracting species are generated from *N*-bromosuccinimide and bromotrichloromethane,[20] it seems plausible that the latter may be involved in a more endothermic reaction.[19,20] In support of this view, the reactivity of phenylacetonitrile toward bromotrichloromethane is found to be 0.94 ± 0.04 times that of toluene. The ratio of labilities of the respective benzylic hydrogens is 1.41:1 as compared with 0.22:1 found in the reaction with *N*-bromosuccinimide.[18]

Experimental Section

Materials. All commercial compounds were distilled prior to use. Physical constants agreed with literature values and GLC analysis indicated minimal purities of 99%. Most of the substituted phenylacetonitriles were prepared similarly to the following example. Purities were comparable to those of the other compounds. Physical properties and IR and NMR spectra were in accord with literature values and/or expectation.

Preparation of (*p*-Methylphenyl)acetonitrile. (*p*-Methylphenyl)acetonitrile was prepared by the addition over 35 min of 50 g (0.43 mol) of *p*-methylbenzyl chloride in 50 g of ethanol to 25 g (0.51 mol) of sodium cyanide dissolved in 23 ml of distilled water. The mixture was refluxed at 82 °C with a water-cooled, glass helices packed condenser for 4 h, after which time the mixture had resolved into a dark-brown upper layer and a dark-amber lower layer. The mixture was cooled and suction filtered to remove the precipitated salt, and approximately 60 ml of ethanol was carefully distilled off at 77 °C. The remaining material was extracted with four times its volume of ethyl ether. The organic material was washed with equal volumes of sulfuric acid, saturated sodium bicarbonate, and concentrated sodium chloride solutions, and dried over a few grams of anhydrous magnesium sulfate. After filtration, the material was fractionally distilled. A yield of 5.5 g (13%) of 99.9% pure product was obtained.

Procedure for Kinetic Runs for the Reaction of Bromotrichloromethane with the Substituted Phenylacetonitriles. Solutions of the two phenylacetonitriles, bromotrichloromethane, and o-dichlorobenzene (or chlorobenzene) were prepared in the approximate molar ratio of 1:1:10:0.5. Approximately 0.75 ml of the solution was placed in each of the several ampules (usually eight ampules were prepared simultaneously). The ampules were cooled to dry ice–isopropyl alcohol temperature until the solutions solidified. The ampules were evacuated at 0.4–1.5 Torr, filled with nitrogen gas, and then warmed to room temperature. This process was repeated three times. After cooling and evacuation, the tubes were sealed and one was reserved for the analysis of the unreacted starting materials. The remainder were placed horizontally just below the surface of a mineral oil constant temperature bath maintained at 70.0 ± 0.5 °C. The samples were irradiated with ultraviolet light provided by a Sylvania 275-W sun lamp placed 20 cm above the surface of the oil. Reaction times varied from 91.25 to 144.25 h, by which time 33.74–89.89% of the phenylacetonitriles had reacted. The ampules were then cooled and opened. Analysis of the mixtures, both before and after reaction, was carried out via GLC on either a 3% SE-30 on Varaport 30 or a 12% Carbowax 20M on Chromosorb P column. Conversion of raw data to relative rate expressions followed standard techniques.[20]

Registry No.—Bromotrichloromethane, 75-62-7.

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The Facile Oxidation of Phenacyl Bromides with *N,N*-Dialkylhydroxylamines

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Received August 17, 1976

Semiionic compounds such as sulfoxides[1a,b] and amine *N*-oxides[1b-d] have been used to oxidize α-halocarbonyl compounds to α-dicarbonyl compounds. It has been shown recently that the reaction of phenacyl bromides (**1**) with 1,1-dimethylhydrazine resulted in the formation of arylglyoxaldimines (**3**) which then underwent further reactions.[2] Inas-

$$\underset{\mathbf{1}}{\mathrm{ArCOCH_2Br}} + \underset{\mathbf{2}}{\mathrm{Me_2NNH_2}} \xrightarrow[-HBr]{-Me_2NH} \underset{\mathbf{3}}{[\mathrm{ArCOCH{=}NH}]} \xrightarrow{-H_2O} \underset{\mathbf{4}}{\mathrm{Ar}\text{-}\overset{\overset{N}{\|}}{\underset{\underset{H}{N}}{\langle}}\text{-}\mathrm{COAr}} \quad (1)$$

much as the net result of this reaction amounts to the conversion of the $-CH_2Br$ group to the $-CH{=}NH$ function, it was reasonable to anticipate that *N,N*-dialkylhydroxylamines might convert phenacyl bromides to the corresponding glyoxals. This note describes the results of our investigations of the reaction of phenacyl bromides with *N,N*-diethyl- and *N,N*-dibenzylhydroxylamines.

The reaction of phenacyl bromide with *N,N*-diethylhydroxylamine (DEHO) in methanol gave a 78% yield of phenylglyoxal as a thick, yellow-orange oil which slowly hydrated on standing, mp 90–91 °C, identical with an authentic sample.[3] Similarly, other phenacyl bromides were converted to the corresponding glyoxals in good to excellent yields (Table I), although no attempts were made to optimize the yields.

To our knowledge, this is the first report of the use of *N,N*-dialkylhydroxylamines as *oxidizing* agents for organic compounds,[4] which is to be contrasted with the recent disclosure of the *reduction* of *p*-benzoquinones to the corresponding hydroquinones with *N,N*-diethylhydroxylamine.[5] By analogy with the reaction of **1** with *N,N*-dimethylhydra-

$$\mathrm{ArCOCH_2Br} + \mathrm{Et_2NOH} \longrightarrow \underset{\mathbf{5}}{[\mathrm{ArCOCH_2\overset{+}{N}(Et)_2}\ \mathrm{Br^-}\ \mathrm{HO}]} \xrightarrow{-HBr} \underset{\mathbf{6}}{[\mathrm{ArCOCH_2\overset{+}{N}(Et)_2}\ \mathrm{O^-}]}$$

$$\rightarrow \underset{\mathbf{7}}{[\mathrm{ArCOCH_2ON(Et)_2} \rightleftharpoons \mathrm{Ar}\text{-}\overset{\overset{O}{\|}}{\underset{\underset{H}{O}}{\langle}}\text{-}\mathrm{NEt_2}]} \longrightarrow \underset{\mathbf{8}}{\mathrm{ArCOCHO}} + \mathrm{Et_2NH{\cdot}HBr} \quad (2)$$

† Taken from the B.A. Thesis of V. E. Gunn, University of Massachusetts at Boston, 1977.

Table I. Oxidation of Phenacyl Bromides with *N,N*-Dialkylhydroxylamine[a]

$ArCOCH_2Br$ (I), Ar	Registry no.	ArCOCHO (yield, %)[b]	Registry no.	Mp of hydrate (lit. mp), °C
Ph	70-11-1	78 (80)[c]	1074-12-0	90–91 (90)[d]
p-BrPh	99-73-0	68 (74)[c]	5195-29-9	119–122 (128–129)[e]
p-PhPh	135-73-9	90 (75)[c]	4974-58-7	113–117 (117–121)[f]
m-MeOPh	5000-65-7	55	32025-65-3	99–100 (98–101)[g]
β-Naphthyl[h]	613-54-7	76	22115-06-6	93–96 (98)[d]

[a] All reactions were carried out in methanol at reflux for 2 h, except as otherwise noted. [b] As the glyoxal hydrates. [c] Yields with *N,N*-dibenzylhydroxylamine, *without* distillation. [d] "Heilbron's Dictionary of Organic Compounds". [e] G. A. Russel and G. J. Mikol, *J. Am. Chem. Soc.*, **88**, 5498 (1966). [f] F. Krohnke and E. Borner, *Ber.*, **69B**, 2006 (1936). [g] R. B. Moffett, B. T. Tiffany, B. D. Aspergren, and R. V. Heinzelman, *J. Am. Chem. Soc.*, **79**, 1687 (1957). [h] Reaction time: 8 h.

zine, one can postulate the initial formation of 1,1-diethyl-1-phenacylhydroxylammonium bromides (**5**)[2,4a] followed by a Meisenheimer rearrangement[6] of the amine *N*-oxides (**6**) to the *O*-phenacylhydroxylamines (**7**).[7] These latter intermediates could then fragment to the arylglyoxals and diethylamine, which was isolated as its hydrobromide salt in each case in nearly quantitative yields. Extension of this oxidation to other α-halo carbonyls has so far been less successful. Although benzil was obtained from the reaction of desyl chloride and DEHO, albeit in only 25% yield, so far only complex products and recovered starting materials have been obtained with 2-chlorocyclohexanone and α-bromopropiophenone. In the case of benzil, a control experiment clearly indicated that *N,N*-diethylhydroxylamine reacted further with benzil to give less than 30% of recovered benzil; no definite product has yet been isolated from the dark residue of this reaction.[8]

The Cope elimination is a competitive reaction when β hydrogens are available in the amine *N*-oxides.[6,9] In order to investigate this possibility, the reaction of phenacyl bromide with *N,N*-dibenzylhydroxylamine[10] was carried out. The reaction proceeded much more slowly (an orangy color develops almost immediately after mixing phenacyl bromide with DEHO) and a longer reflux period had to be used for the reactions to take place. Although the yields of arylglyoxals were not substantially different (see Table I), the undistilled products in these cases were nearly as pure as those obtained with DEHO *after* the distillation. This suggests that the Cope elimination, though not a major problem, may be occurring to a small extent, thus explaining the lesser purity of the products obtained with DEHO.

Thus, the reaction of *N,N*-diethylhydroxylamine with phenacyl bromide offers a useful and mild "nonoxidative" route to arylglyoxals. We are at present investigating the scope and mechanism of this reaction, with particular attention to the possible intervention of radicals in the putative Meisenheimer rearrangement.

Experimental Section

All melting points are uncorrected. *N,N*-Diethylhydroxylamine was obtained from Pennwalt Corp. and was distilled prior to use. *N,N*-Dibenzylhydroxylamine was prepared according to a published procedure.[10] The phenacyl bromides were used as purchased or prepared according to literature directions.

Oxidation of Phenacyl Bromides with *N,N*-Dialkylhydroxylamines. A. With *N,N*-Diethylhydroxylamine. A solution of 8.56 g (0.043 mol) of phenacyl bromide and 3.83 g (0.043 mol) of *N,N*-diethylhydroxylamine in 80 ml of methanol was heated to reflux with stirring for 2 h. Evaporation of the solvent followed by addition of 75 ml of ether to the residue precipitated diethylamine hydrobromide, mp 203–206 °C dec (lit.[11] mp 205 °C), in nearly quantitative yield. Evaporation of the ethereal solution left a residue which was distilled in vacuo to yield 4.5 g (78%) of phenylglyoxal. The other glyoxals reported in Table I were obtained by the same procedure.

B. With *N,N*-Dibenzylhydroxylamine. A solution of 5.00 g (0.025 mol) of phenacyl bromide and 5.33 g (0.025 mol) of *N,N*-dibenzylhydroxylamine in 80 ml of methanol was heated to reflux with stirring for 48 h. Evaporation of the solvent followed by addition of 80 ml of ether to the residue precipitated 5.31 g (76%) of dibenzylamine hydrobromide, mp 262–265 °C (lit.[12] mp 266 °C). Evaporation of the ethereal solution left a residue whose infrared spectrum matched that of the distilled compound above. The other glyoxals reported in Table I were obtained by the same procedure.

Acknowledgment. It is a pleasure to acknowledge generous gifts of *N,N*-diethylhydroxylamine from Mr. L. Gilette of the Pennwalt Co., Philadelphia, Pa.

Registry No.—*N,N*-Diethylhydroxylamine, 3710-84-7; *N,N*-dibenzylhydroxylamine, 621-07-8; dibenzylamine hydrobromide, 103-49-1.

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Heterocyclic Derivatives Formed from 2-Alkoxyimino Aldehydes and 1,2-Disubstituted Ethanes

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Received May 28, 1976

The preparation of 2-alkoxyimino aldehydes, **1**, by selenium dioxide oxidation of alkoxyiminoalkanes[1] provided a functional group adjacent to an oxime which was susceptible to derivatization by nucleophilic reagents.[2] Derivatization of the aldehyde moiety with molecules containing two nucleophilic

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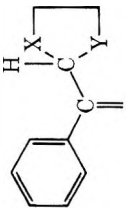
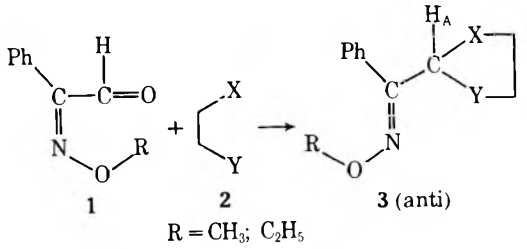
Table I. Compounds Prepared by Reaction of 1,2-Substituted Ethanes with 2-Alkoxyimino Aldehydes



Registry no.	R	X	Y	Bp, °C (Torr)	Refractive index	Mp, °C	Yield, %	Composition	Calcd, %				Found, %			
									C	H	N	S	C	H	N	S
53056-09-0		O	O			81–82	52	$C_{11}H_{13}NO_3$	63.77	6.28	6.76		63.63	6.45	6.56	
60978-34-9		O	O			51–52	45	$C_{12}H_{15}NO_3$	65.16	6.79	6.33		65.04	6.95	6.33	
60978-35-0		O	S	118–123 (0.008)	n^{23} 1.5587		12	$C_{11}H_{13}NO_2S$	59.19	5.83	6.28	14.35	59.08	5.62	6.35	14.40
60978-36-1		O	S	112–113 (0.008)	n^{23} 1.5571		39	$C_{12}H_{15}NO_2S$	60.76	6.33	5.91	13.50	60.55	6.29	5.98	13.61
21504-27-8		S	S			113–114	76.8	$C_{12}H_{14}S_4$	50.21	5.01		44.70	50.15	5.06		44.50

Scheme I



1 2 3 (anti)

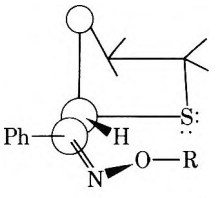
R = CH_3; C_2H_5

sites was carried out to generate heterocyclic systems (Scheme I), adjacent to the oxime function. Reaction of **1** with ethylene glycol (**2**, X = Y = O) and 2-mercaptoethanol (**2**, X = O; Y = S) proceeded to yield the corresponding cyclic acetal (**3**, X = Y = O) and hemithioacetal (**3**, X = O; Y = S), respectively. Starting with a pure geometric isomer of the aldehyde, **1**, the 1,3-dioxolane (**3**, X = Y = O) was synthesized without change in the configuration about the imino double bond. The oxathiolane, formed by reaction with mercaptoethanol (using either BF_3 or *p*-toluenesulfonic acid as catalyst), was a mixture of geometric isomers formed by apparent isomerization of the oxime group as determined by examination of the ^1H NMR spectra of the derivative. The methine proton, H_A, in compound **3** (X = O; Y = S; R = C_2H_5) appears as two single lines at 6.38 and 5.92 ppm, the upfield signal being 2.5 times greater in area than the downfield signal.[3] In addition, the methyl protons (1.2 ppm) appear as a complex multiplet, indicating a mixture of products, although only integrating for three protons.

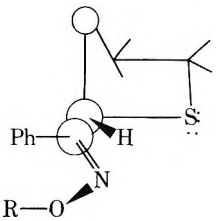
When the spectrum of **3** (X = O; Y = S; R = C_2H_5) was determined in deuteriochloroform or tetrahydrofuran at or above 60 °C, the relative line intensities of the methine ring proton, H_A, changed irreversibly, so that the downfield peak was 1.5 times greater in area than the upfield band.[3] The refractive index of the oxathiolane (determined at 23 °C) had changed from 1.5571 to 1.5634; however, no changes were observed in the mass spectrum or elemental analysis. Similar results were noted with the oximino methyl ether (**3**, X = O; Y = S; R = CH_3) where the refractive index measured at 23 °C changed from 1.5587 to 1.5631. Heating the samples at reflux in nonpolar solvents (benzene, carbon tetrachloride, or carbon disulfide) for 30 min, however, produced no change in the NMR spectrum or refractive index. Apparently, in polar solvents, the product that forms initially undergoes thermal isomerization of the oxime (with or without the concomitant inversion at the asymmetric carbon atom). Isomerization was not observed in nonpolar solvents.

The possibility of simple acid-catalyzed isomerization of the imine was excluded by azeotropic distillation of a chloroform solution of **1** with *p*-toluenesulfonic acid or boron trifluoride. No changes were observed. Variation in ring conformation was ruled out as a possible explanation for the apparent anomalies in the spectra because it was not possible to cause coalescence of the methine peaks on heating. Attempts to resolve the geometric isomers by thin layer or gas–liquid chromatography, however, were unsuccessful.

Assignment of structure of the isomers was tentatively made from chemical shifts, in a manner analogous to that in which configurational identification of isomeric benzaldoximes[4] was made; i.e., from the relative positions of the aldehydic proton absorption bands. The aldehydic proton is always deshielded in the syn form, and therefore appears at a lower field intensity than does the anti isomer. Similar shielding effects can be anticipated with 2-benzoyl-1,3-oxathiolane oxime *O*-alkyl ethers, resulting in the methine proton of the syn isomer (**4a**) absorbing downfield of the corresponding proton of the anti (**4b**) isomer. Accordingly, the major product of the condensation reaction is **4b**, in which the alkoxy group is trans to the



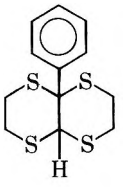
4a



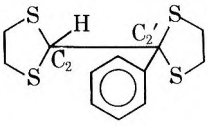
4b

oxathiolane ring. Heating in polar solvents results in predomination of the cis (**4a**) isomer.

Reaction of **1** with ethanedithiol (**2**, X = Y = S) produced a yellow, crystalline product in which the alkoxyimino moiety was no longer present, as determined from an examination of the infrared spectrum. However, characteristic bands for C–S vibration (ν 655 cm^{-1}) were apparent. Low-resolution mass spectral data (obtained at 10 eV) indicated that the compound had a molecular weight of 286, which, with the elemental analysis, was shown to correspond to the molecular formula $C_{12}H_{14}S_4$. It was concluded that 2 mol of 1,2-ethanedithiol had combined with 2-alkoxyiminophenylacetaldehyde, forming either of two structural isomers: a *cis*-naphthodithiane, **5**, or 2-phenyl-2-[2-(1,3-dithiolano)]-1,3-dithiolane (**6**).



5



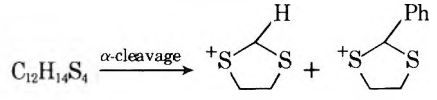
6

Elucidation of the structure of the $C_{12}H_{14}S_4$ compound was made by a mass spectrometric technique capable of distinguishing the pendant from the alternative fused ring system in the determination of the structure of glyoxal bisthioacetals.[5,6,7]

The major fragmentation pathway of the 2,2′-bis(1,3-dithiolanyl) derivative, **6**, involves α-cleavage of the molecular ion resulting in the loss of a 1,3-dithiolane ring fragment by homolysis of the C_2–$C_{2'}$ bond.

$C_{12}H_{14}S_4$ undergoes fission under electron impact at 10 eV[3] to generate the fragments shown in Scheme II. This mode of

Scheme II



m/e 105 (14%) *m/e* 181 (100%)

fragmentation, giving rise to α-cleavage products (*m/e* 181, 105), clearly excludes the fused bicyclic structure, **5**. It must be concluded, then, that the reaction of 2-alkoxyiminophenylacetaldehydes, **1**, with 1,2-ethanedithiol yields 2-phenyl-2-[2-(1,3-dithiolano)]-1,3-dithiolane (**6**).

In conclusion, whereas both sulfur and oxygen nucleophiles react at the carbonyl carbon, only the thiol reacts at the imino carbon. The high nucleophilicity of the soft mercaptan base permits reaction at both the harder Lewis acid (i.e., carbonyl carbon) and softer acid (i.e., imino carbon). Hydroxyl groups are less nucleophilic, harder bases and tend to react at the harder electrophilic (carbonyl) center, rather than the imino carbon, a less reactive, softer acid.[8] Reaction at the imino carbon occurs exclusively with the more nucleophilic, softer sulfur-containing bases. The isomerization of the oxime observed during reaction of **1** with 2-mercaptoethanol may reflect reaction of the thiol moiety at the imino carbon to yield a transient thiocarbinolamine. The free hydroxyl group in this intermediate lacks the reactivity to cause cyclization (with loss of alkoxyamine) but rather eliminates the reactant to re-form the oxime with concomitant loss of stereochemical purity. These results are consistent with the fact that the aldehydic carbonyl group is more polar and generally more reactive toward nucleophilic attack than the corresponding imino function.

The dioxolane and oxathiolane derivatives were submitted for pharmacological testing, and all showed moderate antibacterial activity toward *S. aureus* (Smith strain) and *K. pneumoniae* (AD strain) in an in vivo test.

Experimental Section

Preparation of 2-alkoxyiminophenylacetaldehydes was carried out as previously described and products had physical properties identical with reported values.[1]

General Procedure for Preparation of Heterocyclic Derivatives. The optimum conditions varied from compound to compound, but a general procedure involved heating a benzene solution containing the aldehyde and a 10% molar excess of ethylene glycol, 2-mercaptoethanol, or ethanedithiol in a round-bottom flask equipped with a Dean-Stark trap and a condenser fitted with a calcium chloride for 20 min. Five milligrams of *p*-toluenesulfonic acid or 1 ml of boron trifluoride etherate was added and heating at reflux continued for 24–48 h. The cooled benzene solution was washed with ice-cold saturated $NaHCO_3$ solution, then water and dried over anhydrous magnesium sulfate. The dried solution was decanted and the benzene removed by distillation to yield either a solid which could be recrystallized or an oil which was then purified by distillation.

Registry No.—**1** (R = CH_3), 32349-36-3; **1** (R = C_2H_5), 32349-37-4; **2** (X = Y = O), 107-21-1; **2** (X = O; Y = S), 60-24-2; **2** (X = Y = S), 540-63-6.

Supplementary Material Available. Full NMR data for oxime isomerization studies (3 pages). Ordering information is given on any current masthead page.

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Thermodynamic pK_a's for the Second Ionization of Some Alkylphosphonic Acids[1]

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Received June 18, 1976

There is considerable current interest in determining the curvature of Brønsted plots.[2] A structurally homogeneous set of acid–base catalysts covering a wide pK_a range is required for this purpose, and it is useful also if these catalysts are reasonably transparent to ultraviolet and visible light, for then rate measurements may be made by the very convenient spectroscopic method now in widespread use. Unfortunately, many of the acids and bases commonly employed as catalysts fail to meet these requirements, and it is of interest therefore to develop new catalyst sets.

Simple aliphatic phosphonic acids show considerable promise in this respect. They are readily available, highly stable substances with no strongly chromophoric groups, and in their second dissociation

Table I. Summary of pK_a Determinations

Registry no.	Acid	$[RPO_3H^-]/[RPO_3^{2-}]$	Ionic strength, M	pK_a[a]
993-13-5	$CH_3PO_3H^-$	0.80	0.24–0.081	7.996 ± 0.002
		1.79	0.20–0.068	8.006 ± 0.002
		4.43	0.18–0.062	7.998 ± 0.003
				Av 8.000 ± 0.003
4923-84-6	$(CH_3)_3CPO_3H^-$	0.74	0.22–0.073	8.710 ± 0.003
		1.86	0.20–0.067	8.714 ± 0.003
		4.53	0.18–0.062	8.714 ± 0.003
				Av 8.713 ± 0.001
2617-47-2	$HOCH_2PO_3H^-$	0.60	0.25–0.083	7.369 ± 0.002
		1.25	0.21–0.070	7.363 ± 0.001
		3.20	0.19–0.064	7.362 ± 0.001
				Av 7.364 ± 0.002
2565-58-4	$CH_2ClPO_3H^-$	1.13	0.079–0.0079	6.579 ± 0.003
		2.22	0.16–0.016	6.588 ± 0.001
		3.41	0.15–0.017	6.596 ± 0.002
				Av 6.588 ± 0.005
13113-88-7	$CHCl_2PO_3H^-$	1.28	0.23–0.078	5.606 ± 0.002
		2.58	0.19–0.065	5.606 ± 0.003
		5.63	0.20–0.068	5.601 ± 0.002
				Av 5.604 ± 0.002
5994-41-2	$CCl_3PO_3H^-$	0.99	0.21–0.071	4.930 ± 0.003
		2.94	0.19–0.064	4.934 ± 0.003
		3.79	0.21–0.071	4.926 ± 0.003
				Av 4.930 ± 0.002

[a] Error limits are standard deviations of mean values.

$$RPO_3H^- \rightleftarrows RPO_3^{2-} + H^+ \quad (1)$$

they span a pK_a range which extends from 4 ($CF_2PO_3H^-$) to 9 (t-$BuPO_3H^-$). These monohydrogen phosphonate ions, moreover, because of their negative charge, are likely to be especially effective proton donors toward neutral substrates.[3]

The pK_a's for both the first and the second dissociation of a fair number of phosphonic acids have been determined, and several useful compilations are available.[4] Unfortunately, most of the values reported are apparent rather than thermodynamic ionization constants, i.e., they refer to some finite (and usually unspecified) ionic strength. Since thermodynamic values are needed for the accurate analysis of kinetic data and since thermodynamic values are also preferred for the construction of Brønsted plots, we have determined these for a series of six phosphonate monoanions. The results obtained differ significantly from the apparent pK_a's available in the literature.

Experimental Section

Materials. Methylphosphonic acid was prepared by hydrolyzing dimethyl methylphosphonate (Aldrich Chemical Co.) in refluxing 6 M HCl overnight.[5] *tert*-Butylphosphonic, chloromethylphosphonic, and dichloromethylphosphonic acids were made from the corresponding phosphonyl dichlorides which were themselves prepared by the reaction of phosphorus trichloride and aluminum chloride with either *tert*-butyl chloride, methylene dichloride, or chloroform.[6] Trichlorophosphonic acid was synthesized by the Arbuzov reaction between triethyl phosphite (J. T. Baker Co.) and carbon tetrachloride[7] followed by hydrolysis of the diethyl ester so obtained.[6b] Hydroxymethylphosphonic acid was prepared by treating paraformaldehyde with phosphorus trichloride.[8]

All other reagents were best available commercial grades. Solutions were prepared from distilled, CO_2-free water.

pK_a Determinations. Ionization constants were determined by measuring the pH of successively diluted buffer solutions of the acid and its conjugate base. Buffer ratios, $[RPO_3H^-]/[RPO_3^{2-}]$, were in the range 1–5, and initial concentrations were arranged so that the starting ionic strength was ca. 0.2 M. Measurements were made using a Beckman Research pH meter (Model 1019) operating with a Beckman G.P. glass electrode (Model 39000) and a Beckman calomel reference electrode (Model 39071).

In a typical experiment, the buffer was prepared by combining stock solutions of phosphonic acid and sodium hydroxide of known concentrations. A 10-ml aliquot of this solution contained in a beaker was then placed in a constant temperature bath operating at 25.0 ± 0.02 °C, and, after it had come to thermal equilibrium, its pH was measured. To this solution, 2 ml of pure water was then added, an interval of 2–3 min was allowed for further equilibration, and the pH was measured again. Generally, ten such dilutions were made (total volume of water added 20 ml), which provided pH readings at 11 different buffer concentrations.

Results and Discussion

Since thermodynamic ionization constants refer to infinitely dilute solution, the present measurements, necessarily made at finite concentrations, had to be extrapolated to zero ionic strength. This was done in the following way.

The equilibrium constant for the ionization reaction under study (eq 1), K_a, may be written as

$$K_a = A_{H^+}\frac{[RPO_3^{2-}]}{[RPO_3H^-]}\frac{f^{2-}}{f^-} \quad (2)$$

where A_{H^+} is the activity of the hydrogen ion, brackets denote concentrations on the molarity scale, and f^- and f^{2-} are molar activity coefficients of the mono- and dinegative ions, RPO_3H^- and RPO_3^{2-}. These activity coefficients may be expressed as

$$\log f = \frac{-Az^2I^{1/2}}{1 + I^{1/2}} + BI \quad (3)$$

where A is an electrochemical constant (0.5115 $M^{-1/2}$), z is the charge number of the ion, I is the ionic strength of the solution, and B is a specific ion interaction constant.[9] Taking the logarithm of eq 2 and inserting values for the activity coefficients from eq 3 leads to

$$\log\frac{[RPO_3H^-]}{[RPO_3^{2-}]} + pH + \frac{3AI^{1/2}}{1 + I^{1/2}} = (pK_a)_{app}$$
$$= pK_a + (B^{2-} - B^-)I \quad (4)$$

in which B^- and B^{2-} are specific interaction constants for the RPO_3H^- and RPO_3^{2-} ions. This expression predicts that

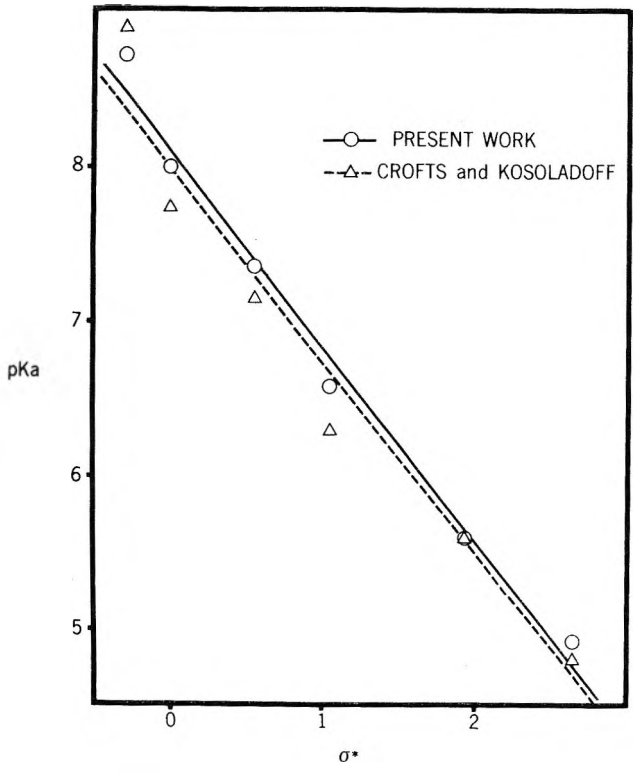

Figure 1. Equilibrium constants for the second ionization of alkylphosphonic acids correlated by the Taft equation.

$(pK_a)_{app}$, whose constituent quantities are all known, will be a linear function of ionic strength with the thermodynamic pK_a as its $I = 0$ intercept.

The data obtained here obey this relationship quite well. Least-squares analysis provides fits whose correlation coefficients are usually 0.98 or 0.99, and never less than 0.95, and whose slopes are generally 0.3 or 0.4; the latter is a reasonable magnitude for the difference $B^{2-} - B^{-}$.[10] These results are summarized in Table I. The average pK_a's listed there are simple unweighted means, and the error estimates given are standard deviations of these means. These probably do not take systematic errors adequately into account, and a more realistic estimate of the reliability of the present results may be 0.005–0.010 pK_a unit.

Thermodynamic pK_a's seem not to have been determined before for any of the acids studied here, but some apparent pK_a values are available. These are due principally to Crofts and Kosolapoff,[6a,b] who carried out potentiometric titrations and used the relationship $pK_a' = pH + \log [RPO_3H^-]/[RPO_3^{2-}]$ to calculate their results. Comparison of this expression with eq 4 shows that this method leaves out the quantity $3AI^{1/2}/(1 + I)^{1/2} - (B^{2-} - B^{-})I$, whose evaluation requires knowledge of the ionic strength at which the measurements were made. Crofts and Kosolapoff do not specify this, but they do say that the mean concentration of phosphonic acids during their titrations was 0.005 M. From this, $I = 0.007$–0.013 M for 20–80% neutralization may be inferred, which leads to −0.12 to −0.14 for the difference $pK_a' - pK_a$. It is significant, therefore, that four of Croft and Kosolapoff's values are lower than the results obtained here: $pK_a' - pK_a$ = −0.26, −0.21, −0.29, and −0.12 for $CH_3PO_3H^-$, $HOCH_2PO_3H^-$, $CH_2ClPO_3H^-$, and $CCl_3PO_3H^-$, respectively. For $CHCl_2PO_3H^-$, however, the difference is zero, and for $(CH_3)_3CPO_3H^-$ it is positive: $pK_a' - pK_a = +0.17$.

Additional apparent pK_a's of 5.58 and 4.71 are available for $CHCl_2PO_3H^-$ and $CCl_3PO_3H^-$.[4b] These are not inconsistent with the present results, but since neither the ionic strength nor the concentrations at which these values were obtained are specified, a more meaningful comparison is not possible.

The present results are correlated moderately well by the Taft equation.[11] Figure 1 shows the relationship obtained by least-squares analysis: $pK_a = (8.10 \pm 0.10) - (1.26 \pm 0.07)\sigma^*$. Although the correlation coefficient for this fit is good, $r = 0.994$, the average deviation from the line corresponds to a 30% difference in K_a or 0.13 pK unit; this is an order of magnitude greater than the estimated experimental uncertainty.

It is significant, however, that the apparent pK_a' values of Crofts and Kosolapoff give a considerably poorer correlation: $pK_a' = (7.98 \pm 0.21) - (1.24 \pm 0.15)\sigma^*$, $r = 0.973$, average deviation in K_a = 70% or 0.23 pK unit. It is interesting, on the other hand, that use of apparent pK_a's produces essentially no change in reaction constant; this is true even if the comparison is extended to a correlation based upon a much larger set of apparent pK_a's (22) which produced $\rho^* = 1.18$.[4b]

References and Notes

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Amplification of Cyanide Ion Production by the Micellar Reaction of Keto Oximes with Phosphono- and Phosphorofluoridates

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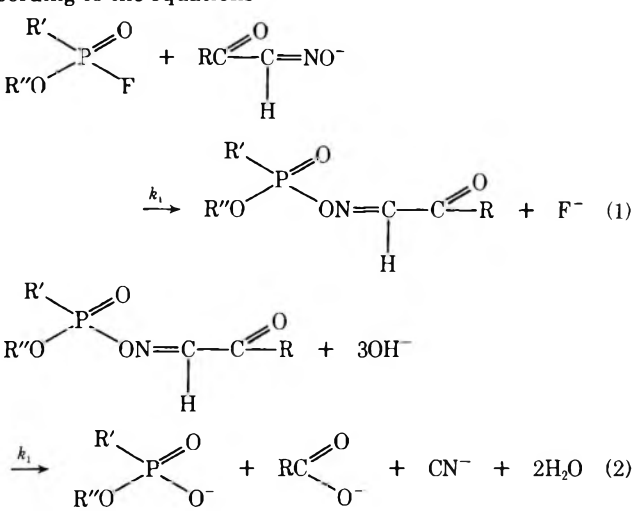
Received August 10, 1976

The reaction of keto oximes with phosphono- and phosphorofluoridates in alkaline aqueous solution proceeds according to the equations[1]



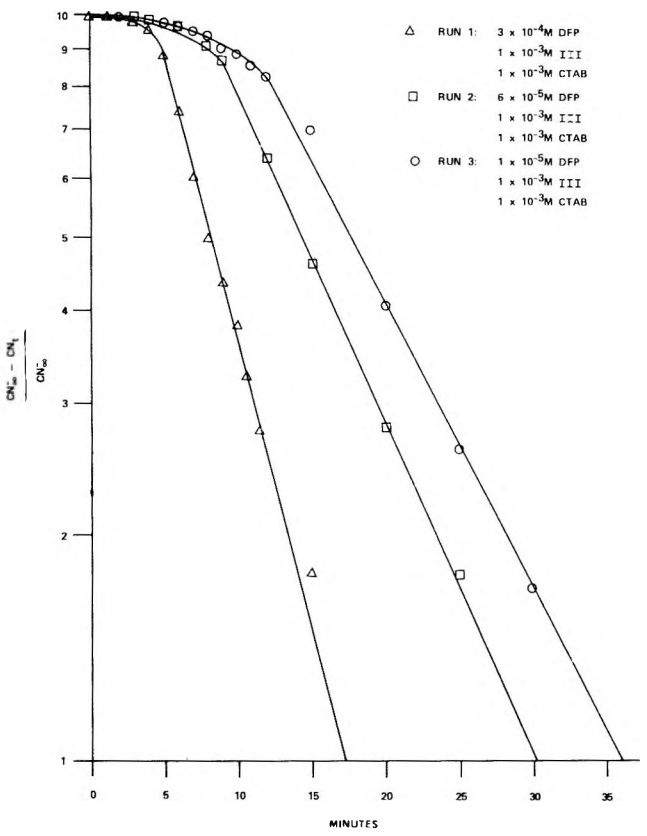


Figure 1. Rate of cyanide ion formation from DFP and III in presence of CTAB.

The production of fluoride (step 1) is rate controlling and 1 mol of cyanide ion is produced per mole of organophosphorus compound reacting. Ford and Watts[2] showed that the reaction between isopropyl methylphosphonofluoridate (I) and 1-phenylbutane-1,2,3-trione 2-oxime (II) produced, depending upon the pH, between 1 and 2 mol of cyanide ion per mole of I reacting. At high pH levels, the reaction was postulated to go through the formation of an acyl cyanide with subsequent hydrolysis to produce 1 mol of cyanide ion per mole of I; at lower pH levels, a reaction between the phosphonylated intermediate and the excess oxime was thought to produce 2 mol of cyanide ion per mole of I reacting. The bimolecular rate constant for the reaction of I and II (k_1 in eq 1) was 72 M^{-1} min^{-1}.

Tabushi et al.[3] reported that the reactivity of the anion of *N*-methyl-*N*-lauroylhydroxamic acid as an ester hydrolysis catalyst was greatly enhanced when used in a cetyltrimethylammonium bromide (CTAB) micelle. In our search for more reactive nucleophiles which would produce cyanide in their reaction with organophosphorus esters, we investigated the reaction of 1-oximino-2-ketononane (III) with I and diisopropyl phosphorofluoridate (DFP) in the presence and absence of micelle-forming compounds.

In the reaction of III with DFP or I in aqueous solution buffered at pH 9.3 with sodium tetraborate–sodium hydroxide buffer, we found that the equations given above adequately explained our observations. The first-order rate constant of the reaction of DFP with 10^{-3} M III, measured by the rate of fluoride ion (fluoride ion electrode) or cyanide ion (cyanide ion electrode) production, was 0.017 min^{-1}, and that of I with III under the same conditions, 0.10 min^{-1}. The reaction of DFP with II under similar conditions gave a first-order rate constant of 0.01 min^{-1} and, from the data of Ford and Watts, II at 10^{-3} M, pH 9.3, might be expected to give a first-order constant of 0.072 min^{-1} with I. Thus III behaves as a normal keto oxime, the small difference in rates between the two oximes being attributable to their pK_a's[4], pK_a (III) = 8.2, pK_a (II) = 7.1.

Table I. Ratio of $[CN^-]/[F^-]$ in Reactions of DFP and I with III (10^{-3} M) at pH 9.3 in Presence of CTAB (10^{-3} M)

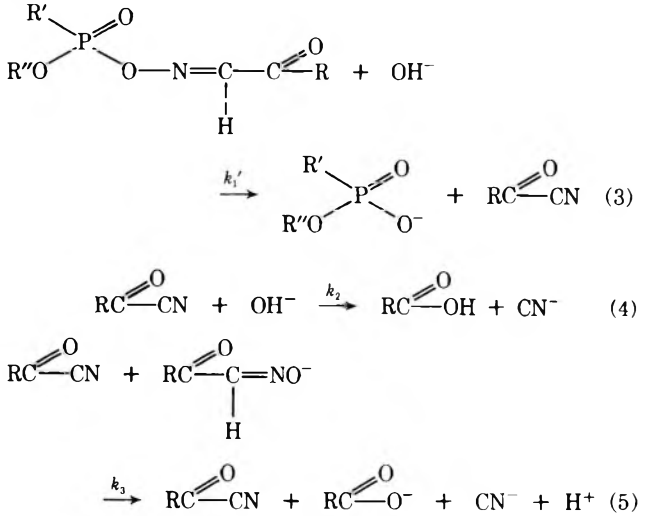
[DFP] mol/l.	[I],[a] mol/l.	$[CN^-]/[F^-]$
3×10^{-4}		3
6×10^{-5}		9.0
1×10^{-5}		13.4
	6.2×10^{-5}	4.7
	6.2×10^{-5} [b]	8.5
	6.2×10^{-5} [c]	4.2
	5.3×10^{-4}	10.9
	0.57×10^{-5}	10.2
	0.057×10^{-5}	19.3

[a] Corrected for hydrolysis. [b] 1% ethylene glycol added to reaction mixture. [c] 1% 1-butanol added to reaction mixture.

In the presence of CTAB, the rate of fluoride ion production was only marginally accelerated (a factor of 2) in the reaction between DFP and III, and not at all in the reaction of I and II. However, in both reactions, many times the 1 to 2 mol of cyanide per mole of organophosphorus compound were produced.

Semilog plots of the fraction of the total cyanide ion formed with time (Figure 1) revealed that after an initial slow release of cyanide, the production rate increased to a point and then followed first-order kinetics, with the time required to reach the portion of the curve showing first-order kinetics increasing with decreasing DFP concentration. The above observations, viz., greater than theoretical production of CN^-, first-order kinetics, and delay time to first-order kinetics, suggested that (a) a second reaction involving the destruction of the oximate ion (Ox^-) with simultaneous formation of cyanide ion was occurring, (b) the compound reacting with oximate was maintaining a constant concentration during the time the formation of cyanide showed first-order kinetics, and hence (c) there is a buildup of the compound to a steady state concentration.

The high yield of cyanide ion was shown not to be due to fluoride or cyanide ions[5] or to the phosphorus or carbon acids resulting from the overall reaction. On the other hand, octanoyl cyanide or octanoyl fluoride did produce the amplification reaction. It was hypothesized, therefore, that, in the micellar medium, octanoyl cyanide is an intermediate and that it reacted simultaneously along two paths, viz., hydrolysis and with the unused oximate anion,[6] and that the equations representing the reactions of III and DFP or I in micellar medium are



where k_1, k_2, and k_3 are rate constants and $k_1 \ll k_1'$.

Under steady state conditions (the concentration of the acyl cyanide remains constant) the ratio of $[CN^-]$ to $[F^-]$ is[7]

$$\frac{[CN^-]}{[F^-]} = 1 + \frac{k_3}{k_2}[Ox^-] \qquad (6)$$

The hydrolysis rate constant (k_2) of octanoyl cyanide at pH 9.3 in presence of 10^{-3} M CTAB was 0.25 min^{-1}; k_3, estimated from the data in Figure 1, was found to be $(4.6 \pm 0.7) \times 10^3$ M^{-1} min^{-1}. Thus, the expected ratio of $[CN^-]/[F^-]$ at constant $[Ox^-] = 10^{-3}$ M is 20.8.

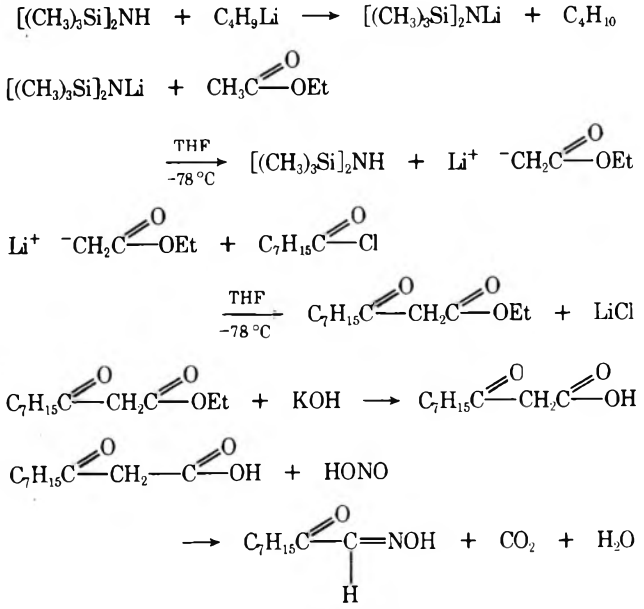
The cyanide to fluoride ratios found for DFP and I in their reaction with III in the presence of CTAB are shown in Table I. The ratio of $[CN^-]$ to $[F^-]$ approaches the calculated value of 21 as the difference in concentrations between III and I or DFP widens.

The reactions of DFP and I with the same oxime were also studied in the presence of the cetyl dimethylglycine (CDG). No acceleration of F^- release was found for either DFP or I in the presence of CDG; the ratios of $[CN^-]/[F^-]$ were ca. 10 for DFP and 7 for I. In all respects CDG and CTAB promoted the same reaction profile leading to cyanide amplification.

There is little (factor of 2) or no enhancement of the nucleophilicity of the keto oximate by a micelle environment. This may be due to poor portioning of the organophosphorus compounds into the micelle. III gives a slight enhancement with DFP, the more lipophilic of the two compounds. The acyl cyanide probably forms in the aqueous phase and then diffuses into the micelle environment where subsequent reaction with III takes place. This could account for the "induction" periods shown in Figure 1. In micellar environment the reaction between III and acyl cyanide is preferred over hydrolysis for two reasons: first, the hydrolysis rate of the acyl cyanide is less in the less polar environment of the micelle than in water, thus making it more available for reaction with III; and secondly, the concentration of III in the micellar phase is relatively high.

Experimental Section

1-Oximino-2-ketononane was prepared as shown in the following equations.[8a]



The procedures were as follows. A 2.46 M solution of n-butyllithium in hexane (122 ml) was added to 66 ml (0.32 mol) of hexamethyldisilazane in 100 ml of dry ether at a rate to maintain a gentle reflux. After addition of the n-butyllithium was complete, the mixture was heated to reflux temperature for an additional 30 min. Removal of the solvents by distillation at atmospheric pressure, followed by vacuum distillation of the residue, gave 40.0 g (240 mmol) of hexamethyldisilizallithium, bp 95 °C (0.3 Torr), lit. 80–84 °C (0.01 Torr),[8b] yield 79.8%.

A THF solution of hexamethyldisilizallithium (50 ml, 1.02 N = 50 mmol) was cooled to −78 °C in a dry ice/acetone cooling bath. Ethyl acetate (2.2 g, 25.0 mmol) was added over 5 min. The solution was allowed to stir at −78 °C for an additional 15 min. n-Octanoyl chloride (4.1 g, 25.0 mmol) was added maintaining the temperature ≤ 65 °C, and the solution was allowed to stir for 30 min following addition. The reaction was quenched at −78 °C with 15 ml of 20% w/w aqueous HCl and warmed to room temperature. The organic layer was separated and the aqueous layer extracted with two 50-ml portions of ether. The combined organic layers were extracted with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated to give 5.1 g of a clear oil. The oil was distilled to give 4.81 g (22.4 mmol) of the desired ethyl 3-oxodecanoate: bp 87–88 °C (0.3 Torr); yield 89.6% based on n-octanoyl chloride; IR (film) 3.44 (s, CH), 5.74 (s, ester C=O), 5.87 (s, ketone C=O), 6.12 (w, enol C=C), 6.84, and 7.12 μ; NMR ($CDCl_3$) δ 0.88 [t, J = 5 Hz, $CH_3(CH_2)_5$, 3], 1.26 [broad peak, $-(CH_2)_5-$ and CH_3CH_2O, 13], 2.55 (t, J = 7 Hz, CH_2CO, 2), 3.45 (s, $COCH_2CO_2$, 2), and 4.34 (q, J = 8 Hz, CH_2O, 2).

Ethyl 3-oxodecanoate was saponified with excess 0.5 N KOH for 24 h at room temperature. The resultant solution was extracted with ether; the acidified water phase gave a white solid, mp 83–84 °C. Titration gave an equivalent weight of 184 (theory 186), pK_a = 5.22.

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.46. Found: C, 64.43; H, 9.46.

Spectra: IR (KBr) 2.94 (w, OH), 3.44 (m, CH), 5.85 (s, C=O), 5.92 (s, C=O), 7.04 and 7.24 μ (m, CH); NMR ($CDCl_3$) δ 0.90 [t, J = 5 Hz, $CH_3(CH_2)_5-$, 3], 1.32 [broad peak, $-(CH_2)_5-$, 10], 2.12 [t, J = 7 Hz, $-(CH_2)_5CH_2CO$, 2], 3.55 (s, $COCH_2CO_2$, 2), 8.08 (broad peak, CO_2H, 1).

Potassium 3-oxodecanoate (1.63 g) was dissolved in 25 ml of distilled water, and 8.53 mmol (0.6 g) of sodium nitrite was added. The resultant clear solution had a pH of 13.0. The solution was treated with 20% w/w aqueous sulfuric acid in the following manner. Acid was added dropwise and precipitate formed and redissolved; this procedure was followed until a pH of 6.0 was obtained. Additional acid was then added to maintain the pH between 4.8 and 5.3. Reaction is complete when the clear (pH 5.3) solution can be taken to pH 4 with no further precipitation (~90 min). The acidic solution was adjusted to pH 12.5 and extracted with ether to remove any 2-decanone formed. The solution was then adjusted to pH 7, extracted with ether, and dried ($MgSO_4$), and the ether concentrated in vacuo to give 0.75 g of the desired keto oxime. The product was recrystallized from petroleum ether to give a white solid: mp 26 °C; IR ($CHCl_3$) 2.82 (s, bonded OH), 3.03 (b, nonbonded OH), 3.44 (s, CH), 5.95 (s, C=O), 6.02 (s, C=N), 6.35 (m, N–O), 6.85 and 7.15 (m, CH), and 10.2 μ (s, C–O); NMR ($CDCl_3$) δ 0.88 (t, J = 5 Hz, CH_3CH_2, 3), 1.3 [broad peak, $-(CH_2)_5-$, 10], 2.75 (t, J = 7 Hz, CH_2CO, 2), 7.57 [s, C(=NOH)H, 1], 8.33 (s, OH, 1).

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.16; H, 10.01; N, 8.18. Found: C, 62.77; H, 10.47; N, 8.07.

The keto oxime was further characterized by preparation of the semicarbazone derivative: mp 142–143 °C; IR ($CHCl_3$ solution) 2.89 (s, NH), 3.03 (s, OH), 3.44 (s, CH), 6.03 (s, C=N), 6.42 (s, C=O), 6.89 (s, CH), and 10.2 μ (s, C–O).

Anal. Calcd for $C_{10}H_{20}N_4O_2$: C, 52.61; H, 8.83; N, 24.54. Found: C, 52.87; H, 8.83; N, 24.32.

NMR spectra were run on a Varian EM360 spectrometer; IR spectra were run on a Perkin-Elmer 247 grating spectrophotometer; and titrations were run using a Metrohm E-436 potentiograph. Reported melting points are uncorrected and were determined on a Fisher-Johns or Mel-Temp melting point apparatus. All elemental analyses were performed by Stanford University.

Organometallic reactions were carried out in glassware that had been dried at 120 °C for 12 h followed by flame drying under nitrogen immediately before use. A nitrogen atmosphere was maintained until reactions were quenched.

All kinetic runs were performed as pseudo-first-order reactions, with the concentration of III being in most cases at least ten times greater than that of DFP or I; reactions were run in borate buffer (pH ~9.3) at 30 °C in a constant temperature bath. Cyanide and fluoride ion productions were monitored with Orion specific ion electrodes using suitable millivoltmeters and recorders.

Acknowledgment. The authors wish to thank Drs. D. Denson and G. Manser for their synthesis of 1-oximino-2-ketononane and Mr. R. Moll for technical assistance.

Registry No.—I, 107-44-8; III, 58040-72-5; III semicarbazone,

61064-12-8; DFP, 55-91-4; cyanide ion, 57-12-5; fluoride ion, 16984-48-8; *n*-butyllithium, 109-72-8; hexamethyldisilazane, 999-97-3; hexamethyldisilazallithium, 4039-32-1; ethyl acetate, 141-78-6; *n*-octanoyl chloride, 111-64-8; ethyl 3-oxodecanoate, 13195-66-9; 3-oxodecanoic acid, 13283-92-6; potassium 3-oxodecanoate, 61-64-11-7.

References and Notes

(1) A. L. Green and B. Saville, *J. Chem. Soc.*, 3887 (1956). The phosphono- and phosphorofluoridates are extremely toxic; extreme care should be exercised in handling these compounds.

(2) B. W. Ford and P. Watts, *J. Chem. Soc., Perkin Trans. 2*, 1009 (1974).

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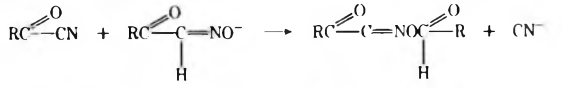
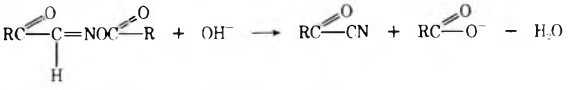
(5) E. V. Crabtree and E. J. Poziomek, *J. Org. Chem.*, **32**, 1231 (1967), were able to produce 8×10^{-3} mol of cyanide ion from a solution containing 2×10^{-4} mol of cyanide ion and 4×10^{-2} mol of II in 6 h, demonstrating the high effectiveness of cyanide ion in catalysis of decomposition of II. In the case reported in this paper, however, direct addition of cyanide ion failed to produce a catalytic effect in the time period of the reaction. Moreover, the observation that the production of cyanide followed first-order kinetics is not consistent with a postulation that cyanide ion is the reactive species. If cyanide were the cause of the decomposition, Figure 1 would have shown an increasing rate with time.

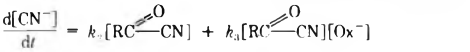
(6) The reaction of the acyl cyanide with oximate ion is considered to be composed of two consecutive reactions

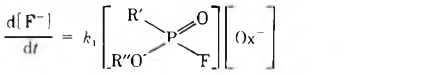


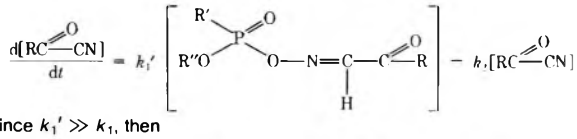


with the first step, i.e., the displacement of cyanide, rate controlling.

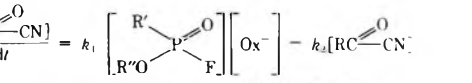
(7) The differential equations for the series of reactions at constant pH are



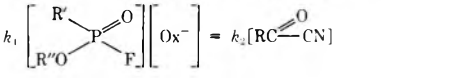




Since $k_1' \gg k_1$, then



and at steady state conditions, i.e., $d[RC(=O)CN]/dt = 0$,



so that

Then

and at t_∞,

(8) (a) M. W. Rathke and J. Deitch, *Tetrahedron Lett.*, 2953 (1971), and references cited therein; (b) E. H. Amonoo-Neizer, R. A. Shaw, D. D. Skovlin, and B. C. Smith, *J. Chem. Soc.*, 2997 (1965).

π-Inductive Effects in Benzyl Compounds

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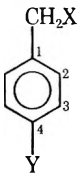
Received August 24, 1976

Considerable interest has been devoted to the nature of the transmission of substituent effects in α-substituted methyl aromatics.[1] The two mechanisms which have been generally proposed to explain the observed results involve hyperconjugative type interactions and π-inductive effects. As both of these mechanisms work in the same direction (for example, they decrease charge density at the para position) it is somewhat difficult to differentiate between them. ^{13}C NMR is well suited to such studies because it has been shown that the para carbon chemical shift is linearly related to the electron density at that position.[2] However, simple inspection of comparative shift data may result in an erroneous conclusion (vide infra). In order to assess the relative importance of hyperconjugative and π-inductive effects, it is instructive to use the dual substituent parameter (DSP) treatment.[3] Here, hyperconjugative interactions become apparent in the importance of the resonance term (**r**), while π-inductive effects appear in the inductive-field parameter (**f**).[3b]

Recently, Taft et al. have reported that for para-disubstituted benzenes, the π-inductive effect is manifest by a nonadditive behavior of the carbon-13 substituent effects.[4] Ab initio calculations have also indicated that π-inductive

Table I. ^{13}C NMR Chemical Shifts in Para-Substituted Benzyl Compounds[a]



Registry no.	X	Y	C_1	C_2	C_3	C_4	CH_2
106-42-3	H	CH_3	134.6	129.0	129.0	134.6	20.9
104-81-4	Br	CH_3	134.8	128.9	129.4	138.3	33.7
104-82-5	Cl	CH_3	134.6	128.5	129.3	138.1	46.1
589-18-4	OH	CH_3	138.0	127.1	129.1	137.6	64.8
106-38-7	H	Br	136.5	130.7	131.1	119.0	20.8
589-15-1	Br	Br	136.7	130.6	131.9	122.4	32.8
589-17-3	Cl	Br	136.4	130.1	131.9	122.4	45.3
873-75-6	OH	Br	139.8	128.5	131.5	121.3	64.3
104-93-8	H	OMe	129.7	129.9	113.8	157.7	20.4
2746-25-0	Br	OMe	130.3	129.9	114.7	159.7	33.9
824-94-2	Cl	OMe	130.0	129.7	114.0	159.6	46.3
105-13-5	OH	OMe	133.4	128.5	113.7	158.9	64.6
99-99-0	H	NO_2	146.2	129.9	123.4	146.2	21.5
100-11-8	Br	NO_2	144.9	129.9	123.9	147.7	30.9
100-14-1	Cl	NO_2	144.5	129.4	123.9	147.8	44.6
619-73-8	OH	NO_2	149.8	127.2	123.6	147.2	63.5
108-88-3	H	H	137.8	129.3	128.5	125.6	21.3
100-39-0	Br	H	137.8	129.0	128.6	129.0	33.4
100-44-7	Cl	H	137.5	128.6	128.5	128.3	46.2
100-51-6	OH	H	140.5	127.2	128.6	127.7	64.9

[a] In parts per million from Me_4Si.

Table II. ^{13}C NMR Substituent Shifts for C_1 and C_4 in Para-Substituted Benzyl Compounds

	Y				
X	CH_3	Br	OMe	NO_2	H
			C_1		
Br	0.2	0.2	0.6	−1.3	0.0
Cl	0.0	−0.1	0.3	−1.7	−0.3
OH	3.4	3.1	3.1	3.6	2.7
			C_4		
Br	3.7	3.4	2.0	1.5	3.4
Cl	3.5	3.4	1.9	1.6	2.7
OH	3.0	2.3	1.2	1.0	2.1

Table III. DSP Analysis of the C_1 and C_4 Carbon Chemical Shifts[a]

	f	r	a^b	b^b	i	$\bar{r}$	Av dev	Range
				C_1				
CH_2OH	5.16	19.55	0.694	0.909	140.5	0.994	0.63	16.4
CH_2Cl	3.63	18.33	0.579	0.944	137.4	0.999	0.20	14.5
CH_2Br	3.74	18.39	0.585	0.942	137.7	0.998	0.24	14.6
CH_2H	4.39	20.57	0.595	0.935	137.8	0.996	0.34	16.5
				C_4				
H	4.33	0.24	0.988	0.065	125.6	0.990	0.15	3.4
CH_3	4.85	−0.99	0.988	−0.449	134.6	1.000	0.01	3.7
Br	4.81	0.07	0.999	−0.297	119.0	0.999	0.05	3.4
OMe	2.82	0.27	0.997	−0.235	157.7	1.000	0.00	2.0
NO_2	2.21	0.13	0.994	−0.263	146.2	0.995	0.05	1.6

[a] $\delta = \mathbf{f}F + \mathbf{r}R + \delta_0$. [b] Correlation coefficient of $\delta = \mathbf{f}F + \delta_0$ (a) or $\delta = \mathbf{r}R + \delta_0$ (b).

Table IV. One-Bond Coupling Constants for the Methylene Carbon

Y	X	J, Hz
H	Br	152.5
Br	Br	152.6
OMe	Br	153.2
NO_2	Br	153.2
Br	OH	142.8
OMe	OH	141.5
H	OH	140.0
H	H	126.0
Br	H	126.7
OMe	H	126.0
NO_2	H	127.1

effects are important in the benzene series.[5] In this light, it was decided to investigate the substituent effects for some para-substituted benzyl compounds,[6] using the DSP treatment.

All of the chemical shift values and the substituent shifts at C_1 and C_4 are given in Tables I and II, respectively. Assignments were made by consideration of substituent effects based on simple benzyl derivatives,[7] para-substituted toluene data, and on the "fingerprint" pattern of the proton coupled spectrum.[8] For instance, each half of the coupled spectrum for C_3 appears as a doublet ($J \approx 3.5$–8.0 Hz, depending on the para substituent), while the C_2 resonance appears as a quintet or a sextet depending on the size of the long-range coupling constants. Full analysis of the spectral patterns was not attempted owing to some second-order effects.

The DSP analysis of the substituent effect observed at C_1, obtained by varying the para substituent, is given in Table III. The result is quite unexceptional indicating that resonance effects are dominant. The relative importance of the **f** and **r** values is seen to vary slightly, suggesting that there may be a small difference in the π-inductive effect of CH_3, CH_2OH, CH_2Br, and CH_2Cl.[4]

The DSP analysis for the C_4 chemical shifts was performed by varying the α-methyl substituent. It is immediately obvious that the para substituent markedly influences the magnitude of the inductive **f** term. The resonance interactions, in comparison, are unimportant and the values given for **r** may be an artifact of the regression analysis. The data strongly suggest that hyperconjugative interactions at the para position are at best a minor contributor to the observed substituent effect in benzyl systems. This observation is consistent with the data based on ^{19}F NMR obtained for p-fluoro-α-substituted toluenes.[9] The influence of the para substituent on the **f** value is seen to be substantial and the trend observed is similar to that found for the para-substituted benzene systems.

The above conclusion is further supported by the one-bond carbon–hydrogen coupling constants for the methylene carbon (Table IV). If hyperconjugative interactions are important, then rehybridization of the methylene carbon from $sp^3 \rightarrow sp^2$-like should occur to some extent. This should result in an increase of this coupling constant value.[10] The values obtained, however, are quite normal and thus inconsistent with the hyperconjugative notion.

Acknowledgment. The financial support of this work by the Robert A. Welch Foundation is gratefully acknowledged.

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Thallium in Organic Synthesis. 46. Oxidative Coupling of Aromatic Compounds Using Thallium(III) Trifluoroacetate. Synthesis of Biaryls[1]

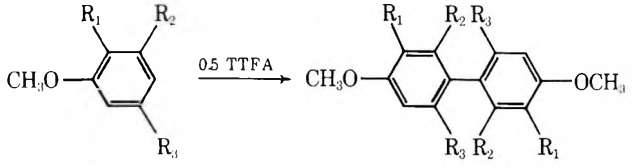
Summary: Treatment of a variety of aromatic compounds with thallium(III) trifluoroacetate in trifluoroacetic acid, carbon tetrachloride, or acetonitrile results in oxidative coupling to give symmetrical biaryls in good to excellent yield.

Sir: There are few preparatively useful procedures for the synthesis of biaryls. The most important, and commonly used, methods are the Ullmann reaction,[2] the Gomberg reaction,[3] the thermal decomposition of aroyl peroxides,[4] and various Kharasch-type reactions in which an aromatic Grignard reagent is treated with an organic halide in the presence of a metal halide.[5] More recent methods which have not yet been widely utilized include the reaction of aromatic Grignard reagents with thallium(I) bromide,[6] treatment of aryllead(IV) triacetates with trifluoroacetic acid in the presence of activated hydrocarbons,[7] reaction of diaryltellurium(IV) dihalides with Raney nickel at 200 °C,[8] treatment of aryl halides with zerovalent nickel complexes,[9] and the coupling of arylmercury(II) salts with copper metal and a catalytic amount of palladium(II) chloride in the presence of pyridine.[10] The requirement that the starting material possess a substituent group which must eventually be lost in the coupling process is the common denominator in *all* of the above biaryl syntheses.[11]

We now report that treatment of a variety of aromatic substrates with thallium(III) trifluoroacetate (TTFA) in trifluoroacetic acid (TFA), or in carbon tetrachloride or acetonitrile containing boron trifluoride etherate results in smooth, rapid, and direct oxidative coupling to give symmetrical biaryls in good to excellent yield.

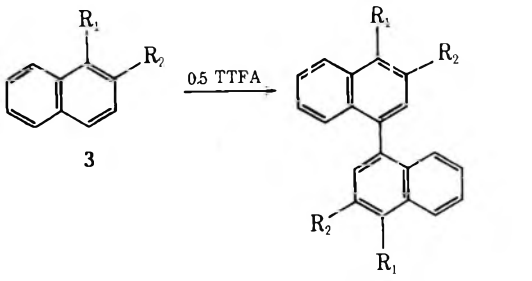
Thus, reaction of 4-bromoveratrole **1a** (1 equiv) with TTFA (0.5 equiv) in TFA is complete within a few minutes; pure 2,2′-dibromo-4,4′,5,5′-tetramethoxybiphenyl **2a** is obtained in 88% yield (92% conversion[12]) after recrystallization from toluene/petroleum ether (bp 100–120 °C).[13] The anisole derivatives **1b–f** react analogously to give the biaryls **2b–f**, and the naphthalene derivatives **3a–g** are smoothly converted into the binaphthyls **4a–g**.[14]

Thus, this method constitutes a simple, effective procedure for the preparation of a variety of highly substituted biaryls in which the ring substituents are either electron-donating or mildly electron-withdrawing groups. Aromatic substrates



1 2

	Conversion, %[11]	Yield, %
a, R_1 = CH_3O; R_2 = H; R_3 = Br	92	88
b, R_1 = CH_3O; R_2 = H; R_3 = I	100	89
c, R_1 = CH_3O; R_2 = H; R_3 = CH_3	85	74
d, R_1 = CH_3O; R_2 = CH_3; R_3 = Br	86	99
e, R_1 = R_3 = CH_3; R_2 = H	63	60
f, R_1 = R_2 = R_3 = CH_3	77	74



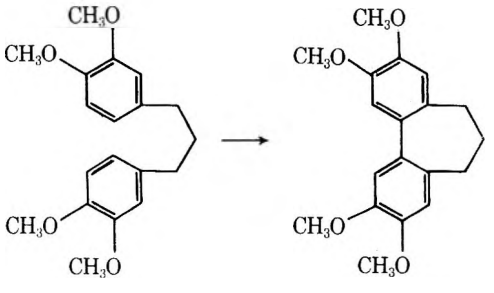
3 4

	Conversion, %	Yield, %
a, R_1 = CH_3; R_2 = H	100	93
b, R_1 = CH_3O; R_2 = H	100	88
c, R_1 = CH_3O; R_2 = CH_3	83	92
d, R_1 = CH_3O; R_2 = Cl	89	82
e, R_1 = CH_3O; R_2 = Br	83	81
f, R_1 = Br; R_2 = H	71	87
g, R_1 = I; R_2 = H	84	94

which contain powerful electron-withdrawing groups (COOR, CN, NO_2) fail to couple under the above conditions. Consequently, the TTFA method is complementary to the Ullmann reaction since the latter procedure usually gives satisfactory yields of biaryls only when the aromatic halides contain powerful electron-withdrawing groups, and is normally an inefficient reaction for the preparation of binaphthyls.

Another important aspect of the present procedure is the facility with which 2,2′,6,6′-tetrasubstituted biaryls can be prepared in good yields. Gibson and Bailey, for example, reported recently that both the Ullmann reaction of the benzyl ether of 2,3,5-trimethyl-4-iodophenol and the Kharasch-type reaction of the corresponding Grignard reagent with cupric chloride failed to yield any biaryl.[15] Treatment of the benzyl ether of 2,3,5-trimethylphenol with TTFA in acetonitrile containing boron trifluoride, however, gives 2,2′,3,3′,6,6′-hexamethyl-4,4′-dibenzyloxybiphenyl in 39% yield (51% conversion) in 10 min.

The effectiveness of this procedure for *intra*molecular coupling is illustrated by the conversion of 1,3-bis(3,4-di-

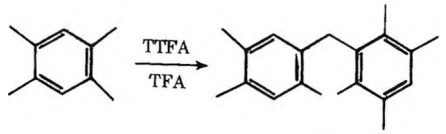


5 6

methoxyphenyl)propane (**5**) to the bridged biphenyl **6** in 81% yield (100% conversion).[16] Applications to the construction of aporphine and homoaporphine alkaloids[17] from 1-benzyl- and 1-phenethyl-1,2,3,4-tetrahydroisoquinolines are under investigation.

The detailed mechanism of this coupling reaction is not yet known, but the available evidence is compatible with the sequence (a) reaction of TTFA with the aromatic substrate and generation of the radical cation $Ar\cdot^+$; (b) reaction of this

electrophile with the aromatic substrate; and (c) oxidative aromatization of the intermediate thus produced by TTFA. Formation of arene radical cations in the reactions of certain alkyl benzenes with TTFA in TFA has been demonstrated by Elson and Kochi,[18] while formation of small amounts of biaryls during electrophilic aromatic thallation using TTFA and other thallium(III) salts has been noted on several occasions.[19] Moreover, treatment of durene with TTFA in TFA gives the heptamethyldiphenylmethane 7 (~15% yield), which



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is also one of the products formed by electrochemical oxidation of durene, a process known to proceed via the radical cation.[20] An important consequence of the radical cation mechanism is that the oxidation potential of an aromatic substrate should be one of the major factors governing the particular reaction course which will be followed when that aromatic substrate is treated with TTFA, i.e., electrophilic aromatic thallation or oxidative coupling. Studies to establish this point and to define more rigorously the scope and limitations of this new biaryl synthesis are currently in progress.

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(12) Conversion data are based on the amount of starting material which is recovered, while yield data are based on the amount of starting material which is consumed. Starting material was recovered from all but three of the reactions; in the other cases use of excess TTFA did result in complete oxidation of the starting materials but led to substantially lower yields of biaryls. This is due to competitive reactions in which the starting material and product are oxidized by TTFA to highly colored, polymeric materials.
(13) The following procedure for the preparation of 2,2′-dibromo-4,4′,5,5′-tetramethoxybiphenyl illustrates the general experimental method. 4-Bromoveratrole (4.34 g, 0.02 mol) was added in one portion to a solution of TTFA (5.50 g, 0.01 mol) in TFA (25 ml) at room temperature. The solution immediately turned deep red in color and became warm, and a colorless solid precipitated within a few minutes. The mixture was stirred for 10 min then poured into water and the resulting mixture extracted with chloroform. The chloroform solution was passed through a short column of basic alumina using petroleum ether (bp 40–60 °C)/chloroform (1:1) as eluent to remove highly colored polymeric materials. Evaporation of the eluent under reduced pressure followed by crystallization of the residual solid thus obtained from petroleum ether (bp 100–120 °C)/toluene gave 3.48 g of pure 2,2′-dibromo-4,4′,5,5′-tetramethoxybiphenyl as colorless needles, mp 159–160 °C [lit. mp 160 °C: W. Baker, J. W. Barton, J. F. W. McOmie, R. J. Penneck, and M. L. Watts, *J. Chem. Soc.*, 3986 (1961)]. Concentration of the mother liquors gave 0.35 g (8% recovery) of 4-bromoveratrole. The yield of biaryl based on 92% conversion of the starting material is 88%.
(14) Yields are calculated from percentage conversions as indicated above, and refer to pure recrystallized materials. Satisfactory spectroscopic and microanalytical data were obtained for all new compounds.
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Received November 12, 1976

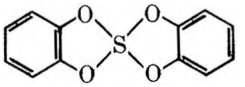
Sulfuranes. The Use of Tetraoxysulfuranes in the Formation of Olefins and Ethers from Alcohols

Summary: Phenylene orthosulfite synthesized from SF_4 and the dilithium salt of catechol reacts with alcohols to form olefins probably by means of a cyclic elimination route.

Sir: Interest in alkoxysulfuranes has been stimulated by reports of their utility as dehydrating reagents.[1-6] The dialkoxysulfurane $[C_6H_5C(CF_3)_2O]_2S(C_6H_5)_2$ reacts with primary alcohols to form unsymmetrical ethers of the type $C_6H_5C(CF_3)_2OR$ and with secondary alcohols to form olefins preferentially by trans coplanar elimination.[1]

We report results indicating that considerable control over the stereochemistry of elimination and the products formed from primary alcohols may be possible by a judicious choice of the sulfurane reagent.

Tetraoxysulfurane **1** reacts rapidly with cyclohexanol in $CDCl_3$ solution at room temperature to provide cyclohexene.



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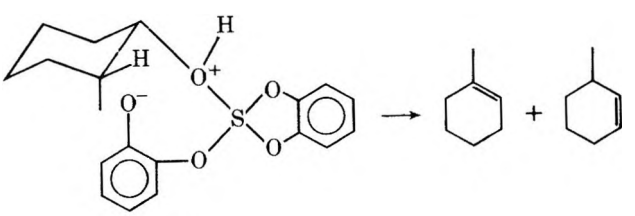
Both the cis and trans isomers of 2-methylcyclohexanol provide a 1:1 mixture of 1-methyl- and 3-methylcyclohexene together with *o*-phenylene sulfite. The sulfite is incapable of effecting the dehydration, and the olefins are stable under the reaction conditions.

This result is inconsistent with expectations for either an E1 or E2 elimination route. A trans coplanar elimination of the trans isomer could produce only 3-methylcyclohexene. By analogy with the phosphoric acid catalyzed dehydration of the isomeric 2-*tert*-butylcyclohexanols,[7] the trans isomer of 2-methylcyclohexanol would be expected to give a mixture of 1- and 3-methylcyclohexene but the cis alcohol should give mainly 1-methylcyclohexene. The observed result is consistent with a cyclic elimination mechanism similar to that found for amine oxide pyrolyses.[8]

In this mechanism the sulfurane undergoes ligand exchange with the alcohol to form **2** with the sulfurane group occupying the equatorial position of the cyclohexane ring by virtue of its



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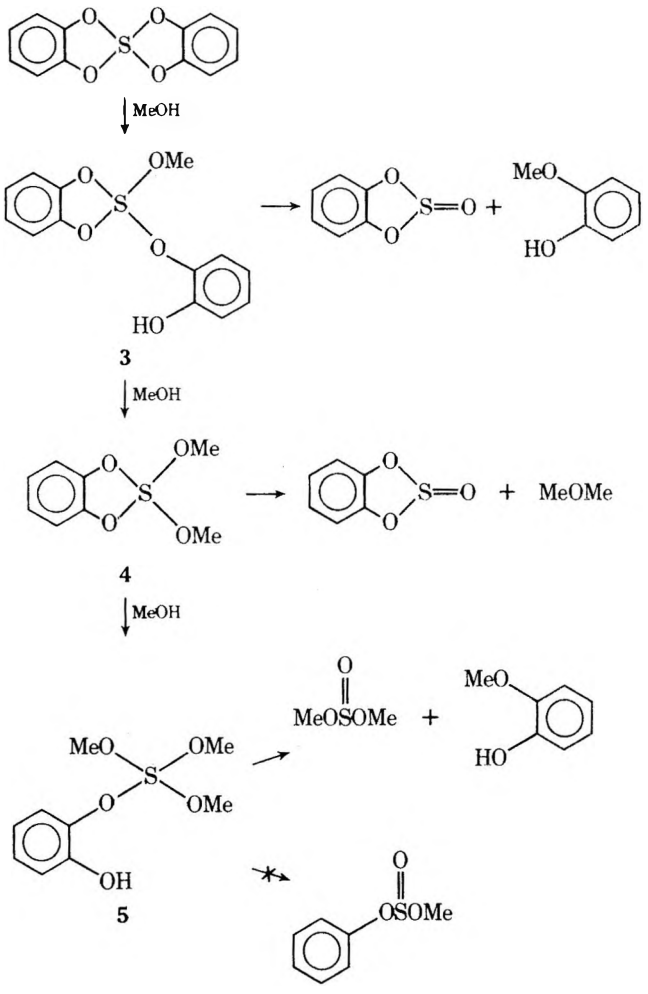
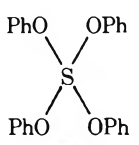
bulk. Elimination then proceeds by a cyclic process initiated by the phenolic oxygen.

The reaction of tetraoxysulfurane **1** with methanol provided a set of products (Scheme I), explicable by internal coupling

Scheme I



reactions of sulfuranes generated by successive ligand exchange. Thus methanol reacts with an equimolar quantity of sulfurane **1** in $CDCl_3$ solution within seconds at room temperature to form guaiacol, dimethyl ether, and dimethyl sulfite in a 30:26:20 ratio in addition to *o*-phenylene sulfite and the normal sulfurane hydrolysis product, catechol. A possible sequence is presented in Scheme I for ether formation but others including methanol and catechol attack on intermediate sulfuranes or sulfonium salts are not presently excluded by our data. Mixed sulfite **6** was not observed, and it cannot be a precursor of dimethyl sulfite by methanol attack because this reaction was shown independently to require 3 h at 60 °C to reach 90% completion. The inclusion of **3**, **4**, and **5** in the ligand coupling scheme is necessary because the ratio of guaiacol to dimethyl sulfite is significantly different from unity which it would be if ligand combination of **3** were excluded. Although we have no compelling evidence, it is possible that tetramethoxysulfurane is also an intermediate. Under similar conditions, Arhart and Martin[3] observed only a mixed ether from the reaction of methanol with their dialkoxydiphenylsulfurane. Thus, it appears that tetraoxysulfuranes have lifetimes commensurate with more extensive ligand exchange than do the dioxysulfuranes. Tetraoxysulfurane **1** is formed by addition of a premeasured quantity of sulfur tetrafluoride to the lithium salt of catechol in scrupulously dry ether at −78 °C under a rigorously dry and oxygen-free nitrogen atmosphere. After removal of excess sulfur tetrafluoride by the nitrogen stream, the inorganic salt is removed by room temperature filtration in a glove bag filled with dry, oxygen-free nitrogen and the sulfurane is isolated by crystallization at −78 °C. The method is of general utility



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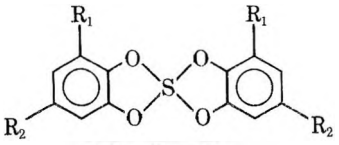
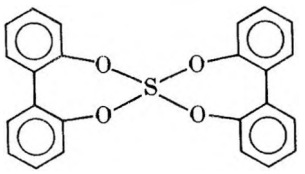


1, $R_1 = R_2 = H$
8, R_1 = Me; $R_2 = H$
9, $R_1 = R_2 = t$-Bu



10

and we have also obtained sulfuranes **7**–**10** in good yield.[9] All the sulfuranes are exceptionally sensitive to moisture, decomposing to sulfite and the phenol. However, all are stable for several days at room temperature in the absence of moisture, and at −5 °C they have half-lives of several weeks.

Sulfurane **1** shows a molecular ion at *m/e* 248.017 (calcd 248.016). The NMR spectrum at 220 MHz in $CDCl_3$ consists of a tight AA′BB′ pattern, 6.95 ppm downfield from TMS, downfield of the AA′BB′ pattern for catechol at 6.82 ppm but upfield of the singlet at 7.20 ppm for phenylene sulfate, and the tight AA′BB′ pattern at 7.14 ppm for phenylene sulfite, respectively. At 60 MHz the sulfurane pattern is a sharp singlet. The 220-MHz NMR pattern is inconsistent with all alternative covalent nontetracoordinate sulfur compounds of the same molecular weight, and the position of the resonances relative to those of sulfite and sulfate suggests that the sulfur atom is less effective at electron withdrawal, as expected. Structures of the analogous sulfuranes **7**–**10** were assigned on the basis of the *m/e* of the molecular ion and the NMR spectra.

Acknowledgment. We thank Professor Harold Kwart for the high resolution mass spectrum. We acknowledge support in part by a National Science Foundation Grant GB 12278, and grants from the Research Corporation and the Sloan Foundation to a consortium at the Rockefeller University for a 220-MHz NMR facility. We also thank Mr. Peter Ziegler for obtaining the NMR spectra.

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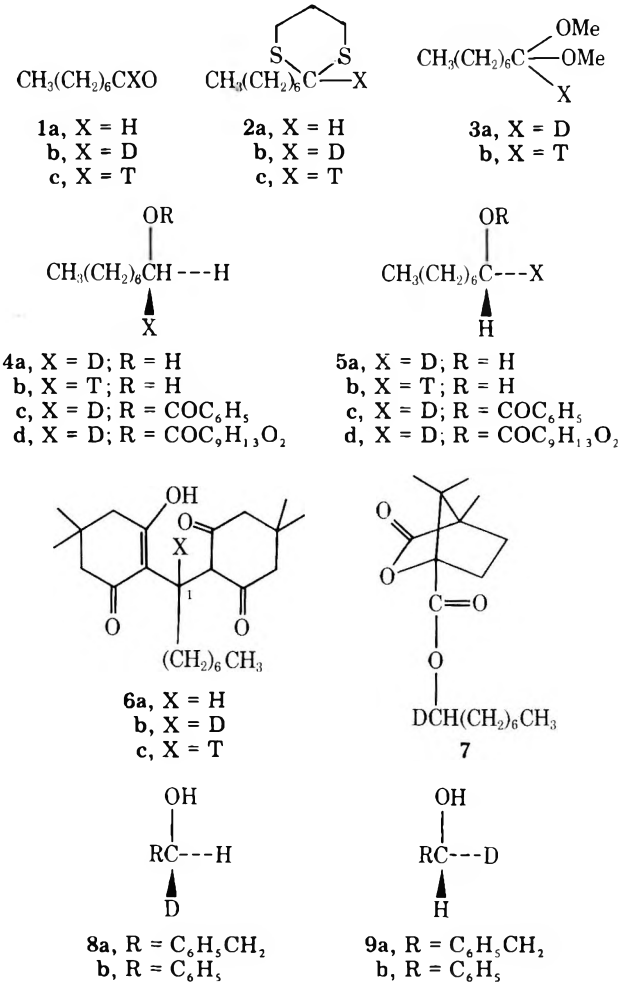
Preparative Scale Synthesis of (1*R*) [1-$^2H_1$] or [1-$^3H_1$] Primary Alcohols of High Optical Purity

Summary: A convenient and rapid procedure for the synthesis of (1*R*)[1-$^2H_1$] or [1-$^3H_1$] primary alcohols from the corresponding (1*S*) alcohols is described.

For studies of mechanisms of enzymatic reactions, we required a general procedure for the synthesis of compounds (hydrocarbons, acetic acids, propionic acids, etc.) containing chiral ("*R*" and "*S*") methyl groups.[1] The approach we chose was to prepare large amounts of (1*R*) and (1*S*) alcohols which would be converted (e.g., via tosylations and LiAl*H_4 hydrogenolyses) to the required chiral methyl groups. Finally, the chiral hydrocarbons could be oxidized (e.g., Kuhn–Roth, RuO_4) to aliphatic acids, as needed.

While the required (1*S*) alcohols[2] are more accessible, there seem to be no convenient methods for the large-scale preparation of the critically important, optically pure (1*R*) alcohols.[3] We report a general, practical procedure for the large-scale synthesis of primary (1*R*) alcohols from (1*S*) alcohols. The method is exemplified by the synthesis of (1*R*)-octanol, (1*R*)-2-phenylethanol, and (1*R*)-benzyl alcohol.

A solution of octanaldithiane (**2a**, 4 g) in dry THF was cooled to −20 °C under N_2 and then *n*-butyllithium (1 equiv)



was added. After 2 h, excess D_2O was added and the deuterated dithiane[4] (**2b**, 4 g; d_0 9%, d_1 91%) was recovered [no triplet at 3.9 ppm for the C-1 (^1H)]. **2b** (4 g), on treatment with HgO (4.4 g) and $HgCl_2$ (11.0 g) in 90% aqueous methanol (900 ml), gave **3a**, which was hydrolyzed (dilute HCl–acetone) to [1-^2H]-octanal (**1b**) [no signal at 9.15 ppm (−CHO)].[5] The [1-^3H]-octanal (**1c**) (60 mCi) was prepared in a similar manner from **2a** (4 g), using 100 mCi of ^3H_2O.

[1-^2H]-octanal (**1b**, 700 mg), horse liver alcohol dehydrogenase (HLAD, 30 mg), NAD (180 mg) in a 0.01 M phosphate buffer (pH 6.9, 1000 ml) containing EtOH (45 ml), and dioxane (25 ml) was incubated at 30 °C for 72 h under N_2.[6] Following column chromatography of the recovered products (silica gel, hexane–ether, 6:4), (1*S*)[1-$^2H_1$]-octanol (**4a**, 690 mg) (mass spectrum d_0 8%, d_1 92%) was obtained.

The optical purity of the alcohol **4a** was determined enzymatically and by NMR spectroscopy. The (1*S*)[1-$^2H_1$]-octanol (**4a**) (30 mg) was incubated in 0.01 M phosphate buffer (pH 9.7, 65 ml) containing 5,5-dimethyl-1,3-cyclohexanedione (dimedone, 35 mg) with yeast alcohol dehydrogenase (YADH, 14 mg) and NAD (300 mg) for 40 h at 27 °C, in the air.[7] The recovered residue (40 mg) obtained following ether extraction was chromatographed (TLC) [silica gel, hexane–ethyl acetate (1:1)] and, on crystallization (EtOH), gave **6b**: mp 130–132 °C; mass spectrum d_0 10%, d_1 90%; NMR, no signal at 4.1 ppm for the C-1 (^1H). Since in the YADH–NAD oxidation of alcohols the (1-H_R) hydrogen atom is removed,[2a,8] the complete retention of ^2H in **6b** establishes the (1*S*) chirality of the alcohol **4a**.

The enantiomeric purity of **4a** was also determined by NMR, by the method of Gerlach and Zagalak.[9] The (1*RS*)-[1-$^2H_1$]-octanol-(−)-camphanic ester (**7**) was prepared and its 100-MHz NMR spectrum in the presence of Eu(dpm)$_3$[10] was recorded. The enantiotopic C-1 proton of **7a** gave two triplets (J = 6Hz) at 5.8 ppm (H_S)[9] and 5.5 ppm (H_R).[9] The 100-MHz Eu(dpm)$_3$ spectrum of the (1*S*)[1-$^2H_1$]-octanol-(−)-camphanic acid ester (**4d**) showed only *one triplet* equivalent to *one* proton at 5.5 ppm for the (1-H_R) of **4d**. For sensitivity determination, (1*RS*)[1-$^2H_1$]-octanol-(−)-camphanic acid ester (**7a**) was added in increments of 2% [corresponding to 1% (1*R*) and (1*S*) esters] to the (1*S*) ester **4d**. Following the admixture of 10% (1*RS*) ester **7a**, the signal for the (1-H_S) could be detected. Hence, the presence of a minimum of ~5% second enantiomer will be detected by this NMR method. It may, therefore, be inferred that octanol **4a** contains a minimum of 95% excess (1*S*) isomer.

A mixture of (1*S*)[1-$^2H_1$]-octanol (**4a**, 360 mg), triphenylphosphine (1.2 g), diethyl azodicarboxylate (440 μl), and benzoic acid (480 mg) in dry tetrahydrofuran (28 ml) was stirred at room temperature for 15 h under N_2.[11,12] The recovered product was fractionated by column chromatography [silica gel, hexane–ether (9:1)] to give (1*R*)[1-$^2H_1$]-benzoate **5c**. Treatment of **5c** (710 mg) with $LiAlH_4$ in ether provided (1*R*)[1-$^2H_1$]- octanol **5a** (315 mg). Oxidation of **5a** (30 mg) with YADH–NAD, as described above, gave the corresponding dimedone derivative **6a** (8 mg) (NMR triplet at 3.8 ppm for the C-1 hydrogen atom) (mass spectrum d_0 100%). Since 1-H_R is removed in the enzymatic oxidation, the absence of deuterium in **6a** establishes the (1*R*) stereochemistry of **5a**.

The 100-MHz Eu(dpm)$_3$ spectrum[10] of the (1*R*)[1-$^2H_1$]-octanol-(−)-camphanic ester (**5d**) showed a triplet at 5.8 ppm for the (1-H_S). As expected,[9] the (H_S) triplet of **5d** was at a lower field than the H_R triplet of the (1*S*)[1-$^2H_1$]-octanol (**4a**). Indeed, incremental addition of **5d** to the (1*RS*)-camphanic ester **7** resulted in an increase in intensity of the 5.8-ppm triplet. Based on the experimentally determined sensitivity of the method, it follows that the octanol **5a** contains a minimum of 95% excess (1*R*) isomer.

In an analogous sequence of reactions (1*S*)[1-$^3H_1$]-octanol (**4b**) and (1*R*)[1-$^3H_1$]-octanol (**5b**) were prepared. For the determination of their optical purities, the (1*S*)[1-$^3H_1$]-octanol (**4b**) (specific activity 1.95 × 10^7 dpm/mmol) and the (1*R*)[1-$^3H_1$]-octanol (**5b**) (specific activity 4.1 × 10^7 dpm/mmol) were oxidized enzymatically (YADH–NAD) to yield octanal **1c** (specific activity 1.90 × 10^7 dpm/mmol; counted as the dimedone derivative **6c**) and octanal **1a** (specific activity 7.8 × 10^5 dpm/mmol; counted as **6a**), respectively. Clearly the

Table I. NMR Spectra of (−)-Camphanic Acid Esters of the Indicated Alcohols. All Spectra Were Recorded at 100 MHz as CCl_4 Solutions in the Presence of 30 mol % $Eu(dpm)_3$

Esters of	^1H_R[a]	^1H_S[a]
2-Phenylethanol		
a, (1*RS*) [1-$^2H_1$]	5.2 (t, J = 6 Hz)	5.4 (t, J = 6 Hz)
b, (1*S*) [1-^{2}H]	5.2 (t, J = 6 Hz)	ND
c, (1*R*) [1-$^2H_1$]	ND[b]	5.4 (t, J = 6 Hz)
Benzyl alcohol		
a, (1*RS*) [1-$^2H_1$]	5.70 (s)	5.88 (s)
b, (1*S*) [1-$^2H_1$]	5.70 (s)	ND
c, (1*R*) [1-$^2H_1$]	ND	5.88 (s)

[a] Chemical shifts of the enantiotopic hydrogens (in ppm). [b] ND, not detectable.

oxidation of the (1*S*)-octanol **4b** to octanal **1c** proceeded with the complete retention of tritium, while the oxidation of the (1*R*)-octanol **5b** to octanal **1a** involved the loss of 98% tritium.

To test the generality of the inversion procedure, (1*S*)-[1-$^2H_1$]-2-phenylethanol (**8a**) and (1*S*)[1-$^2H_1$]-benzyl alcohol (**8b**) were prepared by HLAD–NAD reduction of the corresponding [1-^{2}H] aldehydes. The (1*S*) alcohols were treated with $(C_6H_5)_3P/C_6H_5CO_2H/EtO_2CN{=}NCO_2Et/THF$, as described above. The resulting (1*R*) benzoates were saponified (methanolic KOH) to give (1*R*)[1-$^2H_1$]-phenylethanol (**9a**) and (1*R*)[1-$^2H_1$]-benzyl alcohol (**9b**) in good yield. The 100-MHz Eu(dpm)$_3$ analyses of the (−)-camphanic acid esters of alcohols **9a** and **9b** indicated the presence of at least 95% excess (1*R*) alcohols in each case (see Table I).

The described procedure represents a facile synthesis of primary (1*R*) alcohols from the more accessible (1*S*) alcohols. In the systems investigated, the reaction proceeds in high yield with complete inversion of configuration. Aldehydes with a high C-1 tritium content can be prepared by quenching the anion derived from **2a** with tritiated water of high specific activity. It follows that by using the described methods, (1*S*) and (1*R*) [1-^{3}H] alcohols and the chiral methyls derived from these alcohols will have a high specific activity of tritium.

Acknowledgment. We wish to thank Dr. Warren G. Anderson for recording the NMR spectra. This work was supported by a NIH grant GM 19882. The incubator used in these studies was purchased with funds from NIH Grant RR-05528.

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(10) The ^{1}H NMR spectra of the (−)-camphanic acid esters were recorded at 100 MHz in CCl_4. Optimal separation of the signals for the enantiomeric protons occurred at 30 mol % of Eu(dpm)$_3$.

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(12) The procedure can be adjusted according to the availability of the (1*S*) alcohol.

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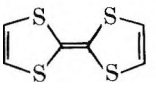
Received November 3, 1976

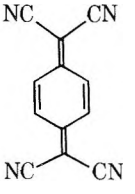
Unsymmetrical Dimethyltetrathiafulvalene[1]

Summary: A hitherto unknown unsymmetrically substituted tetrathiafulvalene (substitution on only one ring) was prepared, isolated, and purified, and its spectroscopic and physical properties are described and compared with those of other members of the family; the title compound forms highly conducting salts with TCNQ and other anions.

Sir: Organic materials whose electrical conductivity in the solid state increases with decreasing temperature belong to the theoretically interesting family of "low dimensional" or "one dimensional metals". Members of this class of substances have in common the peculiar property whereby the molecular charge carriers stack uniformly along a given axis. The solid-state packing arrangement of all known members of this family (whether organic or inorganic) consists of independent, uniform stacks of donors and/or acceptors and are subject to a theoretically predicted solid-phase transition[2a] which eventually converts them to insulators (usually at temperatures below 200 K). Within this class the most highly conducting organic materials are based on TTF (**1**) and TCNQ (**2**).

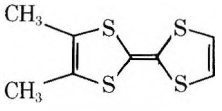


TTF (1)



TCNQ (2)

While an unsymmetrically substituted TCNQ derivative (monomethyl TCNQ), has been prepared and its electrical properties in combination with TTF have been studied,[2b] no such simple unsymmetrical TTF compounds are known. The only previously known asymmetrical TTF compound is the monomethyl dibenzotetrathiafulvalene,[3] a material which does not yield organic metals.[3] This paper is a report on the synthesis, separation, purification, and comparative spectroscopic properties of various potentially interesting methylated TTF molecules, especially the title compound (UDMTTF, **3**). The physical measurements and preparation



UDMTTF (3)

of organic conductors based on these donors will be reported separately.

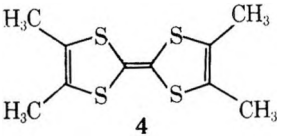
Because monomethyl TTF was expected to have very similar properties to TTF and dimethyl TTF, its synthesis in

Table I

Compd	Mp, °C (corr)	λ_{max} (ϵ),[a] nm	NMR, τ	IR (KBr), cm^{-1}	EPR (propylene carbonate)[b]
TTF (1), orange-yellow needles	119.1–119.3	303 (12 800), 316 (11 400), 368 (2 000), 450 (230)	3.75 (s) [CCl_4 (TMS)]	1530 (w), 1250 (w), 1075 (w), 870 (w), 797 (m), 782 (m), 734 (m)	Quintet (CH_3CN) g = 2.00838 a_H = 1.26 G
UDMTFF (3), orange-yellow needles	117.3–118.8	278 (sh) (10 200), 290 (sh) (12 700), 299 (14 300), 308 (sh) (13 500), 322 (sh) (12 300), 360 (sh) (3 070), 445 (640)	8.08 (s, 6 H), 3.78 (s, 2 H) [CS_2 (TMS)]	2900 (w), 1420 (m), 1180 (w), 1080 (m), 797 (m), 778 (m), 733 (m)	Seventeen lines g = 2.0078 $a_H \simeq$ 1.18 G $a_{CH_3} \simeq$ 0.82 G
SDMTTF (5), orange-yellow needles	109–111	278 (sh) (12 300), 290 (sh) (14 800), 298 (15 800), 308 (14 800), 321 (13 500), 355 (sh) (4 960), 440 (sh) (1 340)	7.95 (d, 6H), 4.18 (q, 2H, J = 1.5 Hz) [$CDCl_3$ (TMS)]	1630 (w), 1480 (w), 1420 (m), 1220 (m), 1110 (s), 1030 (w), 808 (s), 775 (s), 748 (s)	Eleven lines g = 2.0079 $g_{CH_3} \simeq$ 0.64 G $a_H \simeq$ 1.28 G
TMTTF (4), salmon-colored needles	240.5–241.3	287 (sh) (12 000), 297 (sh) (13 000), 315 (14 000), 327 (13 800), 473 (248)[c]	8.13 (s) [CS_2 (TMS)]	2900 (w), 1630 (w), 1420 (m), 1180 (m), 1085 (m), 782 (s)	Thirteen lines g = 2.0077 $a_{CH_3} \simeq$ 0.74 G

[a] In hexane. [b] As fluoroborate salt. [c] In 1,2-dichloroethane.

a manner analogous to reaction 1 was not attempted. On the other hand, we expected **3** to be different enough from TTF and TMTTF [tetramethyl TTF (**4**)][4] so that its separation from the latter would be viable.



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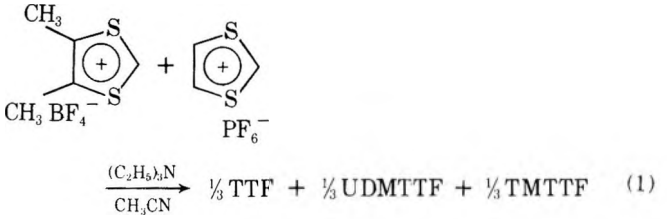
The title compound was prepared by the straightforward approach[4b,5] shown in eq 1.



$$\xrightarrow[CH_3CN]{(C_2H_5)_3N} \tfrac{1}{3}\,TTF + \tfrac{1}{3}\,UDMTTF + \tfrac{1}{3}\,TMTTF \qquad (1)$$

The products TTF and TMTTF are soluble and insoluble (respectively) in cold acetonitrile. Thus, **3** crystallized from a slowly cooling solution of the acetonitrile washings of the crude reaction mixture. Reaction 1 afforded 59% isolated yield of TMTTF and 78% isolated yield of thrice recrystallized **3** (based on a theoretically possible yield of 33% for each component).

Compound **3** is a yellow crystalline solid: mp 117.2–118.5 °C (cf. 119 °C for TTF and 241 °C for TMTTF); mass spectrum (m/e) 232 (parent, plus five isotope peaks in proper ratio), 187, 130 (dimethyldithiolium carbene), 102 (base peak, dithiolium carbene), 76 (CS_2), 54 (dimethylacetylene). There were no peaks at 260 or 204, proving conclusively the absence of contamination by TTF or TMTTF. Interestingly, the dimethyldithiolium species is less stable than the unsubstituted dithiolium based on the relative abundance of the m/e 130 vs. the m/e 54) and fragments of CS_2 and dimethylacetylene.

The electronic spectra of **1**, **3**, and **4** are presented in Table I. Because **3** is the most unsymmetric it exhibits the largest differences as compared to **1** and **4**.

Figure 1 shows the electron spin resonance spectrum of $UDMTTF^+$. The spectrum consists of seventeen lines resulting from the overlap of the lines from two types of H hyperfine couplings.

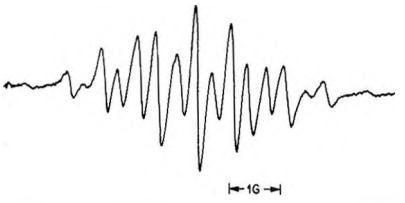
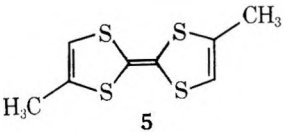


Figure 1. Electron spin resonance spectrum of $UDMTTF(BF_4)_{0.45}$ in propylene carbonate: g = 2.0078, $a_H \simeq$ 1.1 G, $a_{CH_3} \simeq$ 0.8 G.

For comparison, symmetrical dimethyl TTF (SDMTTF, **5**, misnomered ATTF by others) was prepared in a similar



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manner from 4-methyl-1,3-dithiolium fluoroborate and triethylamine. Although two possible isomers are expected (cis and trans), we believe that the isolated material, because of its physical characteristics (lower solubility in acetonitrile, melting point), must be the *trans*-SDMTTF. Previous workers have apparently not been successful in separating the isomers of the SDMTTF.[6] The compound which we isolated exhibits the properties shown in Table I.

As was foreseen, **3** forms highly conducting salts with TCNQ and other anions as does TTF itself.[7] We are currently studying the single-crystal physical properties of its salts and "stereo alloys" of it with unsubstituted and fully methylated TTF.

The experimental procedure[8] follows. To a cooled (0 °C), magnetically stirred solution of 4,5-dimethyl-1,3-dithiolium fluoroborate (1.97 g, 9.04 mmol) and 1,3-dithiolium fluoroborate (or hexafluorophosphate) (1.70 g, 9.04 mmol) in a minimum amount of dry acetonitrile (~15 ml) was added triethylamine, dropwise, until the formation of orange-yellow crystals was obvious (~1.0 g, 10 mmol). After stirring for an additional 10 min, the mixture was poured into 300 ml of water and extracted with cyclohexane (6 × 100 ml). The combined organic layers were washed with water (2 × 100 ml), dried over sodium sulfate, filtered, and then concentrated to dryness under reduced

pressure. The resulting yellowish red solid was washed with ice-cold acetonitrile (~250 ml) to remove TTF and UDMTTF. Recrystallization of the remaining solid from acetonitrile afforded 0.46 g (59%) of tetramethyl TTF.

The acetonitrile washings from above were concentrated to dryness and the resulting solid taken up in a minimum of boiling acetonitrile. Fractional crystallization from this solution afforded several crops of UDMTTF crystals. Two recrystallizations of these combined drops from acetonitrile (Norit, filtration through acid-washed Celite) gave 0.545 g (78% yield) of orange-yellow crystals (mp 117.3–118.5 °C corr). See Table I for additional data.

Acknowledgment. The authors thank Dr. D. J. Freed for performing the mass spectroscopic analyses of some of these compounds.

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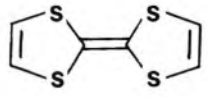
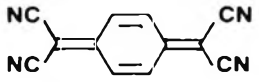
TTF and TCNQ

Components for conductivity

Tetrathiafulvalene (TTF) and several other tetrathioethylenes were originally investigated as possible electron-rich olefins.[1] It was quickly realized that the electrochemistry of **TTF** was by far the most interesting aspect of the compound. Wudl *et al.*[2,3] discovered that **TTF** formed an exceptionally stable radical cation complex with chlorine (TTF•Cl) which exhibited an unusually high electrical conductivity.



TTF

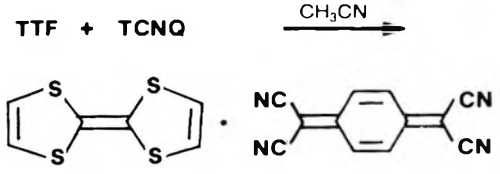


TCNQ

7,7,8,8-Tetracyanoquinodimethane (TCNQ) was first studied for its ability to form radical anions.[4,5,6] Since then, many practical applications have been discovered. For example, **TCNQ** is used in the:

1) colorimetric determination of free radical precursors[7]
2) visualization of certain nitrogen and sulfur compounds on thin-layer and paper chromatograms[7,8]
3) replacement of MnO_2 in aluminum solid electrolytic capacitors[9]
4) construction of heat-sensitive resistors[10]
5) induction of radical polymerizations (in combination with *N,N*-dimethylaniline *N*-oxide)[11]
6) construction of ion-specific electrodes.[12,13]

It was the ability of **TCNQ** to form radical anions that prompted Cowan[14] to combine it with the electron donor **TTF**. The resulting charge-transfer complex was found to contain **TTF** and **TCNQ** in a 1:1 ratio.



This complex behaves electrically and optically like a one-dimensional metal at room temperature. It has one of the highest electrical conductivities known for an organic compound, being highly anisotropic along an axis defined by the colinear stacks of **TTF** and **TCNQ**.[15] Since there was some controversy over the exact value of the conductivity, a study was performed to determine if the chemical purity of the components affected the electrical conductivity of the complex.[16] The workers concluded that crystal perfection rather than chemical purity was the factor chiefly responsible for determining the degree of conductivity. Major research efforts are currently in progress to better understand and find applications for the unusual properties of the **TTF/TCNQ** complex.[17,18,19]

Aldrich has offered **TCNQ** for many years. Now we also offer **TTF!** With the ready availability of these "components for conductivity," the **TTF/TCNQ** complex is more accessible for further studies.

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