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THE JOURNAL OF Organic Chemistry®

VOLUME 40, NUMBER 24 NOVEMBER 28, 1975

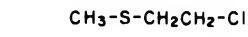
CHLOROETHYL

Chloroethyl ethers, thioethers, sulfones and esters are uniquely activated and interesting compounds. Generally we think of activated organohalides as those attached α- to an unsaturated function (i.e. α-haloketone), but a β-heteroatom is also activating both by inductive and by neighboring group type mechanisms. For example, many of the chloroethyl sulfides offered below are mildly vesicant relatives of the highly reactive Bis (2-chloroethyl) sulfide (Mustard gas!).

These chloroethylsulfides and the corresponding sulfones are particularly useful intermediates for the introduction of a sulfur function into a molecule. The labile chloro is readily displaced by a variety of nucleophiles such as amines, mercaptices, alkoxides, etc. to form the corresponding amines, sulfides or ethers. Due to the electron withdrawing nature of the sulfide or sulfone function these chloroethyl compounds undergo facile dehydrohalogenation to form the vinyl sulfide or sulfone. The vinyls are particularly versatile in that they undergo addition reactions with hydrogen halides, halogens, amines, mercaptans, and alcohols to yield halo, dihalo, amino, thio and alkoxy sulfides or sulfones. In addition they also undergo Michael type additions and, of course, they may be utilized in polymerization processes to form a variety of interesting products.

Because of current intense interest in "Crown Ethers," we have added to our line two Bis (2-chloroethoxy) ethers which are necessary intermediates for the synthesis of 15-crown-5, 18-crown-6, benzo-15-crown-5, cyclohexyl-15-crown-5, dibenzo-27-crown-9, dibenzo-30-crown-10, and nearly as many others as the mind can conceive.

We have pictured below the structures of a few of these interesting chlorethyl compounds as well as some vinyl compounds. If you don't see the precise molecule you need, and you don't have a copy of our catalog, write for one. It lists over 1000 interesting compounds, and to help you visualize their potential usefulness, the structure of the molecule offered is provided with each listing. To help your research budget the price of the molecule offered is also provided with each listing, and the price listed is still the price you pay. Not one compound offered is currently being sold for a price higher than that listed in our catalog. That saves you valuable time because with PARISH there is **no** need to request a quotation, and with PARISH you **don't** receive a reply to your purchase order requesting approval of newer, higher prices before your order can be shipped. **With PARISH you never pay more than the price we list in our catalog!**



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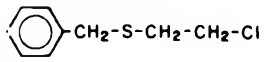
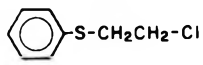


1278 Benzyl 2-chloroethyl sulfide
17.95/25g 55.25/100g



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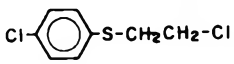
17.35/25g 53.45/100g



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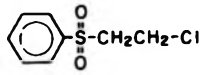

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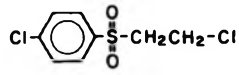

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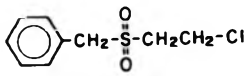
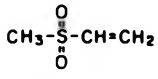
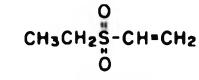


1284 Benzyl 2-chloroethyl sulfone
19.85/25g 61.15/100g



1531 Methyl vinyl sulfone
18.00/10g



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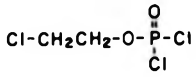
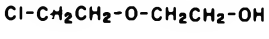


1421 2-Chloroethyl phosphorodichloridate
12.35/25g



2202 2-Chloroethoxyethanol
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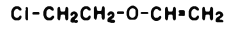

2187 2-Chlorethyl vinyl ether
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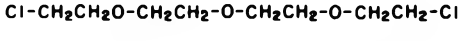
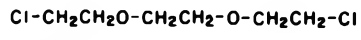


1403 Bis (2-(2-chloroethoxy) ethyl)ether
12.50/25g 38.50/100g



2229 Bis (2-chloroethoxy) ethane
10.00/500g

NOTES

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* In papers with more than one author, the asterisk indicates the name of the author to whom inquiries about the paper should be addressed.

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D-Homo Steroids. Effects of Methyl Substitutions on the Formolysis of an Axial Cyclohexyl Tosylate[1]

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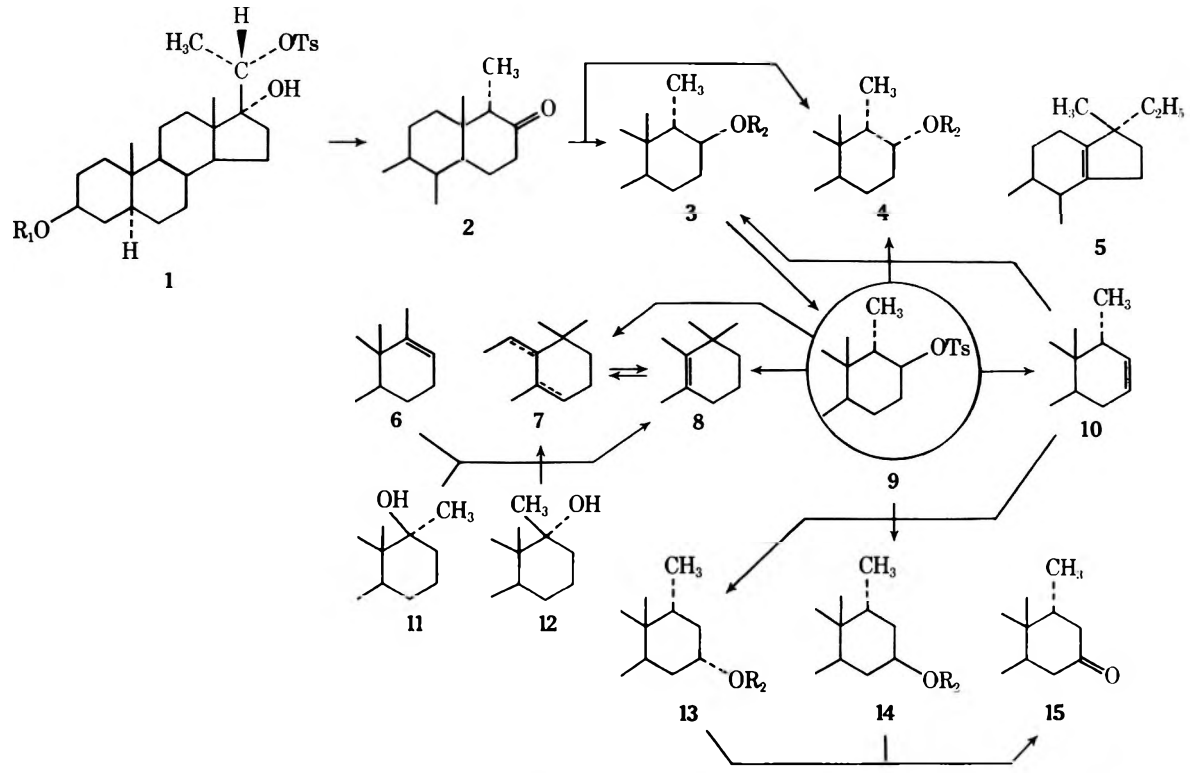
The main products (representing 95% of the material) of the formolysis of 3β-acetoxy-17aα-methyl-*D*-homo-5α-androstan-17β-yl tosylate (**9b**) were identified. The reaction gave the 16-olefin **10b** in 76% yield and only 7% of products that formed by shift or elimination of hydrogen from the more highly substituted C-17a. At C-17 retention was strongly favored over inversion, although this resulted in the unfavorable syn-diaxial interaction of the formoxy with a methyl group. Various explanations for this unusual result were examined. Addition of formic acid to the 16-olefin was negligible during the time required for the formolysis of the tosylate. The hydroboration of the 16-olefin showed only a minor effect of the 17a-methyl on the distribution of the four isomers. This is consistent with the published suggestion that the reaction has an early transition state.

There is a wide divergence of products in the formolyses of the 17a-epimeric 3β-acetoxy-17α-methyl-*D*-homo-5α-androstan-17a-yl tosylates[2] that has not been plausibly explained by the differing positions of the departed tosylate ions. It seemed that the nature of the cationic species involved might be further clarified if new pathways to such 17a cations could be found. With this objective we investigated the solvolysis of a 17aα-methyl-*D*-homo-17β-tosylate (**9b**) because it contains an axial methyl antiparallel to the departing group, an arrangement which might be expected to stabilize itself by a methyl shift to C-17 in concert with the ionization. This migration did not occur. We observed instead the formation of a tertiary C-17a cation which reacted quite unlike the 17a-cationic intermediates which we had studied before.[2-4]

The 17β-hydroxy D-homo steroid (**3e**) required for this investigation was prepared from the known[5,6] 17-ketone **2b**. When we repeated the synthesis of the latter from 3β-acetoxy-17α-hydroxy-5α-pregnan-20α-yl tosylate (**1b**)[6] under the original conditions (potassium acetate in aqueous acetone), we obtained over 40% of the reaction product as the 17α,20β-epoxide,[7] but could suppress its formation by solvolyzing in formic acid. As formolysis gave the desired 17-ketone **2b** in nearly quantitative yield, it follows that the different course of D-homoannulation reported for **1b** and its 17-deoxy analog[4] results from this structural difference and not from the different conditions of solvolysis that had been used heretofore. Reduction of **2b** with lithium tri-*tert*-butoxyaluminohydride gave a single alcohol (**3e**) which was shown to have the 17β configuration by the symmetry[8] of the O–H stretching band at 3611 cm^{-1}; by the narrow NMR signal of the equatorial 17-hydrogen;[9] and by the shifts of ^1H NMR signals on changing the solvent from $CDCl_3$ to C_5D_5N. These changes were large (0.33 ppm downfield) for the 13-methyl but small (0.05 ppm in the same direction) for the 17a-methyl. Comparison of these shifts with those reported by Demarco et al.[10] shows that both the hydroxyl and the 17a-methyl must be axial. This confirms the α configuration of the latter and establishes the chair conformation of the ring. When the reduction was carried out with lithium aluminum hydride both 17-epimeric diols (**3d** and some **4d**) were obtained.

Formolysis of the axial tosylate **9b** gave 85% olefins and a polar fraction which showed strong formate bands. It was hydrogenolized with lithium aluminum hydride and gave six diols on chromatography. Two minor constituents of this fraction had tertiary hydroxyl groups. They may be artifacts resulting from the autoxidation of an olefin and have not been identified. The four other diols could also be obtained by hydroboration of **10b**, the principal olefin derived from **9b**. Two of these diols were identical with **3d** and **4d**, the reduction products of **2**. The two others must also be secondary alcohols because the oxidation of their 3-monoacetates (**13e** and **14e**)[11] gave a common acetoxy ketone (**15b**). We conclude from these observations that C-17 is unsaturated in **10b**, that this olefin has formed from **9b** without rearrangement or configurational change, and that the double bond extends to C-16. The axial isomer (**13e**) of the two 3β-acetoxy-16-hydroxy compounds was identified by the greater symmetry of the O–H stretching frequency; by the lower frequency of the probable stretching band of the C-16–O bond;[12] and by a much greater rate of oxidation with chromic acid.[13] The four 16- and 17-formates derived from **9b** must have arisen by a process of substitution rather than of addition to **10b** because no addition to the double bond was detected during the time required for "complete" solvolysis (9 half-lives). When **10b** was kept in formic acid containing 1 molar equiv of *p*-toluenesulfonic acid for 370 half-lives of the formolysis of **9b**, 12% was recovered as a formate fraction which consisted primarily of the two axial isomers (16α and 17β). This corresponds to 0.3% addition during the formolysis of **9b**.[14]



a, R_1 = H c, C=O instead of $CHOR_1$ e, R_1 = Ac; R_2 = H g, R_1 = Ac; R_2 = HCO
b, R_1 = Ac d, R_1 = R_2 = H f, R_1 = R_2 = Ac

Olefin **10b** comprised 90% of the unsaturated compounds that were derived from tosylate **9b**. Two additional products were isolated from the mother liquors. The major one had no olefinic hydrogen. Its ^{1}H NMR spectrum showed three methyl singlets with the frequencies to be expected from observations[16] on 17a-dimethyl-18-nor-*D*-homo-5α-androst-13-en-3-one (**8c**) (if the published assignments for the 10- and for one of the 17a-methyls are reversed). As in Monneret's[16] work on the 3-ketone, the strongest argument for the 13(14) position of the tetrasubstituted double bond in **8a** lies in the intensity of the $M^+ - CH_3$ peak of the mass spectrum [46% of the base peak (M^+) in our case]. The following observations lend further support to structure **8**. The mass spectrum shows a peak at $M^+ - C_2H_5$ as is to be expected from the work of Aplin et al.[17] Like another 13(14) olefin, **5a** and its acetate **5b**,[18] compounds **8a** and **8b** showed a very intense maximum near 1063 cm^{-1} which in both series disappeared on converting the 3β-ol to the ketone (**5c** and **8c**). As in **5**, the NMR signal of the 19-hydrogens of **8** appears to be essentially unperturbed by the unsaturation. This is not to be expected[19] if the tetrasubstituted double bond occupied the 8(9) position. Because of molecular distortions it may not be justified to exclude the remaining 8(14) location on analogous grounds. However, this position of the double bond is improbable, as it would cause in D-homo steroids a severe interaction between hydrogens at C-7 and C-15.

The French workers[16] obtained the 17a-dimethyl-*D*-homo-13-ene (**8c**) from 17aβ-hydroxy-17a-methyl-*D*-homo-5α-androstan-3-one (**11c**) or from 17a-methyl-*D*-homo-5α-androst-17-en-3-one (**6c**) on treatment with formic acid. When we subjected the corresponding acetoxy compounds **11b** and **6b** as well as **12b** to the conditions of our solvolysis we observed in every instance the formation of **8b** and of the third olefin (**7b**) that we had obtained from the tosylate **9b**. The ir and NMR spectra of **7** showed the presence of olefinic hydrogen. Whereas the C–O stretching frequencies were as expected, the ^{1}H NMR spectrum of **7a** was most unusual as it showed five methyl signals. Four of these had only 1.5 times the area of the olefinic proton or of the one at C-3, while the fifth had three times the area of a single proton. This could signify two magnetically equivalent ethyl groups (J = 6.9 Hz) and one methyl coupled to a single vicinal hydrogen (J = 6.1 Hz). If, however, the strongest signal (0.81 ppm) results from an accidental coincidence of two lines, the spectrum could be consistent with the presence of three $CHCH_3$ groups. Oxidation of the alcohol **7a** to the ketone **7c** eliminated the first of these possibilities, because the assumed coupling pattern did not persist. There were now six peaks of approximately equal intensity, four very close to signals observed for the alcohol (with downfield shifts of 0.01–0.02 ppm) and two displaced downfield by 0.20 or 0.21 ppm. This large shift is consistently observed for the methyl at C-10 in 5α-steroids.[19] As the spatial relationship between C-3 and C-10 is not duplicated for any other position of the methyl group, a rearrangement involving C-10 and leading to a secondary methyl is as improbable on spectrographic as it is on mechanistic grounds. Accordingly we conclude that olefin **7a** in spite of its sharp melting point and its apparent homogeneity on chromatography, is a 1:1 mixture of two secondary–tertiary olefins, each with three tertiary methyl groups. According to ir evidence, **7** also formed when **8** was dissolved in formic acid and this conversion was reversible. This suggests that each one of the three compounds has the 17a-dimethyl group and that they differ in the position of the double bond (13, 14, and 12).[20] Although no isomers could be detected when **5b** was kept in the medium of the formolysis reaction, similar reversible shifts of the double bond must have occurred as a large uptake of isotopic hydrogen was observed.[4]

In Table I the proportions of the four alcohols (**3, 4, 13,** and **14**) that resulted from the hydroboration of **10** are compared with those of the alcohols obtained from another steroidal olefin which has its double bond similarly placed in a terminal ring.[21] In both experiments we observe strong steric hindrance at that facet of an olefinic carbon (17β in i

Table I
Percentages of Alcohols Obtained by Hydroboration

Of 10b			Of 17,17-ethylenedioxy-5α-androst-2-ene[21]		
Atom	Config	%	Atom	Config	%
C-17	β ax	11	C-2	β ax	10
	α eq	21		α eq	26
C-16	α ax	47	C-3	α ax	39
	β eq	21		β eq	24

i ii

and 2β in ii) where the C–B bond would create a syn-diaxial interaction with an angular methyl group. The additional methyl at C-17aα which is present in **10**, although likewise axially oriented in the products, has no inhibitory effect on the α-attack at C-16. This is to be expected if the geometry of the transition state resembles the half-chair conformation of the starting compound as has been deduced for hydroboration by Pasto et al.[22] Only the angular methyls in i and ii have nearly true axial orientations whereas the 17a-methyl shows a major *outward* deflection. This would move the 17a-methyl away from C-16 but would allow it to retard an α-attack on the adjacent C-17 position. The apparently somewhat lower yield of the 17α- than of the 2α-ol suggests the operation of such a vicinal effect.

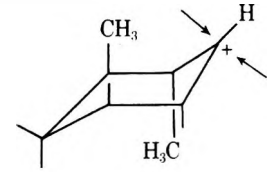
The interpretation of the formolysis of **9b** presents more of a challenge. Pánková et al. explored the acetolysis of a simpler analog, 2β-methyl-4α-*tert*-butylcyclohex-1α-yl tosylate,[23] and observed that the 2β-methyl caused only a minor acceleration but had a major effect on the distribution of the products. The olefins with a vinylic methyl predominated over the one with an allylic methyl, while the esters were confined to substitution products at the site of the tosyloxy group and of the methyl-bearing carbon. In contrast, in the formolysis of **9b** the shift or elimination of a hydrogen from C-16 greatly predominated over the corresponding reactions of the hydrogen at the more highly substituted C-17a (Table II). Our most striking result was an about 5:1 preference for retention over inversion at C-17.

Table II
Solvolyses of Axial Cyclohexyl Tosylates[a]

Products		Substrates			Product
Shifted	Orient	4-BuCy	A-3α	9b	from 9b
		1. Substitution			
−	Axial	0.8	1.2	4.3	3
−	Equat	7.9	4.0	0.9	4
+	Axial	4.3	3.5	6.4	13
+	Equat	0.4	0.1	0.6	14
Unidentified				2.0	
		2. Elimination			
Total		86.5	90.7	84.8	
−		83.5	90.7[b]	76.0	10
+		3.0		7.2	7 + 8

[a] 4-BuCy signifies 4-*cis*-*tert*-butylcyclohexyl tosylate (acetolysis).[24] A-3α, androsterone tosylate (formolysis, corrected for addition).[15] Products are marked shifted (+) if neither the substituted nor either of the unsaturated carbon atoms coincides with the original site of the tosyloxy group. [b] This was a mixture of olefins consisting of the 2-ene and 3-ene in the ratio 9:1.[15]

This may be compared with the 1:8 ratio observed for the cyclohexyl case studied by the Czech workers[23] or the 1:10 ratio obtained for the acetolysis of 4-*cis*-*tert*-butylcyclohexyl tosylate[24] (Table II). This reversal is not simply a solvent effect (cf. the formolysis of androsterone tosylate,[15] Table II) and seems the more remarkable as retention in the substitution of **9b** reintroduces a 1,3-diaxial interaction between the entering ligand and the angular methyl, a feature which is absent in the three other cases. If one postulated that an ion pair in the congested space on the β side of C-17 would dissociate very rapidly, a major obstacle toward retention would be removed. Nevertheless, this would explain the high ratio of **3** to **4** only if one makes the further assumption that a β-attack by the solvent on the C-17 cation would be favored over one from the less hindered α side. This seems most improbable if the ion has the chair conformation (iii).[25]



iii

The interaction between the methyl at C-13 and the ester group would be avoided if the intermediate cation had a nonchair conformation. The spectrum of shapes which this flexible form could assume represents a path of pseudo-rotation between only two boat forms. The first lacks the bow–stern interaction but shows eclipsing effects involving large groups: the 17a-methyl and a methylene (C-12) as well as the 13-methyl and the 17a-hydrogen. In the second boat the 13-methyl causes a particularly severe bow–stern interaction. Both types of destabilizing effects are reduced in the twist form but we still measure distances between nonbonded atoms that are shorter than any found in the chair. It seems hardly possible, therefore, that the transition state of a flexible form of the cation leading to **3g** could have a lower energy than the transition state between the chair conformation of this cation and the equatorial isomer **4g**.

A different mechanism was suggested by Winstein and Holness,[26] who derived the two axial substitution products of 4-*cis*-*tert*-butylcyclohexyl tosylate, the 4-*cis*-*tert*-butyl- and 3-*trans*-*tert*-butylcyclohexyl acetates (or formates) from a hydrogen-bridged cation. Two factors might make such a process more important in our case. The formation of a bridged ion from **9b** would involve the outward and upward movement of the 16α-hydrogen, which can be expected to be favored as it would reduce the 1,3 interaction of this hydrogen with the 17aα-methyl. Moreover, bridging could compensate for any steric hindrance to solvation of a 17-cation that might be caused by the methyl substituents. Actually, the reaction was quite fast, more than ten times faster than the formolysis of androsterone tosylate.[15,27] If a pathway through a bridged ion would indeed have greater importance in the formolysis of **9b** than in the solvolyses of other axial tosylates, this should manifest itself also in a higher yield of the rearranged substitution products. This was the case as our yield of secondary ester formed by hydride shift was exceptionally high.[28]

Olefins **7b** and **8b** must have formed via the tertiary 17a-methyl-17a-cation. This in turn may have formed from the classical C-17 cation or possibly from the 16α-hydrogen-bridged 17-cation by hydride shift. Another conceivable route to the tertiary ion is through protonation of the olefin **6b** which could have formed from **9b** and which was found to be completely isomerized under the conditions of

the solvolysis. Even if all of **7** and **8** were so derived, the total amount of **6** that would have formed in the course of the reaction could not have significantly exceeded the yield of that formolysis product of androsterone tosylate that has a double bond in the corresponding position relative to the ring junctions (5α-androst-3-en-17-one). Therefore the extra methyl at C-17a does not seem to promote the removal of the hydrogen from this site. This too can be rationalized if in a large fraction of the 17-cations the charge was delocalized by a 16α-hydrogen bridge.

Regardless of its origin (**6b, 9b, 11b,** or **12b**), the tertiary cation reacts exclusively by migration of the 13-methyl to C-17a. This distinguishes it from the ion that is generated in the same solvent from uranediol 3-acetate 17a-tosylate. In the latter case, methyl migration, if it occurs at all, still remains to be demonstrated.

Experimental Section

General Procedures. Melting points are corrected. Rotations were measured by means of a Perkin-Elmer polarimeter (Model 141) on solutions in $CHCl_3$, and ir spectra by means of a Perkin-Elmer grating photometer (Model 421) on solutions in CS_2, except the diols which were examined as pressings in KBr. The peaks listed are those characteristic of functional groups and other prominent bands. NMR spectra were recorded for solutions in $CDCl_3$ containing Me_4Si on Model HA-100 or, if the steroid concentrations were low, on Model XL-100 of Varian. Shifts are given in parts per million downfield from Me_4Si. For uv spectra a Beckman spectrophotometer with photomultiplier was used.

Steroids were usually extracted from the diluted reaction mixture with ether; if the medium was formic acid, distribution between benzene and water was used. These organic phases were washed (when appropriate) with dilute hydrochloric acid, sodium carbonate, and water and were taken to dryness under reduced pressure. Chromatography was done on silica gel. Departures from these procedures are indicated in the text.

The homogeneity of the various compounds was deduced from the observation that they and their derivatives gave single spots on TLC and from the constancy of their ir spectra when the purified samples were obtained from different starting materials and when they were subjected to further attempts at fractionation. Yields were determined by the weight of pure material. For this purpose each component that had been separated by chromatography was purified by recrystallization. The mother liquors were fractionated by chromatography on longer columns. The purity of the ensuing fractions was ascertained by ir comparison with the recrystallized reference samples and by TLC. Occasionally very minor fractions were encountered which were still mixtures. Their weight was allotted to their respective components in accordance with the intensity of the spots on TLC.

3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-17-one (2b). 5α-Pregn-(*Z*)-17(20)-en-3β-yl acetate[29] was converted to the 17α,20α-glycol[6] (mp 190.5–192.5°) according to the procedure of Baran[30] and then to its 20-tosylate[6] (**1b**, mp 138–140°). After solvolysis of 82 mg as described by Williams et al.[6] (method A), the product (57 mg) was chromatographed on silica gel which had been deactivated with water and dried by exposure to air. Elution with benzene–hexane (1:1) and with benzene gave 25 mg of **17α,20β-epoxy-5α-pregnan-3β-yl acetate,** mp 172–175° after recrystallization from dilute acetone (reported[6] mp 153–170°).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.83; H, 10.24.

The later eluates (32 mg, obtained with benzene) contained ketone **2b.** An identical product was obtained by keeping a solution of 100 mg of **1b** in 2 ml of benzene and 100 ml of formic acid at 25° for 170 min. The neutral product (71 mg) when chromatographed on deactivated silica gel (see above) gave two unidentified nonketonic products followed by 68 mg of ketone **2b** which was recrystallized from acetone–petroleum ether. Two crystal modifications (mp 120–122.5° and 131.5–132.5°) were observed, $[\alpha]^{30}D$ −27° (reported[5,6] mp 127–129° and 125–129°, $[\alpha]D$ −49°).[31]

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.62; H, 10.13.

Reduction of 3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-17-one (2b). A mixture of **2b** (166 mg), 333 mg of lithium tri-*tert*-butoxyaluminohydride, and 9 ml of dry tetrahydrofuran was kept at room temperature for 17 hr, diluted with solvent, chilled, and treated dropwise with 1 *N* HCl. The neutral reaction product, which was homogeneous on chromatography, was recrystallized from hexane-benzene. **3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-17β-ol (3e)** had mp 167–168°; $[\alpha]^{24}D$ −31°; ^1H NMR ($CDCl_3$) 0.81 (19-H), 0.87 (d, J = 7.4 Hz, 17a-methyl), 1.13 (18-H), 2.01 (H_{OAc}), 3.82 ppm (17-H, m with half-intensity band width 5 Hz as compared to 22 Hz for 3α-H); ^1H NMR (C_5D_5N) 0.74,[32] 0.92 (d, 7.5 Hz), 1.46 (18-H), 2.04, 4.06 ppm (17-H);[10] ir, OH, 3611 (ν_+/ν_- 0.96),[2,8] 985; 3β-OAc, 1736, 1028 cm^{-1}.[33]

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.55; H, 10.81.

When the reduction of **2b** was carried out with lithium aluminum hydride in ether, recrystallization of the reaction product from acetone–methanol gave **17aα-methyl-*D*-homo-5α-androstane-3β,17β-diol (3d):** mp 198–200°; ir 1035 (3β-OH)[33] and 987 cm^{-1}. The mother liquors on TLC yielded, in addition to **3d, 3e, 4d,** and **4e.** (This unusual but to us useful preservation of an ester group evidently was caused by the great age of our preparation of the hydride.) Of the total reaction products 80% had the 17β configuration.

Hydroboration of 17aα-Methyl-*D*-homo-5α-androst-16-en-3β-yl Acetate (10b). Diborane was generated slowly and without heating from $NaBH_4$ and $BF_3{\cdot}Et_2O$. It was passed during 55 min through a solution of 52 mg of **10b** in 4 ml of tetrahydrofuran maintained at 20°. After an additional 1 hr the mixture was diluted with solvent and kept at 1 ± 1° with stirring while 0.7 ml of ice water and then a chilled 3:2 mixture (2.8 ml) of 10% sodium carbonate and 30% H_2O_2 were added dropwise. After 1 hr at this temperature the neutral reaction product was isolated, adsorbed from benzene on silica gel, and eluted with 4% ethyl acetate in benzene to yield material without a hydroxyl group (5%), the four 3β-acetoxy 16- and 17-carbinols (68%) and with 40% ethyl acetate the combined diols (26%). The products are listed in their order of elution.

3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-17β-ol (3e): for characterization see above.

3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-17α-ol (4e) was recrystallized from 95% methanol: mp 172–173.5°; ir 3612 (ν_+/ν_- 0.72), 1733 and 1027 (3β-OAc), 1015 cm^{-1}.

3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-16α-ol (13e) was recrystallized from 95% methanol: mp 156.5–158°; ir 3612 (ν_+/ν_- 1.04), 1732 and 1031 (3β-OAc), 1019 cm^{-1}.

3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-16β-ol (14e) was recrystallized from 90% acetone: mp 162.5–163°; ir 3608 (ν_+/ν_- 0.67), 1732 and 1025 (3β-OAc), 1036 cm^{-1}.

The diol fraction was again adsorbed and fractionated by elution with 20% ethyl acetate in benzene into **3d** (see above), **4d** [mp 201.5–202°; ir 1035 (3β-OH) and 1018 cm^{-1}], **13d** [ir 1039 (3β-OH) and 1021 cm^{-1}], and **14d.** They were identified by converting them and the corresponding monoacetates to the common diacetates. The combined percentages of the four stereoisomeric forms, obtained by hydroboration as diols and monoacetates, are given in Table I. The properties of the diacetates were as follows.

17aα-Methyl-*D*-homo-5α-androstane-3β,17β-diol diacetate (3f) was amorphous: ir 1029 (3β-OAc) and 1013 cm^{-1}.

17aα-Methyl-*D*-homo-5α-androstane-3β,17α-diol diacetate (4f) was recrystallized from methanol: mp 207.5–209°; ir 1027 (3β-OAc) and ~1019 cm^{-1} (shoulder).

Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.21; H, 10.18.

17aα-Methyl-*D*-homo-5α-androstane-3β,16α-diol diacetate (13f) was recrystallized from dilute methanol: mp 136–138°; ir 1031 (3β-OAc) and 1019 cm^{-1}.

Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.37; H, 9.91.

17aα-Methyl-*D*-homo-5α-androstane-3β,16β-diol diacetate (14f) was recrystallized from methanol: mp 174.5–175.5°; ir 1030 (3β-OAc) and ~1021 cm^{-1} (shoulder).

Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.27; H, 10.16.

3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-17β-yl Tosylate (9b). Acetoxycarbinol **3e** (105 mg) and 1.2 g of *p*-toluenesulfonyl chloride were kept in 1.5 ml of pyridine for 3 hr. The neutral reaction product was recrystallized from 96% acetone: mp 135–137°; ir, OAc bands 1734, 1240, 1029; general tosylate bands[2] 1306, 1188, 1177, 1098, 1020; specific tosylate bands 924, 913, 900, 827, 812, 683, 659, 582 cm^{-1}.

Formolysis of 3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-17β-yl Tosylate (9b). A solution of 100 mg of **9b** in 4 ml of benzene was diluted with 200 ml of dry formic acid and kept at 23°

for 70 min. The neutral reaction product (68.8 mg), which showed no tosylate absorption, was adsorbed on deactivated silica gel. Elution with benzene–hexane (1:1) gave 57.6 mg of olefins, with benzene 0.0 mg, and with 12% acetone in benzene 11.7 mg of formates.

The formate fractions from two such runs were hydrogenolized[26] with lithium aluminum hydride to the diols which on recrystallization from acetone–methanol gave **13d** (mp 208–210°). The mother liquors were chromatographed as described for the diols obtained by hydroboration. An incompletely fractionated mixture of **4d** and **13d** was separated by preparative TLC (25% ethyl acetate in benzene). The mother liquors of **3d** and **13d** each contained at least one additional diol which readily separated by acetylation and chromatography because these side products gave monoacetates. They were not identical with **11b** or **12b** or any of the other monoacetates described in this paper.

Diols **3d**, **4d**, **13d**, and **14d** and their diacetates were identified by comparisons (TLC, ir, melting point) with the reduction products of **2b** and the hydroboration products of **10b**. Uranediol and its diacetate, which could not be separated by chromatography from **3d** and **3f**, respectively, were not detected in the mother liquors of **3d** and **3f** by ir spectroscopy.

The olefin fraction (57.6 mg obtained from the formolysis of **9b**) on recrystallization from 95% acetone gave 44.2 mg of **17aα-methyl-*D*-homo-5α-androst-16-en-3β-yl acetate (10b)**: mp 104–106°; $[\alpha]^{28}D$ −139°; ir, olefinic frequencies 3061, 3014 (strong), 1656, 717 (very strong); 3β-acetoxy 1737, 1242, 1029 cm^{-1}.

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.67; H, 10.85.

Another 7.4 mg of **10b** was obtained by chromatographing the mother liquors on silica gel–silver nitrate (prepared by stirring 1.4 g of $AgNO_3$ in 2 ml of water and 12 ml of acetone with 10 g of silica gel, filtering, washing with acetone, and drying at 75° for 4 hr).

On this column **8b** (3.0 mg) and product **7b** (1.9 mg) were eluted ahead of **10b** with benzene–hexane (1:1). The sample of **8b** which was not crystalline had the same ir spectrum as the ones obtained from **6b**, **11b**, and **12b**. It was hydrolyzed with methanolic potassium hydroxide and recrystallized from dilute acetone. **17a-Dimethyl-18-nor-*D*-homo-5α-androst-13-en-3β-ol (8a)** had mp 154.5–155.5°; ^1H NMR 0.76 (19-H), 0.94 and 0.98 ppm (17a-methyls). (A further prominent signal at 1.46 ppm disappeared on adding D_2O.) The ir spectrum agreed with that of the higher melting sample described below.

The next eluate (**7b**) had ^1H NMR peaks at 0.76, 0.83, 0.89, 0.98, 1.05 and 2.03 (very weak curve). Its ir spectrum (3β-OAc, 1026 cm^{-1}) agreed with those of the preparations obtained from **6b**, **11b**, and **12b**. (The relatively high ratio 7:8 observed in the formolysis of **9b** may have been caused by autoxidation of **8b** during the isolation which was much more protracted than the fractionations reported below.)

17a-Methyl-*D*-homo-5α-androst-17-en-3β-yl Acetate (6b). 3β,17aβ-Dihydroxy-17a-methyl-*D*-homo-5α-androstan-17-one (mp 199–201°, reported[34] 200–200.5°) was prepared from 3β-acetoxy-17α-hydroxy-5α-pregnan-20-one by method d (15 min, base 0.2 *N*) of Kirk and Mudd.[35] It was subjected to the Wolff–Kishner reaction under the conditions described by Turner et al.[36] The product gave on chromatography in the early eluates **17a-methyl-*D*-homo-5α-androst-17-en-3β-ol (6a)** (mp 159–161°, reported[37] 159–160°). Its acetate (**6b**) after recrystallization from methanol had mp 131–132°; $[\alpha]^{25}D$ + 48°; ir, 3β-acetoxy 1736, 1241, 1028; =CH 3023, 794; other 1054 cm^{-1}.

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.15; H, 10.52.

3β-Acetoxy-17a-methyl-*D*-homo-5α-androstan-17aβ-ol (11b). The later eluates of the chromatogram of the Wolff–Kishner products contained an impurity with absorption near 3020 cm^{-1} suspected to be the 16,17-dehydro analog of **11a**. It was removed after acetylation by repeated chromatography. Recrystallization of the somewhat less mobile material from methanol gave **11b**: mp 187–188°; $[\alpha]^{24}D$ −15°; ir, 3β-acetoxy 1735, 1244, 1025; 17a-OH 3610 and on the basis of its intensity 1049 cm^{-1}; the band at 1060 cm^{-1} serves best to distinguish **11b** from **12b**.

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.04; H, 10.81.

3β-Acetoxy-17a-methyl-*D*-homo-5α-androstan-17aα-ol (12b). Compound **6b** (20 mg) was treated with 20 mg of *m*-chloroperoxybenzoic acid in 0.6 ml of methylene chloride for 140 min. The resulting **17α,17aα-epoxy-17a-methyl-*D*-homo-5α-androstan-3β-yl acetate** was recrystallized from acetone: mp 157–159° (reported[38] 158–160°, see also ref 39); $[\alpha]^{24}D$ +22°;[40] ir, 3β-acetoxy 1733, 1242, 1027; others 1053, 1042 cm^{-1}.

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.40; H, 10.04.

This epoxide was treated with lithium aluminum hydride under the conditions reported by Ruzicka et al.[41] The product was acetylated and although essentially homogeneous (TLC) was chromatographed. 3β-Acetoxy-17a-methyl-*D*-homo-5α-androstan-17aα-ol (**12b**) had mp 159.5–160° (reported[42] 152.5–154 or 117–118°); $[\alpha]^{24}D$ −25° ($CHCl_3$ or dioxane) (reported[42] −40°, dioxane; for reference data on analogs in $CHCl_3$ see ref 41); ir, 3β-acetoxy 1732, 1244, 1028; 17a-OH 3617, 1019 cm^{-1}. On TLC [SiO_2–$CaSO_4$ dried for 7 hr at room temperature, benzene–ethyl acetate (85:15)] **12b** and **11b** each traveled as a single spot, clearly separated from the other (R_f 0.59 and 0.52, respectively).

Alternative Sources of 7 and 8. Compounds **6b**, **11b**, and **12b** (0.04 mmol) were each dissolved in 0.8 ml of benzene and diluted with 41 ml of formic acid containing 0.04 mmol of *p*-toluenesulfonic acid monohydrate and kept at room temperature for 70 min. The reaction products, which had very similar ir spectra, were adsorbed on silica–silver nitrate. Elution was completed within 2 hr and gave in each case **8b** and **7b**. Product **7b** comprised 20 ± 2% of the total. (This ratio was not altered when **6b** was kept in the formic acid medium for 69 hr.) The fractions with identical ir spectra were combined, hydrolyzed, and recrystallized. **17a-Dimethyl-18-nor-*D*-homo-5α-androst-13-en-3β-ol (8a)** had mp 165–167°; ir, 3β-OH 3610, 1039; 1064 cm^{-1} (equally strong); $[\alpha]^{26}D$ −104°; mass spectrum M^+ (base peak, 24% of intensity sum of spectrum) calcd for $C_{21}H_{34}O$, 302.2610; found, 302.2580; signals with mass >150 and intensity >5% of base peak (except isotopic satellites) $C_{21}H_{33}O$, $C_{20}H_{31}O$, $C_{21}H_{33}$, $C_{20}H_{29}$, $C_{16}H_{23}$, $C_{13}H_{20}$, $C_{13}H_{19}$, $C_{12}H_{17}$; uv in cyclohexane, only end absorption down to 200 nm.

The hydroxy olefins derived from the later eluates gave **7a** with mp 121.5–123.5°; ir, 3β-OH 3612, 1040; =CH 3051, 829; others 1051 cm^{-1}; ^1H NMR 0.74 (19-H), 0.81 (19-H and 17a-methyl), 0.88, 0.98, and 1.04 ppm.

The appearance of the ir bands of **7a** could also be demonstrated after **8a** had been exposed to the formic acid medium (70 min) and the resulting mixture of the 3-formates of **7** and **8** had been hydrolyzed.

Oxidation of Hydroxyolefins 7a and 8a to 3-Ketones. A sample of **8a** (2.8 mg) in 0.5 ml of acetone was stirred at 12° for 1 min after the addition of 5 μl of the CrO_3–H_2SO_4 reagent of Bowers et al.[43] The neutral product (**8c**) [ir 1713 cm^{-1} (C=O) (reported 1720 cm^{-1}),[16] no hydroxyl, other peaks 1215 and 1167 cm^{-1}] was recrystallized from dilute methanol, mp 143–145° [reported 140° (uncorrected)].[16]

Preparation **7a** (3.4 mg) was oxidized under the same conditions. The product contained unwanted absorption near 1670 cm^{-1}. This contaminant was removed by chromatography and recrystallization. Preparation **7c** had ir, C=O 1712; =CH 3052 and 829; other 1223 cm^{-1}; ^1H NMR 0.83, 0.90, 0.95 (19-H), 0.99, 1.01 (19-H), 1.05 ppm.

After exposure of **7c** to the formic acid medium, the ir spectrum changed to that of a mixture of predominantly **8c** with **7c**. On reduction with lithium tri-*tert*-butoxyaluminohydride the strong peak of **8a** at 1064 cm^{-1} appeared.

Oxidations of 13e and 14e. Solutions of 800 μg of 3β-acetoxy-17aα-methyl-*D*-homo-5α-androstan-16α-ol (**13e**) and of its 16-epimer (**14e**) in 1.7 ml of 90% acetic acid were each mixed at zero time with an equal volume of 90% acetic acid containing 323 μg of chromium trioxide. The mixture was maintained at 20.6° while its extinction at 350 nm was measured. The constants (k) of the rates of oxidation follow: **13e**, 2.07; **14e**, 0.112 M^{-1} sec^{-1}; $k = [1.535/(a - b)t] \log[b(a - x)/a(b - x)]$, where a, $a - x$ represent the molar concentrations of CrO_3 at times zero and t, respectively, and b represents ⅔ of the molar concentration of the alcohol at time zero. The rate ratios **13e/14e**: found, 18.5; expected 15.4 from the structural factors given by Schreiber and Eschenmoser.[13] At the end of each run the reaction product (**15b**) was isolated. The ir spectra agreed and showed ν_{max} at 1736, 1711, and 1028 cm^{-1}.

Rate of Formolysis of Tosylate 9b. This process was measured under the same conditions as were specified for the preparative run, but was terminated by distribution between benzene and water after 5 and 10 min, respectively. The fraction of tosylate remaining was determined from the extinctions at 1098 and 683 cm^{-1}. The first-order rate constant was 1.48×10^{-3} sec^{-1}, corresponding to a half-life of 7.8 min. The ir curves after 5, 10, and 70 min showed no bands attributable to an isomeric tosylate.

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Registry No.—**1b**, 1914-30-3; **2b**, 2270-04-4; **3d**, 56665-84-0; **3e**, 56665-85-1; **3f**, 56665-86-2; **4d**, 56665-87-3; **4e**, 56665-88-4; **4f**, 56665-89-5; **6b**, 56665-90-8; **7a** isomer 1, 56665-91-9; **7a** isomer 2, 56665-92-0; **7b** isomer 1, 56665-93-1; **7b** isomer 2, 56665-94-2; **7c** isomer 1, 56665-95-3; **7c** isomer 2, 56665-96-4; **8a**, 56665-97-5; **8c**, 31751-19-6; **9b**, 56665-98-6; **10b**, 56665-99-7; **11b**, 56666-00-3; **12b**, 56666-01-4; **13d**, 56666-02-5; **13e**, 56666-03-6; **13f**, 56666-04-7; **14e**, 56666-05-8; **14f**, 56666-06-9; **15b**, 56666-07-0; 17α,20β-epoxy-5α-pregnan-3β-yl acetate, 56666-08-1; diborane, 18099-45-1; *p*-toluenesulfonyl chloride, 98-59-9; 3β,17aβ-dihydroxy-17a-methyl-*D*-homo-5α-androstan-17-one, 3751-01-7; *m*-chloroperbenzoic acid, 937-14-4; 17α,17aα-epoxy-17a-methyl-*D*-homo-5α-androstan-3β-yl acetate, 56666-09-2.

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Synthesis of α-Methylene Lactones by Reductive Amination of α-Formyl Lactones. Scope and Limitations

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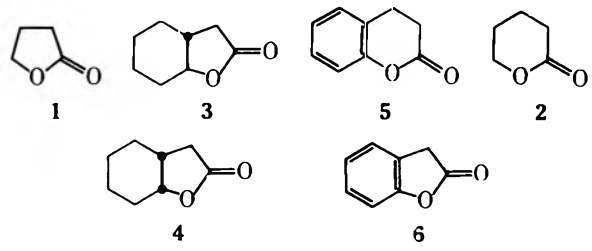
The synthesis of α-methylene lactones by reductive amination of α-formyl lactones with sodium cyanoborohydride and dimethylamine is described with regard to its scope and limitations. The α-methylene lactones α-methylene-δ-valerolactone (**10**), α-methylene-*trans*-2-hydroxycyclohexaneacetic acid γ-lactone (**13**), α-methylene-*cis*-2-hydroxycyclohexaneacetic acid γ-lactone (**16**), and 3-methylene-3,4-dihydrocoumarin (**23**) are prepared from their α-formyl lactones. The α-methylene lactone of 2-coumaranone could not be synthesized by this procedure.

As a counterpart to our development of a synthesis of α-methylene-γ- or -δ-lactones by reductive amination of the corresponding α-formyl lactones,[3a] which enabled an efficient synthesis of tulipalin A and pentaacetyl tuliposide A,[3b] we decided to examine the scope and limitations of this method. In view of the continued great interest in synthetic methods for construction of α-methylene-γ- and -δ-lactone units,[4] which are found in a variety of biologically active natural products,[5] such a study was felt to be necessary to truly define the generality of our synthetic approach. We now report the successes and failures of our investigation.

Results

Our general synthetic format for the preparation of α-methylene-γ- and -δ-lactones is shown in Scheme I. Since it involves the addition of an α-methylene unit to a preformed γ- or δ-lactone, we investigated the "α-methylenation" of lactones 1–4 as representative of the α-methylene lactone systems found in certain natural products,[5] and 5 and 6, whose "α-methylenation" had been attempted by



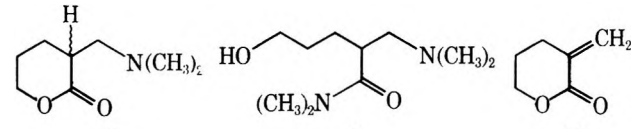
1 3 5 2

4 6

Martin et al.[6] but with unsuccessful results using an α-methylation method based on methyl methoxymagnesium carbonate carboxylation of lactones. For comparative purposes we chose to look at our reductive amination method as comprised of three basic steps: I, lactone formylation; II, reductive amination; and III, quaternization and elimination, although the latter was a trivial distinction.

The synthesis of tulipalin A, the α-methylene analog of 1, has been described.[3a,b] Since steps I and III of its synthesis were carried out essentially quantitatively whereas the yield of α-dimethylaminomethyl-γ-butyrolactone (7)[3b] in step II of the reaction sequence appeared to be variable, a brief study of the effect of experimental conditions on the yield of 7 was undertaken. The results of this study are shown in Table I. Control of the *initial* pH of the reaction mixture between 5 and 7 by addition of absolute methanolic HCl favorably affected the yield of 7 and lessened the amount of the principal by-product, 2-dimethylaminomethyl-4-hydroxybutanoic acid dimethylamide (formed in less than ca. 10% yield[7]), whereas the ratio of dimethylamine to α-formyl butyrolactone and the reaction solvent seemed to be somewhat less critical.

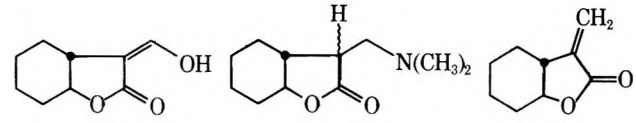
The synthesis of α-methylene-δ-valerolactone[3a] (10) could be achieved in only a 41% overall yield from 2. As with 1, the lowest yield was obtained in step II of the reaction sequence. A similar study (vide supra) of the yield of α-dimethylaminomethyl-δ-valerolactone (8) was done; the



8 9 10

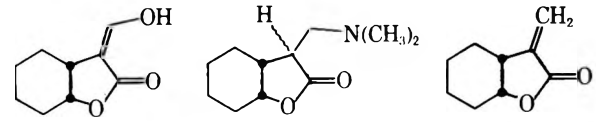
results are shown in Table II. The amount of dimethylamide by-product (9) always represented a greater percentage of the consumed α-formyl-2 than with 1, appearing with 8 in a 1:1 ratio when the reaction solvent was DME. Although the methiodide of 8 could not be obtained crystalline, step III of the reaction sequence could be carried out to give an 80–85% yield of 10.

The method of Newman and Vanderwerf[8] was used to obtain *trans*-2-hydroxycyclohexaneacetic acid γ-lactone (3). This was converted in 90% yield to its α-formyl derivative (11, sodium salt) when diethyl ether was the reaction solvent in step I, and 73% yield when DME was used. Step II of the reaction sequence was shown to be much less variable than for 1 or 2; the yield of 12 ranged from 43% (MeOH) to 57% (DME). Step III was carried out in high yield to give α-methylene-*trans*-2-hydroxycyclohexaneacetic acid γ-lactone (13) in an overall yield of 48% from 3.



11 12 13

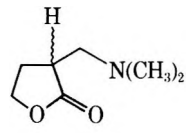
cis-2-Hydroxycyclohexaneacetic acid γ-lactone (4) was prepared according to Klein.[9] Formylation of 4 was accomplished in either diethyl ether or DME as the reaction solvent to give 14 in a 97–100% yield. Two C-2 epimers of 15



14 15 16

were obtained in step II of the reaction sequence in a combined yield of 33–50% when the sodium enolate of 14 was used as starting material to 57% when 14 itself was used. Although the chromatographically separable epimers of 15

Table I
Reductive Amination of Sodium α-Formyl-γ-butyrolactone



7

Expt	Ratio of $(CH_3)_2NH$ to Na enolate[b]	Initial pH	Solvent	Time, hr	Yield of 7, %
1	7:1	*c*	MeOH	96	50
2[a]	6:1	*c*	THF–MeOH (3:1)	96	69
3	1:1	~4	MeOH	1	42
4	2:1	~4	MeOH	1	32
5	2:1	~4	MeOH	18	68
6	2:1	~6	MeOH	18	64
7	2:1	*c*	DME	18	68
8	2:1	~6	DME	24	81
9	2:1	*c*	DME–HMPA (9:1)	18	66
10	2:1	~6	DME–MeOH (15:1)	18	63

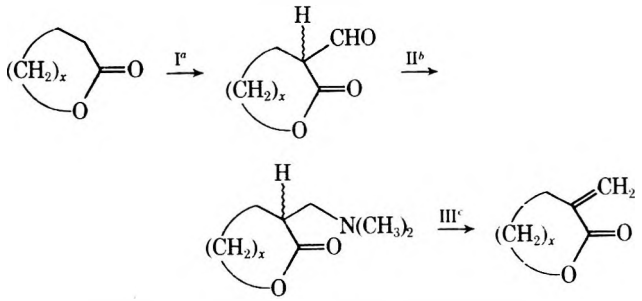
[a] Using purified $NaCNBH_3$;[16] all other runs were done with the commercially available $NaCNBH_3$ used as received. [b] $NaCNBH_3$ always was used in at least 50% excess molar equiv. [c] Initial pH not adjusted.

Table II
Reductive Amination of Sodium α-Formyl-γ-valerolactone

Expt	Ratio of $(CH_3)_2NH$ to Na enolate[a]	Initial pH	Solvent	Time, hr	Yield of 8,[c] %
1	6:1	*b*	MeOH	96	64
2	5:1	*b*	MeOH	24	30
3	2:1	*b*	MeOH	24	35
4	2:1	~6	MeOH	20	49
5	2:1	*b*	DME	24	32
6	2:1	~6	DME–MeOH (10:1)	20	33

[a] $NaCNBH_3$ always was used in at least 50% excess molar equiv. [b] Initial pH not adjusted. [c] Accompanied by varying amounts of 9 (10–20%), which appeared in significant amounts (~32%) in run 5.

Scheme I



[a] Base, $HCO_2C_2H_5$. [b] $NaCNBH_3$, $(CH_3)_2NH$. [c] CH_3I, aqueous $NaHCO_3$.

gave distinctly different methiodides (Experimental Section), their structural distinction spectroscopically was not done largely owing to the close proximity of the resonances from the carbocyclic ring to those of the C-2 hydrogen in the 100-MHz NMR spectra. Each of the epimers of **15**, or their mixture, was carried through step II to give **16** in an overall yield of 50% from **14**.

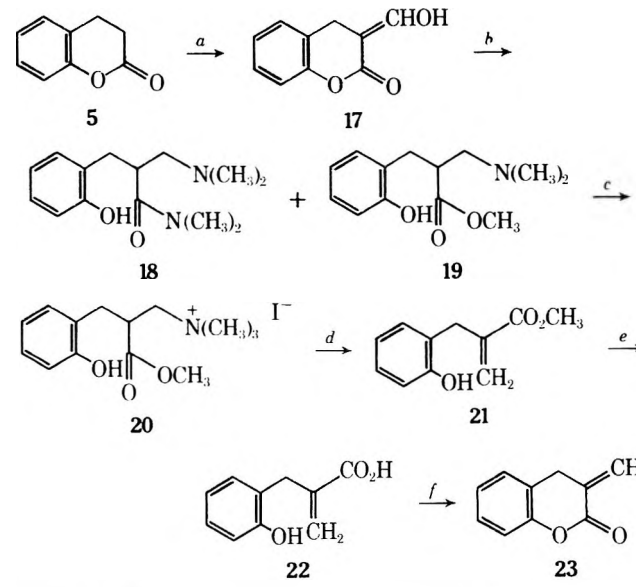
3-Formyl-3,4-dihydrocoumarin (**17**) was prepared in 45% yield essentially as described by Korte and Büchel,[10] although several alternative approaches were examined. Numerous bases and formylating reagents were examined in the hope of finding a combination which would favor the formation of **17** rather than ring-opened products. The combination of lithium 2,2,6,6-tetramethylpiperidide and acetic–formic anhydride[11] produced a 30% yield of **17**. The same base with formic–pivalic anhydride gave only a 27% yield of **17**. Sodium hydride and lithium diisopropylamide produced less satisfactory results. Numerous uncharacterized products were formed in all instances.

The reductive amination of **5** (Scheme II) was carried out more successfully than with **2**–**4** in that the yield of the α-dimethylaminomethyl derivative was as high as 72%. It is unfortunate that the amino lactone was not the reaction product. In all cases the ring-opened methyl ester (**19**) was obtained as the major product, with the corresponding dimethylamide (**18**) as a minor product. In one instance when DME was used as the solvent a nearly 1:1 mixture of **18** and **19** was obtained, **19** arising from initial acidification of the reaction mixture with methanolic hydrogen chloride.

Conversion of **19** to its methiodide (**20**) resulted in the formation of a yellow, amorphous solid. TLC analysis of the reaction mixture after 5 min at room temperature in the dark indicated the presence of unreacted **19** as well as **20**. Two other spots were observed which were not amines, one corresponding to **21**. Treatment of the mixture by shaking with 5% aqueous sodium bicarbonate gave a 62% isolated yield of the α-methylene ester (**21**) based on **17**. Hydrolysis with barium hydroxide and neutralization with 1 *N* sulfuric acid afforded **22**, which was lactonized with *p*-toluenesulfonic acid in refluxing toluene to 3-methylene-3,4-dihydrocoumarin (**23**). A 55% overall yield of **23** was obtained from **17**.

The structure given as **23** was assigned on the basis of the following spectral and analytical data. The ir spectrum contained a strong peak at 1740 cm^{-1}. When compared with the 1773-cm^{-1} peak observed with **5** it was seen that the observed shift of carbonyl absorption corresponded to that observed between other α,β-unsaturated esters and lactones when compared to their saturated analogs.[12] Peaks at 1639 and 810 cm^{-1} suggest a vinylidene group. The NMR spectrum (60 MHz) contained a four-proton multiplet at δ 6.9–7.4 for the aromatic system. A pair of finely split multiplets at δ 5.77 and 6.40 represented the α-methylene protons which were split by the two β protons and by

Scheme II



[a] $Mg[N(i\text{-}Pr)_2]_2$, $HCO_2C_2H_5$. [b] $NaCNBH_3$, $(CH_3)_2NH$, $(CH_3)_2NH_2Cl$. [c] CH_3I. [d] Aqueous $NaHCO_3$. [e] $Ba(OH)_2$. [f] *p*-TSA, Δ.

the magnetically nonequivalent vinylogous twin. Both *J* values are <1 Hz. Finally, the two β methylene protons at δ 3.75 occurred as a triplet (*J* = <1 Hz), being split by the vinylogous protons equally. The two-proton singlet appearing at δ 7.97 in the NMR spectrum of **22** was absent in the spectrum of **23** providing further evidence for the lactonization. High-resolution mass spectrometric analysis on the parent ion of **23** resulted in a value of 160.0527 for the molecular weight. The calculated value of 160.0524 agreed well with the observed value. A satisfactory combustion analysis could not be obtained for this compound.

Attempts to synthesize the α-methylene analog of 2-coumaranone (**6**) uniformly were unsuccessful owing to our inability to formylate it, although the use of several reagents and reaction conditions was explored.[13] It was found that **6**, unlike **5**, could not be deuterated at C-3 by anion formation at −78° in THF with lithium 2,2,6,6-tetramethylpiperidide and subsequent quenching with deuteriotrifluoroacetic acid. On exposure to these conditions **6** was recovered unchanged, whereas **5** easily was converted to its monodeuterio derivative. The use of higher reaction temperatures led to low recovery of **6**, undeuterated, plus the formation of many decomposition products. These results obviated the use of formic–acetic or formic–pivalic anhydride to formylate **6**.

Discussion

The lactone α-formylation reaction generally was quite satisfactory. Excellent yields of the α-formyl lactones of **1**–**4** were obtained and the compounds, as their sodium enolates, were stable, although hygroscopic, compounds. For the cases where this procedure led to only moderate yields (**5**) or was inapplicable (**6**), we felt that the ethoxide anion generated in the reaction was precipitating the problems. It would be expected to nucleophilically attack **5** and **6** forming their corresponding ethyl esters,[10] thereby leading to greatly diminished yields of the α-formyl derivatives. Since acetate would not be expected to have this drawback nor to lead to reversal of the formylation reaction, we attempted to formylate **5** and **6** by quantitative generation of their lithium enolates at low temperatures using lithium 2,2,6,6-tetramethylpiperidide followed by acylation with formic–acetic[11] or formic–pivalic anhydride. However, this approach did not prove to be very efficient for **5**, nor success-

ful for **6**. In the latter case, the lithium enolate of **6** appeared to be very unstable above −78° and unreactive at this temperature.

Although the reductive amination of aldehydes and ketones can be achieved under a variety of conditions,[15] the experimentally most suitable method herein was felt to be that of Borch et al.,[16] since aldehydes are reduced at pH 3–4 by sodium cyanoborohydride whereas the optimum pH range for reductive amination is 6–8. In our hands, Borch's reductive amination method proved to be experimentally convenient although its use lead to somewhat variable yields of the resulting α-dimethylaminomethyl lactones (Tables I and II). The use of the sodium enolates of the α-formylated lactones required the addition of 1 equiv of acid to form the protonated α-formyl lactone, enabling nucleophilic addition of dimethylamine to form the intermediate carbinolamine.[16] This was accomplished by the addition to the reaction of either solid dimethylamine hydrochloride or anhydrous methanolic HCl until a preselected pH was reached. In those instances where the α-formyl lactone itself was utilized, it was found that very poor yields were obtained if dimethylamine hydrochloride was present as the only amine source. This is to be expected on the basis of the reaction's mechanism[16] because of the involvement of the unshared electrons in imminium ion formation.

The variability in yields of the α-dimethylaminomethyl lactones recovered from the reductive amination appears to be sensitive to pH, reaction time, and choice of solvent. During the course of the reaction the pH always increased to a value of 9 or 10 if additional acid was not introduced to lower it. The high pH did not deter the formation of the α-dimethylaminomethyl lactone and in some instances actually increased the yield of it. This was most likely due to a more favorable equilibrium between amine and aldehyde to produce the carbinolamine. A lower pH would result in a more rapid protonation of the resulting enamine[16] but would not favor the carbinolamine formation.

An increased reaction time usually resulted in somewhat increased yields of α-dimethylaminomethyl lactone but the incidence of side reactions also increased. Dimethylamides were most frequently observed after prolonged reactions, especially when δ-lactones were involved. Solvolytic ring opening became important with dihydrocoumarin but did not appear to be time dependent, for its ethyl ester was recovered from all reactions that were attempted. Borch et al.[16] suggested that distilled water could be utilized as the solvent in such cases, which would have eliminated the formation of esters. This was prevented by the insolubility of most of the compounds that were investigated in this study, however.

The amounts of amides as by-products increased with solvent changes from protic to aprotic. This was probably due to decreased solvation of the amine in solution allowing a much closer approach to the carbonyl as well as an increased nucleophilicity. Both of these factors would tend to increase the formation of such by-products.

In order to circumvent the problem with the reductive amination of **5** two other approaches were examined: (1) a direct enamine synthesis by treatment of **5** with dimethylformamide diethyl acetal,[17] and (2) the formation of the enamine from **17** and diethylamine in refluxing benzene with removal of water. Subsequent reduction was anticipated to lead to the desired α-dimethylaminomethyl lactone. Following the addition of dimethylformamide diethyl acetal to dihydrocoumarin and heating, the only product isolated in reasonable yield was ethyl 2-hydroxyphenylpropanoate. No nitrogen-containing compounds other than dimethylformamide were found in any of the reaction mixtures. Similar results were obtained with **1** and **6**.

Borch et al.[16] have reported that enamines and especially their imminium salts are readily reduced to the corresponding amine by $NaCNBH_3$. α-Formyl-γ-butyrolactone[3h] gave a good yield of its diethylenamine when treated with diethylamine in refluxing benzene with constant water removal. Reduction of this diethylenamine in methanol at an initial pH of ca. 3 with sodium cyanoborohydride resulted in a fairly good yield of **7**. Treatment of **17** with diethylamine under the same conditions also resulted in a good yield of its diethylenamine. Attempted reduction of this enamine using $NaCNBH_3$ resulted in hydrolysis of the enamine and very little reduced α-dimethylaminomethyl lactone was obtained. The imminium salt of this diethylenamine could not be isolated by addition of acid or by the method of Leonard and Paukstelis,[18] so this route was subsequently abandoned.

The failures of the reductive amination were not as serious as those found in the formylation step. Although several by-products were obtained in certain instances, these could be lessened by proper choices of solvent and reaction time. If the optimum conditions for the formation of the imminium systems could be met, the reduction could be performed in very high yield making the complete sequence attractive as a synthetic tool.

Throughout the syntheses described in this paper, the quaternization of the α-dimethylaminomethyl lactones using CH_3I in methanol and the subsequent elimination using 5% aqueous $NaHCO_3$ were carried out in 90% or greater yields. The methiodides, when crystalline, proved to be unstable to recrystallization, which always resulted in the formation of small amounts of the corresponding α-methylene lactones.

It is interesting to note the elimination of dimethylamine from **15** during chromatography on silica gel to give **16**. This was undoubtedly the effect of the equilibrium between the Michael adduct—the dimethylaminomethyl lactone—and the Michael acceptor—the α-methylene lactone—being affected by the acidic nature of the silica gel. Dalton and Elmes[19] have suggested that the methylene lactone predominates under acidic conditions and that the Michael adduct is formed under neutral or basic conditions. If this is true in all cases, then the possibility exists that during the work-up of the reductive amination products, a portion of the dimethylaminomethyl lactone may be lost during the acidic wash used to remove neutral compounds. No α-methylene lactones were observed in some of these extracts (TLC) but a careful examination of each was not done.

Experimental Section

General. γ-Butyrolactone, δ-valerolactone, dihydrocoumarin, 2,2,6,6-tetramethylpiperidine, pivaloyl chloride, and miscellaneous organic chemicals were purchased from Aldrich Chemical Co., Cedar Knolls, N.J. Sodium cyanoborohydride, *n*-butyllithium (22% in hexane), and sodium hydride (57% mineral oil dispersion) were purchased from Alfa Inorganics, Beverley, Mass. Deuterium oxide was purchased in 99.8 mol % from Bio-Rad Laboratories, Richmond, Calif. Dimethylamine was purchased from Matheson Gas Products, East Rutherford, N.J.

Adsorbents for preparative and thin layer chromatography (silica gel GF_{254} and silica gel PF_{254}) were purchased from VWR Scientific, Boston, Mass. All solvents for chromatography were distilled prior to use. 1,2-Dimethoxyethane, tetrahydrofuran, and diethyl ether were distilled from lithium aluminum hydride prior to use as reaction solvents. Anhydrous methanol and anhydrous (super-dry) ethanol were prepared according to the method of Vogel.[20]

Nuclear magnetic resonance spectra (60 MHz) were obtained on a Hitachi Perkin-Elmer R-24 spectrometer with deuteriochloroform as solvent. Chemical shifts are reported relative to a Me_4Si internal standard. Infrared spectra were obtained on a Perkin-

Elmer Model 21 spectrophotometer and the wavenumbers are corrected to a polystyrene reference. Mass spectra were obtained on a AEI Scientific, Inc., MS 902 mass spectrometer. Melting points were obtained on either a Kofler hot stage or a Thomas-Hoover Uni-Melt apparatus and are corrected. Gas chromatography was done on a Varian 90-75 gas chromatograph utilizing a thermal conductivity detector and helium as the carrier gas. Refractive indices were obtained on a Bausch and Lomb Abbe 3L refractometer at ambient temperature. In vacuo refers to water aspirator pressures, all evaporations being conducted on a rotary flash evaporator at 25–40°C.

Sodium α-Formyl-δ-valerolactone. A mineral oil dispersion of sodium hydride (57%, 1.1 g, 26 mmol) was placed in a dry 100-ml three-neck round-bottom flask which had been previously evacuated and flushed with dry nitrogen. The mineral oil was removed by washing with petroleum ether (3 × 10 ml) and decanting under nitrogen. The sodium hydride was then suspended in 50 ml of anhydrous diethyl ether by magnetic stirring.

A mixture of **2** (2.5 g, 25 mmol) and ethyl formate (1.85 g, 25 mmol) in 3 ml of diethyl ether was added dropwise to the stirred suspension. Absolute ethanol (0.2 ml) was added to initiate the reaction. Stirring was continued at room temperature for 18 hr, and the resulting mixture was filtered with suction, washed with 15 ml of diethyl ether, and dried under vacuum in a desiccator to yield sodium α-formyl-δ-valerolactone as a light tan powder, 3.8 g (100%).

α-Dimethylaminomethyl-δ-valerolactone (8). The sodium enolate from above (1.5 g, 10 mmol) was dissolved in 30 ml of anhydrous methanol. To this was added a solution of dimethylamine (2.7 g, 4 ml, 60 mmol) and methanolic hydrogen chloride (3 *N*, 10 ml, 30 mequiv). Sodium cyanoborohydride (440 mg, 7 mmol) and 1.5 g of Linde 3A molecular sieves were then introduced and the mixture was stirred at room temperature fitted with a drying tube for 3 days. The reaction mixture was filtered with suction through Celite and the solid remaining on the Celite was washed with methanol (100 ml). The combined filtrates were acidified (pH 2) with concentrated hydrochloric acid, and the methanol was removed in vacuo. The resulting residue was redissolved in distilled water (100 ml) and extracted with CH_2Cl_2 (2 × 100 ml). $NaHCO_3$ was added to the aqueous phase to bring its pH to 8 and the resulting solution was extracted with CH_2Cl_2 (4 × 100 ml). The aqueous solution then was adjusted to ca. pH 10 with Na_2CO_3 and reextracted with EtOAc (4 × 100 ml). The combined basic organic extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4), and the solvent was removed in vacuo to give **8** as a viscous yellow liquid: 1.01 g (64%); ir (neat) 1740 cm^{-1} (lactone); NMR (60 MHz) δ 1.65 (m, 2 H), 2.23 (s, 6 H), 2.7 (m, 2 H), 4.1 (t, J = 7 Hz, 2 H); vapor phase chromatography (VPC), 3% SE-30, 160°, 60 ml/min, crude amine showed greater than 95% one component, retention time 1.9 min. Reaction by-products were isolated and characterized by ir and NMR spectroscopy. α-Dimethylaminomethyl-δ-hydroxyvaleric acid dimethylamide (**9**) and δ-hydroxyvaleric acid dimethylamide were found in the reaction mixture: ir (neat) 3400 (hydroxyl), 1630 (amide I), 1510 (amide II), 1410 cm^{-1} (ν C–N); NMR (60 MHz) δ 3.05 (d, J = 5 Hz, 6 H, dimethylamide).

α-Methylene-δ-valerolactone (10).[21] The tertiary amine (**8**, 300 mg, 2 mmol) was dissolved in 4 ml of methanol and 1.5 ml of methyl iodide was added. No crystals were observed after standing in the dark at room temperature for 24 hr or following the addition of 5 ml of diethyl ether to the solution. The yellow oil that separated after the addition of diethyl ether was isolated by removing the solvent in vacuo; however, all attempts at crystallization were fruitless. The oil was transferred to a separatory funnel containing 10 ml of 5% sodium bicarbonate solution and 20 ml of dichloromethane. After shaking the mixture for 15 min, the aqueous phase was extracted with dichloromethane (6 × 25 ml), the extracts were dried with sodium sulfate, and the solvent was removed in vacuo to yield **10** as a yellowish liquid, 175 mg (81%). The crude product was purified by preparative TLC on silica gel using chloroform–methanol (4:1): ir (neat) 1730 (lactone), 1630 and 814 cm^{-1} (C=CH_2); NMR (60 MHz) δ 2.00 (m, 2 H), 2.71 (m, 2 H), 4.38 (t, J = Hz, 2 H), 5.57 (dd, J_{AB} = $J_{A'B'}$ = 1 Hz, 1 H), 6.40 (dd, J_{AB} = $J_{A'B'}$ = 1 Hz, 1 H); mass spectrum *m/e* (rel intensity) 112 (M^+, 100), 82 (M − CH_2O, 58), 54 (M − C_3H_6O, 94).

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.10; H, 7.26.

***trans*-2-Hydroxycyclohexaneacetic acid γ-lactone (3)** was prepared according to Newman and Vanderwerf:[8] colorless liquid, bp 71.5–72.5° (0.25 mm) [lit.[8] bp 118–119° (6 mm)].

Sodium α-Formyl-*trans*-2-hydroxycyclohexaneacetic Acid γ-Lactone (11). The trans lactone **3** (1.40 g, 10 mmol) and ethyl formate (740 mg, 10 mmol) dissolved in 5 ml of anhydrous diethyl ether was added dropwise to a suspension of oil-free sodium hydride (252 mg, 10.5 mmol) in 50 ml of diethyl ether in a 100-ml three-neck flask. Absolute ethanol (0.1 ml) was introduced to initiate the reaction. After stirring for 15 hr at room temperature the mixture was filtered, washed with ether, and dried in a desiccator under vacuum to give **11** as its sodium enolate, 1.71 g (90%).

α-Dimethylaminomethyl-*trans*-2-hydroxycyclohexaneacetic Acid γ-Lactone (12). The sodium enolate **11** (380 mg, 2 mmol) was suspended in 15 ml of 1,2-dimethoxyethane. To this was added dimethylamine hydrochloride (325 mg, 4 mmol), sodium cyanoborohydride (130 mg, 2 mmol), and 300 mg of Linde 3A molecular sieves. The mixture was stirred at room temperature for 40 hr and filtered through Celite. After extraction of the acidified (pH 2) solution with dichloromethane, the solution was made basic (pH 8) with sodium bicarbonate and again extracted with dichloromethane (5 × 30 ml). The basic extracts were dried over magnesium sulfate and the solvent was removed to obtain **12** as a colorless liquid: 225 mg (57%); ir (neat) 1775 cm^{-1} (lactone); NMR (60 MHz) δ 1.2–2.6 (m, 10 H), 2.25 (s, 6 H), 2.63 (t, J = 6 Hz, 2 H), 3.4–3.8 (m, 1 H); picrate, recrystallized from ethanol, mp 210–211.5°.

Anal. Calcd for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.14. Found: C, 47.96; H, 5.15; N, 13.13.

α-Trimethylaminomethyl-*trans*-2-hydroxycyclohexaneacetic Acid γ-Lactone Iodide. The tertiary amine **12** (279 mg, 1.4 mmol) was dissolved in 2 ml of anhydrous methanol and 1 ml of methyl iodide was added. White crystals were observed after 5 min and the solution was left in the dark at room temperature overnight. The crystals were filtered, washed with diethyl ether, and dried in vacuo to obtain the methiodide: 460 mg (96%); mp 215–216° dec.

α-Methylene-*trans*-2-hydroxycyclohexaneacetic Acid γ-Lactone (13).[22] A portion of the methiodide salt (170 mg, 0.5 mmol) was placed in a separatory funnel with 5 ml of 5% aqueous sodium bicarbonate solution and 10 ml of dichloromethane. After complete dissolution of the salt, the aqueous layer was extracted with dichloromethane (6 × 10 ml) and the combined extracts were dried over sodium sulfate. Evaporation of the solvent yielded **13** as a crystalline solid: 76 mg (99%); mg 38.5–39° (lit.[22] 40–41°); ir ($CHCl_3$ solution) 1770 (lactone), 1675 and 814 cm^{-1} (C=CH_2); NMR (60 MHz) δ 1.1–2.7 (m, 9 H), 3.5–4.0 (m, 1 H), 5.40 (d, J = 3 Hz, 1 H), 6.07 (d, J = 3 Hz, 1 H); mass spectrum *m/e* (rel intensity) 152 (M^+, 9.5), 124 (M − CO, 100).

***cis*-2-Hydroxycyclohexaneacetic acid γ-lactone (4)** was prepared according to Klein[9] as a colorless liquid: bp 95–100° (0.8 mm) [lit.[9] bp 150–155° (20 mm)]; ir 1775 cm^{-1} (lactone).

Sodium α-Formyl-*cis*-2-hydroxycyclohexaneacetic Acid γ-Lactone (14). A solution of **4** (1.40 g, 10 mmol) and ethyl formate (740 mg, 10 mmol) in 5 ml of anhydrous diethyl ether was added dropwise to a suspension of oil-free sodium hydride (252 mg, 10.5 mmol) in 25 ml of diethyl ether in a 100-ml three-neck round-bottom flask. Absolute ethanol (0.1 ml) was added by pipette to initiate the reaction. After stirring at room temperature for 22 hr the mixture was filtered, washed once with 20 ml of diethyl ether, and dried in a desiccator under vacuum to obtain **14** as a dark grayish brown solid, 1.85 g (97%).

α-Formyl-*cis*-2-hydroxycyclohexaneacetic Acid γ-Lactone (14). The sodium enolate of **14** (1.0 g, 5.25 mmol) was slowly added to 10 ml of 2 *N* hydrochloric acid which had been previously cooled in an ice bath. The resulting mixture was extracted with diethyl ether (6 × 15 ml), and the extracts were washed with 10 ml of saturated sodium chloride solution and dried over sodium sulfate. Evaporation of the solvent in vacuo afforded the α-formyl lactone **14** as a light yellow liquid, 890 mg (100%).

α-Dimethylaminomethyl-*cis*-2-hydroxycyclohexaneacetic Acid γ-Lactone (15). The slurry of the sodium enolate of **14** (760 mg, 4 mmol) in 20 ml of methanol was treated with dimethylamine hydrochloride (650 mg, 8 mmol) and sodium cyanoborohydride (195 mg, 3 mmol). Linde 3A molecular sieves (500 mg) was added and the mixture was stirred at room temperature for 18 hr. The mixture was filtered through Celite and the filtrate was acidified (pH 2) with concentrated hydrochloric acid. The methanol was removed in vacuo and 35 ml of distilled water was added. The aqueous acidic mixture was extracted with dichloromethane (3 × 20 ml) and then made basic (pH 8) with sodium bicarbonate. Extraction of the basic solution with dichloromethane (6 × 20 ml) and drying the combined extracts with sodium sulfate yielded **15** as a pale yellow liquid following the evaporation of the solvent in vacuo, 395 mg (50%). TLC analysis on silica gel with chloroform–methanol

(9:1) showed the presence of two amines in a ratio of about 3:2.

Preparative TLC on silica gel with chloroform–methanol (9:1) was used to separate the two amines into relatively pure fractions. A second chromatographic run using the same system with each fraction resulted in the two chromatographically pure amines.

Amine **15a**: R_f 0.47; ir (neat) 1775 cm^{-1} (lactone); NMR (100 MHz) δ 1.37–1.75 (m, 9 H), 2.17 (s, 6 H), 2.45 (br s, 2 H), 2.25–2.6 (m, 1 H), 4.46 (q, J = 6 Hz, 1 H); picrate, recrystallized from ethanol, mp 193–195°.

Anal. Calcd for $C_{17}H_{22}N_4O_8$: C, 47.89; H, 5.20; N, 13.14. Found: C, 47.60; H, 5.33; N, 13.16.

Amine **15b**: R_f 0.63; ir (neat) 1775 cm^{-1} (lactone); NMR (100 MHz) δ 1.30–1.60 (m, 9 H), 2.15 (s, 6 H), 2.44 (d, J = 8 Hz, 2 H), 2.4–2.7 (m, 1 H), 4.31 (q, J = 6 Hz, 1 H); picrate, recrystallized from ethanol, mp 144–145.5°.

Anal. Calcd for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.14. Found: C, 48.00; H, 5.40; N, 13.19.

α-Trimethylaminomethyl-*cis*-2-hydroxycyclohexaneacetic Acid γ-Lactone Iodide. A. A sample of mixed isomers of **15** (228 mg, 1.16 mmol) was dissolved in 1 ml of anhydrous methanol. To this was added 1.5 ml of methyl iodide and the mixture was allowed to stand in the dark at room temperature overnight. The mixture was then cooled to 4° for 1 hr after which the colorless crystals were filtered and washed with diethyl ether to obtain the mixed methiodides, 302 mg (77%). The crystals melted over a wide range.

B. Amine **15a** (91 mg, 0.46 mmol) was dissolved in 1 ml of methanol and 0.5 ml of methyl iodide was added. After standing at room temperature in the dark for 2 hr the colorless crystals were isolated by filtration, washed with diethyl ether, and dried to obtain the methoidide of amine A as shiny plates: 136 mg (87%); mp 228°.

C. Amine **15b** (65 mg, 0.33 mmol) was dissolved in 1 ml of methanol and 0.5 ml of methyl iodide was added. The solution was kept at 4° for 1 hr and then at 25° overnight. The colorless crystals were recovered by filtration, washed with diethyl ether, and dried to yield the methiodide of amine B: 98 mg (88%); mp 215–215.5°.

α-Methylene-*cis*-2-hydroxycyclohexaneacetic Acid γ-Lactone (16).[22] Each sample of the methiodides above was treated separately by shaking with 5% aqueous sodium bicarbonate and dichloromethane and extracting with dichloromethane (5 × 10 ml). After drying the extracts with magnesium sulfate and evaporating the solvent in vacuo, **16** was obtained as a pale yellow liquid from each sample. The following yields were realized.

Methiodide salt of	α-Methylene lactone (16)
Amine mixture, 15 (300 mg)	93 mg (70%)
Amine 15a (100 mg)	40 mg (88%)
Amine 15b (90 mg)	40 mg (99%)

Spectral data: ir (neat) 1774 (lactone), 1670 and 817 cm^{-1} (C=CH_2); NMR (60 MHz) δ 1.1–2.1 (m, 8 H), 2.8–3.2 (m, 1 H), 4.4–4.75 (m, 1 H), 5.52 (d, J = 3 Hz, 1 H), 6.17 (d, J = 3 Hz, 1 H); mass spectrum m/e (rel intensity) 152 (M^+, 14), 124 (M − CO, 100). These values agree with the data given in the literature for *cis*-**16**.[22]

Preparative TLC on silica gel with chloroform–methanol (9:1) of the mixed amines of **15** resulted in the recovery of a small amount of **16** identical with that obtained through the methiodide salts (NMR).

3-Formyl-3,4-dihydrocoumarin (17). A. 17 was prepared from ethyl formate and **5** using $MgN(i\text{-}Pr)_2$ according to Korte and Büchel[10] as a yellowish powder: 2.4 g (45%); mp 138–142° [lit.[10] 140–141°]; ir (KBr) 1700 cm^{-1} (lactone); NMR (acetone-d_6) δ 3.6 (brs, 2 H), 7.2 (m, 4 H), 7.9 (t, J = 2 Hz, 1 H), 9.9 (s, 1 H).

B. From Acetic-Formic Anhydride. 2,2,6,6-Tetramethylpiperidine (141 mg, 1 mmol) was mixed with 15 ml of anhydrous tetrahydrofuran in a dry nitrogen-flushed flask. The mixture was cooled to −15° in an ice–acetone bath and n-butyllithium (2.05 M, 0.5 ml, 1.02 mmol) was introduced. After stirring at −15° for 10 min, the flask was cooled to −78° in a Dry Ice–acetone bath and a mixture of **5** (148 mg, 1 mmol) and acetic–formic anhydride[24] (130 mg, 1.5 mmol) in 5 ml of anhydrous tetrahydrofuran was added dropwise. The mixture was stirred at −78° for 10 min and was then warmed to −15°, at which time 50 ml of 0.2 N hydrochloric acid was introduced. The acidic solution was extracted with dichloromethane (3 × 40 ml), the extracts were dried with sodium sulfate, and the solvent was evaporated in vacuo to afford a yellow liquid which was approximately 30% **17** by TLC analysis on silica gel using chloroform–methanol (50:1).

C. From Formic–Pivalic Anhydride. A solution of 2,2,6,6-tetramethylpiperidine (141 mg, 1 mmol) in 10 ml of anhydrous THF was treated with n-butyllithium (2.05 M, 0.5 ml, 1.02 mmol) at −15°. After stirring for 10 min the mixture was cooled to −78° and **5** (148 mg, 1 mmol) dissolved in 3 ml of anhydrous THF was added slowly. This solution was stirred for 5 min at −78° and then formic–pivalic anhydride[25] dissolved in 1,2-dimethoxyethane (0.5 ml, 1.25 mmol) was added. After 10 min the mixture was warmed to −15°, poured into 50 ml of 0.1 N hydrochloric acid, and extracted with dichloromethane (3 × 40 ml). The combined extracts were dried with sodium sulfate and the solvent was removed in vacuo to obtain an oily residue which was chromatographed on silica gel with chloroform–methanol (50:1). Isolation of the band corresponding to **17** yielded 43 mg (27%) of a yellowish solid, mp 140–142°.

Methyl α-Dimethylaminomethyl-β-(2-hydroxyphenyl)propanoate (19). A solution of **17** (350 mg, 2 mmol) was prepared in 4 ml of 1,2-dimethoxyethane and a solution of dimethylamine (880 mg, 1.2 ml, 20 mmol) and methanolic hydrogen chloride (3 N, 3 ml, 9 mequiv) in 4 ml of anhydrous methanol was added. The pH was adjusted with methanolic hydrogen chloride to the transition point of Bromthymol Blue (pH 6) and then sodium cyanoborohydride (130 mg, 2 mmol) and 400 mg of Linde 3A molecular sieves were introduced. The pH was maintained near 6 by the repeated dropwise addition of 3 N methanolic HCl for 2 hr and the mixture was then stirred at room temperature for 15 hr. After filtering through Celite the solution was acidified (pH 2) with concentrated hydrochloric acid and extracted with dichloromethane (3 × 15 ml). The aqueous phase was then treated with sodium bicarbonate (pH 8) and extracted with dichloromethane (5 × 20 ml). After the combined basic extracts were dried with sodium sulfate and the solvent was removed in vacuo, **19** was obtained as a greenish liquid: 340 mg (72%); ir (neat) 3300, 1200 (phenol), 1733 (ester), 1167 cm^{-1} (tertiary amine); NMR δ 2.31 (s, 6 H), 2.5–3.0 (m, 5 H), 3.69 (s, 3 H), 6.6–7.3 (m, 4 H), 9.2 (br s, 1 H); δ 0.2 peak disappeared on addition of D_2O; mass spectrum m/e (high resolution) calcd for $C_{13}H_{19}NO_3$, 237.1360; found, 237.136.

The amide by-product (**18**) was obtained by preparative TLC of crude amine mixture on silica gel with chloroform–methanol (9:1). It was obtained as a pale yellow liquid: NMR δ 2.32 (s, 6 H), 2.47–3.2 (m, 5 H), 2.99 (d, J = 3 Hz, 6 H), 6.7–7.3 (m, 4 H), 8.95 (br s, 1 H). The absence of a three-proton singlet at δ 3.6 negated the presence of a methyl ester and the appearance of the δ 2.99 doublet strongly suggested the presence of a dimethylamide group; mass spectrum m/e (high resolution) calcd for $C_{14}H_{22}N_2O_2$, 250.1676; found, 250.1674.

Methyl α-Methylene-β-(2-hydroxyphenyl)propanoate (21). A solution of **19** (155 mg, 0.63 mmol) in 1 ml of anhydrous methanol was treated with 1 ml of methyl iodide and the solution was placed in the dark at room temperature for 48 hr. The solvent was removed in vacuo and the residue was triturated with ether to give **20** as a yellowish, amorphous solid, 224 mg (94%).

The crude methiodide salt (**20**) was placed in a separatory funnel, 5 ml of 5% sodium bicarbonate solution and 10 ml of dichloromethane were added, and the mixture was agitated for 5 min. The solution was extracted with dichloromethane (6 × 10 ml), the combined extracts were dried with magnesium sulfate, and the solvent was removed in vacuo to obtain **21** as a white solid: 97 mg (91%); mp 32.5–33° (following preparative TLC on silica gel with chloroform–methanol, 50:1); ir (film) 3380, 1220 (phenol), 1724 (ester), 1631, 818 cm^{-1} (C=CH_2); NMR δ of 3.60 (s, 2 H), 3.76 (s, 3 H), 5.79 (s, 1 H), 6.25 (s, 1 H), 6.7–7.3 (m, 4 H); mass spectrum m/e (rel intensity) 192 (M^+, 32), 160.0523 (M − CH_3OH, 98; calcd for $C_{10}H_8O_2$, 160.0522), 131.0497 (M − H, HCO_2CH_3 100, calcd for C_9H_7O, 131.0495).

α-Methylene-β-(2-hydroxyphenyl)propanoic Acid (22). The methyl ester **21** (148 mg, 0.77 mmol) was dissolved in 8 ml of methanol and 4.1 ml of saturated aqueous barium hydroxide was added. The solution was purged with nitrogen and stirring was continued at room temperature for 18 hr. The solution was acidified (Methyl Red) with 1 N sulfuric acid and 10 ml of distilled water was added. The methanol was removed in vacuo and the remaining aqueous mixture was extracted with dichloromethane (4 × 15 ml). The mixture was adjusted to pH 2 with 1 N sulfuric acid and was extracted with dichloromethane (3 × 15 ml). The combined extracts were dried with sodium sulfate and the solvent was removed in vacuo to obtain **22** as a white solid: 123 mg (90%); mp 79–81°; ir ($CHCl_3$) 3300 (phenol), 1700 (carboxylic acid), 1631 and 823 cm^{-1} (C=CH_2); NMR δ 3.54 (s, 2 H), 5.76 (s, 1 H), 6.31 (s, 1 H), 6.7–7.4 (m, 4 H), 7.97 (s, 2 H). An elemental analysis was not obtained.

3-Methylene-3,4-dihydrocoumarin (23). A solution of **22** (123

mg, 0.69 mmol) in 60 ml of toluene was treated with 50 mg of *p*-toluenesulfonic acid. The flask was fitted with a Dean-Stark constant water separator and the mixture was heated at reflux for 10 min. After removal of the toluene in vacuo the residue was chromatographed on silica gel with benzene–ethyl acetate (8:1) and the band corresponding to **23** was isolated to obtain the product as a crystalline solid: 108 mg (98%); mp 67.5–68° (sublimation and then recrystallization from ether–pentane); ir ($CHCl_3$) 1740 (lactone), 1639 and 810 cm^{-1} (C=CH_2); NMR (60 MHz) δ 3.75 (t, J = <1 Hz, 2 H), 5.77 (dt, J = <1 Hz, 1 H), 6.40 (dt, J = <1 Hz, 1 H), 6.9–7.4 (m, 4 H); mass spectrum *m/e* (high resolution) calcd for $C_{10}H_8O_2$, 160.0524; found, 160.0527; *m/e* (rel intensity) 160 (M^+, 83), 131 (M − CHO, 100). A satisfactory elemental analysis for this compound could not be obtained despite repeated crystallizations form diethyl ether–pentane and sublimation (60°, 0.06 mm). The mass spectrum showed the presence of traces of higher molecular weight material in the purified compound which may have arisen via polymerization during the purification.

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Registry No.—**2**, 542-28-9; **3**, 27345-71-7; **4**, 24871-12-3; **8**, 56783-31-4; **10**, 42023-19-8; **11**, 56783-32-5; **12**, 55643-46-4; **12** MeI, 56783-33-6; **12** picrate, 56783-45-0; **13**, 3727-53-5; **14**, 56783-34-7; **15a**, 56783-35-8; **15a** MeI, 56783-36-9; **15a** picrate, 56783-46-1; **15b**, 56783-37-0; **15b** MeI, 56783-38-1; **15b** picrate, 56783-47-2; **16**, 16822-06-3; **17**, 56783-39-2; **18**, 56783-40-5; **19**, 56783-41-6; **21**, 56783-42-7; **22**, 56783-43-8; **23**, 56783-44-9; sodium α-formyl-δ-valerolactone, 53761-41-4; ethyl formate, 109-94-4; dimethylamine, 124-40-3; acetic–formic anhydride, 2258-42-6; 2,2,6,6-tetramethylpiperidine, 768-66-1; formic–pivalic anhydride, 10535-67-8.

References and Notes

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(25) Sodium formate (750 mg, 11 mmol), finely powdered and dried at 125° for 4 hr was mixed with pivaloyl chloride (1.20 g, 10 mmol) and 3 ml of anhydrous 1,2-dimethoxyethane in a tightly stoppered flask. The flask was heated at 47° for 45 min and then stirred overnight at room temperature. The mixture was filtered and used without further purification: NMR (60 MHz) δ 1.31 (s, 10 H), 9.07 (s, 1 H). Distillation of the anhydride at 18 mmHg, ambient temperature, resulted in decarbonylation and recovery of pivalic acid.

New Germacranolide Sesquiterpene Dilactones from the Genus *Melampodium* (Compositae)

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The isolation of four germacranolide sesquiterpene dilactones from the three white-rayed *Melampodium* species is reported. Melampodin B (**1a**) is found in all three species, and 4(5)-dihydromelampodin B (**4a**) only in *M. cinereum* DC. Cinerenin (**2a**) occurs in both, *M. cinereum* and *M. argophyllum* (A. Gray ex Robinson) Blake, and melampodin C (**3a**) is typical of the latter species. Artemetin is a common constituent of *M. cinereum* and *M. argophyllum*. The structures, configurations, and conformations of the new dilactones were determined by chemical transformations, correlations, and spectral methods.

In connection with our biochemical systematic study of the white-rayed complex of the genus *Melampodium* (Compositae, Heliantheae)[1] we have analyzed multiple populations of *M. cinereum* DC. and *M. argophyllum* (A. Gray ex Robinson) Blake for their sesquiterpene lactone content. In this communication we describe the isolation and structure elucidation of four closely related germacranolide type sesquiterpene dilactones, which we named melampodin B (**1a**), cinerenin (**2a**), melampodin C (**3a**), and 4(5)-dihydromelampodin B (**4a**). The flavonoid artemetin[2] is a common constituent in both *M. cinereum* and *M. argophyllum*.

Melampodin B and Derivatives. Melampodin B (**1a**), $C_{17}H_{18}O_7$, mp 226–228°, the major, most polar constituent, was present in most populations of *M. cinereum* and *M. argophyllum* and was also found in several west Texas populations of *M. leucanthum*.[3] The structure of melampodin B has been described in a previous communication[4] and was mainly deduced on the basis of correlations of 25.5-MHz ^{13}C and 300-MHz ^1H NMR spectra obtained in acetone-d_6 and pyridine-d_5. The ^{13}C NMR data were obtained under proton noise decoupled (PND) and single-frequency off-center decoupled (SFOCD) conditions.[5] The ^1H NMR spectral data of **1a**, which included extensive double resonance experiments, are tabulated in Table I.

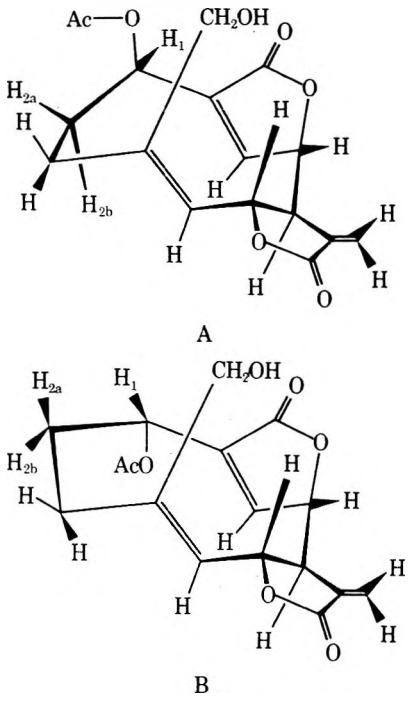
The stereochemical and conformational assignments in melampodin B require further comments. Two initial assumptions were made in the structural assignments of me-

Table I
^{1}H NMR Spectral Parameters[a] of Melampodin B and Analogs

Compd	H-1	H-2[e]	H-3[e]	H-5	H-6	H-7	H-8	H-9	H-13a	H-13b	H-15	Miscellaneous
1a[d,f]	5.96 br dd (6.5; 6.5)	(a) 1.92 m (b) 2.45 m	2.2 m	5.99 br d (10.0)	4.99 dd (10.0; 10.0)	3.56 br ddd (10.0; 3.5; 3.0)	5.95 br	7.63 br	5.93 d (3.0)	6.47 d (3.5)	(a) 4.34 br d (15.0) (b) 4.40 br d (15.0)	2.02 (Ac) 6.60 (OH)
1b[d]	~5.9[g]	*g*	*g*	5.69 br (9.5)	4.93 dd (9.5; 9.5)	3.52 m	~5.9[g]	7.58 br	5.89 d (3.0)	6.41 d (3.5)	4.69 br[e]	2.02 (Ac)
1c[d]	5.83 br dd (7.0; 7.0)	*g*	*g*	6.60 br d (9.5)	5.12 dd (9.5; 9.5)	3.82 m	6.02 br	7.71 br	5.98 d (3.0)	6.47 d (3.5)	9.49 br	1.92 (Ac)
2a[d,f]	4.42 m	(a) 1.84 m (b) 2.34 m	(a) 2.08 m (b) 2.20 m	5.95 br d (9.0)	4.94 dd (10.0; 10.0)	3.52 br ddd (9.0; 3.5; 3.0)	5.97 br	7.58 br	5.96 d (3.0)	6.51 d (3.5)	(a) 4.3 br d (15.0) (b) 4.39 br d (15.0)	1.11 tr (5.5; CH_3'), 3.42 q[h] (5.5; CH_2'), 7.16 (OH)
2b[b]	4.33 m	*g*	*g*	5.47 br d (10.0)	4.60 dd (10.0; 10.0)	3.16 m	5.59 br	7.24 br	5.82 d (3.0)	6.48 d (3.5)	4.60 br[e]	1.21 tr (7.0; CH_3'), 3.53 q[h] (5.5; CH_2')
2c[c]	4.23 m	*g*	*g*	6.58 dd (10.0; 1.5)	4.72 dd (10.0; 10.0)	3.78 m	5.97 br	7.62 br	6.05 d (3.0)	6.38 d (3.5)	9.46 d (1.5)	1.07 tr (7.0; CH_3'), 3.44 q[h] (7.0; CH_2')
3a[c]	5.55 br dd (15.5; 6.5)	*g*	*g*	5.60 br d (10.0)	4.61 dd (10.0; 10.0)	3.49 m	5.86 br	7.54 dd (~1.0; ~1.0)	5.92 d (3.0)	6.27 d (3.2)	4.14 br[e]	1.13 d (7.0; CH_3')[i] 1.15 d (7.0; CH_3'')[i] 2.58 h (7.0; C-H′)
3b[b]	5.66 br dd (15.5; 6.5)	*g*	*g*	5.49 br d (10.0)	4.65 dd (10.0; 10.0)	3.16 m	5.57 br	7.14 br	5.80 d (3.0)	6.66 d (3.5)	4.61 br[e]	1.18 d (7.0; CH_3')[i] 1.19 d (7.0; CH_3'')[i] 2.11 (Ac) 2.53 h (7.0, CH′)
3c[b]	5.62[g]	*g*	*g*	6.41 d (10.0)	4.82 dd (10.0; 9.5)	3.38 m	5.62[g]	7.12 br	5.90 d (3.0)	6.52 d (3.5)	9.48 d (1.0)	1.14 d (7.0; CH_3')[i] 1.15 d (7.0); CH_3'')[i] 2.5 h (7.0; CH′)
4a[c]	5.30 m	*g*	*g*	*g*	3.50 m	3.37 m	5.92 br	8.03 d (1.5)	6.00 d (3.0)	6.31 d (3.5)	3.70 m[e]	2.02 (Ac)
4b[b]	5.37 ddd (10.0; 5.0; 1.5)	*g*	*g*	*g*	3.76 m	3.13 m	5.61 br	7.51 d (1.5)	5.82 d (3.0)	6.44 d (3.5)	3.87 d[e] (7.0)	2.06 (Ac)
5[c]	5.61 m	*g*	*g*	5.50 br d (10.0)	4.91 m	2.95 m	5.60 br	7.33			4.17 d (6.0)	1.40 d (8.0; C-11 CH_3) 2.08 (Ac) 4.91 m (H-11)
6[c]	5.39 ddd (5.5; 5.5; 1.0)	*g*	*g*	*g*	3.97 m	3.35 m	5.58 br	7.84 dd (1.0; 1.0)			3.37 d (6.0)	1.33 d (8.0; C-11 CH_3) 2.03 (Ac), 2.93 m (H-11)
7[c]	4.83 br dd (5.5; 11.5)	*g*	*g*	5.68 br d (9.5)	4.47 dd (9.5)	3.09 ddd (11.0; 9.5; 3.0)	5.73 dd (3.0; 1.5)	7.89 dd (1.5; ~1.0)			(a) 4.10 br d (10.0) (b) 4.27 br d (10.0)	3.5 d tr (11.0; 4.0; H-11) 3.93 d (4.0; 2 H-13[e])

[a] Spectra were run at 100 MHz except where indicated. Me_4Si was used as internal standard and values are recorded in parts per million relative to Me_4Si. Singlets are unmarked, multiplets are designated as follows: d, doublet; t, triplet; q, quartet; h, heptet; m, multiplet whose center is given; br, broad. Figures in parentheses are coupling constants or line separations in hertz. [b] $CDCl_3$. [c] Acetone-d_6. [d] Pyridine-d_5. [e] Intensity two protons. [f] Run at 300 MHz. [g] Obscured by superimposed signals. [h] Appearing as a doublet of a quartet owing to the nonequivalence of the C-2′ methylene hydrogens of the ethoxy group. [i] Pairs of diastereotopic methyls of the isobutyric acid moiety.

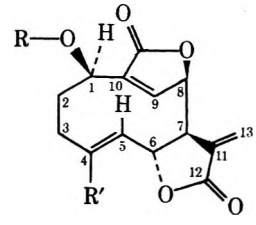
Chart I
Possible Configurations of Melampodin B



lampodin B. From biogenetic considerations and the cooccurrence of melampodin A,[3,6] a compound with known absolute configuration,[7,8] H-7 was assumed to have an α configuration and the C-4(5) double bond to adopt a trans configuration. From the inspection of models with a 4,5-cis double bond, a torsional angle of about 45° and a coupling constant between H-7 and H-8 greater than 5 Hz would have been predicted. In contrast, a skeletal arrangement with a 4,5-trans double bond dictates a torsional angle of 80° between H-7 and H-8, a value that correlates well with the observed coupling constant ($J_{7,8}$ = 2.5 Hz).

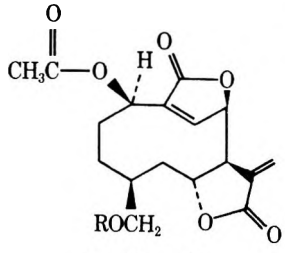
The stereochemical assignments at C-1 in **1a** are mainly based on the torsional angles between H-1 and the C-2a and C-2b protons, with the torsional angle between the H-1 and H-9 providing supporting evidence for the orientation of the side chain at C-1. The observed J values ($J_{1,2a}$ = $J_{1,2b}$ = 5.5 Hz) can be explained if the C-1 hydrogen bisects the two C-2 hydrogens with torsional angles between H-1 and H-2a and H-2b being approximately 45°. Stereomodels indicated that there exist two possible configurations each with two different conformations around the C_3–C_2–C_1 carbon centers. Both could be in agreement with the above J values (compare A and B in Chart I). In order to distinguish between the two possible configurations in melampodin B, the torsional angle dependence of the allylic coupling between the C-1 and C-9 protons was used. Maximum allylic coupling (>3.0 Hz) is observed when the two protons that are allylically coupled are perpendicular to one another.[9] The small coupling constant ($J_{1,9}$ = 1.0 Hz) found in melampodin B indicated that the torsional angle between H-1 and H-9 should be substantially smaller than 90°. From inspection of stereomodels of melampodin B a torsional angle of about 45° was derived which seems to be in good agreement with the observed coupling constants. Conversely, if the medium ring had contained an α-oriented C-1 substituent in a conformation as shown in B, the torsional angle between H-1 and H-9 would have been near 90°, thus a $J_{1,9}$ value of about 3 Hz should have been observed for melampodin B. Additional evidence for a syn orientation of the acetoxy group at C-1 and the hydroxyl group at C-15 as shown in Chart I, A, was derived from comparison of ir spectral data of melampodin B (**1a**) and cinerenin (**2a**). The OH absorption in the ir spectrum of **1a** appears as a sharp peak at 3450 cm^{-1}, indicating strong intramolecular hydrogen bonding between the OH group at C-15 and the C-1′ carbonyl function attached to C-1. This interaction does not occur in cinerenin, which has, as will be shown later, a β-oriented ethoxy group. On the basis of the above arguments, we tentatively assigned a β configuration of the acetoxy group at C-1 in **1a**, and a conformation as shown in A in Chart I.

Correlation of the spectral data of **1a** with its derivatives provided further support for the correctness of the previous structural assignments. Acetylation of **1a** caused a significant downfield shift of the broadened doublets at 4.34 and 4.40 ppm due to the two diastereotopic C-15 protons. Oxidation of **1a** with Sarett's reagent[10] resulted in a loss of the above absorptions and the appearance of an aldehyde proton signal at 9.49 ppm. The H-5 signal at 5.99 ppm in **1a** was shifted downfield to 6.60 ppm in **1c**, a position typical of a β hydrogen at an α,β-unsaturated aldehyde, thus indicating the presence of a primary, allylic alcohol group in **1a**.

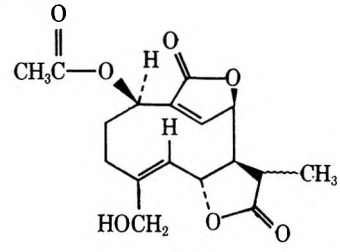


1a, R = Ac; R′ = CH_2OH **2a**, R = C_2H_5; R′ = CH_2OH
b, R = Ac; R′ = CH_2OAc **b**, R = C_2H_5; R′ = CH_2OAc
c, R = Ac; R′ = CHO **c**, R = C_2H_5; R′ = CHO

3a, R = $(CH_3)_2CHCO$; R′ = CH_2OH
b, R = $(CH_3)_2CHCO$; R′ = CH_2OAc
c, R = $(CH_3)_2CHCO$; R′ = CHO



4a, R = H
b, R = Ac



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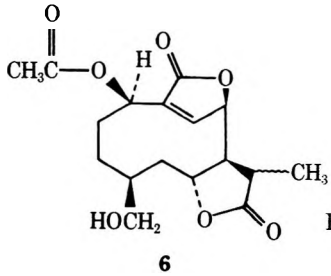

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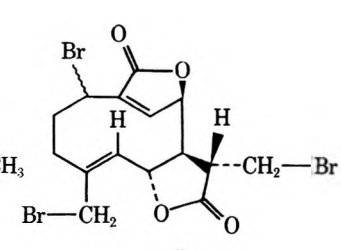

7

The strong uv maximum at 215 nm and the observed allylic coupling between H-5 and H-15 in **1c** also corroborated the above assignments. The mass spectrum of melampodin B lacks a parent peak but shows intense peaks at m/e 274, 256 (base peak), and 228. The acetate **1b** gives a parent peak at m/e 376 and a peak at m/e 333 ($M^+ - 43$), which indicates the loss of an acylium ion (CH_3CO^+) from the parent ion. The fragment corresponding to m/e 274 ($M^+ - 102$) could be formed by a sequential or simultaneous loss

of CH_3COOH (60 mu) involving a McLafferty rearrangement of the C-1 acetoxy group and the elimination of ketene (42 mu) from C-15 in **1b**. Further loss of H_2O gives rise to the base peak at *m/e* 256 and the intense peak at *m/e* 228 in **1a** and **1b** must be due to the loss of CO (28 mu) from the fragment *m/e* 256.

Melampodin B was transformed into the tribromide **7** using a saturated solution of HBr in glacial acetic acid, involving substitution reactions at the allylic carbon centers C-1 and C-15 and an acid-catalyzed Michael addition at C-13. The observed coupling constants ($J_{1,2a}$ = 11.5, $J_{1,2b}$ = 5.5 Hz) for the H-1 doublet of doublets centered at 4.83 ppm indicates that one of the C-2 protons (H-2a) is anti periplanar to the C-1 proton while the torsional angle between H-2b and H-1 should be approximately 60°. Stereomodels indicated that these requirements can be met with H-1 adopting either an α or β orientation depending upon the conformation around the carbon atoms 1, 2, and 3 in **7**. Therefore, the configuration at C-1 in **7** could not be determined from the above coupling data. The multiplet at 3.50 ppm ($J_{7,11}$ = 11.0, $J_{11,13a} = J_{11,13b}$ = 4.0 Hz) in **7** was shown by double irradiation to be due to H-11. The large coupling constant ($J_{7,11}$ = 11.0 Hz) suggested that the protons have an anti periplanar orientation; therefore, since on biogenetic grounds H-7 was assumed to be α oriented, H-11 must have a β orientation. Spin decoupling experiments involving the signals of H-1, H-5, H-6, H-7, H-8, H-9, H-11, H-13, and H-15 verified the structural assignments of **7**. The similarities of the coupling constants of H-5, H-6, H-7, H-8, and H-9 in **1a** and **7** appear to be an expression of their stereochemical and conformational similarity.

Cinerenin and Derivatives. Cinerenin (**2a**), $C_{17}H_{20}O_6$, mp 161–163°, is a common constituent in *M. cinereum* and *M. argophyllum*. The ir spectrum of **2a** contained absorptions typical of α,β-unsaturated γ-lactones (1775, 1750 cm^{-1}) while signals at 3450 and 1665 cm^{-1} indicate a hydroxyl group and double bonds, respectively. The ir spectrum of the acetate **2b** exhibited no OH absorption indicating the presence of only one OH group in cinerenin. The OH group had to be primary since oxidation of **2a** with Sarett's reagent gave an aldehyde (**2c**). The NMR spectral features of **2c** were similar to those of the aldehyde **1c** derived from melampodin B (see Table I). Treatment of cinerenin with HBr in glacial acetic acid gave the tribromide **7** which had previously been obtained from melampodin B. This conversion provided strong evidence that **2a** must have a skeletal arrangement similar to melampodin B and the structural difference between the two compounds should be restricted to the side chain at C-1.

Further information which led to the final structure of cinerenin was deduced from correlations of 25.2-MHz ^{13}C NMR, ^1H NMR spectral data, and mass spectral fragmentation patterns. The ^{13}C NMR data obtained under PND and SFOCD conditions and the ^{13}C chemical shift considerations indicated that cinerenin contains 17 carbon atoms and possesses the following skeletal systems: three each of >C= and >CHO, two each of –C(=O)O, –CH=, C–CH_2C, and C–CH_2O, and one each of H_2C=, >CHC, and –CH_3. Extreme similarities of most ^{13}C NMR parameters of **1a** and **2a** strengthened the chemical evidence that melampodin B and cinerenin must have a structurally similar medium ring skeleton. Major differences were apparent for the signals due to C-1 and the possible two-carbon unit attached to C-1. From chemical shift considerations and the residual splitting patterns in the SFOCD spectra of **2a** (triplet at about 65 ppm and quartet at 15.7 ppm) the presence of an ethoxyl moiety in **2a** was suggested. Comparison of the chemical shifts and the splitting patterns of the 300-MHz spectra of melampodin B and cinerenin provided further strong evidence for the structure as shown in **2a**. Double irradiation experiments on cinerenin in acetone-d_6 at 100 MHz led to the structural assignments as summarized for **2a** in Table I. The major differences between the ^1H NMR spectra of **1a** and **2a** were observed for the proton signals due to the medium-ring side chain at C-1. In melampodin B, an acetate methyl signal was observed; instead a three-proton triplet at 1.11 ppm (C-2′) and a two-proton quartet centered at 3.42 ppm (C-1′) are present in cinerenin. In **2a** and its derivatives the quartet due to the two C-1′ methylene hydrogens showed a double pattern, appearing as a narrow-spaced doublet of a quartet, thus indicating the diastereotopic relationship of the two C-1′ methylene hydrogens in cinerenin and analogs. The mass spectral data of **2a** corroborated the above structural assignments. Cinerenin showed major mass spectral peaks at *m/e* 274, 256, and 228, typical of the melampodin B skeleton, and a parent peak at *m/e* 320. The peak at *m/e* 274 could result from a loss of ethanol (46 mu) from the parent ion *m/e* 320 by a McLafferty rearrangement, whereas the peaks at *m/e* 256 and 228 would be due to the subsequent loss of H_2O (18 mu) and CO (28 mu) from the ion *m/e* 274.

Unlike melampodin B, which carries an acetoxy group at C-1, cinerenin contains a C-1 ethoxy substituent. Cinerenin could represent an artifact of melampodin B, possibly by the introduction of the C-1 ethoxy group in the isolation procedure which involves lead acetate in ethanol–water. However, when **1a** was treated under conditions as applied in the isolation process, it was recovered quantitatively and no cinerenin was detected.

The stereochemistry at C-1 in **1a** was shown to have a β configuration of the acetoxy group which might be different in **2a**. In the ir spectrum of **1a**, the OH absorption appears as a sharp peak at 3450 cm^{-1} while in cinerenin the OH band is broadened. It could be argued that the alcohol group at C-15 undergoes intramolecular hydrogen bonding involving the C-1′ carbonyl function in **1a** while in cinerenin, owing to the lack of a C-1′ carbonyl group, the OH absorption is broadened, possibly owing to a stronger intermolecular contribution to the hydrogen bonding of the hydroxyl group at C-15. Alternatively, intermolecular hydrogen bonding in **2a** could be due to the α orientation of the ethoxy group at C-1. The remoteness of the involved atoms would not allow hydrogen bonding between the C-15 hydroxyl group and the C-1 oxygen. However, since the ^1H NMR coupling constants of H-1, H-5, H-6, H-7, H-8, and H-9 in the two compounds indicated close similarity for the corresponding proton interactions, the stereochemistries in the medium-ring skeleton including C-1 in cinerenin can be considered identical with that of melampodin B. This is evident from the 300-MHz ^1H NMR spectral patterns of the signals due to H-1, H-2a, H-2b, and the two H-3. The small allylic coupling between the H-1 and H-9 signals in cinerenin ($J_{1,9} \sim$ 1.0 Hz) indicated that the torsional angle between the two protons is less than 90°, as in melampodin B. From the inspection of stereomodels it was learned that these conditions can be best met when the substituent at C-1 in **2a** is β oriented; thus, the ethoxy group at C-1 in cinerenin seems to have a β configuration. Since both melampodin B and cinerenin appear to have the same configuration at C-1, it is suggestive that in **2a** the ethoxy group is biosynthesized by a reductive process of the acetoxy carbonyl carbon in **1a**. Processes of this kind are rare in terpenoids and, to the best of our knowledge, cinerenin represents the first sesquiterpene lactone containing an ether-linked side chain.

Melampodin C. Melampodin C (**3a**), $C_{18}H_{22}O_7$, mp

199–201°C, cooccurred with melampodin B in *M. argophyllum*, a rare species in the mountains of northern Mexico. ^{1}H NMR spectral parameters and the mass spectral patterns of the new compound exhibited gross similarities with those of melampodin B. The mass spectra of melampodin C and its acetate (**3b**) showed major peaks at *m/e* 274 ($M^+ - 88$), 256, and 228 and parent peaks at *m/e* 362 and 404, respectively, suggesting that **3a** possesses a melampodin B type ring skeleton with the grouping $C_4H_7O_2$ (88 mu) attached to the medium ring. This was further substantiated by the conversion of **3a** into the tribromide **7** and by double irradiation experiments involving H-1, H-5, H-6, H-7, H-8, H-9, and the two H-13 signals in **3a**. In addition, **3a** exhibited two three-proton doublets at 1.13 and 1.15 ppm, respectively. The heptet at 2.5 ppm was coupled to the above two methyl doublets, indicating the presence of an isopropyl group in the side chain. The empirical formula, $C_{19}H_{22}O_7$, together with the chemical, mass spectral, and ^{1}H NMR data, only allows the presence of an isobutyrate group at C-1 in **3a**. On the basis of the extreme similarity of the NMR parameters of **1a** and **3a** and their derivatives, it appears that melampodin C exhibits the same configurational and conformational relationships as melampodin B.

4(5)-Dihydromelampodin B. This new compound (**4a**), $C_{17}H_{20}O_7$, mp 204–205°, was isolated from several populations of *M. cinereum*. It showed ir absorptions similar to those of melampodin B, indicating a hydroxyl group (3400 cm^{-1}), a γ-lactone (1785 cm^{-1}), an α,β-unsaturated ester (1750 cm^{-1}) and double bonds (1665 cm^{-1}). Treatment of **4a** with acetic anhydride in pyridine gave a monoacetate (**4b**), $C_{19}H_{22}O_8$, mp 195–196°. The absence of an OH absorption from the ir spectrum of **4b** indicated the presence of only one OH group in **4a**. The mass spectra of **4a** and **4b** gave parent peaks at *m/e* 336 and 378, respectively. The major peaks at *m/e* 276, 258, and 230 in **4a** and **4b** differed from those of melampodin B (**1a**) and **1b** (*m/e* 274, 256, and 228) by two mass units, strongly suggesting that **4a** represented a dihydro derivative of melampodin B. Further evidence concerning the structure of **4a** was provided by correlations of ^{1}H NMR spectra of melampodin B (**1a**), the acetate (**1b**), and the compounds **4a** and **4b** which involved detailed double-resonance experiments. In **4a**, doublets at 6.00 and 6.31 ppm and a multiplet at 3.37 ppm signified that it represents an α,β-unsaturated γ-lactone. Irradiation of the multiplet at 3.37 (H-7) collapsed the doublets at 6.00 and 6.31 (H-13a and H-13b), simplified the multiplet at 3.50 (H-6), and sharpened the broadened singlet at 5.92 ppm (H-8). Irradiation of the H-8 signal affected the multiplet at 3.37 (H-7) and collapsed the downfield doublet at 8.03 ppm (H-9) to a broadened singlet. At this point, the gross similarities between the ^{1}H NMR data of the new compound and melampodin B (**1a**) were apparent. The major ^{1}H NMR spectral differences between **1a** and **4a** were observed in the C-6 and C-15 proton signals. In melampodin B, the C-6 lactonic proton appeared as a sharp triplet at 4.99 while the H-6 signal in **4a** represented a complex multiplet at 3.50 ppm. This implied that more than one proton is attached to C-5 in **4a**. Further evidence that **4a** represents a dihydro derivative of melampodin B was provided by a two-proton signal at 3.70 ppm suggesting the presence of methylene protons (two C-15 protons) which are coupled to a proton at C-4. Double irradiation of **4b** at the center of the signals at 3.87 ppm (C-15 protons) affected the envelope at about 2.00 ppm, while irradiation at 2.00 ppm (H-4) caused the doublet at 3.87 ppm to collapse, indicating that **4a** and **4b** contain a proton at C-4. The mass spectral data and the above ^{1}H NMR spectral assignments suggest that the structural differences between melampodin B and **4a** lies in the absence of a 4(5) double bond in **4a**.

The stereochemistry of the new chiral center at C-4 in **4a** could not be obtained from the above spectral data. If melampodin B represents the biological precursor for the dihydro compound **4a**, then, from a fixed conformation of **1a** with a β-oriented C-15 moiety, the biological reducing reagent should attack from the outer face of the 4(5) double bond in **1a** and directly lead to a product with an α-oriented H-4, as is shown for **4a**.

Experimental Section[11]

Isolation of Melampodin B (1a) and Cinerenin (2a). A collection of *M. cinereum* DC. var. *cinereum* was made on July 19, 1973 (T. F. Stuessy and N. H. Fischer, No. 2015) 8.6 miles northeast of Hebbronville, Duval County, Texas, on route 359.

Dried leaves (1475 g) were extracted with cold chloroform and worked up as described before.[3] The crude syrup was allowed to stand at room temperature for several days, resulting in a partial crystallization of the syrup. Filtration and washing of the residue with ether gave a yellow, crystalline solid. Repeated trituration of this material with hot ethyl acetate (EtOAc) left 2.7 g of crude melampodin B (**1a**): mp 226–228° dec.; strong uv end absorption; CD (*c* 6.2×10^5, MeOH), $[\theta]_{216}$ -8.3×10^3, $[\theta]_{238}$ $+5.4 \times 10^3$, $[\theta]_{277}$ -5.4×10^2; ir ν_{max} (Nujol) 3420 (OH), 1780 (γ-lactone), 1730 (ester), 1655 cm^{-1} (double bonds); low-resolution mass spectrum *m/e* 274 (M − 60), 256 (M − 18 − 60, base peak), 245, 228, 227, 210, 165, 162, 91, and 43.

Anal. Calcd for $C_{17}H_{18}O_7$: C, 61.07; H, 5.43; mol wt, 334. Found: C, 61.28, H, 5.63.

The combined ethyl acetate extracts provided a final yield of 4.0 g of crude cinerenin (**2a**). Recrystallization from EtOAc gave colorless crystals: mp 161–163°; uv λ (MeOH) 205 nm (ε 2.7×10^{-4}) (end absorption); CD (c 6.25×10^{-5}, MeOH), $[\theta]_{218}$ -4.1×10^4, $[\theta]_{240}$ $+4.7 \times 10^4$; ir ν_{max} (Nujol) 3400 (broad, OH), 1770 (γ-lactone), 1750 (α,β-unsaturated ester), 1660 cm^{-1} (double bonds); low-resolution mass spectrum *m/e* 320 (M^+), 274 (M − 46), 256 (M − 18 − 46), 228, 227, 199, 179, 165, 147, 112 (base peak), 91, and 43; ^{13}C NMR (acetone-d_6)[12] 173.2 (C-14),[13a] 169.6 (C-12),[13a] 153.9 d (C-9), 148.1 (C-10), 136.6 (C-4), 133.0 (C-11), 122.3 d (C-5), 122.3 t (C-13), 79.1 d (C-8), 73.4 d (C-6),[13b] 73.2 d (C-1),[13b] 65.3 t (C-1′),[13c] 65.1 t (C-15),[13c] 49.5 d (C-7), 28.3 t (C-3), 23.2 t (C-2) and 15.7 q (C-2′).

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29; mol wt, 320. Found: C, 63.54; H, 6.20.

Melampodin B Acetate (1b). A solution of **1a** (103 mg) was heated in 1 ml of pyridine until all of the crystals were dissolved and then 1 ml of Ac_2O was added. The solution was left overnight at room temperature and then evaporated under reduced pressure to give a white residue. Water (5 ml) and a drop of concentrated HCl were added and the slurry was extracted three times with 50-ml portions of $CHCl_3$; the combined $CHCl_3$ extracts were dried ($MgSO_4$), filtered, and evaporated. The residual white powder was recrystallized from EtOAc, providing 70 mg of **1b**: mp 202–204°; uv λ_{max} (MeOH) 206 nm (ε 3×10^4); CD (*c* 7.1×10^{-4}, MeOH) $[\theta]_{216}$ -2.9×10^4, $[\theta]_{233}$ $+4.5 \times 10^4$; ir ν_{max} (Nujol) 1790, 1770 (γ-lactones), 1735, 1230 (acetate), 1660 cm^{-1} (double bonds); low-resolution mass spectrum *m/e* 376 (M^+), 333 (M − 43), 274 (M − 42 − 60), 256 (M − 18 − 42 − 60), 228, 165, 162, 147, 91, and 43 (base peak).

Anal. Calcd for $C_{19}H_{20}O_8$: C, 60.64; H, 5.32; mol wt, 376. Found: C, 60.55; H, 5.41.

11(13)-Dihydromelampodin B (5). A solution of 100 mg of **1a** in 90 ml of MeOH was hydrogenated for 1 hr over 5 mg of 10% Pd/C. After filtration and evaporation, the residue was chromatographed over silica gel using EtOAc as an eluent. The fractions were analyzed by TLC and combined appropriately. The crude residue was recrystallized from EtOAc, providing 30 mg of 11(13)-dihydromelampodin B (**5**): mp 200–202°; ir ν_{max} (Nujol) 3420 (OH), 1775 (γ-lactone), 1735 and 1245 cm^{-1} (acetate).

Anal. Calcd for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99; mol wt, 336. Found: C, 60.90; H, 5.95; mol wt, 336 (MS).

Oxidation of 1a with Sarett's Reagent. Melampodin B (100 mg) in 50 ml of acetone under nitrogen was treated with an excess of Sarett's reagent[10] in acetone. After 4 hr the brown precipitate was filtered and the acetone evaporated. Water (5 ml) was added

and the slurry extracted twice with 75 ml of $CHCl_3$ and once with 50 ml of EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated. The impure brownish crystals were dissolved in acetone and chromatographed over silica gel–CH_2Cl_2. The column was eluted with CH_2Cl_2, CH_2Cl_2–EtOAc (1:1), and finally with pure EtOAc. The recovered crystals were recrystallized from acetone–2-propanol, providing 45 mg of colorless, crystalline **1c**: mp 241–245° dec; uv λ_{max} (MeOH) 215 nm (ϵ 3.2 × 10^4); ir ν_{max} (Nujol) 1775 (γ-lactone), 1740 (acetate), 1660 (double bonds), 1700, and 1240 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}O_7$: C, 61.45; H, 4.82; mol wt, 332. Found: C, 61.26; H, 4.84; mol wt, 332 (MS).

Reaction of 1a with Lead(II) Acetate. Melampodin B (100 mg) was stirred overnight at room temperature in a mixture of 50 ml of 5% lead(II) acetate in H_2O and 50 ml of EtOH. The solution was filtered and the filtrate evaporated to approximately 30 ml and then extracted three times with 30 ml each of $CHCl_3$. The combined $CHCl_3$ extracts were dried and filtered and the solvent evaporated. A crude white residue was left, which after recrystallization from acetone gave unchanged **1a**, characterized by melting point, mixture melting point, ir, and NMR with authentic material.

Reaction of 1a with HBr. A solution of melampodin B (100 mg) in 25 ml of glacial acetic acid and 3.0 ml of a saturated solution of HBr in glacial acetic acid was refluxed for 20 hr. The solvent was evaporated and ethyl ether was added which resulted in the precipitation of a white solid. Recrystallization from 2-propanol yielded 85 mg of pure **7**: mp 215–217°; ir ν_{max} (Nujol) 1775 (γ-lactone), 1650 (double bonds), 1200, and 1000 cm^{-1}.

Anal. Calcd for $C_{15}H_{15}O_4Br_3$: C, 36.08; H, 3.01; Br, 48.10; mol wt, 499. Found: C, 36.1; H, 3.07; Br, 48.00; mol wt, 499 (MS).

Cinerenin acetate (2b) was obtained from 100 mg of **2a** as described above for **1b**. Recrystallization of the crude material from 2-propanol gave 60 mg of pure **2b**: mp 187–189°; ir ν_{max} (Nujol) 1780 and 1770 (γ-lactones), 1740, 1235, 1225 (acetate), and 1665 cm^{-1} (double bonds); low-resolution mass spectrum *m/e* 362 (M^+), 333 (M − 29), 316 (M − 46), 274 (M − 42 − 46, base peak), 256 (M − 18 − 42 − 46), 228, 178, 165, 162, 147, 112, and 43.

Anal. Calcd for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12; mol wt, 362. Found: C, 62.89; H, 6.11.

Oxidation of 2a with Sarett's Reagent. To a solution of 105 mg of **2a** in 25 ml of acetone in a nitrogen atmosphere an excess of Sarett's reagent was added. After 4 hr, the brown precipitate was filtered and the acetone was removed by evaporation. Water (5 ml) was added and the slurry was extracted twice with 50 ml of $CHCl_3$ and once with 50 ml of EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. The crude brownish crystals were taken up in acetone and chromatographed over silica gel; the column was eluted with CH_2Cl_2, CH_2Cl_2–EtOAc (1:1), and finally with pure EtOAc, which gave colorless crystals. Recrystallization from 2-propanol–$CHCl_3$ gave 50 mg of pure **2c**: mp 218–221° dec; uv λ_{max} (MeOH) 216 nm (ϵ 2.7 × 10^4); ir ν_{max} (Nujol) 1770 (γ-lactones), 1700 (α,β-unsaturated aldehyde), 1655 (double bonds), and 1110 cm^{-1}.

Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70; O, 30.16; mol wt, 318. Found: C, 63.93; H, 5.59; O, 30.35; mol wt, 318 (MS).

Reaction of **2a** (105 mg) with HBr under conditions described above for **1a** gave 80 mg of **7**.

Isolation of Melampodin C (3a) from *M. argophyllum*. A collection of *M. argophyllum* was made on July 3, 1974 (T. F. Stuessy No. 3599) 30 miles southeast of the Coahuila-Nuevo León border on route 53 in the state of Nuevo León, Mexico. Dried leaves (1350 g) were extracted and worked up as described before.[3] The crude syrup (22 g), when allowed to stand at room temperature for 3 weeks, partially crystallized, providing 2.5 g of crude melampodin B. The remaining crude syrup (10 g) was chromatographed over 300 g of silica gel (Brinkmann 7734) collecting 20-ml fractions. The column was eluted using the following solvent mixtures: 1000 ml of CH_2Cl_2–EtOAc (9:1); 500 ml of CH_2Cl_2–EtOAc (4:1); 450 ml of CH_2Cl_2–EtOAc (2:1); 700 ml of CH_2Cl_2–EtOAc (1:1); 300 ml of EtOAc; 500 ml of 5% MeOH in EtOAc; and 500 ml of 15% MeOH in EtOAc. The following fractions were collected and combined according to TLC analysis. Fractions 21–40 contained 610 mg of artemetin (5-hydroxy-3,4′,5′,6,7-pentamethoxyflavone). Fractions 71–100 provided 1.23 g of melampodin C (**3a**). Recrystallization from EtOAc–Et_2O gave colorless crystals: mp 199–201°; uv λ (MeOH) 205 nm (ϵ 2.9 × 10^{-4}) (end absorption); CD (c 5.5 × 10^{-5}, MeOH) $[\theta]_{218}$ −5.2 × 10^4, $[\theta]_{238}$ +3.8 × 10^{-4}, $[\theta]_{280}$ −9.3 × 10^2; ir ν_{max} (Nujol) 3450 (OH), 1770 (γ-lactone), 1725 (ester), and 1655 cm^{-1} (double bonds); low-resolution mass spectrum *m/e* 362 (M^+), 344 (M − 18), 274 (M − 88), 256 (M − 18 − 88), 228, 165, 147, 91, 43 (base peak).

Anal. Calcd for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12; O, 30.91; mol wt, 362. Found: C, 63.07; H, 6.00; O, 30.77.

Fractions 116–130 gave 890 mg of **2a** and 3.0 g of **1a** was obtained from fractions 140–160.

Melampodin C acetate (3b) was obtained from 170 mg of **3a** as described above for **1b**. Recrystallization of the crude product from 2-propanol provided 160 mg of **3b**: mp 151–153°; ir ν_{max} (Nujol) 1780, 1765 (γ-lactones), 1225 cm^{-1} (acetate); low-resolution mass spectrum *m/e* 404 (M^+), 361 (M − 43), 316 (M − 88), 274 (M − 42 − 88), 256, (M − 18 − 42 − 88), 228, 165, 147, 91, 71, 43 (base peak).

Anal. Calcd for $C_{21}H_{24}O_8$: C, 62.37; H, 5.98; O, 31.65; mol wt, 404. Found: C, 62.55; H, 5.96; O, 31.57.

Oxidation of Melampodin C with Sarett's Reagent. Melampodin C (150 mg) was dissolved in 25 ml of acetone under nitrogen and an excess of Sarett's reagent, suspended in acetone, was added. After 4 hr, the brown precipitate was filtered and the acetone was removed by evaporation. The crude residue was chromatographed over 25 g of silica gel. The column was eluted with 300 ml of CH_2Cl_2–EtOAc (9:1), then with 200 ml of CH_2Cl_2–EtOAc (1:1). Evaporation of later fractions gave a white powder. Recrystallization from EtOAc provided 71 mg of the pure aldehyde **3c**: mp 207–209°; ir ν_{max} (Nujol) 1785 (γ-lactone), 1735 (ester), 1245, and 1145 cm^{-1}; low-resolution mass spectrum *m/e* 360 (M^+), 359 (M^+ − 1) 329, 315, 274, 256, 212, 91, 77, 71, 43, 29 (base peak).

Anal. Calcd for $C_{19}H_{20}O_7$: C, 63.33; H, 5.59; O, 31.08; mol wt, 360. Found: C, 63.46; H, 5.64; O, 30.84.

Reaction of **3a** (100 mg) with HBr under conditions described above for **1a** gave 60 mg of compound **7**.

Isolation of 4(5)-Dihydromelampodin B (4a). A collection of *M. cinereum* var. *cinereum* was first made on Oct 4, 1971 (N. H. Fischer No. 12) 12 miles south of George West, Texas, on Highway 59 and again on July 7, 1973 (N. H. Fischer No. 29). NMR spectra of the crude extracts indicated the presence of the same constituents in the above collections.

The dried leaves (200 g) were extracted and worked up as described before,[3] providing 18 g of crude terpenoid-containing syrup. The crude syrup (9 g) was chromatographed over 300 g of silica gel (Baker 3405) collecting 15-ml fractions and using the following solvent mixtures: fractions 1–40 (CH_2Cl_2–EtOAc, 9:1), 41–60 (CH_2Cl_2–EtOAc, 4:1), 61–100 (CH_2Cl_2–EtOAc, 3:1), 100–170 (CH_2Cl_2–EtOAc, 1:1), 171–190 (CH_2Cl_2–EtOAc, 1:4), 191–220 (pure EtOAc), 220–260 (5% MeOH in EtOAc), and 260–289 (MeOH–EtOAc, 1:1). The following fractions were combined according to TLC analysis. Fractions 40–57 gave 50 mg of artemetin, mp 159–160°, identical with an authentic sample by mixture melting point and spectral comparison (ir, NMR). Fractions 227–261 provided 300 mg of 4(5)-dihydromelampodin B (**4a**): mp 204–205°; uv λ_{max} (EtOH) 202 nm (ϵ 3.2 × 10^{-4}); CD (c 1 × 10^{-5}, MeOH) $[\theta]_{220}$ −106 × 10^3, $[\theta]_{265}$ 1.60 × 10^3; ir ν_{max} (Nujol) 3400 (OH), 1785 (γ-lactone), 1750 (ester), and 1665 cm^{-1} (double bonds); low-resolution mass spectrum *m/e* 336 (M^+), 276 (M − 60), 258 (M − 18 − 60), 230, 228, 201, 165, 162, 91, 43 (base peak).

Anal. Calcd for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99; mol wt, 336. Found: C, 61.01; H, 6.31.

4(5)-Dihydromelampodin B acetate (4b) was obtained from 100 mg of **4a** as described for **1b**. Recrystallization of the crude product from EtOAc–Et_2O provided 95 mg of **4b**: mp 195–196°; ir ν_{max} (Nujol) 1777 (γ-lactone), 1245 (acetate), and 1070 cm^{-1}; low-resolution mass spectrum *m/e* 378 (M^+) 335 (M − 43), 276 (M − 42 − 60), 258 (M − 18 − 42 − 60), 230, 165, 162, 149, 111, 91, and 43 (base peak).

Anal. Calcd for $C_{19}H_{22}O_8$: C, 60.32; H, 5.82; O, 33.86; mol wt, 378. Found: C, 60.40; H, 5.80, O, 33.73.

4(5),11(13)-Tetrahydromelampodin B (6). A solution of 100 mg of 4(5)-dihydromelampodin B in 75 ml of MeOH and 5 mg of 10% Pd/C were placed in a 100-ml round-bottom flask. After removal of air in vacuo the stirred mixture was hydrogenated under rapid uptake of hydrogen for about 15 min. The reaction was terminated after 1 hr; filtration and evaporation of MeOH provided a syrup which was chromatographed by preparative layer chromatography using propyl acetate as developing solvent. The band at R_f 0.3 was extracted from the silica gel and the resulting crude material recrystallized from acetone, giving 35 mg of **6**: mp 220–222°; ir ν_{max} (Nujol) 3500 (OH), 1770, 1750 (γ-lactone), 1725, and 1240 cm^{-1} (acetate).

Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55; mol wt, 338. Found: C, 60.42; H, 6.27; mol wt, 338 (MS).

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Registry No.—**1a**, 51419-54-6; **1b**, 51212-98-7; **1c**, 56650-61-4; **2a**, 56650-62-5; **2b**, 56650-63-6; **2c**, 56650-64-7; **3a**, 56650-65-8; **3b**, 56650-66-9; **3c**, 56650-67-0; **4a**, 56650-68-1; **4b**, 56650-69-2; **5**, 56650-70-5; **6**, 56650-71-6; **7**, 56650-72-7; lead(II) acetate, 301-04-2; HBr, 10035-10-6.

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(12) The spectra were determined on a Varian XL-100-15 spectrometer operating Fourier transform mode with proton decoupling. Me_4Si was used as internal standard and the values are in parts per million relative to Me_4Si. The number of lines in the single-frequency off-center decoupled spectra are designated as follows: d, doublet; t, triplet; q, quartet. Unmarked signals are singlets.
(13) (a)–(c) Vice versa.

Acanthospermal A and Acanthospermal B, Two New Melampolides from *Acanthospermum* Species[1]

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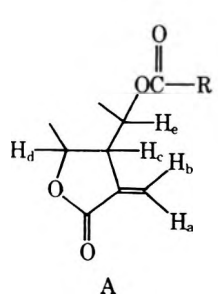
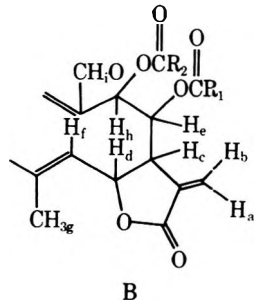
The isolation and structure determination of acanthospermal A (**1a**) from *Acanthospermum australe* (L.) Kuntze and acanthospermal B (**4a**) from *A. hispidum* DC. is reported. Both compounds belong to the melampolide subgroup of germacradienolides. **1a** is the first sesquiterpene lactone to possess an α-hydroxyisobutyric acid ester side chain.

In continuation of our search for sesquiterpene lactones with potential biological activity in Compositae we have examined two local *Acanthospermum* species (tribe Heliantheae, subtribe Melampodiinae). This resulted in the isolation of two closely related noncrystalline melampolides, acanthospermal A (**1a**) from *Acanthospermum australe* (L.) Kuntze and acanthospermal B (**4a**) from *A. hispidum* DC. Structures and stereochemistry were established by chemical transformations and extensive use of ^1H and ^{13}C NMR spectrometry.



A

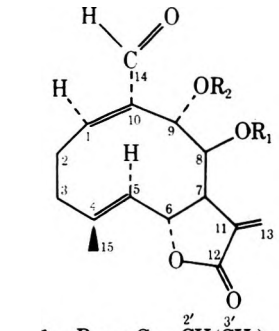


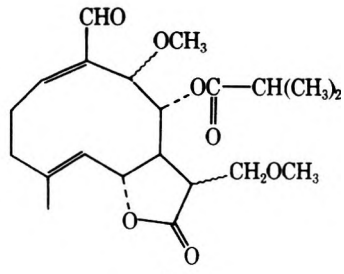
B

Acanthospermal A (**1a**), $C_{23}H_{30}O_8$ (high-resolution mass spectrum and elemental analysis), $[\alpha]_{Hg}^{25}$ −54°, was an α,β-unsaturated aldehyde (ir band at 1690 cm^{-1}, NMR signal at 9.45 ppm) and an α,β-unsaturated lactone of the type shown in A as evidenced by the usual criteria (strong uv end absorption due to superposition of the two chromophores, ir bands at 1780 and 1620 cm^{-1}, narrowly split NMR doublets of H_a and H_b at 6.25 and 5.73 ppm). Attempts to locate H_c by spin decoupling were complicated by overlapping of signals in the $CDCl_3$ spectrum, but a solution of **1a** in benzene-d_6 afforded excellent separation of signals (see Table I) and permitted determination of the entire carbon framework.

The location of H_c as a multiplet at 2.30 ppm was established by double irradiation at the frequency of H_a and H_b. Irradiation at the frequency of H_c collapsed H_a and H_b into singlets and also converted a triplet at 4.97 ppm ($J_1 = J_2 =$ 10 Hz) into a doublet and a narrowly split doublet of doublets at 6.99 ppm ($J_1 = 9$, $J_2 = 1.5$ Hz) into a clean doublet ($J = 9$ Hz). Thus H_d and H_e were at 4.97 and 6.99 ppm, respectively, or the reverse. The chemical shift of the lower field proton suggested that it was under an ester rather than under the lactone oxygen, especially since the ir spectrum indicated the presence of additional carbonyl functions near 1740 cm^{-1} associated with esters. Hence the signal at 4.97 ppm was provisionally assigned to H_d and the signal at 6.99 ppm to H_e. The reason for the unusual paramagnetic shift of H_e will be discussed subsequently.

Irradiation at the frequency of H_d converted H_c into a broad singlet and also changed a broadened doublet at 4.39 ppm ($J = 10$ Hz, H_f) into a broadened singlet. The broadening was due to allylic coupling with a vinylic methyl (H_g) which appeared as a narrowly split doublet at 1.63 ppm. Irradiation at the frequency of H_e slightly sharpened H_c and





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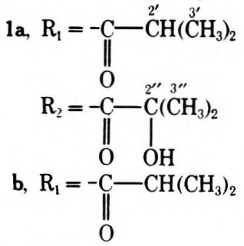
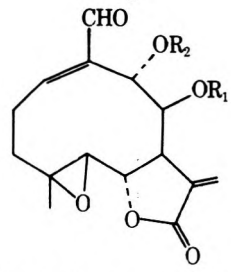


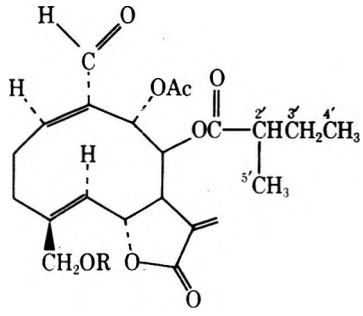
1a, $R_1 = -C(=O)-C(OH)(CH_3)_2$, $R_2 = -C(=O)-CH(CH_3)_2$

b, $R_1 = R_2 = -C(=O)-CH(CH_3)_2$

c, $R_1 = R_2 = Ac$

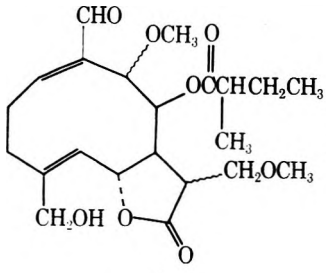


3, R_1, R_2 same as in **1a**



4a, R = H

b, R = Ac



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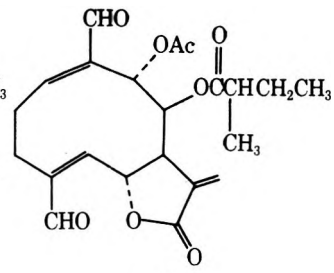

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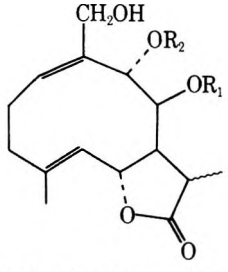
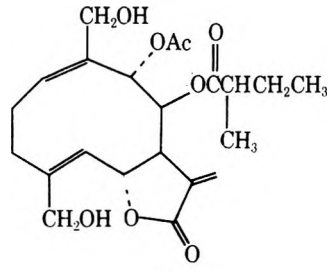


7, R_1, R_2 same as in **1a**

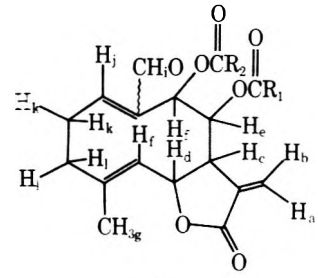


8

also converted a doublet of doublets at 5.10 ppm (H_h, J_1 = 9, J_2 = 2 Hz) into a doublet (J = 2 Hz). The smaller coupling of H_h could be traced to the aldehyde proton H_i. The chemical shift of H_h suggested that it might be either olefinic, with allylic coupling to the aldehyde proton (in which case H_h would have to be β to the aldehyde and less deshielded than usual) or under an ester oxygen with W coupling to the aldehyde proton as in frutescin.[2] The ambiguity was decided in favor of the second alternative by a single-frequency off-resonance decoupling experiment in the ^{13}C NMR spectrum (Table II); irradiation at the frequency of H_h collapsed a doublet at 67.8 ppm, clearly associated with carbon attached to oxygen by a single bond, and not one of the doublets (at 159.2 and 126.8 ppm) identifiable with -CH=. In a similar vein, irradiation at the frequency of H_e collapsed a doublet at 72.0 ppm, thus showing that in spite of its unusually low shift H_e was attached to a carbon atom carrying two carbons and one oxygen. Consequently partial structure A could be expanded to B.

The NMR spectrum further exhibited a one-proton doublet of doublets (H_j) at 5.79 ppm (J_1 = 10, J_2 = 9 Hz), presumably the proton β to the aldehyde function.[3] The identity of this signal was confirmed by single-frequency off-resonance decoupling in the ^{13}C NMR spectrum which resulted in collapse of the doublet at 159.2 ppm to a singlet. Irradiation at the frequency of H_j also simplified two well-separated multiplets at 2.54 and 1.78 ppm which were obviously associated with geminally coupled protons (H_k). Decoupling experiments further showed that the methylene group of H_k was adjacent to another methylene group whose protons (H_l) appeared as multiplets at 1.80 and 1.41 ppm.

Consideration of these results permitted extension of B to C. In accordance with this formula, epoxidation of acan-



C

thospermal A gave a monoepoxide (3), in whose NMR spectrum (Table I) the split vinylic methyl signal was replaced by a sharp methyl signal at 1.70 ppm and the H_d and H_f frequencies had shifted upfield to 4.27 and 2.60 ppm, respectively.

The nature of R_1 and R_2 was deduced as follows. The NMR spectrum exhibited two methyl doublets at 0.86 and 0.87 ppm, each coupled to a one-proton multiplet at 2.11 ppm, thus pointing to the possibility of an isobutyryl side chain. This was confirmed by the loss of 88 mass units and the appearance of peaks corresponding to 87, 71, and 43 mass units in the mass spectrum. The second ester side chain had to correspond to $C_4H_7O_3$ to fit the molecular formula, the extra oxygen atom deriving from a hydroxyl group (ir frequency at 3510 cm^{-1}) which appeared to be tertiary (carbon singlet at 72.2 ppm) and could not be accommodated in the ten-membered ring. Since the NMR spectrum displayed two additional methyl singlets at 1.22 and 1.28 ppm, presumably methyls on carbon carrying single-bonded oxygen, it was concluded that the second side chain was α-hydroxyisobutyrate. In accord with this conclusion, the high-resolution mass spectrum also showed an important peak corresponding to loss of α-hydroxyisobutyric acid; moreover, the base peak corresponded to the combined loss of isobutyric and α-hydroxyisobutyric acid.

The following experiments permitted placement of these two ester side chains. Attempted acetylation of acanthospermal A with pyridine–acetic anhydride furnished a substance **1b**, $C_{21}H_{26}O_7$, by replacement of the α-hydroxyisobutyryl side chain with an acetyl function (NMR spectrum, see Table I). Hydrolysis of **1a** with sodium methoxide in methanol gave a single product $C_{21}H_{30}O_7$ whose NMR spectrum (Table I) fitted in well with structure 2 (exclusive of stereochemistry). Apart from methanol addition to the

Table I
^{1}H NMR Spectra of Acanthospermals and Derivatives[a]

Compd	H-1	H-2	H-3	H-5	H-6	H-7	H-8	H-9	H-13	H-14	H-15	Misc
1a	6.80 dd (10, 9)	2.84 m (14, 10, 10, 2) 2.5 m[c] (14, 9, 2)	2.50 dd[c] (14, 2) 2.09 ddd (14, 10, 2)	5.00 d br (10)	5.07 t (10)	2.63 m[c]	6.73 dd (9, 1.5)	5.15 dd (9, 2)	6.25 d (3.5) 5.73 d (3.5)	9.45 d (2)	2.00 br	1.08 d (7)[d] (H-3′); 1.27[b], 1.29[b] (H-3′); 2.50 m[c] (H-2′)
1a[e]	5.79 dd (10, 9)	2.54 m (14, 10, 10, 2) 1.78 m (14, 9, 2)	1.80 dd (14, 2) 1.41 ddd (14, 10, 2)	4.39 d br (10)	4.97 t (10)	2.30 m	6.99 dd (9, 1.5)	5.10 dd (9, 2)	6.22 d (3.5) 5.66 d (3.5)	9.00 d (2)	1.63 br	0.86 d (7),[b] 0.87 d (7)[b] (H-3′); 1.22,[b] 1.28[b] (H-3″); 2.11 m (H-2′)
1b	6.77 dd (10, 9)	2.81 m (14, 10, 10, 2) 2.46 m[c]	2.59 m[c] 2.07 ddd (14, 10, 2)	4.91 d br (10)	5.05 t (10)	2.59 m[c]	6.70 dd (9, 1.5)	5.25 dd (9, 2)	6.25 d (3.5) 5.73 d (3.5)	9.47 d (2)	2.00 br	1.09 d (7)[d] (H-3′) 1.95[b] (Ac); 2.46 m[c] (H-2′)
2	6.78 dt (10, 9)	2.66 m[c] 2.30 m[b]	2.39 m[c] 2.05 ddd (14, 10, 2)	4.90[c]	4.90[c]	2.30[c]	6.12 dd (9, 1.5)	3.56 dd (9, 2)	3.70[f]	9.43 d (2)	1.90 br	1.20 d (7)[d] (H-3′) 2.39 m[b] (H-2′) 3.35[b] (OMe)
3	6.97 dd (10, 9)	3.17 2.70 m	2.43 m 1.24 m	2.60 d br (10)	4.27 t	2.80 m	6.78 dd (9, 1.5)	5.64 dd (9, 2)	6.35 d (3.5) 5.87 d (3.5)	9.52 d (2)	1.70 br	1.06 d (7), [b] 1.08 (7)[b] (H-3′); 1.32, [b] 1.34[b] (H-3″); 2.50 m (H-2′) 1.60 (–OH)
4a	6.81 dd (10, 9)	2.89 m[c] 2.65 m[c]	2.89 m[c] 2.00 ddd (14, 10, 2)	5.03 br (10)	5.27 t (10)	2.65 m[c]	6.69 dd (9, 1.5)	5.32 dd (9, 2)	6.26 d (3.5) 5.78 d (3.5)	9.45 d (2)	4.50[f]	0.87 t (7)[b] (H-4′); 1.09 d (7)[b] (H-5′) 1.60 m, 1.43 m (H-3′) 1.98[b] (Ac); 2.35 m (H-2′)
4a[e]	5.73[c]	2.63 m (14, 10, 10, 2) 1.80 m (14, 9, 2)	2.48 dd (14, 10) 1.41 ddd (14, 10, 2)	4.44 d br (10)	5.21 t (10)	2.32 m	7.00 dd (9, 1.5)	5.30 dd (9, 2)	6.23 d (3.5) 5.75 d (3.5)	9.05 d (2)	4.21[f]	0.68 t (7)[b] (H-4′); 0.90 d (7)[b] (H-5′); 1.00 m, 1.19 m (H-3′) 1.50[b] (Ac), 2.07 m (H-2′)
4b	6.78 dd (10, 9)	2.92 m (14, 10, 10, 2) 2.5–2.7[c]	2.5–2.7[c] 2.12	2.86 d br (10)	5.08 t (10)	2.5–2.7[c]	6.68 dd (9, 1.5)	5.28 dd (9, 2)	6.28 d (3.5) 5.82 d (3.5)	9.47 d (2)	5.00[f]	0.85 t (7)[b] (H-4′), 1.08 d (7)[b] (H-5′), 1.45 m, 1.60 m (H-3′), 1.95[b], 2.12[b] (Ac), 2.36 m (H-2′)

5	6.80 dd (10, 9)	2.82 m	2.66 m	4.98 d br (10)	5.05 t (10)	2.55 m	6.11 d br (9)	3.79 d br	3.70[f]	9.50 d (2)	4.40[f]	0.94 t (7)[b] (H-4′); 1.17 d (7)[b] (H-5′); 1.52 m, 1.70 m (H-3′); 2.47 m (H-2′); 3.10, [b] 3.37[b] (OMe)
		2.32 m	2.00 m									
6	6.78 dd (10, 9)	2.76 m[e]	2.76 m[e]	6.05 d br (10)	5.00 t (10)	3.20 m	6.71 dd (9, 1.5)	5.00 dd (9, 2)	6.36 d (3.5) 5.89 d (3.5)	9.48 d (2)	10.22 br	0.83 t (7)[b] (H-4′); 1.05 d (7)[b] (H-5′); 1.45 m, 1.61 m[c] (H-3′); 1.90 (Ac); 2.33 m (H-2′)
		1.61 m[c]	1.82 dd (14, 10, 2)									
7	5.75 dd (10, 9)	2.42 m (14, 10, 10, 2)	2.27 m[c]	4.90 d br (10)	5.00 t (10)	2.27 m[c]	5.78 dd (9, 1.5)	5.34 d (9)	1.25 d[b] (7)	4.20[f]	1.94 br	1.17 t (7)[b] (H-3′); 1.32 d (H-3′′); 2.17 m (H-2′); 2.58 m (H-11)
		1.94 m[c]	1.94 m[c]									
8	5.75 dd (10, 9)	2.1–2.8 m[c]	2.1–2.8 m[c]	5.00 d br (10)	5.20 t (10)	2.1–2.8 m[c]	5.70 dd (9, 1.5)	5.42 d (9)	1.25 d[b] (7)	4.23[f]	4.44[f]	0.90 t (7)[b] (H-4′); 1.15 d (7)[b] (H-5′)
		2.8 m[c]	1.85 ddd (14, 10, 2)									1.44 m, 1.64 m (H-3′) 2.1–2.8 m (H-2′ and H-11)

[a] Run in $CDCl_3$ at 270 MHz on a Bruker HX-270 instrument with Me_4Si as internal standard, unless otherwise specified. Values are in parts per million: d, doublet; t, triplet; br, broadened singlet; m, multiplet. Unmarked signals are singlets. [b] Intensity three protons. [c] Signal partially obscured or superimposed. [d] Intensity six protons. [e] Run in C_6D_6. [f] Intensity two protons, center of AB system.

Table II
^{13}C NMR Spectra of Acanthospermal A and B[a]

1a	Assignment[b]	4a	Assignment[b]
193.5 d	C-14	193.9 d	C-14
176.2	C-1′	176.0	C-1′
175.4	C-1′′	170.3	Ac
169.0	C-12	168.4	C-12
159.2 d	C-1[c]	158.4 d	C-1
140.8	C-10	141.5	C-10
138.3	C-4	141.0	C-4
134.2	C-11	134.1	C-11
126.8 d	C-5	128.5 d	C-5
121.8 t	C-13	122.0 t	C-13
74.9 d	C-6[c]	73.6 d	C-6
72.2	C-2′′	70.3 d	C-8
72.0 d	C-8	68.1 d	C-9
67.8 d	C-9[c]	60.4 t	C-15
51.0 d	C-7	51.2 d	C-7
36.9 t	C-3[c]	41.4 d	C-2′
34.1 d	C-2′	32.4 t	C-3
26.8 t	C-2	27.6 t	C-3′
26.8 q	C-3′[c]	26.6 t	C-2
26.8 q	C-3′[c]	20.7 q	Ac
19.0 q	C-3′′	16.8 q	C-5′
18.8 q	C-3′′	11.5 q	C-4′
16.8 q	C-15[c]		

[a] Run in $CDCl_3$ on Bruker HX-270 instrument. Unmarked signals are singlets. [b] Assignments based on predicted shifts and comparisons with data in the literature and in our files. [c] Assignment established by single frequency off-resonance decoupling.

methylene group of the conjugated lactone, the α-hydroxyisobutyryl group had been replaced by a methoxyl. The signal of H_h now appeared at 3.56 ppm, whereas the chemical shift of H_e (6.12 ppm) indicated that the corresponding carbon atom retained the remaining ester side chain, i.e., the isobutyrate unit. Therefore, in acanthospermal A the isobutyrate side chain must be at C-8 and the easily displaced α-hydroxyisobutyrate chain at C-9.

Before delineating the stereochemistry of acanthospermal A, we shall discuss acanthospermal B (**4a**), $C_{22}H_{28}O_8$ (high-resolution mass spectrum), $[\alpha]_{Hg}^{25}$ −33°, whose spectral properties were very similar to those of **1a** and indicated the presence of an α,β-unsaturated lactone, an α,β-unsaturated aldehyde, two ester side chains, and a hydroxyl group. Comparison of the chemical shifts of the various protons[4] showed the essential identity of the basic germacradiene system, but in acanthospermal B the vinylic methyl of **1a** was replaced by a hydroxymethylene group (AB quartet at 4.50 shifted downfield to 5.00 ppm on acetylation to **4b**).

The two ester groups were also different. One was an acetate (singlet at 1.98 ppm); the second—a five-carbon unit to be accommodated in the molecular formula—was an α-methyl butyrate as evidenced by the presence of a methyl doublet (1.09 ppm) coupled to a one-proton multiplet at 2.35 ppm. This was also coupled to two one-proton multiplets at 1.60 and 1.43 ppm, each of which was coupled in turn to a methyl triplet at 0.87 ppm. In accordance with these deductions the high-resolution mass spectrum exhibited diagnostically important peaks at *m/e* 318.1121 (M − $C_5H_{10}O_2$), 300.0994 (M − $C_5H_{10}O_2$ − H_2O), 276.1004 (M − $C_5H_{10}O_2$ − C_2H_2O), 258.0886 (M − $C_5H_{10}O_2$ − $C_2H_2O_2$), and 240.0787 (M − $C_5H_{10}O_2$ − $C_2H_4O_2$ − H_2O) and the base peak at *m/e* 85 (C_5H_9O).

Hydrolysis of acanthospermal B with sodium methoxide–

methanol afforded a substance $C_{22}H_{32}O_8$ (**5**) as the result of methanol addition to the lactone and replacement of the acetate by methoxyl. Just as in the case of **1a**, displacement of methoxyl was accompanied by an upfield shift of the H-9 signal from 5.15 to 3.79 ppm, whereas the shift of H-8, from 6.69 to 6.11 ppm, was considerably less and not compatible with conversion of an ester to an ether function. Consequently acanthospermal B had formula **4a** exclusive of stereochemistry.

We now turn to the stereochemistry of **1a** and **4**, which because of the similarity of chemical shifts and coupling constants had to be the same. The chemical shift of the aldehyde proton (H-14) which appeared near 9.45 ppm indicated clearly that the 1(10) double bond was cis rather than trans, a trans aldehyde proton being found at 10 ppm or higher.[5,6] To determine the geometry of the 4,5 double bond, acanthospermal B was oxidized (MnO_2) to the dialdehyde **6**, whose NMR spectrum (Table I) exhibited the new aldehydic proton at 10.22 ppm indicating that the 4,5 bond was trans. Studies of possible NOE's between the C-15 aldehyde proton of **6** (or the C-15 methyl group of **1a** or the $-CH_2OH$ of **4a**) and H-5 produced the negative results expected for a trans double bond. Hence the acanthospermals belong to the melampolide[7] subgroup of germacranolides.[8]

If the usual assumption be made that the C-7 side chain is equatorial and β as in all sesquiterpene lactones of authenticated stereochemistry, the large values of $J_{5,6}$ and $J_{6,7}$ (see Table I) require that H-6 be trans to H-7 and β, and that H-5 be trans to H-6 and α, i.e., that the lactone ring be trans fused. This conclusion is reinforced by the magnitude of $J_{7,13a}$ and $J_{7,13b}$ (>3 Hz) which according to Samek's rule[12] (apparently applicable to melampolides[2,7,9-11]) indicates the presence of a trans lactone ring. Such a lactone might be expected to exhibit a negative Cotton effect if the absolute configuration is as depicted in the formulas.[13] However, the α,β-unsaturated aldehyde chromophore seems to exert a dominant effect on the CD curves which display a negative maximum at 224 nm (θ −5400 for **1a** and −40200 for **4a**), the much weaker Cotton effect of the unsaturated lactone function usually found near 250 nm having been swamped.

The stereochemistry at C-8 and C-9 was deduced by comparison of the observed coupling constants with those deduced from dihedral angles in Dreiding models. The small value of $J_{7,8}$ (1.5 Hz) can be accounted for only by α orientation of H-8, whereas the large coupling constant between H-8 and H-9 (9 Hz) shows that H-9 is trans to H-8 and β. This stereochemistry places H-9 and H-14 into a W relationship if the aldehyde carbonyl is oriented such that there is maximum overlap between the π orbitals of the 1(10) carbon–oxygen double bonds, an arrangement which accounts for the long-range coupling between H-9 and H-14.

In this orientation of the aldehyde carbonyl group, H-8 lies in the plane of the carbonyl, relatively close to the carbonyl oxygen, and should be strongly deshielded as actually observed. That this was the correct explanation for the paramagnetic shift of H-8 could be verified experimentally. $NaBH_4$ reduction of **1a** gave the tetrahydro derivative **7** whose NMR spectrum exhibited the H-8 signal at a normal frequency of 5.78 ppm and H-1 at 5.75 ppm, as expected. Similarly, $NaBH_4$ reduction of **4a** gave **8** which had H-8 at 5.70 and H-1 at 5.75 ppm.

Thus not only the oxidation pattern, but also the stereochemistry of the acanthospermals is identical with that of five other melampolides whose stereochemistry has been established by X-ray analysis,[7,10] either directly or by chemical correlation.[9,11] Possible implications of this finding will be discussed elsewhere.

Experimental Section

Experimental details have been specified previously.[14]

Extraction of *Acanthospermum australe*. Above-ground parts of *A. australe* (L.) Kuntze, wt 6.3 kg, collected by Mr. R. Lazor on July 16, 1969 along the Dog Lake Fire Tower Road near Tallahassee, Fla. (Lazor no. 3742), was extracted with $CHCl_3$ and worked up in the usual manner.[15] The crude gum, wt 15 g, was chromatographed over 500 g of silicic acid (Mallinckrodt 100 mesh), 50-ml fractions being collected. The $CHCl_3$–MeOH (3%) eluates (fractions 10–15) gave a gummy residue which was fairly homogeneous and was purified by repeated preparative TLC over silica gel (Merck PF 254–356) using $CHCl_3$–MeOH (6%) to give pure acanthospermal A (**1a**, 1.1 g) as a colorless gum which could not be induced to crystallize: $[\alpha]_{Hg}^{25}$ −54° (c 0.328, $CHCl_3$); CD curve $[\theta]_{300}$ 0, $[\theta]_{250}$ −8590, $[\theta]_{235}$ −31500, $[\theta]_{224}$ −54400, $[\theta]_{215}$ −401100, $[\theta]_{205}$ 0 (last reading); ir bands at 3510 (–OH), 1770, 1620 (conjugated lactone), 1740, 1730 (esters), 1690 (conjugated aldehyde), 1460, 1065, 990, and 880 cm^{-1}; uv strong end absorption rising from 250 nm onwards (ϵ_{230} 8700, MeOH). For unknown reasons, the carbon analysis was consistently low, but the high-resolution mass spectrum afforded the correct composition.

Anal. Calcd for $C_{23}H_{30}O_8$: C, 63.58; H, 6.96; O, 29.46; mol wt, 434.1940. Found: C, 61.58; H, 6.64; O, 29.01; mol wt, 434.1975 (MS).

Extraction of *Acanthospermum hispidum*. Above-ground parts of *A. hispidum* DC., wt 5 kg, collected by Mr. R. F. Doren on August 9, 1972 in Gadsden County, Fla. (Doren no. 1500), was extracted with $CHCl_3$ and worked up in the usual manner. The crude gum, wt 10 g, was dissolved in $CHCl_3$ and chromatographed over 400 g of silicic acid, 50-ml fractions being collected. The $CHCl_3$–MeOH (2%) eluates gave a gummy residue, wt 1 g, which appeared to be reasonably homogeneous and was purified by preparative TLC (silica gel, $CHCl_3$–MeOH, 6%) to give 0.6 g of acanthospermal B (**4a**) as a colorless gum: $[\alpha]_{Hg}^{25}$ −33° (c 0.092, $CHCl_3$); CD curve $[\theta]_{300}$ 0, $[\theta]_{250}$ −8940, $[\theta]_{235}$ −24600, $[\theta]_{224}$ −40200, $[\theta]_{215}$ −29100, $[\theta]_{208}$ 0 (last reading); ir bands at 3480 (–OH), 1750, 1630 (conjugated lactone), 1740, 1730 (esters), 1685 (conjugated aldehyde), 1450, 1370, 1130, 990, and 910 cm^{-1}; uv strong end absorption (ϵ_{230} 14000).

Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.59; H, 6.65; O, 29.85; mol wt, 420.1783. Found: C, 62.85; H, 6.71; O, 30.44; mol wt, 420.1766 (MS).

Preparation of 1b and 4b. Acetylation of 0.1 g of **1a** in 1 ml of pyridine and 1 ml of acetic anhydride followed by the usual workup gave a gum (**1b**, 0.06 g) which was purified by preparative TLC (silica gel, $CHCl_3$–MeOH, 4%) and had ir bands at 1770, 1740, 1690, 1620, 1220, 1150, and 990 cm^{-1}. The low-resolution mass spectrum had significant peaks at *m/e* 390 (M^+), 348 (M − C_2H_2O), 330 (M − $C_2H_4O_2$), 319 (M − C_2H_2O − CHO), 302 (M − $C_4H_8O_2$), 260 (M − C_2H_2O − $C_4H_8O_2$), 242 (base peak, M − $C_4H_8O_2$ − $C_2H_4O_2$), 231 (M − $C_4H_8O_2$ − C_2H_2O − CHO), 213 (M − $C_4H_8O_2$ − $C_2H_4O_2$ − CHO), and 71 (C_4H_7O).

Anal. Calcd for $C_{21}H_{26}O_7$: 64.60; H, 6.71; O, 28.68. Found: C, 63.82; H, 6.75; O, 28.27.

Acetylation of 0.05 g of **4a** in the same manner and purification of the crude product by preparative TLC ($CHCl_3$–MeOH, 4%) gave **4b** as a gum. It had ir bands at 1770, 1740, 1690, 1620, 1360, 1230, and 990 cm^{-1}.

Anal. Calcd for $C_{24}H_{30}O_9$: C, 62.33; H, 6.54; O, 31.13. Found: C, 61.62; H, 6.42; C, 30.50.

Preparation of 2 and 5. A solution of 0.1 g of **1a** in 10 ml of anhydrous MeOH containing 0.08 g of CH_3ONa was stirred at room temperature in a nitrogen atmosphere, the reaction being monitored by TLC. After 1 hr, when the starting material had disappeared completely, the solution was acidified with dilute acetic acid, diluted with water, and extracted with ethyl acetate. The washed and dried extract was evaporated and the residue purified by preparative TLC ($CHCl_3$–MeOH, 6%). The gummy product (**2**, 0.03 g) had ir bands at 1770–1720 (broad), 1690, 1620, 1460, 1390, 1310, and 990 cm^{-1}. The mass spectrum exhibited significant peaks at *m/e* 394 (M^+), 365 (M − CHO), 306 (M − $C_4H_8O_2$), 277 (M − $C_4H_8O_2$ − CHO), 71 (C_4H_7O), and 43 (base peak).

Anal. Calcd for $C_{21}H_{30}O_7 \cdot \frac{1}{2}H_2O$: C, 62.53; H, 7.69; O, 29.75. Found: C, 62.88; H, 7.41; O, 29.71.

Treatment of 0.06 g of **4a** with MeOH–MeONa in a similar fashion and purification of the product by preparative TLC ($CHCl_3$–

MeOH, 5%) gave 22 mg of gummy **5**, ir bands at 3510, 1770, 1730, 1690, and 990 cm^{-1}. The mass spectrum exhibited significant peaks at *m/e* 424 (M^+), 395 (M − CHO), 322 (M − $C_5H_{10}O_2$), 304 (M − $C_5H_{10}O_2$ − H_2O), 293 (M − $C_5H_{10}O_2$ − CHO), 85 (base peak, C_5H_9O), and 57 (C_4H_9).

Anal. Calcd for $C_{22}H_{30}O_8$: mol wt, 424.2097. Found: mol wt, 424.2106 (MS).

Acanthospermal A Epoxide (3). A solution of 0.05 g of **1a** in 5 ml of $CHCl_3$ was stirred with 0.05 g of *m*-chloroperbenzoic acid at room temperature for 48 hr and extracted with $CHCl_3$. The extracted was washed with sodium metabisulfite and water, dried, and evaporated. Purification of the crude product by preparative TLC ($CHCl_3$–MeOH, 8%) yielded **3** as a gum, ir bands at 3500, 1770, 1730, 1690, 1620, and 990 cm^{-1}. The mass spectrum exhibited significant peaks at *m/e* 450 (M^+), 362 (M − $C_4H_8O_2$), 347 (M − $C_4H_7O_3$), 276 (M − C_4H_7O − $C_4H_7O_3$), 260 (M − $C_4H_7O_3$ − $C_4H_7O_2$), 71 (C_4H_7O), 59 and 43 (base peak).

Anal. Calcd for $C_{23}H_{30}O_9$: mol wt, 450.1890. Found: mol wt, 450.1894 (MS).

$NaBH_4$ Reductions of 1a and 4a. A solution of 0.05 g of **1a** and 0.05 g of $NaBH_4$ in 10 ml of MeOH was stirred at 0° for 4 hr, acidified with dilute acetic acid, evaporated at reduced pressure, diluted with water, and extracted with ethyl acetate. The washed and dried extract was evaporated and the residue was purified by preparative TLC ($CHCl_3$–MeOH, 8%) to give **7** as a gum, ir bands at 3540, 3500, 1770, 1740, 1460, 1370, and 990 cm^{-1}. The mass spectrum exhibited significant peaks at *m/e* 438 (M^+), 350 (M − $C_4H_8O_2$), 324 (M − $C_4H_8O_3$), 316 (M − $C_4H_8O_3$ − H_2O), 246 (M − $C_4H_8O_2$ − $C_4H_8O_3$), 228 (base peak, M − $C_4H_8O_2$ − $C_4H_8O_3$ − H_2O), 71, 59, and 43.

Anal. Calcd for $C_{23}H_{34}O_8$: mol wt, 438.2253. Found: mol wt, 438.2257 (MS).

Reduction of 0.1 g of **4a** with 0.1 g of $NaBH_4$ followed by work-up in the same way gave, after preparative TLC ($CHCl_3$–MeOH, 8%), **8** as a gum, ir bands at 3540, 3490, 1770, 1760, 1730, 1460, 1230, and 990 cm^{-1}. The mass spectrum exhibited significant peaks at *m/e* 424 (M^+), 322 (M − $C_5H_{10}O_2$), 280 (M − $C_5H_{10}O_2$ − C_2H_2O), 262 (M − $C_5H_{10}O_2$ − $C_2H_4O_2$), 244 (M − $C_5H_{10}O_2$ − $C_2H_4O_2$ − H_2O), 85 (C_5H_9O), 57 (base peak), and 43.

Anal. Calcd for $C_{22}H_{32}O_8$: mol wt, 424.2097. Found: mol wt, 424.2102 (MS).

Oxidation of 4a to 6. A solution of 0.05 g of **4a** in 10 ml of spectral grade $CHCl_3$ was stirred at room temperature with 0.1 g of active MnO_2, the reaction being monitored by TLC. After 24 hr, when the reaction did not appear to proceed further, the mixture was filtered and the precipitate washed repeatedly with $CHCl_3$. The combined filtrate and washings were evaporated and the residue developed as a preparative TLC plate using $CHCl_3$–MeOH (6%) as solvent. The major band yielded 40 mg of starting material. A minor band yielded 6 mg of the dialdehyde **6** as a gum, ir bands at 1770, 1730, 1690, 1680, 1460, 1240, and 1000 cm^{-1}. The mass spectrum exhibited significant bands at *m/e* 360 (M − 2CHO), 258 (360 − $C_5H_{10}O_2$), 85 (C_5H_9O), and 57.

Anal. Calcd for $C_{22}H_{26}O_8$: mol wt, 418.1628. Found: mol wt, 418.1632 (MS).

Registry No.—**1a**, 56689-33-9; **1b**, 56679-16-4; **2**, 56679-17-5; **3**, 56679-18-6; **4a**, 56679-19-7; **4b**, 56679-20-0; **5**, 56679-21-1; **6**, 56679-22-2; **7**, 56679-23-3; **8**, 56679-24-4.

References and Notes

(1) This work was supported in part by Grant CA-13121 from the U.S. Public Health Service through the National Cancer Institute.
(2) W. Herz and S. V. Bhat, *Phytochemistry*, **11**, 1829 (1972).
(3) In $CDCl_3$ this signal appeared at 6.80 ppm. A similarly large diamagnetic shift on passing from $CDCl_3$ to C_6D_6 was observed earlier for H-2 of frutescin.[2]
(4) Since the results of spin-decoupling experiments on **4a** were similar to those performed on **1a**, they are not discussed in detail.
(5) For references see W. Herz and R. P. Sharma, *J. Org. Chem.*, **40**, 192 (1975).
(6) The proximity of the H-1 signal to H-8 (in $CDCl_3$) and to H-13b (in C_6D_6) interfered with attempts to verify the expected nuclear Overhauser effect between H-1 and H-14.
(7) N. H. Fischer, R. Wiley, and J. D. Wander, *J. Chem. Soc., Chem. Commun.* 137 (1972); S. Neidle and D. Rogers, *ibid.*, 140 (1972).
(8) Other members of this subgroup are polydalin and uvedalin,[9] enhydrin,[10] maculatin,[11] and frutescin.[2]
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(15) W. Herz and G. Hogenauer, *J. Org. Chem.*, **27**, 905 (1962).

Synthesis of Tabtoxinine-δ-lactam

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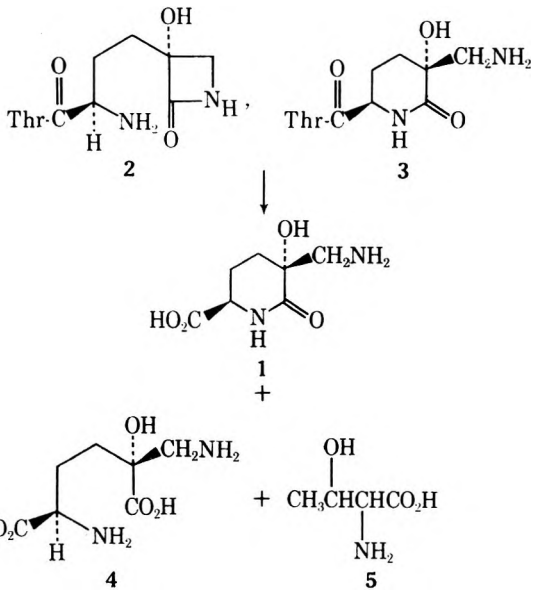
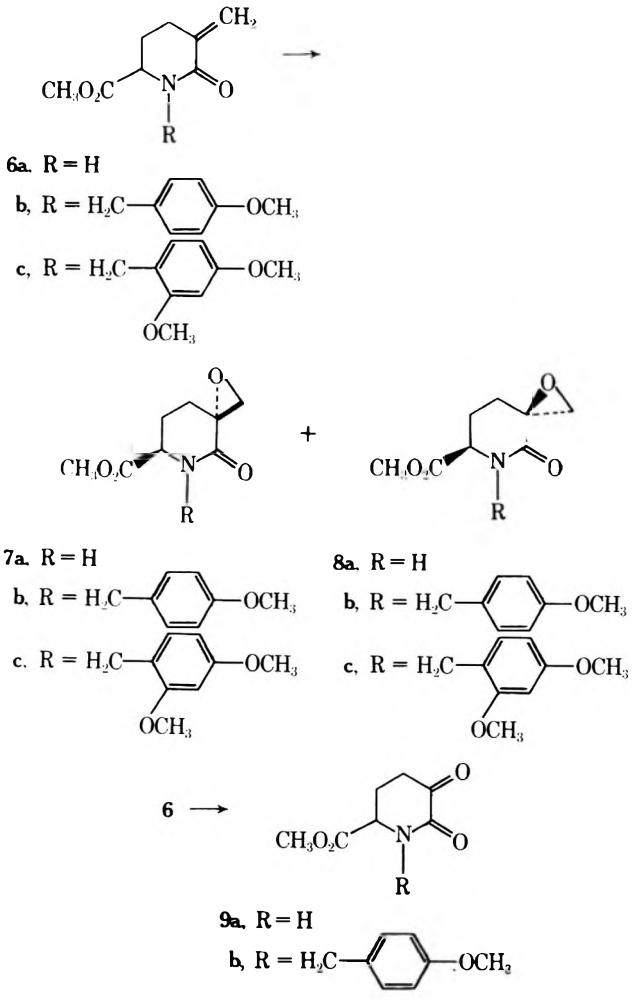
The synthesis is described of tabtoxinine-δ-lactam, an amino acid produced by various Pseudomonad species and also formed on hydrolysis of tabtoxin. The key intermediate in the synthesis is 1-anisyl-6-methoxycarbonyl-3-methylene-2-piperidone, which is easily obtained by application of the α-methylenelactam rearrangement to dimethyl 1-anisyl-2,5-piperidinedicarboxylate. Epoxidation gave a mixture of cis and trans oxides which were individually treated with ammonia. From the trans epoxide, the major isomer, the corresponding 3-aminomethyl-3-hydroxy compound was isolated. Removal of the anisyl protecting group gave the amino acid, *cis*-3-aminomethyl-6-carboxy-3-hydroxy-2-piperidone, identical with tabtoxinine-δ-lactam. This synthesis confirms the structure of, and establishes the aminomethyl and carboxy groups as cis in, the natural amino acid.

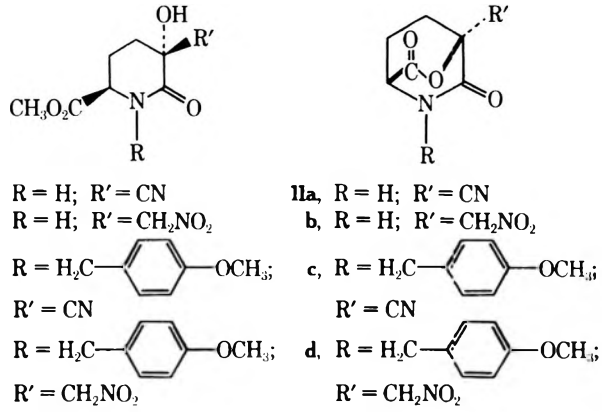
Tabtoxinine-δ-lactam (**1**) is an amino acid produced by various Pseudomonad species and is one of the compounds found in the hydrolysis of tabtoxin (**2**) or isotabtoxin (**3**).[1,2] The other hydrolysis products are tabtoxinine (**4**) and threonine (**5**).[1-3] Tabtoxin (**2**), the chlorosis-inducing exotoxin produced by *Pseudomonas tabaci, P. coronafaciens*, and other phytopathogenic *Pseudomonas*, is the component responsible for the toxicity of these bacteria to various plants (e.g., tobacco, soybean, oat, timothy). Tabtoxin (**2**) is relatively unstable, and at room temperature and pH 7 the biological activity of toxic solutions decreases with a half-life of about 1 day[3] as ready translactamization occurs to the more stable and nontoxic δ-lactam isomer, isotabtoxin (**3**).[1,3] Presented here is the total synthesis of (±)-tabtoxinine-δ-lactam (**1**) which further confirms the structure assigned to isotabtoxin (**3**) and to tabtoxin (**2**), and establishes the relative stereochemistry as shown in structures **1**, **2**, **3**, and **4**.



Results and Discussion

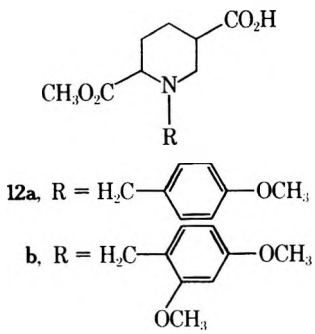
A key intermediate for the synthesis of tabtoxinine-δ-lactam (1) appeared to be an α-methylenelactam of the general type 6. Epoxidation of these α-methylenelactams for which there was precedent[4,5] would then yield the epoxides 7 and 8. Opening of these epoxides by attack at the least substituted carbon with ammonia or an amine would afford the desired lactam 1 or some derivative of it. Alternately, these α-methylenelactams 6 can be ozonolyzed to the corresponding α-ketolactams 9,[4] which potentially can





be elaborated with hydrogen cyanide or nitromethane to yield the adducts 10 and/or 11. Reduction of the adducts 10 would then yield the α-hydroxy-α-aminomethyllactam 1 or some derivative of it. Also, the α-ketolactams could be treated with dimethyloxosulfonium methylide to produce the epoxides 7 and/or 8.

Preparation of the α-methylenelactams 6 appeared to offer an ideal application of the α-methylenelactam rearrangement, i.e., 12 → 6.[6] Since the rearrangement occurs

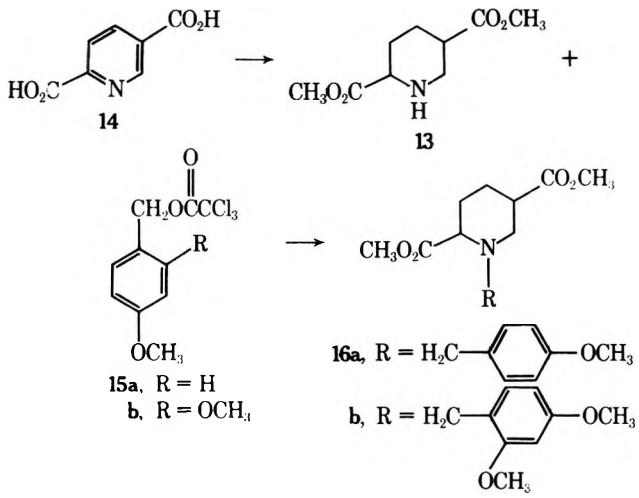


only when the amino group in the starting cyclic β-amino acid is tertiary, the preparation of the N-substituted amino acids 12a and 12b was undertaken. The anisyl group (An) and the 2,4-dimethoxybenzyl group (Dmb) were chosen as the nitrogen protecting groups because they did not interfere with the rearrangement[6] and they are easily removable at the lactam stage[7] to afford the desired NH lactams.

Preparation of these cyclic β-amino acids 12 was accomplished by first reducing isocinchomeronic acid (14) and esterifying the piperidine-2,5-dicarboxylic acid. Alkylation with anisyl chloride or 2,4-dimethoxybenzyl chloride afforded the *N*-benzyl derivatives 16a and 16b in very poor yields owing to the extreme ease with which these benzyl chlorides polymerize. To circumvent this problem, the trichloroacetates, which would be less prone to SN1 type dissociation, of anisyl alcohol 15a or 2,4-dimethoxybenzyl alcohol 15b were employed to give the corresponding benzyl derivatives 16a and 16b, now in respectable yields. Selective alkaline hydrolysis of the less hindered β ester then yielded the β amino acids 12a and 12b.

Rearrangement of the acid 12a and 12b to the respective α-methylenelactams 6b and 6c was readily accomplished in refluxing acetic anhydride. Debenzylation of either lactam 6b or 6c to afford 6a was effected in comparable yield by heating the benzyllactams in trifluoroacetic acid at reflux in the presence of anisole.[7]

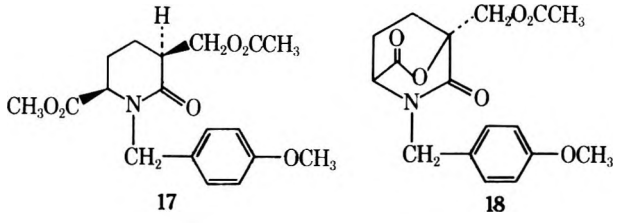
Reaction of the α-methylenelactam 6a with *m*-chloroperbenzoic acid (MCPBA) failed to yield the epoxides 7a or 8a in good yield. This is surprising since the corresponding demethoxycarbonyl compound (3-methylene-2-piperidone) is convertible to epoxide. Evidently overoxidation of the lactam 6a readily occurs because there is continued peracid



consumption beyond 100 mol %. The NMR spectrum of the crude reaction mixture revealed many new absorptions in the olefinic region, indicative of pyridone formation and perhaps initiated at the labile α-H at C-6.

Oxidation of α-methylenelactam **6b** with MCPBA proceeded smoothly to yield the trans and cis epoxides, **7b** and **8b**, in a ratio of 8:1, respectively. The epoxides could be separated via column chromatography (silica gel) with significant loss of material owing to the sensitivity of these epoxides to silica gel. Efforts to alter the epoxide ratio by varying the solvent (ether, ethyl acetate, and carbon tetrachloride) or by employing benzonitrile–hydrogen peroxide had little or no effect.

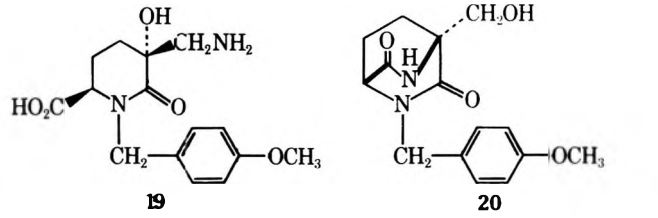
The stereochemistry of epoxides **7b** and **8b** was established by heating them in acetic acid. Trans epoxide **7b** exclusively afforded acetate **17**, and cis epoxide **8b** gave as the sole product the lactone acetate **18**.



Reaction of the *N*-2,4-dimethoxybenzyl α-methylenelactam **6c** with MCPBA also failed to produce any epoxide. Examination of the reaction mixture revealed almost complete disappearance of the aryl methoxy groups and the appearance of numerous new absorptions in the vinyl region. This evidence was suggestive of oxidation of the electron-rich dimethoxyphenyl nucleus to quinoid-type intermediates.

Ozonolysis of the α-methylenelactams **6a** and **6b** produced the respective α-ketolactams **9a** and **9b** in high yield. Reaction of the α-ketolactam **9b** with dimethyloxosulfonium methylide afforded the epoxides **7b** and **8b** in a ratio of 4:1; however, since other products were present, purification was difficult and this method for epoxide formation was not explored further. Treatment of the α-ketolactam **9b** with nitromethane and sodium methoxide afforded a nitro adduct which by NMR appeared to be the nitrolactone **11d** (appearance of a two-proton multiplet at δ 4.5–5.3 for the $-CH_2NO_2$ group and the clean disappearance of the methyl ester); however, the mass spectrum of this adduct was not commensurate with this structure. Treatment of the α-ketolactam **9b** with hydrogen cyanide produced what appeared to be the cyanohydrin **10c** but subsequent attempts to reduce it to the amine failed. Treatment of the α-ketolactam **9a** with dimethyloxosulfonium methylide failed to produce any epoxide, and reaction with nitromethane and sodium methoxide also failed to yield a nitro adduct.

As a result of these failures to obtain synthetically useful products from the α-ketolactams, we focused our efforts on the epoxide **7b**. Opening of the epoxide **7b** with ammonium hydroxide occurred at both carbons of the epoxide and provided the aminol acid **19** (with retention) and the diketopiperazine **20** (with inversion) in a ratio of 2:1, respectively.



An alternative explanation for the formation of diketopiperazine **20** would be initial formation of the amide from ester **7b** and intramolecular attack of the amide nitrogen to open the epoxide. This path is less likely since none of the corresponding amide of **19** was formed. Heating the aminol acid **19** in trifluoroacetic acid at reflux in the presence of anisole afforded tabtoxinine-δ-lactam (**1**).

The characterization of the synthetic material was totally consistent with its proposed structure. Most notable in its NMR spectrum is a set of doublets at δ 3.2 with a coupling constant of J = 13 Hz which is shown by the natural compound and is characteristic of these α-hydroxy-α-aminomethylcarbonyl systems.[1,3] Its mass spectra exhibited major peaks at $M^+ - H_2O$ and $M^+ - (CH_2{=}NH)$ as does the natural product and is also characteristic of these α-hydroxy-α-aminomethylcarbonyl systems.[1,3] Finally, our synthetic (±)-tabtoxinine-δ-lactam showed the same R_f values as the natural amino acid in three different systems.

Experimental Section[8]

Dimethyl 2,5-Piperidinedicarboxylate (13). A mixture of 2,5-pyridinedicarboxylic acid monohydrate (**14**, 37 g, 0.2 mol), concentrated ammonium hydroxide (20 ml), water (200 ml), and rhodium on alumina (10 g of 5%) was hydrogenated at 1–3 atm for 25 hr. The mixture was filtered through super-cel, the filtrate was evaporated to dryness, water (100 ml) was added to the residue, and the solution was again evaporated to dryness. To the residue was added methanol (500 ml) and concentrated sulfuric acid (30 ml), and this solution was heated to reflux for 16 hr. The solution was cooled and then poured into 400 ml of a cooled potassium carbonate solution. After the basic aqueous solution was extracted with chloroform (3 × 400 ml), the combined chloroform extracts were dried ($MgSO_4$) and then evaporated to an oily residue which was distilled to produce 32 g (80%) of the dimethyl ester **13**, bp 87–90° (0.1 mm) [lit.[9] bp 104–106° (0.4 mm)].

***p*-Methoxybenzyl Trichloroacetate (15a).** To a solution of anisyl alcohol (13.8 g, 0.1 mol) and *N,N*-dimethylaniline (12.1 g, 0.1 mol) in 150 ml of toluene at 0° was added trichloroacetyl chloride (18.2 g, 0.1 mol) in 50 ml of toluene over a period of 30 min. After stirring for an additional 1 hr at room temperature, the reaction mixture was poured into 200 ml of ice–water and the organic layer was washed sequentially with 10% sulfuric acid and aqueous sodium bicarbonate. After drying ($MgSO_4$), the toluene solution was evaporated to afford a quantitative yield of the trichloroacetate **15a**: NMR δ 3.80 (s, 3 H), 5.32 (s, 2 H), 6.86 (d, 2 H, J = 9 Hz), 7.28 (d, 2 H, J = 9 Hz). This crude acetate was used without further purification in the alkylation reaction; an analytical sample was obtained by column chromatography (silica gel, 1:1 hexane–ether, R_f 0.73).

Anal. Calcd for $C_{10}H_9O_3Cl_3$: C, 42.4; H, 3.2. Found: C, 42.4; H, 3.0.

2,4-Dimethoxybenzyl Trichloroacetate (15b). The acetate **15b** was prepared in a manner analogous to the procedure described above using 2,4-dimethoxybenzyl alcohol in place of anisyl alcohol. This acetate is relatively unstable and exhibits a high propensity to polymerize when not in solution. Thus it must be used

immediately or stored in the cold as a solution: NMR (CCl_4) δ 4.64 (s, 3 H), 4.70 (s, 3 H), 5.25 (s, 2 H), 6.25–6.46 (m, 2 H), 7.10–7.30 (m, 1 H); ir (neat) 1760 cm^{-1}.

Dimethyl 1-(*p*-Methoxybenzyl)-2,5-piperidinedicarboxylate (16a). A mixture of the diester **13** (15 g, 75 mmol), potassium carbonate (13.8 g, 0.1 mol), the trichloroacetate **15a** (29 g, 0.1 mol), and 400 ml of toluene was heated at reflux under nitrogen for 70 hr. The reaction mixture was cooled, the toluene was removed in vacuo, the residue was dissolved in chloroform (200 ml), and the chloroform solution was washed first with 200 ml of a potassium carbonate solution and then with 200 ml of 10% HCl. Evaporation of the chloroform solution produced 15.6 g of the crude piperidine hydrochloride as a yellow solid. Boiling this crude precipitate in hexane furnished white crystals which on recrystallization from 150 ml of ethanol afforded 12.5 g (52%) of analytically pure **16a** hydrochloride: mp 168–170°; NMR δ 1.3–2.8 (m, 5 H), 3.3–3.9 (m, 4 H), 3.64 (s, 3 H), 3.74 (s, 6 H), 4.23–4.44 (m, 2 H), 6.70 (d, 2 H, J = 9 Hz), 7.50 (d, 2 H, J = 9 Hz); mass spectrum m/e 321 (M^+ − HCl).

Anal. Calcd for $C_{17}H_{24}NO_5Cl$: C, 57.1; H, 6.8; N, 3.9. Found: C, 57.3; H, 6.8; N, 3.9.

An analytical sample of the free amine, obtained by treatment of the hydrochloride with K_2CO_3, was obtained by GC (glass column 10 ft 3% OV-17, 240°C, flow rate 50 ml/min, retention time 5.7 min): NMR δ 1.4–3.5 (m, 8 H), 3.56 (s, 3 H), 3.64 (s, 3 H), 3.70 (s, 3 H), 3.57–3.69 (m, 2 H), 6.75 (d, 2 H, J = 9 Hz), 7.15 (d, 2 H, J = 9 Hz).

Anal. Calcd. for $C_{17}H_{23}NO_5$: C, 63.5; H, 7.2; N, 4.4. Found: C, 63.7; H, 7.3; N, 4.4.

Dimethyl 1-(2,4-Dimethoxybenzyl)-2,5-piperidinedicarboxylate (16b). A mixture of the amino ester **13** (32 g, 0.16 mol), the trichloroacetate **15b** (62 g, 0.2 mol), potassium carbonate (28 g, 0.2 mol), and 400 ml of toluene was heated at reflux under nitrogen for 4 hr. The reaction mixture was cooled, washed with 200 ml of an aqueous potassium carbonate solution, dried ($MgSO_4$), and evaporated in vacuo to furnish an oily residue. Chromatography of the residue on 1600 g of silica gel employing 4% methanol–chloroform as the eluent produced 44 g (64%) of the alkylated amine **16b**: TLC (2% CH_3OH–$CHCl_3$) R_f 0.4; NMR (CCl_4) δ 1.42–3.8 (m, 8 H), 3.55 (s, 2 H), 3.61 (s, 3 H), 3.69 (s, 9 H), 6.20–6.42 (m, 2 H), 6.92–7.24 (m, 1 H); ir (neat) 1730, 1625, 1600 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.5; H, 7.2; N, 4.0 Found: C, 61.6; H, 7.2; N, 4.1.

1-Anisyl-6-methoxycarbonyl-3-methylene-2-piperidone (6b). A solution of the piperidine hydrochloride **16a** (3.47 g, 9.65 mmol), sodium hydroxide (0.80 g, 20 mmol), methanol (100 ml), and water (5 ml) was stirred at room temperature for 20 hr. The solution was evaporated to dryness in vacuo, and the residue along with triethylamine (10 g, 0.1 mol) and acetic anhydride (100 ml) was heated at reflux under nitrogen for 4 hr. The acetic anhydride and triethylamine were removed in vacuo, the residue was dissolved in chloroform and washed with water, and the oil obtained after evaporation of the chloroform was chromatographed on 80 g of silica gel employing 1:1 hexane–ethyl acetate as the eluent, yield 2.2 g (79%) of lactam **6b**: TLC (1:1 hexane–ethyl acetate) R_f 0.43; NMR δ 1.6–2.2 (m, 2 H), 2.22–2.6 (m, 2 H), 3.60 (s, 3 H), 3.67 (s, 3 H), 3.86–4.06 (m, 2 H), 5.13–5.34 (m, 1.5 H), 5.40 (s, 0.5 H), 6.30–6.45 (m, 1 H), 6.69 (d, 2 H, J = 9 Hz), 7.03 (d, 2 H, J = 9 Hz). An analytical sample was obtained by GC (glass column, 10 ft, 3% OV-17, 240°, flow rate 50 ml per min, retention time 6.2 min).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6; N, 4.8. Found: C, 66.2; H, 6.8; N, 4.9.

Methoxycarbonyl-3-methylene-2-piperidone (6a). A solution of the α-methylenelactam **6b** (4.8 g, 16.5 mmol), anisole (4.3 g, 40 mmol), and trifluoroacetic acid (100 g) was heated at reflux under nitrogen for 48 hr. After the trifluoroacetic acid and anisole were removed in vacuo, the residue thus obtained was chromatographed on 300 g of silica gel using ethyl acetate as the eluent to produce 2.1 g (75% yield) of the α-methylenelactam **6a**: TLC (ethyl ether) R_f 0.24; NMR (CCl_4) δ 1.84–2.3 (m, 2 H), 2.31–2.7 (m, 2 H), 3.67 (s, 3 H), 4.0–4.25 (m, 1 H), 5.1–5.26 (m, 1 H), 5.95–6.15 (m, 1 H), 7.57–7.58 (s, 1 H); ir (neat) 1730, 1660, 1610 cm^{-1}. An analytical sample was obtained by GC (glass column, 10 ft, 3% OV-17, 190°, flow rate 50 ml/min, retention time 6.0 min).

Anal. Calcd for $C_8H_{11}NO_3$: C, 56.8; H, 6.6; N, 8.3. Found: C, 56.6; H, 6.4; N, 8.2.

1-Anisyl-3-keto-6-methoxycarbonyl-2-piperidone (9b). Into a solution of the α-methylenelactam **6b** (0.90 g, 3 mmol) and methanol (50 ml) at −78° was passed a stream of ozone for 40 min (O_3 content, 0.1 mmol/min). Dimethyl sulfide (1 ml) was added to the solution, which was left standing for 22 hr at −78° under nitrogen. After warming to room temperature, the methanol and excess dimethyl sulfide were evaporated, the residue was dissolved in 100 ml of ether, and the ethereal solution was washed with water (3 × 50 ml). Evaporation of the ethereal solution after drying ($MgSO_4$) and chromatography of the crude material on 50 g of silica gel employing 5% methanol–ethyl acetate as the eluent gave 0.42 g of purified α-ketolactam which crystallized on standing. Recrystallization from methylene chloride–ethyl ether afforded analytically pure α-ketolactam **9b**: mp 81–83°; mass spectrum m/e 291 (M^+); NMR δ 2.0–2.66 (m, 4 H), 3.50 (s, 3 H), 3.60 (s, 3 H), 3.5–4.3 (m, 2 H), 4.84 (d, 1 H, J = 15 Hz), 6.55 (d, 2 H, J = 8 Hz), 6.95 (d, 2 H, J = 8 Hz); ir (Nujol) 1735, 1680 cm^{-1}.

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.8; H, 5.9; N, 4.8. Found: C, 61.7; H, 5.9; N, 4.9.

3-Keto-6-methoxycarbonyl-2-piperidone (9a). Ozone (flow rate 0.1 mmol per min) was passed through a solution of the α-methylenelactam **6a** (1.1 g, 6.5 mmol) and methanol (50 ml) at −78° for 65 min. Dimethyl sulfide (5 ml) was added, and the solution was left under nitrogen at −78° for 22 hr. Evaporation of the methanol and excess dimethyl sulfide afforded the crude α-ketolactam **9a**, which was chromatographed on 100 g of silica gel using 10% methanol–ethyl acetate as the eluent, yield 0.19 g (17%) of the purified α-ketolactam **9a**: mass spectrum m/e 171 (M^+); NMR δ 2.2–2.8 (m, 4 H), 3.73 (s, 3 H), 4.2–4.5 (m, 1 H), 8.0–8.2 (s, 1 H).

Anal. Calcd for $C_7H_9NO_4$: C. 49.1; H, 5.3; N, 8.2. Found: C, 48.9; H, 5.3; N, 8.2.

6-Methoxycarbonyl-3-epoxymethylene-1-(*p*-methoxybenzyl)-2-piperidone (7b) and 8b. A solution of the α-methylenelactam **6b** (5.0 g, 17 mmol), *m*-chloroperbenzoic acid (6.0 g, 34 mmol), and methylene chloride (100 ml, distilled from P_2O_5) was stirred at room temperature for 40 hr. A precipitate of *m*-chlorobenzoic acid was obtained after 24 hr. The mixture was diluted with chloroform (100 ml), and this methylene chloride–chloroform solution was washed with a sodium bisulfite solution (5.2 g in 100 ml of water, 50 mmol) and then with a saturated sodium bicarbonate solution. After drying ($MgSO_4$), the chloroform was evaporated to yield 5.2 g of the crude epoxides present in a ratio of 8:1, **7b** to **8b**, by NMR. The epoxides were separated by column chromatography (silica gel, 400 g, Camag D-O) with ethyl acetate as the eluent.

Trans epoxide **7b**: yield 3.6 g (69%); TLC (ethyl acetate) R_f 0.7; NMR δ 1.5–2.5 (m, 4 H), 2.60 (d, 1 H, J = 7 Hz), 3.40 (d, 1 H, J = 7 Hz), 3.58–3.67 (m, 3 H), 3.69 (s, 3 H), 3.70–4.18 (m, 2 H), 5.07–5.43 (m, 1 H), 6.70 (d, 2 H, J = 9 Hz), 7.05 (d, 2 H, J = 9 Hz).

Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.9; H, 6.3; N, 4.6. Found: C, 62.7; H, 6.5; N, 4.5.

Cis epoxide **8b**: yield 0.92 g (17.7%); TLC (ethyl acetate) R_f 0.6; NMR ($CDCl_3$) δ 1.46–2.4 (m, 4 H), 2.63 (d, 1 H, J = 7 Hz), 3.20 (d, 1 H, J = 7 Hz), 3.70 (s, 3 H), 3.74 (s, 3 H), 3.75–4.15 (m, 2 H), 5.09 (s, 0.5 H), 5.33 (s, 0.5 H), 6.72 (d, 2 H, J = 9 Hz), 7.06 (d, 2 H, J = 9 Hz); high-resolution mass spectrum, calcd for $C_{16}H_{19}NO_5$ (M^+), 305.1263; found, 305.1264.

3-Acetoxymethyl-6-methoxycarbonyl-3-hydroxy-1-(*p*-methoxybenzyl)-2-piperidone (17). A solution of epoxide **7b** (0.30 g, 1 mmol) and acetic acid (25 ml) was heated at reflux under nitrogen for 16 hr. The solution was cooled, and the acetic acid was removed under reduced pressure. The residue was dissolved in chloroform (25 ml) and washed with a solution of saturated sodium bicarbonate (20 ml). After drying ($MgSO_4$), the chloroform was evaporated to afford 0.37 g (100%) of the acetate **17**, crystallized from hexane–ethyl ether: mp 110–112°; mass spectrum m/e 365 (M^+); NMR δ 1.62–2.6 (m, 4 H), 1.97 (s, 3 H), 3.3–4.2 (m, 4 H), 3.61 (s, 3 H), 3.69 (s, 3 H), 5.0–5.4 (m, 1 H), 6.63 (d, 2 H, J = 9 Hz), 7.02 (d, 2 H, J = 9 Hz).

Anal. Calcd for $C_{18}H_{23}O_7N$: C, 59.2; H, 6.4; N, 3.8. Found: C, 59.2; H, 6.3; N, 3.9.

3-Acetoxymethyl-6-carboxy-3-hydroxy-1-(*p*-methoxybenzyl)-2-piperidone Lactone (18). The epoxide **8b** was treated as above with acetic acid to quantitatively yield the lactone acetate **18**: NMR δ 1.6–2.4 (m, 4 H), 2.13 (s, 3 H), 3.6–4.8 (m, 3 H). 3.77 (s, 3 H), 4.57 (s, 2 H). 6.77 (d, 2 H, J = 9 Hz), 7.12 (d, 2 H, J = 9 Hz); high-resolution mass spectrum, calcd for $C_{17}H_{19}O_6N$ (M^-), 333.1212; found, 333.1207.

Opening of Epoxide 7b with Ammonia. 6-Carboxy-3-hydroxy-1-(*p*-methoxybenzyl)-3-aminomethyl-2-piperidone (19) and 3-Amino-6-carboxy-1-(*p*-methoxybenzyl)-3-hydroxymethyl-2-piperidone Lactam (20). A mixture of epoxide **7b** (3 g, 10 mmol) and concentrated ammonium hydroxide (40 ml) was stirred at room temperature for 3 days. The resulting homogeneous solution was evaporated to dryness in vacuo, water was

added to the residue, and the aqueous solution (pH 6–7) was extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and evaporated to afford 0.95 g (33%) of the diketopiperazine **20**, crystallized from ethanol: mp 171–173°; TLC (95% ethanol) R_f 0.55; mass spectrum *m/e* 290 (M^+), 291 ($M^+ + 1$); NMR δ 1.8–2.6 (m, 4 H), 3.34 (s, 2 H), 3.77 (s, 3 H), 3.7–4.0 (m, 1 H), 4.24 (d, 1 H, J = 13 Hz), 4.61 (s, 1 H), 4.90 (d, 1 H, J = 13 Hz), 6.43 (s, 1 H), 6.77 (d, 2 H, J = 7 Hz), 7.13 (d, 2 H, J = 7 Hz); ir (Nujol) 3380, 3300, 1670, 1650 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.0; H, 6.2; N, 9.6. Found: C, 61.9; H, 6.1; N, 9.6.

The aqueous layer was evaporated to dryness, and the residue (~2 g) was chromatographed on 150 g of silica gel using 3:1 1-propanol–water as the eluent to yield 1.6 g (54%) of the aminol **19**, crystallized from 95% ethanol: mp 206–208°; TLC (3:1 1-propanol–water, v/v, ninhydrin visualization) R_f 0.51; mass spectrum *m/e* 308 (M^+), 290 ($M^+ - H_2O$); NMR (D_2O) δ 1.6–2.2 (m, 4 H), 3.04 (d, 1 H, J = 13 Hz), 3.36 (d, 1 H, J = 13 Hz), 3.44–4.04 (m, 2 H), 3.64 (s, 3 H), 5.01 (s, 1 H), 5.25 (s, 1 H), 6.77 (d, 2 H, J = 9 Hz), 7.04 (d, 2 H, J = 9 Hz).

Anal. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.4; H, 6.5; N, 9.1. Found: C, 58.3; H, 6.5; N, 9.1.

Tabtoxinine-δ-lactam (1). A solution of the aminol **19** (200 mg, 0.65 mmol), anisole (400 mg, 3.7 mmol), and trifluoroacetic acid (5 ml) was heated at reflux for 44 hr under nitrogen. After cooling to room temperature, the excess trifluoroacetic acid was removed under reduced pressure, a solution (25 ml) of KH_2PO_4 (1 g) and K_2HPO_4 (1 g) was added to the residue, and the aqueous solution was extracted with chloroform. After again evaporating the aqueous layer to dryness, the resulting residue was digested in hot methanol. The hot methanolic mixture was filtered, and the filtrate evaporated to dryness. The residue thus obtained was chromatographed on silica gel (10 g) employing 3:1 1-propanol-water as the eluent to afford 0.080 g (66%) of (±)-tabtoxinine-δ-lactam (**1**). An analytical sample was obtained by dissolving the crude crystals in hot ethanol–water (1:1 v/v), allowing the solution to cool, and inducing crystal formation by the addition of acetone. Repetition of this procedure afforded the pure aminol **1**: mp 234–236°; TLC (3:1 1-propanol–water, ninhydrin visualization) R_f (silica gel Camag) 0.15; mass spectrum *m/e* 170 ($M^+ - H_2O$, 8.98% RA, 0.37% TI), 159 ($M^+ - CH_2{=}NH$, 29.14% RA, 1.20% TI), 43 (100.00% RA, 4.12% TI); NMR (D_2O) δ 1.70–2.35 (m, 4 H), 3.07 (d, 1 H, J = 13 Hz), 3.38 (d, 1 H, J = 13 Hz), 3.81–4.12 (m, 1 H).

Anal. Calcd for $C_7H_{12}N_2O_4$: C, 44.7; H, 6.4; N, 14.9. Found: C, 44.8; H, 6.2; N, 14.6.

The R_f's of the synthetic and natural material were identical in three different systems: (1) silica gel G, 2:1 1-propanol–water, R_f 0.24 (lit.[10] R_f 0.24); (2) Whatman No. 1, 2:1 1-propanol–water, R_f 0.23 (lit.[10] R_f 0.23); (3) Whatman No. 1, 4:1 phenol–water, R_f 0.49 (lit.[10] R_f 0.48).

Registry No.—**1**, 56599-17-8; **6a**, 56599-18-9; **6b**, 56599-19-0; **7b**, 56599-20-3; **8b**, 56599-21-4; **9a**, 56599-22-5; **9b**, 56599-23-6; **13**, 2207-52-5; **14**, 100-25-5; **15a**, 56599-24-7; **15b**, 56650-75-0; **16a**, 56599-25-8; **16a** HCl, 56599-26-9; **16b**, 56599-27-0; **17**, 56650-76-1; **18**, 56599-29-1; **19**, 56599-29-2; **20**, 56599-30-5; trichloroacetyl chloride, 76-02-8; anisyl alcohol, 105-13-5; 2,4-dimethoxybenzyl alcohol, 7314-44-5; ozone, 10028-15-6; *m*-chloroperbenzoic acid, 937-14-4.

References and Notes

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(7) F. Weygand, W. Steglich, J. Bjarnason, R. Akhtar, and N. Chytil, *Chem. Ber.*, **101**, 3623 (1968).
(8) Solvent evaporations were carried out in vacuo using a Berkeley rotary evaporator. All melting points are uncorrected. Infrared (ir) spectra were measured on a Perkin-Elmer 137 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained with a Varian T-60 spectrometer; peak positions are given as δ values in $CDCl_3$ (unless otherwise noted) downfield from tetramethylsilane as internal standard, expect that sodium trimethylsilylpropanesulfonate was used as internal standard in aqueous solutions. Mass spectra were obtained on an AEI MS-12 and high-resolution mass spectra were obtained on a CEC 21-110B spectrometer. Gas chromatography was performed on a Varian 90-P chromatograph. Thin layer chromatography (TLC) was performed on plates utilizing Camag D-5 silica gel unless otherwise specified. E. Merck silica gel 60 was employed for column chromatography. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.
(9) S. de Groot and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **80**, 944 (1961).
(10) Referred to as compound "282" in ref 2 and later shown to be identical with tabtoxinine-δ-lactam (**1**): ref 1.

General Methods of Alkaloid Synthesis. XI. Total Synthesis of the Sceletium Alkaloid A-4 and an Improved Synthesis of (±)-Mesembrine

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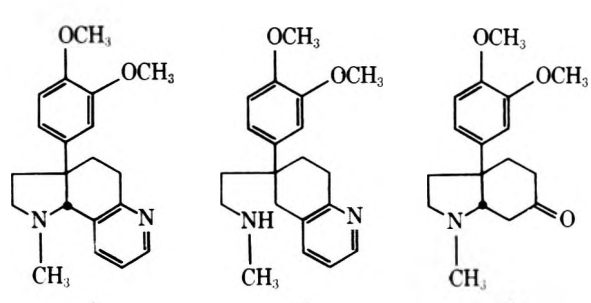
An efficient total synthesis of the pharmacologically interesting alkaloid Sceletium A-4 (**1**) is presented together with an improved synthesis of mesembrine (**3**). Key steps in these syntheses utilize the acid-promoted rearrangement of cyclopropylimine **9** to 2-pyrroline **10** and acid-catalyzed annelation of this intermediate with methyl vinyl ketone or methyl 5-oxohept-6-enoate.

Interest in the so-called Mesembrine alkaloids[3] has been renewed with the discovery[4–7] of several new bases found in various *Sceletium* species. Extracts of these plants are used by the natives of Southwest Africa in the preparation of a pharmacologically interesting drug known as "Channa" or "Koegoed". Since nearly all of the alkaloids from these plants which have been isolated thus far are not available in sufficient quantity for biological evaluation, we have been actively pursuing a program of total synthesis.[8,9] Of particular interest in the present study are the pyridine alkaloids Sceletium A-4 (**1**) and its seco analog tortuosamine (**2**).[6,7] These two substances represent completely new structural types and differ from the more common Mesembrine alkaloids such as mesembrine itself (**3**) by the interesting addition of a fused pyridine ring.



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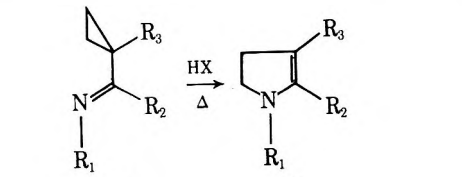
Our synthetic planning was dictated by two fundamental considerations. The first of these involves the previously demonstrated[8,9] utility of the acid-catalyzed rearrangement of cyclopropylimines (4) to 2-pyrrolines (5) and the annelation of these as well as other endocyclic enamines with methyl vinyl ketone or analogs thereof as effective methods for the generation of cis-fused[10] hydroindolones or hydroquinolones (6) common to a whole host of otherwise superficially unrelated alkaloid families. Secondly, from



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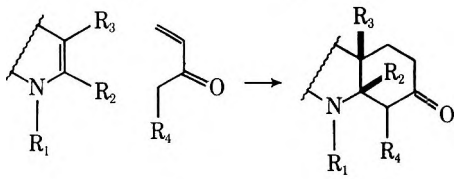

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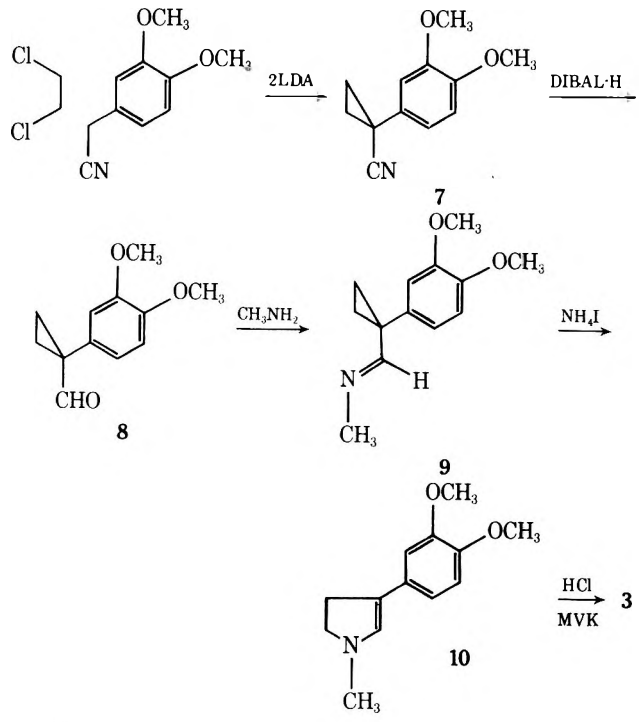
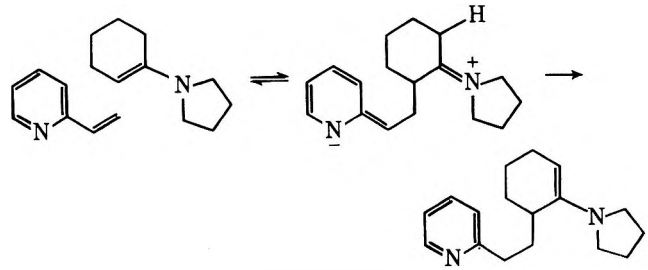
what we know about the probable mode of biosynthesis of these substances,[6] there appears to be a very distinct possibility that dihydropyridone 14 might also be a natural product—a possibility sufficiently attractive to prompt us to employ an appropriate intermediate (12) capable of transformation into this substance.

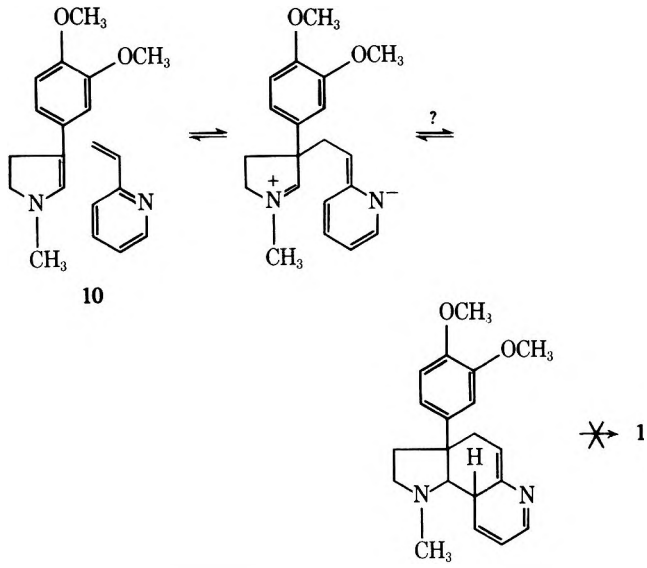
The synthesis of the required 2-pyrroline (10) was executed by methods described previously[8,9] with the very important difference that the cyclopropanation of 3,4-dimethoxybenzyl cyanide was improved dramatically by employing ethylene dichloride as the alkylating agent and lithium diisopropylamide (LDA) as the base instead of ethylene dibromide and lithium amide. In this fashion almost pure cyclopropane 7 was obtained without need for further purification. Selective reduction of this nitrile to the corresponding aldehyde (8) employing diisobutylaluminum hydride (DIBAL-H) and subsequent imine formation proceeded smoothly as did the ammonium iodide induced rearrangement of cyclopropylimine 9 to the required 2-pyrroline 10. Annelation of this intermediate with methyl vinyl ketone (MVK) employing the improved HCl-catalyzed procedure[9,11] provided racemic mesembrine (3) in vastly improved overall yield.



With substantial supplies of endocyclic enamine 10 available, we were now in a position to employ this important synthon in the synthesis of Sceletium A-4. In principle, this could be accomplished in a single step[12] by annelation with 2-vinylpyridine. This prospect appeared rather attractive, since it had been demonstrated previously[14] that *exo*cyclic enamines do react with 2-vinylpyridine in the manner outlined below. Thus, there appeared to be



ample precedence for the Michael addition step. However, in the case of *endo*cyclic enamine 10, after the initial Michael addition the proton transfer step is constitutionally impossible, thus rendering annelation a feasible possibility. Unfortunately, we have been unable to effect this desirable transformation under a variety of conditions.



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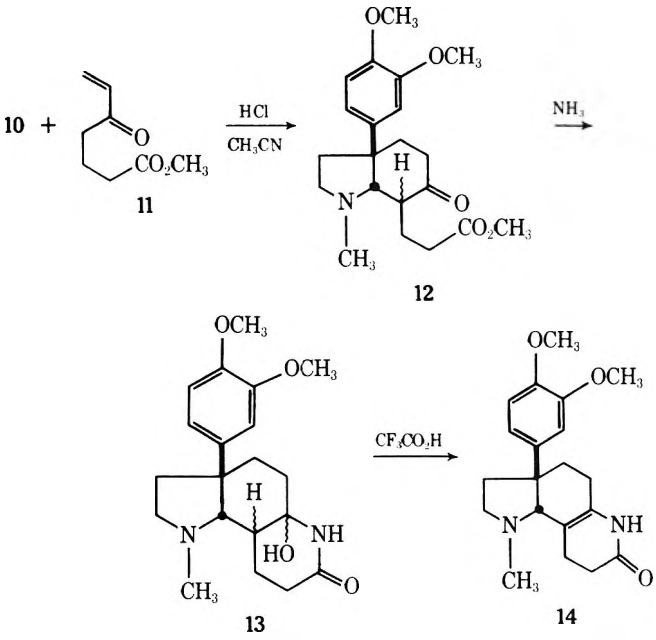
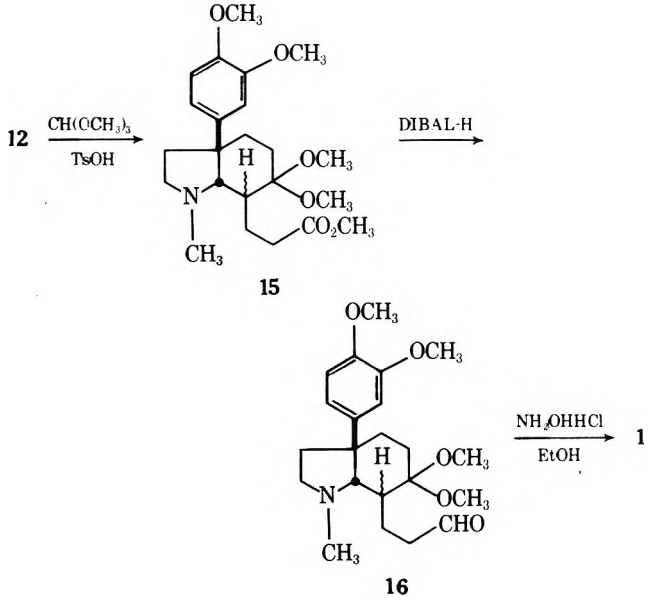
In contrast to this disappointing result, annelation of the hydrochloride salt of 10 with enone 11[15] in refluxing acetonitrile provided hydroindolone 12 as a readily separated and interconvertible mixture of epimers at C-3. The assignment of cis stereochemistry to the ring fusion is based on *all* previous annelations of this type[10] and ultimately on the success of the synthesis. Treatment of this epimeric mixture with ammonia in methanol smoothly transformed it into the isomeric carbinolamides (13) which, without purification, was dehydrated in neat CF_3CO_2H to dihydropyridone 14, thus completing the first synthesis of the basic nucleus of Sceletium A-4. The possibility mentioned above that this substance might also be a naturally occurring alkaloid is presently under investigation.[16]

Completion of the synthesis of Sceletium A-4 itself required adjustment of the oxidation state of the ester side chain in 12 to an aldehyde. This was accomplished in high yield by protection of the ketone as its dimethyl acetal (15)



and selective reduction of the ester with DIBAL-H. We had originally envisaged hydrolysis of the acetal back to the ketone, since it had been demonstrated previously[17] that 1,5-dicarbonyl systems can be converted to pyridines by treatment with hydroxylamine. We were pleasantly surprised to discover that the hydrolysis step was unnecessary—treatment of acetal **16** with hydroxylamine hydrochloride in re-



fluxing ethanol gave Sceletium A-4 directly identical in all respects with the natural product.[18]

Experimental Section

Infrared spectra were obtained on a Beckman IR-8 spectrometer. ^{1}H NMR spectra were secured from a Varian A-56/60 spectrometer in $CDCl_3$ using trimethylsilane as internal standard. Mass spectra were recorded on a Consolidated Electrodynamics Corp. 21-110 high-resolution instrument. Melting points and boiling points are uncorrected.

1-(3,4-Dimethoxyphenyl)cyclopropanecarbonitrile (7). Improved Procedure. To a cold solution of diisopropylamine (67.2 ml, 0.476 mol) in 700 ml of dry THF under N_2 was added an equivalent amount of *n*-butyllithium in hexane. The solution was stirred at 0° for 0.5 hr and then cooled to −76°. Dry hexamethylphosphoramide (88 ml, 0.515 mol) was added dropwise followed by 30 g (0.17 mol) of (3,4-dimethoxyphenyl)acetonitrile in 150 ml of THF after which the temperature was allowed to rise to −20° and 1,2-dichloroethane (70 ml, 0.89 mol) was added slowly. After addition was complete the mixture was cooled again to −76° and stirred overnight, allowing the temperature to rise slowly to 25°. The solvents were removed under reduced pressure and 200 ml of H_2O added cautiously to the residue. The mixture was extracted with benzene and washed with water (4 × 20 ml) and the solvent was removed in vacuo, leaving a dark mass which was sublimed (100°, 0.07 mm) providing 29.6 g (86%) of pure nitrile **7**.

Hydroindolone 12. The hydrochloride salt (290 mg, 1.33 mmol) of pyrroline **10** and methyl 5-oxohept-6-enoate (**11**, 625 mg, 4 mmol) were dissolved in 25 ml of dry acetonitrile and the mixture was refluxed for 24 hr, after which the solvent was removed under reduced pressure and the residue dissolved in benzene and extracted with dilute hydrochloric acid. The aqueous phase was neutralized with solid $NaHCO_3$ and extracted with CH_2Cl_2. After drying over Na_2SO_4 the solvent was removed and the residue chromatographed on neutral alumina (activity III) using ethyl acetate as eluent. Hydroindolone **12** (270 mg, 54%) was obtained as an oil: ir (neat) 1735, 1710 cm^{-1}; ^{1}H NMR major singlets at δ 6.9 (3 H), 3.93 (6 H), 3.68 (3 H), and 3.43 (3 H); mass spectrum *m/e* 375 (M^+), 344 ($M - OCH_3$), 302 ($M - C_3H_6O_2$), 219.

Carbinolamide 13. The keto ester **12** (227 mg, 0.605 mmol) was dissolved in dry methanol (5 ml) and placed in a pressure vessel at −78°. Approximately 5 ml of liquid NH_3 was condensed into the vessel, which was then sealed and allowed to warm to room temperature and the contents stirred magnetically until homogeneous. After 18 hr, the vessel was again cooled to −78°, opened, and allowed to warm up very slowly. Excess NH_3 and methanol were evaporated, leaving a yellow foam (230 mg, 100%). TLC (silica gel, CH_3OH) indicated that a minimum of three diastereomers were present. The foam crystallized from benzene–pentane as a white solid (mp 110–116°, with softening at 105°): ir (CH_2Cl_2) 1665 cm^{-1}; ^{1}H NMR δ 6.95 (m, 3 H), 3.86 (s, 6 H), the rest of the spectrum integrates to 19 H; mass spectrum *m/e* 360 (M^+), 342 ($M - H_2O$), 327, 251, 221, 219.

Dihydropyridone 14. The mixture of isomeric carbinolamides (**13**, 1.68 g, 4.67 mmol) was cooled in an ice bath and 15 ml of CF_3CO_2H was added slowly. The solution was stirred under N_2 at room temperature for 4.5 hr and the CF_3CO_2H removed in vacuo. The residue was dissolved in CH_2Cl_2 and extracted four times with 1 *N* HCl. Neutralization of the combined aqueous extracts with solid $NaHCO_3$ and extraction with CH_2Cl_2 provided 1.27 g (79%) of pure dihydropyridone **14** as a pale yellow oil: ir ($CHCl_3$) 3420, 1675, 1588, and 1511 cm^{-1}; ^{1}H NMR δ 7.52 (s, 1 H), 6.80 (s, 3 H), 3.92 (s, 6 H), 2.5 (s, 3 H); mass spectrum, calcd, 342.1943; found, 342.1972.

Acetal 15. Hydroindolone **12** (479 mg, 1.28 mmol) was dissolved in 4 ml of dry methanol containing 2 ml of trimethyl orthoformate and 342 mg (1.8 mmol) of *p*-toluenesulfonic acid and the resultant dark red solution stirred overnight. After addition of solid $NaHCO_3$, 15 ml of water was added and the solution extracted with benzene. Removal of the solvent in vacuo left 488 mg (90%) of essentially pure acetal: ir (neat) 1738, 1110, 1040 cm^{-1}; ^{1}H NMR δ 6.6–7.0 (m, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.54 (s, 3 H), 3.18 (s, 3 H), 3.12 (s, 3 H), 2.33 (s, 3 H); mass spectrum, calcd, 421; found, 390 ($M - CH_3O$).

Aldehyde 16. To a cooled (Dry Ice–acetone) solution of 298 mg (0.71 mmol) of acetal **15** in 20 ml of toluene was added slowly a pentane solution of diisobutylaluminum hydride (0.75 mmol). After stirring for 1 hr, 15 ml of a pH 2 sulfuric acid solution was carefully added and the mixture stirred for 0.5 hr. Methylene chloride was added and the mixture was neutralized with solid $NaHCO_3$ and extracted three times with methylene chloride. Removal of the solvent left 258 mg (92%) of crude aldehyde which was sufficiently pure for use in the next step: ir (neat) 1726, 1110, 1040 cm^{-1}; ^{1}H NMR δ 9.44 (t, 1 H), 6.5–7.0 (m, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.27 (s, 3 H), 3.22 (s, 3 H), 2.77 (s, 3 H).

(±)-Sceletium A-4 (1). A solution of 110 mg (0.28 mmol) of aldehyde **16** and hydroxylamine hydrochloride (70 mg, 1 mmol) in 4 ml of ethanol was refluxed under N_2 for 2 days. The solution was then made basic with 2 *N* NaOH and the ethanol removed in vacuo. Additional water was added and the solution extracted with methylene chloride. After removal of the solvent the crude product was chromatographed on neutral alumina (activity III) using benzene–chloroform (7:30) as eluent. In this manner 50 mg (55%) of pure Sceletium A-4 was obtained which could be recrystallized from ethyl acetate: mp 149–151°. The ir, ^{1}H NMR, and mass spectra were identical with those of the natural product as was the TLC behavior in several solvents; mass spectrum calcd for $C_{20}H_{24}N_2O_2$, 324.1837; found, 324.1828.

Acknowledgments. The authors are grateful to The Robert A. Welch Foundation and the National Science Foundation for financial support.

Registry No.—**1**, 56782-26-4; **3**, 6023-73-0; **7**, 20802-15-7; **10** HCl, 56744-06-0; **11**, 34990-33-5; **12**, 56744-07-1; **13**, 56744-08-2; **14**, 56744-09-3; **15**, 56744-10-6; **16**, 56744-11-7; (3,4-dimethoxyphenyl)acetonitrile, 93-17-4; 1,2-dichloroethane, 107-06-2.

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(1) National Science Foundation Fellow, 1968–1972.
(2) Fellow of the National Research Council, Canada, 1973–present.
(3) For an earlier review see A. Popelak and G. Lettenbauer "The Alkaloids", Vol. IX, R. H. F. Manske, Ed., Academic Press, New York, N.Y., 1967, p 467.
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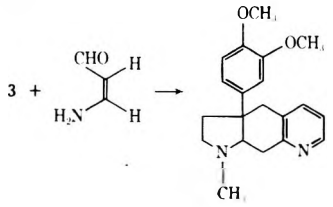
(12) The equally attractive possibility of employing mesembrine itself was abandoned when it was discovered that the major product isolated from the reaction of this substance with β-aminoacrolein[13] was the isomerically fused pyridine.



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(16) In collaboration with Professor A. Wiechers of the University of Pretoria, Pretoria, South Africa.
(17) H. Stobbe and H. Volland, *Chem. Ber.*, **35**, 3973 (1902).
(18) We are indebted to Professor Jeffs of Duke University for providing us with this data and a sample of Sceletium A-4.

A Convenient Synthesis of 2,3′-Imino-1-(β-D-lyxofuranosyl)uracil and Its Derivatives Using Azide Ion

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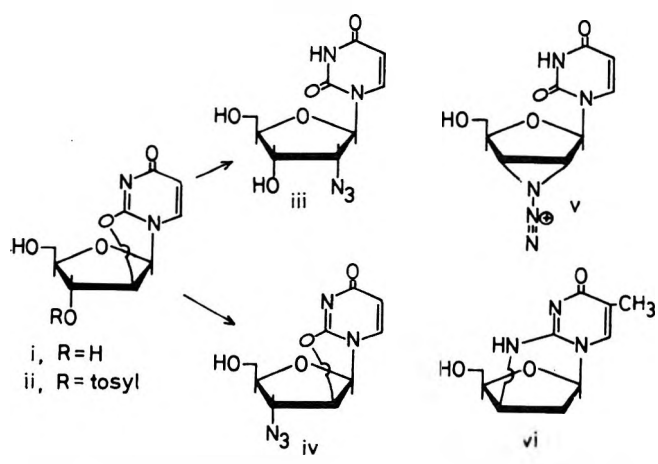
To exploit azide chemistry in the nucleoside area, a variety of derivatives of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil were synthesized as substrates for the reaction of azide ion. These contain 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)-5-bromouracil (**1b**), 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-tosyl-β-D-arabinofuranosyl)uracil (**1c**) and its 5′-chloro-5′-deoxy analog (**1e**), and analogous 2,2′-anhydro nucleoside with 5′-*O*-trityl and 3′-*O*-mesyl substituents (**1d**). These anhydro nucleosides as well as the known 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (**1a**) with in situ generated ammonium azide gave 2,3′-imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (**3a**), its 5-bromo (**3b**) and 5′-*O*-trityl analog (**3c**). An analogous anhydro nucleoside with the 5′-azido group (**3e**) was obtained from 5′-chloro-5′-deoxy-2′,3′-di-*O*-tosyluridine (**4**). **3a** and **3c** were deprotected to 2,3′-imino-1-(β-D-lyxofuranosyl)uracil (**3d**). **3a** was derived to its 2′-*O*-acetyl (**5**) and 4-thioxo analogs (**6**). In contrast, 2,2′-anhydro-1-(5′-*O*-trityl-β-D-arabinofuranosyl)uracil (**7**) with the same reagent afforded 1-(2′-azido-2′-deoxy-5′-*O*-trityl-β-D-ribofuranosyl)uracil (**9**), which was converted to the 3′-*O*-mesyl derivative (**10**) for the NMR measurement.

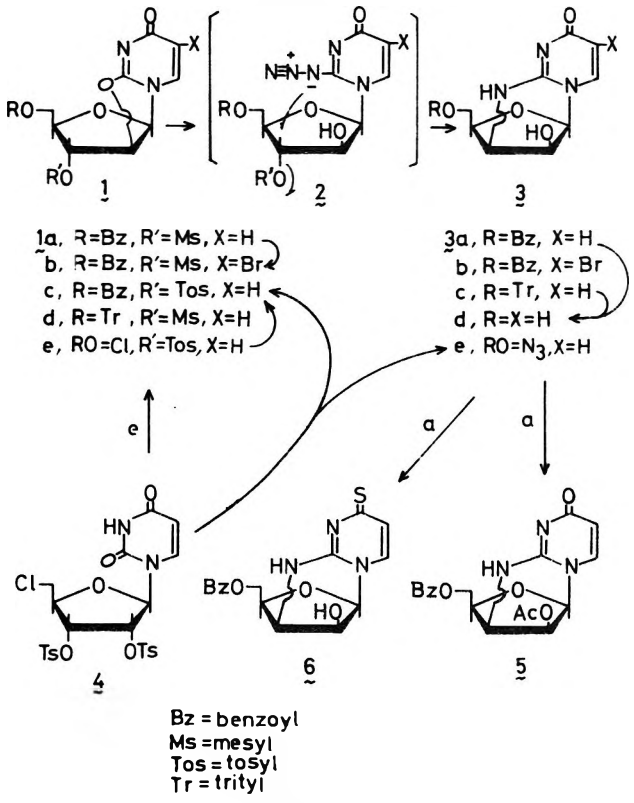
Introduction of an azide group followed by reductive cleavage has long been one of the standard methods for the syntheses of amino sugars and amino sugar nucleosides, while the use of other aspects of an azide reaction for the alterations of nucleosides is notably missing; an azide is known to have multiple reactivity leading to a nitrene, imine, and/or triazole depending upon reaction conditions and the character of a substrate.[1] Hence, our recent concern has been turned to exploitation of intramolecular nucleophilic reactions by an azide group in the nucleoside field, which would occur with or without decomposition of the introduced nitrogen chain. This paper describes a facile, selective, one-step synthesis of the derivatives of 2,3′-imino-1-(β-D-lyxofuranosyl)uracil (**3d**, Scheme II) from readily available 2,2′-anhydrouracil arabinosides.

Moffatt et al.[2] have shown that the reaction of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (i) with lithium azide gives 2′-azido-2′-deoxyuridine (iii), while Hirata[3] obtained 2,2′-anhydro-1-(3′-azido-3′-deoxy-β-D-arabinofuranosyl)-uracil (iv) from 2,2′-anhydro-1-(3′-*O*-tosyl-β-D-arabinofuranosyl)uracil (ii) and sodium azide (Scheme I). For the latter reaction an azidonium intermediate (v) has been proposed by Fox and coworkers[4] without any direct evidence. The proposed intermediate (v) was, however, interesting to us, since it suggested eventual synthesis of a compound with a "down" 2′,3′-imino function under appropriate conditions.

Scheme I



Scheme II



In a trial experiment using 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (**1a**)[5] and in situ generated ammonium azide,[6] a highly crystalline compound of mp 250–252° (**3a**, Scheme II) was obtained as a single product, no other products being detected by TLC using silica gel and 20% ethanol in benzene, 10% methanol in chloroform, and a couple of other solvent systems. This product did indicate the incorporation of one nitrogen atom with loss of the leaving group, no azide absorption in the infrared spectrum, and ultraviolet absorptions at 217 and 261 nm, the latter band being a low-intensity shoulder (see Table I). This characteristically weak second absorption was also observed in the spectrum of the debenzoylated compound (**3d**) and hence was no uridine absorption. This absorption pattern is quite similar to that of 2,3′-imino-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (vi),[7] which absorbs at 213 and 257–269 nm with ε 22700 and 4000 (sh), respectively. The structure of this product was thus assigned as 2,3′-imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (**3a**). The NMR signals of **3a** with some structural significance were the one-proton triplet at 3.84 ppm ($H_{4'}$) and the doublet at 5.35 ppm ($H_{1'}$) (see Experimental Section). The coupling constant, $J_{1',2'}$ = 4.0 Hz, was reasonably predicted from a model study, on the basis of which the dihedral angle between $H_{1'}$ and $H_{2'}$ is expected to be approximately 40°, while for a xylo configuration it reaches as large a value as 70°. The signals of $H_{2'}$, $H_{3'}$, and 5′-methylene overlapped each other as a complex multiplet. Accordingly, **3a** was acetylated to 2,3′-imino-1-(2′-*O*-acetyl-5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (**5**), in the spectrum of which the signal of $H_{2'}$ appeared at 5.38 ppm ($J_{1',2'}$ = 4.0 Hz), clearly separated from the others. In this acetylation reaction, formation of two products was indicated by TLC but the faster moving one, most probably *N*,*O*-diacetate, was unstable and easily collapsed to **5** on attempted separation by silica gel chromatography or on treatment with aqueous acetic acid.

Table I
Ultraviolet Absorption Maxima of 2,3′-Imino Cyclonucleosides, 3a–e, 5, and 6, in Methanol

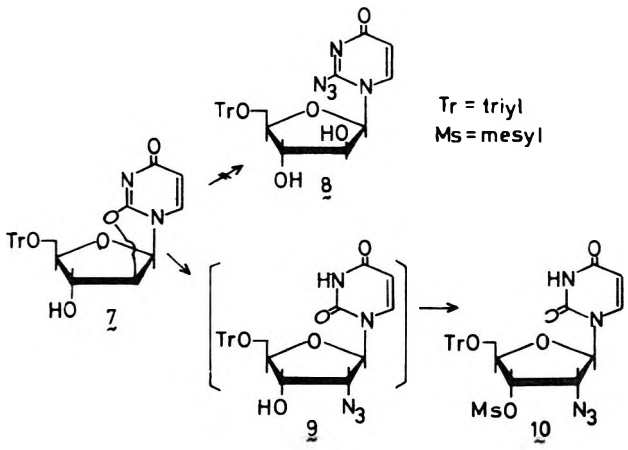
Compd	λ_{max}, nm	ε
3a	217, 261	33300, 4000 sh
3b	220, 267	29400, 5700 sh
3c	258	5200 sh
3d	215, 260	31100, 3700 sh
3e	212, 263	36600, 4080 sh
5	216, 261	39400, 4400 sh
6	228, 324	27600, 19400

Spurred by the finding of the new synthesis of an imino-bridged nucleoside, **3a**, specificity of this reaction was examined using a variety of substituted analogs of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (i). Thus, 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)-5-bromouracil (**1b**) was obtained from **1a** and *N*-bromoacetamide. The brominated position was confirmed by the ultraviolet absorption at 227 and 256 nm, and by the appearance of the NMR signal of H_6 as a singlet at 8.51 ppm which was compatible with the signal at 8.59 ppm shown by that of 2,2′-anhydro-1-(5′-*O*-acetyl-3′-*O*-benzoyl-β-D-arabinofuranosyl)-5-bromouracil.[8] The 3′-*O*-tosyl analog (**1c**) was synthesized from 2,2′-anhydro-1-(5′-chloro-5′-deoxy-3′-*O*-tosyl-β-D-arabinofuranosyl)uracil (**1e**) or directly from 5′-chloro-5′-deoxy-2′,3′-di-*O*-tosyluridine (**4**)[9] by treatment with sodium benzoate, the former (**1e**) being obtained in an excellent yield by treating the latter (**4**) with potassium carbonate. The 5′-*O*-trityl analog (**1d**) was also prepared by the standard method as described in the Experimental Section. Compounds **1c–e** showed uv absorptions at around 225 and 248 nm characteristic for a 2,2′-anhydro structure.

Reaction of excess ammonium azide with **1c**, **1b**, and **1d** gave the above obtained **3a**, 2,3′-imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)-5-bromouracil (**3b**), and 2,3′-imino-1-(5′-*O*-trityl-β-D-lyxofuranosyl)uracil (**3c**), respectively, but no other by-products discernible by TLC. Acidic treatment of **3c** gave 2,3′-imino-1-(β-D-lyxofuranosyl)uracil (**3d**) above obtained from **3a** with methanolic ammonia. Compound **3d** resisted attempted hydrolytic cleavage of the imino bridge by 2 *N* hydrochloric acid or 3 *N* potassium hydroxide, and this stability coincides with the previous observations with the thymine analog (vi) and its *N*-methyl derivative.[7] Treatment of **1e** with a large excess of ammonium azide gave 2,3′-imino-1-(5′-azido-5′-deoxy-β-D-lyxofuranosyl)-uracil (**3e**), which was, however, always contaminated with unseparable halogen-containing compounds. It was eventually found that **3e** was obtainable in pure form directly from **4** as exemplified in the Experimental Section. The structures of all these 2,3′-imino nucleosides were established in terms of uv (see Table I), ir, and NMR spectra. Thiation of compound **3a** afforded 2,3′-imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)-4-thiouracil (**6**).

The formation of **3a–e** from **1a–e** is rationalized by the initial attack of azide ion at C-2 followed by intramolecular nucleophilic displacement at C-3′ with release of a nitrogen molecule as visualized in formula **2**. Such an introduction of an azide group into pyrimidine bases through O^2-anhydro nucleosides is unprecedented and seemed to be directed by the presence of a leaving group at C-3′. Hence, a few trial experiments were done using known 2,2′-anhydro-1-(5′-*O*-trityl-β-D-arabinofuranosyl)uracil (**7**)[10] to ascertain the former observation with compound i.[2] Reaction between **7** and excess ammonium azide was rather sluggish even at a higher temperature (110°) but gave a reasonable yield (59%) of 1-(2′-azido-2′-deoxy-5′-*O*-trityl-β-D-ribofuranosyl)uracil (**9**) (Scheme III) and the starting material

Scheme III



(33%). Compound **9**[11] showed a uridine absorption at 257 nm but failed to give a clear-cut NMR spectrum at 60 MHz principally owing to the overlapping of $H_{2'}$ and $H_{3'}$ signals. A more convincing spectrum was obtained with the mesylated derivative, 1-(2′-azido-2′-deoxy-3′-*O*-mesyl-5′-*O*-trityl-β-D-ribofuranosyl)uracil (**10**), $H_{3'}$ being extensively deshielded relative to $H_{2'}$. Thus, **10** showed a separate triplet for $H_{3'}$ at 5.31 ppm with $J_{2',3'}$ (= $J_{3',4'}$) = 5.2 Hz and a doublet for $H_{1'}$ at 5.96 ppm with $J_{1',2'}$ = 4.3 Hz. While some uncertainty attended the assignments of the signals for $H_{2'}$ and $H_{4'}$, the ill-resolved signal envelope at 4.33 ppm contained splittings of 4.3 and 5.2 Hz. Although a reasonable analysis value was not obtained for this foamy compound and its further derivatization was abandoned owing to the material shortage, the above NMR data are sufficient to assign the structure. Thus, nucleophilic attack by azide ion on **7** occurred exclusively at C-2′, no side product corresponding to **8** being detected. It seems that the leaving group at C-3′ exerts, irrespective of 5′ substituent, a striking "through bond" electronegative influence to C-2, whereas the contrasted behavior of ii (Scheme I) is rather surprising.[12]

Experimental Section

All the melting points are uncorrected. The electronic spectra were measured on a Jasco Model ORD/UV-5 spectrophotometer. The nuclear magnetic resonance spectra were determined using a JNM C-60 HL spectrometer and tetramethylsilane as an internal standard,[13] while a few of the 100-MHz spectra were recorded with a Varian HA-100 spectrometer in the laboratory of the Takeda Chemical Industries Co., Ltd., for which we are grateful. Elemental analyses were carried out by Miss Y. Kawai using a Perkin-Elmer 240 elemental analyzer in this laboratory. Wakogel B-5 silica gel and Mallinkrodt silicic acid (100 mesh) were used for thin layer and column chromatography, respectively.

2,2′-Anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)-5-bromouracil (1b). *N*-Bromoacetamide (300 mg, 2.15 mmol) was added to a solution of **1a**[5] (500 mg, 1.22 mmol) in *N*,*N*-dimethylformamide (DMF) (20 ml) and the mixture was stirred at room temperature for 2 days. The yellow solution was evaporated in vacuo below 40° to a solid residue, which was digested with ice–water (15 ml) to give a pale-yellow precipitate. An aliquot of the collected solid was examined by TLC using 20% ethanol in benzene to show a single product. Crystallization from methanol gave 270 mg (62%) of colorless needles (**1b**): mp 252.5–254°; λ_{max} (MeOH) 227 nm (ε 27600) and 256 (12400); NMR (Me_2SO-d_6) δ 3.39 (3 H, s, mesyl), 5.56–5.80 (4 H, m, 5′-CH_2, $H_{4'}$ and $H_{3'}$ or $H_{2'}$), 5.37–5.51 (2 H, m, $H_{1'}$ and $H_{2'}$ or $H_{3'}$), 7.47–8.03 (5 H, m, benzoyl), and 8.51 (1 H, s, H_6).

Anal. Calcd for $C_{17}H_{15}N_2O_8SBr$: C, 41.90; H, 3.10; N, 5.75. Found: C, 41.81; H, 3.17; N, 5.77.

2,2′-Anhydro-1-(5′-*O*-benzoyl-3′-*O*-tosyl-β-D-arabinofuranosyl)uracil (1c). Method A. A mixture of **1e** (1.90 g, 4.74 mmol) and sodium benzoate (2.05 g, 14.22 mmol) in DMF (30 ml) was stirred at 90° for 7 hr and cooled. The mixture was evaporated in vacuo and the residue thoroughly triturated with ice–water (80 ml). The insoluble solid was collected by suction, air dried, and recrystallized from methanol to give 1.47 g (64%) of **1c** as colorless needles: mp 199–201°; λ_{max} (MeOH) 224 nm (ε 12700) and 249 (8600, shoulder).

Anal. Calcd for $C_{23}H_{20}N_2O_8S$: C, 57.02; H, 4.16; N, 5.78. Found: 57.13; H, 4.33; N, 5.87.

Method B. A mixture of **4**[9] (2.30 g, 4.03 mmol) and sodium benzoate (2.30 g, 16.0 mmol) in DMF (30 ml) was stirred at 95–100° for 6 hr. The solvent was evaporated off and the residue was extracted with ethyl acetate (3 × 100 ml) in the presence of water (80 ml). The ethyl acetate solution was dried over sodium sulfate and evaporated to give a paste, which was purified by preparative TLC using a silica gel plate (20 × 20 cm, 2 mm thick) and 5% methanol in chloroform. Elution of the main band with acetone and crystallization of the obtained solid from methanol gave 620 mg (32%) of crystals, mp 199–200°, identical with the product in method A in terms of infrared and ultraviolet spectroscopy.

2,2′-Anhydro-1-(5′-*O*-trityl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (1d). To a solution of 5′-*O*-trityluridine (1.23 g, 2.53 mmol) in dry pyridine (20 ml) at −20° was added dropwise methanesulfonyl chloride (0.44 ml, 5.67 mmol) under stirring. After standing at 0° overnight, the mixture was treated with methanol (5 ml) at room temperature for 30 min and evaporated to a syrup, which was dissolved in methanol (10 ml) and precipitated into ice–water (150 ml). The precipitate was collected by suction, washed with water (50 ml), and air dried (1.6 g, 95%). TLC of an aliquot of the product revealed a single product with a slight amount of trityl alcohol.

A mixture of the above obtained crude 5′-*O*-trityl-2′,3′-di-*O*-mesyluridine (1.60 g, 2.49 mmol) and anhydrous potassium carbonate (0.35 g, 2.54 mmol) in dry acetone (10 ml) was heated to reflux for 2 hr. After cooling, the insolubles were filtered off and the filtrate evaporated in vacuo to a syrup, which was extracted with chloroform (3 × 100 ml) in the presence of water (80 ml). The chloroform solution was dried over sodium sulfate, concentrated, and applied on a silica gel column (3 × 15 cm). Elution with chloroform–methanol (95:5 v/v) gave 0.75 g (55%) of a practically homogeneous foam. The analytical sample was purified by TLC over silica gel ($CHCl_3$–EtOAc, 2:1): λ_{max} (MeOH) 248 nm (ε 14300, shoulder).

Anal. Calcd for $C_{29}H_{26}N_2O_7S$: C, 63.72; H, 4.80; N, 5.12. Found: C, 63.43; H, 5.06; N, 4.97.

2,2′-Anhydro-1-(5′-chloro-5′-deoxy-3′-*O*-tosyl-β-D-arabinofuranosyl)uracil (1e). A mixture of **4**[9] (0.7 g, 1.23 mmol) and anhydrous potassium carbonate (415 mg, 3 mmol) in acetonitrile (12 ml) was heated to reflux for 2 hr. After cooling, the insolubles were filtered off, and the filtrate was treated with Norit and concentrated in vacuo to give 0.43 g (ca. 90%) of crystals homogeneous by TLC (mp 227–229°), which were recrystallized from methanol as colorless needles: mp 232–234°; λ_{max} (MeOH) 226 nm (ε 22100) and 248 (8300).

Anal. Calcd for $C_{16}H_{15}N_2O_6SCl$: C, 48.16; H, 3.79; N, 7.03. Found: C, 47.91; H, 3.79; N, 6.86.

2,3′-Imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (3a). Method A. To a solution of **1a** (1.02 g, 2.5 mmol) in DMF (20 ml) was added sodium azide (980 mg, 15 mmol) and ammonium chloride (810 mg, 15 mmol), and the mixture was stirred at 90° for 10 hr. After cooling, the insoluble materials were filtered off and the filtrate was evaporated in vacuo below 40° to a solid residue, which was thoroughly digested with ice–water (10 ml). The insoluble part was collected by suction and the aqueous filtrate was extracted with chloroform (2 × 100 ml) after adding ca. 20 ml of water. The extract was combined with the above obtained solid and recrystallized from methanol to give 570 mg (70%) of **3a** as colorless needles: mp 250–252°; NMR (Me_2SO-d_6) δ 3.84 (1 H, t, $H_{4'}$), 4.26–4.58 (4 H, m, $H_{2'}$, $H_{3'}$, and 5′-methylene), 5.35 (1 H, d, $J_{1',2'}$ = 4.0 Hz, $H_{1'}$), 5.46 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 6.18 (1 H, br s, 2′-OH), 7.32–7.98 (6 H, m, H_6 and benzoyl), and 8.45 (1 H, br s, NH).

Anal. Calcd for $C_{16}H_{15}N_3O_5$: C, 58.36; H, 4.59; N, 12.76. Found: C, 58.10; H, 4.67; N, 12.70.

Method B. A mixture of **1c** (500 mg, 1.03 mmol), sodium azide (335 mg, 5.15 mmol), and ammonium chloride (290 mg, 5.15 mmol) in DMF (10 ml) was stirred at 90° for 17 hr. The reaction mixture was worked up as in method A to give 190 mg (56%) of **3a** after recrystallization from methanol. Its identity with the above obtained product was confirmed by mixture melting point and infrared spectra.

2,3′-Imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)-5-bromouracil (3b). A mixture of **1b** (1.25 g, 2.5 mmol), sodium azide

(1.0 g, 1.54 mmol), and ammonium chloride (810 mg, 1.53 mmol) in DMF (20 ml) was stirred at 90° for 37 hr and cooled. TLC of an aliquot of the mixture using 20% ethanol in benzene showed the persistence of a small amount of the starting material and another product which moved slightly slower than the former. The inorganic materials were filtered off and the filtrate evaporated in vacuo below 40° to a solid residue, which was collected after digestion with ice–water (15 ml). Extraction of the filtrate with chloroform (2 × 50 ml) gave an additional crop. The total product was repeatedly recrystallized from methanol to give 390 mg (38%) of colorless needles of mp 260–261°: NMR (Me_2SO-d_6) δ 3.87 (1 H, m, $H_{4'}$), 4.24–4.61 (4 H, m, $H_{2'}$, $H_{3'}$, and 5′-methylene), 5.42 (1 H, d, $J_{1',2'}$ = 4.0 Hz, $H_{1'}$), 6.19 (1 H, d, 2′-OH), 7.36–8.01 (6 H, m, H_6 and benzoyl), and 8.45 (1 H, br s, NH).

Anal. Calcd for $C_{16}H_{14}N_3O_5Br$: C, 47.06; H, 3.47; N, 10.28. Found: C, 46.92; H, 3.55; N, 10.27.

2,3′-Imino-1-(5′-*O*-trityl-β-D-lyxofuranosyl)uracil (3c). A mixture of **1d** (550 mg, 1 mmol), sodium azide (400 mg, 6.15 mmol), and ammonium chloride (330 mg, 6.17 mmol) in DMF (10 ml) was stirred at 90° for 23 hr, and the reaction mixture was worked up similarly as for **3a** and **3b**. TLC of the crude product showed a small amount of the starting material and another slower moving product (10% methanol in chloroform). Crystallization from methanol gave 260 mg (55%) of **3c** as colorless needles: mp 270–271°; NMR (Me_2SO-d_6) δ 3.67 (2 H, m, 5′-methylene), 4.17–4.56 (3 H, m, $H_{2'}$, $H_{3'}$, and $H_{4'}$). 5.23–5.61 (2 H, m, $H_{1'}$ and H_5), 6.13 (1 H, br s, OH), 7.08–7.66 (16 H, m, trityl and H_6), and 7.76 (1 H, br s, NH).

Anal. Calcd for $C_{28}H_{25}N_3O_4$: C, 71.93; H, 5.39; N, 8.99. Found: C, 72.02; H, 5.48; N, 8.98.

2,3′-Imino-1-(β-D-lyxofuranosyl)uracil (3d). Method A. A suspension of powdered **3a** (200 mg, 0.61 mmol) in a mixture of concentrated ammonium hydroxide and methanol (1:3 v/v) (25 ml) was stirred at room temperature for 4 hr. The resulting solution was evaporated in vacuo at room temperature and the residue was triturated with a small amount of ether to give a crystalline solid, which was filtered and recrystallized from methanol to give needles (**3d**) which became slightly brown colored at above 282° but did not melt even at 290°: yield 137 mg (73%); NMR (Me_2SO-d_6) δ 3.54 (2 H, t, 5′-methylene), 3.76 (1 H, t, $H_{4'}$), 4.17 (1 H, m, $H_{2'}$), 4.49 (1 H, t, $H_{3'}$), 4.98 (1 H, br s, 5′-OH), 5.33 (1 H, d, $J_{1',2'}$ = 3.5 Hz, $H_{1'}$), 5.51 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 6.16 (1 H, br s, 2′-OH), 7.42 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_6), and 9.42 (1 H, br s, NH).

Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 48.01; H, 4.94; N, 18.40.

Method B. A suspension of **3c** (146 mg, 0.31 mmol) in a mixture of ether (5 ml), chloroform (5 ml), and saturated hydrogen chloride solution in dioxane (1 ml) was stirred at room temperature for 30 min. The resulting solution was evaporated in vacuo at room temperature and the residue triturated with ether (10 ml) to give a crystalline solid. The collected solid was dissolved in ethanol and neutralized with saturated ethanolic ammonia and the solvent was evaporated off to give a solid residue, which was digested with water (1 ml) and the insoluble part was collected. Recrystallization from methanol gave 45 mg (64%) of needles (**3d**), identical with the product obtained by method B in terms of infrared and ultraviolet spectra.

2,3′-Imino-1-(5′-azido-5′-deoxy-β-D-lyxofuranosyl)uracil (3e). A mixture of compound **4** (1.75 g, 3.08 mmol), sodium azide (1.18 g, 18.4 mmol), and ammonium chloride (990 mg, 18.4 mmol) in DMF (20 ml) was stirred at 90–95° for 8 hr. The mixture was evaporated in vacuo and the residue digested with ice–water (7 ml). The sparingly soluble part was collected by suction (0.33 g) and repeatedly crystallized from hot water to give 0.29 g (37%) of **3e** as needles, which decomposed at around 275° under black coloration, ir (KBr) νN_3 2130 cm^{-1}.

Anal. Calcd for $C_9H_{10}N_6O_3 \cdot \frac{1}{2}H_2O$: C, 41.70; H, 4.25; N, 32.42. Found: C, 41.98; H, 4.11; N, 32.15.

2,3′-Imino-1-(2′-*O*-acetyl-5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (5). A mixture of **3a** (200 mg, 0.61 mmol) and acetic anhydride (0.33 ml, ca. 3.3 mmol) in dry pyridine (6 ml) was warmed at 50° for a while to effect a solution. The solution was left at room temperature overnight and evaporated in vacuo to a paste, which was repeatedly coevaporated with ethanol. TLC at this stage using a silica gel plate and 20% ethanol in benzene as a developer showed two spots in approximately equal amounts. The syrupy mixture was then warmed with 20% acetic acid at 90° for 10 min. An aliquot was taken, thoroughly evaporated, and examined by TLC using the same solvent system to show only one spot, the faster moving one having now disappeared. The mixture was again evaporated to a gum, which was repeatedly coevaporated with ethanol to give a crystalline residue. Recrystallization of the collected solid from a mixture of methanol and ethanol gave 195 mg (86%) of prisms of mp 263–266° dec: NMR (Me_2SO-d_6) δ 4.20 (1 H, t, $H_{4'}$), 4.38 (2 H, m, 5′-methylene), 4.61 (1 H, m, $H_{3'}$), 5.38 (1 H, t, $J_{1',2'}$ = 4.0 Hz, $H_{2'}$), 5.51 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 5.72 (1 H, d, $J_{1',2'}$ = 4.0 Hz, $H_{1'}$), 7.34–7.99 (6 H, m, H_6 and 5′-benzoyl), and 8.72 (1 H, br s, NH).

Anal. Calcd for $C_{18}H_{17}N_3O_6$: C, 58.22; H, 4.61; N, 11.32. Found: C, 58.22; H, 4.84; N, 11.47.

2,3′-Imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)-4-thiouracil (6). Phosphorus pentasulfide (112 mg, 0.5 mmol) in dry pyridine (5 ml) was stirred at 95° for 30 min, and to this was added **3a** (110 mg, 0.33 mmol). After stirring at this temperature for 3 hr, the mixture was cooled and evaporated to a syrup, which was digested with water (3 ml) and the separated solids were collected. TLC of an aliquot of the solids indicated one main product with a couple of minor by-products. Purification by preparative TLC over silica gel (10 × 20 cm, 2 mm thick, benzene–EtOH, 8:2) gave, after elution of the main band with acetone, needles which were recrystallized from methanol to give 35 mg (30%) of **6** as methanolate: mp 181–183°; NMR (Me_2SO-d_6) δ 3.19 (3 H, s, methanol), 4.22 (1 H, m, $H_{4'}$), 4.32–4.84 (4 H, m, $H_{2'}$, $H_{3'}$, and 5′-methylene), 5.52 (1 H, d, $J_{1',2'}$ = 4.0 Hz, $H_{1'}$), 6.39 (1 H, br s, 2′-OH), 6.43 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 7.23–8.17 (6 H, m, benzoyl and H_6), and 9.22 (1 H, br s, NH).

Anal. Calcd for $C_{16}H_{15}N_3O_4S \cdot CH_3OH$: C, 54.10; H, 5.07; N, 11.13. Found: C, 54.30; H, 5.03; N, 11.17.

1-(2′-Azido-2′-deoxy-5′-*O*-trityl-β-D-ribofuranosyl)uracil (9). A mixture of **7**[10] (500 mg, 1.08 mmol), sodium azide (350 mg, 5.38 mmol), and ammonium chloride (300 mg, 5.60 mmol) in DMF (15 ml) was stirred at 110° for 20 hr. After cooling, the mixture was filtered and the filtrate evaporated in vacuo to a syrup, which was digested with ice–water (10 ml). The separated precipitate was filtered by suction, dried by pressing on a porous plate, and taken into chloroform (10 ml). The sparingly soluble solid collected by suction proved to be practically homogeneous starting material (167 mg, 33%). The filtrate was concentrated and submitted to preparative TLC using a silica gel plate (20 × 20 cm, 2 mm thick) and 10% methanol in chloroform. Elution of the faster moving main band with acetone gave 320 mg (59%) of a homogeneous foam (**9**) which resisted crystallization and hence was directly used for the next step: ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 257 nm (ε 9400).

1-(2′-Azido-2′-deoxy-3′-*O*-mesyl-5′-*O*-trityl-β-D-ribofuranosyl)uracil (10). Methanesulfonyl chloride (0.06 ml, 0.77 mmol) was added to a precooled solution (at −20°) of **9** (320 mg, 0.63 mmol) in pyridine (4 ml) under stirring and the mixture was left at −20° overnight, treated with methanol (1 ml) at room temperature for 1 hr, and then evaporated in vacuo. The residue was extracted with chloroform (3 × 50 ml) in the presence of water (20 ml) and the chloroform extract applied on a silica gel column (2 × 17 cm). Elution with chloroform–ethyl acetate (5:1 v/v) gave 300 mg (80%) of a practically homogeneous foam (**10**), a portion of which was further purified by TLC over silica gel (10% MeOH in $CHCl_3$) for the elemental analysis and spectral measurements: ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 257 nm (ε 10100); NMR ($CDCl_3$) δ 3.05 (3 H, s, mesyl), 3.56 (2 H, br s, 5′-methylene), 4.33 (2 H, triplet-like q, J = 4.3 and 5.2 Hz, $H_{2'}$ and $H_{4'}$), 5.31 (1 H, t, $J_{2',3'}$ = 5.2 Hz, $H_{3'}$), 5.49 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 5.96 (1 H, d, $J_{1',2'}$ = 4.3 Hz, $H_{1'}$), 7.33 (15 H, s, trityl), 7.76 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_6) and 9.10 (1 H, br s, NH).

Registry No.—**1a**, 56687-59-3; **1b**, 56615-01-1; **1c**, 56615-02-2; **1d**, 56615-03-3; **1e**, 56615-04-4; **3a**, 56615-05-5; **3b**, 56615-06-6; **3c**, 56615-07-7; **3d**, 56615-08-8; **3e**, 56615-09-9; **4**, 56615-10-2; **5**, 56615-11-3; **6**, 56615-13-5; **7**, 3249-94-3; **9**, 34407-66-4; **10**, 56615-14-6; *N*-bromoacetamide, 79-15-2; sodium benzoate, 532-32-1; 5′-*O*-trityluridine, 6554-10-5; methanesulfonyl chloride, 124-63-0; sodium azide, 26628-22-8.

References and Notes

(1) S. Patai, Ed., "The Chemistry of Azide Group", Interscience, New York, N.Y., 1970.
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(3) M. Hirata, *Chem. Pharm. Bull.*, **16**, 291 (1968).
(4) J. J. Fox and K. A. Watanabe, *Chem. Pharm. Bull.*, **17**, 211 (1969).
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(6) Less basic ammonium azide was considered preferable to sodium azide so as not to injure the 5'-ester portions and some other sensitive parts of products and also of the starting material (**1a**). According to our experiences, the former reagent seems to be more soluble in DMF than the latter, and the aqueous washings of the reaction mixtures after evaporation of the reaction solvent usually indicated a practically neutral pH, when equimolar amounts of ammonium chloride and sodium azide were used. The uses of some other soluble azide salts have been described: W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).
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(10) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1964).
(11) This compound has previously been obtained via another route and fully characterized by 100-MHz NMR spectroscopy [D. Wagner, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **37**, 1876 (1972)]. The shortage of our sample has hampered repeating the measurement at 100 MHz for comparison. The authors are indebted to one of the referees for the information of the above publication.
(12) It must be added that in a trial experiment with **1b** and sodium azide in DMF **3b** was isolated in a low yield from a rather complex mixture.
(13) Measurements after D_2O exchange were also carried out for all the compounds containing labile protons.

Photochemical Formation of Spiro and Bicyclo 1-Acylaminoazetidin-2-ones. Models for the Syntheses of Penicillin-like Systems. II[1]

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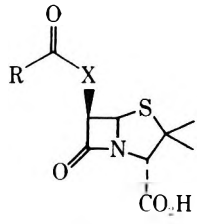
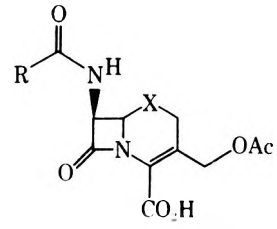
The syntheses and photochemistry of spiro 2-acetylpyrazolidin-3-ones **1d, 2d,** and **13d,** spiro 1-acetylpyrazolidin-3-one 8, and N-unsubstituted spiro pyrazolidin-3-one **1a** were studied. Upon irradiation these systems were shown to give 1-acetamidoazetidin-2-ones **6, 5, 15, 6,** and 1-aminoazetidin-2-one 7, respectively, in good yields. A cis-fused bicyclo pyrazolidin-3-one **33a** was also synthesized and irradiated to give bicyclo β-lactam **34a** in 45% isolated yield. β-Lactam **34a** was also synthesized by a second route which involved amination of β-lactam **35a** obtained from the reaction of chlorosulfonyl isocyanate and cyclohexene. The stereochemistry and some reactions of these systems are discussed.

There has been considerable interest in the syntheses of molecules related to the penicillin and cephalosporin antibiotics over the last several decades.[2] During this time many "established" structure–activity relationships concerning these antibiotics have evolved including, among others, the necessity of having the 6-amido group in penicillin (Ia) or the ring sulfur in cephalosporin (IIa) in order to maintain activity. Recent reports on the syntheses of fundamentally different active "penicillin-like" (Ib–d)[3] and "cephalosporin-like" (IIb,c)[4] systems indicate, however, the tentative nature of some of these "established" relationships and the need for continuing studies of different structural analogs of these antibiotics.

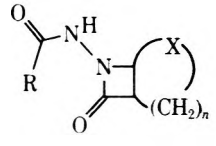


Ia, X = NH, penicillin
b, X = O
c, X = CH$_2$
d, X = NHNH

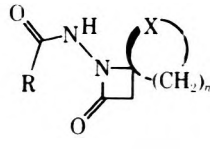


IIa, X = S, cephalosporin
b, X = O
c, X = CH$_2$

Our interests in this area include approaches to the syntheses of 6-azapenicillins (III, n = 2), 7-azacephalosporins (III, n = 3), and related spiro systems (IV).[5]



III, X = S, CH$_2$
n = 2, 3



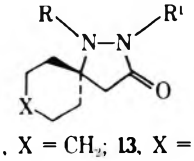
IV, X = S, CH$_2$
n = 3, 4

Toward these goals we have been examining methods applicable to the synthesis of the *N*-acylaminoazetidin-2-one moiety, which is the dominant feature of both III and IV. Previously we reported on the photochemical rearrangement of monocyclic 2-acyl 5,5-dimethylpyrazolidin-3-ones to give *N*-acylaminoazetidin-2-ones in isolated yields as high as 65%.[1,6] We have now examined the effects of several structural features on this photochemical ring contraction reaction as well as the presence of a remote sulfur atom. This report includes our findings on the syntheses and photochemical reactions of an assortment of 5- and 6-spiro pyrazolidin-3-ones and a 6-fused bicyclo pyrazolidin-3-one as well as the preparation of an *N*-acylaminoazetidin-2-one related to III (X = CH_2) using a procedure which involves amination and acylation of an azetidin-2-one.

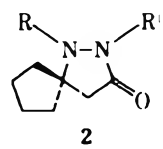
Carbon Spiro Systems. Starting with the known α,β-unsaturated esters, ethyl cyclohexylideneacetate[7] and ethyl cyclopentylideneacetate,[8] carbon spiro systems **1a** and **2a** were prepared by condensation of the respective esters with hydrazine.

While **1a** was obtained in quite good yield, the yield of **2a,** the 5-spiro system, was generally 15–20% lower, presumably because of the increased strain involved in the ring closure step. Both of these acyl hydrazides were solids and were significantly more stable to air oxidation than 5,5-dimethylpyrazolidin-3-one which we had prepared previously.[1] Condensation of either **1a** or **2a** with 2,2,2-trichloroethoxycarbonyl chloride (TrOCCl)[9] under Schotten–Baumann conditions gave 1,2-diacylhydrazides **1b** and **2b,** respectively, in good yields.

Acylation of **1b** or **2b** with acetyl chloride and triethylamine in tetrahydrofuran solvent gave *O*-acyl derivatives **3** and **4,** which were easily rearranged to their corresponding

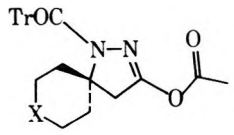


1, X = CH$_2$; 13, X = S

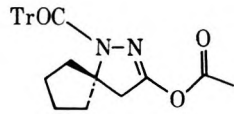


2

a, R = R^1 = H; b, R = TrOC, R^1 = H;
c, R = TrOC, R^1 = CH$_3$CO; d, R = H, R^1 = CH$_3$CO



3. X = CH_2; 14. X = S



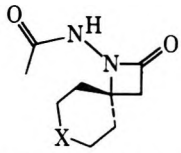
4

N-acyl isomers **1c** and **2c** by heating them neat under nitrogen at 100–120° for 2 hr.

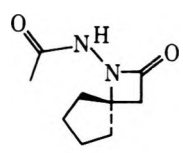
The TrOC protecting group was removed from **1c** and **2c** with zinc dust in acetic acid and the respective 2-acylpyrazolidin-3-ones **1d** and **2d** were extracted from cold aqueous carbonate with chloroform and purified by column chromatography on silicic acid. Sublimation gave **1d** and **2d** analytically pure as low-melting solids. These 5,5-disubstituted 2-acylpyrazolidin-3-ones, which are 1,1-diacylhydrazides, were shown not to rearrange to their 1-acyl isomers upon heating.

It is interesting to compare the ^{13}C chemical shifts of the junction carbon of 6-5 spiro molecules **1a** and **1d** with 5-5 spiro molecules **2a** and **2d** (see Scheme I). We believe that the ca. 10 ppm difference observed for the chemical shift of the junction carbon in these two systems is the result of increased sp^2 character for that carbon in the 5-5 spiro because of its increased strain. This trend continues in the more strained spiro β-lactam (6-4, 5-4) systems (see Experimental Section).

Irradiation of either **1d** or **2d** (see Scheme II) in degassed methanol with a Hanovia 450-W immersion lamp equipped with a Vycor filter for 2 hr gave β-lactams **5** and **6**, respectively, in 50–55% isolated yield. Isolation was performed by column chromatography using silicic acid. The yields of spiro β-lactams **5** and **6** were only slightly lower than those obtained for the monocyclic 5,5-dimethyl system (see Table I).



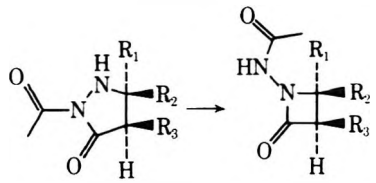
5, X = CH_2; 15, X = S



6

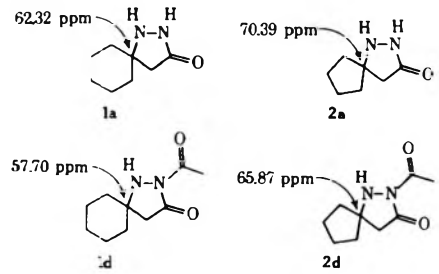
The 6-spiro β-lactam **5** was also obtained in high yield by acetylation of 1-aminoazetidin-2-one **7**, which was prepared by two independent methods. The first involved photolysis of nitrogen unsubstituted pyrazolidin-3-one **1a** for 20 hr in degassed methanol. Column chromatography of the crude photolysis mixture obtained after removal of solvent gave **7** in 15% yield. Amine **7** was found to rearrange at 25° in acidic methanol back to pyrazolidin-3-one **1a**. The second preparation of **7** involved removal of the acetyl group from the exocyclic nitrogen of **5**.[10] Reaction of **5** with 1 equiv of

Table I

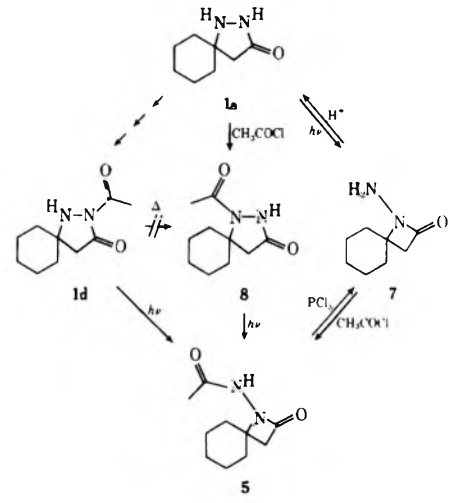


Pyrazolidin-3-one		Azetidin-2-one	R_1	R_2	R_3	Isolated yield of β-lactam, %
	Ref 1		CH_3	CH_3	H	65
			CH_3	H	H	45
2d	–	**6**		$-(CH_2)_4-$	H	50
1d	–	**5**		$-(CH_2)_5-$	H	55
13d′	–	**15**		$-(CH_2)_2S(CH_2)_2-$	H	45
33a	–	**34a**	H	$-(CH_2)_4-$		45

Scheme I

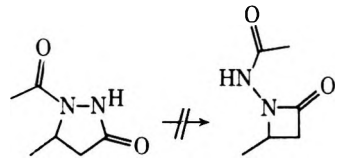


Scheme II



PCl_5 and quinoline in methylene chloride at 25° followed by addition of excess 1-butanol and finally water gave **7** in low yield. No attempt was made to maximize the yield of this reaction.

Interestingly, we found that β-lactam **5** could also be isolated in 30% yield from the photolysis, in degassed methanol for 20 hr, of 1-acetylpyrazolidin-3-one **8**, which was prepared by reaction of **1a** and acetyl chloride. This is the first report of the photochemical ring contraction reaction of a 1-acylpyrazolidin-3-one to give a 1-acylaminoazetidin-2-one. Success of this approach seems to depend at least on the presence of 5,5 disubstitution, since irradiation of 1-acetyl-5-methylpyrazolidin-3-one (**9**) gave no β-lactam **10**. (While not established unambiguously, the aromatic *N*-acetylhydroxypyrazole appears to be the major product in this case.)

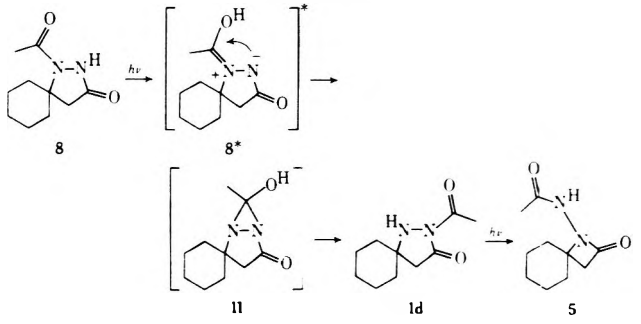


9 10

Scheme III outlines a rationale for the formation of β-lactam **5** from the photolysis of 1-acetylpyrazolidin-3-one **8**. Irradiation of **8** gives **8*** which, upon cyclization, would give the bicyclic intermediate **11**.[11] Rearrangement of **11** to **1d** would be expected to occur occasionally; however, we feel that rearrangement back to **8** should be the predominant reaction of **11** since the "amide type" nitrogen of the hydrazide is the better leaving group. The low concentration of **1d** would account for the long reaction times required for this transformation. The photochemical rearrangement of 2-acylpyrazolidin-3-ones, such as **1d**, to 1-acylaminoazetidin-2-ones has been discussed previously.[1]

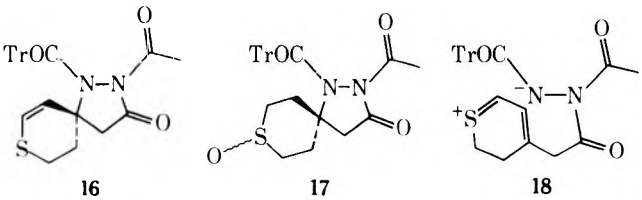
Sulfur-Containing Spiro Systems. Sulfur-containing

Scheme III



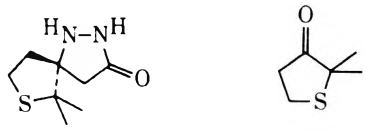
spiro pyrazolidin-3-one **13** was prepared in a manner similar to that described for carbon spiro systems **1** and **2**. The α,β-unsaturated ester, ethyl 4′-thiacyclohexylideneacetate (**12**), was synthesized in good yield via a Horner modification of the Wittig reaction[12] using triethyl phosphonate and thiacyclohexan-4-one.[13] Condensation of the α,β-unsaturated ester with hydrazine gave pyrazolidin-3-one **13a** in moderate yield. Acylation of the 1 position of **13a** with TrOCCl occurred readily to give **13b**, which was treated with acetyl chloride and triethylamine to give the *O*-acyl derivative **14**. Heating **14** neat at 150° for 2 hr gave **13c** in moderate yield. In contrast to the carbon spiro systems, however, the sulfur-containing spiro system **14** turned very dark upon heating. Removal of the protecting group from **13c** to give **13d** required addition of zinc dust in several portions. Only partial removal of the protecting group was observed when the zinc was added in one portion. Presumably sulfur "poisons" the surface of the zinc metal. After its purification by column chromatography, **13d** was irradiated, in a manner similar to that described above for **1a** and **2a**, to give β-lactam **15** in 45% isolated yield. Relative to the carbon spiro systems, the presence of the sulfur atom in system **13** had only a slight lowering effect on the yield of β-lactam (see Table I). That this would be the case was not obvious, since sulfides have been shown to undergo photochemical reaction with carbonyl chromophores via both intra- and intermolecular electron transfer processes.[13,14]

In order to further examine structural modifications related to pyrazolidin-3-one system **13**, thiovinyl ether **16** was synthesized via a Pummerer reaction[15] on sulfoxide **17**. Re-



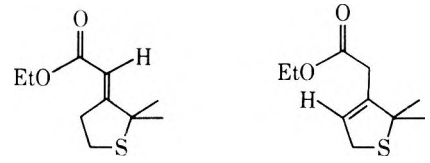
action of sulfur spiro system **13c** with *m*-chloroperoxybenzoic acid in methylene chloride at 0° gave sulfoxide **17** in 40% yield, probably as a mixture of isomers. Treatment of **17** with refluxing acetic anhydride gave, after work-up, a crude material whose ^{1}H NMR spectra indicated formation of some of the desired thiovinyl ether **16**. However, every effort to purify this material resulted in its decomposition. We feel that the facile decomposition of **16** can be explained in terms of an initial elimination of the good triacyl hydrazide anion to give an unstable diene **18** which would be expected to undergo further decomposition. The orbital alignment of the π bond with the C–N bond of the spiro system should favor such an elimination process.

In addition to the sulfur-containing 6-spiro system **13a**, we were also interested in the hindered sulfur-containing



5-spiro pyrazolidin-3-one **19**. This was to be synthesized from olefin **20** via ketone **21**. Ketone **21** was synthesized from ethyl 2,2-dimethyl-3-thiahexanedioate by Dieckmann cyclization[16] and decarboxylation of the intermediate β-keto ester.

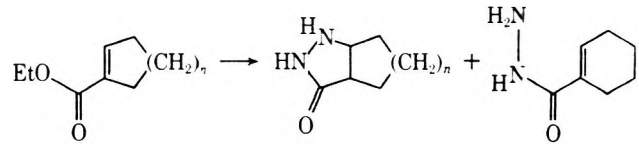
Wittig reaction of ketone **21** with triethyl phosphonoacetate required long reaction times but gave a moderate yield of a mixture of two esters with similar GLC retention times. Ir, ^{1}H NMR, and mass spectral data from GLC collected samples of the two products indicated that they were olefinic esters **20** and **22**. These isomers could be distin-



guished by either their ir or ^{1}H NMR spectra. The α,β-unsaturated ester **20** had a carbonyl band in its ir spectrum at 1707 cm^{-1}, while the β,γ-unsaturated isomer **22** had a carbonyl band in its ir spectrum at 1731 cm^{-1}. The ^{1}H NMR spectrum of **20** contained two triplet absorptions with coupling constants of 7 Hz, one of which was also coupled to the vinyl proton as determined by double resonance, while the ^{1}H NMR spectra of **22** had absorptions for the two methylene groups with only fine coupling. It is interesting to note that the olefinic proton absorptions of **20** and **22** have the same chemical shift. The presence of only the *E* isomer of **20** is not surprising, since the Wittig reaction is known to be affected by steric factors.[12]

Because of the difficulty in the separation of esters **20** and **22**, hydrazine was condensed with a mixture of the two. Reaction under a variety of conditions produced, however, only intractable material from which no product with the properties expected for **19** could be isolated.

Carbon Bicyclo Systems. Although a large number of monocyclic pyrazolidin-3-ones have been prepared, a search of the literature reveals no examples of a nitrogen-unsubstituted pyrazolidin-3-one ring fused to another ring. We therefore prepared the two cyclic α,β-unsaturated esters 1-ethoxycarbonylcyclopent-1-ene (**23**)[17] and 1-ethoxycarbonylcyclohex-1-ene (**24**)[18] in order to examine their reactions with hydrazine. From reaction of the cyclopentene system with hydrazine under a variety of conditions we were unable to isolate any products with the properties expected for bicyclo compound **25**. In contrast, from the reaction of the cyclohexene system with 1 equiv of hydrazine at 120° for 6 hr we were able to obtain, after column chromatography, a low yield (5–10%) of the desired bicyclo pyrazolidin-3-one **26**. Also isolated from this reaction was a small amount of the α,β-unsaturated hydrazide **27** which was identified by comparison with a sample prepared by an unambiguous route.[19] The bulk of the material was polymeric.



23, $n = 1$ **25**, $n = 1$ **27**
24, $n = 2$ **26**, $n = 2$

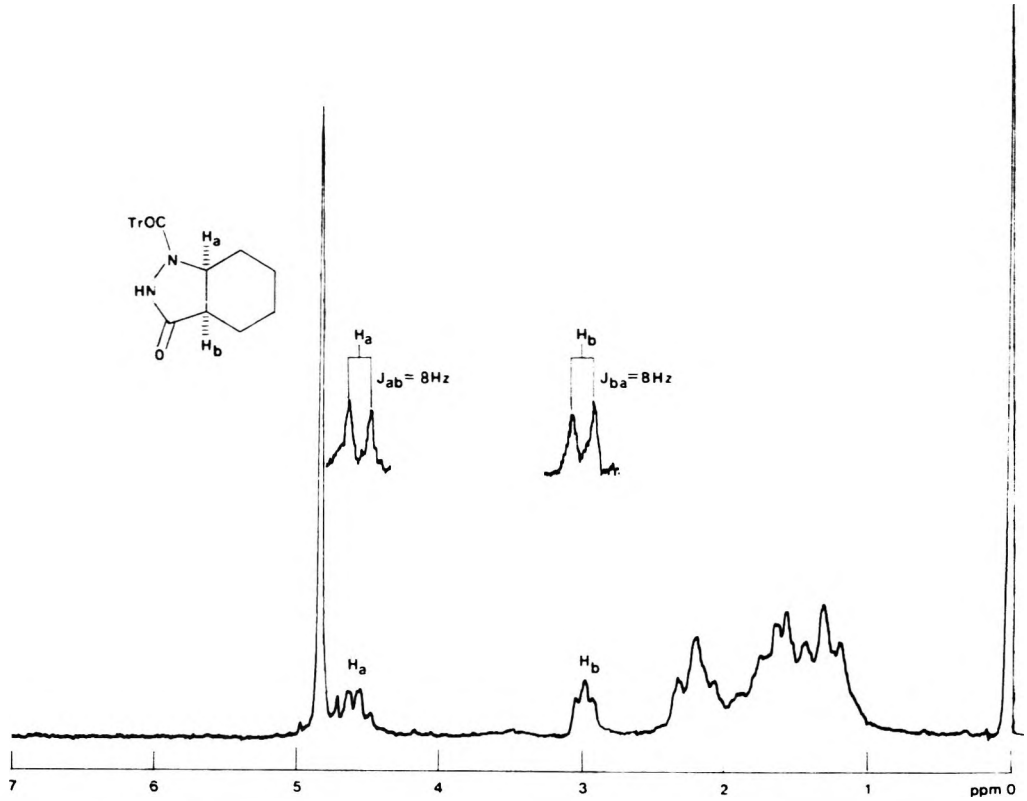


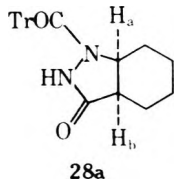
Figure 1. ^{1}H NMR spectrum of *cis*-1-(2,2,2-trichloroethoxycarbonyl)indazolidin-3-one (**28a**) in CCl_3D at room temperature. Inserts are the absorptions of the bridgehead protons decoupled from the corresponding adjacent methylene (for H_a, $H_2 \approx 210$ Hz; H_b, $H_2 \approx 160$ Hz).

These results on the hydrazine condensation of esters **23** and **24** indicate that pyrazolidin-3-one formation by this method is strongly affected by the strain of a fused ring and does not represent a good approach to systems like **26.**

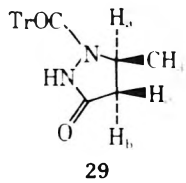
Although we were able to obtain **26** pure off a column, the best yields of 1-acylated **26** were obtained by using partially purified material (see Experimental Section). Acylation of partially purified **26** with TrOCCl gave a product which was determined by ^{13}C NMR to be mainly one diastereomer of **28** containing some of the other diastereomer. Recrystallization removed the minor isomer. The identity of the major isomer was determined to be the desired *cis*-**28** (**28a**) by comparison of its ^{1}H NMR spectra with the ^{1}H NMR spectra of compound **29** (see Figures 1 and 2). After correction for the methine vs. methylene difference, H_a and H_b in **29** have the same chemical shifts as the two bridgehead protons of **28a,** while the absorption for H_c in **29** is upfield. Also the coupling constant of the two bridgehead protons of **28a** is the same as the two "cis" (H_a, H_b) protons in **29.**

The isolation of predominantly **28a** from acylation of the cis/trans **26** (**26a,b**) mixture indicates that the predominant isomer formed in the hydrazine condensation was probably **26a** (^{13}C NMR data indicated that one major diastereomer was formed). Formation of predominantly **26a** can be rationalized by favored axial protonation of intermediate **30** which can close to give the cis product.[20]

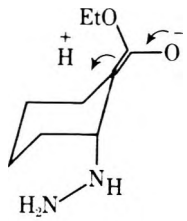
Reaction of **28a,** which is a 5-monosubstituted pyrazolidin-3-one, with acetyl chloride and triethylamine in tetrahydrofuran gave a 70:30 mixture of *N*-acetyl *cis*-**31** (**31a**)



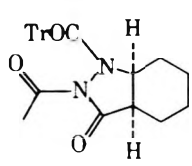
28a



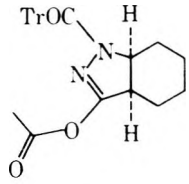
29



30



31a

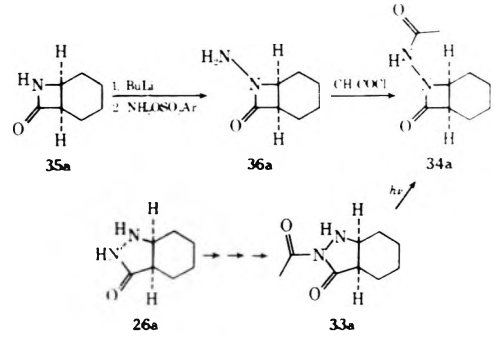


32a

and *O*-acetyl *cis*-**32** (**32a**) isomers. This is in contrast with the behavior of the 5,5-disubstituted pyrazolidin-3-ones **1b, 2b,** and **13b,** which, when acylated under similar conditions, gave exclusively *O*-acyl derivatives. Heating the mixture of **31a** and **32a** at 110° for 3 hr gave pure *N*-acetyl **31a.** Removal of the protecting group from **31a** with zinc gave *cis*-**33** (**33a**) (see Scheme IV). Irradiation of **33a** gave *cis*-**34** (**34a**), which was isolated by column chromatography in 45% yield. The presence of a fused six-membered ring apparently has only a small effect on the photochemical ring contraction reaction (see Table I).

β-Lactam **34a** was also prepared from N-unsubstituted β-lactam *cis*-**35** (**35a**),[21] which was prepared by reaction of chlorosulfonyl isocyanate with cyclohexene followed by re-

Scheme IV



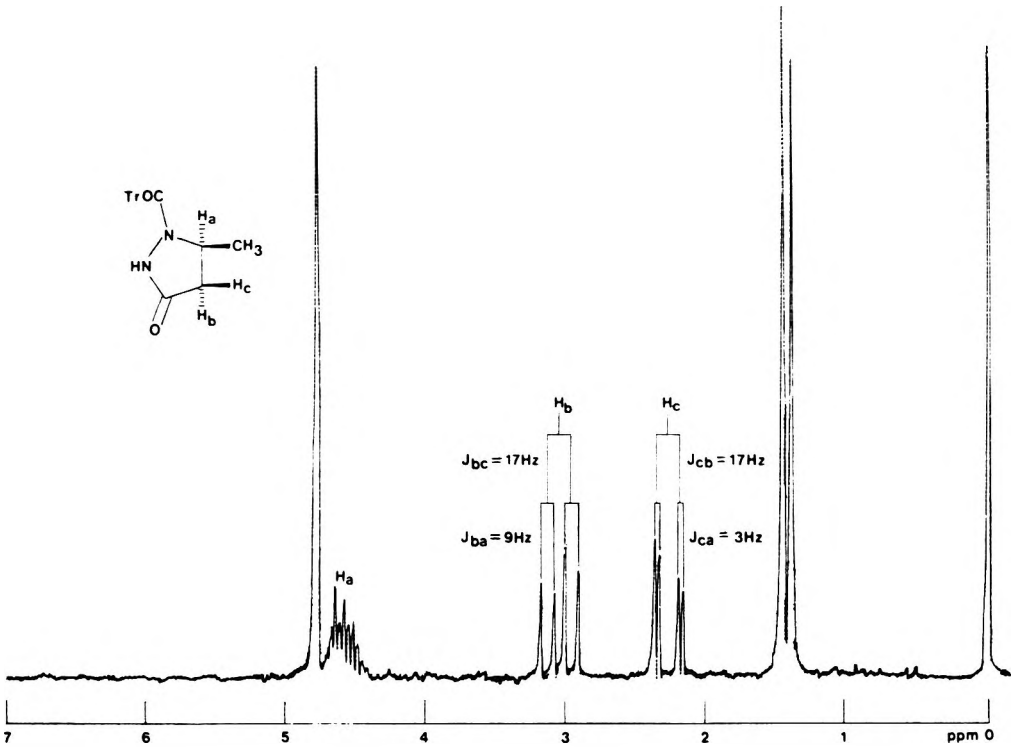


Figure 2. ^1H NMR spectrum of 1-(2,2,2-trichloroethoxycarbonyl)-5-methylpyrazolidin-3-one (**29**) in CCl_3D at room temperature.

moval of the chlorosulfonyl moiety with NaOH–Na_2SO_3.[22] Amination of the anion of **35a** with 1 equiv of *O*-mesitylene sulfonylhydroxylamine[23] resulted in 1-amino β-lactam *cis*-**36** (**36a**). Acylation of **36a**, using conditions similar to those used for the acylation of 1-amino β-lactam **10**, gave **34a** which was identical by ir, ^1H NMR, and TLC with the photoproduct of **33a**.

Further studies on systems of the generalized structure III are underway in our laboratories and will be reported at a later time.

Experimental Section

Melting points were taken in capillary tubes on a Thomas-Hoover Unimelt and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457A spectrometer. The ^1H NMR spectra were taken either on a Varian A-60 spectrometer or on a Perkin-Elmer JEOL MH-100 spectrometer and are reported in parts per million downfield from tetramethylsilane. The ^{13}C NMR spectra were taken on a Varian CFT-20 spectrometer and are reported in parts per million downfield from tetramethylsilane. The abbreviations s, singlet; d, doublet; t, triplet, q, quartet refer to the multiplicity of the absorption in an off-resonance decoupled spectrum. Mass spectra were determined on a Perkin-Elmer Hitachi RMU-6D spectrometer. Ultraviolet spectra were taken on a Cary 14 recording spectrophotometer. Gas chromatography was carried out using programmed temperature control on a Hewlett-Packard 5750 B instrument equipped with 8- and 10-ft stainless steel columns packed with SE-30 on 80–100 mesh Chromosorb P. Mallinckrodt AR 100 mesh silicic acid was used for all column chromatography. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Irradiations were carried out using a Hanovia 450-W immersion lamp equipped with a Vycor filter unless otherwise specified.

Pyrazolidin-3-one-5-spirocyclohexane (1a). To 95% hydrazine (3.05 g, 89.5 mmol) cooled to 0° under a nitrogen atmosphere was added dropwise ethyl cyclohexylideneacetate[7] (15.00 g, 89.5 mmol). After the addition was complete, the mixture was allowed to warm to room temperature and to stir for 1 hr. The mixture was then heated at 120° for 6 hr. Immediately after removing the oil bath aspirator vacuum was applied to the reaction vessel to remove the ethanol formed. When the reaction vessel had cooled to room temperature, it was placed under high vacuum. The crude solid (13.7 g, 99%) obtained from this procedure was acylated directly without further purification. An analytical sample was obtained by recrystallization from ethanol. For **1a**: mp 138–140°; ir (CCl_3H) 3430, 3230 (broad), 2930, 2855, 1700 (broad), 1450, 1380, 1310, 1110, 990, 950, 880 cm^{-1}; ^1H NMR (CCl_3D) δ 1.20–1.85 (m, 10), 2.30 (s, 2); ^{13}C NMR (CCl_3D) δ 22.70 (t), 25.57 (t), 43.33 (t), 62.32 (s), 178.00 (s); mass spectrum (70 eV) *m/e* (rel intensity) 154 (43, M^+), 139 (4), 125 (7), 123 (19), 112 (25), 111 (100), 98 (61), 97 (10), 96 (8), 95 (24), 83 (14), 81 (20), 79 (10), 68 (12), 67 (26), 55 (22), 54 (13), 53 (11), 41 (28); uv (EtOH) 203 nm (ε 3900), shoulder 219 (2100).

Anal. Calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.11; H, 9.08; N, 18.10.

1-(2,2,2-Trichloroethoxycarbonyl)pyrazolidin-3-one-5-spirocyclohexane (1b). To a solution of crude pyrazolidin-3-one-5-spirocyclohexane (**1a**, 13.7 g, 89.0 mmol) in a mixture of aqueous 2 *N* NaOH (45 ml) and tetrahydrofuran (45 ml) cooled to 10–20° under a nitrogen atmosphere was added dropwise 2,2,2-trichloroethoxycarbonyl chloride (18.8 g, 89.0 mmol). After the addition was complete, the mixture was allowed to warm to room temperature and to stir for 2 hr. The precipitate which formed during the reaction was filtered off and washed with a little water. Recrystallization of the solid from ethanol gave 16.5 g (57%) of pure **1b**: mp 193–194°; ir (CCl_3H) 3410, 2940, 2860, 1710 (broad), 1450, 1390, 1340, 1300, 1140, 910 cm^{-1}; ^1H NMR (CCl_3D) δ 1.00–2.60 (m, 10), 2.76 (s, 2), 4.84 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 328 (6, 3-Cl, M^+), 207 (6), 181 (6), 154 (10), 153 (8), 123 (25), 122 (43), 111 (25), 98 (22), 97 (16), 96 (26), 95 (100), 94 (43), 81 (57), 79 (21), 68 (23), 67 (54), 61 (22), 55 (35), 54 (26), 44 (43), 41 (39).

Anal. Calcd for $C_{11}H_{15}N_2O_3Cl_3$: C, 40.08; H, 4.59; N, 8.56. Found: C, 39.90; H, 4.64; N, 8.42.

2-Acetyl-1-(2,2,2-trichloroethoxycarbonyl)pyrazolidin-3-one-5-spirocyclohexane (1c) via 3-Acetoxy-1-(2,2,2-trichloroethoxycarbonyl)-2-pyrazoline-5-spirocyclohexane (3). To a solution of 1-(2,2,2-trichloroethoxycarbonyl)pyrazolidin-3-one-5-spirocyclohexane (**1b**, 16.5 g, 50.1 mmol) and triethylamine (5.10 g, 50.1 mmol) in tetrahydrofuran (300 ml) at room temperature under a nitrogen atmosphere was added dropwise over a period of 30 min acetyl chloride (3.95 g, 40.1 mmol). The mixture was stirred for an additional 6 hr and the precipitated triethylamine hydrochloride salt was filtered off. Concentration of the filtrate left a solid which was dried under high vacuum. ^1H NMR analysis revealed this to be the O-acylated product **3**: ^1H NMR (CCl_3D) δ 1.00–2.00 (m, 10), 2.28 (s, 3), 3.13 (s, 2), 4.87 (s, 2).

Without further purification the O-acylated material was heated neat under a nitrogen atmosphere at 110° for 3 hr. Upon cooling was obtained a white solid which upon recrystallization from Et_2O gave 14.6 g (73%) of pure **1c**: mp 117.5–118.5°; ir (CCl_3H) 2940, 2860, 1740 (broad), 1500, 1370, 1260, 970 cm^{-1}; ^1H NMR (CCl_3D) δ 1.10–2.40 (m, 10), 2.52 (s, 3), 2.76 (s, 2), 4.79 (s, 2); mass spectrum

(70 eV) *m/e* (rel intensity) no parent, 326 (trace, 3-Cl), 293 (trace, 3-Cl), 271 (trace, 3-Cl), 154 (13), 140 (12), 122 (6), 111 (18), 98 (22), 97 (20), 96 (25), 81 (48), 68 (22), 67 (45), 61 (30), 60 (57), 55 (25), 54 (26), 45 (92), 44 (98), 43 (100), 42 (51), 41 (39).

Anal. Calcd for $C_{13}H_{17}N_2O_4Cl_3$: C, 42.01; H, 4.61; N, 7.54. Found: C, 42.04; H, 4.56; N, 7.57.

2-Acetylpyrazolidin-3-one-5-spirocyclohexane (1d). To a solution of 2-acetyl-1-(2,2,2-trichloroethoxycarbonyl)pyrazolidin-3-one-5-spirocyclohexane (**1c**, 5.00 g, 13.5 mmol) in acetic acid (30 ml) at room temperature under a nitrogen atmosphere was added all at once an equal quantity by weight of zinc dust. Cooling with an ice bath was applied as necessary to prevent any warming. After stirring for 2 hr at room temperature, the mixture was carefully poured into ice-cold water (120 ml) containing K_2CO_3 (90 g). The heterogeneous mixture was extracted well with chloroform, which was evaporated to leave an oil. Column chromatography of the oil on silicic acid with Et_2O eluent gave 1.59 g (60%) of a colorless oil which was shown to be pure **1d**: ir (CCl_3H) 3280, 2930, 2855, 1749, 1700, 1412, 1375, 1310, 1280, 970, 905 cm^{-1}; ^1H NMR (CCl_3D) δ 1.30–1.90 (m, 10), 2.48 (s, 6), 2.64 (s, 2), 4.44 (broad s, 1, NH); ^{13}C NMR (CCl_3D) δ 22.70 (t), 24.00 (q), 25.53 (t), 35.52 (t), 45.51 (t), 57.72 (s), 167.50 (s), 173.01 (s); mass spectrum (70 eV) *m/e* (rel intensity) 196 (7, M^+), 178 (3), 155 (8), 154 (75), 125 (7), 112 (46), 111 (100), 98 (94), 97 (13), 95 (8), 81 (11), 79 (8), 68 (7), 67 (14), 58 (8), 55 (13), 54 (8), 53 (9), 43 (57), 41 (26); uv (EtOH) 226 nm (ϵ 3800), 240 (2750).

Anal. Calcd for $C_{10}H_6N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 60.95; H, 8.03; N, 14.26.

1-Acetamidoazetidin-2-one-4-spirocyclohexane (5). From Irradiation of 1d. A solution of 2-acetylpyrazolidin-3-one-5-spirocyclohexane (**1d**, 1.30 g, 6.65 mmol) in methanol (250 ml) was degassed with a stream of nitrogen for 2 hr, after which it was irradiated for 2 hr. TLC analysis [silicic acid plates with Et_2O–EtOH (90:10 mixture by volume) developer] showed the loss of starting material (detected by uv and I_2) and the appearance of a new spot of slightly smaller R_f (detected by I_2). Stripping of the solvent left an oil which slowly crystallized. Column chromatography of the solid on silicic acid with Et_2O–EtOH (90:10 mixture by volume) eluent resulted in the isolation of 0.705 g (55%) of a white solid which was shown to be pure **5**: mp 147.5–148.5°; ir (CCl_3H) 3410, 2935, 2860, 1769, 1710, 1455, 1370, 1305, 1090, 997 cm^{-1}; ^1H NMR (CCl_3D) δ 1.00–1.92 (m, 10), 2.00 (s, 3), 2.60 (s, 2), 8.90 (broad s, 1, NH); ^{13}C NMR (CCl_3D) δ 20.71 (q), 24.10 (t), 25.02 (t), 34.43 (t), 45.42 (t), 65.90 (s), 168.01 (s), 170.02 (s); mass spectrum (70 eV) *m/e* (rel intensity) 196 (9, M^+), 178 (11), 154 (40), 123 (16), 122 (78), 112 (18), 111 (37), 100 (23), 98 (40), 96 (37), 95 (73), 94 (33), 81 (100), 79 (43), 75 (50), 68 (42), 67 (88), 56 (23), 55 (56), 54 (40), 53 (31), 43 (89), 41 (55).

Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 61.09; H, 8.34; N, 14.20.

From Irradiation of 8. A solution of 1-acetylpyrazolidin-3-one-5-spirocyclohexane (**8**, 0.100 g, 0.50 mmol) in methanol (40 ml) was degassed with a stream of nitrogen for 2 hr, after which it was irradiated for 20 hr. Stripping of the solvent left an oil. Column chromatography of the oil on silicic acid with Et_2O–EtOH (90:10 mixture by volume) eluent resulted in 0.031 g (31%) of a solid. The solid was shown to be pure **5** by ir, TLC, and ^1H NMR comparison to **5** obtained from the irradiation of **1d**.

From Acylation of 7. To a solution of 1-aminoazetidin-2-one-4-spirocyclohexane (**7**, 0.023 g, 0.15 mmol) and triethylamine (0.016 g, 0.15 mmol) in benzene (1 ml) under a nitrogen atmosphere and cooled to 10° was added slowly acetyl chloride (0.012 g, 0.15 mmol). After the addition was complete, the mixture was stirred for 1 hr at 10° and 5 hr at room temperature. Additional benzene (5 ml) was added, the mixture was filtered, and the solvent was evaporated to leave an oil which was shown to be 95% 1-acetamidoazetidin-2-one-4-spirocyclohexane (**5**) by ir, ^1H NMR, and TLC comparison to **5** obtained from the irradiation of **1d**.

Pyrazolidin-3-one-5-spirocyclopentane (2a). Compound **2a** was prepared in 90% yield in a manner similar to that described for **1a**. For **2a**: mp 95–97°; ir (CCl_3H) 3430, 3225 (broad), 2945, 2865, 1702 (broad), 1455, 1375, 1339, 1080, 962, 880 cm^{-1}; ^1H NMR (CCl_3D) δ 1.55–1.90 (m, 8), 2.48 (s, 2); ^{13}C NMR (CCl_3D) δ 24.04 (t), 37.08 (t), 43.51 (t), 70.39 (s), 178.04 (s); mass spectrum (70 eV) *m/e* (rel intensity) 140 (23, M^+), 111 (37), 109 (18), 108 (9), 98 (100), 97 (21), 82 (21), 81 (11), 68 (31), 58 (15), 41 (29).

Anal. Calcd for $C_7H_{12}N_2O$: C, 59.98; H, 8.63; N, 19.98. Found: C, 59.92; H, 8.56; N, 19.93.

1-(2,2,2-Trichloroethoxycarbonyl)pyrazolidin-3-one-5-spirocyclopentane (2b). Compound **2b** was prepared in 41% yield in a manner similar to that described for **1b**. For **2b**: mp 196–197°; ir (CCl_3H) 3400, 2945, 2865, 1709 (broad), 1450, 1385, 1340, 1285, 1130 cm^{-1}; ^1H NMR (CCl_3D) δ 1.5–2.10 (m, 6), 2.30–2.65 (m, 2), 2.75 (s, 2), 4.86 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 314 (5, 3-Cl, M^+), 167 (8), 139 (16), 131 (10, 3-Cl), 111 (15), 109 (31), 108 (49), 98 (27), 97 (23), 96 (29), 95 (15), 81 (28), 80 (88), 79 (27), 78 (21), 77 (17), 68 (17), 67 (100), 61 (35), 55 (23), 54 (31), 53 (20), 44 (67), 41 (47).

Anal. Calcd for $C_{10}H_{13}N_2O_3Cl_3$: C, 38.06; H, 4.15; N, 8.88. Found: C, 38.06; H, 4.13; N, 8.81.

2-Acetyl-1-(2,2,2-trichloroethoxycarbonyl)pyrazolidin-3-one-5-spirocyclopentane (2c) via 3-Acetoxy-1-(2,2,2-trichloroethoxycarbonyl)-2-pyrazoline-5-spirocyclopentane (4). Compound **2c** was prepared in 66% yield via compound **4** in a manner similar to that described for **1c** and **3**. For **4**: ^1H NMR (CCl_3D) δ 1.45–2.10 (m, 6), 2.23 (s, 3), 2.35–2.70 (m, 2), 3.16 (s, 2), 4.90 (s, 2). For **2c**: mp 87.5–88.5°; ir (CCl_3H) 2955, 1740 (broad), 1450, 1370, 1260, 1155, 1115, 970 cm^{-1}; ^1H NMR (CCl_3D) δ 1.50–2.10 (m, 6), 2.15–2.45 (m, 2), 2.53 (s, 3), 2.77 (s, 2), 4.80 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) no parent, 312 (trace, 3-Cl), 280 (trace, 3-Cl), 238 (trace, 3-Cl), 225 (3), 182 (1), 140 (12), 114 (12), 111 (8), 99 (10), 98 (30), 96 (14), 86 (10), 82 (23), 81 (14), 79 (9), 67 (60), 61 (17), 60 (100), 54 (16), 45 (94), 44 (91), 43 (96).

Anal. Calcd for $C_{12}H_{15}N_2O_4Cl_3$: C, 40.30; H, 4.23; N, 7.83. Found: C, 40.22; H, 4.28; N, 7.72.

2-Acetylpyrazolidin-3-one-5-spirocyclopentane (2d). Compound **2d** was prepared in 51% yield in a manner similar to that described for **1d**. For **2d**: mp 69–71°; ir (CCl_3H) 3260, 2925, 2870, 1750, 1700, 1410, 1375, 1340, 1290, 975, 840 cm^{-1}; ^1H NMR (CCl_3D) δ 1.50–1.95 (m, 8), 2.44 (s, 3), 2.74 (s, 2), 5.06 (broad s, 1, NH); ^{13}C NMR (CCl_3D) δ 23.96 (q), 37.22 (t), 45.83 (t), 65.87 (s), 167.00 (s), 172.40 (s); mass spectrum (70 eV) *m/e* (rel intensity) 182 (10, M^+), 141 (9), 140 (100), 112 (12), 111 (59), 109 (8), 99 (12), 98 (84), 97 (32), 82 (17), 81 (14), 79 (11), 67 (43), 60 (23), 54 (22), 45 (21), 44 (18), 43 (50), 41 (32); uv (EtOH) 225 nm (ϵ 3700), 244 (2250).

Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.27; H, 7.68; N, 15.35.

1-Acetamidoazetidin-2-one-4-spirocyclopentane (6). Compound **6** was prepared in 50% yield in a manner similar to that described for **5**. For **6**: mp 95–96°; ir (CCl_3H) 3400, 2950, 2870, 1769, 1710, 1453, 1368, 1333, 1091, 907 cm^{-1}; ^1H NMR (CCl_3D) δ 1.40–2.00 (m, 8), 2.00 (s, 3), 2.79 (s, 2), 9.14 (broad s, 1, NH); ^{13}C NMR (CCl_3D) δ 20.59 (q), 24.12 (t), 33.91 (t), 47.21 (t), 71.53 (s), 168.51 (s), 170.00 (s); mass spectrum (70 eV) *m/e* (rel intensity) 182 (2, M^+), 164 (44), 163 (33), 149 (6), 140 (10), 121 (6), 111 (9), 108 (8), 100 (15), 98 (32), 83 (21), 82 (35), 81 (23), 80 (12), 79 (24), 67 (100), 62 (31), 61 (13), 60 (12), 59 (27), 58 (12), 44 (13), 43 (35), 41 (32).

Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.13; H, 7.58; N, 15.26.

1-Aminoazetidin-2-one-4-spirocyclohexane (7). From Irradiation of 1a. A solution of freshly recrystallized pyrazolidin-3-one-5-spirocyclohexane (**1d**, 1.00 g, 6.50 mmol) in methanol (250 ml) was degassed with a stream of nitrogen for 2 hr after which it was irradiated for 20 hr. Stripping of the solvent left an oil which was column chromatographed on silicic acid with Et_2O–EtOH (80:20 mixture by volume) eluent. From the column was obtained 0.171 g (17%) of an oil which was identified from its spectra to be **7**: ir (CCl_3H) 2920, 1745, 1300, 1000, 905 cm^{-1}; ^1H NMR (CCl_3D) δ 1.10–2.10 (m, 10), 2.48 (s, 2), 3.80 (broad s, 2, NH_2); ^{13}C NMR (CCl_3D) δ 24.08 (t), 24.93 (t), 33.33 (t), 45.68 (t), 62.80 (s), 167.59 (s); mass spectrum (70 eV) *m/e* (rel intensity) 154 (35, M^+), 151 (12), 139 (16), 138 (14), 123 (34), 122 (100), 111 (15), 110 (25), 99 (16), 96 (18), 95 (84), 94 (23), 81 (55), 79 (26), 68 (21), 67 (51), 55 (45), 54 (26), 41 (34).

Compound **7** was acetylated to give **5**, for which a correct analysis was obtained (see above, **5**).

From Deacylation of 5. To a solution of PCl_5 (0.470 g, 2.2 mmol) and quinoline (0.516 g, 4 mmol) in methylene chloride (20 ml) cooled to 0° under a nitrogen atmosphere was added slowly a solution of 1-acetamidoazetidin-2-one-4-spirocyclohexane (**5**, 0.370 g, 1.9 mmol) in methylene chloride (1 ml). After the addition was complete, the mixture was allowed to warm to room temperature and to stir for 2 hr. The mixture was then cooled to 0° and *n*-BuOH (2.96 g, 40 mmol) was added dropwise. After the addition was complete, the mixture was allowed to warm to room temperature and to stir for 2 hr. After cooling the solution to 0° NaCl-saturated water (20 ml) was added dropwise. The mixture was stirred at 0° for 2 hr, after which the organic and aqueous layers were separated. The aqueous layer was extracted with methylene chloride and the combined organic layers washed with aqueous 2 *N* NaOH and dried over anhydrous K_2CO_3. Evaporation of the solvent left

an oil which was column chromatographed on silicic acid with Et_2O–EtOH (80:20 mixture by volume) eluent. From the column was isolated 0.045 g (15%) of an oil which was shown to be **7** by ir, ^1H NMR, and TLC comparison to **7** obtained from the photolysis of **1a**.

1-Acetylpyrazolidin-3-one-5-spirocyclohexane (8). To a solution of pyrazolidin-3-one-5-spirocyclohexane (**2a**, 1.54 g, 0.010 mol) and triethylamine (0.79 g, 0.010 mol) in methylene chloride (20 ml) cooled to 0° under a nitrogen atmosphere was added acetyl chloride (1.01 g, 0.010 mol) over a period of 15 min. The resultant mixture was stirred for 4 hr at 0° and 12 hr at room temperature after which it was heated to boiling and the insoluble triethylamine hydrochloride salt was filtered off. Evaporation of the benzene left a white solid. Recrystallization from Et_2O gave 0.571 g (29%) of pure **8**: mp 175.0–176.0°; ir (CCl_3H) 3385, 2915, 1707, 1630, 1382, 1300, 1270, 980 cm^{-1}; ^1H NMR (CCl_3D) δ 1.08–1.52 (m, 3), 1.60–2.04 (m, 5), 2.20 (s, 3), 2.20–2.64 (m, 2), 2.78 (s, 2); ^{13}C NMR (CCl_3D) δ 22.93 (q), 23.25 (t), 24.72 (t), 34.17 (t) 42.88 (t), 66.83 (s), 162.91 (s), 167.90 (s); mass spectrum (70 eV) *m/e* (rel intensity) 196 (30, M^+), 154 (100), 122 (21), 112 (24), 111 (69), 101 (24), 98 (65), 86 (100), 81 (31), 67 (22), 58 (25), 57 (27), 55 (27), 43 (46), 41 (31); uv (EtOH) 239 nm (ϵ 11000).

Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 61.46; H, 8.38; N, 14.08.

1-Acetyl-5-methylpyrazolidin-3-one (9). Compound **9** was prepared in 24% yield from 5-methylpyrazolidin-3-one[24] in a manner similar to that described for **8**. For **9**: mp 138.5–139.5°; ^1H NMR (CCl_3D) δ 1.40 (d, J = 6 Hz, 3), 2.11 (s, 3), 2.28 (d, J = 17 Hz, 1), 3.14 (doublet of doublets, J = 9 and 17 Hz, 1), 4.34–4.82 (m, 1), 10.52 (broad s, 1, NH); ^{13}C NMR (CCl_3D) δ 19.48 (q), 20.67 (q), 39.00 (t), 52.59 (d), 161.89 (s), 168.92 (s); mass spectrum (70 eV) *m/e* (rel intensity) 142 (16, M^+), 100 (64), 85 (32), 69 (35), 58 (29), 57 (23), 43 (100); uv (EtOH) 238 nm (ϵ 9800).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.64; H, 7.01; N, 19.61.

Ethyl 4′-Thiacyclohexylideneacetate (12). To a mixture of 57% dispersion of sodium hydride in mineral oil (4.2 g, 0.100 mol) in dry benzene (50 ml) under a nitrogen atmosphere was added dropwise over a 45-min period triethyl phosphonoacetate (23.5 g, 0.105 mol). Cooling was applied as necessary to keep the temperature below 35°. After the addition of the triethyl phosphonoacetate was complete, the almost clear solution was stirred for 1 hr at room temperature. To this preformed anion was added thiacyclohexan-4-one[13] (11.6 g, 0.100 mol) over a 45-min period. Cooling was applied as necessary to keep the temperature below 25°. After addition of the ketone was complete, the mixture was heated to 60–70° for 15 min. It was then cooled and the liquid decanted off. The gummy precipitate was worked three more times with hot benzene. The combined benzene layers were distilled to give 15.1 g (81%) of product. GLC analysis revealed this to he mainly **12** containing a small amount (ca. 5%) of unreacted triethyl phosphonoacetate which could not be removed by simple distillation. The product was therefore used in the next step without further purification. A pure sample was obtained by preparative GLC. For **12**: bp 88–90° (0.20 mm); ir (CCl_4) 2980, 2900, 1715, 1650, 1430, 1378, 1309, 1271, 1249, 1203, 1165 (broad), 1130, 1040, 862 cm^{-1}; ^1H NMR (CCl_3D) δ 1.26 (t, J = 7 Hz, 3), 2.40–2.90 (m, 6), 3.10–3.35 (m, 2), 4.12 (q, J = 7 Hz, 2), 5.66 (broad s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 186 (68, M^+), 157 (24), 141 (38), 139 (11), 125 (12), 114 (10), 113 (100), 112 (81), 111 (23), 99 (14), 97 (21), 85 (16), 79 (39), 77 (12), 67 (15), 55 (11), 47 (10), 45 (16), 41 (17).

Pyrazolidin-3-one-5-spiro[4′-thiacyclohexane] (13a). Compound **13a** was prepared in 92% yield in a manner similar to that described for **1a**. For **13**: mp 137.5–138.5°; ir (CCl_3H) 3430, 3235 (broad), 2905, 2835, 1701 (broad), 1378, 1270, 972, 860 cm^{-1}; ^1H NMR (CCl_3D) δ 1.85–2.10 (m, 4), 2.30 (s, 2), 2.35–2.65 (m, 2), 2.70–3.05 (m, 2); ^{13}C NMR (CCl_3D) δ 24.65 (t), 36.22 (t), 43.98 (t), 61.14 (t), 177.02 (s); mass spectrum (70 eV) *m/e* (rel intensity) 172 (6, M^+), 156 (2), 144 (3), 139 (4), 114 (100), 100 (75), 87 (78), 86 (30), 82 (17), 80 (28), 68 (27), 67 (45), 65 (15), 57 (18), 53 (23), 45 (24), 44 (48), 41 (30).

Anal. Calcd for $C_7H_{12}N_2O$ S: C, 48.81; H, 7.02; N, 16.26. Found: C, 48.64; H, 7.06; N, 15.97.

1-(2,2,2-Trichloroethoxycarbonyl)pyrazolidin-3-one-5-spiro[4′-thiacyclohexane] (13b). Compound **13b** was prepared in 31% yield in a manner similar to that described for **1b**. For **13b**: mp 225–226° dec; ir (CCl_3H) 3410, 2910, 1711 (broad), 1385, 1342, 1312, 1280, 1135 cm^{-1}; ^1H NMR (CCl_3D) δ 2.00–2.30 (m, 2), 2.50–2.90 (m, 6), 2.72 (s, 2), 4.85 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) no parent, 254 (4), 196 (2, 3-Cl), 154 (12), 114 (90), 111 (24), 99 (90), 98 (47), 96 (53), 86 (88), 85 (41), 81 (34), 79 (46), 68 (36), 67 (67), 65 (24), 63 (33), 61 (100), 60 (28), 53 (40), 47 (32), 45 (50), 44 (57), 43 (36), 41 (60).

Anal. Calcd for $C_{10}H_{13}N_2O_3Cl_3S$: C, 34.55; H, 3.77; N, 8.06. Found: C, 34.39; H, 3.71; N, 7.97.

2-Acetyl-1-(2,2,2-trichloroethoxycarbonyl)pyrazolidin-3-one-5-spiro[4′-thiacyclohexane] (13c) via 3-Acetoxy-1-(2,2,2-trichloroethoxycarbonyl)-2-pyrazoline-5-spiro[4′-thiacyclohexane] (14). Compound **13c** was prepared in 44% yield via compound **14** in a manner similar to that described for **1c** and **3**. For **14**: ^1H NMR (CCl_3D) δ 1.95–2.20 (m, 2), 2.24 (s, 3), 2.55–2.90 (m, 6), 3.10 (s, 2), 4.88 (s, 2). For **13c**: mp 97–99°; ir (CCl_3H) 2910, 1745 (broad), 1375, 1320, 1280, 1123, 1035 cm^{-1}; ^1H NMR (CCl_3D) δ 1.85–2.20 (m, 2), 2.35–3.10 (m, 6), 2.52 (s, 3), 2.74 (s, 2), 4.81 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) no parent, 142 (8), 114 (18), 100 (19), 99 (14), 96 (10), 86 (17), 85 (17), 67 (10), 61 (12), 60 (96), 59 (12), 45 (93), 44 (79), 43 (100), 42 (19), 41 (31).

Anal. Calcd for $C_{12}H_{15}N_2O_4Cl_3S$: C, 36.99; H, 3.88; N, 7.19. Found: C, 37.03; H, 3.85; N, 6.96.

2-Acetylpyrazolidin-3-one-5-spiro[4′-thiacyclohexane] (13d). Compound **13d** was prepared in 43% yield in a manner similar to that described for **1d**. For **13d**: mp 100.5–101.5°; ir (CCl_3H) 3255, 2905, 2835, 1747, 1699, 1407, 1370, 1275, 972 cm^{-1}; ^1H NMR (CCl_3D) δ 1.85–2.10 (m, 4), 2.30–2.68 (m, 2), 2.45 (s, 3), 2.61 (s, 2), 2.70–3.05 (m, 2), 4.96 (broad s, 1, NH); ^{13}C NMR (CCl_3D) δ 23.91 (q), 24.76 (t), 36.42 (t), 45.86 (t), 56.34 (s), 167.00 (s), 171.91 (s); mass spectrum (70 eV) *m/e* (rel intensity) 214 (24, M^+), 173 (8), 172 (89), 195 (100), 116 (8), 112 (8), 111 (74), 100 (13), 99 (16), 98 (53), 97 (17), 86 (7), 85 (13), 60 (18), 45 (24), 43 (63), 41 (20); uv (EtOH) 226 nm (ϵ 4140), 246 (2500).

Anal. Calcd for $C_9H_{14}N_2O_2S$: C, 50.45; H, 6.59; N, 13.07. Found: C, 50.34; H, 6.49; N, 13.01.

1-Acetamidoazetidin-2-one-4-spiro[4′-thiacyclohexane] (15). Compound **15** was prepared in 45% yield in a manner similar to that described for **5**. For **15**: mp 151–154°; ir (CCl_3H) 3390, 3240 (broad), 2910, 1770, 1705, 1368, 1270, 1085, 965 cm^{-1}; ^1H NMR (CCl_3D) δ 2.00 (s, 3), 2.09 (t, J = 5 Hz, 4), 2.62 (s, 2), 2.70 (t, J = 5 Hz, 4), 8.64 (s, 1, NH); ^{13}C NMR (CCl_3D) δ 20.63 (q), 26.92 (t), 33.91 (t), 45.03 (t), 64.54 (s), 168.30 (s), 170.81 (s). mass spectrum (70 eV) *m/e* (rel intensity) 214 (22, M^+), 196 (11), 172 (76), 144 (71), 114 (77), 112 (65), 111 (62), 99 (82), 98 (56), 86 (59), 67 (45), 43 (100), 41 (42).

Anal. Calcd for $C_9H_{14}N_2O_2S$: C, 50.45; H, 6.59; N, 13.07. Found: C, 50.22; H, 6.58; N, 13.06.

2-Acetyl-1-(2,2,2-trichloroethoxycarbonyl)pyrazolidin-3-one-5-spiro[4′-thiacyclohexane] 4′-Oxide (17). To a solution of 2-acetyl-1-(2,2,2-trichloroethoxycarbonyl)pyrazolidin-3-one-5-spiro[4′-thiacyclohexane] (**13c**, 1.00 g, 2.58 mmol) in methylene chloride (25 ml) cooled to 0° under a nitrogen atmosphere was added dropwise *m*-chloroperoxybenzoic acid (0.44 g, 2.58 mmol) in methylene chloride (5 ml). After stirring at 0° for 12 hr the mixture was allowed to warm to room temperature, after which it was washed three times with 15-ml portions of saturated aqueous sodium bicarbonate. The methylene chloride was dried over $MgSO_4$ and evaporated to give an oil. Column chromatography of the oil on silicic acid using Et_2O–EtOH (90:10 mixture by volume) gave 0.41 g (39%) of a colorless oil which was shown to be **17**: ir (CCl_3H) 2925, 1742 (broad), 1375, 1325, 1290, 1120, 1022 cm^{-1}; ^1H NMR (CCl_3D) δ 1.90–2.35 (m, 2), 2.40–3.30 (m, 6), 2.55 (s, 3), 2.72 (broad s, 2).

Anal. Calcd for $C_{12}H_{15}N_2O_5Cl_3S$: C, 35.53; H, 3.73; N, 6.91. Found: C, 35.65; H, 3.71; N, 7.05.

Reaction of 2-Acetyl-1-(2,2,2-trichloroethoxycarbonyl)pyrazolidin-3-one-5-spiro[4′-thiacyclohexane] 4′-Oxide (17) with Acetic Anhydride. A solution of 2-acetyl-1-(2,2,2-trichloroethoxycarbonyl)pyrazolidin-3-one-5-spiro[4′-thiacyclohexane] 4′-oxide (**17**, 0.085 g, 0.208 mmol) in acetic anhydride (5 ml) was heated at 120° for 2 hr under a nitrogen atmosphere. Immediately after removing the oil bath, aspirator vacuum was applied to the reaction vessel to remove the acetic anhydride solvent. When the reaction vessel had cooled to room temperature, it was placed under high vacuum for a short period of time. ^1H NMR analysis of the crude product resulted in a spectrum which contained major signals for two olefin protons, a doublet at δ 5.64 (J = 10 Hz) and a doublet at 6.56 (J = 10 Hz), along with the other signals expected for **17**. Attempts to purify the sample by column chromatography on silicic acid or by recrystallization resulted in samples in which the olefin signals were either greatly reduced or absent.

2,2-Dimethyl-3-thiacyclopentan-1-one (21). To a solution of NaOH (62 g) in a mixture of water (400 ml) and EtOH (250 ml) at room temperature under a nitrogen atmosphere was added all at once 2-mercaptopropionic acid (82 g, 0.77 mol). After the solution

had cooled to room temperature ethyl 2-bromoisobutyrate (150 g, 0.77 mol) was added all at once. The resulting solution was stirred at room temperature for 5 hr, after which it was cooled in an ice bath and aqueous 12 *N* HCl (100 ml) was added. The resulting acidic solution was extracted with Et_2O which was dried over anhydrous $MgSO_4$ and distilled up to 80°. To the residue was added EtOH (1500 ml) and the mixture refluxed overnight. To the still warm reaction mixture was added Na_2CO_3 (25 g) after which the EtOH was distilled off. To the residue cooled in an ice bath was added aqueous 2 *N* NaOH (100 ml). The basic solution was extracted with Et_2O which was dried over anhydrous $MgSO_4$ and distilled to give 153 g (81%) of the sulfide of α-isobutyric acid β-propionic acid diethyl ester: bp 160° (30 mm); mass spectrum (70 eV) *m/e* 248 (M^+). The sulfide (153 g, 0.62 mol) in Et_2O (350 ml) was dripped slowly into a suspension of NaOEt (84 g, 1.24 mol) in Et_2O (1250 ml) heated at 50°. During the addition the mixture became almost clear and then turned cloudy. The mixture was heated at 50° overnight, after which most of the Et_2O was distilled off. The residue was poured into ice-cold water (200 ml) and aqueous 12 *N* HCl was added slowly until the pH of the solution was strongly acidic. The acidic solution was extracted with Et_2O which was dried over anhydrous $MgSO_4$ and distilled to give 81 g (65%) of foul-smelling 5-ethoxycarbonyl-2,2-dimethyl-3-thiacyclopentan-1-one: bp 71° (0.5 mm); mass spectrum (70 eV) *m/e* 202 (M^+).

The β-keto ester (30 g, 0.148 mol) in a mixture of water (225 ml) and sulfuric acid (25 ml) was refluxed for 4 hr. The cooled solution was saturated with NaCl and extracted with Et_2O. The combined Et_2O was washed with aqueous Na_2CO_3 and then dried over anhydrous $MgSO_4$ and distilled to give 13.94 g (72%) of pure **21**: bp 80° (20 mm); ir (CCl_4) 2970, 1740, 1460, 1405, 1381, 1364, 1275, 1140, 1060, cm^{-1}; ^1H NMR (CCl_3D) δ 1.36 (s, 6), 2.56–2.80 (m, 2), 2.84–3.08 (m, 2); mass spectrum (70 eV) *m/e* (rel intensity) 130 (63, M^+), 112 (72), 75 (7), 74 (100), 59 (65), 45 (8), 41 (12).

An analysis was obtained on the *p*-toluenesulfonic acid hydrazone of ketone **21**, mp 157–159°.

Anal. Calcd for $C_{13}H_{18}N_2O_2S_2$: C, 52.32; H, 6.08; N, 9.39. Found: C, 52.22; H, 6.01; N, 9.26.

Ethyl 2′,2′-Dimethyl-3′-thiacyclopentylideneacetate (20) and Ethyl 5′,5′-Dimethyl-4′-thia-1′-cyclopenten-1′-ylacetate (22). A Wittig reaction on 2,2-dimethyl-3-thiacyclopentan-1-one (**21**) in a manner similar to that used to prepare compound **12** resulted in a 76% yield of distilled product. ^1H NMR analysis revealed this to be a mixture of approximately 60% **20** and 40% **22**. Spectral data were obtained on GLC collected samples of the two esters. For **20**: ir (CCl_3H) 1707 cm^{-1}; ^1H NMR (CCl_3H) δ 1.28 (t, *J* = 8 Hz, 3), 1.50 (s, 3), 2.95 (t, *J* = 7 Hz, 2), 3.40 (doublet of triplet, *J* = 4 and 7 Hz, 2), 4.18 (q, *J* = 8 Hz), 5.70 (t, *J* = 4 Hz, 1); mass spectrum (70 eV) *m/e* (rel intensity) 200 (41, M^+), 185 (72), 155 (14), 139 (46), 127 (100), 111 (53), 93 (23), 77 (26). For **22**: ir (CCl_3H) 1731 cm^{-1}; ^1H NMR (CCl_3H) δ 1.28 (t, *J* = 8 Hz, 3), 1.48 (s, 3), 3.00–3.10 (m, 1), 3.62–3.72 (m, 1), 4.18 (q, *J* = 8 Hz, 2), 5.63–5.75 (m, 1); mass spectrum (70 eV) *m/e* (rel intensity) 200 (46, M^+), 185 (100), 139 (44), 127 (21), 113 (26), 112 (25), 111 (79), 97 (19), 77 (18), 41 (31).

***cis*-Indazolidin-3-one (26a), *trans*-Indazolidin-3-one (26b), and Cyclohex-1-enecarboxylic Acid Hydrazide (27).** 1-Carboethoxycyclohex-1-ene[18] (**24**) was treated with hydrazine in a manner similar to that described for the preparation of **1a**. Column chromatography of the crude product on silicic acid resulted in the isolation of 0.70 g (5%) of a white solid which was identified as cyclohex-1-enecarboxylic acid hydrazide (**27**) by comparison to a sample prepared below and 0.98 g (7%) of an oil which was identified to be a 90:10 mixture of **26a–26b**: ir (CCl_3H) 3425, 2930, 2860, 1705, 902 cm^{-1}; ^1H NMR (CCl_3D) δ 1.00–2.40 (m, 8), 2.48–2.78 (m, 1, one of **26a** bridgehead proton absorptions), 3.40–3.72 (m, 1, one of **26a** bridgehead proton absorptions), 6.60 (broad s, 2, NH). Trace multiplet absorptions at δ 2.20 and 2.98 were assigned as the two bridgehead protons of **26b**; ^{13}C NMR (CCl_3D) absorptions at δ 42.0 (d) and 58.0 (d) were assigned to **26a** while absorptions at δ 49.0 (d) and 56.5 (d) were assigned to **26b**. The relative intensities of the **26a** to **26b** signals were approximately 9:1; mass spectrum (70 eV) *m/e* (rel intensity) 140 (100, M^+), 125 (16), 109 (71), 98 (67), 97 (43), 81 (67), 71 (24), 67 (32), 54 (22), 41 (22).

The best yields of acylated **26** were obtained by taking the crude reaction mixture and pouring it into ice-cold 2 *N* HCl (90 ml). After washing with Et_2O the acidic aqueous layer was poured into ice-cold 2 *N* K_2CO_3 (100 ml). The basic solution was extracted with CCl_3H which was dried over K_2CO_3 and stripped to leave an oil. The Et_2O soluble (approximately 100 ml Et_2O) portion of this oil was used in the acylation reaction.

Cyclohex-1-enecarboxylic Acid Hydrazide (27). To cyclohex-1-enecarboxylic acid (2.7 g, 0.021 mol) in methylene chloride (50 ml) was added 1.50 g (0.011 mol) of anhydrous K_2CO_3. This mixture was stirred until no gas evolution (CO_2) was observed (ca. 12 hr), at which time it was cooled to 0° and ethyl chloroformate (2.5 g, 0.23 mol) in chloroform (10 ml) containing 1% pyridine was added dropwise. After the mixture was allowed to stir for several hours at 0°, it was poured into a solution of 95% hydrazine (1.0 g, 0.03 mol) in methylene chloride (50 ml) and allowed to stir for another 12 hr. Acid–base work-up gave 1.8 g (60%) of hydrazide **27** as a white solid: mp 78–79° (Bz); ir ($CHCl_3$) 3480, 3340, 2930, 1670, 1625, 1475, 960, and 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61 (m, 4), 2.2 (m, 4), 4.08 (broad s, 2, absent D_2O, NNH_2), 6.70 (broad s, 1, C=CH), and 7.9 (broad s, 1, absent D_2O, $CONHNH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 140 (12, M^+), 125 (3), 109 (100), 81 (73), 79 (29), 77 (8), 53 (25).

Anal. Calcd for $C_7H_{12}N_2O$: C, 59.97; H, 8.63. Found: C, 59.82; H, 8.87.

1-(2,2,2-Trichloroethoxycarbonyl)-*cis*-indazolidin-3-one (28a). A partially purified 90:10 mixture of *cis*- and *trans*-indazolidin-3-one (**26a–26b**) was acylated in a manner similar to that described for the acylation of **1a** to give **1b**. Column chromatography of the crude product on silicic acid resulted in the isolation of 0.65 g (13%) of a white solid which was identified as **28a**: mp 173.5–175.5°; ir (CCl_3H) 3415, 2940, 2860, 1710 (broad), 1450, 1380, 1325, 1125, 905 cm^{-1}; ^1H NMR (CCl_3D) δ 1.00–2.40 (m, 8), 2.88–3.12 (m, 1), 4.44–4.80 (m, 1), 4.87 (s, 2), 9.60 (broad s, 1); ^{13}C NMR (CCl_3D) δ 21.84 (t), 21.92 (t), 22.33 (t), 27.35 (t), 41.19 (d), 58.27 (d), 75.26 (t), 95.03 (s), 151.83 (s), 173.01 (s); mass spectrum (70 eV) *m/e* (rel intensity) 314 (12, 3-Cl, M^+), 272 (8, 3-Cl), 184 (11), 167 (13), 139 (99), 131 (46, 3-Cl), 109 (60), 81 (79), 67 (82), 44 (100), 41 (60).

Anal. Calcd for $C_{10}H_{13}N_2O_3Cl_3$: C, 38.06; H, 4.15; N, 8.88. Found: C, 37.95; H, 4.13; N, 8.88.

1-(2,2,2-Trichloroethoxycarbonyl)-5-methylpyrazolidin-3-one (29). Compound **29** was prepared in 57% yield from 5-methylpyrazolidin-3-one[24] in a manner similar to that described for **1b**. For **29**: mp 165.5–166.5°; ir (CCl_3H) 3410, 2940, 1720 (broad), 1382, 1332, 1080 cm^{-1}; ^1H NMR (CCl_3D) δ 1.45 (d, *J* = 7 Hz, 3), 2.29 (doublet of doublets, *J* = 17 and 3 Hz, 1), 3.07 (doublet of doublets, *J* = 17 and 9.5 Hz, 1) 4.45–4.75 (m, 1), 4.80 (s, 2), 9.10 (broad s, 1, NH); mass spectrum (70 eV) *m/e* (rel intensity) 274 (3-Cl, 3, M^+), 240 (3-Cl, trace), 131 (3-Cl, 8), 100 (32), 97 (20), 69 (27), 61 (36), 44 (100), 42 (47), 41 (55).

Anal. Calcd for $C_7H_9N_2O_3Cl_3$: C, 30.52; H, 3.29; N, 10.17. Found: C, 30.37; H, 3.17; N, 10.15.

2-Acetyl-1-(2,2,2-trichloroethoxycarbonyl)-*cis*-indazolidin-3-one (31a). 1-(2,2,2-Trichloroethoxycarbonyl)-*cis*-indazolidin-3-one (**29**) was acetylated in a manner similar to that described for the acylation of **1b** to give **3**. ^1H NMR analysis of the crude product revealed it to be a 70:30 mixture of the *N*-acetyl derivative **31a** and the *O*-acetyl derivative **32a** as determined by integration of the acetyl methyl singlet absorptions assigned to the two isomers. Heating of the mixture of the two isomers neat under a nitrogen atmosphere at 110° for 3 hr resulted in exclusively the *N*-acetyl isomer. Column chromatography resulted in 0.611 g (58%) of an oil which was identified as **31a**: ^1H NMR (CCl_3D) δ 1.00–1.96 (m, 6), 2.08–2.44 (m, 2), 2.54 (s, 3), 2.92–3.16 (m, 1), 2.56–2.92 (m, 1), 2.82 (AB pattern, *J* = 12 Hz, 2); ^{13}C NMR (CCl_3D) δ 21.62, 22.50, 23.76, 27.38, 43.29 (d), 58.87 (d), 75.61 (t), 94.75 (s), 154.51 (s), 166.04 (s), 172.64 (s).

Anal. Calcd for $C_{12}H_{15}N_2O_4Cl_3$: C, 40.30; H, 4.23; N, 7.83. Found: C, 40.25; H, 4.15; N, 7.77.

2-Acetyl-*cis*-indazolidin-3-one (33a). Compound **33a** was prepared in 46% yield in a manner similar to **1d**. For **33a**: mp 84–86°; ir (CCl_3H) 2920, 2850, 1748, 1695, 1378, 1286, 1108, 980, 910 cm^{-1}; ^1H NMR (CCl_3D) δ 1.00–2.40 (m, 8), 2.44 (s, 3), 2.80–3.08 (m, 1), 3.48–3.80 (m, 1), 5.52 (broad s, 1, NH); ^{13}C NMR (CCl_3D) δ 22.12, 22.41, 22.82, 23.74, 27.56 (t), 44.65 (d), 53.29 (d), 167.15 (s) 173.21 (s); mass spectrum (70 eV) *m/e* (rel intensity) 182 (5, M^+), 154 (16), 140 (61), 112 (11), 111 (27), 98 (41), 97 (100), 84 (14), 81 (13), 67 (14), 55 (10), 54 (10), 41 (29); uv (EtOH) 227 nm (ε 3582), 246 (2885).

Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.08; H, 7.74; N, 15.38.

1-Acetamido-*cis*-perhydrobenz[*c*]azetidin-2-one (34a). From Irradiation of 33a. Compound **34a** was prepared in a 45% yield in a manner similar to that described for **5**. For **34a**: ir (CCl_3H) 3410, 3230 (broad), 2940, 2860, 1768, 1702, 1450, 1370, 1105 cm^{-1}; ^1H NMR (CCl_3D) δ 1.34–1.98 (m, 8), 1.98 (s, 3), 3.10–3.36 (m, 1), 4.12–4.32 (m, 1), 9.18 (broad s, 1, NH); mass spectrum (70 eV) *m/e* (rel intensity) 182 (5, M^+), 140 (91), 97 (67), 81 (40), 67 (56), 54 (43), 43 (100), 41 (46).

Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.41; H, 7.87; N, 15.32.

From Acetylation of 36a. 1-Amino-*cis*-perhydrobenz[c]azetidin-2-one (**36a**) was acetylated in a manner similar to that described for the acetylation of compound 7 to give 5. A 90% yield of an oil was isolated which was shown to be **34a** by ir, ^1H NMR, and TLC comparison to **34a** obtained from the irradiation of **33a**.

1-Amino-*cis*-perhydrobenz[c]azetidin-2-one (36a). To a solution of *cis*-perhydrobenz[c]azetidin-2-one (**35a**, 0.69 g, 0.56 mmol) in tetrahydrofuran (which was freshly distilled from lithium aluminum hydride) under a nitrogen atmosphere and cooled to 0° was added over a 10-min period 2.6 *M* BuLi (0.216 ml). The resultant heterogeneous mixture was then stirred for 1 hr at 0°, after which a solution of *O*-mesitylene sulfonylhydroxylamine in tetrahydrofuran (1 ml) was added over a 5-min period. The resultant solution was stirred at 0° for 10 min and then poured in ice-cold aqueous 2 *N* K_2CO_3 (20 ml). The aqueous mixture was extracted with CCl_3H which was dried over K_2CO. Evaporation of the solvent left an oil which was column chromatographed on silicic acid with Et_2O–EtOH (80:20 mixture by volume) eluent. From the column was obtained 11 mg (14%) of an oil which was identified as **36a**: ir (CCl_3H) 2930, 1745 cm^{-1}; ^1H NMR (CCl_3D) δ 1.20–2.00 (m, 8), 2.92–3.16 (m, 1), 3.68–3.88 (m, 1), 3.92 (broad s, 2 NH_2); mass spectrum (70 eV) *m/e* (rel intensity) 140 (81, M^+), 109 (22), 108 (46), 82 (37), 81 (100), 67 (80), 54 (47), 41 (41).

Compound **36a** was acetylated to give **34a** for which a correct analysis was obtained (see above, **34a**).

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Registry No.—**1a**, 56700-30-2; **1b**, 56700-31-3; **1c**, 56700-32-4; **1d**, 56700-33-5; **2a**, 56700-34-6; **2b**, 56700-35-7; **2c**, 56700-36-8; **2d**, 56700-37-9; **3**, 56700-38-0; **4**, 56700-39-1; **5**, 56700-40-4; **6**, 56700-41-5; **7**, 56700-42-6; 8, 56700-43-7; **9**, 56700-44-8; **12**, 56700-45-9; **13a**, 56700-46-0; **13b**, 56700-47-1; **13c**, 56700-48-2; **13d**, 56700-49-3; **14**, 56700-50-6; **15**, 56700-51-7; **17**, 56700-52-8; **20**, 56700-53-9; **21**, 52662-41-6; **21** *p*-toluenesulfonic acid hydrazone, 56700-54-0; **22**, 56700-55-1; **24**, 1617-22-7; **26a**, 56700-56-2; **26b**, 56700-57-3; **27**, 56700-58-4; **28a**, 56700-59-5; **29**, 56700-60-8; **31a**, 56700-61-9; **33a**, 56700-62-0; **34a**, 56700-63-1; **35a**, 22031-53-4; **36a**, 56700-64-2; hydrazine, 302-01-2; cyclohexylidene acetate, 1552-91-6; 2,2,2-trichloroethoxycarbonyl chloride, 17341-93-4. 5-methylpyrazolidin-3-one, 10234-76-1; 2-mercaptopropionic acid, 79-42-5; ethyl 2-bromoisobutyrate, 600-00-0; α-isobutyric acid-β-propionic acid diethyl ester sulfide, 52662-42-7; 5-ethoxycarbonyl-2,2-dimethyl-3-thiacyclopentan-1-one, 52704-93-5; cyclohex-1-ene-1-carboxylic acid, 636-82-8.

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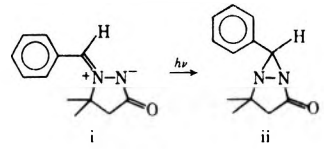

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Aspects of the Chemistry of 1-Aminoazetidin-2-ones and Pyrazolidin-3-ones

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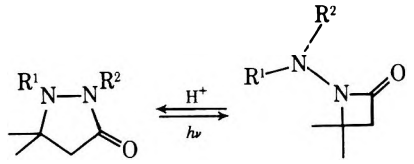
Several reactions of 1-amino-4,4-dimethylazetidin-2-one (**5**) and 1-acetamido-4,4-dimethylazetidin-2-one (**2**) have been examined and their chemistry compared with that of isomeric 5,5-dimethylpyrazolidin-3-ones. The 1-amino β-lactam system was found to undergo ring expansion reactions under a variety of conditions. The irradiation of several 2-alkylpyrazolidin-3-ones to give 1-alkylamino β-lactams in low yields is also discussed.

As part of our work toward the development of approaches to 1-amino- and 1-acylaminoazetidin-2-ones,[1] which we hope to incorporate into total syntheses of penicillin-like systems,[2] we found that these molecules undergo some interesting chemistry, particularly their ring-expansion reactions. While not a well-known class of molecules, 1-aminoazetidin-2-one derivatives have been prepared (1) by photolysis of nitrogen-unsubstituted[1,2] and various 1- or 2-substituted[1,2,3] pyrazolidin-3-ones, (2) by amination of nitrogen unsubstituted azetidin-2-ones,[2,4] (3) by cycloaddition of an acyl hydrazone with ketene,[5] (4) by reaction of an in situ generated 1,1-disubstituted hydrazine with a 3-halo acid chloride,[6] and (5) by an unusual *N*-amino triazole decomposition route.[7]

Results

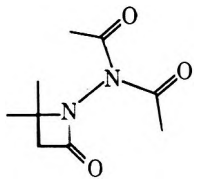
We have previously reported that 2-acetyl-5,5-dimethylpyrazolidin-3-one (1) undergoes photochemical reaction upon irradiation to give 1-acetamidoazetidin-2-one (2) in 65% yield.[1] Since that time, we have found that irradiation

Scheme I



	R^1	R^2		R^1	R^2
1	H	CH_3CO	2	H	CH_3CO
3	CH_3CO	H	5	H	H
4	H	H	21	H	CH_3
10	H	CH_3CH_2	22	H	CH_3CH_2
19	H	CH_3			
20	H	CH_2Ph			

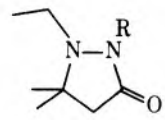
of 1-acetyl-5,5-dimethylpyrazolidin-3-one (**3**) gives **2** also, in 30% yield. Furthermore, irradiation of the nitrogen unsubstituted 5,5-dimethylpyrazolidin-3-one (**4**) gives the parent system 1-aminoazetidin-2-one (**5**) in 15% yield. When amine **5** was acetylated under heterogeneous conditions involving acetyl chloride and solid potassium carbonate in methylene chloride at 25°, the desired β-lactam **2** was not obtained but rather a mixture of products was produced from which 1-acetylpyrazolidin-3-one (**3**) was isolated as the major product (see Scheme I). Ring expansion was found not to occur, however, when the reaction was carried out under basic homogeneous conditions. Reaction of **5** with 1 equiv of acetyl chloride in triethylamine allowed isolation of β-lactam **2** in high yield. When 2 equiv of acetyl chloride and triethylamine were employed, diacetylated β-lactam **6** was obtained. We believed that under the heterogeneous acylation conditions, a low concentration of acid developed which catalyzed the rearrangements of **5**. This contention was supported when it was observed that treatment of 1-aminoazetidin-2-one (**5**) with ethanol–HCl for several hours at 25° resulted in the formation of pyrazolidin-3-one (**4**). Furthermore, 1-acetamidoazetidin-2-one (**2**) underwent a similar reaction to give **4**. We were unable, however, to decide whether hydrolysis of the acetyl group of **2** occurred before or after rearrangement since 2-acetylpyrazolidin-3-one (**1**) also hydrolyzes to give **4** when treated under similar conditions.



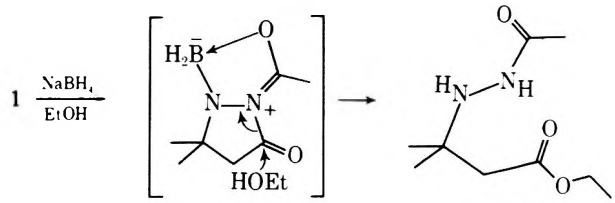
6

In contrast to their behavior under acidic conditions, β-lactams **2** and **5** were shown to be stable to mild base such as sodium ethoxide in ethanol for several hours at 25° or sodium borohydride ($NaBH_4$) in ethanol for 1 hr at 0°. β-Lactams **2**, **5**, and **6** were also thermally stable, since ir spectra of GLC collected samples (200°C) were identical with ir spectra of samples obtained by column chromatography using silicic acid.

While 1,2-diacylhydrazides **2** and **3** were stable to $NaBH_4$ in ethanol at 0°, 1,1-diacylhydrazide **1** reacted to give hydrazide ester **7** as the major product along with two unidentified minor products.[8] Since neither 1-ethyl-2-acetyl-5,5-dimethylpyrazolidin-3-one (**8**), prepared from 1-ethyl-5,5-dimethylpyrazolidin-3-one (**9**), nor 2-ethyl-5,5-dimethylpyrazolidin-3-one (**10**) reacted under similar conditions, we feel that a complexed species such as **11** might have been important in facilitating the reaction of **1**.

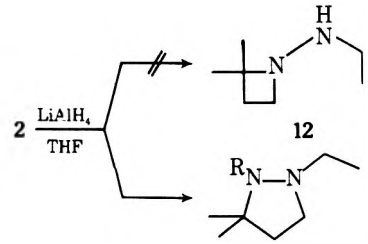


8, R = CH_3CO; **9**, R = H



11 **7**

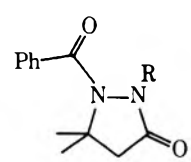
More vigorous reduction of acetamido β-lactam **2** using lithium aluminum hydride in refluxing tetrahydrofuran did not give the expected azetidine **12** but rather gave 2-ethyl-5,5-dimethylpyrazolidine (**13**) resulting not only from reduction but also rearrangement. Because this trialkylhydrazine was readily oxidized in air, it was converted to its 1-benzoyl derivative **14**.[9] The reduction–rearrangement product **13** was synthesized unequivocally by $LiAlH_4$ reduction of 2-ethyl-5,5-dimethylpyrazolidin-3-one (**10**) prepared via 1-benzoyl-5,5-dimethylpyrazolidin-3-one (**15**)[10] as described below. These reactions were found necessary at early stages of our work to ensure correct assignment of rearrangement isomers.



12

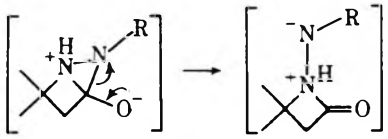
13, R = H; **14**, R = PhCO

Finally, to complete our photochemical studies on pyrazolidin-3-ones with various N substituents, the photochemistry of several 2-alkylpyrazolidin-3-ones was examined. The 2-methyl- (**19**), 2-ethyl- (**10**), and 2-benzyl- (**20**) 5,5-dimethylpyrazolidin-3-ones were synthesized by alkylation of **15**,[10] to give **16**–**18**, followed by removal of the benzoyl groups using acid hydrolysis. Irradiation of either the methyl **19** or ethyl **10** compound for 20 hr in degassed methanol with a Hanovia 450-W immersion lamp equipped with a Vycor filter allowed isolation, after careful column chromatography, of alkylamino β-lactams **21** and **22** in low yields (5% at best; see Scheme I). These β-lactams were characterized by their spectral properties (see Experimental Section). Although loss of starting material was not complete after 20 hr in these photolyses, longer irradiation times or variation of other parameters did not improve the yields of β-lactam. In contrast to **19** and **10**, irradiation of 2-benzyl 5,5-dimethylpyrazolidin-3-one (**20**) under a variety of conditions gave no β-lactam product. In this case 1- and 1,2-dibenzyl substituted pyrazolidin-3-ones were isolated in varying yields. Apparently cleavage of the 2-benzyl



15, R = H; **16**, R = Et; **17**, R = Me; **18**, R = CH_2Ph

group competed effectively with ring contraction. A similar problem was encountered in the photolysis of 2-phenylacetyl-5,5-dimethylpyrazolidin-3-one.[11] Photolysis results obtained for the 2-alkylpyrazolidin-3-ones are in line with the electron transfer quenching mechanism proposed for the photochemical ring contraction reaction of other 2-substituted pyrazolidin-3-ones.[1] If group R (the original 2 substituent) in intermediate **23** can stabilize the negative charge in ylide **24** (e.g., an acyl moiety), good yields of β-lactam are usually obtained. On the other hand, R groups which cannot stabilize the negative charge of ylide **24** (e.g., an alkyl moiety) result in low yields of β-lactam even with longer irradiation times. In these cases side reactions often become important.



23 **24**

Experimental Section

Melting points were taken in capillary tubes on a Thomas-Hoover Unimelt and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 A spectrometer. The ^1H NMR spectra were taken either on a Varian A-60 spectrometer or on a Perkin-Elmer JEOL MH-100 spectrometer and are reported in parts per million downfield from tetramethylsilane. Mass spectra were determined on a Perkin-Elmer Hitachi RMU-6D spectrometer. Ultraviolet spectra were taken on a Cary 14 recording spectrometer. Gas chromatography was carried out using programmed temperature control on a Hewlett-Packard 5750 B instrument equipped with 8- and 10-ft stainless steel columns packed with SE-30 on 80–100 mesh Chromosorb W. Mallinckrodt AR 100 mesh silicic acid was used for all column chromatography. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Irradiations were carried out using a Hanovia 450-W immersion lamp equipped with a Vycor filter unless otherwise specified.

1-Diacetylamino-4,4-dimethylazetidin-2-one (6). To a solution of 1-acetamido-4,4-dimethylazetidin-2-one (**2**, 0.156 g, 1.00 mmol) and triethylamine (0.101 g, 1.00 mmol) in a mixture of benzene (5 ml) and tetrahydrofuran (2 ml) under nitrogen was added with cooling acetyl chloride (0.078 g, 1.00 mmol) in benzene (1 ml) over a period of 30 min. The mixture was stirred for 8 hr at room temperature, after which the triethylamine hydrochloride salt was filtered off, washed with a little benzene, and the combined filtrates concentrated. The residue was taken up in ice-cold aqueous 2 *N* sodium hydroxide and extracted well with chloroform. The chloroform was dried over K_2CO_3 and evaporated to leave a white solid. Recrystallization of the solid from Et_2O gave 0.106 g (54%) of 1-diacetylamino-4,4-dimethylpyrazolidin-3-one (**6**): mp 92–93°; ir (CCl_3H) no NH, 2960, 1780, 1730, 1319, 1225 (broad), 1100, 1000 cm^{-1}; ^1H NMR (CCl_3D) δ 1.49 (s, 6), 2.43 (s, 6), 2.84 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 198 (trace, M^+), 157 (9), 156 (35), 114 (66), 101 (8), 100 (10), 99 (75), 83 (18), 72 (20), 56 (17), 55 (16), 43 (100), 42 (12), 41 (17).

Anal. Calcd for $C_9H_{14}N_2O_3$: C 54.53; H, 7.13; N, 14.13. Found: C, 54.73; H, 7.26; N, 13.98.

Ethyl 3-(2′-Acetylhydrazino)-3-methylbutyrate (7). To a solution of 2-acetyl-5,5-dimethylpyrazolidin-3-one[1] (**2**, 1.00 g, 6.5 mmol) in ethanol (40 ml) cooled to 0° under a nitrogen atmosphere was added $NaBH_4$ (1.32 g, 39.0 mmol) all at once. After stirring for 1 hr the mixture was poured into ice-cold water (40 ml) and extracted with chloroform. The chloroform was dried over K_2CO_3 and evaporated to leave an oil. Column chromatography of the oil in silicic acid with Et_2O–EtOH (90:10 mixture by volume) eluent resulted in the isolation of 598 mg (45%) of an oil which was shown to be pure **7**: ir (CCl_3H) 3430, 2960, 1720, 1670, 1370, 1320, 1110, 1022, 850 cm^{-1}; ^1H NMR (CCl_3D) δ 1.18 (s, 6), 1.26 (t, *J* = 7 Hz, 3), 1.98 (s, 3), 2.39 (s, 2), 4.11 (q, *J* = 7 Hz, 2); mass spectrum (70 eV) m/e (rel intensity) no parent ion, 156 (10), 114 (50), 99 (100), 83 (10), 72 (10), 56 (10), 55 (8), 43 (25).

Anal. Calcd for $C_9H_{18}N_2O_3$: C, 53.44; H, 8.97; N, 13.85. Found: C, 53.26; H, 9.06; N, 13.83.

2-Acetyl-1-ethyl-5,5-dimethylpyrazolidin-3-one (8). To a solution of 1-ethyl-5,5-dimethylpyrazolidin-3-one (**9**, 1.00 g, 7.1 mmol) and triethylamine (0.72 g, 7.1 mmol) in tetrahydrofuran (100 ml) was added dropwise a solution of acetyl chloride (0.56 g, 7.1 mmol) in tetrahydrofuran (5 ml). The mixture was stirred at room temperature for 6 hr, after which it was filtered to remove the precipitated triethylamine hydrochloride salt. Evaporation of the solvent left an oil which was column chromatographed on silicic acid using Et_2O–EtOH (90:10 mixture by volume) eluent to give 0.74 g (58%) of a pure oil which was identified as **8**: ir (CCl_3H) 2970, 1750, 1710, 1375, 1305, 1230 (broad), 1130, 1085, 955, 945 cm^{-1}; ^1H NMR (CCl_3D) δ 1.10 (t, *J* = 7 Hz, 3), 1.35 (s, 6), 2.50 (s, 3), 2.52 (s, 2), 3.04 (q, *J* = 7 Hz, 2); mass spectrum (70 eV) *m/e* (rel intensity) 184 (trace, M^+), 143 (3), 142 (31), 129 (7), 128 (100), 109 (5), 99 (14), 85 (2), 83 (5), 71 (2), 56 (5), 55 (4), 43 (12), 42 (6), 41 (7); uv (EtOH) end absorption 200 nm (ε 3200), 227 (3800), 262 (1000).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.51; H, 8.87; N, 15.03.

1-Ethyl-5,5-dimethylpyrazolidin-3-one (9). To a solution of 1-benzoyl-5,5-dimethylpyrazolidin-3-one[10] (**15**, 11.4 g, 0.10 mol) in EtOH (150 ml) cooled to 10° under a nitrogen atmosphere was added all at once acetaldehyde (13.2 g, 0.30 mol). The resulting solution was stirred at room temperature for 1 hr and then cooled to 0°. To the cooled solution was added $NaBH_4$ (20 g, 0.53 mol) in several portions at short intervals. After the last addition the mixture was allowed to warm to room temperature and to stir at that temperature for 30 min. The solution was again cooled and water was added. The mixture was extracted well with chloroform which was dried over K_2CO_3. Evaporation of the solvent left a solid. Column chromatography of the solid on silicic acid using Et_2O–EtOH (90:10 mixture by volume) eluent gave 4.3 g (30%) of pure **9**: mp 113.5–114.5; ir (CCl_3H) 3430, 2970, 1695, 1370, 1305, 1100 cm^{-1}; ^1H NMR (CCl_3D) δ 1.15 (t, *J* = 7.5 Hz, 3), 1.30 (s, 6), 2.38 (s, 2), 2.71 (q, *J* = 7.5 Hz, 2); mass spectrum (70 eV) *m/e* (rel intensity) 142 (27, M^+), 128 (8), 127 (100), 99 (36), 85 (10), 84 (7), 83 (24), 71 (9), 57 (12) 56 (14), 55 (13), 35 (8), 44 (7), 42 (13), 41 (18).

Anal. Calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.00; H, 10.05; N, 19.77.

2-Ethyl-5,5-dimethylpyrazolidin-3-one (10). A solution of 1-benzoyl-2-ethyl-5,5-dimethylpyrazolidin-3-one (**16**, 20.0 g, 0.082 mol) in a mixture of 12 *N* aqueous HCl (240 ml) and EtOH (80 ml) was refluxed under a nitrogen atmosphere for 20 hr. The solution was washed with Et_2O, after which it was cooled in an ice bath and solid NaOH was added to it until the pH was strongly basic. The basic water was extracted well with CCl_3H which was dried over K_2CO_3. Evaporation of the solvent left an oil which upon distillation gave 8.84 g (76%) of pure **10**: bp 65° (1 mm); ir (CCl_3H) 2920, 1680, 1460, 1400, 1300, 940, 910, 887 cm^{-1}; ^1H NMR (CCl_3D) δ 1.12 (t, *J* = 7 Hz, 3), 1.25 (s, 6), 2.31 (s, 2), 3.41 (q, *J* = 7 Hz, 2), 4.88 (broad s, 1, NH); mass spectrum (70 eV) *m/e* (rel intensity) 142 (51, M^+), 127 (66), 99 (58), 85 (90), 83 (81), 58 (42), 56 (100), 55 (36), 43 (50), 41 (42); uv (EtOH) 206 nm (ε 5330), 222 (3765).

Anal. Calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.14; H, 9.82; N, 19.70.

2-Benzoyl-1-ethyl-3,3-dimethylpyrazolidine (14). From 2. To a solution of 1-acetamido-4,4-dimethylazetidin-2-one[1] (**2**, 0.100 g, 0.640 mmol) in tetrahydrofuran (3 ml) cooled to 0° under a nitrogen atmosphere was added in several portions lithium aluminum hydride (0.292 g, 7.7 mmol). The mixture was allowed to warm to room temperature during a period of 30 min after which it was refluxed for 24 hr. At the end of the reflux period the mixture was cooled in an ice bath and water (10 ml) was added. The aqueous mixture was extracted well with Et_2O which was dried over K_2CO_3. Evaporation of the solvent left an oil which was taken up in methylene chloride (5 ml). In this solution cooled to 10–20°C under a nitrogen atmosphere was suspended a small quantity of anhydrous K_2CO_3. Benzoyl chloride (0.200 g, 14.0 mmol) was then added to the suspension and the resultant mixture stirred at room temperature for 6 hr. At the end of the reaction period the mixture was filtered and to the filtrate, cooled in an ice bath, was added aqueous 2 *N* HCl (approximately 4 ml). The mixture was extracted twice with Et_2O. To the aqueous layer, cooled in an ice bath, was added aqueous 2 *N* NaOH (approximately 6 ml). The resulting solution was extracted well with chloroform which was dried over K_2CO_3. Evaporation of the solvent left 0.030 g of an oil which was identified to be **14** (20% based on **2**) by comparison to **14** prepared by reduction–benzoylation of 2-ethyl-5,5-dimethylpyrazolidin-3-one (**10**).

From 10. To a suspension of lithium aluminum hydride (26.0 mmol, 1.00 g) in tetrahydrofuran (25 ml) cooled to 0° under a ni-

trogen atmosphere was added a solution of 1-ethyl-5,5-dimethylpyrazolidin-3-one (**10**, 7.00 mmol, 1.00 g) in tetrahydrofuran (5 ml) over a period of 30 min. The mixture was allowed to warm to room temperature during a period of 30 min after which it was refluxed for 40 hr. At the end of the reflux period the mixture was cooled in an ice bath and water (25 ml) was added. The mixture was extracted with chloroform which was dried over K_2CO_3. Evaporation of the solvent left an extremely air-sensitive oil. Distillation of the oil gave 0.576 g (64%) of 1-ethyl-3,3-dimethylpyrazolidine (**13**): ^1H NMR (CCl_3D) δ 1.11 (t, J = 7.5 Hz, 3), 1.22 (s, 6), 1.79 (t, J = 7 Hz, 2), 2.65 (q, J = 7.5 Hz, 2), 2.78 (t, J = 7 Hz, 2).

To a solution of 1-ethyl-3,3-dimethylpyrazolidine (**13**, 0.500 g, 3.90 mmol) in aqueous 1 *N* NaOH (5 ml) cooled to 10° under a nitrogen atmosphere was added dropwise benzoyl chloride (0.550 g, 3.90 mmol). After the addition was complete the mixture was allowed to warm to room temperature and was stirred for 6 hr. At the end of the reaction period the mixture was extracted well with chloroform which was dried over K_2CO_3. Evaporation of the solvent left 0.154 g (11% based on **10**) of an oil which was shown to be pure **14**: ir (CCl_4) 2970, 1645, 1410, 1245, 1135, 1025, 910 cm^{-1}; ^1H NMR (CCl_3D) δ 0.68 (t, J = 7 Hz, 3), 1.68 (s, 6), 2.16 (t, J = 8 Hz, 2), 2.63 (q, J = 7 Hz, 2), 3.08 (t, J = 8 Hz, 2), 7.28–7.48 (m, 3), 7.68–7.88 (m, 2); mass spectrum (70 eV) *m/e* (rel intensity) 232 (5, M^+), 128 (9), 127 (100), 122 (4), 105 (9), 99 (10), 97 (6), 77 (15), 70 (3), 56 (7), 55 (5), 51 (7), 44 (3), 43 (7), 42 (7), 41 (8).

Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.06; H, 8.74; N, 12.03.

1-Benzoyl-2-ethyl-5,5-dimethylpyrazolidin-3-one (16). To a solution of 1-benzoyl-5,5-dimethylpyrazolidin-3-one[10] (**15**, 38.5 g, 0.176 mol) in 0.4 *N* ethanolic NaOH (75 ml) under a nitrogen atmosphere was added ethyl iodide (27.5 g, 0.176 mol). The resultant solution was heated to 80° for 12 hr and then cooled. Evaporation of the solvent left a solid which was taken up in water (100 ml). The water was extracted with CCl_3H which was dried over K_2CO_3 and evaporated to leave a white solid which was recrystallized from Et_2O to give 21.1 g (49%) of pure **16**: mp 146–147°; ir (CCl_3H) 2960, 1715, 1670, 1340, 1290, 1245, 1175, 1080 cm^{-1}; ^1H NMR (CCl_3D) δ 1.15 (t, J = 7.5 Hz, 3), 1.28 (s, 6), 2.49 (s, 2), 3.72 (q, J = 7.5 Hz, 2), 7.3–7.8 (m, 5); mass spectrum (70 eV) *m/e* (rel intensity) 246 (5, M^+), 141 (13), 106 (9), 105 (100), 99 (8), 83 (5), 77 (24), 56 (4), 55 (3), 51 (7), 43 (4), 42 (3), 41 (4).

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.58; H, 7.43; N, 11.30.

1-Benzoyl-2,5,5-trimethylpyrazolidin-3-one (17). To a solution of 1-benzoyl-5,5-dimethylpyrazolidin-3-one[10] (**15**, 9.50 g, 43.5 mmol) in aqueous 2 *N* NaOH (22 ml) cooled to 10–20° under a nitrogen atmosphere was added dropwise over a period of 30 min dimethyl sulfate (5.50 g, 43.5 mmol). After the addition the mixture was allowed to warm to room temperature and to stir for 6 hr. The mixture was then extracted with CCl_3H which was dried over K_2CO_3 and evaporated to leave a white solid. Recrystallization of the solid from Et_2O gave 6.55 g (65%) of pure **17**: mp 125–126°; ir (CCl_4) 2970, 1715, 1665, 1415, 1325, 1275, 1170, 1090, 945 cm^{-1}; ^1H NMR (CCl_3D) δ 1.29 (s, 6), 2.51 (s, 2), 3.18 (s, 3), 7.30–7.85 (m, 5); mass spectrum (70 eV) *m/e* (rel intensity) 232 (7, M^+), 127 (25), 106 (28), 105 (100), 85 (39), 83 (15), 78 (11), 77 (75), 56 (26), 55 (17), 51 (45), 50 (13), 44 (14), 43 (28), 42 (17), 41 (27).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.39; H, 6.90; N, 12.12.

1-Benzoyl-2-benzyl-5,5-dimethylpyrazolidin-3-one (18). A solution of 1-benzoyl-5,5-dimethylpyrazolidin-3-one[10] (**15**, 12.90 g, 0.059 mol) and benzyl bromide (9.90 g, 0.059 mol) in 0.4 *N* ethanolic NaOH (188 ml) was refluxed for 7 hr. After cooling the solution was stripped to leave a white solid to which was added ice-cold water (100 ml). After stirring for 15 min the undissolved solid was filtered off and washed with a little ether. Recrystallization from ether–ethanol gave 9.10 g (50%) of pure **18**: mp 176–177°; ir (CCl_3H) 3030, 2960, 1715, 1360, 1450, 1420, 1380, 1340, 1275, 1245, 1180 cm^{-1}; ^1H NMR (CCl_3D) δ 1.91 (s, 6), 2.5 (s, 2), 4.94 (s, 2), 7.39 (s, 5), 7.45 (s, 5); mass spectrum (70 eV) *m/e* (rel intensity) 308 (5, M^+), 205 (1), 204 (5), 203 (6), 162 (1.5), 106 (9.5), 105 (100), 92 (4), 91 (45.5), 77 (24), 65 (4.5), 55 (3), 55 (2), 51 (5), 44 (2), 41 (4).

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H,6.54; N, 9.09. Found: C, 73.97; H, 6.59; N, 9.14.

2,5,5-Trimethylpyrazolidin-3-one (19). A solution of 1-benzoyl-2,5,5-trimethylpyrazolidin-3-one (**17**, 15.15 g, 65.0 mmol) in a mixture of aqueous 12 *N* HCl (180 ml) and EtOH (60 ml) was refluxed for 20 hr. After cooling the aqueous solution was washed with Et_2O, cooled in an ice bath, and solid NaOH was added to it until the pH was strongly basic. The basic aqueous solution was extracted well with CCl_3H which was dried over K_2CO_3 and evaporated to leave an oil. Distillation of the oil gave 5.00 g (60%) of pure **19**: bp 51° (0.1 mm); ir (CCl_4) 2960 1690, 1380, 1090 cm^{-1}; ^1H NMR (CCl_3D) δ 1.25 (s, 6), 2.31 (s, 2), 2.99 (s, 3), 5.05 (broad s, 1, NH); mass spectrum (70 eV) *m/e* (rel intensity) 128 (89, M^+), 113 (100), 85 (12), 84 (39), 82 (51), 72 (14), 57 (28), 56 (86), 55 (39), 46 (28), 45 (32), 44 (21), 43 (26), 42 (61), 41 (61); uv (EtOH) shoulder on end absorption at 214 nm (ϵ 3150).

Anal. Calcd for $C_6H_{12}N_2O$: C, 56.23; H, 9.44; N, 21.86. Found: C, 56.19; H, 9.42; N, 21.69.

2-Benzyl-5,5-dimethylpyrazolidin-3-one (20). A solution of 1-benzoyl-2-benzyl-5,5-dimethylpyrazolidin-3-one (**18**, 15.35 g, 0.050 mol) in a mixture of 12 *N* aqueous HCl (150 ml) and ethanol (50 ml) was refluxed for 20 hr. After cooling the mixture was extracted with Et_2O to remove the benzoic acid which was formed. The aqueous layer was neutralized with NaOH and extracted again with Et_2O. This Et_2O was dried over K_2CO_3 and distilled to give 5.90 g (60%) of pure **20**: bp 158° (3 mm); ir (CCl_3H) 3030, 2965, 1695, 1390, 1370, 1280 cm^{-1}; ^1H NMR (CCl_3D) δ 1.11 (s, 6), 2.18 (s, 2), 4.35 (broad s, 1, NH), 4.45 (s, 2), 7.30 (s, 5); mass spectrum (70 eV) *m/e* (rel intensity) 204 (36, M^+), 189 (8), 113 (25), 111 (8), 105 (9), 100 (13), 91 (100), 85 (5), 93 (10), 77 (8), 71 (12), 65 (12), 57 (12), 56 (12), 55 (12), 46 (29), 45 (64), 43 (21), 41 (18); uv (EtOH) shoulder on end absorption at 222 nm (ϵ 3350), 280 (150).

Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.55; H, 7.90; N, 13.71. Found: C, 70.47, H. 8.03; N, 13.60.

1-Methylamino-4,4-dimethylazetidin-2-one (21). A solution of 2,5,5-trimethylpyrazolidin-3-one (**19**, 1.28 g, 0.010 mol) in methanol (250 ml) was degassed with a stream of nitrogen for 2 hr, after which it was irradiated for 20 hr with a Hanovia 450-W immersion lamp equipped with a Vycor filter. TLC analysis indicated the formation of one product with a slightly greater R_f value than the starting material. (Loss of starting material was not complete but longer irradiation times did not significantly change the ratio). Evaporation of the solvent followed by columns chromatography on silicic acid with Et_2O–EtOH (80:20 mixture by volume) eluent resulted in the isolation of 0.064 g (ca. 5%) of an oil which was identified from its spectra to be **21**: ir (CCl_3H) 2970, 1755, 1378, 1278 cm^{-1}; ^1H NMR (CCl_3D) δ 1.40 (s, 6) 2.56 (s, 2), 2.80 (s, 3), 4.21 (broad s, 1, NH); mass spectrum (70 eV) *m/e* (rel intensity) 128 (12, M^+), 86 (66), 84 (100), 72 (29), 56 (17), 47 (25), 44 (21).

1-Ethylamino-4,4-dimethylazetidin-2-one (22). A solution of 2-ethyl-5,5-dimethylpyrazolidin-3-one (**10**, 1.42 g, 0.010 mol) in methanol (250 ml) was treated in a manner similar to the reaction of 2,5,5-trimethylpyrazolidin-3-one (**19**) described above. From the column was isolated 0.043 g (3%) of an oil which was identified by its spectra to be **22**: ir (CCl_3H) 2965, 1750 cm^{-1}; ^1H NMR (CCl_3D) δ 1.22 (t, J = 7 Hz, 3), 1.40 (s, 6), 2.50 (s, 2), 3.12 (q, J = 7 Hz, 2), 4.31 (s, 1, NH).

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Registry No.—**2**, 53992-45-3; **6**, 56678-92-3; **7**, 56678-93-4; **8**, 56678-94-5; **9**, 26485-97-2; **10**, 56678-95-6; **13**, 56678-96-7; **14**, 56678-97-8; **15**, 49629-13-2; **16**, 56678-98-9; **17**, 56678-99-0; **18**, 56679-00-6; **19**, 56679-01-7; **20**, 53992-50-0; **21**, 56679-02-8; **22**, 56679-03-9.

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Chemistry of Heterocyclic Compounds. 21. Synthesis of Hexa(2-pyridyl)benzene and the Related Phenyl(2-pyridyl)benzenes. Characterization of Corresponding Substituted Cyclopentenolone Intermediates[1a]

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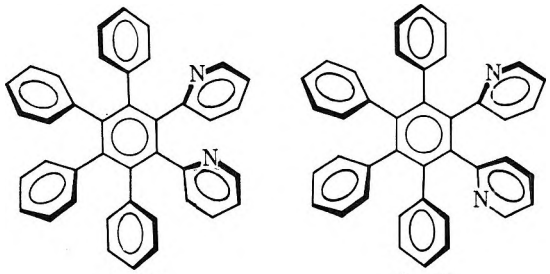
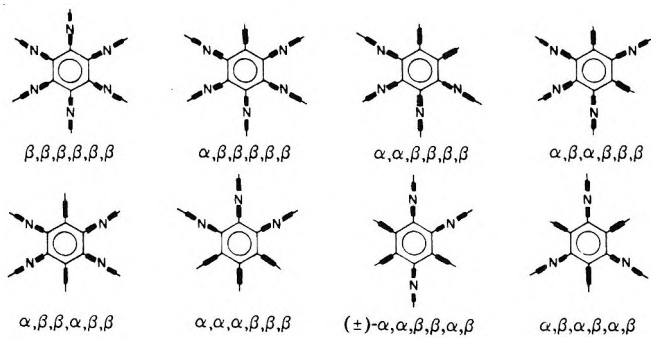
The synthesis and some physical properties of hexa(2-pyridyl)benzene (**41**) and the related phenyl(2-pyridyl)benzenes **30–40** are reported. These compounds were prepared via Diels–Alder reaction of the appropriate acetylene **26–28** with the intermediary dienones **16–25**, which were generated in situ from the corresponding enolones **7–15**. These enolones **7–15** were characterized by analysis of their spectral data.

At the onset of this project, it was hoped that certain stable conformations of poly-2-pyridylbenzenes could be isolated owing to the predicted large barrier to free rotation. Such examples of atropisomerism have not been previously demonstrated. One of the simplest examples is 1,2-di(2-pyridyl)tetraphenylbenzene, which can exist as either β,β



$\beta.\beta$-31 $\beta.\alpha$-31

or α,β isomer; whereas hexa(2-pyridyl)benzene (**41**) should exist as eight nonsuperimposable conformational isomers including one enantiomeric pair (Figure 1).



$\beta,\beta,\beta,\beta,\beta,\beta$ $\alpha,\beta,\beta,\beta,\beta,\beta$ $\alpha,\alpha,\beta,\beta,\beta,\beta$ $\alpha,\beta,\alpha,\beta,\beta,\beta$

$\alpha,\beta,\beta,\alpha,\beta,\beta$ $\alpha,\alpha,\alpha,\beta,\beta,\beta$ $(\pm)$-$\alpha,\alpha,\beta,\beta,\alpha,\beta$ $\alpha,\beta,\alpha,\beta,\alpha,\beta$

Figure 1. Top view of the possible hexa(2-pyridyl)benzenes. —N— (β) = 2-pyridyl nitrogen above the plane of the central benzene ring; - - - (α) = 2-pyridyl nitrogen below and the 3-pyridyl hydrogen above the plane of the central benzene ring.

We herein describe the utilization of the Diels–Alder reaction of cyclopentadienones with the appropriate acetylenes to prepare the previously unknown hexa(2-pyridyl)benzene (**41**) as well as the complete series of related phenyl(2-pyridyl)benzenes (**30–40**) (Figure 2). Although several phenyl(2-pyridyl)cyclopentadienones and cyclopentenolones are known, faulty and/or limited literature data make an accurate interpretation of these known compounds rather tenuous at best. In this paper, we also report the structural assignment of the intermediate substituted cyclopentenolones (**7–15**).

Experimental Section[2]

Substituted Acetones. 2-Pyridylacetonitrile was prepared (80%) from 2-chloromethylpyridine[3] [bp 100–104° (12 mm)] with potassium cyanide in anhydrous dimethyl sulfoxide: bp 79–81° (0.4 mm) [lit.[4] bp 118–120° (13 mm)]; NMR ($CDCl_3$) δ 3.85 ($PyCH_2$–, s, 2 H), 6.95–7.8 (PyH, m, 3 H), 8.45 (6-PyH, d, 1 H); ir (neat) 2220 cm^{-1} (C≡N).

1,3-Di(2-pyridyl)acetone (6) was prepared (60%) from 2-pyridylacetonitrile with 2-picolyllithium in anhydrous ether: bp 115–120° (0.01 mm) [lit.[5] bp 130–135° (0.05 mm)]; mp 80–81° (ether); NMR (CCl_4) δ 3.6 [CH_2 (enol, 60%), s], 3.95 [CH_2CO (keto), s], 5.32 (vinyl H), 6.7–7.7 (PyH, m), 8.1–8.5 (6-PyH, m); ir (CCl_4) 1720 (C=O, w), 1640 (C=H, s), 1460, and 1325 cm^{-1}.

1-Phenyl-3-(2-pyridyl)propan-2-one (5) was synthesized (33%) from phenylacetonitrile with 2-picolyllithium in anhydrous ether: bp 167–173° (3.5 mm) [lit.[6] bp 140–142° (3 mm)]; NMR ($CDCl_3$) δ 3.56 [$PhCH_2$– (enol, 22%), s], 3.79 ($PhCH_2CO$, s), 3.90 ($PyCH_2CO$, s), 5.2 (vinyl H, s), 6.6–7.65 [ArH and –OH (exchanged with D_2O)]; ir (neat) 1720 (C=O), 1650 cm^{-1} (C=COH).

Substituted α-Diketones. Phenyl(2-pyridyl)glyoxal (2) was prepared from *trans*-stilbazole[7] [mp 90–91° (ethanol)] via selenium oxide[8] or concentrated nitric acid[9] oxidation: bp 128–130° (0.2 mm); mp 72–73° (ethanol–petroleum ether, lit.[8] mp 72–72.5°).

2-Pyridil (3) was obtained from commercial sources and recrystallized from absolute ethanol, mp 154–156°.

Substituted Acetylenes. Diphenylacetylene was obtained from commercial sources, mp 59–61°.

Phenyl(2-pyridyl)acetylene was prepared (60% overall) from *trans*-stilbazole via 1-phenyl-2-(2-pyridyl)-1,2-dibromoethane [mp 185–186° (benzene), lit.[7] mp 185–186°], then treated with alcoholic potassium hydroxide: bp 120–122° (0.3 mm) [lit.[7] bp 160–164° (3–4 mm)]; NMR ($CDCl_3$) δ 6.92–7.7 (ArH and PyH, m, 8 H); ir (neat) 2350 cm^{-1} (C≡C).

Di(2-pyridyl)acetylene was prepared from either *trans*-1,2-di(2-pyridyl)ethene[10] or 2-pyridil[11] in greater than 80% yield, mp 69–71° (petroleum ether, lit.[10b] mp 69–70°).

Substituted 4-Hydroxy-2-cyclopenten-1-ones. The following procedure illustrates the general preparation of aryl- and heteroaryl-4-hydroxy-2-cyclopenten-1-ones.

A mixture of 2-pyridil (2.12 g, 0.01 mol), 1,3-di(2-pyridyl)acetone (2.12 g, 0.01 mol), and potassium hydroxide (500 mg) in absolute ethanol (20 ml) was refluxed for 30 min. The mixture was cooled and upon standing crystals formed. Recrystallization from benzene–ethyl acetate afforded a mixture (95:5) of (4*SR*,5*SR*)- and (4*SR*,5*RS*)-4-hydroxy-2,3,4,5-tetra(2-pyridyl)-2-cyclopenten-1-one: mp 147–148°; NMR ($CDCl_3$) δ 4.68 and 4.82 (CO^5CH, 2 s, 1 H), 6.65–7.90 (PyH and –OH, m, 13 H), 8.22–8.70 (6-PyH, m, 4 H); ir ($CHCl_3$) 3350 (–OH), 1700 cm^{-1} (C=O).

All of the substituted 4-hydroxy-2-cyclopenten-1-ones are tabulated with their physical and spectral data in Table I.

Substituted Cyclopentadienones. 2,3,4-Triphenyl-5-(2-pyridyl)cyclopentadienone (19). Enolone **10** (1.05 g, 2.5 mmol) in ethylene glycol (5 ml) was refluxed for 10 min. Upon cooling, trituration with methanol precipitated dark red crystals, which were collected, washed with cold methanol, and recrystallized from methanol, affording (50%) 500 mg of **19**: mp 220–221° (lit.[12] mp 225–226°); NMR ($CDCl_3$) δ 6.8–7.8 (ArH and PyH, m, 18 H), 8.42–8.53 (6-PyH, bd, 1 H); ir (Nujol) 1685 cm^{-1} (C=O); uv–visible (MeOH) 290 nm (ϵ 13100), 241 (13900), 443 (12940).

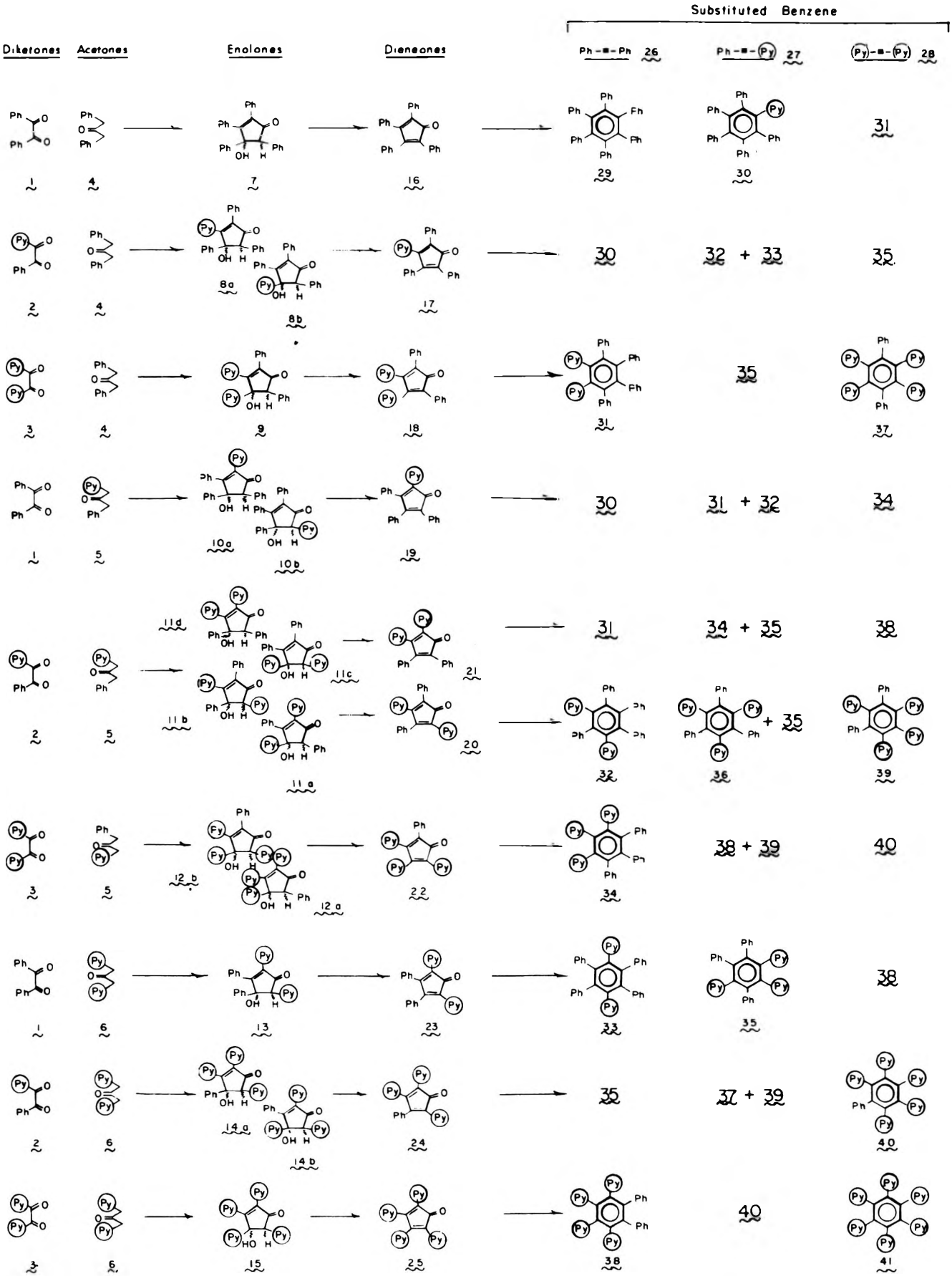


Figure 2.

Anal. Calcd for $C_{28}H_{19}NO$: C, 87.25; H, 4.97; N, 3.64. Found: C, 86.99; H, 4.89; N, 3.60.

2,5-Diphenyl-3,4-(2-pyridyl)cyclopentadienone (18) was prepared (55%) in a similar manner: mp 200–201° (lit.[13] mp 200–201°); NMR ($CDCl_3$) δ 6.50–8.80 (ArH and PyH, m); ir (KBr) 1720 cm^{-1} (C=O); uv-visible (MeOH) 250 nm (ε 18950), 493 (643).

Anal. Calcd for $C_{27}H_{18}N_2O$: C, 83.92; H, 4.70; N, 7.25. Found: C, 83.72; H, 4.55; N, 7.20.

Table I
Substituted 4-Hydroxy-2-cyclopenten-1-ones[a]

Starting materials: α-Diketone	Starting materials: Acetone	Enolone product	Substituents: 2	3	4	5	Mp, °C (solvent)	Yield,[b] %	Product distribution: trans	cis	NMR, δ[c] ppm: C5 H	6-Py H: C2	C3	C4	C5	Ir,[d] cm⁻¹ (C=O)
1	4	7[e]	Ph	Ph	Ph	Ph	210 (EtOH)	90	100	0	4.51					1700
2	4	8a[f]	Ph	2-Py	Ph	Ph	139–140 (EtOH)	60	100	0	4.57		8.37			1700
		8b	Ph	Ph	2-Py	Ph		0								
3	4	9[g,h]	Ph	2-Py	2-Py	Ph	188–189 (C_6H_6-EtOH)	80	100	0	4.34		8.28	8.36		1700
1	5	10a	2-Py	Ph	Ph	Ph	147–148 (EtOAc)	83	100	0	4.56	8.60				1630
		10b	Ph	Ph	Ph	2-Py		0								
2	5	11a	2-Py	Ph	2-Py	Ph	148–149 (EtOH)	27	100	0	4.27	8.65		8.40		1700
		11b	Ph	2-Py	Ph	2-Py		3	*i*		4.82		*i*	*i*	*i*	*i*
		11c	Ph	Ph	2-Py	2-Py										
		11d	2-Py	2-Py	Ph	Ph										
3	5	12a	2-Py	2-Py	2-Py	Ph	146–149 (EtOH)	80	90		4.83	8.60	8.28	8.38		1700
		12b	Ph	2-Py	2-Py	2-Py			(10)[i,j]		4.66	*i*	*i*	*i*	*i*	*i*
1	6	13	2-Py	Ph	Ph	2-Py	170–171 (EtOAc)	80	100	0	4.73	8.62			8.49	1660
2	6	14a	2-Py	2-Py	Ph	2-Py	136–137 (EtOH)	70	100	0	4.74	*k*	*k*	*k*	*k*	1725
		14b	2-Py	Ph	2-Py	2-Py										
3	6	15	2-Py	2-Py	2-Py	2-Py	147–148 (EtOH)	80	95		4.68	8.66	8.32	8.42	8.50	1700
										5	4.82	*i*	*i*	*i*	*i*	*i*

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Reported yields refer to actual isolated crystalline products. [c] 10% w/v. in deuteriochloroform. [d] In chloroform. [e] Lit.[15] mp 208°. [f] Lit.[16] mp 138–140°. [g] Lit.[16] mp 186°. [h] Lit.[13] mp 178–180°. [i] Cannot be determined from limited available data. [j] Either *cis*-12a or *trans*-12b. [k] Broad overlapping multiplet of three hydrogens (δ 8.24–8.69).

Table II
Hexasubstituted Benzenes[a]

Benzene	Starting materials[b]: Enolone (0.01 mol)	Acetylene (mol)	Reaction temp, °C	Yield,[c] %	Mp,[d] °C	Ir,[e] cm⁻¹	Uv,[f] λ, nm (ε × 10³)	NMR, δ ppm[g]: 6-PyH	ArH, PyH
29	7 [16]	26	300	90	465	1450, 1350, 780, 725, 692	247 (59.0)		6.81–7.11
30	7 [16]	27 (0.03)	300	80	466[j]	1580, 1550, 793, 737, 692	247 (52.0)	8.23[h]	6.82–7.15
31	9 [18]	26 (0.025)	350	95	468[k]	1580, 792, 734, 697	246 (62.0)	8.15[h]	6.70–7.46
32	11a, b [20]	26 (0.03)	350	50	476	1590, 790, 745, 695	245 (73.0)	8.21[i]	6.82–7.26
33	13 [23]	26 (0.03)	320	75	474	1600, 790, 740, 695	244 (58.0)	8.22[h]	6.80–7.28
34	12 [22]	26 (0.03)	350	80	473	1580, 784, 731, 695	245 (75.5)	8.20[i]	6.76–7.41
35	13 [23]	27 (0.03)	300	60	470[l]	1595, 1150, 800, 735, 695	246 (58.0)	8.21[h]	6.68–7.18
36	11a, b [20]	27 (0.02)	300	50	479	1570, 1500, 790, 730, 695	245 (62.0)	8.20[i]	6.76–7.43
37	9 [18]	28 (0.02)	300	57	479	1575, 1550, 800, 745, 695	245 (77.5)	8.22[h]	6.74–7.47
38	15 [25]	26 (0.025)	275	75	479	1590, 800, 730, 692	244 (72.5)	8.20[i]	6.76–7.64
39	11a, b [20]	28 (0.025)	300	35	481	1580, 785, 730, 700	244 (60.5)	8.17[i]	6.69–7.43
40	14 [24]	28 (0.03)	250	65	484	1575, 1530, 805, 745, 695	245 (62.0)	8.15[i]	6.62–7.12
41	15 [25]	28 (0.025)	200	70	486	1595, 1150, 810, 755, 720	247 (58.0)	8.16[h]	6.72–7.46

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in the table. [b] Preferred starting materials; however, alternate combinations have been successful; number in brackets in first column designates enone intermediate. [c] Reported yields refer to the actual isolated recrystallized product, from dimethylformamide. [d] DTA values, uncorrected. [e] In Nujol. [f] In 1,2-dichloroethane. [g] Ca. 10% w/v, in dimethylacetamide at 110°, Me_4Si as standard. [h] Observed doublet (J = 2 Hz). [i] Center of the observed two doublets (J = 2 Hz each). [j] Lit.[16] mp 455°. [k] Lit.[16] mp 455°. [l] Lit.[16] mp 468–470°.

Hexasubstituted Benzenes. The following procedure illustrates the general preparation of aryl- and/or heteroarylbenzenes.

A mixture of 4-hydroxy-2,3,4,5-tetra(2-pyridyl)-2-cyclopenten-1-one (4.1 g, 0.01 mol) and di(2-pyridyl)acetylene (4.5 g, 0.025 mol) was heated under nitrogen to 200° for 15 min. After gas evolution and subsequent cooling, the residue was washed with benzene and recrystallized from anhydrous dimethylformamide, affording (70%) analytically pure hexa(2-pyridyl)benzene: mp 486°; NMR (*N,N*-dimethylacetamide, 150°) Figure 3.

All of the aryl- and/or heteroaryl substituted benzenes are tabulated with their physical and spectral data in Table II.

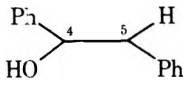
Results and Discussion

Synthesis of Enolones. Classically, cyclopentenolones have been prepared by base-catalyzed condensation of the appropriately substituted 1,3-disubstituted acetones with α-diketones; the general reaction has been reviewed[14] and best exemplified[15] by condensation of **1** with **4** to prepare (90%) tetraphenyl-4-hydroxy-2-cyclopentenone (**7**). 2,5-Diphenyl-3,4-di(2-pyridyl)cyclopentenolone (**9**) was previously synthesized[13,16] from α-pyridil (**3**) and dibenzyl ketone (**4**) in the presence of ethanolic potassium hydroxide at 78°. Although the major isolated reaction product was not structurally assigned, the gross structure of **9** was assigned as based on its thermal conversion to **18**, which also was not isolated but rather trapped by an appropriate dienophile. Similarly, phenyl(2-pyridyl)glyoxal (**2**) was condensed with **4** affording the enolone **8**, whose configuration was assigned to *trans*-**8a** as based on the strong hydrogen bonding exhibited in the ir spectrum of the major isolated product.[16]

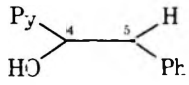
All of the substituted 4-hydroxy-2-cyclopenten-1-ones were prepared in an analogous manner and the physical and spectral data are given in Table I.

Characterization of Enolones. The gross structure proof of the 2-pyridylenolones was established by their thermal dehydration to the corresponding dienones, which were trapped by a symmetrical acetylene such as diphenylacetylene (**26**). Two additional configurational questions need to be clarified: (1) cis or trans C_4–C_5 substituent orientation, and (2) reaction regioselectivity. The structural assignments of **7**–**15** were determined by NMR spectroscopy coupled with corroborative ir data. In several of the condensation reactions, product mixtures are possible; however, product analysis indicated strong stereoselectivity and regioselectivity. Normally a single isomer was formed either solely or at least predominantly. In the cases where mixtures were formed, the isomers were inseparable. Typical chromatography and recrystallization techniques, which normally would effect separation of such mixtures, were unsuccessful. Presence of the minor isomers was detected by their spectral data.

In addition to the aromatic and hydroxylic hydrogens, the NMR spectrum of **7** exhibited a one-proton singlet at δ 4.51 for the C_5 benzylic hydrogen. Condensation of **2** and **4** afforded a single isolated product, which was assigned *trans*-**8a** as based on the C_5 hydrogen chemical shift (δ 4.57) similarity with **7** suggesting the moiety

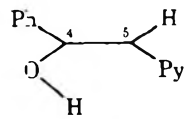


The regioselectivity was established by (1) strong hydrogen bonding (with C_3 pyridyl group) exhibited in the ir spectrum of **8a** and (2) the chemical shift of the C_3 6-pyridyl hydrogen. The benzylic hydrogen is cis to the C_4 phenyl group as indicated by its higher field due to shielding of the aromatic ring;[17] thus, a trans C_4–C_5 diphenyl juxtaposition. Condensation of **1** with **5** afforded *trans*-**10a** as assigned by chemical shift of the C_5 benzylic hydrogen (δ 4.56) and the isolated C_2 6-pyridyl hydrogen (δ 8.60). Dibenzyl ketone (**4**) was condensed with **3** affording a single isolated regioisomer **9**, whose NMR spectrum indicated a single benzylic C_5 hydrogen (δ 4.34) assigned to the moiety



The C_3 6-pyridyl hydrogen chemical shift (δ 8.28) and ir spectral data confirm strong hydrogen bonding (with C_3 pyridyl group).

Condensation of benzil (**1**) and 1,3-di(2-pyridyl)acetone (**6**) gave a single isolated product *trans*-**13**, whose C_5 picolyl hydrogen (δ 4.76) was shifted to lower field indicating the moiety



The strong hydrogen bonding exhibited in the ir spectrum of **13** substantiated the expected cis C_4–C_5 hydroxyl–pyridyl configuration. Reaction of **2** and **6** afforded **14**, whose NMR spectrum confirmed the C_5 picolyl hydrogen (δ 4.74). Since the 6-pyridyl hydrogens exhibited a broad three-proton multiplet, it was impossible to distinguish between structures **14a** and **14b**; however, the probable trans C_4–C_5 phenyl–pyridyl configuration was assigned on steric basis and the hydrogen bonding

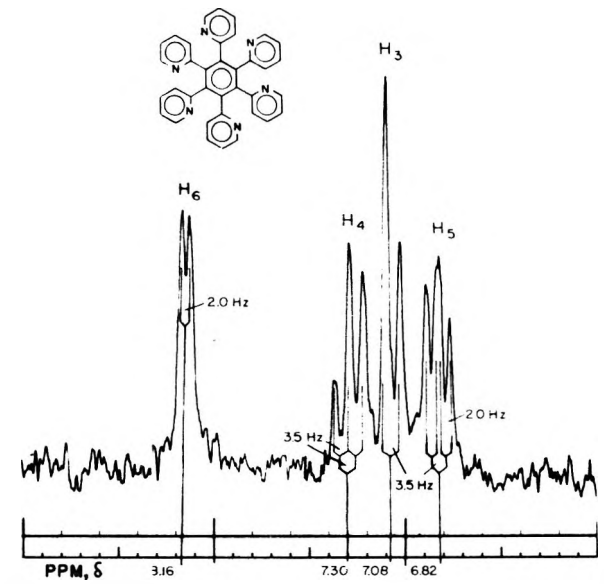
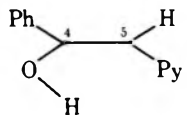
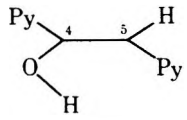


Figure 3. NMR spectrum of hexa(2-pyridyl)benzene in dimethylacetamide at 150°C.



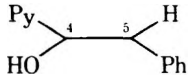
Fortuitously, either **14a** or **14b** affords the single dienone **24**.

Only three condensation reactions afforded inseparable reaction mixtures. Condensation of **3** and **6** generated a mixture of **15** whose isomer distribution cannot arise from regioisomers, thus must be the cis, trans C_4–C_5 substituent geometrical isomers. The NMR spectrum of **15** exhibited the C_5 picolyl hydrogens at δ 4.68 and 4.82 (trans:cis 95:5) whose assignments were based on a greater shielding of the C_5 hydrogen by the C_4 pyridyl group. The second isomeric mixture arose from condensation of **3** and **5** affording **12**. Although two regioisomers are possible, the chemical shift (δ 4.38) of the major isomer is indicative of the moiety



(compare with **9**). The minor (10%) isomer was assigned to either *cis*-**12a** or *trans*-**12b** but, owing to limited data, a distinction cannot be made.

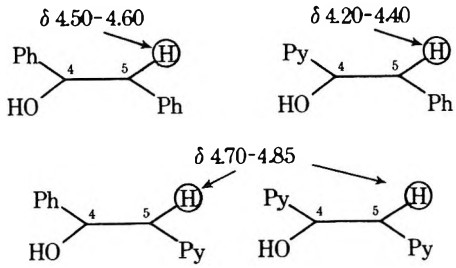
Condensation of **2** and **5** led to a complex mixture of enolones **11**. Pyrolysis of this mixture in the presence of **26** gave predominantly **32**, which was synthesized via an alternate route; thus, the major isomers were **11a** and/or **11b**. The NMR spectrum of **11** exhibited a strong singlet at δ 4.27 indicating the moiety



(compare with **9** or **12a**); thus **11a** is the major isomer. The minor (ca. 3–5%) isomer was assigned either **11b** or **11c** as based on limited spectral data.

Certain generalizations can be drawn from the NMR data of these enolones. (a) Chemical shift data of the C_5 hydrogen singlet, shown in Figure 2, afforded direct evidence to the substituents at C_4 and C_5 on the five-membered ring. (b) The major isolated product preferences under these reaction conditions are shown in Chart I. (c) The chemical

Chart I



shift of the 6-pyridyl hydrogen also depends, albeit to a lesser extent, upon the location of the 2-pyridyl group on the five-membered ring, as shown in Table I.

Synthesis of the Cyclopentadienones. The isolation of pure dienone **16** from enolone **7** is well documented.[15] However, isolation of the 2-pyridyl substituted dienones in an analytical form was the exception rather than the rule. Although the dienones **17–20** and **22–25** were all generated in situ, only **9** and **10a** gave crystalline dienones **18**[18] and **19**,[19] respectively. All other enolones either resisted normal dehydration procedures or, if the desired dienone was generated, it either added water during work-up or was contaminated with starting enolones.

Synthesis of Heteroarylbenzenes. The Diels–Alder condensation[20] of substituted cyclopentadienones (**16–25**), generated in situ from the corresponding tetraaryl- or -heteroarylcyclopentenolones, with acetylenes **26–28** at 200–350° resulted in the formation of the complete series of hexa(2-pyridyl)- and phenyl(2-pyridyl)benzenes. Although the majority of the pyridyl-containing benzenes were readily available from several different combinations, the symmetrical benzene **36** can be synthesized by only one combination of enolone and acetylene. Pyrolysis of cyclopentenolones **11**, consisting of predominantly isomer **11a**, afforded **20** along with the minor isomer **21** (<5% from **11c**). The generation of the preponderant isomer **20** permitted an unambiguous route to **32** and **39** and afforded fortuitously the unique regioisomer **36** when condensed with the unsymmetrical acetylene **27**. The regioselectivity of this Diels–Alder condensation is in agreement with frontier orbital predictions.[21]

All of these hexaaryl–heteroarylbenzenes are colorless, high-melting solids with similar spectral data (Table II). In the uv absorption spectra, all of these compounds have absorption maxima between 245 and 247 nm. The similarity of electronic spectra of pyridylbenzenes **30–41** with hexaphenylbenzene **29** suggest that the steric arrangement of the aryl–heteroaryl substituents are nearly orthogonal to the central benzene ring.[22] The absence of a higher wavelength absorption also indicates the lack of appreciable conjugation. Thus, these heteroarylbenzenes, like hexaphenylbenzene,[22] are semirigid in that the peripheral rings oscillate approximately 10° from orthogonality.

NMR variable temperature studies of these compounds were performed using *N,N*-dimethylacetamide as solvent in the temperature range 70–150°. Owing to the extreme insolubility of these compounds at temperatures below 70°, the NMR spectral data are available only over a limited range. In general, there was no discernible change in the NMR spectral patterns of **30–41** over this limited temperature range.

In summary, the complete series of 2-pyridylbenzenes (**30–41**) has been synthesized in an unambiguous manner from the corresponding characterized cyclopentenolones (**8–15**). From the current spectral and physical data on **31–41**, little useful information can be ascertained concerning their atropisomeric properties. However, from our limited selective complexation studies coupled with high-pressure liquid chromatography, several isomeric mixtures of the less complicated compounds (e.g., **31**) can be detected. Details of these results will be reported later.

Acknowledgments. The authors gratefully acknowledge partial financial support of this work by the Public Health Service grant from the National Institute of Health and National Science Foundation. We also thank Mr. John Martin for variable temperature ^{1}H NMR spectral data.

Registry No.—**1**, 134-81-6; **2**, 13474-48-1; **3**, 28348-69-8; **4**, 102-04-5; **5**, 50550-53-3; **6**, 23580-81-6; **7**, 56650-39-6; **8a**, 56650-40-9; **9**, 56650-41-0; **10a**, 56650-42-1; **11** major isomer, 56650-43-2; **11** minor isomer, 56630-16-1; **12** major isomer, 56650-44-3; **12** minor isomer, 56630-17-2; **13**, 56650-45-4; **14a**, 56650-46-5; **14b**, 56650-47-6; (4*SR*,5*SR*)-**15**, 56679-40-4; (4*SR*,5*RS*)-**15**, 56679-39-1; **16**, 479-33-4; **17**, 56650-48-7; **18**, 14678-71-8; **19**, 50550-55-5; **20**, 56650-49-8; **21**, 56650-50-1; **22**, 56650-51-2; **23**, 56650-52-3; **24**, 56650-53-4; **25**, 56650-54-5; **26**, 501-65-5; **27**, 13141-42-9; **28**, 28790-65-0; **29**, 992-04-1; **30**, 13867-34-0; **31**, 13698-27-6; **32**, 56650-55-6; **33**, 56650-56-7; **34**, 56650-57-8; **35**, 13698-24-3; **36**, 56679-38-0; **37**, 56679-37-9; **38**, 56650-58-9; **39**, 56650-59-0; **40**, 56650-60-3; **41**, 56679-15-3; 2-pyridylacetonitrile, 2739-97-1; 2-chloromethylpyridine, 4377-33-7; potassium cyanide, 151-50-8; 2-picolyllithium, 1749-29-7; phenylacetonitrile, 140-29-4; *trans*-stilbazole, 538-49-8; *trans*-1,2-di(2-pyridyl)ethene, 13341-40-7.

References and Notes

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(2) All melting points were taken in capillary tubes with a Thomas-Hoover Unimelt and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 621 spectrophotometer and ^{1}H NMR spectra on a Varian Associates HA-100 spectrometer. Tetramethylsilane was used as an internal standard. Microanalyses were performed by Mr. R. Seab in these laboratories. Satisfactory analytical data were obtained on all of the new compounds.
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(19) Dienone **19** was previously synthesized in situ[13] without isolation. Isolation of **19** has been realized;[12] however, their sample was probably contaminated with **16**, since the analytical data are outsice the normal deviation.
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Reaction of Enedione Epoxides with Base[1]

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Epoxides of bridged enediones, such as adducts of cyclopentadiene and cyclohexadienes with *p*-benzoquinones, undergo Favorskii-type ring contraction to γ-carbethoxy-α,β-unsaturated cyclopentenones on treatment with ethanolic sodium hydroxide. Thermal decarboxylation of the corresponding acids to α,β-unsaturated cyclopentenones involves an anionic-type transition state. Epoxides of unbridged enediones, i.e., adducts of butadienes with *p*-benzoquinone, do not undergo Favorskii-type ring contraction with ethanolic sodium hydroxide, but nucleophilic displacement to yield hydroxybenzoquinones.

In the course of earlier work[2] we transformed the epoxide **1** to **2a** by treatment with base and thence, by hydrolysis and decarboxylation, to the cyclopentenone **3**. It occurred to us that this series of reactions, whose first step involved the Favorskii rearrangement of an enedione epoxide, might offer a general route to alicyclic systems incorporating a cyclopentenone moiety, since the starting materials are readily prepared by the Diels–Alder reaction. In the present paper we report our study of this procedure with some model compounds.

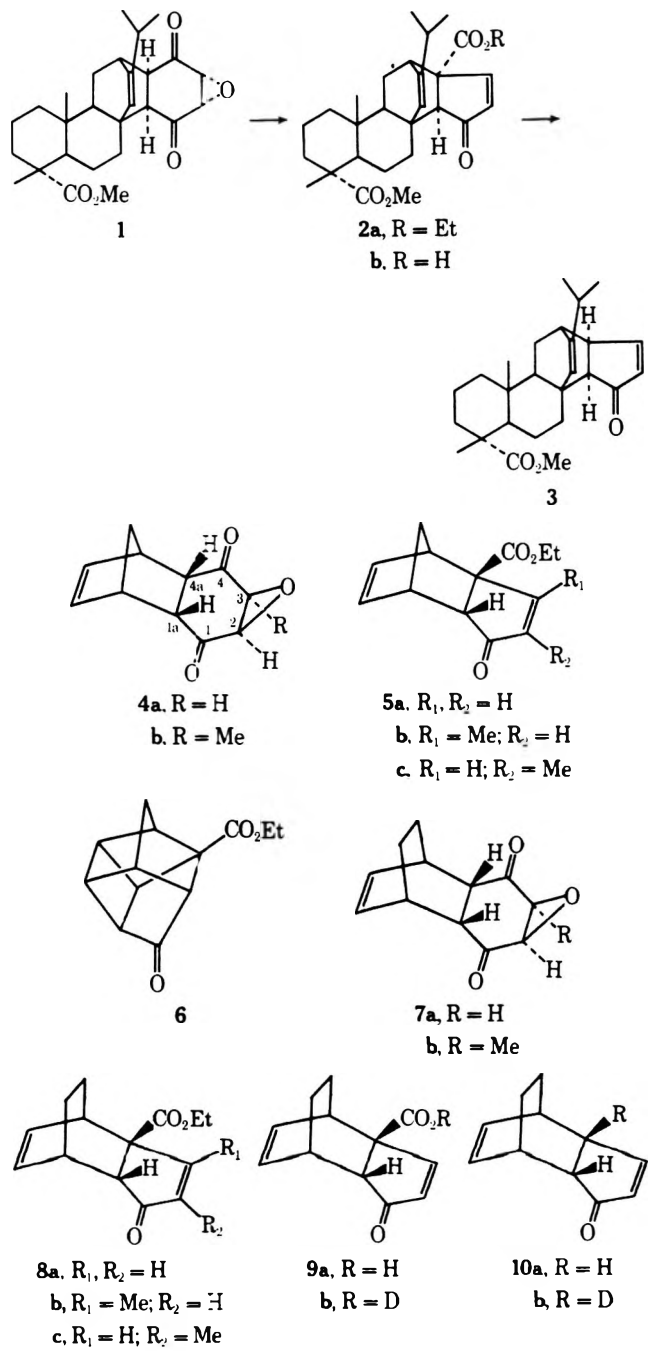
Reaction of **4a** and **7a** with a small amount of sodium hydroxide in ethanol indeed resulted in rearrangement to esters **5a** and **8a** in high yield. In the case of **5a**, the stereochemistry of the rearrangement product was verified by photolytic conversion to the cage isomer **6** and is in accord with the discussion presented earlier.[2]

Rearrangement of **4b** afforded two isomeric esters in the ratio 3:2. The major product **5c** and the minor product **5b** were easily distinguishable by NMR spectrometry, since the cyclopentenone vinyl proton of **5c** should resonate at lower field than that of **5b** (7.1 vs. 5.8 ppm) and since these signals can be identified readily by being coupled allylically to the vinyl methyl group. Similarly, rearrangement of **7b** gave **8c** and **8b** in the ratio 3:2, the distinction being made on the same grounds (6.9 vs. 5.9 ppm).

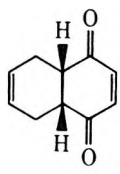
In terms of the Loftfield mechanism for the Favorskii rearrangement, **5b** and **8b** arise through displacement of an oxirane bond by the enolate of C_{7a} and **5c** and **8c** by the enolate at C_{4a}. In contrast to the situation prevailing in the case of **1**, there is obviously little regioselectivity in the simple substances under discussion here, although the products arising from attack of enolate on the tertiary center are formed in somewhat larger amounts.

The hydrolysis and decarboxylation step was examined in the case of **8a**. Hydrolysis to **9a** followed by pyrolysis afforded **10a** in excellent yield. We have not previously commented on the details of the decarboxylation step, which, because it results in the exclusive formation of an α,β- instead of a β,γ-unsaturated cyclopentenone, is not likely to proceed via the cyclic mechanism of Linstead[3] and Barton[4] or the β-carbonium ion mechanism of Johnson.[5] We assume that the presence of the ketone group is responsible for this departure from the path by which β,γ-unsaturated acids normally undergo decarboxylation and that, in the case of **2b** and **9a**, pyrolytic decarboxylation is initiated by (for steric reasons) intermolecular proton transfer from the carboxyl to the ketone group. Subsequent decarboxylation would lead to an incipient carbanion (stabilized to some extent by the protonated carbonyl) which is in turn protonated exclusively at the γ position by a second intermolecular proton transfer.[6]

Evidence against a mechanism involving initial formation of a β,γ-unsaturated cyclopentenone was also provided by the following experiment. Pyrolysis of **9b** afforded a substance **10b** containing the deuterium label exclusively at the γ position, as evidenced in the NMR spectrum by collapse of the H-2 and H-3 doublets of doublets to doublets. Any series of steps involving intra- or intermolecular



proton transfer from the carboxyl group to C-2 and subsequent double bond isomerization to an α,β-unsaturated cyclopentenone would have resulted in scrambling of label between C-2 and C-4.



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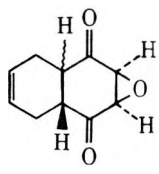
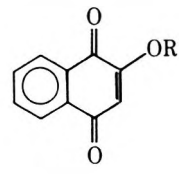
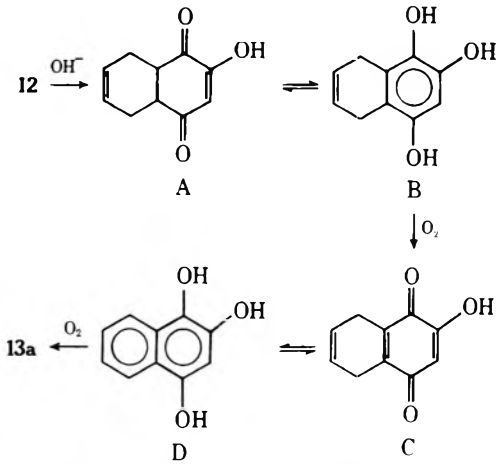


12a, β-H
b, α-H

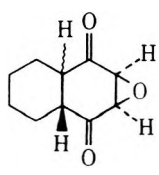


13a, R = H
b, R = Me

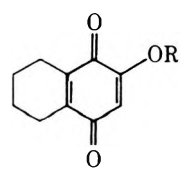
Under the conditions successfully used for the rearrangement of **4a, 4b, 7a,** and **7b, 12a** and the more stable trans isomer **12b** were recovered unchanged. Use of excess sodium hydroxide in aqueous ethanol resulted in formation of a highly colored aromatic substance identified as **13a** by methylation to **13b.** This is obviously the result of bimolecular nucleophilic displacement by external hydroxide ion and subsequent elimination in the manner demonstrated earlier[7,8] for the reaction of 4 and 7 with thiols. In base, the initially formed hydroxyenedione A tautomerizes to the anion of B which may undergo air oxidation to C. Further tautomerization to D and another oxidation step would lead to **13a.** Thus, exclusion of air resulted in formation of a yellow intermediate, possibly A or B, but exposure to air during work-up again produced **13a.**



Similarly, reaction of **14a** and **14b** obtained from **12a** by hydrogenation (ethyl acetate–10% Pd/C) and subsequent isomerization gave **15a** which was characterized as **15b.**



14a, β-H
b, α-H



15a, R = H
b, R = Me

Thus bridged enedione epoxides uniformly undergo the Favorskii rearrangement with base, possibly because of steric interference with approach of the nucleophile from the endo side, whereas unbridged relatively unhindered enedione epoxides like 12 and 14 react by the bimolecular displacement–elimination pathway. This behavior would seem to limit severely the utility of enedione epoxides as precursors of substituted cyclopentenones, although increased substitution on the epoxidic carbon atoms might conceivably direct the reaction into the Favorskii rearrangement path.[10]

Experimental Section

Epoxidations. Epoxidations of the Diels–Alder adducts of cyclopentadiene and cyclohexadiene with *p*-benzoquinone and methyl-p-benzoquinone were carried out as described in the literature[7,8,12] to give **4a, 4b, 7a,** and **7b** in essentially quantitative yield.

Epoxidation of the butadiene–*p*-benzoquinone adduct required low temperature and short reaction time and was carried out as follows. To a solution of 8 g of **11** in 20 ml of acetone immersed in a freezing mixture was added with stirring (N_2 atmosphere) 10 ml of ice-cold freshly prepared 20% sodium carbonate solution followed immediately by 40 ml of 30% hydrogen peroxide. After 3 min of stirring at low temperature, the mixture was diluted with water and extracted with ether. The washed and dried ether layer was evaporated and the residue crystallized from petroleum ether, yield 5 g (68%) of **12a** after recrystallization from petroleum ether, mp 72°, NMR signals at 5.6 br (vinyl protons), 3.55 (protons under epoxide), 3.25 m (protons at ring junction), and 2.1 in (methylenic protons).

Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66; O, 26.94. Found: C, 67.00; H, 5.62; O, 27.28.

Chromatography of 1 g of **12a** over alumina and elution with chloroform produced a 3:1 mixture of **12b** and **12a.** Recrystallization of the mixture from chloroform–ether afforded **12b,** mp 172°, NMR signals at 5.6 c (vinyl protons) and 3.65 ppm (epoxidic protons). The methylene and methinyl region was complex.

Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66, O, 26.94. Found: C, 67.38; H, 5.62; O, 27.28.

Favorskii Rearrangements. Rearrangements of **4a, 4b, 7a,** and **7b** were carried out as described below for **1a.** To a solution of 2 g of **4a** in 30 ml of absolute ethanol was added 0.5 ml of saturated sodium hydroxide solution. After 0.5 hr, the highly colored solution was evaporated and reduced pressure, diluted with water, and extracted with ether. The washed and dried ether layer was evaporated and the residue was chromatographed over Florisil to furnish 1.8 g of gummy **5a** which had ir bands at 1720 (ester), 1695, and 1640 cm^{-1} (conjugated cyclopentenone); λ_{max} 230, 325 nm (ϵ 12600, 60), NMR signals at 7.50 d ($J \simeq 5$ Hz, β proton), 5.95 d (AJ, α proton), 6.00 (2 H, vinylic protons of bridge), 4.27 q (J = 7 Hz, $-OCH_2CH_3$), 3.00 br (methine), 1.82 (center of AB system, J = 11 Hz, methylene), 1.30 t ppm (7, methyl).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47; O, 21.99. Found: C, 71.20; H, 6.46; O, 21.89.

Rearrangement of **4b** gave a quantitative yield of **5b** and **5c** (2:3 ratio). The two compounds were separated by preparative TLC (chloroform–ethyl acetate, 9:1). The less polar substance (**5b**) was a gum: ir bands at 1725, 1690, and 1640 cm^{-1}; λ_{max} 240, 330 nm (ϵ 12800, 70); NMR signals at 6.05 br (2 H, vinyl protons of bridge), 5.8 br (α-vinyl proton), 4.25 q (2 H, $-OCH_2CH_3$), 3.4 br (proton α to carbonyl) 3.2 br (bridgehead protons), 2.00 br (vinyl methyl), 1.8 (center of AB, J = 12 Hz, methylene) 1.30 ppm t (7, $-OCH_2CH_3$).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; O, 20.60. Found: C, 72.50; H, 6.85; O, 20.40.

The more polar product (**5c**) was a gum: ir bands at 1725, 1690, 1635 cm^{-1}; λ_{max} 235, 325 nm (ϵ 12500, 70); NMR signals at 7.1 br (β proton), 6.00 br (bridge vinyl protons), 4.25 q (J = 7 Hz, $-OCH_2CH_3$), 3.3 br (3 H, bridgehead proton and proton α to carbonyl), 1.8 (center of AB, J = 12 Hz, methylenes), 1.65 (α-vinyl methyl), 1.30 ppm t (7, $-OCH_2CH_3$).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; O, 20.60. Found: C, 72.00; H, 6.70; O, 20.59.

Rearrangement of **7a** gave **8a** as a gum in 95% yield: ir bands at 1720, 1700, and 1640 cm^{-1}; NMR signals at 7.41 d and 6.05 d (J = 6 Hz, β and α protons of cyclopentenone), 5.95 (J = 3 Hz, 2 vinyl protons of bridge), 4.15 q and 1.25 ppm t (J = 7 Hz, ethoxyl).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 71.88; H, 6.90.

Hydrolysis of **8a** with 10% methanolic sodium hydroxide solution, removal of solvent at reduced pressure, acidification of the residue, and recrystallization from methanol afforded **9a:** mp 134–135°; ir bands at 3300 (broad) and 1710 (carboxyl), 1705, and 1645 cm^{-1} (cyclopentenone); NMR signals similar to those of **8a** except for the absence of the ethoxyl.

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.99; H, 6.10.

Rearrangement of **7b** in the same manner gave a mixture of gummy **8b** and **8c** (90%, 2:3 ratio) which was separated by preparative TLC as described for **5b** and **5c.** The less polar substance **8b** had ir bands at 1725, 1695, and 1635 cm^{-1}; λ_{max} 238, 328 nm (ϵ 12000, 70); NMR signals at 5.9 m (superimposed α-vinyl and vinyl

bridge protons), 2.00 ppm br (β-vinyl methyl), and the usual ethoxyl resonances.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; O, 19.49. Found: C, 72.83; H, 7.38; O, 19.72.

The more polar product **8c** had ir bands at 1720, 1690, 1635 cm^{-1}; λ_{max} 235, 330 nm (ε 11800, 68); NMR signals at 6.90 br (β-vinyl proton), 5.9c (two vinyl protons), 1.7 ppm br (α-vinyl methyl), and the usual ethoxyl resonances.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; O, 19.49. Found: C, 72.89; H, 7.51; O, 19.49.

Catalytic Reduction of 12a and 12b. A solution of 2 g of **12a** in 30 ml of ethyl acetate was hydrogenated for 24 hr in the presence of 0.2 g of Pd/C. Filtration, evaporation at reduced pressure, and recrystallization from ether–hexane afforded **14a** in quantitative yield: mp 60–61°; ir band at 1720 cm^{-1}; NMR signals at 3.65 (2 H, epoxidic protons), 3.15 m (proton at ring junction), 1.58 ppm m (methylenes).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71; O, 26.64. Found: C, 66.75; H, 6.77; O, 26.37.

Reduction of **12b** in the same fashion and recrystallization of the crude product from hexane afforded **14b**, mp 53–54°, ir band at 1720 cm^{-1}. The same substance was obtained by chromotography of **14a** over alumina and elution with chloroform.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71; O, 26.64. Found: C, 67.00; H, 6.70; O, 26.30.

Reactions of 12 and 14 with Base. Reaction of **12a** with base under the conditions described for **4a**, **4b**, **7a**, and **7b** resulted in recovery of starting material **12a** and **12b**; hence excess base was employed. To a solution of 1.0 g of **12a** in 30 ml of 95% ethanol was added with stirring at ice bath temperature (nitrogen atmosphere) 15 ml of 10% sodium hydroxide solution. After 20 min, the mixture was diluted with water, acidified with HCl, and filtered. Methylation of the brown solid **13a** with diazomethane in the usual fashion afforded 0.9 g of **13b**, mp 183° (lit.[13] mp 183.5°). Treatment of **12b** with base followed by methylation also gave **13b** in 90% overall yield.

Reaction of **14a** or **14b** with base in the manner described in the previous paragraph followed by methylation of the crude product with diazomethane gave **15** in 90% yield, mp 170–171° (lit.[14] mp 171°, 172°).

Photocyclization of 5a. A solution of 0.5 g of **5a** in 50 ml of methanol was irradiated for 20 hr in a photochemical reactor with a Hanovia 450 lamp using a Pyrex filter. The solution was evaporated at reduced pressure and the residue chromatographed over 20 g of alumina. Elution with benzene afforded 0.45 g of noncrystalline **6**: ir band at 770 cm^{-1} (strained cyclopentanone); λ_{max} 285 nm (ε 68); NMR signals at 4.20 q (2 H) and 1.28 t (3 H, J = 7 Hz, ethoxyl), 2.2–3 ppm c (9 H, methinyl and methylene protons).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47; O, 21.99. Found: C, 71.25; H, 6.40; O, 21.80.

Decarboxylation of 9a. Decarboxylation was achieved by heating the substance in a slow stream of nitrogen at 150° for 15 min until CO_2 evolution had ceased. Trituration of the product (**10**) with methanol resulted in crystallization. The material, mp 103°, was homogeneous on TLC, and had significant NMR signals at 7.60 dd (J = 6 Hz, 3, β proton) and 6.30 ppm dd (J = 6 Hz, 2, α proton).

Anal. Calcd for $C_{11}H_{12}O$: C, 87.46; H, 7.55. Found: C, 82.78; H, 7.51.

A solution of 0.1 g of **9a** in 3 ml of $CDCl_3$ was mixed with 2 ml of D_2O and stirred thoroughly. After 15 min, a portion of the mixture was transferred to an NMR sample tube; the NMR spectrum exhibited no OH absorption. The mixture was dried by addition of anhydrous sodium sulfate, filtered, and evaporated. The residue (**9b**) was pyrolyzed as described in the preceding paragraph. The NMR spectrum of the crude product (**10b**) now displayed the β- and α-cyclopentenone protons as doublets at 7.60 and 6.30 ppm (J = 6 Hz). On thin layer examination, **10b** exhibited R_f values identical with those of **10a**.

Registry No.—**4a**, 15052-12-7; **4b**, 15052-13-8; **5a**, 56689-06-6; **5b**, 56689-07-7; **5c**, 56689-08-8; **6**, 56689-09-9; **7a**, 56711-55-8; **7b**, 56711-56-9; **8a**, 56689-10-2; **8b**, 56689-11-3; **8c**, 56689-12-4; **9a**, 56689-13-5; **10a**, 56689-14-6; **11**, 35043-92-6; **12a**, 56689-15-7; **12b**, 56711-57-0; **14a**, 56689-16-8; **14b**, 56711-58-1.

References and Notes

(1) Supported in part by grants from the National Science Foundation (GP-12582) and the donors of the Petroleum Research Fund, administered by the American Chemical Society.
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Epoxydiazo Ketones. Synthesis and Reactions

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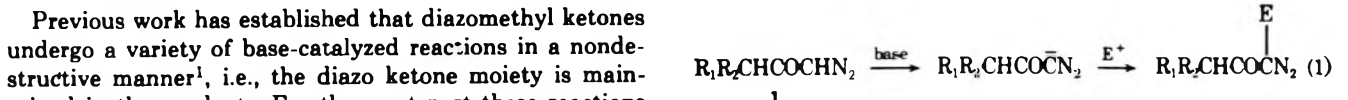
Darzens condensation of 3-chloro-1-diazopropanone with nonenolizable aldehydes and base in equal molar amount yielded 1-diazo-4-R-3,4-epoxy-2-butanones (**7**) [**a**, R = Ph; **b**, R = 4-$NO_2C_6H_4$; **c**, R = 4-$CH_3OC_6H_4$; **d**, R = (*E*)-PhCH=CH; **e**, R = 2-thienyl]. Under conditions of higher base and excess aldehyde molar ratios, **7** and diadducts of 2-diazo-1,5-di-R-4,5-epoxy-1-hydroxy-3-pentanones (**8**) were produced. The reactions of **7a–c** with hydrogen chloride gas in ether generated α-chloro ketones and opened the epoxide ring in the case of **7a** and **7c**. Photolysis of **7a** in methanol gave methyl 4-hydroxy-4-phenyl-2-butenoate (**32**). Pyrolysis of **7a** in refluxing methanol gave 1,1-dimethoxy-4-phenyl-3-buten-2-one (**34**).

Previous work has established that diazomethyl ketones undergo a variety of base-catalyzed reactions in a nondestructive manner[1], i.e., the diazo ketone moiety is maintained in the products. For the most part these reactions result from the facile formation of an anion at the diazomethyl carbon followed by reaction with electrophile (reaction 1).

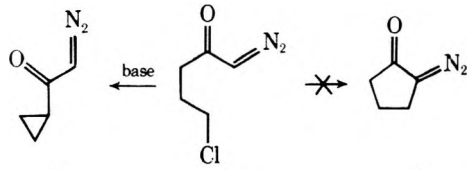


$$R_1R_2CHCOCHN_2 \xrightarrow{\text{base}} R_1R_2CHCOC\bar{N}_2 \xrightarrow{E^+} R_1R_2CHCOC(E)N_2 \quad (1)$$

1

In cases where anion formation could take place at either the diazomethyl or the 3 carbon, the greater acidity of the diazomethyl hydrogen directed condensation to this posi-

tion. Only one case has been reported where reaction occurs at the 3 carbon, that of the 5-chloro-1-diazo-2-pentanone (3), where apparently favorable entropy factors and the greater reactivity of the 3-carbon anion make formation of 2 preferred over 4.[1c]



2 3 4

We have attempted to find structural factors which will direct reaction to the 3 carbon of diazomethyl ketones. Substitution of a phenyl group on carbon 3, however, did not increase the acidity of the 3-carbon hydrogen sufficiently to allow reaction of that center.[1d] Aldol reaction of 1 (R_1 = Ph; R_2 = H) took place at the diazo carbon exclusively.

This report contains our success in directing reaction to carbon 3 by substitution of a chlorine (1, R_1 = Cl; R_2 = H) at that carbon. This allows further reaction of the initial aldol adduct to form epoxydiazomethyl ketones, overall a Darzens condensation. The reactions of these novel compounds under acidic, thermal, and photochemical conditions were also examined.[1e,f,2]

Results and Discussion

Base-Catalyzed Reaction. Treatment of the ω-chlorodiazomethyl ketone 3 with sodium hydroxide and benzaldehyde diverted reaction from formation of the intramolecular product 2 to the aldol product 6-chloro-2-diazo-1-hydroxy-1-phenyl-3-hexane (5). This indicated that formation of 2 in the absence of aldehyde resulted from the special properties of 3 and not an inversion in acidity of the diazomethyl and the 3-carbon hydrogen.

$$3 + PhCHO \xrightarrow{^-OH} Cl(CH_2)_3COCN_2CHOHPh$$

5

A real competitive increase in acidity of the 3-carbon hydrogen was observed, however, with 3-chloro-1-diazopropanone (6) and led to a general synthesis of epoxydiazo ketones 7.[2] By control of conditions, with certain aldehydes, only 7 or a mixture of 7 with the aldol product was formed (Scheme I).

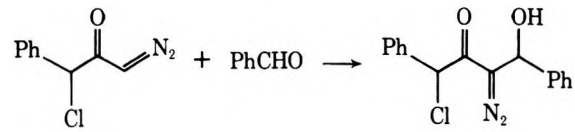
When chlorodiazo ketone 6 was treated with equal molar amounts of benzaldehyde in methanol and aqueous sodium hydroxide solution, 1-diazo-3,4-epoxy-4-phenyl-2-butanone (7a) was formed in 69% yield. The analytical and spectral data were all consistent with this structural assignment (cf. Experimental Section). The size of the coupling constant (J = 1.5 Hz) for the epoxymethine protons supports trans stereochemistry for the epoxide ring.[3] Thus, the behavior of 6 is entirely comparable to Darzens condensation of chloroacetone.[4]

The scope of the reaction is exemplified by reaction of 6 with the aldehydes shown in Scheme I in the indicated yields. Attempts to extend reaction to o-phthalaldehyde and glucose have so far proved unrewarding. No other aldehydes having α hydrogens have been investigated.

When 6 was treated with a moderate molar excess of sodium hydroxide and a large excess of benzaldehyde, two products were isolated. The epoxydiazo ketone 7a and a diastereomeric mixture of 2-diazo-1,5-diphenyl-4,5-epoxy-1-hydroxy-3-pentanone (8a) were formed in 44 and 41% yields, respectively. Separation of the diastereomeric mixture was effected by fractional crystallization to give two isomers. The NMR spectral properties of the mixture and of the pure isomers were identical except for one epoxymethine proton which differed for the two isomers. Further confirmation of the diadduct nature of 8a was supplied by the basic retro-aldol cleavage[5] of the diastereomeric mixture of 8a, and both pure isomers to give 7a in 87–91% yield.

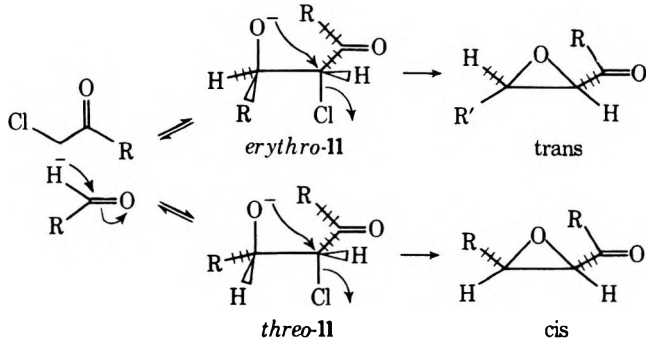
A diastereomeric mixture 8d of the diadduct of (*E*)-cinnamaldehyde and 6 was isolated by a similar procedure in 49% yield. No attempt was made to separate the component stereoisomers of 8d. The structural assignment was made on the basis of analogy to 8a, on the physical data, and the fact that this mixture was also cleanly cleaved to the Darzens product 7d by aqueous base in 70% yield. Undoubtedly the diadducts of other aldehydes could also have been prepared but these reactions were not attempted.

In contrast to the ready Darzens condensation of 6 with aldehydes, 3-chloro-1-diazo-3-phenyl-2-propanone (9) underwent only aldol condensation with benzaldehyde and aqueous sodium hydroxide solution. The oily product, a diastereomeric mixture of 1-chloro-1,4-diphenyl-4-hydroxy-2-butanone (10), was characterized spectroscopically.

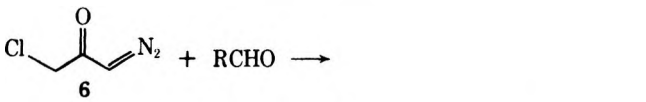


9 10

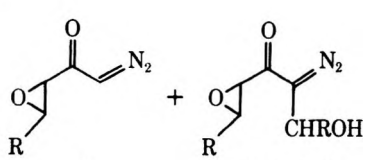
Mechanism of Base-Catalyzed Condensation. The mechanism postulated for the Darzens condensation[4b] to explain the observed stereospecificity involves initial aldol condensation of the chloro ketone anion with the aldehyde to form a keto halohydrin intermediate (or its anion). This can occur in two distinct ways to form *erythro*-11 and *threo*-11. Steric hindrance between the substituent groups is greater in the transition state between *threo*-11 and cis epoxide than between *erythro*-11 and trans epoxide. Thus, through the equilibrium, *erythro*-11 reacts more rapidly forming the trans product. The exclusive formation of



Scheme I



6



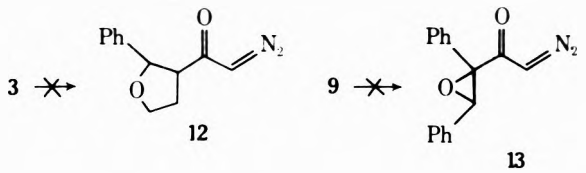
7 8a and d

a, R = C_6H_5 (69%)
b, R = 4-$NO_2C_6H_4$ (88%)
c, R = 4-$CH_3OC_6H_4$ (35–55%)
d, R = C_6H_5CH=CH (40%)
e, R = 2-thienyl (61%)

trans epoxides from 6 and aldehydes supports a similar interpretation for reaction of this chlorodiazo ketone.

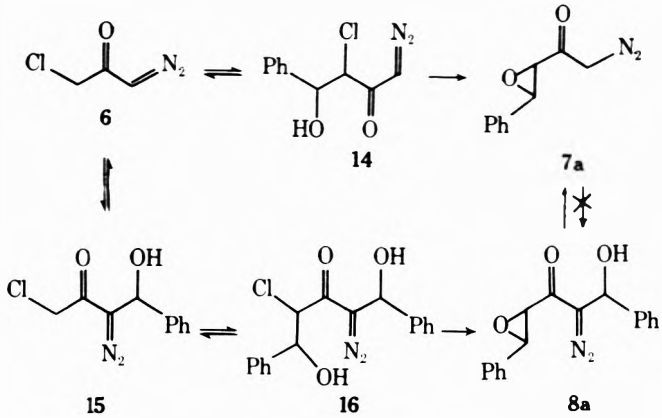
The substituent effects observed for Darzens condensation of phenacyl chloride and para-substituted benzaldehydes[6] are also consistent with more facile reaction of electron-poor aldehydes. The relative yields of 7a, 7b, and 7c support a similar trend for the reactivity of 6. The yield of 7c also increased from 35 to 55% on tripling the reaction time, consistent with this interpretation.

The lack of irreversible formation of 12 and 13 from 3 and 9, respectively, with benzaldehyde probably reflects the steric interaction of disubstitution at one α carbon on the other observed previously.[1b] Diazo ketones of the general type $RR'CHCOCHN_2$ do not form aldol products nearly as readily as monosubstituted diazo ketones. Low equilibrium concentration of the aldol intermediates does not allow subsequent cyclization to 12 and 13.



The effect of base and benzaldehyde molar ratios on formation of the mono- and diadducts was also investigated. The diazo carbon proton in 6 was more acidic than the chloromethylene protons as demonstrated by the deuterium exchange (D_2O and Na_2CO_3) exclusively at the diazo carbon. Thus, when equal molar amounts of 6, base, and benzaldehyde are allowed to react, initial establishment of the aldol equilibrium at the diazo carbon forming 15 seems most likely (see Scheme II). Slower reaction of 6 at the

Scheme II



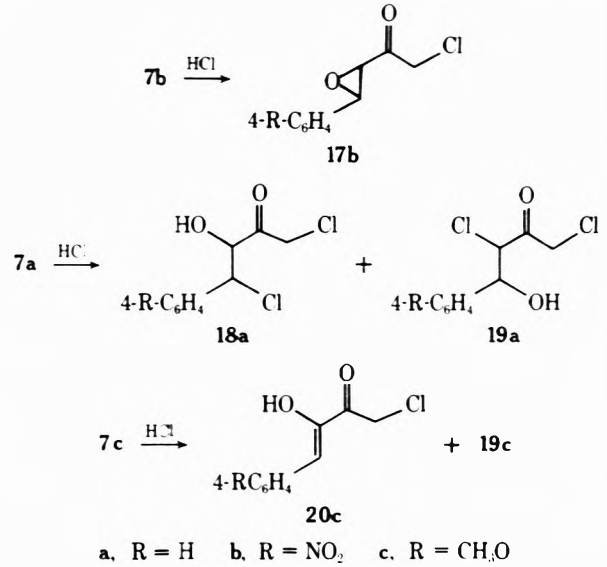
chloromethylene carbon by the Darzens condensation via a low equilibrium concentration of 14 would siphon off 6, converting it irreversibly to 7a, which is stable to base. Once 7a is formed, it can not undergo aldol reaction to form 8a as treatment of 7a under the reaction conditions showed. This result is consistent with the hindering of aldol reaction at one α carbon by disubstitution at the other discussed above. Some of the 7a formed, however, could come from Darzens condensation of 15 to the diadduct 8a via 16 in an irreversible reaction followed by retro-aldol at the diazo carbon to form 7a. Both paths to 7a must be operating. Isolation of a 4% yield of the diadduct 8a worked up after a short period of time supports this view.

When 6 was treated with a moderate excess of base and a large excess of benzaldehyde, the retro-aldol reaction of 8a to 7a became unimportant, a contention supported by the lack of cleavage of 8a under these reaction conditions. Some retro-aldol reaction of 15 to 6 probably occurs in order for the formation of 7a to compete with the initial formation of 15. Both 7a and 8a are then formed by irreversible reactions and cannot be interchanged, a contention consistent with the invariance in the 7a/8a ratio with time. No evidence for the presence of 14, 15, or 16 could be found nor can the possibility of a 14 $\rightleftharpoons$ 16 equilibrium be assessed at this time.

The lack of retro-aldol reaction of 8a when benzaldehyde is in excess of hydroxide implies that the predominant base is the anion formed by addition of hydroxide to benzaldehyde. This base is strong enough to allow the 6 $\rightleftharpoons$ 15 equilibrium and the Darzens condensation to take place but not for the cleavage of 8a to 7a. The basis for this selectivity is not clear.

Reactions with Hydrogen Chloride. In order to ascertain if the diazo group and the epoxy group would react independently or if some intramolecular interaction would take place, the diazo ketones 7a, 7b, and 7c were treated with hydrogen chloride gas in anhydrous ether. The results are summarized in Scheme III. The *p*-nitrophenylepoxydiazo ketone 7b reacted only at the diazo carbon to give 1-chloro-3,4-epoxy-4-(4′-nitrophenyl)butanone (17b).[2]

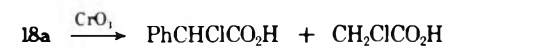
Scheme III



a, R = H b, R = NO_2 c, R = CH_3O

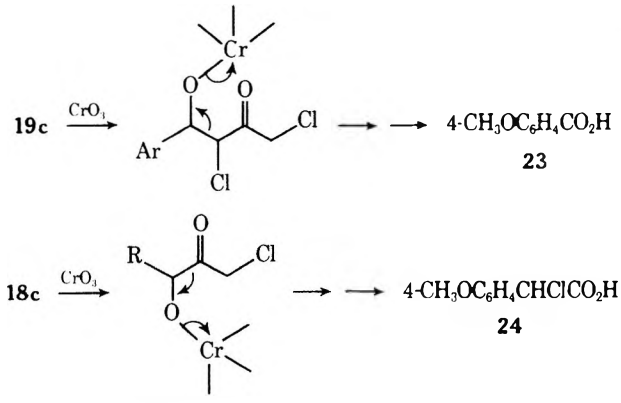
The phenylepoxydiazo ketone 7a reacted with hydrogen chloride to form 1,4-dichloro-3-hydroxy-4-phenyl-2-butanone (18a) as the major product and the isomer 1,3-dichloro-4-hydroxy-4-phenyl-2-butanone (19a) as a minor by-product, although the latter could not be isolated but was identified spectroscopically in the mixture. The reaction of 7c with hydrogen chloride gave mainly 1,3-dichloro-4-hydroxy-4-(4′-methoxyphenyl)-2-butanone (19c) with a smaller amount of 1-chloro-3-hydroxy-4-(4′-methoxyphenyl)-3-buten-2-one (20c). Neither 18a nor 19c gave satisfactory elemental analyses, probably because of their unstable nature and the time necessary to obtain analytical data. They did have sharp melting points and satisfactory parent ions in their mass spectra, however, consistent with the assigned molecular formula.

The structure of 18a is based on the presence of $PhCHCl^+$ ions in its mass spectrum which is consistent with cleavage of structure 18a. Furthermore, Jones oxidation[7] of 18a gave chlorophenylacetic acid (21) and chloroacetic acid (22) in 68 and 67% yields, respectively. When a mixture of 18a and 19a was oxidized, the NMR spectrum of the reaction mixture contained peaks other than those of



21 and 22, strongly suggesting that **19a** was isomerically rather than diastereomerically related to **18a**.

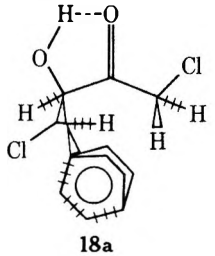
Jones oxidation of the *p*-methoxy derivative **19c**, however, resulted in cleavage to 4-methoxybenzoic acid (**23**). Although spectroscopic evidence was adduced for the other fragment, chloropyruvic acid, it was not isolated. This distinguished structure **19c** from its isomer **18c**. The latter should be oxidized to **24** instead of **23** as with the oxidation of **18a** to **21**.



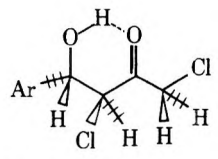
Another line of evidence supporting structure **19c** comes from a comparison of the NMR spectra of **18a**, **19a**, and **19c** given in Table I. Note that the CHOH and CHCl absorptions are quite similar in all three compounds but that in **18a** the two CH_2Cl protons are nonequivalent whereas they are equivalent in **19a** and **19c**. Furthermore, one of

Table I
Chemical Shifts (δ, ppm)

Proton	18a	19a	19c
CHOH	4.75	4.72	4.70
CHCl	5.20	5.45	5.38
CH_2Cl	4.33, 3.83	4.38	4.35



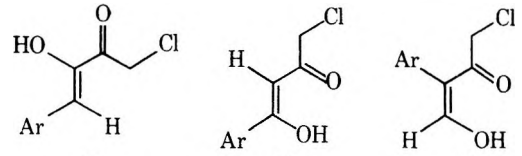
18a



19a, Ar = Ph
c, Ar = 4-$CH_3OC_6H_4$

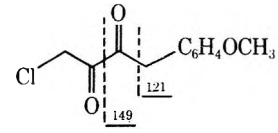
these protons in **18a** has roughly the same chemical shift as those in **19a** and **19c**, whereas the other CH_2Cl proton is shielded by 0.50 ppm. This difference can be rationalized if one considers the intramolecular hydrogen bonded form of the hydroxy ketone portion of the structure (the diastereomers shown are those predicted for stereospecific opening of the trans epoxides). In the case of **18a** one conformation allows the phenyl moiety to come close to the CH_2Cl group. Partially restricted rotation as well as some conformation preference could readily explain the shielding of one CH_2Cl proton. In the case of **19a** and **19c**, however, the hydroxy ketone hydrogen bond holds the aromatic ring away from the CH_2Cl group and provides no basis for shielding. Thus, the CH_2Cl protons in **19a** and **19c**, should be equivalent, as was found.

The structure assigned the minor product from hydrogen chloride reaction of **7c** is based on a detailed consideration of the physical data. Basically, the mass spectrum, the elemental analysis, and spectral data restrict consideration to structures **20c**, **25**, and **26**. The vinyl and hydroxyl absorp-

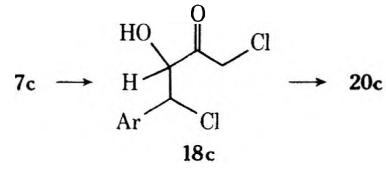


20c **25** **26**

tions at δ 6.39 and 6.9 ppm (the latter was under part of the aromatic absorption) respectively argue against structures **25** and **26**. The hydroxyl proton of **25** and **26** should appear near δ 15 ppm;[1d,8,9] the vinyl proton of **26** would be expected near δ 8 ppm.[9] The infrared spectrum of **20c** showed typical enolic hydroxyl adsorption at 2.91 μ[10] but the hydroxyl absorption of **25** and **26** would be expected at longer wavelengths.[1d,11] The ultraviolet spectrum of **20c** showed two maxima at 235 (ε 7060) and 343 nm (ε 25000) which shifted to 245 (ε 10000) and 383 nm (ε 14500) on addition of sodium hydroxide solution. This behavior, particularly the bathochromic shift on addition of base, is typical of an enolic α-diketone[12] but inconsistent with a β-diketone.[13] The mass spectrum of **20c** showed, in addition to a parent ion containing one chlorine atom, a base peak at *m/e* 121 and a weak peak at *m/e* 149. These peaks are consistent only with structure **20c** in the diketo form.



The structure assigned **20c** also supports the structure assigned **19c**. The mechanism of formation of **20c** (reaction 2) could reasonably involve initial formation of isomer **18c**

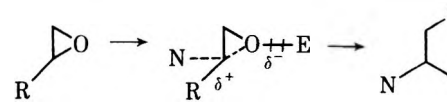


(2)

18c

followed by elimination of hydrogen chloride to **20c**. If **19c** was diastereomeric with **18c**, then it is difficult to see why **19c** would also not be unstable and give rise to **20c**. Therefore, **19c** and **18c** must be isomeric. Furthermore, treatment of **19c** with base gave a mixture which did not contain the characteristic NMR spectral peaks of **20c**.

Mechanistically the formation of **18a** with **19a** from **7a** with hydrogen chloride in ether is understandable in terms of the push–pull mechanism postulated for epoxide ring opening (reaction 3).[14] The transition state under acidic

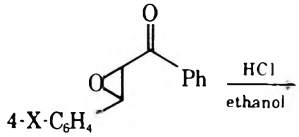


(3)

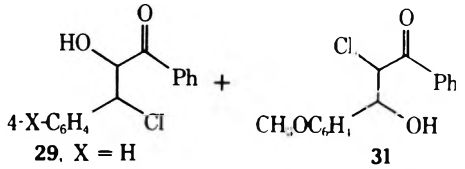
conditions is characterized by partial bond formation to an electrophile (E) and with a nucleophile (N) simultaneously with former predominating. R groups which allow dispersion of the partially developed positive charge tend to favor epoxy ring opening at that carbon under acidic conditions. Thus, product **18a** is the expected isomer on this basis from **7a**.

The major production of **19c** from **7c**, however, is not consistent with this interpretation. A similar result has

been observed before. In the case of **27** and **28**, **27** gave rise only to **29**[15] when treated with hydrogen chloride in ethanol, while the *p*-methoxyl series **28** gave both **30** and **31** al-



27, X = H
28, X = CH_3O

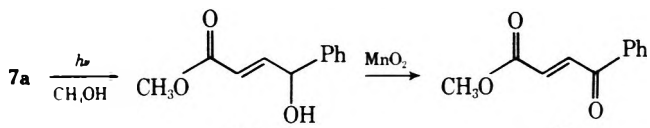


29, X = H
30, X = CH_3O **31**

though the yields were not reported.[16] In view of the fact that the push–pull mechanism was derived from reactions of aryl epoxides,[14] not aryl acyl epoxides, and because of the dearth of examples of reactions in the literature other than those above, it seems imperative that further investigation of such systems be made before more definitive mechanistic conclusions may be drawn.

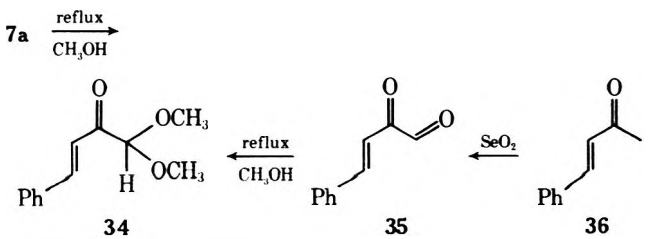
The apparent relative reactivity of the epoxy and diazo functions and the observed products indicate that the diazo group probably reacts first followed by independent reaction of the epoxide ring. Under aqueous conditions this is apparently not true.[2a]

Photo and Thermal Decomposition. Irradiation of the epoxydiazo ketone **7a** in methanol gave methyl 4-hydroxy-4-phenyl-2-butenoate (**32**) as a brown liquid in 62% yield.[2b] Confirmation of structure **32** came from the manganese dioxide oxidation of the allylic hydroxyl group to the known[17] methyl 4-oxo-4-phenyl-2-butenoate (**33**) in 74% yield.



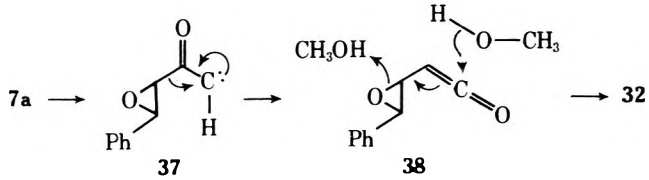
32 **33**

Pyrolysis of **7a** in refluxing benzene gave an intractable red oil.[2b] Refluxing in methanol over 48 hr, however, gave an 83% yield of 1,1-dimethoxy-4-phenyl-3-buten-2-one (**34**). The keto acetal **34** was synthesized from 4-phenyl-3-buten-2-one (**36**) by selenium dioxide oxidation[18] to the 4-phenyl-2-oxo-3-butenal (**35**) followed by refluxing in methanol, thus confirming the structural assignment.



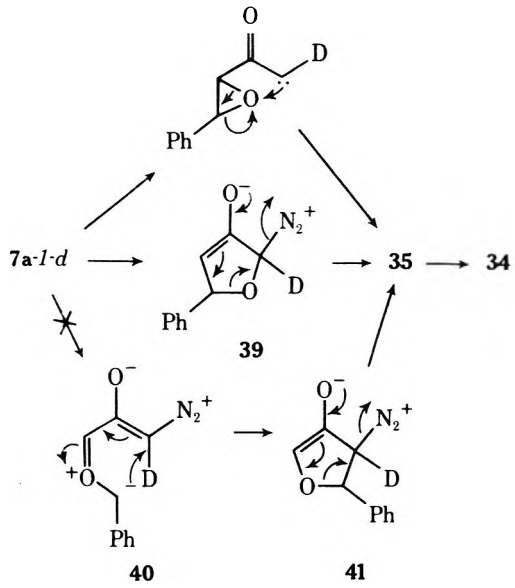
34 **35** **36**

Mechanistically the photochemical reaction of **7a** probably proceeds by normal Wolff rearrangement[19] via the ketocarbene **37** to the epoxy ketene **38**. Nucleophilic attack



37 **38**

Scheme IV



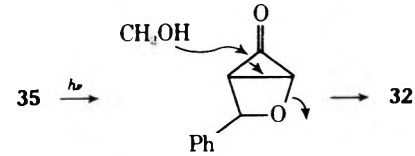
40 **41**

by methanol on **38** could open the epoxide as shown to give the observed product **32**. An epoxy ketene has been isolated by others[2b] on irradiation of **7a** in a hydrocarbon matrix at low temperature, supporting this mechanism.

The mechanism of the thermal rearrangement probably involves initial formation of **35** followed by acetal formation in refluxing methanol. The rearrangement of **7a** to **35** could be brought about by direct intramolecular abstraction of oxygen by a thermally generated ketocarbene[20] or by cyclization before loss of nitrogen to **39** followed by ring opening concerted with nitrogen loss to **35** (Scheme IV).[21] Both mechanisms are consistent with the results of a deuterium labeling experiment where the diazo carbon hydrogen of **7a** was replaced with deuterium.[22] Pyrolysis of **7a**-*1-d* in methanol *O-d* gave **34**-*1-d* with no change in deuterium content. This result eliminates the carbon–carbon epoxide ring cleavage mechanism observed for vinyl oxiranes[23] which would have given **34**-*3-d* for rearrangement of **7a** via **40** and **41** (Scheme IV).

If both the thermal and photochemical reactions proceeded through the ketocarbene **37** it is difficult to see why the products are different unless the multiplicity of the carbene generated in the two ways is different.[24] The Wolff rearrangement normally takes place through a singlet carbene.[25] If the thermal reaction took place through a triplet ketocarbene, then irradiation of **7a** with a triplet sensitizer should give high yields of the thermal product **34** or **35**.[26] Irradiation of **7a** with benzophenone as sensitizer gave a mixture which lacked the characteristic peaks of **32**, **34**, or **35**. This result implies that neither **32** nor **35** is formed through a triplet ketocarbene.

It is possible that **35** is a common intermediate in both thermal and photo processes. Formation of **32** could take place by rapid secondary irradiation of **35** through an intramolecular Paterno–Büchi reaction[27] (reaction 4) followed by opening of the cyclopropanone intermediate as indicated to form **32**. Irradiation of **35** in methanol gave an intractable mixture, however, which lacked the characteristic peaks of **32** in the NMR spectrum.



(4)

Thus, the most probable mechanism for the photolysis of **7a** is the Wolff rearrangement through a singlet ketocarbene. The pyrolysis reaction probably occurs by cyclization to **39** prior to nitrogen loss followed by rearrangement to **35** and addition of methanol to **34**.

Experimental Section

General. Melting points were determined on a Fisher-Jones hot stage; ir spectra with a Beckman IR-12 or IR-33(i); NMR with a Varian A-60; mass spectra with a CEC 491; uv spectra with a Cary 14. Microanalyses were performed by Midwest Microlabs.

Diazomethane. Diazomethane was prepared from bis(*N*-methyl-*N*-nitroso)terephthalamide by a standard procedure.[28] The yield was estimated by standardization of an aliquot by the benzoic acid acid procedure.[28]

1-Chloro-3-diazopropanone (6). Literature preparation[29] of **6** from chloroacetyl chloride and diazomethane was followed by fractional vacuum distillation. After the first 40% was discarded (which contained an impurity, probably dichloroacetone), **6** was collected as a yellow oil (52%): bp 45–47° (1 mm); NMR (CCl_4) δ 5.90 (s, 1 H, CHN_2), 3.96 ppm (s, 2 H, CH_2Cl); ir (neat) 4.79 (m, C=N_2), 6.17 μ (s, C=O).

3-Chloro-1-diazo-3-phenyl-2-propanone (9). Literature preparation[30] of **9** from chlorophenyl acetyl chloride and diazomethane gave a 61% yield, recrystallized from ether–pentane: mp 60–61° (lit.[30] 62°); NMR δ 7.32 (s, 5 H, Ph), 5.65 (s, 1 H, CHN_2), and 5.18 ppm (s, 1 H, CHCl); ir ($CHCl_3$) 4.78 (s, C=N_2), 6.18 μ (s, C=O).

6-Chloro-2-diazo-1-hydroxy-1-phenyl-3-hexanone (5). To an ice-cold, stirred solution of 0.50 g (3.4 mmol) of **3**[12] in 30 ml of methanol and 3 ml of benzaldehyde was added 0.14 g (3.4 mmol) of sodium hydroxide dissolved in 5 ml of water. After 20 min water was added, the mixture extracted with methylene chloride, the solvent distilled, and the residue chromatographed on alumina (activity II, 100 g). Elution with hexane removed starting material, with benzene gave 0.39 g (45%) of **5** as a yellow oil: NMR ($CDCl_3$) 7.40 (s, 5 H, Ph), 6.05 (s, 1 H, CHOH), 4.02 (br s, 1 H, CHOH), 5.08 (t, 2 H, CH_2Cl), 2.28–1.95 ppm (m, 4 H, $COCH_2CH_2$); ir (neat) 2.93 (w, OH), 4.75 (s, C=N_2), 6.18 μ (s, C=O).

1-Chloro-3-diazo-1,4-diphenyl-4-hydroxy-2-butanone (10). To an ice-cold, stirred solution of 0.5 g (2.6 mmol) of **9** in 30 ml of methanol and 3 ml of benzaldehyde was added 0.11 g (2.6 mmol) of sodium hydroxide dissolved in 4 ml of water. After stirring for 30 min, the mixture was poured into 30 ml of water and extracted thrice with 50-ml portions of methylene chloride. After removal of the solvent, the extract was chromatographed (basic alumina, activity II, 100 g). Elution with carbon tetrachloride and benzene gave unreacted benzaldehyde and **9**, respectively. Elution with ether–ethyl acetate (2:3) gave on solvent removal 0.39 g (25%) of a diastereomeric mixture of **10**: NMR (CCl_4) δ 7.35 (d, 10 H, 2 Ph), 5.93 (s, CHOH, isomer A), 5.09 (s, sum A + B = 1 H, CHOH, isomer B), 5.53 (s, CHCl, isomer B), 5.50 (s, sum A + B = 1 H, CHCl, isomer A), 4.22 ppm (br s, 1 H, CHOH); ir ($CHCl_3$) 2.93 (w, OH), 4.75 (s, C=N_2), 6.17 μ (s, C=O).

Darzens Reaction of Aldehydes with 6. General Procedure. To an ice-cold, stirred solution of 0.5 g (4.2 mmol) of **6** and 4.2 mmol of aldehyde in 20 ml of methanol was added 0.17 g (4.2 mmol) of sodium hydroxide in 4 ml of water. After stirring for 30 min, 50 ml of water was added, and the precipitate was filtered off and recrystallized from methanol–water.

1-Diazo-3,4-epoxy-4-phenyl-2-butanone (7a). Reaction of **6** with benzaldehyde gave 69% of **7a** as yellow crystals mp 95–96°; NMR ($CDCl_3$) δ 7.33 (s, 5 H, Ph), 5.58 (s, 1 H, CHN_2), 3.91 (d, 1 H, J = 1.5 Hz, epoxymethine), 3.48 ppm (d, 1 H, J = 1.5 Hz, epoxymethine); NMR ($CDCl_3$, D_2O, Na_2CO_3) same as above except lacking δ 5.58 peak; ir ($CHCl_3$) 4.76 (s, C=N_2), 6.13 μ (s, CO); uv max (MeOH) 280 nm (ϵ 15600), 235 (20800); mass spectrum (30 eV, 90°) *m/e* (rel intensity) 188 (0.6, $C_{10}H_8O_2N_2$), 160 (5, P − N_2), 159 (12), 120 (12), 106 (39), 105 (100), 103 (11), 91 (12), 90 (11), 77 (11). Anal. Calcd for $C_{10}H_8O_2N_2$: C, 63.83; H, 4.25; N, 14.87. Found: C, 63.77; H, 4.52; N, 14.85. In a second run the reaction was terminated after 5 min, then the mixture was extracted with methylene chloride. After concentration, the crystalline precipitate was filtered off and recrystallized to give 33% of **7a**. The filtrate was chromatographed on Florisil (activity II, 20 g) eluted with hexane, which gave benzaldehyde and **6**, and with benzene–ether (9:1), which afforded 4% of the diastereomeric mixture of **8a**, mp 79–102°, identified by the characteristic NMR spectrum.

1-Diazo-3,4-epoxy-4-(4′-nitrophenyl)-2-butanone (7b). Reaction of **6** with 4-nitrobenzaldehyde gave 88% of **7b** as yellow crystals: mp 134–135°; NMR ($CDCl_3$) δ 8.13 (m, 2 H, 4′-nitrophenyl), 7.50 (m, 2 H, 4′-nitrophenyl), 5.82 (s, 1 H, CHN_2), 4.13 (d, 1 H, J = 1.5 Hz, epoxymethine), 3.50 ppm (d, 1 H, J = 1.5 Hz, epoxymethine); ir (Nujol) 4.78 (s, C=N_2), 6.18 μ (s, C=O). Anal. Calcd for $C_{10}H_7N_3O_4$: C, 51.52; H, 3.00; N, 18.02. Found: C, 51.28; H, 3.25; N, 17.95.

1-Diazo-3,4-epoxy-4-(4′-methoxyphenyl)-2-butanone (7c). Reaction of **6** with 4-methoxybenzaldehyde gave 30% of **7c** as a yellow solid: mp 83–84°; NMR ($CDCl_3$) δ 7.25 (m, 2 H, 4′-methoxyphenyl), 3.76 (s, 3 H, OCH_3), 3.88 (d, 1 H, J = 1.5 Hz, epoxymethine), 3.50 ppm (d, 1 H, J = 1.5 Hz, epoxymethine); ir (Nujol) 4.75 (s, C=N_2), 6.20 μ (s, C=O). Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.57; H, 4.58; N, 12.84. Found: C, 60.33; H, 4.80; N, 12.64. A second run as above except for the 1.5-hr reaction time gave a 55% yield of **7c**.

1-Diazo-3,4-epoxy-6-phenyl-5-hexen-2-one (7d). Reaction of **6** with (*E*)-cinnamaldehyde gave a 46% yield of **7d** as yellow crystals: mp 77–78°; NMR ($CDCl_3$) δ 7.33 (s, 5 H, Ph), 6.86 (d, 1 H, J = 16 Hz, PhC**H**=), 5.85 (dd, 1 H, J = 16, J' = 7.5 Hz, PhCH=C**H**–), 3.58 (dd, J' = 7.5, J'' = 2 Hz, =CHC**H**O–), 3.47 ppm (d over 3.58 dd, sum 2 H, J'' = 2 Hz, –COC**H**O–); ir (Nujol) 4.74 (s, C=N_2), 6.17 μ (s, C=O). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.31; H, 4.67; N, 13.08. Found: C, 67.03; H, 4.82; N, 13.25.

1-Diazo-3,4-epoxy-4-(2′-thienyl)-2-butanone (7e). Reaction of **6** with 2-thiophene carboxaldehyde gave a 61% yield of **7e** as yellow crystals: mp 100.5–101.5°; NMR ($CDCl_3$) δ 7.18 (m, 4 H, thienyl), 5.56 (s, 1 H, CHN_2), 4.16 (d, 1 H, J = 1.5 Hz, epoxymethine), 3.65 ppm (d, 1 H, J = 1 Hz, epoxymethine); ir (Nujol) 4.75 (s, C=N_2), 6.17 μ (s, C=O). Anal. Calcd for $C_8H_6N_2O_2S$: C, 49.48; H, 3.11; N, 14.42; S, 16.51. Found: C, 49.37; H, 3.34; N, 14.22; S, 16.39.

Diadducts. 2-Diazo-1,5-diphenyl-4,5-epoxy-1-hydroxy-3-pentanone (8a). To an ice-cold, stirred solution of 0.50 g (4.2 mmol) of **6** and 2 ml of benzaldehyde in 20 ml of methanol was added 0.34 g (8.4 mmol) of sodium hydroxide dissolved in 8 ml of water. After stirring for 30 min, 30 ml of water was added and the solution extracted with three 50-ml portions of methylene chloride. After removal of the solvent, the residue was chromatographed on Florisil (activity II, 60 g). Elution with hexane gave unreacted starting materials; with carbon tetrachloride, the epoxydiazo ketone **7a** in 44% yield; with benzene–ether, the diadduct **8a** (0.50 g, 41%) as a diastereomeric mixture with mp 77–106°; NMR ($CDCl_3$) δ 7.35 (d, 10 H, 2 Ph), 6.12 (d, 1 H, CHOH), 4.25 (d, 1 H, CHOH), 4.10 (d, J = 1.5 Hz, epoxymethine, isomer A), 4.02 (d, sum of A + B = 1 H, J = 1.5 Hz, epoxymethine, isomer B), 3.70 ppm (d, 1 H, J = 1.5 Hz, epoxymethine); NMR ($CDCl_3$–D_2O) same as above except for δ 6.12 (s, 1 H, CHOD) and lacking the δ 4.25 ppm peak; ir ($CHCl_3$) 2.95 (w, OH), 4.77 (s, C=N_2), 6.19 μ (s, CO); mass spectrum (30 eV, 80°) *m/e* (rel intensity) 266 (36, $C_{17}H_{14}O_3$), 248 (40), 247 (37), 246 (25), 199 (10), 197 (10), 161 (10), 160 (81), 159 (10), 147 (10), 120 (21), 119 (19), 118 (84), 106 (34), 105 (37), 103 (23), 91 (100), 90 (15), 77 (21), 75 (13), 69 (11), 62 (94), 61 (37), 59 (10). Anal. Calcd for $C_{17}H_{14}O_3N_2$: C, 69.41; H, 4.76; N, 9.52. Found: C, 69.17; H, 4.78; N, 9.40.

Fractional crystallization of the diastereomeric mixture of **8a** from ether gave 80 mg of isomer A: mp 110.5–111.5°; NMR same as above except δ 4.10 integrated for one proton and lacked the δ 4.02 peak. The filtrate from isomer A crystallization was cooled in ether–hexane to give 120 mg of isomer B: mp 78.5–80°; NMR as above except the δ 4.02 peak integrated for one proton and lacked the δ 4.10 peak.

A second run with the same amounts of reagents was stirred for 90 min and worked up as before to give 0.30 g (37%) of epoxydiazo ketone **7a** and 0.44 g (36%) of the diastereomeric mixture of the diadducts **8a** identified by the NMR spectrum.

4-Diazo-6,7-epoxy-3-hydroxy-1,9-diphenyl-1,8-nonadien-4-one (8d). To an ice-cold, stirred solution of 0.50 g (4.2 mmol) of **6** and 2 ml of (*E*)-cinnamaldehyde in 30 ml of methanol was added 0.34 g (8.4 mmol) of sodium hydroxide dissolved in 8 ml of water. After 30 min, the precipitation of a solid was completed by addition of 30 ml of water. The solid was filtered and recrystallized from acetone to give 0.72 g (49%) of a diastereomeric mixture of **8d** as a yellow solid: mp 124–130°; NMR (Me_2SO) δ 7.60–5.9 (m, 15 H, 2 Ph, 4 vinyl, OH), 5.55 (d, 1 H, CHOH), 4.15–3.75 ppm (m, 2 H, epoxymethine); ir (Nujol) 2.94 (w, OH), 4.72 (s, C=N_2), 6.16 μ (s, C=O). Anal. Calcd for $C_{21}H_{18}O_3N_2$: C, 72.83; H, 5.20; N, 8.26. Found: C, 73.04; H, 5.36; N, 8.26.

Base Cleavage of 8a. To an ice-cold stirred solution of 200 mg (0.68 mmol) of the diastereomeric mixture of **8a** in 5 ml of methanol was added 0.35 ml of a 2 *M* (0.68 mmol) aqueous sodium hydroxide solution. After stirring for 15 min the precipitated solid was filtered to give 115 mg (90%) of **7a**, mp 95–96°.

When the above reaction was carried out with 0.5 ml of benzaldehyde added, followed by addition of water and extraction with methylene chloride, the NMR spectrum of the solvent-free reaction mixture showed only adsorptions due to benzaldehyde and the starting diastereomeric mixture **8a** but lacked the characteristic peaks of **7a**.

Cleavage of 8a, Isomer A. Treatment of 100 mg (0.34 mmol) of **8a** isomer A, with 0.17 ml of 2 *M* aqueous sodium hydroxide solution as above gave 55 mg (87%) of **7a**, mp 94.5–96°.

Cleavage of 8a, Isomer B. Treatment of 100 mg (0.34 mmol) of **8a**, isomer B, with 0.17 ml of 2 *M* sodium hydroxide solution as above gave 58 mg (91%) of **7a**, mp 95–96°.

Cleavage of 8d. Treatment of 0.50 g (1.4 mmol) of the diastereomeric mixture **8d** in 250 ml of methanol with 0.74 ml of 2 *M* sodium hydroxide solution followed by the above extractive work-up gave on concentration and crystallization from methanol–water 100 mg (70%) of **7d**, identified by mp (77–78°), mmp (77–78°), and NMR spectrum with an authentic sample.

Hydrogen Chloride Reactions of Epoxydiazo Ketones. 1-Chloro-3,4-epoxy-4-(4′-nitrophenyl)-2-butanone (17b). Dry hydrogen chloride gas was bubbled through a stirred solution of 250 mg (1.07 mmol) of **7b** in 250 ml of anhydrous ether. After 45 min the reaction mixture was washed with water, dried, and distilled to a solid residue which was crystallized from methanol–water to give 180 mg (71%) of **17b**: mp 101–102°; NMR ($CDCl_3$) δ 8.35 (m, 2 H, 4′-nitrophenyl), 7.52 (m, 2 H, 4′-nitrophenyl), 4.28 (s, 2 H, CH_2Cl), 4.21 (d, 1 H, J = 1.5 Hz, epoxymethine), 3.77 ppm (d, 1 H, J = 1.5 Hz, epoxymethine); ir ($CHCl_3$) 5.79 μ (s, C=O); mass spectrum *m/e* (rel intensity) 243 (2, $C_{18}H_8{}^{37}ClNO_4$), 241 (6, $C_{10}H_8{}^{35}ClNO_4$), 201 (6), 200 (34), 176 (6), 165 (6), 154 (9), 153 (10), 152 (100), 150 (12), 136 (52), 135 (81), 118 (9), 107 (12), 106 (14), 92 (10), 91 (6), 90 (11), 89 (19), 84 (16), 77 (30). Anal. Calcd for $C_{10}H_8ClNO_4$: C, 49.69; H, 3.31; N, 5.71; Cl, 14.70. Found: C, 49.41; H, 3.48; N, 5.88; Cl, 14.96.

Reaction of 7a with Hydrogen Chloride. A solution of 500 mg of **7a** in 30 ml of anhydrous ether was treated as above with hydrogen chloride gas for 10 min and worked up as above. The crude product was crystallized from ether–hexane, then from chloroform to give 330 mg (54%) of 1,4-dichloro-3-hydroxy-4-phenyl-2-butanone (**18a**) mp 100–101°; NMR δ 7.38 (s, 5 H, Ph), 5.20 (d, 1 H, J = 5 Hz, CHCl), 4.75 (br d, 1 H, CHOH), 4.33 (d, 1 H, J = 16 Hz, HCHCl), 3.83 (d, 1 H, J = 16 Hz, HCHCl), 3.48 ppm (br, 1 H, CHOH); NMR ($CDCl_3$–D_2O) same as above except δ 4.75 (d, 1 H, J = 5 Hz, CHOD) and lacking the δ 3.48 peak; ir ($CHCl_3$) 2.83 (w, OH), 5.74 μ (s, C=O); mass spectrum (24 eV, 150°) *m/e* (rel intensity) 236 (0.47, $C_{10}H_{10}{}^{37}Cl_2O_2$), 234 (3, $C_{10}H_{10}{}^{35}Cl^{37}ClO_2$), 232 (5, $C_{10}H_{10}{}^{35}Cl_2O_2$), 128 (2.5), 127 (33, $C_7H_6{}^{37}Cl$), 126 (9), 125 (100, $C_7H_6{}^{35}Cl$), 120 (6), 119 (9), 91 (91). Anal. Calcd for $C_{10}H_{10}O_2Cl_2$: C, 51.53; H, 4.32; Cl, 30.42. Found: C, 50.71, 51.02; H, 4.68, 4.55; Cl, 30.55. Removal of solvent from the above filtrates gave 110 mg of the isomeric mixture of chlorohydrin **18a** and 1,3-dichloro-4-hydroxy-4-phenyl-2-butanone (**19a**) which could not be separated cleanly. The NMR of this mixture showed peaks due to **18a** and in addition had peaks of δ 5.45 (d, 1 H, J = 3 Hz, CHCl), 4.72 (br d, 1 H, CHOH), 4.38 (s, 2 H, CH_2Cl), 3.20 ppm (br, 1 H, CHOH); NMR ($CDCl_3$–D_2O) same as above except for δ 4.72 (d, 1 H, J = 3 Hz, CHOD) and lacking 3.20-ppm peak. The integral area ratio of the δ 5.20 peak of **18a** to the 5.45 peak of **19a** was 1:3. Total yield of **18a** was 58% and of **19a** was 13% based on the NMR ratio.

Reaction of 7c with Hydrogen Chloride. Treatment of 560 mg (2.6 mmol) of **7c** with hydrogen chloride as above gave a yellow oil which was crystallized from ether–hexane, then from ether. Filtration gave 320 mg (42%) of 1,3-dichloro-4-hydroxy-4-(4′-methoxyphenyl)-2-butanone (**19c**): mp 80–81°; NMR ($CDCl_3$) δ 7.41 (m, 2 H, 4′-methoxyphenyl), 6.88 (m, 2 H, 4′-methoxyphenyl), 5.37 (d, 1 H, J = 3 Hz, CHCl), 4.68 (d, 1 H, J = 3 Hz, CHOH), 4.33 (s, 2 H, CH_2Cl), 3.77 (s, 3 H, OCH_3), 3.20 ppm (br, 1 H, CHOH); ir ($CHCl_3$) 2.87 (w, OH), 5.80 μ (s, C=O); mass spectrum (70 eV, 50°) *m/e* (rel intensity) 264 (0.18, $C_{11}H_{12}O_3{}^{35}Cl^{37}Cl$), 262 (0.3, $C_{11}H_{12}O_3{}^{35}Cl_2$), 229 (4, $C_{11}H_{12}O_3{}^{37}Cl$), 227 (1.1, $C_{11}H_{12}O_3{}^{35}Cl$), 157 (14), 155 (38), 136 (24, $C_8H_8O_2$), 135 (38), 121 (100, C_8H_9O), 91 (14), 77 (29), 76 (10). Anal. Calcd for $C_{11}H_{12}Cl_2O_3$: C, 50.21; H, 4.60; Cl, 26.95. Found: C, 50.19; H, 4.83; Cl, 25.81, 25.55. In a second run 300 mg (1.38 mmol) of **7c** was treated with hydrogen chloride and worked up as before. Crystallization of the crude pale yellow oil from ether–hexane gave 50 mg of **20c** (16%), mp 103–108°. Recrystallization from benzene gave colorless crystals which turned yellow on drying in vacuo. When heated slowly the yellow crystals turned white and melted at 107–108°:[31] ir ($CHCl_3$) 2.91 (m, OH), 5.94, 6.10, 6.22 (m, m, s, enolic dicarbonyl), 6.59, 7.92, 8.48 μ; NMR (CCl_4) δ 7.73 (m, 2 H, 4′-$CH_3OC_6H_4$), 6.8 (m, 3 H, 4′-$CH_3OC_6H_4$ and –C=H, latter removed on deuteration with D_2O), 6.38 (s, 1 H, vinyl), 4.43 (s, 2 H, CH_2Cl), 3.82 ppm (s, 3 H, CH_3O); uv (C_2H_5OH) max 234–237 (7060), 342–343.5 nm (25000), which changed to 244.5–246 (10600), 381–385 nm (14500) on addition of one drop of 3 *N* sodium hydroxide solution; mass spectrum (70 eV, 80°) *m/e* (rel intensity) 228 (6.8), 226 (19.5), 163 (4.4), 149 (8.6), 148 (3.1), 121 (100), 120 (3), 91 (5.4), 78 (4.9), 77 (6.4), 51 (5.7). Anal. Calcd for $C_{11}H_{11}O_3Cl$: C, 58.29; H, 4.89; Cl, 15.64. Found: C, 58.10; H, 5.05; Cl, 15.67.

Chromic Acid Oxidations of 18a. To a stirred solution of 150 mg of **18a** in 5 ml of reagent grade acetone was added 2 ml of a 1 *M* aqueous chromium trioxide solution containing 0.1 ml of concentrated sulfuric acid. After 8 hr chromium salts were filtered off followed by addition of 10 ml of water. The mixture was extracted twice with ether, distilled to a viscous oil, then evaporatively distilled at 40° (1 mm) to give 40 mg (67%) of *β*-chloroacetic acid (**22**): mp 56–57° (lit.[32] mp 57°); NMR ($CDCl_3$) δ 11.56 (s, 1 H, COOH), 4.16 ppm (s, 2 H, CH_2Cl); mass spectrum (70 eV, 40°) *m/e* (rel intensity) 96 (13, $C_2H_3{}^{37}ClO_2$), 94 (40, $C_2H_3{}^{35}ClO_2$), 51 (40), 50 (42), 49 (40), 48 (21), 45 (100), 42 (47), 34 (55).

The residue after distillation was triturated, then recrystallized from hexane to give 75 mg (68%) of the inactive form of chlorophenylacetic acid (**21**): mp 77–78° (lit.[33] mp 79°); NMR ($CDCl_3$) δ 9.84 (br, 1 H, CO_2H), 7.40 (m, 5 H, Ph), 5.36 ppm (s, 1 H, CHCl); mass spectrum (70 eV, 50°) *m/e* (rel intensity) 172 (4, $C_8H_7{}^{37}ClO_2$), 170 (13, $C_8H_7{}^{35}ClO_2$), 125 (86), 91 (100), 90 (52), 89 (36), 77 (43).

When 70 mg of a mixture of **18a** and **19a** in 3 ml of acetone were oxidized with 1 ml of 1 *M* aqueous chromium trioxide solution containing 0.05 ml of concentrated sulfuric acid for 6 hr followed by a work-up as above, a yellow oil resulted, the NMR of which showed peaks due to **21**, **22**, and additional peaks at δ 8.08 (m) and 4.35 ppm (s).

Chromic Acid Oxidation of 1,3-Dichloro-4-hydroxy-4-(4′-methoxyphenyl)-2-butanone (19c). Following the procedure used for **18a** above, 160 mg of **19c** was oxidized with 2 ml of acidic 1 *M* chromium trioxide solution over 6 hr. The crude product isolated as above was crystallized from ether to give 67 mg (73%) of 4-methoxybenzoic acid (**23**): mp 184–185° (lit.[34] mp 185°); NMR ($CDCl_3$) δ 10.50 (br, 1 H, COOH), 7.98 (m, 2 H, $CH_3OC_6H_4$), 6.98 (m, 2 H, $CH_3OC_6H_4$), 3.68 ppm (s, 2 H, OCH_3); ir ($CHCl_3$) 3.30 (br, OH), 5.86 μ (br, C=O); parent ion in mass spectrum at *m/e* 152. The filtrate showed in addition to the acid **23** peaks, δ 4.10 ppm (s).

Irradiation of 7a. Methyl 4-Hydroxy-4-phenyl-2-butenoate (32). A solution of 500 mg (2.6 mmol) of **7a** in 150 ml of methanol was irradiated in a test tube-like apparatus under a slow stream of nitrogen with a Pyrex, 450 W Hanovia medium pressure lamp in a water-cooled, test tube-like, immersion well for 30 min. After removal of the solvent the residue was chromatographed on Florisil (activity II, 50 g). Elution with hexane–ether (4:1) afforded 330 mg (62%) of **32** as a brown liquid: NMR (CCl_4) δ 7.28 (s, 5 H, Ph), 6.92 (q, 1 H, CH=CHCHOH, J = 16 J' = 5 Hz), 6.00 (q, 1 H, CH=CHCHOH, J = 16 J'' = 2 Hz), 5.15 (q, 1 H, CH=CHCHOH, J' = 5 J'' = 2 Hz), 3.65 (s, 3 H, OCH_3), and 3.12 ppm (s, 1 H, CHOH); ir (neat) 2.88 (w, OH), 5.82 μ (br, C=O). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.75; H, 6.25. Found: C, 68.81; H, 6.02. A second irradiation in 150 ml of benzene with 500 mg of **7a** over 30 min gave a light yellow oil which by TLC had at least three components but which proved intractable. Attempted chromatography on silica gel, alumina, or Florisil resulted in total decomposition (see ref 2b for characterization).

Methyl 4-Oxo-4-phenyl-2-butenoate (33). A solution of 200 mg (1 mmol) of **32** in 10 ml of anhydrous ether was stirred with 400 mg of activated[35] manganese dioxide for 8 hr. Filtration and removal of the solvent gave a yellow oil which was crystallized from ether–pentane to give 148 mg (74%) of **33** as yellow crystals: mp 28.5–29.5° (lit.[17] mp 29°); NMR (CCl_4) δ 8.15–7.20 (m, Ph and one vinyl proton), 6.79 (d, 1 H, J = 16 Hz, vinylic), 3.75 ppm (s, 3 H, OCH_3); ir ($CHCl_3$) 5.83 (s, ester C=O), 5.99 μ (s, keto C=O).

Sensitized Irradiation of 7a. With Benzophenone. A methanol solution (50 ml), 0.0256 *M* in **7a** and 0.404 *M* in benzophenone, was divided equally into five 15-ml Pyrex test tubes. A sixth tube contained 10 ml of 0.0265 *M* solution of **7a** only. The solutions were purged with nitrogen for 15 min, sealed, and irradiated at 25° ± 3° in a Rayonet Merry-Go-Round reactor with a medium pressure Hanovia 450-W lamp through a Corning C. S. 7-83 filter to isolate the 3660-Å mercury line. Tubes were withdrawn periodically, the solvent removed, and the NMR spectrum run. After 108 hr

all the **7a** in the unsensitized tube had been decomposed mainly to the ester **32** as revealed by the NMR spectrum. The NMR spectrum of a sensitized sample, after removal of excess benzophenone by crystallization from cold ether, was complex but lacked the characteristic peaks of **32**.

Attempted Sensitization with Michler's Ketone. The experiment was set up and carried out as above employing a solution 2.5 $\times 10^{-3}$ *M* in Michler's ketone and 2.5 $\times 10^{-2}$ *M* in **7a**. After irradiation for 96 hr the unsensitized sample was decomposed but the sensitized sample showed the NMR spectrum of only starting **7a**.

1,1-Dimethoxy-4-phenyl-3-buten-2-one (34). From 7a. A solution of 500 mg (2.6 mmol) of **7a** in 20 ml of methanol was refluxed for 48 hr.[36] Removal of the solvent gave a reddish oil which was chromatographed on alumina (activity II, 50 g). Elution with hexane–ether (7:3) afforded 440 mg (83%) of **34** as a yellow oil: bp 247–248.5° (capillary); n^{27}D 1.5641; NMR (CCl_4) δ 7.70 (d, 1 H, *J* = 16 Hz, vinylic), 7.40 (m, 5 H, Ph), 6.98 (d, 1 H, *J* = 16 Hz, vinylic), 4.50 [s, 1 H, C**H**(OCH_3)], 3.38 ppm (s, 6 H, OCH_3); ir (neat) 6.17 μ (s, C=O). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 69.67; H, 6.84.

From 36. 4-Phenyl-2-oxo-3-butenal (35). Following the procedure of Schank,[18] 11 g of **36** was treated with 8.2 g of selenium dioxide. Distillation gave 7 g (60%) of **35**: bp 140–143° (2 mm) [lit.[18] bp 120–121° (1 mm)]; NMR ($CDCl_3$) δ 9.50 (s, 1 H, HC=O), 8.02 (d, 1 H, *J* = 16 Hz, vinylic), 7.83–7.00 (m, 6 H, Ph and one vinylic); ir (neat) 5.82 (s, HC=O), 5.98 μ (s, keto C=O). When 1.0 g (6.2 mmol) of **35** was refluxed in 20 ml of methanol for 10 hr, followed by solvent removal and chromatography of the resultant brown oil on alumina (activity II, 50 g), the fraction eluted with hexane–ether (7:3) afforded 1.0 g (75%) of **34** with physical properties identical with those above.

Irradiation of 35. In Methanol. A solution of 390 mg (2.6 mmol) of **35** in 150 ml of methanol was irradiated (same procedure as for **7a**) for 30 min. After solvent removal, the NMR revealed a complex spectrum but lacking the characteristic peaks of **32**.

In Benzene. **35** was irradiated essentially as above but substituting benzene for methanol. The NMR of the reaction mixture was not the same as that for irradiation of **7a** in benzene.

Preparation and Thermolysis of 7a-*1-d*. To a solution of 0.10 g of **7a** in 10 ml of methylene chloride was added ca. 0.05 g of anhydrous sodium carbonate and ca. 1 ml of D_2O (99.5% deuterium). After stirring overnight the aqueous layer was separated and the organic phase dried with anhydrous magnesium sulfate. Two more treatments in the same way gave **7a**, mp 93–94°, containing 96.5–100% deuterium on C-1 as judged by NMR integration. This sample in a carefully dried apparatus was dissolved in 5 ml of methanol-*o*-*d* (99.5% deuterium). The solution was refluxed for 48 hr.[36] Removal of the solvent under reduced pressure gave a crude brown oil. The NMR spectrum of this mixture showed less than 4% of hydrogen on C-1 of **34**. Integration clearly established the 1:1 ratio of the protons on C-3 and C-4.

Registry No.—**3**, 28488-90-6; **5**, 56468-30-5; **6**, 20485-53-4; **7a**, 50629-66-8; **7b**, 50629-68-0; **7c**, 50629-69-1; **7d**, 50801-37-1; **7e**, 50629-70-4; **8a** isomer A, 50763-76-3; **8a** isomer B, 50629-67-9; **8d** isomer A, 56467-94-8; **8d** isomer B, 56498-04-5; **9**, 54497-04-0; **10** isomer A, 56467-95-9; **10** isomer B, 56467-96-0; **17b**, 56467-97-1; **18a**, 56467-98-2; **19a**, 56467-99-3; **19c**, 56468-00-9; **20c**, 56468-01-0; **21**, 4755-72-0; **22**, 79-11-8; **23**, 100-09-4; **32**, 55980-63-7; **33**, 14274-07-8; **34**, 55980-64-8; **35**, 6784-05-0; **36**, 122-57-6; benzaldehyde, 100-52-7; 4-nitrobenzaldehyde, 555-16-8; 4-methoxybenzaldehyde, 123-11-5; (*E*)-cinnamaldehyde, 14371-10-9; 2-thiophenecarboxaldehyde, 98-03-3; sodium hydroxide, 1310-73-2; hydrogen chloride, 7647-01-0; chromium trioxide, 1333-82-0; benzophenone, 119-61-9.

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Substituent Effects on the Solvolysis of α,α'-Dichloroazoalkanes. Evidence for Open Aza-allylic Ion Intermediates on Reaction Pathway[1]

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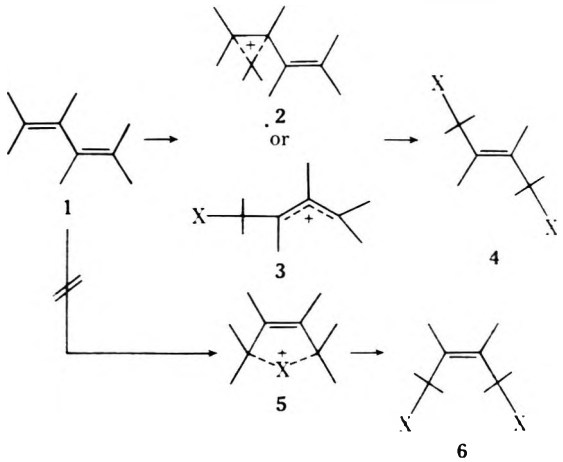
Reaction of α,α'-dichloroazoalkanes **9** in 7:3 dioxane–water at 25° shows consecutive kinetics. The spectrophotometrically detected intermediate is shown to be a 1-aryldiazoethane (**11** or **13**); this is stable in basic solution but undergoes rapid nitrogen loss in acid. The rate-determining step in the conversion of α,α'-dichloroazoalkanes to diazoalkanes was investigated in detail and shown to be the formation of a stabilized carbonium ion species. This is consistent with a large solvent effect (m = 1.20) and the observation of a rate depression by chloride ion. With symmetrically disubstituted substrates (**9**, $Ar^1 = Ar^2$), electron-donating groups aid reaction ($\rho = -3.68$). However, when the substrates **9** are not symmetrically substituted ($Ar^1 \neq Ar^2$) the data deviate markedly from a simple Hammett relationship and this is rationalized in terms of the formation of an open aza-allylic intermediate (**10**) rather than a symmetrical chloronium ion (**19**). The intermediate **10** does not give the expected diazoalkane (**11**) directly on fragmentation; instead the isomeric material (**13**) is formed preferentially. To explain these results a mechanism for the formation of diazoalkane **13** from **10** is suggested involving the chloronium ion **19** as an intermediate or transition state.

Extensive mechanistic studies have been carried out on the 1,4 addition of halogens to 1,3-dienes (**1**), including butadiene,[2] isoprene,[3] and their 2,3-diaza analogs.[4] In all cases the ionic reaction is stereospecific, leading only to the trans isomer **4**. This observation has been used to rule out the intermediacy of a bridged cyclic intermediate of type **5**, since it has been rationalized that nucleophilic attack by halide ion on **5** would necessarily lead to a cis product **6**. Instead an open vinyl cation (**3**) or a 1,2-bridged cation (**2**) has been proposed as intermediate. However, recent work at low temperature in SbF_5–SO_2 has clearly established the existence of tetramethylenehalonium ions, which are the saturated analogs of **5**.[5,6] Moreover, solvolysis studies have indicated 1,4-halogen participation in the solvolysis of ω-halo-2-alkyl tosylates.[7]

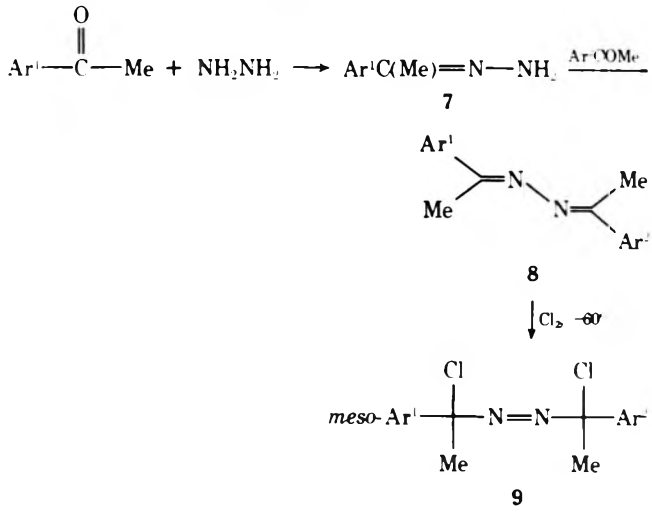


We have investigated in some detail the mechanism of solvolysis of the dichlorides **9**. These are the diaza analogs of the dihalides **4**. It has been suggested[4] that the pathway for the chlorination of the diene and the solvolysis of the dichlorides are similar; thus our observation of both open and bridged chloronium ion species in the solvolysis of **9** is also relevant to the preferred pathway followed in the halogenation of **1**.

Results and Discussion

A. Preparation of α,α'-Dichloroazoalkanes. The symmetrical 2,3-diazabuta-1,3-diene ("ketazine") substrates **8** were prepared directly by the reaction of 2 mol of the appropriate aromatic ketone with 1 mol of hydrazine. However, when a ketazine was required with two different substituents in Ar^1 and Ar^2, the intermediate hydrazone **7** had to be isolated. Such unsubstituted hydrazones are normally unstable, rapidly disproportionating to give the ketazine and hydrazine. However, electron-withdrawing substituents in Ar^1 (e.g., Ar^1 = p-$NO_2C_6H_4$ or p-ClC_6H_4) provide some stability to the hydrazone and where possible the synthetic route used (Scheme I) took advantage of this.

Scheme I



Several methods are available for the chlorination step. Thus, for example, reaction is reported to proceed well when the ketazine is dissolved in petroleum ether,[8] methylene chloride,[4] sulfur dioxide, or acetyl chloride, and treated with chlorine.[4] Earlier workers[9] chlorinated the ketazine at −60° in the absence of solvent and we have found this to be the preferred procedure for the preparation of the novel unsymmetrical materials **9** ($Ar^1 \neq Ar^2$).

Malament and McBride[4] have shown that in solution the diazabutadiene **8** ($Ar^1 = Ar^2$) exists at equilibrium in the preferred configuration shown, with the bulky aryl groups remote from each other. The chlorination is stereospecific (see below) so that only one product, the meso isomer **9** ($Ar^1 = Ar^2$ = Ph), is formed. Although the stereochemistry of the dichloride formed was not investigated as part of this work, we found no kinetic evidence that mixtures of isomers were present.

We were unable to obtain the normal chlorination products **9** when *both* aromatic rings had strongly electron-withdrawing groups. Thus the ketazine **8** with $Ar^1 = Ar^2$ =

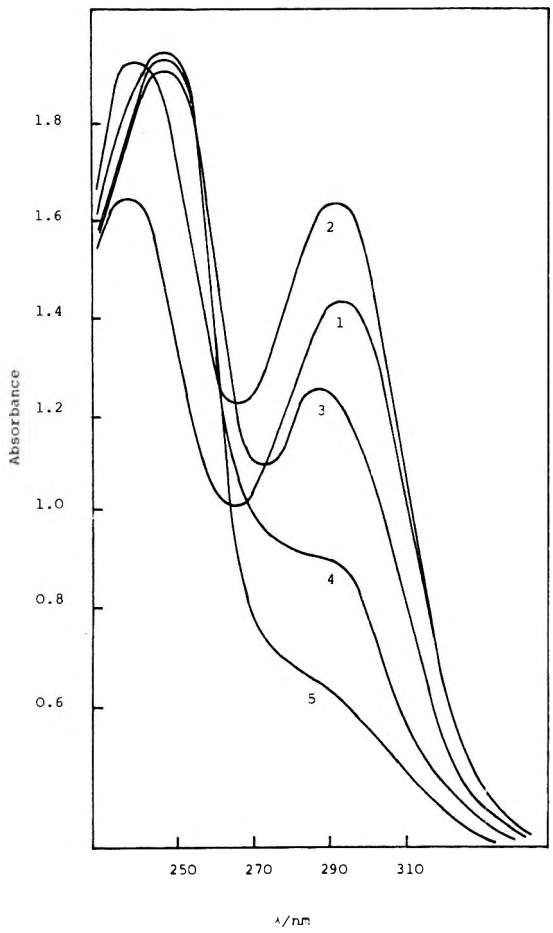


Figure 1. Repetitive scans of the ultraviolet spectrum of **9** (Ar^1 = Ar^2 = p-ClC_6H_4) in 7:3 dioxane–water at 25°; the time interval between the various scans is ca. 2 min.

p-$NO_2C_6H_4$ remained unchanged when treated with chlorine at −60° after 6 hr. At higher temperature extensive decomposition occurred. The m-nitroazine (**8**, Ar^1 = Ar^2 = m-$NO_2C_6H_4$) behaved similarly, but the o-nitro material (**8**, Ar^1 = Ar^2 = o-$NO_2C_6H_4$) gave a high yield of the hydrochloride of the starting ketazine on attempted chlorination.

B. Kinetic Experiments. The solvolyses of α,α'-dichloroazoalkanes **9** were studied in 7:3 (v/v) dioxane–water at 25°. Under these conditions with a typical substrate (**9**, Ar^1 = Ar^2 = p-ClC_6H_4) two consecutive reactions were observed. This is clearly shown by the absence of tight isosbestic points in repetitive scans of the ultraviolet region (see Figure 1 for a typical example). This result is surprising in view of Benzing's report that the solvolysis of 2,2′-dichloro-2,2′-azopropane (followed by N_2 evolution) in 85% aqueous acetone gives good kinetics.[9]

Although the spectral change with time on solvolysis of **9** (Ar^1 = Ar^2 = p-ClC_6H_4) at a single wavelength showed an initial increase in absorbance followed by a decrease (or vice versa), it was possible to follow both reactions by a careful choice of wavelength. Thus no spectral change was observed at 260 nm for the second reaction; the change in optical density at this wavelength was thus used to follow the first reaction. Similarly the first reaction showed little change in optical density at 310 nm and the second reaction was best followed at this wavelength when the first reaction was essentially complete. It was more difficult to estimate the rate constant for the second reaction when its rate was equal to or faster than that of the initial reaction; under these conditions it was usually possible to estimate the rate constant using the τ_{max} technique for series first-order reactions of Frost and Pearson.[10] Normally, however, the reaction conditions could be manipulated (see below) so that just one of the steps was rate determining and good first-order kinetics were then obtained.

Table I
Observed Rate Constants for the Solvolysis of 9 (Ar^1 = Ar^2 = p-ClC_6H_4) in 7:3 Dioxane–Water at 25°

Salt (0.01 M)	$10^3 k_1$,[a] sec^{-1}	$10^3 k_2$,[b] sec^{-1}
NaN_3	7.2	[c]
NaOAc	7.2	[c]
$NaClO_4$	11.0	8.9
NaCl	2.6	3.6
NaOH	4.5	[c]
$HClO_4$	6.0	[c]

[a] Followed at 260 nm. [b] Followed at 310 nm. [c] No subsequent rate observed.

Table II
Rate Constants for the Solvolysis of 9 (Ar^1 = Ar^2 = p-ClC_6H_4) in 7:3 Dioxane–Water at 25° in Presence of Added Chloride Ion

[NaCl], M[a]	[$NaClO_4$], M	$10^3 k_{obsd}$, sec^{-1}
0.00	0.10	11.0
0.02	0.08	6.9
0.05	0.05	4.9
0.08	0.02	3.4
0.10	0.00	2.6

[a] 0.01 M NaOH added to suppress second reaction ($k_2 \sim 0$).

A schematic reaction Scheme II is presented. A is the starting dichlorodiazoalkane **9**; we have carried out a detailed kinetic study to determine the nature of the ultimate products C and the intermediate B and of the rate-determining steps for the first and second reactions, k_1 and k_2, respectively.

Scheme II

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

1. Solvolysis under Neutral and Basic Conditions (k_1). The observed rates of solvolysis of **9** (Ar^1 = Ar^2 = p-ClC_6H_4) in 7:3 dioxane–water in the presence of various added salts are presented in Table I. As regards the first step (k_1), perhaps the most significant observation is that the reaction shows a remarkable insensitivity to the presence of acid or base. Also the rate is increased by salts such as sodium perchlorate and shows a depression in the presence of sodium chloride, a salt with a common ion.[11] The latter effect was examined in more detail (Table II); these measurements were made, for convenience, in the presence of 0.10 M added hydroxide ion in each case since this suppresses the second reaction and good first-order kinetics were obtained in each case.

In addition, the rate of the first reaction is very sensitive to the aqueous fraction of the solvent, increasing sharply with the ionizing power of the medium (Table III). The Grunwald–Winstein m value calculated is 1.20; a value of this magnitude (m for *tert*-butyl chloride is 1.0) is strong evidence for an SN1 dissociative-type mechanism for the first step.[12]

These data, taken together, support a mechanism involving rate-determining C–Cl bond fission for the first step (Scheme III) and confirm the earlier work of Benzing.[9] The charge on the ion formed, **10** (Ar^1 = Ar^2 = p-ClC_6H_4), can be stabilized by delocalization onto the adjacent azo nitro-

Scheme III

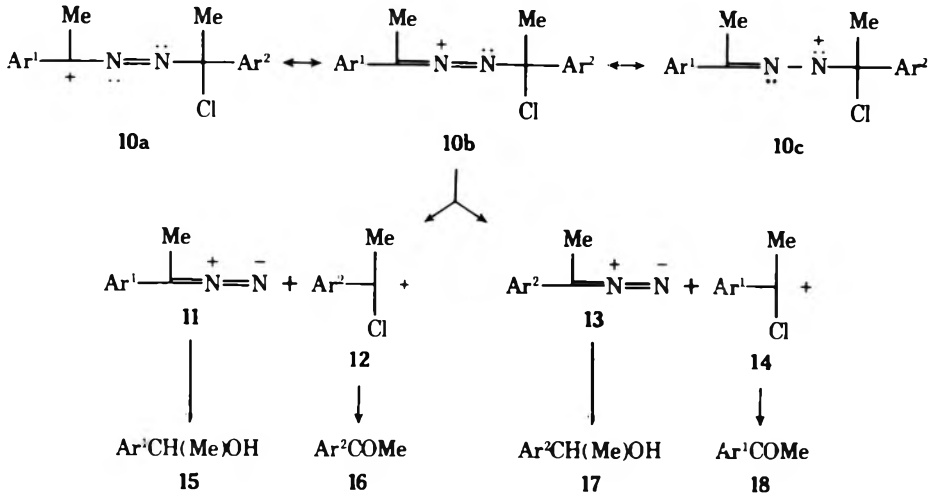


Table III
Rate Constants for the Solvolysis of 9 ($Ar^1 = Ar^2 = p\text{-}ClC_6H_4$) in Varying Dioxane–Water Mixtures[a]

Dioxane-water	$10^3 k_{obsd}$, sec^{-1}
55:45	62
60:40	28
65:35	10
70:30	4.5
75:35	2.2

[a] Measured at 25° at 260 nm; 0.01 *M* NaOH added to suppress second reaction ($k_2 \sim 0$).

gens (**10b** and **10c**). The formation of **10** is also consistent with the substituent effects discussed in detail below.

2. The Intermediate B (k_2). The first structure considered for the spectrophotometrically observable intermediate B was the azocarbonium ion **10.** This is, however, unlikely since such a species would be highly reactive in basic solution where B is the observed final product of reaction. Also no second reaction was observed in the presence of acetate or azide ion; the salts (NaN_3 and NaOAc) raise the pH of the medium, slowing the second reaction. In acidic solution no second rate was observed but in this case the final spectrum observed is that of the normal final products of solvolysis, viz., C. It is clear therefore that B is stable in base but reacts rapidly in acid.

The reaction solution containing B in base is pink (indeed Benzing[9] noted the transitory formation of pink solutions during his experiments). This, together with the kinetic data suggested that the intermediate B was in fact the diazoalkane **11,** formed by fragmentation of the carbonium ion **10.** Several pieces of evidence support this. Thus the uv spectrum of B formed from **9** ($Ar^1 = Ar^2 = p\text{-}ClC_6H_4$) in 7:3 dioxane–water containing 0.10 *M* NaOH was identical with the spectrum of a mixture of *p*-chlorophenyldiazoethane (**11,** $Ar^1 = p\text{-}ClC_6H_4$) and *p*-chloroacetophenone (which would be formed from **12,** $Ar^2 = p\text{-}ClC_6H_4$, on reaction with water) measured under the same conditions. In a separate experiment B (formed from **9,** $Ar^1 = Ar^2 = p\text{-}ClC_6H_4$) was extracted with methylene chloride and showed a strong absorption at 2043 cm^{-1} in the ir, characteristic of diazoalkanes.[13]

The diazoalkane was actually isolated in one case. Thus 1,1′-dichloro-1-(*p*-nitrophenyl)-1′-phenyl-1,1′-azoethane (**9,** $Ar^1 = p\text{-}NO_2C_6H_4$; Ar^2 = Ph) was solvolyzed on a large scale in the presence of 0.1 *M* hydroxide. The resulting red solution was extracted with ether and the solid isolated was identical with 1-(*p*-nitrophenyl)diazoethane as shown by melting point, mixture melting point, ir, and uv comparison with an unambiguously prepared sample.

It is well established[13,14] that diazoalkanes are hydrolyzed in aqueous solution by an acid-catalyzed mechanism to give the corresponding alcohol (in the absence of nucleophiles other than water). Thus the ultimate products of hydrolysis of **9** should be a substituted acetophenone and 1-arylethanol formed in a 1:1 ratio in neutral and acidic solution. This was confirmed for **9** ($Ar^1 = Ar^2$ = Ph and $Ar^1 = Ar^2 = p\text{-}ClC_6H_4$) by GLC analysis.

Finally the rates of reaction of an unambiguously prepared sample of diazoalkane (**11,** $Ar^1 = p\text{-}ClC_6H_4$) in 7:3 dioxane–water were compared with the measured subsequent rate (k_2 values) for the solvolysis of **9** ($Ar^1 = Ar^2 = p\text{-}ClC_6H_4$), measured under the same conditions. The observed rate constants were the same in both cases (within experimental error) and varied in the same way with pH (over the pH region 4.9–6.3).

Thus it has been established that **9** solvolyzes by an SN1 mechanism involving the azocarbonium intermediate **10** in aqueous dioxane. This step is neither acid nor base catalyzed, ruling out competing mechanisms involving nucleophilic attack on the substrate. Under neutral or basic conditions diazoalkanes (such as **11**) lie on the reaction pathway. These are also probably formed from **9** in acidic solution but their rapid further reaction (to form alcohols) under these conditions precludes their isolation.

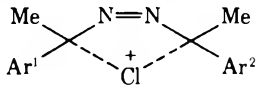
The relative magnitudes of the two rate constants, k_1 and k_2, can, however, be varied since k_1 is very sensitive to the ionizing power of the medium whereas k_2 remains relatively unchanged. Alternatively, changing the pH can also affect the balance between k_1 and k_2; k_1 is insensitive while k_2 is increased in acid and tends towards zero in base. Finally k_1 is depressed by the addition of a salt containing chloride ion, while this has no special effect on k_2.

C. Substituent Effects. 1. Kinetic Studies. In Table IV are summarized the data for the solvolysis of the dichlorides **9** measured under standard conditions (7:3 dioxane–water, 25° in the presence of 0.10 *M* sodium hydroxide); under these conditions $k_2 = 0$ and steady and reproducible infinity values were obtained. When the symmetrically disubstituted substrates (**9,** $Ar^1 = Ar^2$) are taken alone, and log k_1 is plotted against the σ value[15] of the substituent, then an excellent correlation ($r = 0.998$) is obtained (Figure 2). The slope or Hammett ρ value is −3.68, implying a transition state in which there is a build-up of considerable positive charge in the transition state.

Table IV
Observed Rate Constants for the Solvolysis of 9 in 7:3 Dioxane–Water at 25° (μ = 0.10, NaOH)

Ar^1	Ar^2	$10^3 k$, sec^{-1}	Registry no.
C_6H_5	C_6H_5	35	56688-54-1
p-MeC_6H_4	p-MeC_6H_4	110	56587-95-2
p-ClC_6H_4	p-ClC_6H_4	4.5	56587-96-3
m-ClC_6H_4	m-ClC_6H_4	1.1	56587-97-4
p-BrC_6H_4	p-BrC_6H_4	4.5	56587-98-5
m-BrC_6H_4	m-BrC_6H_4	0.74	56587-99-6
p-ClC_6H_4	m-ClC_6H_4	3.9	56588-00-2
p-ClC_6H_4	p-MeC_6H_4	31	56588-01-3
p-MeC_6H_4	p-$NO_2C_6H_4$	10	56588-02-4
p-ClC_6H_4	p-$NO_2C_6H_4$	0.98	56588-03-5
C_6H_5	p-ClC_6H_4	8.1	56588-04-6
C_6H_5	p-$NO_2C_6H_4$	4.0	56588-05-7

Besides **10** another limiting structure **19** can be visualized for the intermediate carbonium ion. In **19** the charge is



19

symmetrically distributed throughout the molecule so that both aryl rings bear an equal fraction of the charge. These two possibilities can be distinguished as follows.

When data for unsymmetrically disubstituted substrates **9** ($Ar^1 \neq Ar^2$) are plotted against the sum of the σ values of both substituents, it is seen (Figure 2) that wide scatter results; the datum points lie above and below the correlation line for the symmetrical compounds. No combination of alternative σ values (e.g., σ^+, σ^-, etc.) succeeded in bringing all the data onto the correlation line.

However, when the data in Table IV are broken down as follows certain patterns emerge. Thus when substrates **9** with one p-nitrophenyl group (Ar^1 = p-$NO_2C_6H_4$) are considered then a plot of log k_1 vs. the σ value of the substituent in the other aryl ring (Ar^2) gives a good correlation with $\rho = -2.50$ ($r = 0.997$). Alternatively, when these substrates with Ar^1 = p-MeC_6H_4 are chosen a similar plot (of log k_1 vs. σ value of substituent in Ar^2) gives a very much reduced $\rho = -1.10$ ($r = 0.998$). Good correlations were not always obtained by this technique. Thus when Ar^1 = Ph or Ar^1 = p-ClC_6H_4 plots of log k_1 vs. σ value of the substituent in Ar^2 are curved.

These data are readily explicable only in terms of an unsymmetrical transition state (of type **10**). In the substrate **9** when $Ar^1 \neq Ar^2$, two parallel reactions occur but it is clear that the C–Cl bond cleaved preferentially is that which locates the charge adjacent to the aryl group carrying the most electron-donating group. The p-Me and p-NO_2 substituents are respectively the most electron-donating and -withdrawing groups used. Thus when Ar^2 = p-$NO_2C_6H_4$ the charge is located adjacent to Ar^1 giving the high ρ value for substituents in Ar^1.[16] The opposite situation exists when Ar^1 = p-MeC_6H_4; charge is then located adjacent to Ar^1 (see **10**) and the ρ value for Ar^2 is small. When substrates in which a p-ClC_6H_4 group is present are considered, the second substituent may have a stronger (e.g., p-MeC_6H_4) or weaker (e.g., p-$NO_2C_6H_4$) electron-donating power. Ionization at both sites is then competitive and the position of preferred bond cleavage will therefore change throughout the series leading to the observed curved log k_1 vs. σ plots.

The direct application of the Hammett equation to such curved plots is complex since the observed rate constant

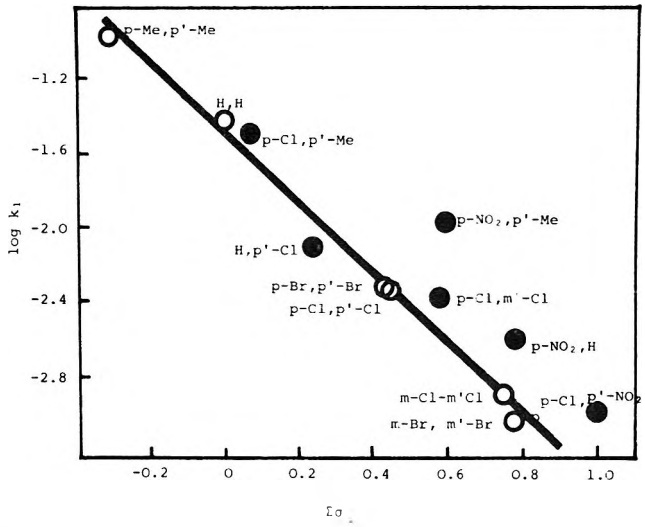
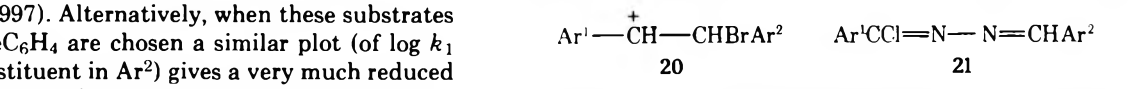


Figure 2. Hammett plot of log k_{obsd} vs. $\Sigma\sigma$ for solvolysis of $XC_6H_4CMeClN{=}NCMeClC_6H_4Y$ in 7:3 dioxane–water at 25° (μ = 1.0, NaOH). The solid line has slope −3.68 and correlates data for symmetrically disubstituted substrates (X = Y, open circles).

represents the *sum* of two rate constants for parallel reactions, each of which varies as the substituent is changed. This difficulty is discussed in detail by Ruasse and Dubois.[17] However, the following simple deduction can be made. In a symmetrically disubstituted substrate the observed ρ value (−3.68) is composite representing the contribution of the remote and adjacent substituent to the stabilization of the ion formed. These individual contributions can be estimated as −2.50 and −1.10 (the ρ values for ionization essentially at a single site adjacent to or remote from aryl group in which the substituent is changed). There is thus unequivocal kinetic evidence available to support the formation of an open (**10**) rather than symmetrical (**19**) carbonium ion intermediate, with preferential C–Cl bond cleavage occurring at a site remote from the most electron-withdrawing group.

The formation of an open carbonium ion (**20**) rather than a bridged bromonium ion has also been noted by Dubois



20 **21**

and Ruasse in the bromination of stilbenes.[16] In this case the ρ values for electron-withdrawing and electron-donating substituents are different, since the carbonium ion which is preferentially formed always locates the charge adjacent to the most electron-donating aryl group.

The transition state for the formation of **10** may, of course, involve some bridging (i.e., partial **19** formation) but this is unlikely in view of the following evidence. Any degree of bridging by the chlorine in **10** would tend to reduce the ρ value for substituents in Ar^1. A good test would therefore involve comparison with a substrate in which participation is unlikely, e.g., compound **9** in which one of the Cl groups was replaced by Me. We were, however, unable to synthesize such 1-chloroazoalkanes. On the other hand, data are available for the related system **21** and this provides a good model. Thus the ρ values reported for azocarbonium ion formation from **21** are −2.3 and −1.2 for Ar^1 and Ar^2, respectively (measured in 2:3 dioxane–water).[18] These values are remarkably close to those which we have obtained for **9**, and since bridging cannot occur in **21**, neither is it likely to be an important contribution for the reaction of **9**.

On an absolute scale **9** is solvolyzed ca. 120-fold more slowly than the very reactive imidoyl halides.[17] However **9** is still hydrolyzed ca. tenfold more readily than diphenyl-

Table V
Ultraviolet Absorption Maxima for Products Formed in Basic 7:3 Dioxane-Water from Dichlorodiazoalkanes 9

Substrate 9				
Ar^1	Ar^2	λ_{max},[a] nm	Diazoalkane	λ_{max}, nm
C_6H_5	p-$NO_2C_6H_4$	410	11, Ar^1 = p-$NO_2C_6H_4$	410
p-MeC_6H_4	p-$NO_2C_6H_4$	410		
p-ClC_6H_4	p-$NO_2C_6H_4$	410		
p-MeC_6H_4	p-ClC_6H_4	300	5, Ar^1 = p-ClC_6H_4	300

[a] Absorption maximum of diazoalkane formed.

Table VI
Relative Amounts of Two Substituted Acetophenones (16 and 18) Formed from Unsymmetrically Disubstituted Dichloroazoalkanes 9[a,b]

Substrate 3			
Ar^2	Ar^1	Ar^2COMe, %	Ar^1COMe, %
C_6H_5	C_6H_5	50	50
p-ClC_6H_4	C_6H_5	30	70
p-ClC_6H_4	p-MeC_6H_4	17	83
p-$NO_2C_6H_4$	p-ClC_6H_4	8	92
p-$NO_2C_6H_4$	p-MeC_6H_4	2	98

[a] Reaction medium: 7:3 dioxane-water at 25°. [b] Products analyzed by GLC (column: 2 m, 15% Carbowax 20M on Chromosorb 80-100 mesh).

carbinyl chlorides,[19] indicating that the azo group can provide considerable stabilization by electron donation to an adjacent carbonium ion center.

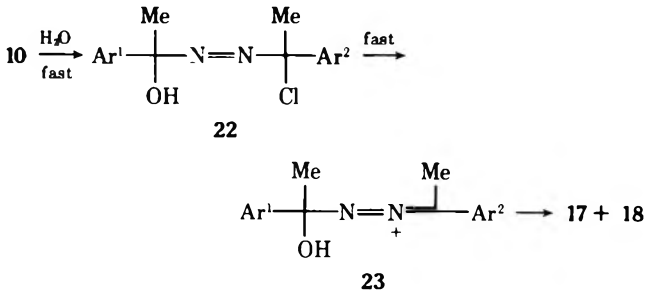
2. Product Analysis. Since it has been demonstrated that the carbonium ion **10** lies on the reaction pathway, it is expected to fragment to give the diazoalkane **11** and ultimately the alcohol **15** and ketone **16.** However, the actual products isolated in major amounts were the isomeric materials **17** and **18.** This result was quite unexpected but was supported by data for several substrates. Two methods of product analysis were used: (a) spectrophotometric determination of the diazoalkanes formed (in base) and (b) GLC analysis of the ketones and alcohols.

Method a gave best results only in those cases in which one of the possible diazoalkane intermediates carried a p-nitrophenyl group, since this absorbed at an appreciably longer wavelength than the other diazoalkanes (typically 410 vs. 290 nm). The results are summarized in Table V and indicate that in all cases the diazoalkane formed preferentially is substituted by the more electron-withdrawing aryl group present in the original dichloroazoalkane **9.** Quantitative studies indicate 80–100% p-nitrophenyldiazoalkane formation.

Method b was more rigorous and could be used with any dichloroazoalkane substrate; for convenience in most cases the relative amounts of the two possible ketones **16** and **18** ($Ar^1 \neq Ar^2$) were estimated, since the separation was better than in the case of the alcohols. However, the results obtained by estimation of either ketone or alcohols were consistent. The results (Table VI) indicate that the ketone formed in largest amount was that with the most electron-donating group. This complements the uv data which indicated that the diazoalkane (and consequently the alcohol) formed has the most strongly electron-withdrawing group.

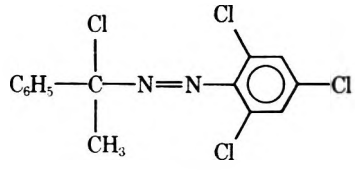
There is thus an apparent dichotomy between the kinetic results and the product studies. Thus while the kinetics clearly show that, say, **10** is formed preferentially from **9** (Ar^1 more electron-donating than Ar^2), there is equally

Scheme IV



clear evidence that the carbonium ion **10** does not break down to give **11** and **12** preferentially but rather to give **13** and **14.** We therefore propose that an extra step(s) must be involved before the azocarbonium ion fragments; the three most likely are considered below.

(1) Benzing[9] proposed a mechanism (Scheme IV) in which the carbonium ion reacts with water to form the chlorohydroxy material **22.** If this pathway is followed then rapid loss of Cl^- from **22** gives **23** and eventually the correct products **17** and **18** (Ar^1 more electron-donating than Ar^2). The formation of **22** is not unreasonable, since we have found that solvolysis of the chloride **24** under similar conditions also occurs via an azacarbonium ion mechanism and leads to the formation of the azocarbinol **25.**[20] How-



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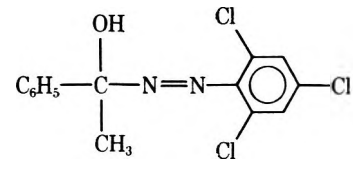
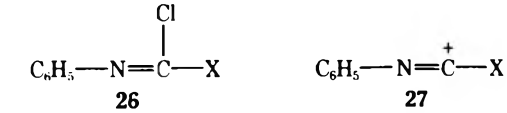
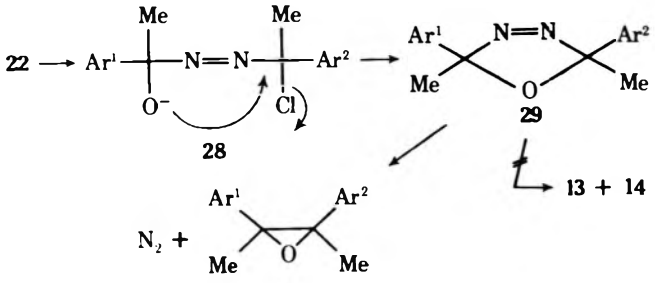


25

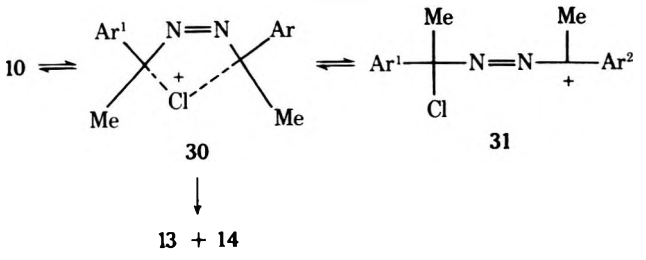
ever, for the mechanism of Scheme IV to be viable then all steps subsequent to the formation of **10** must be rapid, since no intermediates were detected spectrophotometrically in the conversion of **9** to **17.** In particular, repetitive scans of the ultraviolet spectrum of **9** (Ar^1 = p-MeC_6H_4; Ar^2 = p-$NO_2C_6H_4$) showed tight isosbestic points in 7:3 dioxane–water containing 0.01 M $HClO_4$ and good first-order kinetics were obtained at all wavelengths [although the spectral difference between the model compounds **24** and **25** is small, there is sufficient difference at 300 nm so that the presence of **22** would be detectable from nonlinear log (absorbance) vs. time plots]. Therefore either (a) the intermediate **22** is not present on the reaction pathway or (b) its further reaction (**22** → **23**) is faster than the formation of **10** from **9.** We regard the latter as unlikely, since this would require that the second ionization, which occurs adjacent to a relatively electron-withdrawing (e.g., Ar^2 = p-$NO_2C_6H_4$) group, should be faster than the first adjacent to Ar^1 (electron donating, such as p-MeC_6H_4). In addition **22** has an OH group in place of the Cl group in **9.** This should, however, have a relatively minor effect on the rates of ionization of the remote C–Cl bond. Thus **26** (X = Cl) actually ionizes 10^2-fold faster to give **27** (X = Cl) than does **26** (X



Scheme V



Scheme VI



= -OAr).[21] On the other hand, the Cl group is inductively more electron withdrawing than the OH group (the difference in Taft σ^* values is 0.49),[22] but is insufficient to counter the larger difference in electron-withdrawing power between p-$NO_2C_6H_4$ and p-MeC_6H_4.

(2) The mechanism in Scheme V modifies Scheme IV by inclusion of a rapid intramolecular displacement of Cl^- by the OH group (or its conjugate base **28**) to give the Δ^3-1,3,4-oxadiazoline **29**. Such materials have been reported as unstable;[23] however, nitrogen loss gives rise to epoxides (which are relatively stable and would have been detected) rather than the observed products **17** and **18**.

(3) The mechanism presented in Scheme VI is favored on the basis of available evidence. This involves migration (or partial migration) of chloride ion from one carbon site to the other (possibly via the bridged ion **30**). This step must occur *after* the initial rate-determining formation of **10**. Complete transfer (to **31**) is unlikely (since this is *less* stable than **10**) so that fragmentation probably occurs directly from **30**. The extra driving force for bridging by chloride ion is provided by the formation (on fragmentation) of the most stable carbonium ion **14** (Ar^1 is electron donating) and diazoalkane **13** (Ar^2 is electron withdrawing). This is clearly shown in Figure 3, where the log of the relative

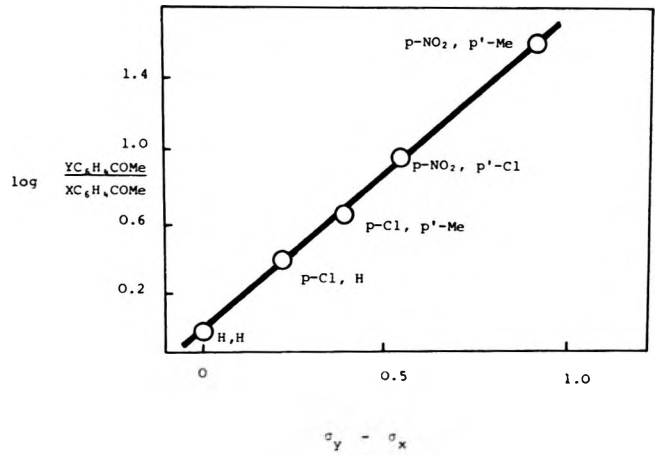
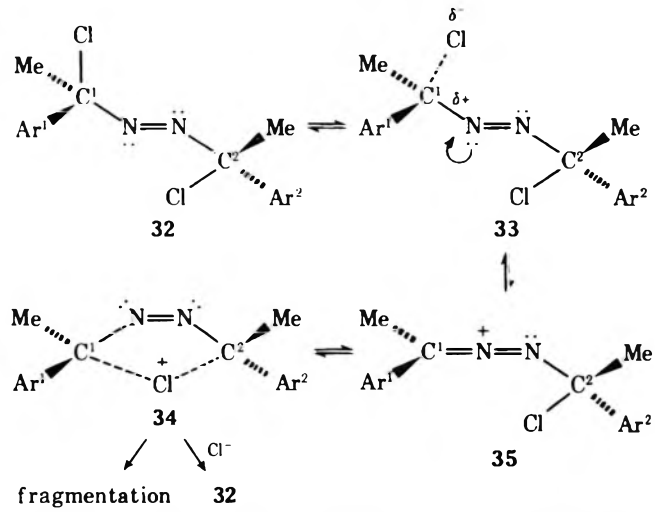


Figure 3. Plot of the log of the relative amounts of ketones formed on solvolysis of dichloroazoalkanes ($XC_6H_4CMeClN{=}NCMeClC_6H_4Y$) vs. the difference in the σ values of substituents X and Y.

Scheme VII



amounts of the two ketones formed [i.e., log ([Ar^1COMe]/[Ar^2COMe])] from **10** is shown to vary with the difference in electron-donating power of Ar^1 and Ar^2. The slope of the correlation (or ρ value) is +1.70; this is most satisfactory, since it indicates that the presence of an electron-withdrawing group in Ar^2 accelerates rearrangement of the initially formed carbonium ion **10**. Since the ρ value (for Ar^1) for the formation of **10** is −2.5 and that for the subsequent rearrangement is +1.70, most of the charge in the transition state for the formation of **10** from **9** is lost in the transition state for the subsequent formation of **13** and **14**. The proposed chloronium ion **30**, either as a transition state or intermediate, is consistent with this.

The question might be asked: if the chlorine participates in the stabilization of the azocarbonium ion during fragmentation, then why does it not provide stabilization in the initial reaction, loss of Cl^- from **9**.[2] A possible answer arises from the stereochemistry of the system.

There is good evidence[4] that the starting azo materials **9** are in the more stable trans configuration **32** (Scheme VII). In the transition state for azocarbonium ion formation (**33**) there is partial C^1–Cl bond fission; also C^1 has moved partly down into the N–N plane to allow eventual overlap of the vacant p orbital with the filled (lone pair) orbital on nitrogen (**35**). It is clear from molecular models that the distance between the Cl group attached to C^2 and C^1 is too great to allow appreciable bond formation in the transition state **34**. However once the azocarbonium ion **35** is actually formed, the Cl–C^1 bond distance can be further reduced to allow bonding to occur (see **34**). Although it is proposed that both the azocarbonium ion **35** and the chloronium ion **34** lie on the reaction pathway, we have no evidence as to their relative stabilities. However, a priori, there is no reason to expect that **34** is more stable than **35** since (a) in **34**, being a cis configuration, there is some steric interaction between the groups attached to carbon, (b) the possibility of stabilization of the carbonium ion by electron donation from nitrogen is minimized in **34**, and (c) this structure (**34**) places a partial positive charge on C^2, the carbon carrying the most electron-withdrawing substituent (Ar^2).

However, the existence of some bridging by chlorine such as **30** on the reaction pathway provides an elegant explanation for Malament and McBride's observation[4] that the chlorination of diazabutadienes is stereospecific. Chlorination of the diazabutadiene **8** under ionic conditions leads to the formation of the same azocarbonium ion (**34, 35**) as formed in the solvolysis of the dichloride **32**. If the stereochemistry of the intermediate is maintained by bridging by the remaining chlorine on the side remote from the depart-

Table VII
The Ketazines 8 ($Ar^1 \neq Ar^2$)

Substituent			Calcd, %				Found, %		
Ar^1	Ar^2	Mp, °C	C	H	N	Formula	C	H	N
p-$NC_2C_6H_4$	*p*-MeC_6H_4	138	69.15	5.76	14.23	$C_{17}H_{17}N_3O_2$	68.80	5.43	14.41
p-$NO_2C_6H_4$	C_6H_5	125	68.32	5.33	14.94	$C_{16}H_{15}N_3O_2$	68.00	5.48	15.14
p-$NO_2C_6H_4$	*p*-ClC_6H_4	155	60.95	4.44	13.33	$C_{16}H_{14}ClN_3O_2$	61.20	4.52	13.30
p-MeC_6H_4	*p*-ClC_6H_4	138	71.83	5.98	9.75	$C_{17}H_{17}ClN_2$	71.49	5.96	9.85
p-ClC_6H_4	*m*-ClC_6H_4	112	62.95	4.59	9.18	$C_{16}H_{14}Cl_2N_2$	62.75	4.62	9.54

Table VIII
The Dichlorides 9

Substituent			Calcd, %					Found, %			
Ar^1	Ar^2	Mp, °C	C	H	Cl	N	Formula	C	H	Cl	N
m-BrC_6H_4	*m*-BrC_6H_4	88	41.74	3.01	49.66[a]	6.02	$C_{16}H_{14}Br_2Cl_2N_2$	40.83	3.02	49.26	6.31
m-ClC_6H_4	*p*-ClC_6H_4	106	51.06	3.72	37.76	7.44	$C_{16}H_{14}Cl_4N_2$	50.32	3.57	38.00	7.55
p-MeC_6H_4	*p*-ClC_6H_4	115	57.46	4.78	29.85	7.88	$C_{17}H_{17}Cl_3N_2$	56.97	4.84	29.92	8.31
p-$NO_2C_6H_4$	C_6H_5	75	54.54	4.26	20.17	11.43	$C_{16}H_{15}Cl_2N_3O_2$	54.01	4.27	20.33	11.88

[a] Tota. halogen (Br + Cl).

ing Cl^- (see **34**) then chloride ion attack on **34** gives (by microscopic reversibility) the product of chlorination with the observed trans configuration.

Experimental Section

Substrates. 1,4-Diaryl-1,4-dimethyl-2,3-diazabuta-1,3-dienes. The symmetrically disubstituted ketazines (**8**, $Ar^1 = Ar^2$) were prepared by the reaction of 1 mol of hydrazine hydrate with 2 mol of substituted acetophenone in 95% ethanol and recrystallized to constant melting point in this solvent. The following hydrazones were also prepared: *p*-nitroacetophenone hydrazone, mp 152° (lit.[24] 151°); *p*-chloroacetophenone hydrazone, mp 51° (lit.[24] 55°); *m*-nitroacetophenone hydrazone, mp 75° (lit.[24] 77°). The unsymmetrical azines (**8**, $Ar^1 \neq Ar^2$) were prepared from these using 1 mol of the hydrazone and 1 mol of substituted acetophenone; analytical and melting point data are summarized in Table VII.

1,1′-Dichloro-1,1′-diaryl-1,1′-azoethanes. The following is a typical example. Acetophenone azine **8** ($Ar^1 = Ar^2$ = Ph) (2.36 g) was thoroughly dried and finely ground; liquid chlorine at −60° (Dry Ice–acetone) was added and the mixture was maintained at this temperature for 30 min. The apparatus was protected from moisture and light was excluded. The mixture was then allowed to warm to room temperature and the residual chlorine was removed in vacuo to give the dichloride **9** ($Ar^1 = Ar^2$ = Ph) in near-quantitative yield, mp 110°. The other dichlorides were prepared similarly; melting point and analytical data were in agreement with literature values where available;[8] otherwise the data are summarized in Table VIII.

Kinetic Studies. Measurements were made in 7:3 dioxane–water at 25°, unless otherwise stated. The ionic strength was maintained at 0.10 *M* by the addition of sodium perchlorate or sodium hydroxide. The dioxane was BDH Analar grade, used without further purification. The water used was deionized and then twice distilled from alkaline permanganate. The rates of reaction were measured spectrophotometrically using Unicam SP800 or SP1800 ultraviolet spectrometers; initial repetitive scans established suitable wavelength at which the reactions could be followed. The analytical wavelengths used are noted in the tables. The substrate was dissolved initially (ca. 10^{-2} *M*) in dioxane and a drop of this solution was added to the reaction solution in a 3-ml cuvette. The apparatus and treatment of results have been described in detail elsewhere.[25]

Product Analysis. *p*-Nitrophenyldiazoethane was prepared by a literature procedure[14] involving the oxidation of *p*-nitroacetophenone hydrazone with silver oxide and had mp 87° (70%) (lit.[14] 87–88[6]). The *p*-bromophenyl and *p*-chlorophenyl diazoethanes were similarly prepared but not actually isolated from the ethereal solution; ir analysis showed the presence of a strong absorption at 2049 cm^{-1} and the absence of absorption at ca. 3200 cm^{-1} which are present in the starting hydrazones. *p*-Nitrophenyldiazoethane was also isolated as a solvolysis product of a dichloride **9** as follows. 1,1′-Dichloro-1-phenyl-1′-(*p*-nitrophenyl)-1,1′-azoethane (**9**, Ar^1 = Ph; Ar^2 = *p*-$NO_2C_6H_4$) (0.328 g) was dissolved in dioxane (25 ml) and added dropwise at 25° to 7:3 dioxane–water (75 ml) containing sodium hydroxide (0.10 *M*) over 30 min. The red reaction mixture was extracted with ether. Evaporation of the dried ethereal extracts gave *p*-nitrophenyldiazoethane, mp 84–87°; on recrystallization from ether this had mp 87° (59% yield) and was shown to be identical with an authentic sample.

Solvolysis of Dichlorides 9, under Neutral or Acidic Conditions. The following represents a typical procedure. 1,1′-Dichloro-1,1′-diphenyl-1,1′-azoethane (**9**, $Ar^1 = Ar^2$ = Ph) (0.307 g) was dissolved in dioxane (70 ml) and water (30 ml) was added dropwise with stirring over 30 min. After 4 hr, stirring was discontinued and the reaction mixture was extracted with ether (3 × 100 ml). The combined ether extracts were dried and reduced to ca. 50 ml. Samples (5 μl) were analyzed using a Perkin-Elmer F11 gas chromatograph with a 2 m 15% Carbowax 20M on Chromosorb 80–100 mesh at 110°. Authentic samples of the ketone and alcohol were similarly made up in ether and analyzed; integration then gave the relative amounts of the two (or four) products formed. The ketones were also analyzed by the formation of *p*-nitrophenylhydrazone or 2,4-dinitrophenylhydrazone. Control experiments showed ca. 90% product recovery in this case and when allowance was made for this the results were in agreement with those reported for the GLC method (Table VI).

Acknowledgment. We are grateful to Dr. D. S. Malament for helpful discussion.

Registry No.—**8** ($Ar^1 = Ar^2 = C_6H_5$), 56587-83-8; **8** ($Ar^1 = Ar^2$ = *p*-MeC_6H_4), 56587-84-9; **8** ($Ar^1 = Ar^2$ = *p*-ClC_6H_4), 56587-85-0; **8** ($Ar^1 = Ar^2$ = *m*-ClC_6H_4), 56587-86-1; **8** ($Ar^1 = Ar^2$ = *p*-BrC_6H_4), 56587-87-2; **8** ($Ar^1 = Ar^2$ = *m*-BrC_6H_4), 56587-88-3; **8** (Ar^1 = *p*-ClC_6H_4; Ar^2 = *m*-ClC_6H_4), 56587-89-4; **8** (Ar^1 = *p*-ClC_6H_4; Ar^2 = *p*-MeC_6H_4), 56587-90-7; **8** (Ar^1 = *p*-MeC_6H_4; Ar^2 = *p*-$NO_2C_6H_4$), 56587-91-8; **8** (Ar^1 = *p*-ClC_6H_4; Ar^2 = *p*-$NO_2C_6H_4$), 56587-92-9; **8** ($Ar^1 = C_6H_5$; Ar^2 = *p*-ClC_6H_4), 56587-93-0; **8** ($Ar^1 = C_6H_5$; Ar^2 = *p*-$NO_2C_6H_4$), 56587-94-1; hydrazine, 302-01-2; acetophenone, 98-86-2; *p*-methylacetophenone, 122-00-9; *p*-chloroacetophenone, 99-91-2; *m*-chloroacetophenone, 99-02-5; *p*-bromoacetophenone, 99-90-1; *m*-bromoacetophenone, 2142-63-4; *p*-nitroacetophenone hydrazone, 28153-22-2; *p*-chloroacetophenone hydrazone, 40137-41-5; *m*-nitroacetophenone hydrazone, 56588-06-8; *p*-nitrophenyldiazoethane, 30009-43-4.

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Acid-Catalyzed Isomerization of 1-Acyl- and 1-Thioacylaziridines. III. 2-Phenylaziridine Derivatives

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Acid-catalyzed isomerizations of (*R*)-1-(*N*-phenylcarbamyl)- (**1a**) and (*R*)-1-(*N*-phenylthiocarbamyl)-2-phenylaziridine (**1b**) were investigated to see the effect of the ring phenyl group on the orientation of the ring opening and the stereochemistry at the asymmetric carbon atom. Throughout the isomerizations of **1a** and **1b**, exclusive N–CHPh bond cleavage was observed. With protonic acids, **1a** gave partially (40%) racemized 2-anilino-5-phenyl-2-oxazoline (**2a**), and with boron trifluoride etherate, it gave highly (95%) racemized **2a**. The thiourea **1b** gave 2-anilino-5-phenyl-2-thiazoline (**2b**) in good yields with protonic acids and in a poor yield with boron trifluoride etherate.

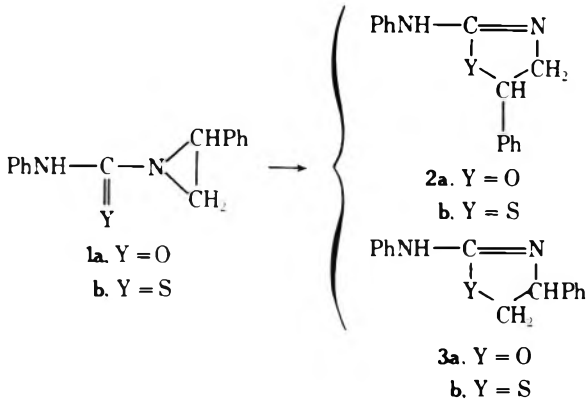
A variety of acid-catalyzed isomerizations of 1-acyl- and 1-thioacylaziridines to 2-oxazolines[1] or thiazolines[1a,f,2] have been observed, and mechanistic studies of these reactions have been done by several workers. Heine and coworkers[1e] found that 1-aroyl-2,2-dimethyl- or 1-aroyl-2-phenylaziridine isomerized in cold sulfuric acid to 2-aryl-5,5-dimethyl- or 2-aryl-5-phenyl-2-oxazoline, respectively. Deutsch and Fanta[2a] reported that the isomerization of 1-(*N*-phenylthiocarbamyl)-2,2-dimethylaziridine with hot concentrated hydrochloric acid gave 2-anilino-5,5-dimethyl-2-thiazoline. These reactions were considered to proceed via a carbonium ion from the orientation of the ring opening (so-called "abnormal" cleavage).

Our previous study[3] was planned to see if an "abnormal" cleavage would always give rise to a carbonium ion in the acid-catalyzed isomerizations of 1-acyl- or 1-thioacylaziridines, and further to correlate the orientation with the mechanism of the ring opening. (*S*)-1-(*N*-Phenylcarbamyl)-2-methylaziridine (**1a'**) isomerized to 2-anilino-5-methyl-2-oxazoline (**2a'**) with 100% retention of configuration either with protonic acids or with boron trifluoride etherate in refluxing benzene. This means that the conversion of (*S*)-**1a'** to (*S*)-**2a'** ("abnormal" cleavage) has not proceeded via a free carbonium ion. As for the orientation of the ring opening, very puzzling results were obtained and no correlation could be found between the orientation and the mechanism of the ring opening deduced from the stereochemistry: **1a'** gave **2a'** as the major product (80–90%), while 1-(*N*-phenylthiocarbamyl)-2-methylaziridine (**1b'**) gave nearly equal amount of 2-anilino-5-methyl-2-thiazoline (**2b'**) and 2-anilino-4-methyl-2-thiazoline (**3b'**). Optically active **1b'** gave racemic **2b'** in some cases in contrast with **1a'**.

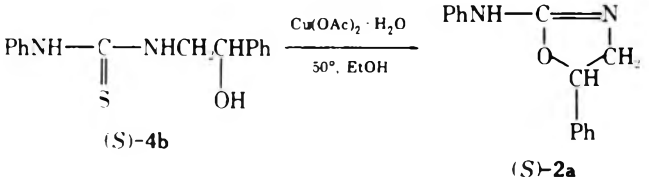
Replacing the 2-methyl group with a phenyl group seemed interesting from the following two points: (1) whether in this case, also, the "abnormal" cleavage would give the oxazoline with retention of configuration, and (2) what would be the orientation of the ring opening especially with the thiourea derivative. Heine and Kaplan[1e] reported that the thermal isomerization of *cis*-1-(*p*-nitrobenzoyl)-2,3-diphenylaziridine gave *cis*-2-(*p*-nitrophenyl)-4,5-diphenyl-2-oxazoline, and the corresponding trans compound gave the trans oxazoline. So far, no stereochemical investigation of the acid-catalyzed isomerization of 2-aryl- or 2,3-diarylaziridine derivatives has been reported.

The present study deals with the isomerization of (*R*)-1-(*N*-phenylcarbamyl)- (**1a**) and (*R*)-1-(*N*-phenylthiocarbamyl)-2-phenylaziridine (**1b**). (*R*)-2-Phenylaziridine was prepared from (*R*)-2-amino-2-phenylethyl alcohol by the Wenker method. Reaction of (*R*)-2-phenylaziridine with phenyl isocyanate gave **1a**. (*R*)-1-(*N*-Phenylthiocarbamyl)-2-phenylaziridine (**1b**) which was prepared from the same aziridine and phenyl isothiocyanate could not be recrystallized owing to the tendency to polymerize in solution.

Authentic samples of the isomerization products (**2a, 2b, 3a,** and **3b**) were prepared. Optically pure samples of (*R*)-2-anilino-4-phenyl-2-oxazoline (**3a**) and (*R*)-2-anilino-4-phenyl-2-thiazoline (**3b**) were prepared from (*R*)-1-(1'-phe-



nyl-2′-hydroxyethyl)-3-phenylurea and the corresponding thiourea by dehydration with polyphosphoric acid (PPA). However, dehydration of both (*S*)-1-(2′-hydroxy-2′-phenylethyl)-3-phenylurea (**4a**) and the thiourea derivative (**4b**) under the same conditions gave racemic **2a** and **2b**. It was previously[4] found that the reaction of 1-(3′-phenoxy-2′-hydroxypropyl)-3-phenylthiourea with cupric acetate in refluxing ethanol gave 2-anilino-5-phenoxymethyl-2-oxazoline in 73% yield. Treatment of **4b** under the same conditions led to extensive decomposition, but at 50°, we obtained an optically pure sample of (*S*)-**2a** from (*S*)-**4b** pre-



(*S*)-**4b**

(*S*)-**2a**
$[\alpha]^{30}D$ +77° (0.2298 g/10 ml in dioxane)

pared from (*S*)-1-phenyl-2-aminoethanol and phenyl isothiocyanate. We have not succeeded in the preparation of optically pure sample of **2b** so far.

The isomerization of (*R*)-**1a** was tried with *p*-toluenesulfonic acid, picric acid, and boron trifluoride etherate in refluxing benzene. In all cases, the rearranged product was composed of 100% **2a**, and no trace of **3a** was found by the NMR analysis. The specific rotations of the products are shown in Table I. The reaction of (*R*)-**1b** with *p*-toluenesulfonic acid, picric acid, or boron trifluoride etherate was carried out in the same way, and gave 100% **2b** in every case, though in a very low yield with boron trifluoride etherate. Results are summarized in Table I.

The isomerization of **1a** to **2a** proceeded with 60% retention of configuration on the asymmetric carbon atom with protonic acids, and 5% with boron trifluoride etherate. The 60% retention with protonic acids suggests that the conjugate bases of the acids should have participated in the reaction. An ion-pair formation between the conjugate base of the acid and the forming carbonium ion might explain the partial retention of configuration since an addition–elimination process should lead to a complete retention of configuration. Under similar conditions, *p*-nitrobenzoic acid and **1a** gave an addition product which was found to be 1-[2′-(*p*-nitrobenzoyloxy)-2′-phenylethyl]-3-phenylurea (**5**). Comparison of the optical rotations of authentic (*S*)-**5** and the addition product showed that the addition reaction had taken place with complete inversion of configuration. An intramolecular ion pair seems less likely as an intermediate of the isomerization of **1a** to **2a** with protonic acids, since **1a** gave highly (95%) racemized **2a** with boron trifluoride etherate. The latter reaction must have proceeded via a free carbonium ion.

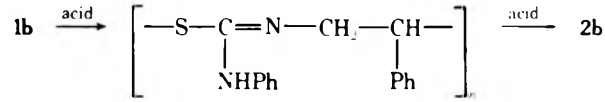
Table I
Isomerization of 1a and 1b with Acids

	Acid	Yield of **2**, %	$[\alpha]D^a$	% of retention[b]
(*R*)-**1a**	*p*-Toluenesulfonic	86	−47	61
	Picric	76	−46	60
	$BF_3 \cdot OEt_2$	69	−4	5
(*R*)-**1b**	*p*-Toluenesulfonic	81	+95	
	Picric	75	+97	
	$BF_3 \cdot OEt_2$	9	+100	

[a] Measured in dioxane, at 28° in the case of **2a**, and 24° with **2b**. [b] Calculated from the equation $-100[\alpha]D/77$, where 77 is a value for the specific rotation of (*S*)-**2a**.

It is noted in the isomerization of **1b** that the specific rotations of **2b** are almost the same in three cases. Therefore, the optical purity of **2b** from the isomerization of (*R*)-**1b** is supposed to be fairly high. The ir spectra (in KBr pellets) of **2b** thus obtained are different from that of (*R,S*)-**2b**, and a similar difference is also found between the spectra of (*S*)- and (*R,S*)-**2a**. Participation of the conjugate bases of protonic acids is not likely, since boron trifluoride etherate gave **2b** of similar specific rotation. Three ways may be conceivable which would explain the results: (1) an intramolecular ion-pair formation, (2) participation of another molecule of **1b** as a nucleophile, and (3) intervention of a polymer of **1b** with iminothioether structures. There has been no fact which would favor or disfavor any one of the three. However, we would like to think of 1 only after the other possibilities have been crossed out, since the structure of such an ion pair is highly strained.

Previous papers[5,6] have shown that 1-thioacylaziridines polymerize to give polymers with iminothioether structures, and such polymers give thiazolines on heating with acids. A low molecular polymer of (*R*)-**1b** ($\eta_{sp/c}$ = 0.1) obtained by allowing a solution of **1b** to stand with a small amount of boron trifluoride etherate gave **2b** in 55% yield



on heating with *p*-toluenesulfonic acid in refluxing benzene, and the specific rotation of **2b** thus obtained was +101°. When the reaction of **1b** with *p*-toluenesulfonic acid was stopped in 5 min, **1b** was not recovered but **2b** and some polymeric material were obtained from the reaction mixture. These facts coupled with the results reported previously[5,6] suggest that 3 could be possible.

As a summary, the effect of the ring phenyl group definitely appeared in the orientation of the ring opening: throughout the isomerizations of **1a** and **1b**, exclusive N–CHPh bond cleavage was observed. This is in marked contrast to the case with **1a′** and **1b′**, where always N–CHMe and N–CH_2 bond cleavages were taking place at the same time in varying ratios depending upon the materials and the reaction conditions. Stereochemically, **1a** gave **2a** with 60% retention of configuration with protonic acids, while **1a′** isomerized to **2a′** with complete retention under the same conditions. Moreover, in contrast to the fact that (*S*)-**1a′** gave optically pure (*S*)-**2a′** with boron trifluoride or boron trifluoride etherate under varying conditions (presumably by an SNi mechanism), (*R*)-**1a** gave almost racemic **2a** on heating with boron trifluoride etherate in refluxing benzene. These facts may be explained by the greater ion-stabilizing and the steric effects of the phenyl group in **1a** than those of the methyl in **1a′**, which would tend to favor SN1 reaction rather than SN2 or SNi.

Experimental Section

All melting and boiling points are uncorrected. Ir spectra were recorded on a Shimazu Model IR-27G instrument. NMR spectra were obtained on a Hitachi Model R-20B spectrometer. Optical rotations were determined on a Jasco Model DIP-SL automatic polarimeter.

Preparation of (*R*)-2-Phenylaziridine. Reduction of (*R*)-2-phenylglycine with $LiAlH_4$ in THF gave (*R*)-2-amino-2-phenylethanol, mp 76.6–77.8° (lit.[7] 78–79°), $[\alpha]^{23}D$ −27.6° (0.9928 g/10 ml, EtOH) [lit.[7] $[\alpha]^{15}D$ −27.5 ± 0.5° (0.993 g/10 ml, EtOH)]

The cyclization of the amino alcohol to (*R*)-2-phenylaziridine was carried out according to the Wenker method via the hydrogen sulfate. When an aqueous solution of the sulfuric acid salt of the amino alcohol was evaporated under reduced pressure, the salt sometimes crystallized out, and this crystallization prevented smooth dehydration of the salt to the ester. Therefore, the bath temperature was quickly raised to 150° before the crystallization began. Starting from 23 g of the amino alcohol, 17 g (84%) of (*R*)-2-phenylaziridine was obtained, bp 73° (4 mm).

That racemization was not taking place during the synthesis was shown by the fact that the specific rotation was practically the same with samples from two separate preparations: $[\alpha]^{26}D$ −43.4° (1.0062 g/10 ml, EtOH) and −42.7° (1.0123 g/10 ml, EtOH).

(*R*)-1-(*N*-Phenylcarbamyl)-2-phenylaziridine [(*R*)-1a] was obtained by the reaction of (*R*)-2-phenylaziridine with phenyl isocyanate in ether, and recrystallized from benzene and *n*-hexane: mp 114.0–116.0°; ν (KBr) 1655 cm^{-1} (C=O); δ ($CDCl_3$) 2.13 (δ_A), 2.74 (δ_M), 3.35 (δ_X) (AMX, J_{AM} = 0.7, J_{AX} = 3.9, J_{MX} = 6.8 Hz, 3, ring H), 7.20 (m, 10, aromatic H), 7.67 (s, 1, NH); $[\alpha]^{26}D$ −262° (0.5078 g/10 ml, dioxane).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.78; H, 5.93; N, 11.82.

(*R*)-1-(*N*-Phenylthiocarbamyl)-2-phenylaziridine [(*R*)-1b]. To a solution of 1.3 g (9.6 mmol) of phenyl isothiocyanate in 20 ml of petroleum ether (bp 35–80°) was added a solution of 1.3 g (10.9 mmol) of (*R*)-2-phenylaziridine in 12 ml of ether dropwise at −10°. After addition, the reaction mixture was stirred for 1 hr at −10°. Meanwhile crystals separated out. They were collected on a filter, washed with cold ether–petroleum ether mixture, and dried at 0° to give 2 g of crude (*R*)-**1b**. All attempts to recrystallize the crude product failed. Crude (*R*)-**1b** melted at about 80°; δ ($CDCl_3$) (at −10°) 2.54 (δ_A), 2.78 (δ_M), 3.39 (δ_X) (AMX, J_{AM} = 0, J_{AX} = 5.0, J_{MX} = 3.2 Hz, 3, ring H), 6.8–7.4 (m, 10, aromatic H), 9.31 (s, 1, NH). Deterioration of the sample was noted while the NMR was taken, and no crystalline material was recovered after evaporation of $CDCl_3$ from the solution. Optical rotation was measured with the crude samples right after preparation: $[\alpha]^{24}D$ −177° (0.3442 g/10 ml, dioxane) and −174° (0.0604 g/10 ml, dioxane).

Anal. Calcd for $C_{15}H_{14}N_2S$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.73; H, 5.58; N, 10.83.

Preparation of (*R*)-2-anilino-4-phenyl-2-oxazoline [(*R*)-3a] and (*R*)-2-anilino-4-phenyl-2-thiazoline [(*R*)-3b]. From (*R*)-2-amino-2-phenylethanol and phenyl isocyanate, (*R*)-1-(1′-phenyl-2′-hydroxyethyl)-3-phenylurea was obtained, mp 164.0–165.5°, ν (KBr) 1637 cm^{-1} (C=O).

A mixture of 7 g of PPA and 7 ml of dioxane was kept at 80°. To this was added 1.0 g (3.9 mmol) of above-obtained urea, and the mixture was stirred for 8 hr at 80°. Then the reaction mixture was poured into ice-cold 2 *N* NaOH. Extraction of the basified aqueous layer with benzene and evaporation of the solvent gave 0.8 g of crude (*R*)-**3a**. Recrystallization from a benzene–petroleum ether mixture gave 0.7 g (75%) of an analytically pure sample: mp 119.0–120.5°; ν (KBr) 1695–1707 cm^{-1} (C=N); δ ($CDCl_3$) 4.05 (δ_X), 4.58 (δ_A), 5.00 (δ_B) (ABX, J_{AB} = 8.7, J_{AX} = 7.7, J_{BX} = 7.4 Hz, 3, ring H), 7.0–7.3 (m, 10, aromatic H), 8.51 (s, 1, NH); $[\alpha]^{23}D$ −164° (0.4960 g/10 ml, dioxane).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.67; H, 5.75; N, 11.83.

In a similar manner, (*R*)-**3b** was prepared from (*R*)-1-(1′-phenyl-2′-hydroxyethyl)-3-phenylthiourea (mp 96–100°). Crude product was recrystallized from benzene and petroleum ether to give an analytical sample: mp 132.7–135.0°; ν (KBr) 1639 cm^{-1} (C=N); δ ($CDCl_3$) 3.07 (δ_B), 3.39 (δ_A), 4.88 (δ_X) (ABX, J_{AB} = 10.5, J_{AX} = 6.8, J_{BX} = 8.4 Hz, 3, ring H), 6.9–7.3 (m, 10, aromatic H), 8.23 (s, 1, NH); $[\alpha]^{24}D$ −224° (0.5080 g/10 ml, dioxane).

Anal. Calcd for $C_{15}H_{14}N_2S$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.90; H, 5.55; N, 11.11.

2-Anilino-5-phenyl-2-oxazoline (2a) and 2-Anilino-5-phenyl-2-thiazoline (2b). 1-Phenyl-2-aminoethanol was prepared by the $LiAlH_4$ reduction of mandelic amide in THF according to the literature[8], bp 107–114° (3 mm) [lit.[8] bp 116–117° (2 mm)].

Reaction of phenyl isocyanate with the amino alcohol gave 1-(2′-hydroxy-2′-phenylethyl)-3-phenylurea (**4a**), mp 184.0–185.0°, ν (KBr) 1633 cm^{-1} (C=O). Dehydration of **4a** with PPA and the subsequent treatment as mentioned in the preparation of **3a** gave **2a** in a quantitative yield. Recrystallization from benzene and petroleum ether gave a pure sample: mp 124.0–125.0°; ν (KBr) 1642, 1665 (C=N), 3210, 3260 cm^{-1} (NH); δ ($CDCl_3$) 3.73 (δ_B), 4.17 (δ_A), 5.50 (δ_X) (ABX, J_{AB} = 11.6, J_{AX} = 8.9, J_{BX} = 7.7 Hz, 3, ring H), around 7.3 (m, 10, aromatic H), 8.10 (s, 1, NH).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N 11.76. Found: C, 75.35; H, 5.91; N, 11.74.

Similarly, 1-(2′-hydroxy-2′-phenylethyl)-3-phenylthiourea (**4b**, mp 127–129°) was prepared from the same amino alcohol and phenyl isothiocyanate, and dehydrated to give **2b**. Recrystallization from benzene and petroleum ether gave a sample melting at 113–116°; ν (KBr) 1625 (C=N), 3200, 3250 cm^{-1} (NH); δ ($CDCl_3$) 3.77 (δ_B), 3.99 (δ_A), 4.83 (δ_X) (ABX, J_{AB} = 11.2, J_{AX} = 6.9, J_{BX} = 8.0 Hz, 3, ring H), 7.0–7.4 (m, 10, aromatic H), 7.97 (s, 1, NH).

Anal. Calcd for $C_{15}H_{14}N_2S$: C, 70.85, H, 5.55; N, 11.02. Found: C, 70.62; H, 5.48; N, 11.01.

Preparation of (*S*)-2-Anilino-5-phenyl-2-oxazoline [(*S*)-2a]. (*S*)-1-Phenyl-2-aminoethanol was prepared in the same way as mentioned in the preparation of (*R,S*)-amino alcohol starting from (*S*)-mandelic acid. Crude amino alcohol was recrystallized from ether and petroleum ether, mp 61–63° (lit.[8] mp 61–62°), $[\alpha]^{23}D$ +44.8° (0.2088 g/10 ml, EtOH) [lit.[8] $[\alpha]^{18}D$ +44.6 ± 2.2° (0.206 g/10 ml, EtOH)].

Reaction of the amino alcohol with phenyl isocyanate gave (*S*)-**4a** melting at 199.0–200.7°, ν (KBr) 1631 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.55; H, 6.37; N, 10.84.

Compound (*S*)-**4a** had no appreciable optical rotation. Dehydration of (*S*)-**4a** with PPA gave (*R,S*)-**2a**.

(*S*)-1-(2′-Hydroxy-2′-phenylethyl)-3-phenylthiourea [(*S*)-**4b**] was obtained by the reaction of the (*S*)-amino alcohol with phenyl isothiocyanate. Crude (*S*)-**4b** was recrystallized from benzene and petroleum ether to give a pure sample, mp 83–87°.

Anal. Calcd for $C_{15}H_{16}N_2OS$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.54; H, 5.99; N, 10.32.

A mixture of 680 mg (2.5 mmol) of (*S*)-**4b**, 500 mg (2.5 mmol) of $Cu(OAc)_2 \cdot H_2O$, and 20 ml of EtOH was stirred at 50–55° for 3 hr. After the black precipitate of CuS was removed by centrifuge, the ethanolic solution was evaporated by rotary. The residue was dissolved in benzene, and the benzene solution was extracted with 2 *N* HCl three times. The aqueous layer was cooled and basified with NaOH, and was extracted with benzene. Drying the benzene solution with Na_2SO_4 and evaporation by rotary left a brown residue. The residue was dissolved in $CHCl_3$, and the solution was quickly passed through a silicic acid column. Evaporation of the solvent and recrystallization of the residue from benzene and petroleum ether gave 105 mg (17%) of (*S*)-**2a**, mp 124.0–125.0°, $[\alpha]^{30}D$ +77° (0.2298 g/10 ml, dioxane). Another cyclization reaction gave a sample, $[\alpha]^{28}D$ +84° (0.1062 g/10 ml, dioxane). The ir of (*S*)-**2a** in a KBr pellet was much different from that of (*R,S*)-**2a**, especially in the C=N and NH regions: ν (KBr) 1649, 1687 (C=N), 3110, 3175 cm^{-1} (NH). In $CHCl_3$, their ir spectra were completely identical: ν ($CHCl_3$) 1673 cm^{-1} (C=N).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.75, 75.71; H, 5.95, 5.95; N, 11.48, 11.51.

Dehydration of (*S*)-**4b** with PPA gave (*R,S*)-**2b**.

Isomerization Reaction of (*R*)-1a with *p*-Toluenesulfonic Acid. A solution of 1.0 g (5.9 mmol) of *p*-TosOH in 10 ml of benzene was stirred in a 100-ml three-necked flask with an addition funnel, a reflux condenser, and a stirrer, and the solution was heated to reflux. To the solution was added a solution of 1.27 g (5.1 mmol) of (*R*)-**1a** in 10 ml of benzene dropwise in 5 min, and the mixture was refluxed for 1 hr with stirring. After cooling, the benzene solution was washed with 2 *N* NaOH and then with water, and dried with Na_2SO_4. Evaporation of the solvent by rotary left 1.1 g (87%) of white residue. The NMR spectrum of the residue was completely identical with that of **2a**, and no trace of **1a** or **3a** was detected.

The crude product was dissolved in 2 *N* H_2SO_4, and the acidic solution was cooled and basified with NaOH. Extraction of the aqueous suspension with benzene and concentration of the benzene solution gave white crystals. After drying, the optical rotation of the crystalline product was measured.

Other isomerization reactions were carried out and the products

were treated in much the same manner. In the case of the reaction of **1b** with BF_3·OEt_2, the crude reaction product was mostly polymeric, though it had peaks of **2b** in the NMR spectrum. Extraction of the crude product with 2 *N* H_2SO_4, treatment of the acidic solution with NaOH, and the subsequent extraction of the alkaline suspension with benzene gave crystalline **2b** in 9% yield on evaporation of the solvent. The ir spectrum (KBr pellet) of **2b** thus obtained was different from that of (*R,S*)-**2b** especially in the NH regions: ν (KBr) 3090 cm^{-1} (NH). However, the C=N regions were almost the same: ν (KBr) 1624 cm^{-1} (C=N).

Reaction of 1a with *p*-Nitrobenzoic Acid. A solution of 476 mg (2 mmol) of (*R*)-**1a** and 368 mg (2.2 mmol) of *p*-nitrobenzoic acid in 10 ml of benzene was refluxed for 8 hr. After cooling, crystals were collected on a filter and the filtrate was concentrated to give an additional crop. The crude product was dissolved in ethyl acetate, and the solution was washed with 1*N* NaOH and water and dried with Na_2SO_4. Evaporation of the solvent gave 90 mg (12%) of **5** melting at 175–180°, $[\alpha]^{22}D$ +12.4° (0.1770 g/10 ml, THF). Recystallization of the crude product from $CHCl_3$–petroleum ether gave a sample: mp 181.0–183.0°; ν (KBr) 1631 (urea C=O), 1727 (ester C=O), 3350 cm^{-1} (NH); δ (in a 1:1 mixture of $CDCl_3$–Me_2SO-d_6) 3.77 (dd, 2, CH_2), 6.10 (t, 1, CH), 6.27 (d, 1, NH), 6.7–7.7 (m, 10, aromatic H), 7.7 (s, 1, NH), 8.23 (s, 4, aromatic H).

Anal. Calcd for $C_{22}H_{19}N_3O_5$: C, 65.18; H, 4.72; N, 10.37. Found: C, 65.48; H, 4.74; N, 10.60.

When the addition product **5** (20 mg) was treated with a solution of KOH (30 mg) in aqueous ethanol (2 ml) at room temperature, (*S*)-**4a** was obtained, mp 199–201°. [As mentioned before, authentic (*S*)-**4a** melts at 199.0–200.7°, and (*R,S*)-**4a** at 184.0–185.0°.] The mixture melting point with authentic (*S*)-**4a** was 199–201°.

An authentic sample of (*S*)-**5** was prepared by refluxing a solution of (*S*)-**4a** (1 mmol), *p*-nitrobenzoyl chloride (2 mmol), and Et_3N (2 mmol) in 10 ml of THF for 4 hr. Recrystallization of the crude product from $CHCl_3$–petroleum ether gave a sample, mp 182–183°, $[\alpha]^{22}D$ +11.9° (0.0505 g/10 ml, THF).

The above obtained addition product **5** was found to be identical with (*S*)-**5** in all respects.

Polymerization of (*R*)-1b, and the Reaction of the Polymer with *p*-TosOH. A solution of 635 mg (2.5 mmol) of (*R*)-**1b** and 4 mg of BF_3·OEt_2 in 10 ml of benzene was kept at 5° for 1 week. The solution was washed with 1 *N* NaOH and water and dried (Na_2SO_4). Evaporation of the solvent left a pale yellow residue. The residue was dissolved in a small amount of benzene, and the solution was poured into a large volume of ether to give white precipitate, which was filtered and dried. The polymer weighed 313 mg (50%), melted at about 145°, and had an absorption at 1610 cm^{-1} (presumably C=N) in the ir (KBr pellet). The viscosity in benzene solution (c 1 g/100 ml) was determined at 30°.

Anal. Calcd for $(C_{15}H_{14}N_2S)_n$: C, 70.85; H, 5.55; N, 11.02; S, 12.58. Found: C, 70.99; H, 5.56; N, 10.83; S, 12.60.

The polymer (254 mg) and *p*-TosOH (189 mg) were dissolved in 5 ml of benzene, and the solution was refluxed for 2 hr. The solution was washed with 2 *N* NaOH and water, dried (Na_2SO_4), and evaporated to give 140 mg (55%) of crystalline **2b**, $[\alpha]^{22}D$ +101°.

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Registry No.—(*R*)-**1a**, 33815-64-4; (*R*)-**1b**, 56533-11-0; (*R*)-**1b** polymer, 56533-12-1; (*R,S*)-**2a**, 56533-13-2; (*S*)-**2a**, 56586-18-6; (*R,S*)-**2b**, 56533-14-3; (+)-**2b**, 56533-15-4; (*R*)-**3a**, 56533-16-5; (*R*)-**3b**, 56533-17-6; (*R,S*)-**4a**, 56533-18-7; (*S*)-**4a**, 56586-19-7; (*R,S*)-**4b**, 56533-19-8; (*S*)-**4b**, 56586-20-0; (*S*)-**5**, 56533-20-1; (*R*)-2-phenylaziridine, 18142-08-0; phenyl isocyanate, 103-71-9; phenyl isothiocyanate, 103-72-0; (*R*)-2-amino-2-phenylethanol, 56613-80-0; (*R*)-1-(1′-phenyl-2′-hydroxyethyl)-3-phenylurea, 56533-21-2; (*R*)-1-(1′-phenyl-2′-hydroxyethyl-3-phenylthiourea, 56533-22-3; (*R,S*)-1-phenyl-2-aminoethanol, 1936-63-6; (*S*)-1-phenyl-2-aminoethanol, 56613-81-1; (*S*)-mandelic acid, 17199-29-0; *p*-toluenesulfonic acid, 104-15-4; BF_3·OEt_2, 109-63-7; *p*-nitrobenzoic acid, 62-23-7; picric acid, 88-89-1.

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Reaction of Nitriles with Thionyl Chloride in the Presence of Hydrogen Chloride. Formation of Sulfinyl and Sulfenyl Chlorides and Phenyl Cyanosulfine

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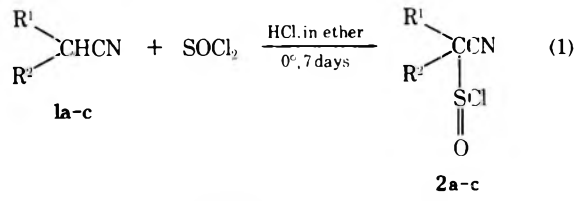
The reaction of nitriles with thionyl chloride in the presence of hydrogen chloride was investigated. The electrophilic attack of thionyl chloride occurred at the α carbon of nitriles rather than the nitrogen atom to give various products. 2-Methylpropionitrile and 2-methylbutyronitrile gave α-cyano-α-methylethane- and α-cyano-α-methylbutanesulfinyl chloride in 48 and 11% yield, respectively. α-Chlorophenylacetonitrile and 2-phenylpropionitrile gave the corresponding succinonitrile derivatives. On the other hand, some nitriles with two α hydrogens gave α-chloro-α-cyanoalkanesulfenyl chlorides in 4–44% yield. Phenylacetonitrile gave also *trans*-phenyl cyanosulfine in 5% yield when a smaller amount of hydrogen chloride was used. It was confirmed by H–D exchange experiment that nitriles were in equilibrium with α-chloroenamines under the reaction conditions. The reaction mechanisms were also discussed.

Reactions of nitriles with electrophiles in the presence of hydrogen chloride are generally initiated by the nitrogen attack of the electrophiles,[1] and there seem to be few examples which involve initial electrophilic attack at the α carbon atom.

In this paper we wish to report the reaction of nitriles with thionyl chloride in the presence of hydrogen chloride to give α-cyanosulfinyl and α-cyanosulfenyl chlorides and phenyl cyanosulfine via α carbon attack by thionyl chloride.

Results

Reaction of Nitriles Possessing one α Hydrogen. When 2-methylpropionitrile (**1a**) was allowed to react with thionyl chloride (3 equiv) in the presence of an excess of hydrogen chloride (ca. 6 equiv) at 0° for 7 days using diethyl ether as a solvent, α-cyano-α-methylethanesulfinyl chloride (**2a**) was obtained in 50% yield (based on the nitrile), and 37% of the starting nitrile was recovered.



(1)

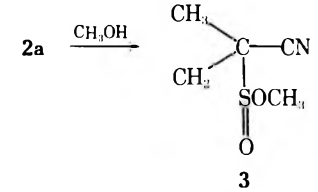
1a-c **2a-c**

a, $R^1 = R^2 = CH_3$
b, $R^1 = CH_3$; $R^2 = CH_3CH_2$
c, $R^1 = R^2 = CH_3CH_2$

The sulfinyl chloride was identified on the basis of its ir and NMR spectra and elemental analyses (Table I). The ir spectrum showed, in addition to a C≡N stretching band at 2230 cm^{-1}, a strong S=O stretching band at 1165 cm^{-1} characteristic of sulfinyl chlorides.[2] The NMR spectrum (CCl_4) showed two peaks at δ 1.80 and 1.75 with an area ratio of 1:1; the magnetic nonequivalence of the two methyl groups may be attributed to asymmetry at the sulfinyl sulfur.[3]

The structure of **2a** was further confirmed by converting it into sulfinate ester **3** according to the method of Douglass.[4]

The NMR spectrum of **3** measured in CCl_4 showed one singlet at δ 1.50 due to the two methyl groups attached to the α carbon atom. In benzene, however, two singlets were observed at δ 0.95 and 1.10 due to the magnetically nonequivalent two methyl groups.[3] The solvent effect is explained in terms of the anisotropy as in the case of methyl 2-propanesulfinate.[5]



2a → **3**

The reaction was extended to some other nitriles with one α hydrogen in order to determine the scope and limitations as a route to sulfinyl chlorides. 2-Methylbutyronitrile (**1b**) and 2-ethylbutyronitrile (**1c**) gave the corresponding sulfinyl chlorides **2b** and **2c** in low yields (12% and trace, respectively) and most of the starting nitriles were recovered[6] (Table I). 2-Chloromethylpropionitrile (**1d**), however, did not afford the expected sulfinyl chloride and 78% of the starting nitrile was recovered. 2-Phenylpropionitrile (**1e**) gave, instead of the expected sulfinyl chloride, 2,3-dimethyl-2,3-diphenylsuccinonitrile (**4e**) in 16% yield (recov-

Table I
Sulfinyl Chlorides 2a,b[a] and Sulfenyl Chlorides 7a–d

Compd	Yield (recovery of nitriles[b]), %	Bp, °C (mm)	NMR (CCl_4), δ, ppm
2a	50(37)	82–83(4)	1.80 (s, 1 H), 1.75 (s, 1 H)
2b	12(76)	73(3)	1.25 (t, 3 H)[d] 1.70 (s) and 1.75 (s) (total 3 H), 1.8–2.3 (m, 2 H)
7a	44(3)	94.5–95.5(0.7)	7.3–7.9 (m)
7b[c]	17(19)	116–116.5 (0.8)	7.4–7.9 (m)
7c	23(62)	45(5)	2.30 (s)
7d	4(80)	45–46(2)	1.35 (t, 3 H),[d] 2.10–2.65 (m, 2 H)

[a] All the sulfinyl chlorides **2a–c** showed a S=O stretching band at 1165 cm^{-1}. [b] Recovery of the starting nitriles was determined by NMR for **7a** and **7b** and by GLC for the others. [c] Mp 47–48°. [d] J = 6.8 Hz. Satisfactory analytical values (±0.3% for C, H, and N) were reported for all compounds in Table. Ed.

The reaction was extended to some other nitriles with one α hydrogen in order to determine the scope and limitations as a route to sulfinyl chlorides. 2-Methylbutyronitrile (**1b**) and 2-ethylbutyronitrile (**1c**) gave the corresponding sulfinyl chlorides **2b** and **2c** in low yields (12% and trace, respectively) and most of the starting nitriles were recovered[6] (Table I). 2-Chloromethylpropionitrile (**1d**), however, did not afford the expected sulfinyl chloride and 78% of the starting nitrile was recovered. 2-Phenylpropionitrile (**1e**) gave, instead of the expected sulfinyl chloride, 2,3-dimethyl-2,3-diphenylsuccinonitrile (**4e**) in 16% yield (recov-

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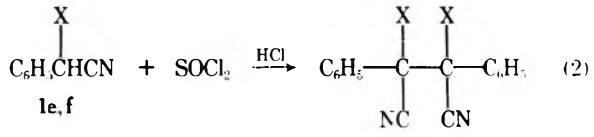
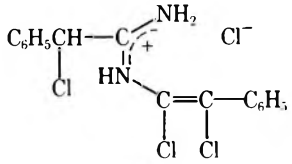


1e,f 4e,f (2)

e. X = CH_3
f. X = Cl

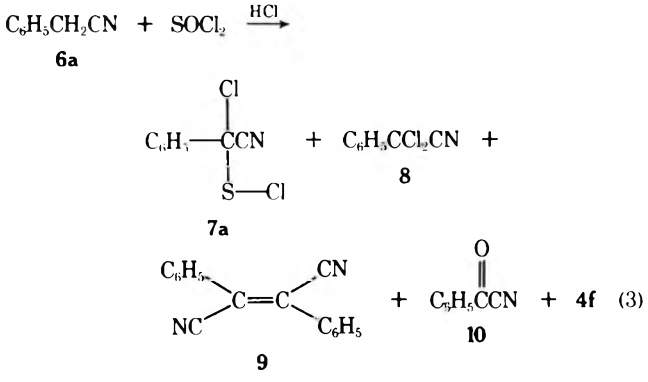
ery of **1e** 75%) (eq 2). The nitrile **4e** was found to be a mixture of meso and *dl* isomers (ratio 79:7) by NMR.[7] α-Chlorophenylacetonitrile (**1f**) gave only nitrile–hydrogen chloride adduct **5**[8] in 40% yield under the same reaction conditions (recovery of **1f** 27%). On the other hand, the reaction of **1f** at 50° in chlorobenzene afforded a 5% yield of 2,3-dichloro-2,3-diphenylsuccinonitrile (**4f**) together with a 27% yield of **5** (recovery of **1f** 43%). In this case, the diastereomer ratio was not determined.

In view of the above results, the sulfinyl chloride formation is limited to secondary cyanides bearing only alkyl substituents.



5

Reactions of Nitriles with Two α Hydrogens. When phenylacetonitrile (**6a**) was allowed to react with thionyl chloride in the presence of hydrogen chloride under the same conditions as described in the previous section, α-chloro-α-cyanophenylmethanesulfenyl chloride (**7a**) was obtained in 44% yield together with low yields of succinonitrile derivative **4f**, α,α-dichlorophenylacetonitrile (**8**), *trans*-α,β-dicyanostilbene (**9**), and benzoyl cyanide (**10**) (recovery of **6a** 3%) (eq 3).



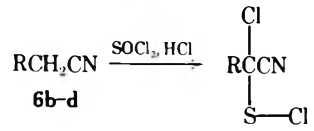
6a **7a** **8** **9** **10** **4f** (3)

Sulfenyl chloride **7a** was isolated by fractional distillation, and identified by its ir and NMR spectra and elemental analyses. The ir spectrum showed a C≡N and two S–Cl bands at 2240, 528, and 498 cm^{-1}, respectively. The NMR spectrum exhibited no peaks other than aromatic proton signals.

The sulfenyl chloride is thermally unstable and it was readily pyrolyzed at 145–150° under nitrogen to give a mixture of **4f** (39%), **8** (39%), **9** (4%), and sulfur; this transformation also supports the sulfinyl chloride structure.

Products **8**–**10** were characterized by spectral and elemental analyses or by comparison with authentic samples (see Experimental Section).

In order to determine the scope and limitations of the reaction, the reaction of some other nitriles with two α hydrogens were also carried out under the same reaction conditions. *p*-Chlorophenylacetonitrile (**6b**), propionitrile (**6c**), and *n*-butyronitrile (**6d**) afforded the corresponding sulfenyl chlorides **7b–d** in 17, 23, and 4% yield, respectively (eq 4) (Table I).



6b–d **7b–d** (4)

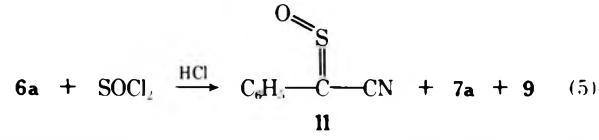
b. R = *p*-ClC_6H_4
c. R = CH_3
d. R = CH_3CH_2

Although the reaction of **6b** yielded a fair amount of by-products, they were not characterized. In the case of **6c** and **6d**, only a small amount of tar was produced as a by-product and fair amounts of the starting nitriles were recovered (Table I).

Chloroacetonitrile (**6e**), 3-chloropropionitrile (**6f**), 3-phenylpropionitrile (**6g**), and ethyl cyanoacetate (**6h**) failed to give the corresponding sulfenyl chlorides. Nitrile **6e** gave a nitrile–hydrogen chloride 2:3 adduct[8] in 71% yield. The reactions of both **6f** and **6g** resulted in a 70% recovery of the starting nitriles. Nitrile **6h** afforded only an intractable tar (recovery of **6h** 23%).

Thus, the sulfenyl chloride formation is limited to phenylacetonitriles and unsubstituted primary alkyl cyanides.

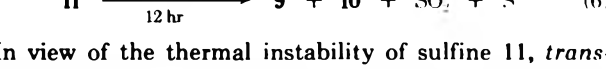
Formation of Phenyl Cyanosulfine. It is of much interest that a new type of sulfine, i.e., phenyl cyanosulfine (thiobenzoyl cyanide *S*-oxide, **11**), was obtained in 5% yield together with *trans*-α,β-dicyanostilbene (**9**, 7%) and sulfenyl chloride **7a** from the reaction of phenylacetonitrile (**6a**) with thionyl chloride (3 equiv) in the presence of a smaller amount of hydrogen chloride (3 equiv) at 0° for 3 days (eq 5); the recovery of the starting nitrile was 56%.



6a **11** **7a** **9** (5)

The reaction in the presence of 6 equiv of hydrogen chloride for both 3 and 6 days also yielded a trace amount of **11**, the formation of which was confirmed by ir analyses of the reaction mixtures.

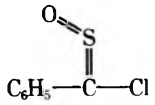
The structures of the sulfine was established by spectral and elemental analyses, and by its disproportionation reaction. The ir spectrum exhibited, in addition to the absorption at 767 and 682 cm^{-1} due to the monosubstituted benzene, two C≡N bands at 2215 and 2205 cm^{-1}, and C=S=O bands at 1140 and 998 cm^{-1}.[9,10] The mass spectrum showed the molecular ion peak at *m/e* 163 and the deoxygenated peak at *m/e* 147, and the NMR spectrum ($CDCl_3$) showed aromatic proton signals at δ 7.3–7.8 (m) and 8.1–8.4 (m) with relative areas of 3:2. In addition, by analogy to the behavior of some sulfines,[9,11] sulfine **11** decomposed gradually on heating with evolution of sulfur dioxide to give *trans*-α,β-dicyanostilbene (**9**). Thus, when a benzene solution of **11** was heated under reflux for 12 hr, a 54% yield of **9** was obtained together with benzoyl cyanide (**10**) (trace) and sulfur (recovery of the starting material 7%) (eq 6).



11 **9** **10** (6)

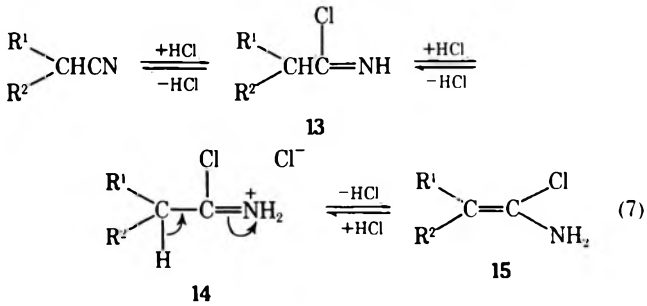
In view of the thermal instability of sulfine **11**, *trans*-α,β-dicyanostilbene (**9**) in eq 5 must be formed through the decomposition of **11** during work-up.

If two substituents are different, it is possible for sulfines to exist in two geometrical isomers.[12] In the present case, cyanosulfine **11** probably has the trans configuration, i.e., the oxygen is trans to the cyano group, in view of the close resemblance of chemical shifts and patterns of its NMR signals to those of *trans*-phenyl chlorosulfine (**12**).[10,12]



12

H–D Exchange of the α Hydrogens of Nitriles in the Presence of Deuterium Chloride. Simchen and Krämer postulated that nitriles with at least one α hydrogen atom were in equilibrium with α-chloroenamine **15** in the presence of hydrogen chloride as shown in eq 7.[13]



13

14 **15** (7)

Their postulation is based on the observation that α deuteriums of nitriles are replaced by hydrogens in the presence of hydrogen chloride.[13]

Since also in the present reactions the α-chloroenamine seemed to play an important role, the H–D exchange reaction of α hydrogens of nitriles was investigated to obtain mechanistic information.

Nitriles were treated with 3 equiv (for nitriles with one α hydrogen) or 6 equiv (for nitriles with two α hydrogens) of deuterium chloride in diethyl ether at 0° for 4 days. The degree of deuterium exchange was determined by NMR. Results are shown in Table II. It is obvious from the table that most nitriles examined except for **1c** are in equilibrium with the corresponding α-chloroenamine **15** under the reaction conditions.

Table II
H–D Exchange of α Hydrogens of Nitriles Nitrile $R^1(R^2)CHCN$

Compd	R^1	R^2	% deuteration
1a	CH_3	CH_3	45
1b	CH_3	CH_3CH_2	18
1c	CH_3CH_2	CH_3CH_2	0
1d	CH_3	$ClCH_2$	82
1e	C_6H_5	CH_3	76
6a	C_6H_5	H	85
6c	CH_3	H	80
6f	$ClCH_2$	H	86

Whereas almost maximum deuterations (80–85%) were obtained for nitriles with two α hydrogens independent of the α substituents, deuterations of secondary cyanides varied significantly, depending on the nature of the α substituents.

For secondary alkyl cyanides, the extent of deuteration decreased dramatically on going from **1a** to **1c**, and this order is consistent with the order of the decrease in yields of the sulfinyl chlorides **2a–c**. However, it was difficult to generally correlate the deuterations with product yields.

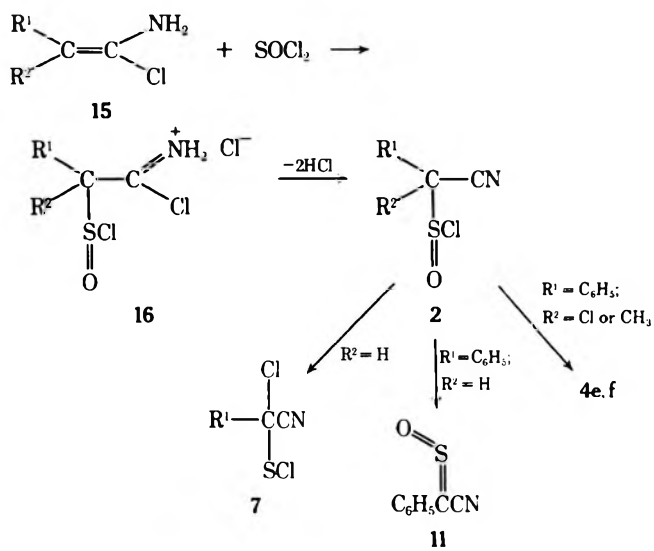
Discussion

Since the nitriles failed to react with thionyl chloride in the absence of hydrogen chloride, it is evident that hydrogen chloride plays a very important role in the present reactions. In other words, activated species derived from the reaction of nitriles with hydrogen chloride, i.e., nitrile–hydrogen chloride adducts **13–15**, take part in the reaction. Among them, α-chloroenamine **15** seems to be the most plausible species that is subjected to the electrophilic attack by thionyl chloride in view of the fact that the decrease in the yield of sulfinyl chlorides **2a–c** is in line with the decrease in percent deuteration of the starting nitriles **1a–c**. Nitriles **1d** and **1f**, however, failed to give the corresponding sulfinyl or sulfenyl chloride in spite of their high percent deuteration. This may be ascribed to low nucleophilicity of the β carbon of the corresponding α-chloroenamine **15** as a result of substitution of a chlorine atom on the adjacent saturated carbon atom.

The above speculation that α-chloroenamine **15** is attacked rather than **13** and **14** is reasonable in view of the resemblance of the present reactions to acid-catalyzed halogenation of ketones[14] and α-chlorosulfenylation of carboxylic acid chlorides and ketones,[15,16] in which enols (oxygen analogs of enamines) rather than ketones or acid chlorides themselves are subjected to the electrophilic attack.

The most plausible routes of the present reactions are depicted in Scheme I.

Scheme I



15 **16** **2** **7** **11**

The reaction probably proceeds by the initial electrophilic attack of thionyl chloride at the β carbon of α-chloroenamine **15** to produce iminium salt **16**, followed by elimination of hydrogen chloride to give sulfinyl chloride **2** as the final product for nitriles **1a–c** or as the intermediate for nitriles **6a–d**. The succinonitrile derivatives **4e** and **4f** might also be produced via **2**. In the case of nitriles with two α hydrogens, the initially formed sulfinyl chloride further reacts with thionyl chloride to give the sulfenyl chloride **7** possibly via the Pummerer type reaction proposed by Krubsack et al. for the chlorosulfinylation of acid chlorides and ketones by thionyl chloride.[15,16]

In the case of phenylacetonitrile, phenyl cyanosulfine (**11**) is also produced, the yield of which is very low as a result of suppression of dehydrochlorination from sulfinyl

chloride **2** ($R^1 = C_6H_5$; $R^2 = H$) when a large excess (6 equiv) of hydrogen chloride is used.

At a glance, sulfine **11** seems to be in equilibrium with sulfinyl chloride **2** ($R^1 = C_6H_5$; $R^2 = H$). If that is the case, sulfenyl chloride **7a** would be produced also from sulfine **11**. However, treatment of **11** with thionyl chloride in the presence of hydrogen chloride resulted in the almost quantitative recovery of the starting material. Thus, the sulfine is not in equilibrium with the sulfinyl chloride; this is consistent with the result of Strating et al.[17]

The present reaction is of synthetic use since sulfenyl or sulfinyl group is introduced into nitriles by one process under mild conditions.

Experimental Section[18]

General Procedure. Anhydrous HCl (ca. 11 g, 0.30 mol) was dissolved into a solution of a nitrile (0.05 mol) in anhydrous ether (30 ml) in a 115-ml glass tube under ice cooling, followed by addition of thionyl chloride (17.85 g, 0.15 mol). After sealing the tube, the mixture was allowed to stand at 0° for 7 days. After the gaseous products were purged, the solvent and other volatile materials were removed under reduced pressure (ca. 20 mm) at room temperature, then the resulting liquid was fractionally distilled to give a sulfinyl chloride or sulfenyl chloride. The distillation residue was chromatographed on either alumina or silica gel to give crystalline products.

In the case of α-chlorophenylacetonitrile (**1f**) and chloroacetonitrile (**6e**), the corresponding nitrile–hydrogen chloride adducts precipitated in the reaction mixture.

Sulfinate Ester 3. To a solution of **2a** (3.03 g, 0.02 mol) in anhydrous ether (10 ml) was added 1.0 g (0.031 mol) of methanol at −30° and the mixture was stirred for 30 min. After removal of the solvent, the resulting liquid was distilled under reduced pressure to give 2.53 g (86%) of **3** (colorless liquid): bp 88–89° (5 mm); ir (liquid film) 2230, 1460, 1160, 980, and 730 cm^{-1}; NMR (CCl_4) δ 1.50 (s, 6 H) and 3.85 (s, 3 H); NMR (C_6H_6) δ 0.95 (s, 3 H), 1.1 (s, 3 H), and 3.25 (s, 3 H).

Anal. Calcd for $C_5H_9NO_2S$: C, 40.80; H, 6.16; N, 9.52. Found: C, 40.76; H, 6.34; N, 9.95.

Reaction of 2-Phenylpropionitrile (1e). According to the general procedure, **1e** (6.55 g, 0.05 mol) was allowed to react with thionyl chloride. The liquid, obtained after removal of the volatile material, was distilled under reduced pressure to give 4.92 g (75%) of the starting nitrile. The distillation residue was chromatographed on alumina. Elution with CCl_4 gave 1.07 g (16%) of a mixture of *meso*- and *dl*-2,3-dimethyl-2,3-diphenylsuccinonitrile (**4e**), which was recrystallized from benzene to give colorless prisms: mp 234–235°; ir (KBr) 2230, 1500, 1450, 1230, 1805, 790, 745, and 695 cm^{-1}; NMR ($CDCl_3$) δ 1.80 (s, CH_3 of meso isomer) and 2.08 (s, CH_3 of *dl* isomer)[7] (area ratio 79:7); mass spectrum (70 eV) *m/e* (rel intensity) 260 (M^+), 130 (100, $M^+/2$), 103 (50), and 77 (30).

Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.05; H, 6.20; N, 10.76. Found: C, 83.04; H, 6.26; N, 10.99.

Reaction of α-Chlorophenylacetonitrile (1f) at 50° in Chlorobenzene. Anhydrous HCl (0.80 g, 0.022 mol) was dissolved into **1f** (4.55 g, 0.03 mol) in a 80-ml Pyrex tube, and then a mixture of thionyl chloride (10.7 g, 0.09 mol) and chlorobenzene (6 ml) was added. After sealing the tube, the mixture was heated at 50° for 2 days on an oil bath. The precipitates formed were filtered, washed with a small portion of ether, and dried in vacuo to give 1.53 g (27%) of **5**, which was identified by comparison with an authentic sample.[8] The filtrate was concentrated and distilled under reduced pressure to give 1.94 g (43%) of **1f**. The distillation residue was chromatographed on silica gel. Petroleum ether–benzene (4:1 v/v) eluted 0.4 g (5%) of 2,3-dichloro-2,3-diphenylsuccinonitrile (**4f**), which was recrystallized from benzene to give colorless prisms: mp 188–189°; ir (KBr) 1495, 1445, 1180, 1000, 845, 795, 725, and 690 cm^{-1}; NMR ($CDCl_3$) δ 7.1–7.8 (m); mass spectrum (70 eV) *m/e* (rel intensity) 300 (M^+), 265 ($M^+ - Cl$), 230 (100, $M^+ - 2Cl$), 215 (32), 203, and 150 (60, $M^+/2$).

Anal. Calcd for $C_{16}H_{10}N_2Cl_2$: C, 63.81; H, 3.35; N, 9.30; Cl, 23.54. Found: C, 63.88; H, 3.15; N, 9.62; Cl, 23.82.

Reaction of Phenylacetonitrile (6a) in the Presence of 6 Equiv of HCl. Phenylacetonitrile (**6a**, 5.85 g, 0.05 mol) was allowed to react according to the general procedure. The liquid obtained after removal of the volatile materials was fractionally distilled to give 2.53 g of a forerun and 4.85 g (44%) of α-chloro-α-cyanophenylmethanesulfenyl chloride (**7a**, a yellow liquid). The forerun was a mixture of **6a**, **7a**, **8**, and **10**. Nitriles **8** (ir 1500, 1457, 1200, 1022, 870, 797, 727, and 688 cm^{-1}) and **10** (ir 2320 and 1690 cm^{-1}) were identified by comparison of the GLC retention time and ir spectrum with those of authentic samples.[19,20] The distillation residue was chromatographed on silica gel. Sulfur (0.05 g), 2,3-dichloro-2,3-diphenylsuccinonitrile (**4f**, 0.32 g, 4%), and a trace amount of α,β-dicyanostilbene (**9**) were eluted with petroleum ether–benzene (4:1 v/v) and petroleum ether–benzene (1:1 v/v), respectively. Dicyanostilbene **9** was recrystallized from EtOH to give colorless needles: mp 160–162°; ir (KBr) 2200 (C≡N), 1495, 1250, 755, and 690 cm^{-1}. The mixture melting point of **9** and an authentic sample[21] showed no depression.

Pyrolysis of 7a. Sulfenyl chloride **7a** (8.72 g, 0.04 mol) was placed in a 15-ml two-necked flask equipped with a gas inlet tube and a gas outlet tube and it was heated on an oil bath at 145–150° for 3 hr. A continuous stream of nitrogen was passed through the reaction mixture during the pyrolysis. The precipitates formed were filtered, washed with a small portion of ether, and dried in vacuo to give a mixture of sulfur, **4f**, and **9**. The filtrate was distilled under reduced pressure to give 2.88 g (39%) of **8**, bp 82.5–83° (3.5 mm). The mixture obtained by filtration and the distillation residue were combined and chromatographed on silica gel. Sulfur (0.5 g), **4f** (2.36 g, 39%), and **9** (0.17 g, 4%) were eluted with petroleum ether, petroleum ether–benzene (9:1 v/v), and petroleum ether–benzene (1:1 v/v), respectively.

Reaction of Phenylacetonitrile (6a) with Thionyl Chloride in the Presence of 3 Equiv of HCl. A solution of **6a** (5.85 g, 0.05 mol) in 30 ml of anhydrous ether was placed in a 115-ml glass tube, then anhydrous HCl (5.6 g, 0.15 mol) was dissolved into the solution, followed by the addition of thionyl chloride (17.85 g, 0.15 mol). After sealing the tube, the mixture was allowed to stand at 0° for 3 days. After removal of the volatile materials, the residual oil was distilled under reduced pressure to give two fractions, the first 3.45 g (55–85°, 0.1 mm) and the second 1.60 g (85–95°, 0.1 mm). The second fraction partially solidified when it was left standing at room temperature. The solid that formed was filtered, washed with a small portion of *n*-hexane, and dried in vacuo to yield 0.5 g (6%) of *trans*-phenyl cyanosulfine (**11**, a yellow powder), which was recrystallized from *n*-hexane–CCl_4 (10:3 v/v) to give fine yellow needles: mp 69.5–70°; ir (Nujol)[22] 2215, 2205, 1592, 1583, 1445, 1283, 1190, 1140, 1110, 1604, 998, 767, and 682 cm^{-1}; NMR ($CDCl_3$) δ 7.3–7.8 (m, 3 H) and 8.1–8.4 (m, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 163 (100, M^+), 147 (38, $M^+ - 0$), 135 (42), and 115 (30); λ_{max} (CH_3CN)[23] (log ε) 227 (3.78), 273 (3.43), and 341 nm (4.07).

Anal. Calcd for C_8H_5NOS: C, 58.80; H, 3.09; N, 8.58; S, 19.65. Found: C, 58.64; H, 2.99; N, 8.52; S, 19.27.

The filtrate of the second fraction and the first fraction were combined, and percent recovery of the starting nitrile was determined by NMR to be 56%.

Pyrolysis of *trans*-Phenyl Cyanosulfine (11). A solution of sulfine **11** (335 mg, 2.1 mmol) in 2 ml of benzene was heated under reflux for 12 hr on an oil bath (bath temperature 110–120°). The solvent was removed under reduced pressure (ca. 20 mm) at room temperature and the residue was chromatographed on silica gel. Elution with petroleum ether gave 25 mg of sulfur, and further elution with petroleum ether–benzene (2:1 v/v) gave a trace amount of benzoyl cyanide (**10**), 23 mg (7%) of *trans*-phenyl cyanosulfine (**11**), and 128 mg (54%) of *trans*-α,β-dicyanostilbene (**9**), successively.

H–D Exchange of α Hydrogens of Nitriles. DCl was prepared by dropping D_2SO_4 (96–98%) into a mixture of dried NaCl and DCl solution (20%) in D_2O and it was dried by passing through a P_2O_5 column. DCl was dissolved into diethyl ether and two DCl–ether solutions of different concentration, solution A (3.04 mmol DCl/ml) and solution B (5.60 mmol DCl/ml), were prepared. Solutions A and B were used for nitriles with one α hydrogen and for those with two α hydrogens, respectively. A mixture of a nitrile (10 mmol) and 10 ml of the DCl–ether solution in a 20-ml sealed glass tube was allowed to stand at 0° for 4 days. After removal of the solvent, the residual liquid was distilled at ordinally or reduced pressure to give a mixture of undeuterated and deuterated nitriles. The percent deuteration was determined by NMR analysis of the mixture.[24]

Registry No.—**1a**, 78-82-0; **1b**, 18936-17-9; **1e**, 1823-91-2; **1f**, 22259-83-2; **2a**, 56630-18-3; **2b**, 56630-19-4; **3**, 56630-20-7; *meso*-**4e**, 16510-37-5; *dl*-**4e**, 16510-36-4; **4f**, 52819-60-0; **6a**, 140-29-4; **6b**, 140-53-4; **6c**, 107-12-0; **6d**, 107-74-0; **7a**, 56630-21-8; **7b**, 56630-22-9; **7c**, 56630-23-0; **7d**, 56630-24-1; **8**, 40626-45-7; **9**, 2450-55-7; **10**,

613-90-1; **11**, 56630-25-2; thionyl chloride, 7719-09-7; methanol, 67-56-1.

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Chemical Purity and the Electrical Conductivity of Tetrathiafulvalinium Tetracyanoquinodimethanide

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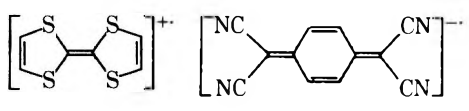
A critical evaluation using high-pressure liquid chromatography is made of three purification techniques for the neutral precursors of the highly conducting organic charge-transfer salt TTF-TCNQ (**1**). The purification techniques examined are (a) recrystallization, (b) sublimation, and (c) gradient sublimation. It is demonstrated that for the compounds studied gradient sublimation offers no significant advantage over more conventional sublimation techniques, and in fact is less efficient than simpler methods. Direct current conductivity data for crystals obtained from TTF^0 and $TCNQ^0$ of the varying purity are also presented. Only in extremely dirty samples do we see any significant change in electrical conductivity. We conclude that for impurity concentrations likely to be achieved routinely in most laboratories, crystal perfection rather than chemical purity chiefly determines the sample-dependent conductivity of TTF-TCNQ.

The best organic conductors of electricity known are the charge-transfer salt TTF-TCNQ (tetrathiafulvalinium tetracyanoquinodimethanide, **1**), first prepared in these



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laboratories,[2-8] and several of its derivatives[9] and analogs.[10,11] The chain-like structures[5] of these materials lead to conductivities which are highly anisotropic, but metallic in magnitude along the chain axis. Since the propagation of conduction electrons is thus restricted effectively to one dimension, it is natural to expect chemical impurities and lattice defects to influence transport more profoundly here than in conventional three-dimensional metals.

Interest in the problem of purification has sharpened with the observation[2,12-14] that the conductivity of TTF-TCNQ is strongly sample dependent. Although it now appears that early reports[12] of truly giant conductivities in occasional crystals were overstated,[15-17] the variation among specimens is still large enough that the intrinsic conductivity of TTF-TCNQ remains in some doubt. Compounding the uncertainty are claims by at least one laboratory[12,13,18] of extreme chemical purity, based solely upon accounts of the methods of purification and care employed in synthesis.

Toward a resolution of these questions, we have undertaken to evaluate the methods currently used by various laboratories for purification of the neutral molecules TTF^0 and $TCNQ^0$. Using newly available techniques of high-pressure gel permeation chromatography, we obtain separations of 4000–5000 theoretical plates, and by differential ultraviolet detection we are able to monitor impurity concentrations as low as 1 ppm. We find that conventional techniques of recrystallization and sublimation are sufficient to reduce impurity levels in TTF^0 below the sensitivity of our instruments. The same is true of $TCNQ^0$ except for a tendency to complex weakly with acetonitrile. The acetonitrile is removed upon formation of the TTF-TCNQ salt. The gradient sublimation technique introduced by McGhie et al.[18] offers no improvement for TTF^0 or $TCNQ^0$. The conductivities of TTF-TCNQ crystals of maximum purity are the same as reported previously,[2,14,15] and not significantly different from those of deliberately contaminated samples. The latter, however, appear more susceptible to inhomogeneous current distributions which give rise to spurious giant apparent conductivities.[15,16] We conclude that most of the variation in conductivity among samples of TTF-TCNQ is due to lattice imperfections rather than chemical purity.

Results and Discussion

Three methods of purification were examined in this study: (a) recrystallization in an inert atmosphere using dry, purified solvents, (b) nonfractionating sublimation onto Teflon,[19] and (c) fractionating, or gradient sublimation onto Teflon.

A critical evaluation of these techniques was accomplished by the use of high-pressure liquid chromatography[20] (HPLC). Through the use of a differential uv detector operated at 254 nm, this method allowed detection of as little as 10^{-9} g, depending on the absorbtivity of the sample. The use of μ-styragel[21] gel-permeation[22] columns, which are capable of separating molecules of moderate molecular weights on the basis of effective size (including solvation sphere), gave chromatographs of both TTF^0 and $TCNQ^0$ which demonstrated the presence of characteristic impurities. In addition, these columns avoided the difficulties encountered when more conventional columns were used. For example, in the case of TTF^0, "normal phase" (i.e., liquid–solid absorption) HPLC proved to be unsatisfactory because of the low affinity of silica toward TTF^0. "Reverse phase" (i.e., liquid–liquid partition) HPLC using a permanently bonded hydrocarbon on silica phase gave satisfactory retention volumes for TTF^0 but proved useless owing to the sensitivity of TTF^0 to water (aqueous acetonitrile is required for the separation). Reverse phase HPLC was similarly unsatisfactory for $TCNQ^0$, as was normal phase owing to the possible presence of nonobservable highly polar impurities.

HPLC Analysis. For the analytical runs using TTF^0, recrystallized, sublimed, and gradiently sublimed TTF^0 (samples a, b, and c, respectively, see Experimental Section) were injected as approximately 0.5 *M* solutions in dry, deoxygenated THF. A solution of the starting material was prepared similarly. The resulting chromatographs are presented in Figures 1 and 2. (All figures appear as supplementary material in the microfilm edition. See paragraph at end of paper for details.) Figure 1 is the chromatography of the starting TTF^0. The Δuv traces are of particular interest. For the starting TTF, we note a significant impurity at a retention volume (RV) of 15 ml. This peak is due to a molecule *larger* than TTF^0, smaller compounds being eluted later owing to greater penetration of the gel pores. This impurity is essentially removed (Figure 2a) after three recrystallizations. After one sublimation onto Teflon using a vertical sublimator, we note that this impurity has, within the limits of detection, disappeared (Figure 2b). Thus it appears that recrystallization and a simple sublimation provide TTF^0 of excellent purity. Figure 2c demonstrates that gradient sublimation provides no advantage over the simpler method.

In contrast, gradient sublimation of TTF which has not been extensively recrystallized does not remove the small impurity present at RV 15 (Figure 3). Approximately the same amount of impurity was present before and after two gradient sublimations. Thus gradient sublimation of itself does not provide TTF^0 of exceptional purity, and can be exceeded in purifying ability by much simpler methods.

The analysis of $TCNQ^0$ was carried out essentially as that for TTF^0. A minor change was made owing to the low solubility of $TCNQ^0$ in THF. Since a saturated solution at room temperature was only about 0.01 *M*, injections of 100 μl were used. This did not cause any significant peak broadening.

The results of the analysis are presented in Figures 4 and 5. Figure 4 is a chromatograph obtained from the starting $TCNQ^0$. This material, which had been sublimed once, exhibited three extraneous peaks at RV 13.5, 18.5, and 20 ml. Multiple recrystallization under argon yielded material (Figure 4a) in which the impurities were somewhat reduced. Sublimation onto Teflon using the vertical sublimator yielded material (Figure 4b) from which essentially all of the impurities at RV 13.5 and 18.5 ml had been removed. The residual peak near RV 15 ml may be due to dihydro-TCNQ (*p*-bisdicyanomethylbenzene).[23] However, the peak at RV 20 ml had not been diminished significantly. Even gradient sublimation (Figure 4c) did not remove this impurity. Likewise, as in the case of TTF^0, gradient sublimation did not afford material significantly purer than a simpler sublimation method.

The persistence of the peak at RV 20 ml is particularly troublesome. For some reason the peak does not seem to be susceptible to removal by sublimation. Its composition can be inferred by reference to Figure 4. First of all, the impurity is smaller than $TCNQ^0$, being eluted very close to the totally included volume of the column (that is, the volume which includes all the accessible pores of the gel). Second, the relative intensities of the ΔRI and Δuv detector responses suggest a compound having an absorbence at 254 nm only slightly different from that of THF. In view of the above facts, a likely candidate is acetonitrile, the recrystallization solvent.[25] A reason for its persistence even during sublimation might be a weak charge-transfer interaction with TCNQ.[26] This hypothesis is supported by the observation of a typical –CN absorption at ~2220 cm^{-1} in the ir spectrum of the peak at RV 20 ml. In addition, gas chromatographic and mass spectrometric evidence is consistent with the presence of acetonitrile. The presence of acetonitrile is sublimed $TCNQ^0$ presents a potential source of contamination in crystals of TTF-TCNQ. However, HPLC of crystals of the salt (which had been grown in acetonitrile) showed no evidence of the solvent, indicating at least a 20-fold decrease in the amount of acetonitrile present.

While certainty remains impossible, we feel strongly that no significant impurities have gone undetected in either TTF^0 or $TCNQ^0$. This statement is supported by three observations. The first is the high theoretical plate values[29] obtained for TTF^0 (~5000) and $TCNQ^0$ (~4000). Second, recycling the TTF^0 or $TCNQ^0$ peak in excess of five times provided no evidence for any impurities not observed in one pass through the columns. Third, HPLC traces obtained at wavelengths other than 254 nm (220, 280, 330, 450, and 500 nm) gave no evidence of new impurities. It is important to note at this point that the particular impurities present will in general depend on the method of preparation and handling of any given sample.

Conductivities. As a test of the importance of impurities in the TTF-TCNQ salt, we compared the conductivity of impure crystals to that of crystals grown under rigorously clean conditions. One of the reasons that other workers[12-14,18] claimed to have obtained extraordinarily pure TTF-TCNQ was their use of a quartz apparatus during crystal formation, thus reducing the possibility of leeching salts from borosilicate glass. In order to further reduce this possibility, we coated the interior of two inverted U-tube crystallizers with Teflon. We placed several crystals of NaCl in one of these to imitate the leeched salts. The other was kept clean. Crystals of the salt were grown by diffusion of acetonitrile solutions of gradiently sublimed TTF^0 and $TCNQ^0$. Crystals were also obtained from the starting TTF^0 and $TCNQ^0$.

The dc conductivities of representative "clean", "salty", and "dirty" crystals, measured by conventional four-probe techniques,[30] are summarized in Table I. No significant differences are observed among the three types of crys-

Table I

Crystal no.	Crystal type[a]	σ_{max},[b] 10^3 ohm^{-1} cm^{-1}	$\sigma_{max}{}^{b}/\sigma_{RT}$	T_{max}, K
40	Salty	6.27	15.5	59
41	Salty	5.34	14.2	59
42	Clean	8.48	17.5	59
43	Clean	7.67	14.5	59
44	Clean	11.6	20.4	58
45	Salty	5.45	13.1	60
46	Clean	3.08	7.4	59
47	Clean	6.41	13.9	58
51	Clean	3.08	16.3	59
52	Clean	8.08	12.5	59
53	Clean	8.01	14.8	58
55	Salty	3.24	16.6	59
56	Salty	4.53	14.4	58
57	Salty	3.37	13.6	59
91	Dirty	3.53	9.6	65
95	Dirty	5.04	10.3	61
96	Dirty	5.80	16.5	58
97	Dirty	7.74	23.3	56
39	Salty	71.9[c,d]	120.[c,d]	59

[a] "Clean" indicates crystallization of TTF-c and TCNQ-c from CH_3CN in a Teflon-coated inverted U-tube. "Salty" indicates crystallization of TTF-c and TCNQ-c from CH_3CN containing NaCl in a Teflon-coated U-tube. "Dirty" indicates crystals obtained from the starting TTF^0 and $TCNQ^0$ using a glass apparatus. [b] Average values of σ_{max} taken as the temperature was decreased and then increased. [c] These results do not represent the true conductivity of this crystal. See text. [d] Value taken as the temperature was decreased. Upon warming this crystal exhibited two peaks, 3.4×10^5 ohm^{-1} cm^{-1} at 53 K and 1.3×10^5 ohm^{-1} cm^{-1} at 66 K.

tals.[31] However, a substantial variation in the ratio of the conductivity at the maximum to the room temperature conductivity (σ_{max}/σ_{RT}) is observed within each type; this we attribute to crystalline imperfections. Among the "dirty" crystals there is also considerable variation in the temperature at which σ_{max} occurs. Here the lowest conductivity peaks appear at the highest temperatures, consistent with previous observations.[13]

One crystal of the "salty" variety, no. 39, does not fit the generally consistent conductivity behavior we observed. This crystal was particularly large and apparently well formed. As the temperature was lowered, it displayed a single, sharp maximum in the apparent conductivity of 7.2×10^4 Ω^{-1} cm^{-1} (σ_{max}/σ_{RT} ~120) at 59 K. This behavior essentially duplicates that of the occasional crystals to which Coleman et al.[12] assigned giant intrinsic conductivities. In this case, however, continuous monitoring of the voltage checks suggested by Schaefer et al.[15] revealed the giant conductivity to be an artifact due to inhomogeneous current distributions. A detailed analysis of these results will be presented elsewhere.[16] With repeated thermal cycling the apparent σ_{max}/σ_{RT} rose to ca. 350, then rapidly deteriorated, with auxiliary conductivity maxima appearing at higher temperatures. The voltage checks continued to show that none of the cycles measured the true conductivity of the specimen.

Experimental Section

General. Gas chromatography was performed on a Hewlett-Packard Model 402 GC using a flame ionization detector. Two columns were employed: 5% UC-W98 on Chromosorb P and 20% Carbowax on Chromosorb W. Mass spectra were obtained on a Hitachi RMU-6 mass spectrometer operated at 70 eV.

All manipulations of the TTF^0 and $TCNQ^0$ samples were carried out under an argon atmosphere, using either dry Schlenk apparatus or glove bag techniques.[32] The purified samples were stored prior to analysis in argon-filled vials, under argon at −30°.

The solvents used were all dry and oxygen free. Acetonitrile (Burdick and Jackson spectrograde) was passed through 50 g of Super I Al_2O_3 (Woelm) and deoxygenated by bubbling argon through it for 15 min.[33] Petroleum ether (Fisher, bp 60–64°) was purified by shaking three times with concentrated H_2SO_4, distillation, and finally passage through Super I Al_2O_3, and deoxygenated using argon. Tetrahydrofuran (Fisher reagent grade) was purified by stirring with $LiAlH_4$ and then distilled under argon. All solvents were used immediately after purification.

Sublimations were carried out in two ways.

(1) Vertical Tube Sublimation. Into a sublimator consisting of a 25 × 1.5 cm tube fitted with a vacuum connection and lined with a piece of Teflon sheeting (5 × 20 cm) was placed a sample of TTF or TCNQ. The tube was placed on an efficient vacuum line in a vertical position and evacuated and then the lower 2 cm was heated using an oil bath. After the sublimation was judged complete, the tube was cooled and filled with Ar. The Teflon sleeve was taken out and the sublimate was removed for subsequent treatment.

(2) Gradient Sublimation. A gradient sublimation apparatus was constructed using as a model McGhie's[18] design. Vacuum connections were made via an O-ring high-vacuum seal and a high-vacuum Teflon stopcock to further reduce changes of contamination. For a typical run the apparatus was lined with a Teflon sheet (10 × 60 cm) fitted with a Teflon cap to assure that no glass surface was available to the substrate. After being dried with a flame under vacuum, the tube was filled with Ar and the sample was introduced via a Teflon boat. The apparatus was evacuated and placed in a gradient heater[18] which had been preequilibrated to the appropriate conditions. When the sublimation was complete, the tube was cooled and filled with argon and the sample was removed as above. Only that portion of the sublimate present as large crystals was collected.

Liquid Chromatography. The instrument used for the HPLC was a Waters Associates ALC-201 chromatograph fitted with a U-6K septumless injector. The detection system consisted of a differential refractive index detector followed by a differential uv detector operated at 254 nm. Two 30 cm long 100-Å μ-styragel columns were used. The eluting solvent was tetrahydrofuran, the flow rate was 1 ml/min, and the temperature was ambient. HPLC traces at wavelengths other than 254 nm were obtained using a Schoeffel Model SF770 spectroflow monitor coupled with a Model GM770 monochromator.

Purification. Tetrathiafulvalene. The starting material was prepared by coupling dithiolium perchlorate using triethylamine,[35] and had been recrystallized once from hexane (mp 119.1–119.5). TTF-a was obtained after three crystallizations from ligroin. TTF-b was obtained after vertical tube sublimation of TTF-a at 75°. Finally TTF-c was obtained from TTF-b by sublimation over a gradient of 80° to 25°. In each case a small amount of the sample was removed and stored under Ar at −30° before proceeding to the next step.

Tetracyanoquinodimethane. The starting material was obtained from Aldrich[39] and had been sublimed once in a conventional manner prior to use (mp 294–296°). TCNQ-a was prepared by recrystallization three times from acetonitrile. TCNQ-b was prepared from TCNQ-a by vertical sublimation at 155°. TCNQ-c was prepared from TCNQ-b by sublimation over a gradient of 150° to 100°. A small amount of each sample was removed and stored under Ar at −30° before proceeding to the next step.

HPLC Analysis. Samples for HPLC analysis were prepared by placing a small amount of each in a weighed vial fitted with a serum cap. Sufficient THF was injected into the vials to give, in the case of TTF^0, a 100 mg/ml solution. In the case of $TCNQ^0$, approximately 500 μl was injected into each vial. The prepared samples were kept in the dark under an Ar atmosphere prior to use. The analyses were carried out by injecting 15 μl of the TTF^0 solution or 100 μl in the cases of $TCNQ^0$. Repetitive injections were made to check the reproducibility of the chromatographic traces.

Complex Formation and Conductivity Measurements. The complex of TTF^0 and $TCNQ^0$ was formed by diffusive crystallization of their solutions in an inverted U-tube crystallizer. The crystallizers were Teflon coated by the following procedure.[41] The U-tube, scrupulously clean, was evacuated on an efficient vacuum line. After thorough flame drying, approximately 2 Torr of CF_2CF_2, obtained from the pyrolysis of Teflon chips, was introduced into the tube. Approximately 25 Torr of di-*tert*-butyl perox-

ide was then added, and the tube was isolated from the vacuum line and heated at 150° until a faint opalescence was apparent. Success of the procedure was determined by placing a drop of distilled water in the tube. If any surface was wetted, the process was repeated.

For the "salty" crystals, ca. 0.1 mg of reagent grade NaCl was placed in each side of the crystallizer.

Conductivity measurements were performed using standard four-probe techniques.[30]

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Registry No.—TTF-TCNQ, 40210-84-2; tetrathiafulvalene, 31366-25-3; tetracyanoquinodimethane, 1518-16-7.

Supplementary Material Available Figures 1-5, the HPLC traces, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3544.

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Barriers to Amide Rotation in Piperidides and Related Systems. Unambiguous Assignments Using Carbon-13 Magnetic Resonance

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Variable-temperature carbon-13 magnetic resonance is used to investigate barriers to amide rotation in a series of benzoyl- and carboethoxy-substituted six-membered nitrogen heterocycles. Observed barriers are unambiguously assigned to amide rotation (as opposed to ring reversal or nitrogen inversion) because of the symmetry properties inherent in the carbon-13 technique. Barriers are compared with those obtained by variable-temperature proton magnetic resonance. The amide rotation barriers are relatively insensitive to changes in the nature of the ring substituent γ to the nitrogen, thereby supporting earlier results which suggested little or no 1,4-transannular interaction in six-membered heterocycles.

Application of carbon-13 magnetic resonance spectroscopy (^{13}C NMR)[2] to temperature-dependent phenomena (^{13}C DNMR) is still in its infancy.[2,3] It is the intention herein to use ^{13}C DNMR to provide unambiguous assignment of the nature of a dynamic process in a situation where several processes may occur. Variable-temperature proton magnetic resonance spectroscopy (^{1}H DNMR)[4] will be used to support[5] ^{13}C DNMR studies[6] in two examples.

Table I
Amide Rotation Barriers in Piperidides

Compd	Solvent	T_c, K	$\Delta G^{\ddagger}$, NMR method	Ref
1-Acetyl-4-methylpiperidine	$CDCl_3$	~330	16.4 α-^{1}H	Calcd by ref 9 from ref 8
	$CDCl_3$	~330	16.96 α-^{1}H	Calcd by ref 11a from ref 8
	$CDCl_3$	~343	17.07 α-^{1}H	Calcd here from ref 10
1-Acetyl-4-phenylpiperidine	Toluene-d_8	357	16.96 α-^{1}H	11a
1-Acetyl-2-methylpiperidine	Neat	288	15.3 CH_3-^{1}H	9
	Toluene-d_8	279	15.03 CH_3CO-^{1}H	11a
	Toluene-d_8	290.5	15.09 CH_3-^{1}H	11a
Acetamidomonosaccharides	C_2Cl_4	~360	17.4 α-^{1}H	9
	D_2O	303	16.1 α-^{1}H	9
	D_2O	278	15.7 CH_3CO-^{1}H	9
1-Acetylmorpholine	$CHFCl_2$	305	16.5 β-^{1}H	12
	$CHFCl_2$	315	16.6 α-^{1}H	12
1-Benzoyl-4-methylpiperidine	$CDCl_3$	~285	14.77 axial α-^{1}H	Calcd here from ref 10
	$CDCl_3$	~308	15.07 equat α-^{1}H	Calcd here from ref 10
1-Benzoyl-3-methylpiperidine	$CDCl_3$	~308	15.09 α-^{1}H	Calcd here from ref 10
1-Benzoyl-*cis*-2,6-dimethylpiperidine	$CDCl_3$	~253	12.30 α-^{1}H	Calcd here from ref 10
	CCl_4	~242	12.1 α-^{1}H	11b
	CH_3OH	247	12.5 α-CH_3-^{1}H	11b
	$CDCl_3$	~263	13.16 α-^{1}H	Here
1-Benzoylpiperidine (**1a**)	$CDCl_3$	292	14.82 α-^{1}H	Here
	$CDCl_3$	316	14.94 α-^{13}C	Here
	$CDCl_3$	289	14.75 β-^{13}C	Here
1-Benzoyl-4-piperidone (**1b**)	$CDCl_3$	273	13.97 α-^{1}H	Here
	$CDCl_3$	303[a]	14.32 α-^{13}C	Here
1-Benzoylmorpholine (**1c**)	$CHFCl_2$	276	14.4 β-^{1}H	12
	$CHFCl_2$	283	14.4 α-^{1}H	12
	$CDCl_3$	305	14.39 α-^{13}C	Here
1-Benzoyl-4-methylpiperazine (**1d**)	$CDCl_3$	310[a]	14.64 α-^{13}C	Here
	$CDCl_3$	284	14.65 β-^{13}C	Here
1-Carbomethoxypiperidine (**1e**)	$CHFCl_2$[b]	223[c]	11.88[c] α- and β-^{13}C	Here

[a] Not clearly defined coalescence because of overlapping signals; ±5°. [b] Containing a slight amount of CD_2Cl_2 for external lock. [c] Because of line broadening, the coalescence temperatures are somewhat indefinite here. The T_c's definitely lie between 215 and 235 K, corresponding to $\Delta G^{\ddagger}$ of 11.86 and 12.54, respectively, as outer limits.

Piperidides (**1**) were chosen for investigation since three dynamic processes are possible—amide rotation[4,7-12] (eq 1), ring reversal[4,12-14] (eq 2), and nitrogen inversion[4,14-16] (eq 3). Conformational isomers related by amide rotation (eq 1) should exhibit different ^{13}C NMR chemical shifts for the ring carbons α to the nitrogen, and possibly for the ring carbons β to the nitrogen, under conditions of slow interconversion.[3] Preliminary ^{13}C NMR studies[17] indicated that such conformational equilibria were occurring slowly at room temperature for **1a** and **1b**, but not slowly for **1e** and **1f**. Unless nitrogen inversion has a higher energy requirement than ring reversal, the latter (eq 2) will not be observable by ^{13}C DNMR. Similarly, ^{13}C DNMR will only be useful for nitrogen inversion barriers (eq 3) if ring reversal has a higher barrier. In summary, ^{13}C DNMR can be used to detect amide rotation in **1**, but cannot discriminate between ring reversal and nitrogen inversion.

Examination of the literature suggests that amide rotation should have the highest barrier of the three possible processes in **1**. While solvent, concentration, and method of data analysis are all found to be critical,[4,7,18,19] the overall results indicate free energies of activation at the appropriate coalescence temperatures[20] [$\Delta G^{\ddagger}(T_c)$] in the range of 15–16 kcal/mol for *N,N*-dimethylbenzamides and *N,N*-dimethylcarbamates using ^{1}H DNMR techniques. Available ^{1}H DNMR data in the 1-acylpiperidines[8-11] (Table I) suggest an amide rotation barrier around 16.5 kcal/mol for the 1-acetylpiperidines and a lower barrier for the 1-benzoylpiperidines (although actual barriers were not calculated for the latter compounds[10,21]). LeCam and Sandström's results[12] for partially deuterated acylmorpholines (Table I) support these conclusions and suggest that the nature of the ring substituent in a 1,4 relationship to the nitrogen may be of little significance.

Ring reversal barriers in piperidines, morpholines, and piperazines are observed with $\Delta G^{\ddagger}(T_c)$ of 10–13 kcal/mol,[4,12-14] and should be considerably lower (by 4–5 kcal/mol) in the 4-piperidones.[14,23] Nitrogen inversion barriers in acylpiperidines[15,16,24] should be below the range detectable by ^{1}H DNMR and ^{13}C DNMR studies. Nevertheless, as pointed out by Lambert,[15a] almost all of the ^{1}H DNMR studies of piperidines and piperidides are ambiguous as to the nature of the specific dynamic process being observed. However, as indicated previously, ^{13}C DNMR studies of piperidides (**1**) will provide unambiguous evidence whether a given dynamic process is amide rotation or not. In addition, because of the simplicity of the observed exchange process in the proton-decoupled spectra, the $\Delta G^{\ddagger}(T_c)$ should be obtained with reasonable accuracy.[20,22]

The results for compounds **1** are presented in Table I. In each instance, the benzamides (**1a–d**) exhibit amide rotation barriers of 14–15 kcal/mol under conditions of ^{1}H DNMR and ^{13}C DNMR analysis in $CDCl_3$ solutions. The ^{13}C DNMR method is especially useful for 1-benzoylmorpholine[26] (**1c**), a compound whose ^{1}H NMR spectrum appears as a slightly broadened singlet at both 60 and 100 MHz and is, therefore, not amenable to ^{1}H DNMR analysis without the preparation of deuterated derivatives.[12] On the other hand, ^{1}H DNMR is more useful than ^{13}C DNMR for 1-benzoyl-4-piperidone (**1b**), since overlapping signals in

Table II
^{13}C NMR Data in $CDCl_3$

Compd	Temp, K	α to N[a]	β to N[a]
1a[c]	249	48.5 (524), 42.8 (534)	26.3 (478), 25.5 (475)
	275	48.5 (370), 42.8 (323)	26.4 (443), 25.5 (418)
	287	48.4 (190), 42.9 (186)	26.3 (257), 25.6 (270)
	291	48.4 (152), 42.9 (148)	26.0 (124)
	299	48.4 (118), 42.8 (119)	26.0 (361)
	303	Broad d	26.0 (424)
	315	Coalescence	26.0 (611)
	317	Broad s	26.0 (702)
	321	Broad s	26.1 (822)
	329	45.8 (401)	26.1 (872)
1b[d]	248	46.1 (211), 40.6 (286)	41.3 (475)
	273	46.0 (220), 40.7 (346)	41.1 (516)
	299	Broad d	40.9 (521)
	306	Broad s	40.9 (582)
	311	Broad s	41.0 (712)
	322	43.8 (249)	41.1 (811)
	332	43.9 (237)	41.0 (732)
1c[e]	248	47.9 (383), 42.2 (401)	66.6 (760)
	273	48.0 (92), 42.3 (88)	66.6 (611)
	300	Broad d	66.6 (797)
	305	Coalescence	66.6 (654)
	309	Broad s	66.6 (717)
	333	45.4 (212)	66.7 (816)
1d[f]	248	47.3 (261), 41.6 (246)[b]	54.8 (264), 54.3 (256)[b]
	273	47.4 (165), 41.9 (173)	54.6 (280) d
	281	47.4 (227), 41.7 (247)	54.9 (292), 54.5 (306)
	286	47.3 (182), 41.8 (235)	54.7 (418) broad
	299	47.4 (50), 42.0 (58)	54.9 (412)
	305	Broad d	54.9 (810)
	310	Coalescence	54.9 (1036)
	323	Broad s	54.9 (475)
	331	44.8 (210)	54.8 (1050)
1e[g]	248	44.6 (921)	25.7 (889), 25.5 (879)
	299	44.8 (1893)	25.8 (1814)
1f[h]	248	42.8 (941)	41.1 (783)
	299	43.0 (981)	40.9 (876)
	303	43.0 (233)	41.0 (263)

[a] Relative peak intensities indicated in parentheses where relevant. [b] Signals α and β to the amide nitrogen, respectively, in the columns. [c] Amide CO, 169.8-170.0; γ to N, 24.4-24.5; Ar, 136.2-136.8, 129.2-129.3, 128.2-128.3, 126.6-126.8. [d] Amide CO, 170.3-170.6; ring CO, 206.0-206.9; Ar, 134.8-135.5, 129.9-130.0, 128.4-128.5, 126.8-127.0. [e] Amide CO, 170.0; Ar, 134.9-135.7, 129.6-129.7, 128.4-128.5, 126.9-127.0. [f] Amide CO, 169.5-169.9; NCH_3, 45.7-46.0; Ar, 135.2-136.1, 129.3-129.5; 128.1-128.3; 126.8-127.0. [g] Amide CO, 155.4; γ to N, 24.4-24.6; OCH_2, 60.9-61.1; CH_3, 14.7-14.8. [h] Amide CO, 155.1-155.3; ring CO, 207.2; OCH_2, 61.6-61.7; CH_3, 14.7.

the ^{13}C NMR spectrum interfere with accurate assignment of the coalescence temperature. Neither technique provides an advantage for 1-benzoyl-4-methylpiperazine (**1d**), since overlapping signals are a problem in both approaches.

The urethanes **1e** and **1f** behave somewhat strangely. No change is observed in the ^{13}C NMR spectrum of 1-carboethoxy-4-piperidone (**1f**) on cooling to 248 K in $CDCl_3$ or to 181 K in $CHFCl_2$, at which temperature precipitation begins to occur from each solvent. The behavior of 1-carboethoxypiperidine (**1e**) in $CDCl_3$ is somewhat puzzling. The signal attributed[17] to the ring carbons α to the nitrogen becomes less intense relative to the other signals on cooling, but does not obviously broaden or split. However, a small splitting (5 Hz) is observed at 248 K for the signal of the ring carbons β to the nitrogen. An accurate coalescence temperature could not be obtained but the $\Delta G^{\ddagger}$ at 270 K would be 14.47 kcal/mol. On switching to $CHFCl_2$ as the solvent, splittings of 4.9 Hz are observed for the ring carbons both α and β to the nitrogen. Because of problems caused by line broadenings, coalescence is estimated to occur at 223 K (outer limits are 215 and 235 K), corresponding to $\Delta G^{\ddagger}(T_c)$ of 11.88 kcal/mol (outer limits of 11.86 and 12.54 kcal/mol, respectively). This large solvent effect using quite similar solvents has no obvious explanation.

As previously noted,[7,10] the barriers to rotation are lower in the carbamates than in the benzamides, a result which differs from that observed in the acyclic analogues. The piperidide system differs from the acyclic case in that the six-membered ring minimizes rotation of the nitrogen end of the amide group, leaving C=O rotation as the major isomerization pathway. In addition, as pointed out by LeCam and Sandström,[12] repulsions between the *N*-acyl group and the vicinal equatorial hydrogens would cause more sp^3 character on nitrogen in the piperidides than in the acyclic analogues, leading to a lower barrier to amide rotation in the piperidides than in the *N,N*-dimethylamides, as observed in this work.

It is also apparent that the amide rotation barriers are almost insensitive to the nature of the substituent in the 4 position of the piperidine ring. All of these systems exist in chair conformations;[17] however, changing the atom in the 4 position would change the bond lengths, bond angles, and dihedral angles in the ring, as well as changing the electron

Table III
^{13}C NMR Data in $CHFCl_2$[a]

Compd	Temp, K	α to N[b]	β to N[b]
1e[c]	194	44.9 (280), 44.7 (320)	26.1 (392), 25.9 (348)
	211	45.1 (1726), 44.9 (1899)	26.2 (2070), 26.0 (2071)
	215	45.1 (116), 44.9 (120)	26.2 (144), 26.0 (140)
	223	Multiplicity?	Multiplicity?
	240	45.1 (553)	26.2 (591)
	253	45.3 (509)	26.2 (455)
1f[d]	182	43.1 (283)	41.4 (256)
	211	43.3 (462)	41.4 (443)

[a] Containing a trace of CD_2Cl_2 for field-frequency stabilization. [b] Signals in the ring α and β to the amide nitrogen, respectively. [c] Amide CO, 156.1-156.2; γ to N, 24.7-25.0; OCH_2, 61.6; CH_3, 14.8-14.9. [d] Amide CO, 155.4-155.6; OCH_2, 62.0; CH_3, 14.7-14.8.

distribution. The amide rotation barriers in **1** appear to be insensitive to such changes. The results, therefore, corroborate those determined earlier[17] in that no significant transannular electronic effects are observed between γ positions[28] in saturated six-membered heterocycles by ^{13}C NMR methods.

Experimental Section

All compounds were commercially available or prepared as previously reported[17] except for 1-benzoyl-4-methylpiperazine (**1d**), which was prepared from 1-methylpiperazine and benzoyl chloride by the method of Harfenist.[29]

^1H NMR spectra were recorded on a Varian A-60A spectrometer using deuteriochloroform or 1,1,2,2-tetrachloroethane solutions. Variable-temperature studies were performed with the aid of a Varian 6040 temperature controller. The temperature was calibrated by the peak separation of ethylene glycol,[30] and the instrument was retuned at each temperature by optimization of the aromatic singlet.

^{13}C NMR spectra were recorded on a JEOL PS-100 NMR spectrometer equipped with a JEOL JNM-PFT-100 pulse unit, a JEOL JEC-6 computer, and a JEOL VT-3C temperature controller. Field frequency stabilization was established by the deuterium signal of solvent deuteriochloroform or by the deuterium signal of a trace amount of dideuteriodichloromethane in solvent fluorodichloromethane (Matheson Genetron 21). The chemical shifts are expressed in parts per million relative to internal Me_4Si, and are believed to be accurate to 0.2 ppm. Relative peak intensities are indicated in parentheses after chemical shift values. Temperatures are accurate to ±2°. Results are shown in Tables II and III.

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Registry No.—**1a**, 776-75-0; **1b**, 24686-78-0; **1c**, 1468-28-6; **1d**, 7556-56-1; **1e**, 5325-94-0; **1f**, 29976-53-2.

References and Notes

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Conformational Equilibria in the 1-Amino-1-phenyl-2-propanol and 2-Amino-1-phenyl-1-propanol Systems. III. Nuclear Magnetic Resonance and Infrared Studies[1,2]

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Conformational preferences in the 1-(*N,N*-dialkylamino)-1-phenyl-2-propanol and 2-(*N,N*-dialkylamino)-1-phenyl-1-propanol series of amino alcohols and their benzoate esters have been studied by nuclear magnetic resonance and infrared spectroscopy. The threo amino alcohols reside almost exclusively in the intramolecularly hydrogen bonded form of the anti rotamers, while the erythro alcohols prefer the intramolecularly hydrogen bonded form of the gauche rotamers.

Conformational equilibria in the 2-amino-1,2-diphenylethanol system have been studied in detail by NMR[4] and infrared spectroscopy.[1] These earlier studies led to working hypotheses regarding the factors controlling conformation in that system. The present study was undertaken to test the applicability of these working hypotheses in related systems to further refine our understanding of the controlling factors. The compounds chosen for this study belong to the 1-amino-1-phenyl-2-propanol (I) and 2-amino-1-phenyl-1-propanol (II) systems.

The stereoisomeric *N,N*-dialkylamino alcohols in Table I were prepared by either nucleophilic scission of the C–O bond of *trans*-1-phenyl-1-propene oxide, hydroboration of the appropriate enamine, or reduction of the corresponding amino ketone. The well-documented trans nature of the epoxide opening established the configuration of the erythro[5] amino alcohols in these systems. In each case structure and homogeneity were established by NMR spectroscopy.

The vicinal coupling constants, J_{ab}, were conveniently obtained from the NMR spectra and reflect a weighted mean dependent on the relative populations of the three possible staggered rotamers.[6] This study, as the earlier one, is concerned with identifying trends and evaluating their conformational implications. The calculations of approximate anti to gauche rotamer ratios using the previously suggested working values, J_{anti} = 10.3 and J_{gauche} = 2.6 Hz,[4] are consistent with the objective.

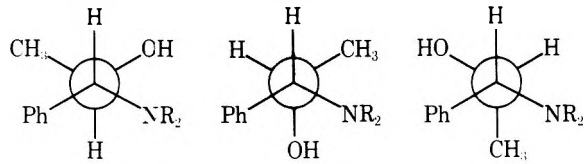
It is apparent from the values of J_{ab} (Table I) that the threo amino alcohols **1** and **3** highly populate the anti rotamers tA and tA′ (Charts I and II), respectively. Intramolecular hydrogen bonding (OH···N) undoubtedly contributes to the stability of these rotamers, already favored on steric grounds. The intrinsic stablizing influence of the division of the four bulkiest groups into two pairs separated from one another by hydrogen atoms has been noted previously in the 2-amino-1,2-diphenylethanol system.[4]

At high dilution in carbon tetrachloride, *only* hydrogen bonded OH stretching bands appear in the infrared spectra of threo piperidino alcohols **1a** and **3a** (Table II); therefore, the highly populated anti rotamers tA and tA′, respectively, exist completely in the intramolecularly hydrogen bonded form. In addition to the strong intramolecular OH···N absorption bands, the corresponding threo pyrrolidino alcohols **1b** and **3b** exhibit weak absorptions at 3590 and 3621 cm^{-1}, respectively. The band at 3590 cm^{-1} (**1b**) assigned to intramolecular OH···π (phenyl), is consistent with a small population of gauche rotamers. Similarly, the appearance of unassociated OH stretching in the spectrum of **3b** is also compatible with the presence of gauche rotamers. These conclusions are consistent with the slightly lower vicinal coupling constants observed for the threo pyrrolidino alcohols, and suggest that the subtle differences in the steric requirements of the piperidine and pyrrolidine groups noted in the more encumbered 2-amino-1,2-diphenylethanol system[4] manifest themselves here as well.

The lower J_{ab} values (<5.1 Hz) observed in the erythro

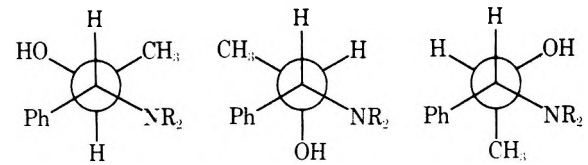
Chart I
Rotamers in the 1-Amino-1-phenyl-2-propanol System (I)

Threo



tA tB tC

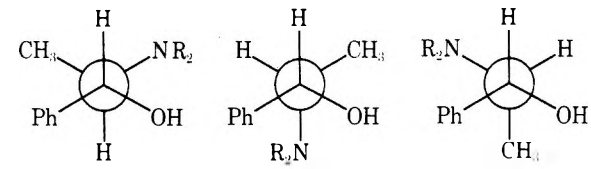
Erythro



eA eB eC

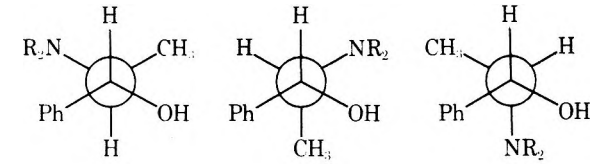
Chart II
Rotamers in the 2-Amino-1-phenyl-1-propanol System (II)

Threo



tA′ tB′ tC′

Erythro



eA′ eB′ eC′

Table I
Nuclear Magnetic Resonance Data[a]

Compd	Chemical shift[b] H_a thr[d]	H_a er[e]	H_b thr	H_b er	CH_3 thr	CH_3 er	J_{ab}[c] thr	J_{ab}[c] er	[anti]/[gauche][d] thr	[anti]/[gauche][d] er
				$C_6H_5—CH_a(X)—CH_b(OR)—CH_3$						
				I						
Amino Alcohols										
1, R = H										
a, X = 1-piperidino	186	183	245	260	55	51	10.2	5.1	*f*	0.47
b, X = 1-pyrrolidino	207	179	248	255	49	49	9.8	3.2	*f*	0.09
Esters										
2, R = benzoyl										
a, X = 1-piperidino	204	211	342	344	62	85	8.8	7.9	4.3	2.2
b, X = 1-pyrrolidino	209	189	337	327	70	65	5.3	3.2	0.54	0.09
				$C_6H_5—CH_a(OR)—CH_b(X)—CH_3$						
				II						
Amino Alcohols										
3, R = H										
a, X = 1-piperidino	253	285	*g*	*g*	46	48	9.9	4.1	*f*	0.23
b, X = 1-pyrrolidino	247	301	*g*	*g*	43	48	9.1	3.2	5.3	0.09
Esters										
4, R = benzoyl										
a, X = 1-piperidino	360	366	180	179	53	68	9.0	5.9	4.9	0.75
b, X = 1-pyrrolidino	268	378	185	*g*	54	68	6.1	3.7[h]	0.82	0.16

[a] Spectra were determined at room temperature on a Varian Model A-60A (60 MHz) spectrometer in CCl_4 or $CDCl_3$ solution at a concentration of ca. 15%. [b] In hertz relative to internal tetramethylsilane. [c] An average of ten runs. Values are accurate to an estimated ±0.1 Hz. [d] Ratio of the population of rotamer A or A′ to the gauche rotamers. [e] thr = *dl*-threo; er = *dl*-erythro. [f] >90% anti. [g] Signal overlaps the NCH_2 signal. [h] Spectrum was determined on 10 mg of sample and the value is accurate to an estimated ±0.2 Hz.

Table II
Infrared Spectral Properties of Amino Alcohols[a]

Compd	ν[b] OH	OH···π	OH···N[d]	$\Delta\nu$, cm^{-1}[c] OH···π	OH···N
threo-**1a**			3415		206
1b		3590 (w)	3425	31	196
3a			3355		266
3b	3621 (w)		3385		236
erythro-**1a**		3600 (s)	3475	21	156
1b		3595 (w)	3515	31	106
3a	3621 (m)		3425		196
3b	3621 (w)		3480		141

[a] All spectra were determined in carbon tetrachloride solution (<0.005 *M*). [b] s = strong; m = medium; w = weak. Probable errors: ±1.5 cm^{-1} for unassociated OH; ±2.5 cm^{-1} for bonded OH absorptions. [c] 3621 cm^{-1} for the free OH stretch is used in calculating these values. [d] Strong, broad absorptions in all cases.

amino alcohols **1** and **3** reflect the dominance of gauche rotamers. In the erythro series, in contrast to the threo amino alcohols, intramolecular hydrogen bonding and steric factors act as opposing forces, with the former effect dominating. This observation serves to underscore the profound role of intramolecular hydrogen bonding in the control of conformation in poor hydrogen acceptor solvents. As in the 2-amino-1,2-diphenylethanol system, the conformational bias toward gauche rotamers is greater in the pyrrolidine than in the piperidine compounds. Space-filling CPK molecular models suggest that this phenomenon has a common origin in the systems studied.[4]

At high dilution the infrared spectra of the erythro amino alcohols **1a** and **1b** confirm the importance of intramolecular hydrogen bonding. In addition to the presence of strong OH···N stretching bands, absorption characteristic of OH···π (phenyl) appears in the spectra of both compounds. The OH···π peak of **1a** is more intense than the OH···N band, but that of **1b** is less intense than the OH···N band. This is consistent with the conclusion, derived on the basis of NMR, that the substitution of pyrrolidine for piperidine in **1** leads to a decrease in the population of the anti rotamer tA, believed responsible for intramolecular OH···π.

The high-dilution spectra of erythro amino alcohols **3a** and **3b** exhibit absorption characteristic of intramolecular OH···N and unassociated OH. The fact that the unassociated OH absorption peak is weaker in **3b** than in **3a** again implicates the greater conformational bias of the pyrrolidine compound for the gauche rotamers.

The reported vicinal coupling constants of the benzoate esters (Table I) permit an analysis of the factors controlling conformation in the absence of the superimposed influence of intramolecular hydrogen bonding. In contrast to the corresponding amino alcohols, both threo and erythro benzoates **2a** heavily populate the anti rotamers tA and eA, respectively, most likely as a result of the stabilization conferred by division of the four bulky groups into two groups separated by hydrogen atoms. However, in the corresponding pyrrolidino esters **2b**, this control is apparently offset by other factors, as gauche rotamers are preferred. An examination of space-filling CPK models suggests a possible explanation of this discrepancy.

Molecular models of the erythro benzoates **2a** and **2b**

Table III
Effect of Substituents on the Coupling Constant in $PhCH_a(OR)CH_b(X)R'$[a]

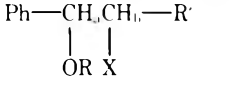
Entry	X	R'	R	$J_{erythro}$[b]	J_{threo}
1	1-Piperidino	Ph	Ms[c]	9.6	10.4
2	1-Piperidino	Ph	Ac	8.7	10.7
3	1-Piperidino	Ph	CH_3	7.7	9.2
4	1-(*N*-Methylpiperidino)	Ph	H	2.9	10.7
5	1-(*N*-Methylpiperidino)	Ph	CH_3	2.2	10.4
6	1-Piperidino	CH_3	Bz	5.9	9.0

[a] Data are taken from ref 4 and Table I of this paper. [b] J_{ab} in hertz. [c] Ms = mesitoyl.

suggest, as in the cases of the erythro pyrrolidino esters in the 2-amino-1,2-diphenylethanol system,[4] that the dominance of the gauche rotamers in the pyrrolidino compound **2b** is the result of unfavorable steric interactions between the pseudo-axial hydrogens at positions 2 and 5 of the pyrrolidine ring and the carbon atoms of phenyl in the anti rotamer eA. In contrast, in the gauche rotamer eB, the most favorable orientation of the amino group about the C–N bond leads to greater steric interaction in the piperidine compound, while the pyrrolidine moiety is relatively strain-free in this conformation.[7] Similar, but apparently not as pronounced, steric influences account for the more highly populated gauche rotamers in threo ester **2b**.

As expected on steric grounds, the NMR data for the threo piperidino ester **4a** reveals a heavily populated anti rotamer tA′. In the erythro piperidino ester **4a** the concentration of the gauche rotamers slightly exceeds that of the anti rotamer. In the absence of intramolecular hydrogen bonding this is unexpected, since in rotamer eA′, just as in tA, the four bulky groups are divided into two pairs separated by hydrogen atoms. This contrasting behavior is explicable in the disposition of the two bulkiest vicinal groups, phenyl and amine; anti in tA′ and gauche in eA′. This unfavorable latter interaction is relieved in eB′, but not in eC′, which is probably negligibly populated.

If the above analysis is valid, conformational equilibria should be quite sensitive to the steric requirements of OR, X, and R′ in *erythro*-**5**, but not in *threo*-**5**. The compounds



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listed in Table III demonstrate that this is indeed the case. In the erythro series (a) a decrease in the steric requirement of the ester group favors rotamer eB′ (entries 1–3); (b) an increase in the size of the amino group increases the proportion of gauche rotamer eB′ (entries 3 and 5); and (c) an increase in the size of R′ favors rotamer eA′ (entries 1, 2, and 6).

The gauche rotamers of the pyrrolidino benzoates (*threo*- and *erythro*-**4b**) are more highly populated than in the corresponding piperidino benzoates **4a**. Inspection of molecular models suggests that in the anti rotamers of ester **4**, the methyl and amino groups occupy the same relative orientation toward one another as the phenyl and amino groups in the tA and eA rotamers of esters **2**. Consequently, the less favorable methyl–amine interaction in the pyrrolidino compounds should destabilize the anti rotamers. Models suggest that the effect should be less pronounced than in ester series **2**, where the more severe amine–phenyl interactions operate. This view is supported by the data, since the anti/gauche ratio for both *threo*- and *erythro*-**4b** is greater than that for *erythro*-**2b**.

Table IV
Properties of the Amino Alcohols and Their Benzoate Esters[a]

Compd	% yield	Mp, °C, or eluent
threo-**1a**	71	95.5–96.5
erythro-**1a**	63	82–83
threo-**1b**	20	81–82
erythro-**1b**	69	82.5–83.5
threo-**2a**	66	Hexane
erythro-**2a**	68	Hexane
threo-**2b**	78	3% EtOAc
erythro-**2b**	80	10% EtOAc
threo-**3a**	39	55–56
erythro-**3a**	1	84–85
threo-**3b**	12	60–61
erythro-**3b**	6	70–71
threo-**4a**	75	10% EtOAc
erythro-**4a**	34	3% EtOAc
threo-**4b**	82	4% EtOAc
erythro-**4b**	34	7% EtOAc

[a] Satisfactory analytical data were obtained for all compounds listed in the table.

Experimental Section

All melting points are uncorrected and were determined on a Mel-Temp melting point apparatus. The nuclear magnetic resonance spectra were recorded on a Varian Associates A-60A spectrometer using tetramethylsilane as an internal standard. Infrared spectra were determined in potassium bromide or as a thin film on a Perkin-Elmer 137 spectrophotometer. High-dilution infrared studies were carried out on a Beckman IR-12 spectrophotometer using previously described techniques.[1] The microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind.

Ring Opening of *trans*-1-Phenyl-1-propene Oxide with Pyrrolidine. A solution of 2.0 g (0.015 mol) of *trans*-1-phenyl-1-propene oxide and pyrrolidine (5 ml) was heated at the reflux temperature for 41 hr. The solvent was removed in vacuo and the residue poured into water (40 ml). The material which solidified was isolated by filtration. Fractional crystallization from hexane afforded the crystalline, isomeric amino alcohols: 2.12 g (69%) of *dl-erythro*-1-(1-pyrrolidino)-1-phenyl-2-propanol (**1b**) and 0.184 g (6%) of *dl-erythro*-2-(1-pyrrolidino)-1-phenyl-1-propanol (**3b**).

Ring Opening of *trans*-1-Phenyl-1-propene Oxide with Piperidine. Using the above procedure with a reaction time of 54 hr, the following amino alcohols were prepared: *dl-erythro*-1-(1-piperidino)-1-phenyl-2-propanol (**1a**) in 50% yield and *dl-erythro*-2-(1-piperidino)-1-phenyl-2-propanol (**3a**) in 1% yield.

1-Phenyl-2-(1-piperidino)-1-propene. Using the method of Munk and Kim,[8] 16.0 g (0.12 mol) of phenylacetone and 34.5 g (0.41 mol) of piperidine afforded 10.9 g (45%) of the enamine: mp 40–42°C; NMR (CCl_4) δ 7.1 (m, 5, Ph), 5.48 (s, 1, CH=), 2.9 (m, 4, CH_2N), 1.89 (s, 3, CH_3), and 1.5 (m, 6, CH_2). Short-path distillation followed by crystallization afforded the analytical sample.

Anal. Calcd for $C_{14}H_{19}N$: C, 83.51; H, 9.53. Found: C, 82.88; H, 9.80.

Hydration of 1-Phenyl-2-(1-piperidino)-1-propene. To a solution of 0.507 g (0.013 mol) of sodium borohydride and 2.057 g (0.010 mol) of 1-phenyl-2-(1-piperidino)-1-propene in dry THF (25 ml) was added dropwise 1.59 g (0.014 mol) of boron trifluoride etherate in THF (7 ml). The solution was heated at the reflux temperature for 1 hr and cooled in an ice bath and water (10 ml) was added followed by 6 ml of sodium hydroxide (1 *N*) and 30% hydrogen peroxide (4 ml). The solution was heated at the reflux temperature for 4 hr, poured into a solution of saturated sodium chloride (50 ml), and extracted with three 50-ml portions of ether. The combined ether extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Crystallization of the residue afforded 0.894 g (39%) of *dl-threo* **3a**.

Hydration of 1-Phenyl-1-(1-piperidino)-1-propene. The above procedure afforded *dl-threo* **1a** in 71% yield.

Hydration of 1-Phenyl-1-(1-pyrrolidino)-1-propene. To a solution of 0.544 g (0.014 mol) of sodium borohydride in dry THF (15 ml) was added dropwise 1.5 ml (0.012 mol) of boron trifluoride

etherate in THF (10 ml). The solution was stirred at room temperature for 2 hr and cooled in an ice bath and 0.953 g (0.053 mol) of 1-phenyl-1-(1-pyrrolidino)-1-propene in THF (10 ml) was added dropwise. The solution was stirred at room temperature for 5 hr and cooled and a solution of 1 *N* sodium hydroxide (4 ml) was added simultaneously with a solution of 30% hydrogen peroxide (3 ml). The solution was stirred for 12 hr, poured into a saturated sodium chloride solution, and extracted with three 50-ml portions of 1 *M* hydrochloric acid and the combined acid extracts were made basic by the addition of sodium hydroxide pellets. The basic solution was extracted with ether and dried ($MgSO_4$) and the solvent was removed in vacuo. Crystallization of the residue from hexane afforded 0.207 g (20%) of *dl-threo*-**1b**.

Reduction of 2-(1-pyrrolidino)-1-phenyl-1-propanone. The sodium borohydride reduction of the amino ketone in methanol afforded a mixture of *dl-threo*- and *dl-erythro*-**3b** in high yields. The *dl*-threo and *dl*-erythro amino alcohols (Table IV) could be isolated in low yields from the mixture by fractional crystallization from hexane.

Benzoate Esters 2 and 4. A solution of benzoic anhydride (0.01 mol), pyridine (2 ml), and amino alcohol (ca. 0.002 mol) was heated on a steam bath for 2–24 hr. The solution was poured into a mixture of saturated sodium bicarbonate (50 ml) and ether (25 ml). The solution was magnetically stirred for ca. 1 hr, extracted with three 50-ml portions of ether, and dried ($MgSO_4$) and the solvent was removed in vacuo. The oily benzoates were purified by chromatography over alumina.

Acknowledgments. We are pleased to acknowledge the partial support of the Research Corporation for a Frederick Gardner Cottrell grant and a grant for partial support from the University of Northern Colorado Faculty Research and Publications Committee. We are indebted to Colorado State University for the use of their Beckman IR-12 spectrophotometer for the infrared studies.

Registry No.—*threo*-**1a**, 56571-81-4; *erythro*-**1a**, 56571-82-5; *threo*-**1b**, 56571-83-6; *erythro*-**1b**, 56571-84-7; *threo*-**2a**, 56571-85-8; *erythro*-**2a**, 56571-86-9; *threo*-**2b**, 56571-87-0; *erythro*-**2b**, 56571-88-1; *threo*-**3a**, 56571-89-2; *erythro*-**3a**, 56571-90-5; *threo*-**3b**, 56571-91-6; *erythro*-**3b**, 56571-92-7; *threo*-**4a**, 56571-93-8; *erythro*-**4a**, 56571-94-9; *threo*-**4b**, 56571-95-0; *erythro*-**4b**, 56571-96-1; *trans*-1-phenyl-1-propene oxide, 23355-97-7; pyrrolidine, 123-75-1; piperidine, 110-89-4; 1-phenyl-2-(1-piperidino)-1-propene, 56571-97-2; 1-phenyl-1-(1-piperidino)-1-propene, 25076-80-6; 1-phenyl-1-(1-pyrrolidino)-1-propene, 31889-28-8; 2-(1-pyrrolidino)-1-phenyl-1-propanone, 19134-50-0.

References and Notes

(1) For previous paper in this series see M. K. Meilahn and M. E. Munk, *J. Org. Chem.*, **34**, 1440 (1969).
(2) M. K. Meilahn, C. N. Statham, J. L. McManaman, and M. E. Munk, Abstracts, First Rocky Mountain Regional Meeting of the American Chemical Society, Fort Collins, Colo., June 1972, p 39.
(3) Taken in large part from the senior research project of C. N. Statham, University of Northern Colorado, 1972.
(4) M. E. Munk, M. K. Meilahn, and P. Franklin, *J. Org. Chem.*, **33**, 3480 (1968).
(5) The term threo and erythro as used in this paper indicate *dl*-threo and *dl*-erythro.
(6) Footnote 7, ref 4, defines the term "rotamer" as used in this paper.
(7) These interactions have been previously discussed and Figures 1 and 2 in ref 4 show these interactions.
(8) M. E. Munk and Y. K. Kim, *J. Am. Chem. Soc.*, **86**, 2213 (1964).

Reactions of Amines. XVIII. The Oxidative Rearrangement of Amides with Lead Tetraacetate[1,2]

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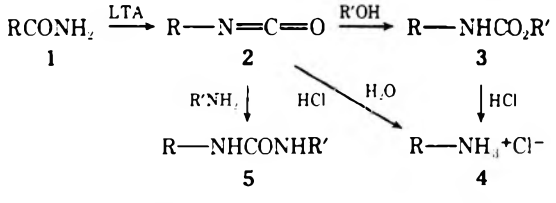
Fourteen primary amides of varying structures were converted to isocyanates by treatment with lead tetraacetate. Generally the isocyanates were not isolated but were converted to carbamates by using a reaction solvent such as benzyl or, preferably, *tert*-butyl alcohol. Alternatively, the reaction was run in dimethylformamide and the isocyanate was converted to the *unsym*-urea by treatment with *tert*-butylamine. The carbamates could be easily cleaved to the corresponding amines (as the hydrochlorides) by treatment with HCl in alcohol, ether, or acetic acid. The rearrangement was shown to proceed with retention of configuration about the migrating carbon atom.

Some years ago we reported[3] the oxidative rearrangement of *N*-aminooxindole to 3-cinnolinol using lead tetraacetate (LTA) as the oxidant. Because this rearrangement appeared to resemble in some aspects the classical Hofmann rearrangement of *N*-halo amides, we next showed[4] that the rearrangement of *N*-aminooxindole could be carried out via the *N*-chloro derivative. These observations led logically to the conclusion and subsequent demonstration[5] that a Hofmann-like oxidative rearrangement of amides (**1**) could be brought about with LTA. By a somewhat different



pattern of reasoning Beckwith[6-9] and his coworkers came independently to the same conclusion. They have described in some detail their investigations of this quite general and immensely practical version of the Hofmann rearrangement.[10]

Even earlier Tscherniac[11] had noted an apparent similarity in the behavior of iodosobenzene and the hypohalites and reported the first example known to us of a Hofmann-like rearrangement using a two-electron oxidant other than positive halogen. This communication describes some of our efforts to explore the scope and limitations of the rearrangement as a practical synthetic method.

As was reported in the preliminary communication,[5] the rearrangement can be run very rapidly in dimethylformamide solution in such as a way as to permit isolation of the intermediate isocyanate (**2**) or to proceed directly via acid hydrolysis to the amine hydrochloride (**4**). However, for many amides isolation of **2** is tedious, if not difficult,[6] and acid-catalyzed hydrolysis of **2** without isolation may result in lower yields of **4** than may be obtained by the less direct routes described here. Nevertheless, the use of dimethylformamide is very advantageous in those rearrangements involving a subsequent reaction with an amine to form a urea[5] (**5**) or a subsequent cyclization of the isocyanate

Table I
Yields of Carbamates and Amine Hydrochloride from the Reactions

$$RCONH_2 + LTA + PhCH_2OH \xrightarrow{Et_3N} RNHCO_2CHPh \xrightarrow[HCl]{HCl} RNH_3Cl$$

Registry no.	R	Scale,[a] mol	Solvent	Temp,[a] °C	Yield, %,[b] carbamate	Yield, %,[b] amine hydrochloride
56730-65-3	Cyclobutyl	0.01	DMF		66	
7137-58-6	Cyclohexyl	0.01	MeCN	40, 80	76	
	Cyclohexyl	0.01	DMF[c]	25, 120	67	
	Cyclohexyl	0.03	DMF	25, 120	72[d]	63[h]
39836-97-4	Benzyl	0.01	DMF	0, 60	65[e]	54[i]
	Benzyl	0.01	DMF[c]	25, 68	64	
	Benzyl	0.01	MeCN[c]	60, 60	38	
3422-02-4	Phenyl	0.01	DMF[c,d]	25, 75	33[f]	

[a] First temperature given is that of oxidation step; second, that of conversion of isocyanate to carbamate. [b] Based on amide. [c] Benzyl alcohol added at start of reaction. [d] Et_3N not used. [e] Mp 95–95.5° (lit.[52] mp 90–91°). [f] Mp 62–63° (lit.[53] mp 64°). [g] Mp 77° (lit.[53] mp 78°). [h] Mp 205–207° (lit.[42] mp 203–204°). [i] Mp 245–247° (lit.[43] mp 246–250°).

group with some other functional group in the same molecule.[9] Dimethylformamide appears to serve both as a good solvent and as a catalyst for the oxidative rearrangement.[5]

In our experiments the rearrangement of amides proceeded slowly in pure benzene, chloroform, and methylene chloride, although the reaction in these solvents could be accelerated by addition of alcohols, triethylamine, or pyridine. Beckwith and coworkers have used benzene–aliphatic acid and benzene–alcohol mixtures successfully in preparing acylamines[7] and carbamates,[8] respectively. The former solvent–reactant mixture gave a relatively slow reaction and the latter a relatively fast reaction.[10] We found that the rearrangement also took place slowly in pure acetic acid. This solvent has been used (usually with benzene) in the preparation of acylamines,[7] but again the times given for disappearance of LTA are quite long compared with those in dimethylformamide[5] or benzene–alcohol mixtures.[8]

Although the use of alcohols as solvent–reactants has certain easily demonstrated disadvantages, we have chosen to concentrate our attention on their use for two reasons: (1) the rearrangement reaction is or can be made quite rapid in the alcohols, and (2) the resultant carbamates (**3**) afford excellent intermediates for clean, high-yield conversion to the corresponding amines or to other useful products. The principal disadvantages in the use of alcohols as solvent–reactants are the preferential oxidation of the alcohol (rather than the amide) in some instances,[5,8] and the difficulty that is sometimes encountered in cleaving primary alkyl carbamates.[12] Thus, for example, LTA reacts with methanol at the reflux temperature at approximately the same rate (or faster) that it reacts with some amides. Acott, Beckwith, and Hassanali[8] have used primary and secondary alcohols successfully with a number of amides and benzene–alcohol mixtures with those for which the alcohol oxidation appeared to be faster than the oxidative rearrangement. They did not obtain satisfactory results with *tert*-butyl alcohol, possibly because their reactions conditions were not optimized. Although simple alkyl carbamates are not readily hydrolyzed in alkaline solutions,[12] acid-catalyzed hydrolysis is generally very satisfactory. Therefore, we have concentrated our attention on alcohols that yield very easily cleaved carbamates, benzyl alcohol and, especially, *tert*-butyl alcohol.

The benzyl carbamates were prepared by oxidative rearrangement of the amide in DMF or acetonitrile solution with LTA, followed by reaction with benzyl alcohol (catalyzed by triethylamine). The carbamates could be hydrolyzed with hydrogen chloride in acetic acid. The results are given in Table I. The reaction was satisfactory with aliphatic amides on a small scale but less so on a large scale, probably because of difficulties associated with the isolation of the product. Benzamide gave unsatisfactory results in this system. Because the concurrent development of the use of *tert*-butyl alcohol appeared to be more promising, the use of benzyl alcohol was not studied further.

The procedure that appears to us to be the simplest and most effective means to date for obtaining amine hydrochlorides from simple amides via LTA oxidation consists of the preparation of the *tert*-butyl carbamates (**3**, R′ = *t*-Bu) followed by cleavage of the carbamate to the corresponding amine hydrochloride by treatment with anhydrous hydrogen chloride. The *tert*-butyl carbamates were obtained in good to excellent yields by treating the appropriate amide (**1**) in anhydrous *tert*-butyl alcohol with LTA at the reflux temperature.[13] This procedure has the advantage of giving a stable, solid intermediate product (**3**) that can be purified by recrystallization or chromatography and then readily and quickly converted to the amine hydrochloride when required.

When cyclohexanecarboxamide was treated with LTA in refluxing *tert*-butyl alcohol for 3 hr, the yield of *tert*-butyl *N*-cyclohexylcarbamate was 64%, but, when phenylacetamide was treated in the same way for only 1 hr, a yield of 83% of *tert*-butyl *N*-benzylcarbamate was obtained. The slower of the two successive reactions, oxidative rearrangement of the amide and addition of the alcohol to the isocyanate, is almost certainly the alcohol–isocyanate reaction in all the examples studied. However, there are a number of catalysts which may be used to accelerate this reaction. Although we have found no study of the catalysis of the *tert*-butyl alcohol–isocyanate reaction, a comparison of the effectiveness of various catalysts for the *n*-butyl alcohol–phenyl isocyanate reaction has been reported.[15,16] The following order of increasing catalyst effectiveness was determined by comparing reaction rates: triethylamine ≪ stannic chloride < di-*n*-butyltin dilaurate.[17] Use of any of these catalysts raised the yield of *tert*-butyl *N*-cyclohexylcarbamate to 80–87%, probably by accelerating the alcohol–isocyanate reaction and minimizing, thereby, the competitive dehydration reaction.[18] The yields of *tert*-butyl carbamates from aromatic carboxamides were not improved by these catalysts, probably because the aryl isocyanates react with *tert*-butyl alcohol almost as rapidly as they are formed. The lower yields of *tert*-butyl carbanilates are attributed to side reactions other than those brought about alcohol dehydration.

The oxidation of aliphatic primary amides with LTA in anhydrous *tert*-butyl alcohol proceeded quite selectively at the amide function except for cinnamamide and *trans*-2-

Table II
Yields of *tert*-Butyl Carbamates and Amine Hydrochlorides Obtained from the Reactions

$$RCONH_2 + LTA + t\text{-BuOH} \xrightarrow{\text{catalyst}} RNHCO_2\text{-}t\text{-Bu} \quad (1)$$

$$RNHCO_2\text{-}t\text{-Bu} + HCl \longrightarrow RNH_3Cl \quad (2)$$

Registry no.	R	Scale, mol	Catalyst	Reaction time for carbamate formation, hr[n]	Yield,[a] *tert*-butyl carbamate, %	Yield,[a] amine hydrochloride, %
1503-98-6	Cyclobutyl	0.277	Et_3N	10.0	87.2	81.5[n]
	Cyclobutyl	0.006	*d*	3.0	*b*	81.9
	Cyclobutyl	0.03	*m*		72.6	
1122-56-1	Cyclohexyl	0.01	None	3.0	63.5	
	Cyclohexyl	0.01	Et_3N[i]	1.3	79.9[f]	
	Cyclohexyl	0.01	Et_3N[i]	1.5	79.4[f,h]	
	Cyclohexyl	0.01	Et_3N	3.0	86.8	
	Cyclohexyl	0.10	Et_3N	9.0	77.6	72.8
	Cyclohexyl	0.01	$SnCl_4$	1.0	84.5	
	Cyclohexyl	0.01	$SnCl_4$	1.5	83.4[f]	
	Cyclohexyl	0.01	*d*	3.0	80.4	
	Cyclohexyl	0.03	*m*		30	
1503-87-3	Cyclohexylmethyl	0.10	Et_3N	10.0	77.9	
56760-76-0	1,2,2-Trimethyl-3-carbomethoxy-1-cyclopentyl	0.0086	$SnCl_4$	19.0	87.1	78.3
	1,2,2-Trimethyl-3-carbomethoxy-1-cyclopentyl	2.13	*d*	13.0	*b*	80.7
103-81-1	Benzyl	0.01	None	0.8	88.8[f]	
	Benzyl	0.10	None	1.0	83.5	
	Benzyl	0.10	*d*	3.0	*b*	90.0
	Benzyl	0.10	Et_3N	10.0	88.7	86.1
102-93-2	2-Phenethyl	0.1	Et_3N	10.0	83.3	74.6
939-88-8	*trans*-2-Phenylcyclopropyl	0.01	None	2.5	12.9[l]	
98-92-0	3-Pyridyl	0.01	None	1.5	78.9[e]	
	3-Pyridyl	0.01	None	2.0	*e*	73.0[c]
	3-Pyridyl	0.01	Et_3N	7.0	61.7	
55-21-0	Phenyl	0.01	None	0.5	76.2	
	Phenyl	0.1	None	1.0	*e*	76.8
	Phenyl	0.1	None	1.5	75.2[g]	
	Phenyl	0.3	None	2.0	*e*	82.7[k]
	Phenyl	0.05	None	2.5	89.1[j]	
	Phenyl	0.01	Et_3N	10.5	68.6	
	Phenyl	0.1	*d*	3.0	*b*	75.5
	Phenyl	0.03	*m*		75.5	75.5
619-56-7	4-Chlorophenyl	0.01	None	1.0	70.6	
	4-Chlorophenyl	0.01	$SnCl_4$	3.0	68.3	
	4-Chlorophenyl	0.03	*d*	10.0	*b*	71.5
	4-Chlorophenyl	0.03	*m*		70.5	
619-80-7	4-Nitrophenyl	0.01	None	0.5	73.1	
	4-Nitrophenyl	0.01	None	1.0	78.5	
	4-Nitrophenyl	0.01	None	3.0	78.9	
	4-Nitrophenyl	0.01	$SnCl_4$	24.0	77.7	75.4[c]
	4-Nitrophenyl	0.03	*m*		35.0	
2008-58-4	2,6-Dichlorophenyl	0.03	None	1.0	*b*	74.8[c]
	2,6-Dichlorophenyl	0.01	$SnCl_4$	10.0	81.6	
4380-68-1	2,4,6-Trimethylphenyl	0.01	$SnCl_4$	9.0	78.3	

[a] Yields are based on the amide. [b] The carbamate was not isolated. [c] "Free" amine. [d] Di-*n*-butyltin dilaurate. [e] The carbamate was purified with activated alumina. [f] The carbamate was precipitated by adding *tert*-butyl alcohol solution to ice water. [g] The carbamate was precipitated by adding acetone solution to ice water. [h] The LTA was added as a 10% acetic acid paste. [i] Added after 15 min at reflux. [j] A fivefold excess of amide was used; yield based on LTA. [k] A threefold excess of amide was used; yield based on LTA. [l] 37% of starting amide recovered. [m] Et_3N used as oxidative rearrangement catalyst (see Experimental Section). [n] Optimum reaction times were not determined; some times are greater than necessary to obtain the maximum yield.

phenylcyclopropanecarboxamide, which suffered some attack at the double bond and three-ring, respectively. Apparently isolated olefinic bonds are not oxidized under similar conditions.[8] The yields of *tert*-butyl carbamate were usually in the range 80–90%. Aromatic amides also gave good yields (60–80%) of *tert*-butyl carbanilates despite the formation of colored by-products, the nature of which was not determined. Our results are summarized in Table II.

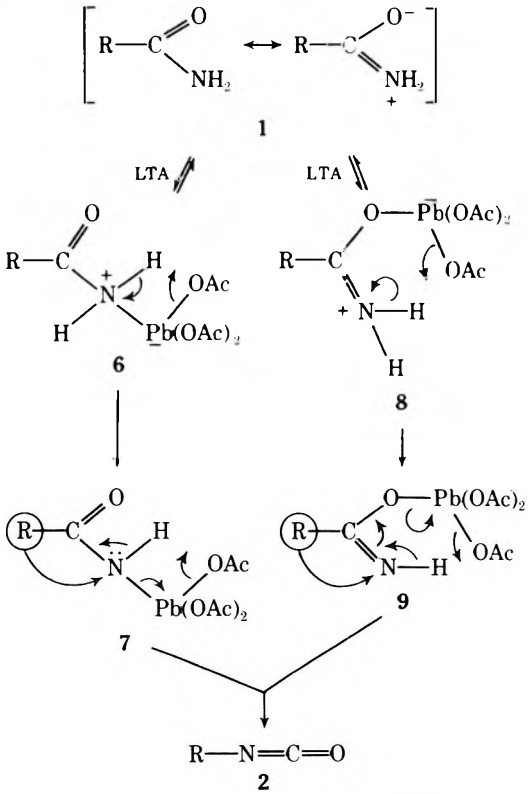
Although Acott, Beckwith, and Hassanali[8] obtained at best a 37% yield of ethyl *N*-pyridylcarbamate from the oxidative rearrangement of nicotinamide in ethyl alcohol or ethyl alcohol–benzene, we experienced no difficulty in preparing the *tert*-butyl carbamate in yields up to 79%.

N-Carbo-*tert*-butoxy protective groups[19] have been removed by treatment of the derivative, usually a peptide, with anhydrous hydrogen chloride in ether,[5] diethyl phos-

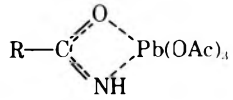
phite,[20] benzene,[20] or nitromethane,[21] as well as with other acids.[22] Although most of the *tert*-butyl carbamates lost the carbo-*tert*-butoxy group when treated with anhydrous hydrogen chloride in ether, we found that cleavage proceeded most satisfactorily in anhydrous ethanol to give high yields of the corresponding amine hydrochloride (Table II).[23]

Incomplete kinetic studies still in progress[25] indicate that in 0.01 M solutions in 1:1 methylene chloride–*tert*-butyl alcohol at 22° the rate of reaction (as measured by disappearance of LTA) is accelerated by the addition of pyridine as a catalyst by roughly a factor of 2–3 at 50% completion of the reaction. However, variations in the rate of this same order of magnitude may result from the use of different batches of LTA (or of *tert*-butyl alcohol in different stages of dryness). It is not known at this time whether pyridine[8,26] (and other bases such as triethylamine[5] and DMF[5]) serves as a catalyst or as a scavenger of acetic acid. Acetic acid does appear to depress the rate of this reaction as it does for other LTA oxidations of organic nitrogen compounds.[27,28] Fortunately, at the reflux temperature of *tert*-butyl alcohol these rate variations are not particularly important, and catalysts for the oxidative rearrangement are not required in practical applications of the method, provided that the amides and solvents used are reasonably dry and the LTA reasonably free from excess acetic acid.

The detailed mechanism of the oxidative rearrangement of amides cannot be specified on the basis of available evidence, although simplified mechanisms have been suggested.[5,8] Two reasonable alternatives consistent with available evidence are summarized in sequences **1** → **6** → **7** → **2** and **1** → **8** → **9** → **2**. These two alternatives could be considered



extreme forms of a third alternative in which the lead atom is bonded to both oxygen and nitrogen in the RCONH-$Pb(OAc)_3$ complex (**10**).

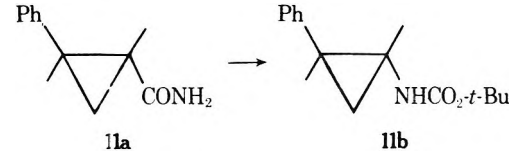


10

In view of the proposed[29] eight-coordinate, distorted dodecahedral structure for LTA in the crystal, **10** would be a reasonable structure. At the time of rearrangement the structure might be distorted toward either **7** or **9**, especially under the influence of nucleophilic solvents (alcohols) or presumed catalysts (pyridine, DMF).

It is also possible that a discrete nitrene intermediate may result from the decomposition of **7**, **9**, or **10**; however, attempts to demonstrate the existence of the nitrene by trapping experiments on the presumed nitrene obtained from the oxidation of urethane (EtO_2CNH_2) with LTA were unsuccessful. Although carboethoxynitrene (from the azide) has been trapped with cyclohexene,[30] cyclohexane,[30] and benzene,[31,32] we have obtained none of the expected cycloaddition or insertion products from the reaction of urethane with LTA in the presence of these hydrocarbons. Acott, Beckwith, and Hassanali[6] reported a similar failure with cyclohexane and urethane. Unfortunately, these negative results provide less than compelling evidence of the absence of an intermediate nitrene, for in our experiments urethane was not oxidized by LTA at an appreciable rate and ultimately the oxidant was consumed in other reactions, presumably with the solvents present. However, attempts to trap the presumed nitrene intermediate in the oxidative rearrangement of cyclohexanecarboxamide with cyclohexane or benzamide with dimethyl sulfoxide[33] also failed. In the latter solvent the principal product was the *sym*-urea.

On the reasonable assumption that the oxidative rearrangement of amides, like the Hofmann[34] and Curtius[35] reactions, proceeds with retention of configuration, Acott, Beckwith, and Hassanali[8] assigned the 17 β configuration to the methyl carbamate obtained from 3β-acetoxyandrost-5-ene-17β-carboxamide. We have established that the reaction does indeed proceed with retention of configuration by the sequence shown in Chart I and by the conversion of *trans*-2-phenylcyclopropanecarboxamide (**11a**) into *tert*-butyl *N*-(*trans*-2-phenylcyclopropyl)carbamate (**11b**) albeit in low yield. After this work had been completed Si-



11a **11b**

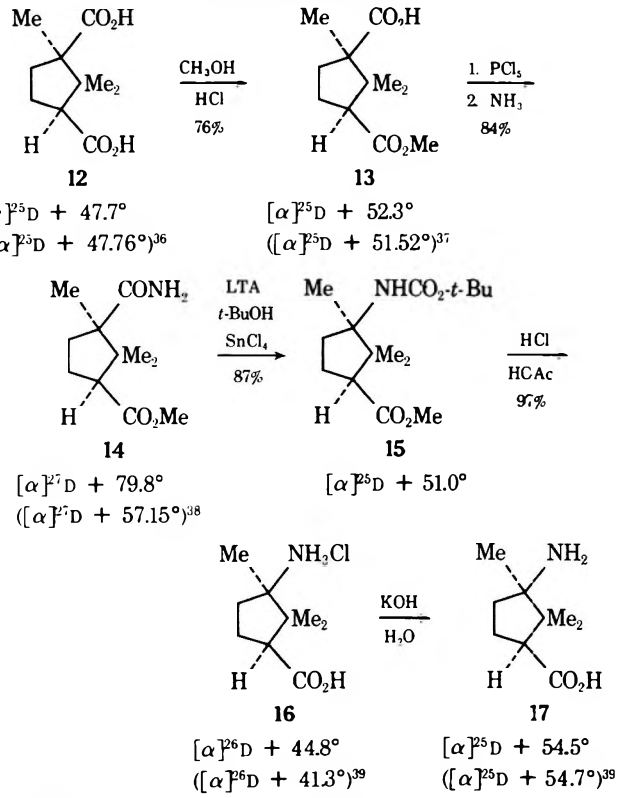
mons[26] reported the apparently stereospecific conversion of *exo*-3-carbamyl-*exo*-2-norborneol to norbornyl[2,3-*d*]-2-oxazolidinone.

From the foregoing discussion it is clear that the oxidative rearrangement of amides using LTA in *tert*-butyl alcohol affords a useful alternative to the classical Hofmann, Schmidt, Curtius, and Lossen rearrangements. The question then arises as to whether or not some other two-electron oxidant, such as iodosobenzene diacetate,[2] might give even better results. A number of other oxidants will be compared in a subsequent communication; however, for most (but not all) purposes LTA appears to be the reagent of choice based on cost, availability, ease of use, and overall results.

Experimental Section

All melting points are uncorrected. The NMR spectra were observed with a Varian A-60 spectrophotometer. Infrared spectra were observed with Perkin-Elmer Models 137 and 237 spectrometers. *tert*-Butyl alcohol was dried by refluxing over calcium hydride (approximately 10 g/l.) for 4–10 hr, followed by distillation. *N,N*-Dimethylformamide (DMF) was dried by refluxing over calcium oxide (approximately 50 g/l.), followed by distillation. Tri-

Chart I
Stereochemistry of Oxidative Rearrangement[a]



[a] Values in parentheses taken from literature.

ethylamine was dried by refluxing over barium oxide, followed by distillation and storage over potassium hydroxide. Acetonitrile (practical grade) and benzyl alcohol were dried by refluxing over phosphorus pentoxide for several hours, followed by distillation. Di-*n*-butyltin dilaurate was purchased from K & K Laboratories, Inc. Lead tetraacetate (LTA) (Arapahoe Chemical Co.) was stored in a desiccator over sulfuric acid (which removes most of the acetic acid stabilizer). The reagent was added as a dry powder in most reactions and directly from the reagent bottle (added in 10% excess to allow for the acetic acid present) in a few instances.

***tert*-Butyl Carbamates. General Procedures.** Most of the reactions were carried out using 0.1 or 0.01 molar equiv of amide and LTA and no catalyst *for the oxidation step*. The 0.1-mol reactions were carried out by warming 250–500 ml of anhydrous *tert*-butyl alcohol with the appropriate amide until dissolution was complete. The reaction flask was equipped with a mechanical stirrer and a reflux condenser protected with a drying tube. The 0.01-mol reactions were run in 50 ml of anhydrous *tert*-butyl alcohol. The reaction flask was equipped with a magnetic stirrer and reflux condenser, protected with a drying tube. When stannic chloride or di-*n*-butyltin dilaurate was used as a catalyst for the isocyanate–alcohol reaction, the catalyst was added via a syringe prior to LTA addition (for example, see the preparation of *tert*-butyl *N*-cyclohexylcarbamate). When triethylamine was used as the catalyst, it was added via a pipette 0.25–2 hr after the addition of LTA (for example, see the preparation of *tert*-butyl *N*-benzylcarbamate). In all reactions, the LTA was weighed as rapidly as possible and added to the *tert*-butyl alcohol–amide solution in one lot. The reaction temperature was then raised to reflux as rapidly as possible.

After the reaction, the *tert*-butyl alcohol was removed on a bench evaporator. The residue was extracted with ether, which was then filtered through Celite. The lead diacetate remaining in the reaction flask was agitated and washed with several portions of ether to remove any entrained carbamate.

In the early experiments, the ethereal filtrate was reduced in volume and washed with 300 ml of 10% potassium carbamate to remove the acetic acid. This was found later to be unnecessary. The ethereal filtrate was evaporated and the carbamate was recrystallized from Skellysolve B (bp 60–69°). If the carbamate was not to be purified, the ethereal filtrate was evaporated, the residue was dissolved in anhydrous ethanol, and the carbamate was converted to the amine hydrochloride as described below. The carbamates were isolated whenever stannic chloride or triethylamine was used as a catalyst, since recovery of the amine hydrochloride was otherwise difficult. Purification of *N*-aryl carbamates was effected by column chromatography in a few instances.

In several small-scale (1–2 g) experiments the *N*-alkyl carbamates were recovered by pouring the cooled mixture into ice water. A modification of the method was found to be effective in recovering *tert*-butyl carbanilates without purification using a column of alumina. After the reaction of the benzamide and LTA was complete, the *tert*-butyl alcohol was removed, the residue was extracted with acetone, and the extract was filtered to remove lead diacetate. The volume of the filtrate was reduced and the concentrated acetone solution was poured into water. The carbanilate which precipitated was considerably cleaner than that obtained when the reaction mixture (*tert*-butyl alcohol as solvent) was poured into water.

The foregoing general procedures are illustrated below with three typical amides: cyclohexanecarboxamide, phenylacetamide, and benzamide. Other examples are summarized in Table II. Properties of the carbamates are given in Table III.

In several experiments triethylamine was used as a catalyst for both the oxidative rearrangement and the alcohol–isocyanate reaction. This procedure would appear to be useful when it is necessary to use the mildest conditions possible. To a solution (or suspension) of 0.03 mol of the amide and 0.03 mol of dry, powdered LTA in 70 ml of dry *tert*-butyl alcohol warmed with stirring to 50° on the steam bath (thermometer in the reaction mixture), 10 ml of triethylamine was added very slowly (ca. one drop every 3–4 sec) with no additional heating. The initial reddish color of the reaction solution faded to colorless (or pale pink) within a few minutes. At this point, the conversion to the isocyanate was essentially complete and the remainder of the triethylamine could be added more rapidly. The reaction mixture was allowed to stand up to several days to permit the isocyanate to react with the *tert*-butyl alcohol. The disappearance of the isocyanate infrared peak at ca. 2260 cm^{-1} could be used as a qualitative test for completeness of conversion. The reaction mixture was evaporated at room temperature to a volume of ca. 30 ml, and this solution was poured into a mixture of crushed ice and 15 ml of acetic acid [to neutralize triethylamine and prevent precipitation of lead(II) salts]. After a few minutes the white or tan urethane was collected by filtration, air dried, and recrystallized from petroleum ether. Examples of carbamates made by this procedure are cited in Table II.

***tert*-Butyl *N*-Cyclohexylcarbamate.** A mixture composed of 1.27 g (0.01 mol) of cyclohexanecarboxamide, 50 ml of anhydrous *tert*-butyl alcohol, and 0.2 ml of stannic chloride, in a 100-ml flask fitted with a magnetic stirrer and a reflux condenser with a drying tube, was stirred at 50° until dissolution of the amide was complete. The addition of 4.43 g (0.01 mol) of LTA was carried out as rapidly as possible, after which the reaction mixture was refluxed for 1 hr. The *tert*-butyl alcohol was removed, the residue was extracted with ether, and the ethereal extract was filtered through Celite, reduced in volume to 15 ml, and diluted with 150 ml of Skellysolve B, whereupon the *tert*-butyl *N*-cyclohexylcarbamate precipitated, yield 1.68 g (84.4%), mp 76–78°.

In another experiment using the same quantities of reagents, 0.1 ml of stannic chloride, and a reflux time of 1.5 hr, the cooled reaction mixture was poured directly into ice water. The carbamate was collected by filtration and recrystallized from Skellysolve B, yield 1.66 g (83.4%), mp 76–78°.

In another experiment 4.87 g (0.01 mol plus 10%) of LTA taken directly from the reagent bottle was added to 1.27 g (0.01 mol) of cyclohexanecarboxamide in 60 ml of anhydrous *tert*-butyl alcohol. After the mixture had been heated under reflux for 15 min, 2.0 ml of triethylamine was added and the mixture was heated under reflux for an additional 1.5 hr. The cooled reaction mixture was poured into ice water, and the carbamate was collected and recrystallized from Skellysolve B, yield 1.58 g (79.4%), mp 76–78°.

***tert*-Butyl *N*-Benzylcarbamate.** A mixture of 1.35 g (0.01 mol) of phenylacetamide and 4.43 g (0.01 mol) of LTA in 25 ml of *tert*-butyl alcohol (no added catalyst) was heated rapidly to reflux and held there for 1 hr. After cooling, the reaction mixture was poured into 250 ml of ice water. The carbamate was recovered by filtration and recrystallized from Skellysolve B, yield 1.84 g (88%), mp 53–54°.

***tert*-Butyl carbanilate** was prepared by treating 2.42 g (0.02 mol) of benzamide with 8.86 g (0.02 mol) of LTA in 50 ml of anhydrous *tert*-butyl alcohol. The reaction mixture was refluxed for 1.5 hr, the alcohol was removed, the residue was extracted with acetone, and the resultant mixture was filtered through Celite to re-

Table III
Properties of Carbamates, $RNHCO_2$-*t*-Bu

Registry no.	R	Mp, °C	Infrared, cm^{-1} [a] ν (NH)	ν (C=O)	Anal., % C Calcd (found)	H Calcd (found)	N Calcd (found)	NMR (CCl_4), δ, ppm δ (*t*-Bu)[f]	δ (NH)[g]	δ (R)
56700-66-4	c-C_4H_7	79–80	3450	1710	63.13 (63.00)	10.00 (10.10)	8.18 (8.20)	1.42	4.80	1.65–2.30[h] (6 H m, ring CH_2's), 4.10 (1 H m, CHN)
3712-40-1	c-C_6H_{11}	77.5–79	3450	1705	66.29 (66.40)	10.62 (10.43)	7.03 (6.96)	1.40	5.40	0.96–2.10[h] (10 H m, ring CH_2's), 4.02 (1 H m, CHN)
56700-67-5	c-$C_6H_{11}CH_2$	50–51	3455	1705	67.56 (67.52)	10.87 (10.81)	6.57 (6.69)			
42116-44-9	$C_6H_5CH_2$	53–54[b]	3455	1710				1.46	4.78	4.24 (2 H d, CH_2), 7.21 (5 H s, C_6H_5)
38427-30-6	$C_6H_5CH_2CH_2$	55–56	3455	1710	70.55 (70.61)	8.65 (8.66)	6.33 (6.22)		4.50	2.71 (2 H t, J = 13 Hz, CH_2) 3.21 (2 H t, J = 13 Hz, CH_2), 7.11 (5 H s, C_6H_5)
3422-01-3	C_6H_5	134–135.5[c]	3460	1715				1.52	6.60	7.32 (5 H t, C_6H_5)
18437-66-6	4-ClC_6H_4[d]	105–106	3435	1730	58.02 (57.91)	6.20 (6.16)	6.16 (6.35)	1.49	6.58	7.2 (4 H s, C_6H_4)
18437-63-3	4-$NO_2C_6H_4$	110.5–111.5	3435	1735	55.45 (55.66)	5.92 (5.92)	11.76 (11.69)	1.57	7.02	7.64 (2 H d, J = 9 Hz, o-CH), 8.25 (2 H d, J = 9 Hz, *m*-CH)
56700-68-6	2,6-$Cl_2C_6H_3$[e]	96–97	3430	1735	50.39 (50.61)	5.00 (4.97)	5.34 (5.53)	1.50	6.12	7.21 (3 H m, C_6H_3)
56700-69-7	2,4,6-$Me_3C_6H_2$	70–71	3440	1720	71.45 (71.32)	9.00 (9.01)	5.95 (6.02)	1.41	6.17	2.11 (6 H s, 2,6-Me_2), 2.21 (3 H s, 4-Me), 6.69 (2 H s, C_6H_2)
56700-70-0	3-C_5H_4N	117–118	3440	1710	61.83 (62.11)	7.27 (7.33)	14.42 (14.41)			

[a] In $CHCl_3$. [b] Lit.[40] mp 57–58°. [c] Lit.[41] mp 136.3–136.5°. [d] Calcd: Cl, 15.57. Found: Cl, 15.50. [e] Calcd: Cl, 27.05. Found: Cl, 26.90. [f] 9 H s. [g] 1 H s, broad. [h] At 60 MHz.

move the lead diacetate. After removal of the acetone, the carbanilate was dissolved in ether, and the ethereal solution was reduced to 75 ml and put on a 2.5 × 50 cm column of activated alumina (80 g) in Skellysolve B (bp 60–69°). After elution with 300 ml of Skellysolve B, followed by 750 ml of ether, 2.98 g (77.3%) of the carbanilate was recovered, mp 134–135.5°. Further elution with 150 ml of 10% methanol–ether yielded 0.294 g (12.1%) of benzamide: mp 127–128.5°; ir ($CHCl_3$) 3510, 3400, 1680, 1580, 1475 cm^{-1}. No other compounds were characterized.

For ordinary preparative purposes the above procedure could be simplified by passing the ethereal solution (without concentration) through 100 g of activated alumina in a Büchner funnel.

In another experiment *tert*-butyl carbanilate was prepared by adding 44.34 g (0.1 mol) of LTA to 12.11 g (0.1 mol) of benzamide in *tert*-butyl alcohol. The reaction mixture was refluxed for 1.5 hr, the alcohol was removed, the residue was extracted with acetone, and the extract was filtered. The volume of filtrate was reduced until the carbanilate was just kept in solution. The solution was poured into 750 ml of ice water. The carbanilate was recrystallized from Skellysolve B, yield 14.52 g (75.2%), mp 134–136°.

Conversion of *tert*-Butyl Carbamates to Amine Hydrochlorides. General Procedure. The *tert*-butyl carbamate was dissolved in the minimum volume of anhydrous ethanol (approximately 35 ml for 0.01-mol reactions, and 150 ml for 0.10-mol reactions). Anhydrous hydrogen chloride was passed into the solution for 1.5–2 hr. The reaction flask was fitted with a magnetic stirrer and a reflux condenser, protected with a drying tube. The volume of ethanol was reduced, and the amine salt was brought out by the addition of ether and recovered by filtration. Subsequent fractions were recovered by removing the ether, reducing the volume of ethanol, and adding more ether. If methanol was substituted for ethanol, two layers sometimes formed at this stage, complicating recovery. If necessary, the amine salts were recrystallized from methanol or ethanol. A large quantity of decolorizing carbon was used to purify the aromatic amine hydrochlorides (2–3 g/10 g of amine hydrochloride) when the carbanilate had not been purified prior to cleavage. This procedure was used in most of the examples in Table II, and was more satisfactory than the following for unpurified carbamates.

Alternatively, dry hydrogen chloride could be passed into a solution of *tert*-butyl carbamate in anhydrous ether (ca. 150 ml/g of carbamate) for 10–15 min. Usually the solution became filled with a fine, white precipitate, which was collected by filtration and dried in over sulfuric acid under mild vacuum, yields 79–90%.

Purification of solid aromatic amines was best carried out by neutralizing the crude hydrochloride with aqueous potassium hydroxide and recrystallizing the amine from Skellysolve B (bp 60–69°).

The amine hydrochlorides obtained gave the following melting points: cyclobutyl, 183–184° (Anal. Calcd for $C_4H_{10}ClN$: C, 44.66; H, 9.37; Cl, 32.95; N, 13.02. Found: C, 44.54, H, 9.35; Cl, 32.68; N, 13.13); cyclohexyl, 205–207° (lit.[42] mp 203–204°); benzyl, 247–248° (lit.[43] mp 246–250°); 2-phenethyl, 218–219° (lit.[44] mp 217°); aniline, 196–198° (lit.[45] mp 198°). The free amines gave the following melting points: *p*-chloroaniline, mp 69–71° (lit.[46] mp 70–71°); *p*-nitroaniline, mp 146–148° (lit.[47] mp 145°); 2,6-dichloroaniline, mp 37–37.5° (lit.[48] mp 39°).

***cis*-3-Carbomethoxy-1,2,2-trimethylcyclopentanecarboxylic acid (13).** *d*-Camphoric acid (12) (Aldrich) was recrystallized[49] from ether: mp 187–188°; $[\alpha]^{20}D$ +47.7° (*l* 2, c 0.04, etha-

Table IV
Preparation of Ureas, RNHCONH-*t*-Bu

Registry no.	R	Yield, %	Mp, °C	Lit. mp, °C	Infrared, cm^{-1} [a] ν(NH)	Infrared, cm^{-1} [a] ν(C=O)
5336-24-3	*tert*-Butyl	96	240 ± 2[b]	242–243[c]	3440	1680
2387-23-7	Cyclohexyl	88	226 ± 2[b]	227[d]	3440	1668
5472-16-2	Cyclohexylmethyl	74	150–151[e]		3440	1670
56700-71-1	2-Methyl-2-phenylpropyl	97	192–193[f]		3435	1665

[a] In $CHCl_3$ solution. [b] On Koeffler hot bench calibrated to accuracy shown. [c] R. N. Lacy, *J. Chem. Soc.*, 1633 (1960). [d] B. Brauner, *Ber.*, 12, 1875 (1879). [e] Anal. Calcd for $C_{12}H_{24}N_2O$: C, 67.89; H, 11.39; N, 13.20. Found: C, 67.57; H, 11.56; N, 12.91. [f] Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.53; H, 9.68; N, 11.28. Found: C, 72.27, H, 9.75; N, 11.61.

nol) [lit.[49] mp 187°; lit.[36] $[\alpha]^{20}D$ +47.76° (*l* 2, *c* 0.93, ethanol)]. Anhydrous hydrogen chloride was passed into a stirred solution of 20.02 g (0.100 mol) of 12 in 250 ml of methanol for 2 hr. The methanol was evaporated and the residue was taken up in 5% aqueous sodium bicarbonate. The sodium bicarbonate solution was added until effervescence ceased, then 100 ml of 5% aqueous sodium hydroxide was added. The diester was removed by extraction with ether and discarded. The aqueous layer was acidified with 10% hydrochloric acid and extracted with ether. The ethereal extract was dried ($MgSO_4$) and evaporated, and the residue was recrystallized from Skellysolve B (bp 60–69°): yield 16.2 (76%); mp 77.0–77.5°; $[\alpha]^{25}D$ +52.3° (*l* 2, *c* 0.04, ethanol) [lit.[37] mp 75–76°; $[\alpha]^{25}D$ +51.52° (*l*, *c* not given)]; ir ($CHCl_3$) 3490, 1720 cm^{-1} (acid C=O and ester C=O, broad peak).

***cis*-3-Carbamoyl-2,2,3-trimethylcyclopentanecarboxylate (14).** To 10.5 g (0.049 mol) of 13 susupended in 60 ml of petroleum ether was added 12 g (0.057 mol) of phosphorus pentachloride, and the mixture was stirred for 1 hr at room temperature. To 250 ml of anhydrous acetonitrile, which had been saturated with anhydrous ammonia at −30°, was added dropwise the mixture of acid chloride and phosphoryl chloride in petroleum ether. The temperature was kept at −35° until addition was complete. The mixture was stirred for 10 min following addition of the acid chloride, the acetonitrile was removed on a bench evaporator, and the residue was taken up in hot ethyl acetate. The solution was filtered through Celite and evaporated. The amide was recrystallized from ethyl acetate: yield 8.83 g (84%); mp 141–142°; $[\alpha]^{27}D$ +79.8° (*l* 2, *c* 0.025, ethanol) (lit.[38] mp 139°, $[\alpha]^{27}D$ +57.15°); ir ($CHCl_3$) 3540, 3410, 2950 (broad), 1725, 1660, 1580 cm^{-1}; NMR ($CDCl_3$) δ 3.70 (3 H s, CH_3O), 2.83 (1 H m), 1.5–2.5 (4 H m), 1.30 (3 H s), 1.21 (3 H s), 0.86 (3 H s).

***tert*-Butyl *N*-(*cis*-1,2,2-trimethyl-3-carbomethoxy-1-cyclopentyl)carbamate (15)** was prepared from 1.85 g (0.0086 mol) of 14, using stannic chloride (0.1 ml) as a catalyst for the alcohol–isocyanate reaction. The reaction mixture was heated under reflux for 19 hr. After removal of the *tert*-butyl alcohol, the residue was taken up in ether and washed with 100 ml of 10% potassium carbonate. The carbamate was recrystallized from Skellysolve B (bp 60–69°); yield 2.5 g (87.1%); mp 78.8–79.2°; $[\alpha]^{25}D$ +51.0° (*l* 2, *c* 0.029, ethanol); ir ($CHCl_3$) 3450, 1715 cm^{-1}; NMR ($CDCl_3$) δ 3.68 (3 H s, CH_3O), 2.63 (1 H m), 2.0 (4 H m), 1.41 (9 H s), 1.33 (3 H s), 1.11 (3 H s), 0.85 (3 H s). Anal. Calcd for $C_{15}H_{27}O_4N$: C, 63.13; H, 9.54, N, 4.91. Found, 63.11; H, 9.46; N, 4.99.

***cis*-3-Amino-2,2,3-trimethylcyclopentanecarboxylic Acid Hydrochloride (16).** A mixture of 2.00 g (0.0070 mol) of 15 and a solution of 10 ml of hydrochloric acid (37%) and 15 ml of glacial acetic acid was heated under reflux for 11 hr, after which the acetic acid, methanol, and water were removed. The amine salt was recrystallized from ethanol and brought out by adding ether: yield 1.41 g (97%); mp 254–256°; $[\alpha]^{26}D$ +44.8° (*l* 2, *c* 0.028, water) [lit.[39] mp 261–222°; $[\alpha]^{26}D$ +41.3° (*c* 0.1, water)]; NMR (D_2O) δ 4.80 (5 H s), 3.00 (1 H m), 2.15 (4 H d), 1.40 (3 H s), 1.20 (3 H s), 1.09 (3 H s).

***cis*-3-Amino-2,2,3-trimethylcyclopentanecarboxylic Acid (17).** To 20 ml of 3% aqueous potassium hydroxide was added 1.57 g (0.0075 mol) of 16. The water was carefully evaporated until the amino acid precipitated. The amino acid was recovered by filtration and washed with water: yield 0.973 g (97%); $[\alpha]^{25}D$ +54.5° (*l* 2, *c* 0.0202, water) [lit.[39] $[\alpha]^{25}D$ +54.7° (*c* 0.05, water)].

***tert*-Butyl *N*-(*trans*-2-phenylcyclopropyl)carbamate** was prepared by treating *trans*-2-phenylcyclopropanecarboxamide (1.61 g, 0.01 mol) with 4.43 g (0.01 mol) of LTA in *tert*-butyl alcohol. After removal of the alcohol and filtration of the ethereal extract, the ethereal filtrate was evaporated and the residue was taken up in hot Skellysolve B (bp 60–69°). The solution was cooled, and the crystalline mixture, which was removed by filtration, was recrystallized from Skellysolve B (bp 60–69°). The solid which was insoluble in Skellysolve B was identified as *trans*-2-phenylcyclopropanecarboxamide (0.594 g, 36.9%): mp 189–191°; ir ($CHCl_3$) 3515, 3405, 1675, 1585 cm^{-1}. Only 0.30 g (12.9%) of the carbamate was recovered: mp 80–81° (lit.[50] mp 80–82°); ir ($CHCl_3$) 3440, 2915, 1715, 1590, 1355 cm^{-1}; NMR ($CDCl_3$) δ 7.2 (5 H s), 4.96 (1 H s), 2.69 (1 H m), 2.05 (1 H m), 1.46 (9 H s), 1.13 (2 H m).

3-Aminopyridine. The oxidation of 12.2 g (0.100 mol) of nicotinamide with 44.39 (0.100 mol) of LTA in 500 ml of *tert*-butyl alcohol was carried out with no catalyst present. The mixture was heated under reflux for 2 hr, and the *tert*-butyl alcohol was removed. To the gummy, red residue was added 400 ml of ether in 100-ml portions, each of which was filtered through Celite to remove the lead diacetate. The combined ethereal filtrates were reduced to a volume of 50 ml and placed on a 4.5 × 25 cm column of 250 g of activated alumina in ether. The column was eluted with 2.5 l. of ether, from which the carbamate was recovered and dissolved in 500 ml of methanol. Anhydrous hydrogen chloride was passed into the solution for 2 hr, after which the mixture was stirred overnight.

The volume of methanol was reduced to 50 ml, 200 ml of ether was added, and the amine dihydrochloride was collected by filtration. The dihydrochloride was neutralized with 10 g of potassium hydroxide in 100 ml of water, and the solution was saturated with sodium chloride and extracted with 250 ml of chloroform. The chloroform extracts were dried ($MgSO_4$), filtered, and reduced to a volume of 75 ml. Addition of 75–100 ml of petroleum ether (bp 30–60°) and cooling yielded 6.87 g (73.1%) of 3-aminopyridine: mp 60–61.5° (lit.[51] mp 64°); ir ($CHCl_3$) 3370, 3380, 1620, 1580 cm^{-1}; NMR ($CDCl_3$) δ 8.1 (2 H m), 7.0 (2 H m), 3.85 (2 H s).

***tert*-Butyl Isocyanate.** To a solution of 10.0 g (0.100 mol) of *tert*-butyl carboxamide in 100 ml of dry DMF was added 44.3 g (0.100 mol) of lead tetraacetate. The mixture was distilled through a 2-ft, heated Vigreux column (with magnetic stirring of the reaction mixture in the still pot). The fraction boiling at 83–85° (lit.[54] bp 85.5°) was collected, yield 4.4 g (44%). When the oil bath temperature reached 150° the distillation was stopped. The infrared spectrum (CCl_4) of the distillate showed the expected peaks at 2980 [ν(CH)], 2260 [ν(N=C=O)], 1540 (*t*-Bu), and 1365 cm^{-1} (*t*-Bu) and no amide ν(C=O) absorption. An infrared spectrum of the still pot residue showed an intense band at 2260 cm^{-1}, indicating that not all of the isocyanate was recovered from the reaction mixture.

Alkyl *tert*-Butyl Ureas. General Procedure. A solution of 0.02 mol of the amide in 100 ml of dry DMF was stirred while 8.86 g (0.02 mol) of dry LTA was added. The addition caused the solution to become light red. As the reaction progressed to completion the temperature rose to ca. 60° and the color faded. When the solution became colorless, 7 ml of *tert*-butylamine was added. Although the product could be isolated by removing the DMF under reduced pressure, usually the solution was poured over ca. 100 g of crushed ice and water, and the urea was collected and washed thoroughly with water The yields and properties of the ureas are summarized in Table IV.

Benzyl Carbamates. General Procedure. A solution of 0.01 mol of the amide in 20–30 ml of dry DMF or dry acetonitrile was stirred while 4.43 g (0.01 mol) of LTA was added. The reaction mixture was kept at the initial temperature (Table I) for 20–90 min, then heated at the final temperature overnight (10–12 hr). The reaction mixture was cooled and poured into 500 ml of ice water. The carbamate was collected and recrystallized from Skellysolve B. For reaction at the 0.1-mol scale, the volume of the reaction mixture was reduced before it was poured into 1 l. of water.

Hydrolysis of Benzyl Carbamates. The benzyl carbamates, prepared as described, were hydrolyzed by refluxing a solution of

the purified carbamates in a mixture of glacial acetic acid and concentrated (37%) hydrochloric acid for 2–4 hr. After removal of the solvent mixture by distillation, the amine salt was taken up in methanol and precipitated by adding ether. The results for these preparations are summarized in Table I.

Registry No.—1 (R = C_6H_5CMeEt), 828-40-0; **4** (R = cyclobutyl), 6291-01-6; **4** (R = cyclohexyl), 4998-76-9; **4** (R = 1,2,2-trimethyl-3-carbomethoxy-1-cyclopentyl, 56700-72-2; **4** (R = benzyl), 3287-99-8; **4** (R = 2-phenethyl), 156-28-5; **4** (R = 3-pyridyl), 462-08-8; **4** (R = phenyl), 142-04-1; **4** (R = 4-chlorophenyl), 20265-96-7; **4** (R = 4-nitrophenyl), 100-01-6; **4** (R = 2,5-dichlorophenyl), 608-31-1; **12**, 124-83-4; **13**, 29607-02-1; **14**, 56760-77-1; **15**, 56760-78-2; **16**, 56700-74-4; **17**, 56700-79-3; *tert*-butyl 1,2,2-trimethyl-3-carboethoxy-1-cyclopentylcarbamate, 56700-73-3; *tert*-butyl *trans*-2-phenylcyclopropylcarbamate, 56700-75-5; lead tetraacetate, 546-67-8; benzyl alcohol, 100-51-6; *tert*-butyl alcohol, 75-65-0; hydrochloric acid, 7647-01-0; *tert*-butylamine, 75-64-9.

Supplementary Material Available. The experimental procedures used to prepare the amides **1** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3554.

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(18) Catalysis of the dehydration of a small amount of the *tert*-butyl alcohol by the isocyanate would not be important, were it not for the water formed which hydrolyses the isocyanate to yield the amine, which reacts rapidly with a second molecule of isocyanate to form the *sym*-disubstituted urea. Formation of the latter is also the basis of the need for absolutely anhydrous reagents and conditions throughout the reaction.

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Nitration of Acetoacetate Esters by Acetyl Nitrate. A High Yield Synthesis of Nitroacetoacetate and Nitroacetate Esters[1]

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Reaction of acetoacetic esters (**3**) with acetyl nitrate (**1**) at −10 to 15° in the presence of catalytic amounts of strong protic acids or Lewis acids afforded 90–97% yields of the corresponding nitroacetoacetic esters (**6**). Under similar conditions, ethyl 3-acetoxy-2-butenoate (**10b**) produced 63% **6b** and 35% 3,4-bis(ethoxycarbonyl)furazan 2-oxide (**9b**) at 15°. In the absence of catalyst, reaction of ethyl acetoacetate (**3b**) was slow at 25° and the yields of **6b** and **9b** were 39 and 52%, respectively. A slow transformation of **6b** to **9b** took place at 22° in the presence of catalytic amounts of H_2SO_4 and the reaction was accelerated by acetic anhydride. Proton exchange evidence indicated that the crucial function of the acid catalyst in the nitration is to protonate **1** to provide an active nitrating species **2**, rather than merely accelerate enolization of **3**. In the presence of water, alcohols, or ammonia **6** cleaved quantitatively to nitroacetate esters and correspondingly acetic acid, acetate ester, or acetamide. The cleavage with water and alcohols was acid catalyzed. The combination of nitration and cleavage reactions affords a practical synthesis of nitroacetate esters.

Reaction of acetoacetate esters with absolute nitric acid in acetic anhydride at about 32° affords moderate (40–50%) yields of nitroacetate esters, the balance consisting mainly of the corresponding 3,4-bis(ethoxycarbonyl)furazan 2-oxides.[2] Nitric acid in acetic anhydride exists largely as acetyl nitrate.[3] In view of the mode of reaction of this reagent with enol esters,[4] it appeared reasonable that nitroacetoacetate esters are formed at least as intermediate species during the reaction with acetoacetate esters. Recently methyl nitroacetoacetate was synthesized by Babievskii et al.[5] by means of condensation reactions of methyl nitroacetate. The authors advanced the hypothesis that failure to prepare nitroacetoacetates by nitration of acetoacetates is due to the hydrolytic instability of the former, by analogy with the known hydrolytic instability of formylnitroacetic ester.[6]

Results and Discussion

Reaction of ethyl acetoacetate (**3b**, Scheme I) with a solution of 99% nitric acid (1 mol) in 2 mol of acetic anhydride (essentially acetyl nitrate in acetic acid) failed to proceed appreciably at 0° and was slow at ambient temperature. Two main products were detected by GLC, identified as ethyl nitroacetoacetate (**6b**) and 3,4-bis(ethoxycarbonyl)furazan 2-oxide (**9b**). In the presence of catalytic amounts of strong inorganic acids, such as sulfuric or perchloric, or Lewis acids, such as boron trifluoride etherate, reaction was fast even at −10° and **6b** was formed in essentially quantitative yield (reaction 1).

$$CH_3COCH_2CO_2R + AcONO_2 \rightarrow CH_3COCHNO_2CO_2R + AcOH \quad (1)$$

p-Toluenesulfonic acid was a less efficient catalyst and **9b** was produced in significant amounts along with **6b** (Table I). The reaction was also carried out using 70% nitric acid, in which case a larger amount of acetic anhydride was used in order to react with the water present in the 70% acid. The product was isolated from the reaction mixture by neutralizing the acid catalyst with anhydrous sodium carbonate and distilling under reduced pressure. If neutralization of the catalyst was omitted, extensive decomposition of **6b** to **9b** with simultaneous formation of acetic acid occurred on heating (vide infra). In similar manner the methyl, isopropyl, and cyclohexyl esters of acetoacetic acid were nitrated to the corresponding nitroacetoacetate esters. The NMR spectra of **6** in chloroform solution indicated the presence of 21–32% enol (**7**) in equilibrium with the keto form (Table II).

The behavior of the enol acetate of ethyl acetoacetate (**10b**, ethyl 3-acetoxy-2-butenoate, a mixture of cis and trans isomers) under the nitration conditions is of interest. In the presence of catalytic amounts of sulfuric acid, reaction was very slow at 0°. At 15° reaction was complete in about 50 min. The products formed were **6b** and **9b** in 63 and 35% yield, respectively. Under the same conditions **3b** gave essentially only **6b** (run 5 in Table I). When the reaction mixture from the nitration of either **3b** or **10b**, containing 1 mol % of sulfuric acid, was allowed to stand with-

Table I
Nitration of $CH_3COCH_2CO_2R$ (3) by $AcONO_2$[a]

Run	R (formula)	Nitration reagent	Catalyst (mol %)	Temp,[b] °C	Time,[b] min	Yield, %[c] 6	9
1	Me (a)	*d*	$HClO_4$ (0.25)	−10	60	97	*e*
2	Et (b)	*f*	$HClO_4$ (0.20)	−10	60	97	2
3	Et (b)	*d*	BF_3 (1.0)	−10	45	98	1
4	Et (b)	*d*	H_2SO_4 (1.0)	−10	60	97	2
5	Et (b)	*d*	H_2SO_4 (1.0)	15	20	96	3
6	Et (b)	*f*	*p*-TSA[g] (2.5)	−5	65	91	7
7	Et (b)	*f*	None	25	60	39	52
8	*i*-Pr (c)	*d*	$HClO_4$ (0.25)	−10	60	93	*e*
9	Cyclohexyl (d)	*d*	$HClO_4$ (0.25)	−10	60	90	*e*

[a] All quantities of chemicals are referred to 3. [b] Temperature at which the last reagent (3 or the catalyst) was added to the nitration mixture, which was then maintained at that temperature for the stated time. [c] Yields determined by GLC. The yield of 6 was very close to the yield of $CH_2NO_2CO_2R$ obtained in a subsequent cleavage with an alcohol or water and isolated by distillation. [d] Ac_2O (6.0 mol) and 70.4% HNO_3 (1.02 mol). [e] Not determined. [f] Ac_2O (2.10 mol) and 99% HNO_3 (1.05 mol). [g] *p*-Toluenesulfonic acid.

Table II
Properties of Nitroacetoacetate Esters $CH_3COCHNO_2CO_2R$ (6) ⇌ $CH_3C(OH)=CNO_2CO_2R$ (7)

R (formula)	Bp, °C (mm)	Ir (neat), cm^{-1}	NMR ($CDCl_3$), δ[a] (multiplicity,[b] number of protons) CH_3CO	$CH_3C=$	$CHNC_2$	R	Enol (7), %[c]
Me (a)	75 (0.5)	1755, 1560	2.36 (s, 2.29)	2.23 (s, 0.71)	6.05 (s, 0.68)	3.81 (s, 3)	27 (32)
Et (b)	75 (0.2)	1750, 1567	2.40 (s, 2.24)	2.26 (s, 0.76)	6.13 (s, 0.69)	1.31 (t, 3) 4.35 (q, 2)	25 (30)
i-Pr (c)	66 (0.1)	1743, 1568	2.39 (s, 2.38)	2.25 (s, 0.62)	6.09 (s, 0.73)	1.32 (d, 6) 5.15 (m, 1)	21 (27)
Cyclohexyl (d)	70 (0.15)	1740, 1560	2.36 (s, 2.13)	2.22 (s, 0.87)	6.07 (s, 0.68)	~1.5 (b, 10) 4.9 (b, 1)	29 (32)

[a] Relative to tetramethylsilane. [b] s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. [c] Calculated from $CH_3C=$ protons; number in parentheses calculated from $CHNO_2$ protons.

out prior neutralization of the acid catalyst, **6b** was slowly transformed to **9b**. The reaction followed first-order kinetics with respect to **6b** with a half-life of 22 hr at 22°. No such transformation took place if the acid catalyst was neutralized by addition of anhydrous sodium carbonate. Pure **6b** in acetic acid solution was indefinitely stable at room temperature but decomposed to **9b** at a similar rate in the presence of 10 mol % of sulfuric acid. The rate increased by one order of magnitude when the solvent was a 1:1 (v/v) mixture of acetic acid and acetic anhydride (Table III).

The following reaction mechanism is consistent with the experimental results of the nitration of **3b** and **10b** and the transformation of **6b** to **9b** (Scheme I). The active nitrating species in a mixture of acetic anhydride and nitric acid is the protonated acetyl nitrate (**2**).[3] The concentration of **2** is greatly increased in the presence of a strong protic acid. A Lewis acid apparently creates an equally strong electrophile by withdrawing electrons from **1**; e.g., in the case of boron trifluoride the species $AcONO_2BF_3$ is assumed. Obviously the role of acid in the nitration also involves catalysis of the enolization of **1** (reaction 2). Proton NMR spectra of a 20 vol % solution of ethyl acetoacetate in acetic acid-d_4 revealed exchange of the active methylene protons at 0° with a half-life equal to 52 min. Addition of 2 mol % of sulfuric acid accelerated the rate of exchange by a factor of about 5 (half-life 10 min). In both cases the ester existed in the enol form, **4b**, to the extent of about 20%. As stated earlier, no appreciable nitration of ethyl acetoacetate took place at 0° in the absence of acid catalyst upon treatment with **1** in acetic acid. It is evident that **1** does not react with **4** unless it is first activated via protonation to **2**. The proton exchange data show that the acid catalyst also accelerates the rate of enolization of **3**. It is clear from the experimental data, however, that the crucial function of the acid is in assisting the formation of the nitrating species **2**. This species adds to **4** with formation of acetic acid to yield the α-nitrohydroxycarbonium ion, **5** (reaction 3). Ejection of a proton from **5** affords nitroacetoacetate ester **6** and/or its enol form **7** (reaction 4). The formation of **9** can be explained by cleavage of **5** to a nitrile oxide **8**, which then dimerizes (reactions 5 and 6). The high yields of **6** obtained during the acid-catalyzed nitration of **3** indicate that reaction 4 is much faster than reaction 5. The first-order transformation of **6b** to **9b** in the presence of acid catalyst is reasonably explained by reversal of reaction 4, followed by reactions 5 and 6.

The increased yields of **9b** obtained during nitration of **10b** can be explained in the following manner. The carbonium ion, **11b**, formed in this case cannot, unlike **5b**, be transformed to **6b** by simple ejection of a proton but must rather eject an acylium ion (reaction 8). Cleavage to acetic anhydride and **8b** (reaction 9) is apparently a competitive alternative. The acceleration of the acid-catalyzed transformation of **6b** to **9b** in the presence of acetic anhydride presumably involves formation of **11b** via **5b** and/or **7b** fol-

Table III
Conversion of Ethyl Nitroacetoacetate (6b) to Diethyl 2-Oxofurazandicarboxylate (9b)[a]

Run	Reaction medium	Additive (mol %)[b]	Half-life, hr
10	AcOH	H_2SO_4 (10)	24
11	AcOH–Ac_2O equal volumes	H_2SO_4 (10)	2.1
12	Aliquot from run 4[c,d]	None[d]	22
13	Aliquot from run 4[c,e]	None[e]	No reaction

[a] Reaction at 22°, concentration of **6b** was 0.25 *M*, unless otherwise mentioned. [b] Referred to **6b**. [c] Concentration of **6b** was ~1.3 *M*; Ac_2O–AcOH ~ 350:400 (molar ratio). [d] Aliquot taken before addition of Na_2CO_3. [e] Aliquot taken after addition of Na_2CO_3.

Scheme I

$$Ac_2O + HNO_3 \underset{AcOH}{\overset{-AcOH}{\rightleftharpoons}} AcONO_2 \underset{-H^+}{\overset{H^+}{\rightleftharpoons}} (AcOHNO_2)^+$$
1 2

$$CH_3COCH_2CO_2R \underset{-H^+}{\overset{H^+}{\rightleftharpoons}} CH_3\overset{+}{C}(OH)CH_2CO_2R \underset{H^+}{\overset{-H^+}{\rightleftharpoons}}$$
3

$$CH_3C(OH)=CHCO_2R \quad (2)$$
4

$$2 + 4 \longrightarrow CH_3\overset{+}{C}(OH)CHNO_2CO_2R + AcOH \quad (3)$$
5

$$5 \underset{H^+}{\overset{-H^+}{\rightleftharpoons}} CH_3COCHNO_2CO_2R \text{ or } CH_3C(OH)=CNO_2CO_2R \quad (4)$$
6 7

$$5 \longrightarrow O\leftarrow N\equiv CCO_2R + AcOH + H^+ \quad (5)$$
8

$$2\,8 \longrightarrow \quad (6)$$
9

$$2 + CH_3C(OAc)=CHCO_2R \longrightarrow$$
10

$$CH_3\overset{+}{C}(OAc)CHNO_2CO_2R + AcOH \quad (7)$$
11

$$11 \underset{Ac^+}{\overset{-Ac^+}{\rightleftharpoons}} 6 \text{ or } 7 \quad (8)$$

$$11 \longrightarrow 8 + Ac_2O + H^+ \quad (9)$$

R = Me (**a**), Et (**b**), *i*-Pr (**c**), cyclohexyl (**d**)

Table IV
Cleavage of Ethyl Nitroacetoacetate (6b)[a]

Run	Nucleophile[b]	Additive (mol %)[c]	Half-life, min	Product[d]
14	MeOH	None	66	AcOMe
15	MeOH	NaOMe (10)	2.3×10^2	AcOMe
16	EtOH	None	5.8×10^2	AcOEt
17	EtOH	Et_3N (140)	$>10^4$	AcOEt
18	EtOH	$HClO_4$ (10)	<1	AcOEt
19	EtOH	$HClO_4$ (1)	5.5	AcOEt
20	H_2O[e]	None	40	AcOH
21	NH_3[f]	None	<1	$AcNH_2$

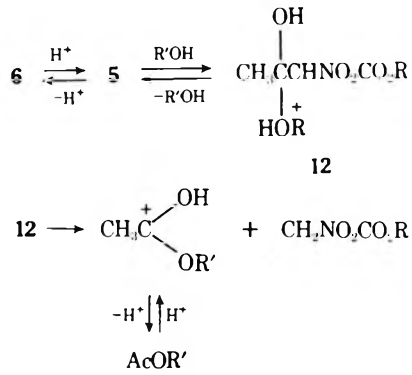
[a] Reaction at 22°, concentration of 6b was 0.5 *M*. [b] Neat, unless otherwise mentioned. [c] Referred to 6b. [d] Besides ethyl nitroacetate. [e] Mixed with two volumes of acetone. [f] As 14 *M* aqueous solution.

lowed by reactions 9 and 6. Formation of oxofurazans during nitration of enol esters of simple ketones has not been observed.[4] It is likely that the role of the ethoxycarbonyl group of 11b is to stabilize the nitrile oxide (8) by delocalizing the C≡N triple bond. Transient formation of nitrile oxides has been postulated in the decomposition of α-nitro ketones with excess strong mineral acid.[7] In that medium the nitrile oxides hydrolyze to carboxylic acids and hydroxylamine salts, which are the products isolated from the reaction mixture.

The nitroacetoacetate esters cleaved quantitatively to nitroacetate esters upon reaction with water, alcohols, or ammonia. The cleavage by water and alcohols was catalyzed by acids and followed first-order kinetics with respect to the substrate. The rate of cleavage decreased in the order water > methanol > ethanol (Table IV). The mechanism that best fits these data is fast protonation of **6** to **5** followed by nucleophilic attack of alcohol or water on **5** and cleavage of the hemiketal, **12**, formed (Scheme II). Hemiketals have been postulated as intermediates in the acid-catalyzed cleavage of α-nitro ketones in alcohol solution.[8] In the presence of base the cleavage of **6b** by alcohols was inhibited. Since base-catalyzed cleavage of α-nitro ketones is known,[9] an explanation is in order. The most likely reason for the inhibition is the fact that **6b** is a relatively strong acid with pK_a estimated to be about 2.4. Owing to the acidity of **6b**, less than stoichiometric amounts of added base are completely neutralized. The acidity of the reaction medium is reduced in the process, and as a result the acid-catalyzed cleavage is hindered without compensation by a base-catalyzed reaction. In the presence of excess base **6b** is completely ionized and therefore less amenable to attack by RO^- or OH^-. Aqueous ammonia, however, cleaved **6b** to ethyl nitroacetate and acetamide in a few minutes at room temperature.

For preparative purposes it is not necessary to isolate **6** in order to obtain nitroacetate esters. Ethyl nitroacetate was very conveniently prepared in over 90% yield by nitrating ethyl acetoacetate in the presence of an acid catalyst and cleaving the nitroacetoacetate formed without isolation by adding ethanol to the reaction mixture after all the acetoacetate had reacted. The catalyst was then neutralized by addition of sodium carbonate and the mixture was fractionally distilled under reduced pressure. Failure to neutralize the catalyst resulted in partial decomposition of ethyl nitroacetate during distillation accompanied by formation of **9b**. The distilled nitroacetate had a faintly yellow color but otherwise was indistinguishable from authentic material. Colorless material could be obtained in an alternate work-up, in which the nitration mixture was treated with water and then extracted with dichloromethane. Ethyl nitroacetate was recovered by fractional distillation of the extract. This work-up is very similar to the practice of early

Scheme II



R = Me (**a**), Et (**b**), *i*-Pr (**c**), cyclohexyl (**d**)
R′ = H, Me, Et

workers[2] and explains why **6b** had not been observed in the past in the nitration products of ethyl acetoacetate.

In conclusion it should be noted that the combination of nitration and cleavage reactions reported here constitutes a practical, high-yield synthesis of nitroacetate esters from acetoacetate esters.

Experimental Section

GLC analyses were carried out on a Packard gas chromatograph using 6-ft, 3-mm i.d. Pyrex columns of 10% SE-30 on acid-washed Chromosorb W or 10% Carbowax 20M on Teflon 6. Proton NMR spectra were recorded on either Varian A-60 MHz or HA-100 MHz instruments. All preparative reactions were routinely carried out under a nitrogen atmosphere.

Methyl acetoacetate (**3a**) and ethyl acetoacetate (**3b**) were purchased from Eastman. Other acetoacetates were prepared from **3a** by base-catalyzed transesterification with the appropriate alcohol; isopropyl acetoacetate (**3c**), bp 55° (4.5 mm); cyclohexyl acetoacetate (**3d**), bp 92–95° (2 mm). Both esters were characterized by NMR spectra. Nitric acid, 70.4%, was Baker and Adamson reagent grade. Nitric acid, 99%, was obtained from Essex Chemical, Clifton, N.J. It was distilled prior to use to afford a colorless fraction.

Proton Exchange of Ethyl Acetoacetate (3b) in Acetic Acid-d_4. Acetic acid-d_4 (0.40 ml) was mixed at 0° with **3b** (0.10 ml) and the NMR spectrum at 100 MHz was recorded at the same temperature immediately and every 15 min thereafter for 1 hr. The intensity of the peaks for $-COCH_2CO-$ (3.47 ppm, s) and $C{=}CH-$ (4.95 ppm, s) diminished with first-order kinetics owing to proton–deuteron exchange. The half-life of the exchange was 52 min. The mole ratio of the enol to keto form, taken as equal to 2 H (4.95)/[2 H (4.95) + H (3.47)], remained essentially constant at 0.22 ± 0.02 during the experiment. When 0.8 μl of D_2SO_4 was added, the half-life of the exchange was reduced to 10 min.

Ethyl 3-Acetoxy-2-butenoate (10b). This was prepared by acetylation of **3b** with acetyl chloride in pyridine.[10] Analysis by GLC and NMR showed that the product consisted of a mixture of two cis–trans isomers in the ratio 30:70. The major component was the isomer with the methyl group cis to the ethoxycarbonyl group: bp 95–97° (10 mm); NMR ($CDCl_3$) δ 1.26 (t) and 1.28 (t, total 3 H), 2.02 (d, J = 1.10 Hz, 1 H) and 2.36 (d, J = 0.92 Hz, 2 H), 2.19 (s, 2.2 H) and 2.24 (s, 0.8 H), 4.13 (q) and 4.18 (q, total 2 H), 5.60 (q, J = 1.10 Hz, 0.35 H) and 5.67 (q, J = 0.92 Hz, 0.65 H). The doublets at δ 2.36 and 2.02 were assigned correspondingly to the methyl groups cis and trans to the ethoxycarbonyl function in accordance with numerous literature examples[11] showing that in similar systems the allylic methyl group of the cis isomer appears at lower field than the corresponding group of the trans isomer.[12] The assignment is consistent with the fact that the vinyl proton cis to the acetoxy function appears at a lower field (δ 5.67) than the corresponding trans proton (δ 5.60).[14]

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.03. Found: C, 56.25; H, 6.96.

Ethyl Nitroacetoacetate (6b). Concentrated H_2SO_4 (0.055 ml, 0.001 mol) was added to 57 ml (0.60 mol) of Ac_2O. The mixture was cooled to 10°, then 6.30 ml (0.102 mol) of 70.4% HNO_3 was added dropwise while the solution was well stirred and the temperature maintained at 10–15° with external cooling. The reaction mixture was cooled to −10° and 13.0 g (0.100 mol) of ethyl acetoacetate

Table V
Spectral Properties of Nitroacetate Esters

R	Ir (neat), cm^{-1}	NMR ($CDCl_3$), δ[a] (multiplicity,[b] number of protons)			Registry no.
		CH_2NO_2	R		
Et	1760, 1567	5.20 (s, 2)	1.28 (t, 3)	4.25 (q, 2)	626-35-7
i-Pr	1750, 1560	5.16 (s, 2)[c]	1.30 (d, 6)	5.1 (m, 1)[c]	31333-37-6
Cyclohexyl	1740, 1560	5.12 (s, 2)	~1.5 (b, 10)	4.9 (b, 1)	75-36-5

[a] Relative to tetramethylsilane. [b] s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. [c] Imperfectly resolved.

(**3b**) was added within 5 min. Temperature was maintained at −10° during addition and subsequently for 1 hr. Then the reaction mixture was allowed to warm to 21° and 0.31 g (0.003 mol) of anhydrous Na_2CO_3 was added. The color changed from pale yellow to yellow-orange. Analysis by GLC indicated that **3b** had reacted completely and that **6b** had been produced in 97% yield and **9b** in 2% yield. The bulk of volatiles was eliminated below 50° in the rotary evaporator. The residue was filtered and distilled under vacuum[15] to give 9.5 g (54%) of yellow liquid **6b**. Physical properties are shown in Table II.

Anal. Calcd for $C_6H_9NO_5$: C, 41.15; H, 5.18; N, 8.00. Found: C, 41.37; H, 5.25; N, 7.66.

Sodium Salt of Ethyl Nitroacetoacetate. A solution of 1.75 g (0.010 mol) of **6b** in 10 ml of MeOH was made and immediately treated at room temperature with a solution of 0.70 g (0.013 mol) of MeONa in 3 ml of MeOH. A white, crystalline precipitate formed. EtOH (30 ml) was added and the reaction mixture was stirred for 10 min and filtered. The product was washed with EtOH and dried in vacuo at 70°, yield 1.46 g (74%), mp 222–224° dec.

Anal. Calcd for $C_6H_8NO_5Na$: C, 36.54; H, 4.09; N, 7.11. Found: C, 36.32; H, 4.37; N, 6.83.

Estimate of the pK_a of Ethyl Nitroacetoacetate (6b). The sodium salt of **6b** (0.197 g, 1.00 mmol) was dissolved in 30 ml of 0.0167 *N* HCl (0.50 mequiv). The pH of the solution was monitored for 10 min at 22° with a combination glass–calomel electrode. The pH drifted from 2.71 to 4.04 during this time. A plot vs. time extrapolated at the origin to pH 2.4, which was taken as equal to the pK_a of **6b**. A second plot was obtained by mixing equimolar quantities of **6b** and its sodium salt dissolved respectively in MeOH and water. The total initial concentration of **6b** and its anion in the mixture was 0.035 *M* and the ratio of MeOH to water was 1:5 by volume. The two plots differed by less than 0.2 pH units at any time point and extrapolated to essentially the same value at the origin.

Ethyl Nitroacetate. A. With 70.4% Nitric Acid. The nitration procedure described in the synthesis of **6b** was repeated on a tenfold scale. *Caution: When working on this scale it is important to control the temperature as closely as possible. Best control was obtained by maintaining a Dry Ice–acetone bath on a jack below the reactor and lifting it as required.* Addition of **3b** was complete in 10 min. At the end of the nitration the temperature was raised to 21° and 500 ml of EtOH was added. The reaction mixture was allowed to remain for 1 hr at 30°, then 2.1 g (0.02 mol) of Na_2CO_3 was added and the mixture was concentrated in the rotary evaporator. The residue was filtered and the filtrate was fractionated under vacuum to yield 125 g (94%) of faintly yellow liquid ethyl nitroacetate: bp 70° (1.5 mm); ir (neat, NaCl plates) 1760, 1567 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (t, 3 H), 4.25 (q, 2 H), 5.20 (s, 2 H). Both spectra were similar to the spectra of a sample of ethyl nitroacetate prepared according to a literature method.[16] Identity was further confirmed by coinjection in two GLC columns with the same sample of ethyl nitroacetate.

B. With 99% Nitric Acid. To 200 ml (2.10 mol) of Ac_2O were added dropwise with good stirring 44 ml (1.05 mol) of colorless distilled 99% nitric acid. The temperature during addition was maintained at 0–5° by external cooling. The mixture was kept at 5° for an additional period of 5 min; then it was cooled to −15° and 130 g (1.00 mol) of **3b** was added at this temperature. No reaction was evident. To the reaction mixture was added dropwise a solution of 0.20 ml (0.002 mol) of 70% $HClO_4$ in 5 ml of acetic acid. Vigorous evolution of heat was evident during addition of catalyst but the temperature was maintained at −10°. Addition was complete in about 10 min. *Caution: It is important to maintain good temperature control. This was best accomplished by maintaining a Dry Ice–acetone bath on a jack under the reaction vessel and lifting it as required. In large-scale reactions with 99% HNO_3 the reaction was best controlled by adding the catalyst last.* After 1 more hr at −10°, the reaction mixture was allowed to reach 21° and was worked up as described under part A. Similar yields of ethyl nitroacetate were obtained and the product was faintly yellow. In an alternate work-up, the nitration mixture was stirred for 2 hr with 500 ml of water at room temperature, the mixture was extracted with methylene dichloride, and the extract was fractionated. The distilled product was colorless in this case, but the yield was the same.

Other Nitroacetoacetate Esters. Methyl nitroacetoacetate (**6a**), isopropyl nitroacetoacetate (**6c**), and cyclohexyl nitroacetoacetate (**6d**) were prepared in a similar manner as **6b** (Table I) and were characterized by ir and NMR spectra (Table II).

Other Nitroacetate Esters. Methyl nitroacetate, isopropyl nitroacetate, and cyclohexyl nitroacetate were obtained by cleavage of the corresponding crude nitroacetoacetates. The yields, based on the nitroacetoacetates charged, were essentially quantitative (GLC). The nitroacetates (except methyl nitroacetate) were characterized by ir and NMR spectra (Table V). The identity of methyl nitroacetate was confirmed by coinjection in two GLC columns with material prepared by a literature method.[16]

3,4-Bis(ethoxycarbonyl)furazan 2-Oxide (9b). This was isolated from the residue remaining after distillation of **6b**: yellow liquid, bp 98° (0.35 mm); NMR ($CDCl_3$) δ 1.39 (t) and 1.44 (t, total 6 H), 4.45 (q) and 4.50 (q, total 4 H).

Anal. Calcd for $C_8H_{10}N_2O_6$: C, 41.74; H, 4.38; N, 12.17. Found: C, 41.71; H, 4.50; N, 12.38.

Nitration of Ethyl 3-Acetoxy-2-butenoate (10b). Concentrated H_2SO_4 (0.011 ml, 0.0002 mol) was added to 11.4 ml of Ac_2O. The mixture was cooled to 10°, then 1.30 ml (0.021 mol) of 70.4% HNO_3 was added dropwise with good stirring while maintaining the temperature at 10–15° with external cooling, followed by 3.44 g (0.020 mol) of **10b**. After 50 min at 15°, Na_2CO_3 (0.10 g, 0.001 mol) was added and the mixture analyzed by GLC. It contained **6b** (63%) and **9b** (35%). The identities of both **6b** and **9b**, were confirmed by coinjection with the authentic compounds in two GLC columns.

Conversion of Ethyl Nitroacetoacetate (6b) to 3,4-Bis(ethoxycarbonyl)furazan 2-Oxide (9b). The conversion of **6b** to **9b** was carried out in vials immersed in a water bath maintained at 22°. The progress of the reaction was monitored by GLC. The concentration of **9b** was plotted vs. time as for a first-order reaction. The fit was reasonably good. The results are summarized in Table III.

Cleavage of Ethyl Nitroacetoacetate (6b). The cleavage of **6b** by various nucleophiles was carried out in vials immersed in a water bath maintained at 22°. The progress of the reaction was monitored by GLC. The concentration of **6b** was plotted vs. time as for a first-order reaction. The fit was reasonably good. First-order kinetics were assumed whenever the reaction was too fast to permit multiple analysis. The results are summarized in Table IV.

Acknowledgments. The author wishes to thank Mr. George E. Babbit for the NMR experiments.

Registry No.—**3a**, 105-45-3; **3b**, 141-97-9; **3c**, 542-08-5; **3d**, 6947-02-0; **6a**, 29291-62-1; **6b**, 51026-98-3; **6b** Na salt, 56689-02-2; **6c**, 51026-99-4; **6d**, 51027-00-0; **7a**, 30414-52-19; **7b**, 56689-03-3; **7c**, 56689-04-4; **7d**, 56689-05-5; **9b**, 18417-40-8; *trans*-**10b**, 27750-19-2; *cis*-**10b**, 26805-39-0; acetyl chloride, 75-36-5.

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Deuterium Isotope Effects and the Influence of Solvent in the Redox and Rearrangement Reactions of 2-Picoline *N*-Oxide and Phenylacetic Anhydride[1]

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The reaction of 2-picoline *N*-oxide with phenylacetic anhydride proceeds by two paths: rearrangement to produce picolyl phenylacetate (**6**), 2-(β-phenylethyl)pyridine (**7**), other minor rearrangement products, and CO_2, and oxidation to give benzaldehyde, 2-picoline, and CO_2. The ratio of the competing processes is sensitive to the incorporation of deuterium at appropriate sites in the reactants, thereby permitting a convenient method for determining hydrogen isotope effects. For rearrangement, a primary kinetic isotope effect value (3.8–4.2) is obtained when reactions of methyl-deuterated and undeuterated 2-picoline *N*-oxide are compared, confirming earlier work on related systems that anhydro base (**5**) formation is rate determining. Oxidation, however, manifests an inverse isotope effect (0.76–0.81, deuterium labeling at the methylene groups of phenylacetic anhydride) which, along with other evidence, suggests reversible enol or enolate formation prior to an SN1′-like rate-determining step to generate the reactive carbocation **3** or its conjugate base. Solvent polarity also significantly, but not dramatically, affects the ratio of the competing pathways. A trend is established which supports the proposed mechanisms if they are modified to include ion pairing phenomena. Furthermore, the influence of solvent polarity is found to be consistent with a dual mode of fragmentation of anhydro base intermediate **5**.

For over two decades there has been considerable interest in both the mechanistic and synthetic aspects of the reactions of carboxylic acid derivatives with the *N*-oxides of pyridine and picoline. The four-electron oxidative decarboxylation of anhydrides (or a mixture of the corresponding acid and acetic anhydride) which possess an acidic α hydrogen by pyridine *N*-oxide produces aldehydes or ketones, carbon dioxide, and pyridine as major products.[2-5] For example, the oxidation of phenylacetic anhydride by pyridine *N*-oxide produces benzaldehyde and proceeds according to the following stoichiometry.

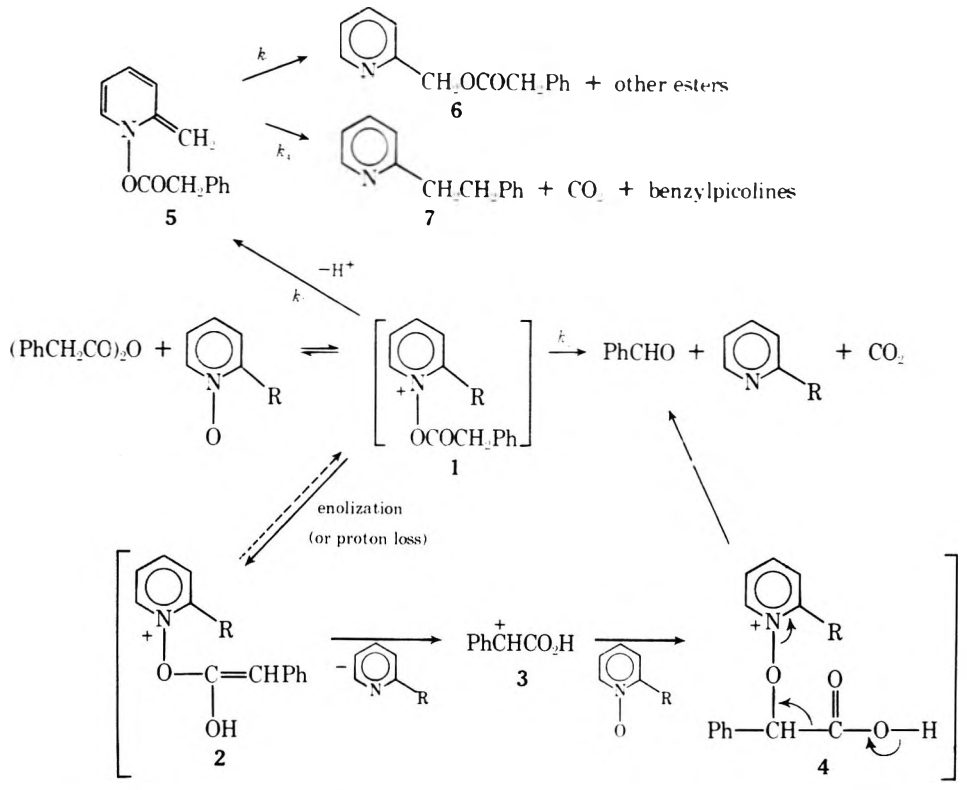
$$(PhCH_2CO)_2O + 2C_5H_5NO \rightarrow PhCHO + 2C_5H_5N + CO_2 + PhCH_2CO_2H$$

The reaction is thought[2-5] to involve acylation of pyridine *N*-oxide, probably reversibly,[6] to yield the *N*-acyloxypyridinium ion **1** (R = H) (Scheme I). The latter cation, by reaction with a second molecule of pyridine *N*-oxide and loss of a pyridine molecule, is then believed to produce the intermediate *N*-(α-carboxybenzyloxy)pyridinium ion **4** (R = H) or the corresponding carboxylate zwitterion.[2-5] Decarboxylative fragmentation of **4** (R = H) (or its conjugate base) as shown would yield benzaldehyde, carbon dioxide, and pyridine.[7]

Although there is substantial evidence for the intermediate **4** (or its conjugate base),[5,8a] the mechanism of the conversion of **1** to **4** is not entirely clear. It has been suggested[2,4,5,8a] that pyridine is displaced from the enol **2** (R = H) of **1** (R = H) by pyridine *N*-oxide in an SN1′ or SN2′ manner. Enolization is consistent with the requirement for an α hydrogen atom.[2b,3c,5] On the basis of the experimental finding that pyridine *N*-oxide is much more nucleophilic than pyridine toward the intermediate, an SN1′ attack involving the α-carboxybenzylcarbenium ion **3**, or its conjugate base, has been favored.[8a] Some such electrophilic intermediate has been trapped by acetic acid and by pyridine, each utilized as solvent.[5] Further evidence for a cationic intermediate of type **3** has been found in the oxidation of 2,3-diphenylpropanoic acid by pyridine *N*-oxide;[8b] in addition to attack by *N*-oxide to ultimately yield the expected oxidation product, the reactive electrophilic species undergoes loss of an adjacent proton to produce an α,β-unsaturated carboxylic acid and it is also attacked by acetate to give the 2-acetoxy derivative of the starting acid.

The reaction of 2-picoline *N*-oxide with phenylacetic anhydride yields, by a similar path, the products of oxidative decarboxylation, benzaldehyde, carbon dioxide, and 2-picoline (Scheme I, R = Me). By an alternative path, the rearrangement products 2-pyridylmethyl phenylacetate (**6**), 3- and 5-phenylacetoxy-2-picoline, 2-(β-phenylethyl)pyridine (**7**), and 3- and 5-benzyl-2-picoline are also obtained[9] (Scheme I). The rearrangement process is thought to pro-

Scheme I[a]



[a] k_1' and k_2' are the corresponding rate constants for the reactions of methyl-labeled N-oxide and benzyl-labeled anhydride, respectively.

ceed through the anhydro base intermediate 5 which arises by proton abstraction from the acylated N-oxide 1 (R = H).[9,10] Dissociation of 5 to a picolyl acylate ion pair,[9,11,12] followed by recombination of the ion fragments, leads to ester products, while homolysis of the N–O bond, with concerted decarboxylation, leads to 7 and benzylpicolines.[9] Traynelis[13a] and Oae[13b] have presented evidence which suggests that anhydro base formation is the rate-limiting step in the rearrangement process when 2-benzylpyridine N-oxide and 2- and 4-picoline N-oxide are treated with acetic anhydride.

The 2-picoline N-oxide–phenylacetic anhydride system readily lends itself to an internal competition method of determining hydrogen isotope effects[14] and identifying rate-determining steps in both the oxidative decarboxylation and rearrangement mechanisms. If 2-picoline N-oxide is treated with phenylacetic anhydride-d_4, and if an α deuterium atom of the anhydride is involved in the rate-determining step of the oxidation process, such as in the formation of an enol or enolate species, or in an equilibrium immediately prior to the rate-determining step, the rate constant for oxidation (k_2', Scheme I) would differ from that (k_2) observed for nonlabeled reactant while the rate constant for rearrangement (k_1) would not be expected to vary.[15] The ratio of rate constants is proportional to the ratio of the yield of oxidation product to that of rearrangement products. A hydrogen isotope effect value, k_H/k_D, may then be calculated for the redox process by comparing the ratio obtained in a control reaction of unlabeled reactants (k_2/k_1) to the one obtained in the labeled reaction (k_2'/k_1). Confirming evidence that anhydro base formation is rate determining in the rearrangement process may be obtained by similarly calculating the hydrogen isotope effect when methyl-deuterated 2-picoline N-oxide is allowed to react with unlabeled phenylacetic anhydride.

The 2-picoline N-oxide–phenylacetic anhydride system is also ideally suited for a study of the effect of solvents on the oxidation and rearrangement mechanisms. Furthermore, if the proposed dual mechanism of fragmentation in the rearrangement process is operative,[9] the degree of homolytic vs. heterolytic cleavage should vary with solvent. In the present paper, we present the results of these kinetic investigations.

It should be noted that in this system the determination of hydrogen isotope effects by the method of competition has an inherent advantage over a direct measurement of k_H and k_D. Variations in product ratios reflect simply the relative rates of decomposition of acylated N-oxide 1 (R = Me), whereas k_H (or k_D) would contain a contribution from a pre-rate-determining equilibrium (acylation) step.[6] The latter could conceivably be subject to a secondary isotope effect when phenylacetic anhydride-d_4 is allowed to react. Determination of hydrogen isotope effects by competition avoids the necessity for knowing the uncertain magnitude of that effect.

Results

The synthesis of 2-trideuteriomethylpyridine N-oxide was attempted by the sodium deuteroxide catalyzed equilibration of the methyl protons of 2-picoline N-oxide with the deuterons of deuterium oxide.[16] However, successive exchanges resulted in the incorporation of deuterium into the α position of the pyridine ring as well as into the methyl group. Since a deuterium atom on the ring should have no significant effect on the reaction mechanism, the compound 2-trideuteriomethyl-6-deuteriopyridine N-oxide was therefore prepared. Analysis by ^{1}H NMR spectroscopy indicated a deuterium content of 98% in the methyl group. Phenylacetic anhydride-d_4 containing 97% deuterium in the benzyl positions was prepared as described in the Experimental Section.

In the first series of reactions the production of benzal-

Table I
Variation in Benzaldehyde and Ester Products with Deuterium Labeling

Reaction[c,d]	% yields[a,b] Benzaldehyde	Picolyl phenylacetates	Ratio of benzaldehyde to picolyl phenylacetates[e]
I	21.5 ± 0.8	25.3 ± 1.3	0.851 ± 0.016
II	36.2 ± 0.8	11.3 ± 0.1	3.21 ± 0.10
III	49.1 ± 0.4	11.6 ± 0.3	4.24 ± 0.10

[a] Yields were determined by VPC (FID). [b] Results are for duplicate experiments, except for I, which was run in triplicate. Reactions were performed simultaneously. [c] I = 2-picoline *N*-oxide, phenylacetic anhydride; II = 2-picoline *N*-oxide-d_4 (98%), phenylacetic anhydride; III = 2-picoline *N*-oxide-d_4 (98%), phenylacetic anhydride-d_4 (97%). [d] 4 equiv of *N*-oxide and 1 equiv of anhydride in 25 ml of benzene heated at reflux under nitrogen for 24 hr. [e] The ratio of each run was determined and the average reported here.

dehyde and esters[17] was taken as a measure of the relative importance of oxidation and rearrangement pathways, respectively, *i.e*, $k_2/k_1 \simeq$ % benzaldehyde/% esters. The yields in control and labeled reactions are presented in Table I. The reaction of labeled *N*-oxide with phenylacetic anhydride (reaction II) gave a ratio of aldehyde to esters (k_2/k_1') of 3.21 ± 0.10. A ratio of 0.851 ± 0.016 was obtained in the nonlabeled control reaction (k_2/k_1) (reaction I). Therefore, a hydrogen isotope effect value of about 3.8 for the rearrangement process may be calculated from eq 1.

$$(k_H/k_D)_{rearr} = k_1/k_1' = (k_2/k_1')/(k_2/k_1) \simeq 3.8 \pm 0.2 \quad (1)$$

Reaction II produced benzaldehyde containing 8% deuterium. The deuterium incorporation probably arose (see below) from the exchange of phenylacetic acid-d_1 (produced in the formation of the anhydro base intermediate) and unreacted phenylacetic anhydride.

When 2-picoline *N*-oxide was allowed to react with the labeled anhydride, the product benzaldehyde was found to contain only 25.5% deuterium. Such a result is suggestive of considerable loss of deuterium in the anhydride by exchange with water, phenylacetic acid, or ester products. It was then shown that under the reaction conditions phenylacetic anhydride readily exchanges α deuterons in the presence of acetic acid, 2-picoline, and water. Because of this exchange *the reaction of 2-picoline N-oxide and labeled anhydride does not permit a direct determination of the hydrogen isotope effect for the oxidative process.*

However, if deuterated anhydride is treated with deuterated *N*-oxide, the ratio of benzaldehyde to ester products is now a measure of k_2'/k_1'. The quotient of this value and the nonlabeled reaction value is

$$k_2'/k_1' \div k_2/k_1 = k_1/k_1' \times k_2'/k_2 \quad (2)$$

where $k_1/k_1' = 3.8 \pm 0.2$ (vide supra).

When the reaction of 2-picoline *N*-oxide-d_4 and phenylacetic anhydride-d_4 (reaction III) was conducted under strictly anhydrous conditions, a ratio of aldehyde to esters of 4.24 ± 0.10 was obtained. Equation 2 may then be solved for k_2/k_2', the hydrogen isotope effect for the oxidation pathway, to give 0.76 ± 0.07, or $(k_D/k_H)_{oxidn} = 1.3 \pm 0.1$.

The k_H/k_D values determined above for both rearrangement and oxidation were checked at an earlier stage of the reaction. When 2-picoline *N*-oxide-d_4 and unlabeled phenylacetic anhydride were heated in refluxing benzene for 30 min, an aldehyde to ester ratio of 3.46 was observed. This corresponds to an isotope effect of 4.1 for the rearrangement process. Comparison of the ester yield with that at the end of 24 hr indicated 70% reaction. Similarly, a mixture of labeled *N*-oxide and labeled anhydride heated in refluxing benzene for only 5 min gave an aldehyde to ester ratio of 4.95, corresponding to a k_H/k_D value of 0.65 for oxidation. The reaction was 38% complete.

Table II
Variation in 2-Picoline and Ester Products with Deuterium Labeling

Reaction[c,d]	% yields[a,b] 2-Picoline	Picolyl phenylacetates	Ratio of 2-picoline to picolyl phenylacetates[e]
I	23.9 ± 0.1	25.6 ± 0.5	0.936 ± 0.020
II	37.0 ± 0.4	9.39 ± 0.16	3.94 ± 0.03
III	53.5 ± 0.7	11.0 ± 0.2	4.87 ± 0.16

[a] Yields were determined by isothermal VPC (TC). [b] Results are for duplicate experiments. [c] Reactions correspond to those in Table I. [d] 4 equiv of 1.0 *M* *N*-oxide (benzene) and 1 equiv of anhydride heated at reflux under nitrogen for 24 hr. [e] The ratio of each run was determined and the average reported here.

Under experimental conditions in which *N*-oxide is the limiting reagent it had been shown that some product benzaldehyde was consumed in a Perkin-type condensation with excess phenylacetic anhydride.[9] Conceivably, then, the variation in benzaldehyde yields in the above series of reactions (particularly reaction III) could reflect an unknown contribution from changes in the amount of product destruction due to a condensation isotope effect. In order to eliminate that uncertainty, a second series of reactions was performed in which 2-picoline was analyzed as a measure of the oxidation pathway. The results are presented in Table II. By the method discussed above, hydrogen isotope effects of 4.2 ± 0.1 and 0.81 ± 0.06 can be calculated for the rearrangement and oxidation processes, respectively. The values are in good agreement with those determined in the first series of reactions.[19]

The effects of several solvents on the ratio of oxidation to rearrangement and of homolytic to heterolytic fragmentation are summarized in Table III.

Discussion

The magnitude of the k_H/k_D value for the rearrangement process (3.8–4.2) is clearly indicative of a primary isotope effect and is further confirmation of the suggestion[13] that removal of a methyl proton from 1 (R = Me) to form the anhydro base intermediate 5 is the rate-determining step in that pathway. Oae et al.,[13b] utilizing a kinetic method which results in an overall isotope effect for the rearrangement rather than an isotope effect proceeding from the *N*-acyloxypicolinium ion as in the present report, found a value of 6.3 for the reaction of acetic anhydride with 2-picoline *N*-oxide in dioxane.

A more striking observation to be noted from the deuterium labeling study is that the replacement of hydrogen by deuterium atoms at the benzylic position of phenylacetic anhydride *enhances* the production of benzaldehyde, i.e., k_D/k_H is 1.2–1.3 for the oxidative decarboxylation process. Such an inverse isotope effect may be readily rationalized if one assumes that the hydrogen transfer step is reversible.[20] Consistent with this assumption is an equilibrium involving formation of an enol or enolate prior to the rate-determining step (Scheme I, with dotted arrow as a real arrow). Since a chemical equilibrium depends upon the rates of the forward and reverse reactions, the position of enol or enolate equilibrium would be slightly affected by the substitution of deuterium for benzylic hydrogen atoms. The direction of shift would be expected to be toward enolization since the zero-point energy for the stretching vibration of the OH bond is greater than for the CH bond.[14a] The equi-

Table III
Variation in Yields of Oxidation and Rearrangement Products with Solvent

Solvent (ϵ)	% yields[a]		Ratio of benzaldehyde to picolyl phenylacetates	2-(β-Phenylethyl)-pyridine, %[a,b]	Ratio of 2-(β-phenylethyl)-pyridine to picolyl phenylacetates
	Benzaldehyde	Picolyl phenylacetates			
Benzene (2.3)	21.5 ± 0.8	25.3 ± 1.3	0.851 ± 0.016	7.01 ± 0.31	0.268 ± 0.004
	(23.1 ± 0.5)[c]	(28.6 ± 1.1)	(0.808 ± 0.013)		
o-Dichlorobenzene (9.9)	22.5	26.7	0.845	*d*	*d*
Benzonitrile (25)	32.5	29.4	1.11	6.40	0.217
Sulfolane (44)	31.0 ± 1.3	20.7 ± 0.5	1.50 ± 0.09	2.75 ± 0.20	0.133 ± 0.006
	(31.7)[c]	(20.1)	(1.58)		

[a] Yields were determined by VPC (FID). Results are for duplicate experiments where ranges are given. [b] Yields are relative, not absolute (see Experimental Section). [c] 2,6-Lutidine added. [d] Not determined.

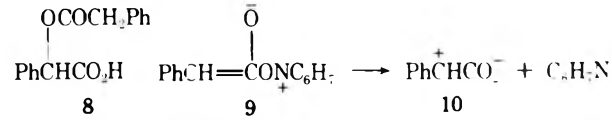
librium constant is increased, and the oxidation reaction rate therefore is accelerated.

The possibility of enolization or enolate anion formation being rate determining is eliminated since a value of $(k_H/k_D)_{oxidn}$ less than unity was obtained (0.76–0.81). In view of the kinetic work by Koenig,[4] in the case of reaction of 4-picoline *N*-oxide with phenylacetic anhydride, in which the disappearance of anhydride was found to be first order in *N*-oxide concentration, and consistent with our earlier study of pyridine and pyridine *N*-oxide nucleophilicities,[8a] the present finding of an inverse isotope effect strongly suggests that the slow step for the oxidation process is the SN1′ attack of pyridine *N*-oxide on the enol **2** (R = Me) or its enolate anion. That is, fragmentation of **2** or its conjugate base to picoline and **3** or its conjugate base is rate determining.

The variation in yields of oxidation and rearrangement products with solvent (Table III) establishes a trend that is in agreement with the postulated mechanisms. One would expect the rate constant for oxidation, k_2, to remain relatively unaffected as solvent polarity is varied, since charge is neither created nor destroyed in the equilibrium step (enolization or enolate formation) or in the rate-determining step (the loss of picoline from the enol or enolate). However, k_1, the rate constant for rearrangement, should decrease significantly as the solvent polarity increases, since the process proceeds through a transition state in which charged species are neutralized (anhydro base formation). The effect of increasing solvent polarity on these rate constants, as reflected in the yield ratio of benzaldehyde to picolyl phenylacetates, is a 31% increase in the rate of oxidation relative to that of rearrangement upon proceeding from benzene to benzonitrile and a corresponding increase of 76% from benzene to sulfolane. The result is thus consistent with a decrease in the rate constant for rearrangement (k_1) with an increase in solvent polarity.

Although the trend is in the expected direction, the magnitude of rate change is somewhat surprising since one might expect k_1 to decrease by several powers of ten when the dielectric constant of the solvent is increased 20-fold (benzene to sulfolane).[21] The observed change in k_2/k_1 of less than twofold might be rationalized by assuming that the cationic intermediate **1** (R = Me) and the phenylacetate anion exist as an ion pair.[22] If this is so, the reaction paths of **1** would only be marginally susceptible to the effect of dielectric change.

If the phenylacetate were indeed a counterion to the α-carboxybenzylcarbenium ion **3**, it would seem that a significant amount of phenylacetylmandelic acid (**8**), resulting from attack of the phenylacetate counterion on the cation **3**, should form. Since this is not the case,[5] we prefer formation of the enolate **9** around which no counteranion is likely to be present. The phenylacetate ion is neutralized by proton abstraction from **1** (R = Me) to give the acid and enolate species (**9**) which then loses 2-picoline to give the zwitterion **10**.[25,26]



In view of the suggestion that intermediate **1** (R = Me) proceeds to react in an ion pair, then the addition of base to the reaction solution, for the purpose of attempting to determine whether an enol or enolate species is involved in the equilibrium prior to the rate-determining step, would not be expected to change k_2/k_1 appreciably. In agreement with this expectation no significant change in the yield ratio of benzaldehyde and esters was observed when 2,6-lutidine was added (in a mole ratio of 1:1 with the anhydride) to the reaction in solvents benzene or sulfolane (Table III).

A final aspect of this study concerns the effect of solvents on the modes of cleavage which the anhydro base **5** may undergo (Table III). Heterolytic fragmentation of the NO bond, k_3 (Scheme I), produces the 2-picolyl cation and phenylacetate anion which recombine to produce picolyl phenylacetates. On the other hand, homolytic fragmentation, k_4 (Scheme I), with concerted decarboxylation, produces 2-picolyl and benzyl radicals, which upon recombination yield 2-(β-phenylethyl)pyridine and benzylpicolines.[9] The rate constant ratio of homolytic to heterolytic fragmentation (k_4/k_3) is proportional to the ratio of the yields of 2-(β-phenylethyl)pyridine[27] and esters. Table III records the yield ratios observed in several solvents.

The rate constant for heterolytic fragmentation (k_3), a process in which ionic species are formed, would be expected to increase as solvent polarity increases, whereas the rate constant for homolytic fragmentation (k_4) should be rather insensitive to solvent changes. As shown in Table III, the yield ratio of 2-(β-phenylethyl)pyridine to picolyl phenylacetates does indeed decrease as solvent polarity is increased. This result reflects the expected increase in k_3 and lends additional support to the proposed dual mechanism of fragmentation of anhydro base intermediate **5**. Furthermore, the 20-fold change in solvent dielectric (benzene to sulfolane) once again has a rather small effect on the ratio of rate constants, which decreases only twofold. The small solvent effect on the competition between heterolysis and homolysis can once again be explained by ion pairing; the anhydro base **5** probably rearranges to the ester **6** by way of a tight ion pair, a suggestion which is consistent with Oae's labeling studies[24] and is in complete accord with current theory.[10-12]

Experimental Section[28]

2-Picoline *N*-Oxide-d_4. To a solution of 50.0 g (2.50 mol) of deuterium oxide (99.8% D, Stohler Isotope Chemicals) and 100 ml of dry dioxane in a flask equipped with a reflux condenser and

magnetic stirrer was added piece by piece 1.4 g of freshly cleaned metallic sodium. The resulting sodium deuterioxide concentration was approximately 5%. Then 54.5 g (0.500 mol) of 2-picoline *N*-oxide was introduced into the two-phase system and the reaction mixture was stirred and heated at reflux (100°) for 3 hr. After being cooled, the aqueous sodium deuteroxide layer was removed by pipet. The remaining solution was filtered, and the filtrate neutralized with a concentrated solution of deuterium chloride in deuterium oxide. (A deuterium chloride solution of approximately 35% concentration was prepared by slowly adding 11 g of freshly distilled thionyl chloride to 20 g of deuterium oxide.) Removal of the cosolvent on a rotatory evaporator left the pale yellow crude liquid *N*-oxide and solid sodium chloride. The crude *N*-oxide was subjected to three additional exchanges. Each exchange utilized 50.0 g (5 equiv) of deuterium oxide, 1.4 g of sodium, and 100 ml of dioxane under the procedure outlined above. Before the final exchange was accomplished, the dioxane was heated at reflux over calcium hydride overnight and distilled at 101°, and all glassware used was flame dried.

Carbon tetrachloride was added to the crude liquid *N*-oxide and sodium chloride suspension, and the salt was removed by filtration through a medium porosity sintered-glass filter. Thorough evaporation of the solvent left the crude *N*-oxide. Vacuum distillation (93–95°, 0.25 mm) of the material afforded 55.0 g (97%) of the pure, white, crystalline product, which was stored in a vacuum desiccator ($CaSO_4$). Decreases in the integrated ^1H NMR signals at τ 1.7 (α-H) and 7.6 ($-CH_3$) indicated 98% deuterium incorporated at each site.

Phenylacetic Anhydride. Phenylacetic anhydride was prepared in 72% yield by the method of Cohen and Fager.[9] The anhydride was further purified by dissolving in ether, washing the solution successively with 10% sodium carbonate solution and water, drying it over calcium sulfate, and cooling in powdered dry ice to give a white, crystalline solid: mp 72.0–72.5° (lit.[9] mp 72.5–73.0°); ^1H NMR (CCl_4) τ 6.4 (s, 4 H), 2.85 (s, 10 H).

Phenylacetic Anhydride-d_4. Phenylacetonitrile-d_2 was prepared as follows. A vigorously stirred solution of 58.5 g (0.500 mol) of phenylacetonitrile, 50.0 g (2.50 mol) of deuterium oxide (99.8% D, Columbia Organic Chemicals), and 150 g of pyridine which had been dried over 4 Å molecular sieve (Linde) was heated at reflux (100°) for 23 hr. Then 10% aqueous hydrogen chloride was added to the reaction mixture until it became acidic to litmus. The solution was extracted with ether, and the combined extracts were dried over Drierite. Evaporation of the solvent left colorless, partially deuterated phenylacetonitrile. The nitrile was subjected to three additional exchanges by the same procedure. Each exchange utilized 5 equiv of deuterium oxide in a 75% pyridine solution. An ir spectrum of the deuterated phenylacetonitrile indicated a decrease in the signal at 3.38–3.44 μ, the appearance of the signal at 4.73 μ, and the disappearance of the signal at 7.08 μ (C–H stretch, C–D stretch, and C–H bend, respectively). An integrated ^1H NMR spectrum was consistent with essentially complete deuteration. No α protons were detectable in the τ 6.25–6.35 region.

To a solution of 30 g (1.5 mol) of deuterium oxide and 120 ml of dry dioxane was added piece by piece 11.5 g (0.50 mol) of freshly cleaned metallic sodium. The phenylacetonitrile-d_2 from above was added, and the solution was vigorously stirred and heated at reflux (100°) for 84 hr. Throughout this period the reaction solution was swept with dry nitrogen to remove ammonia. Evaporation of the solvent left a pink solid. The crude solid was washed with anhydrous[29] ether to whiteness to yield, after drying in an oven at 110°, 78.9 g (98%) of pure white material. An integrated ^1H NMR spectrum of the sodium phenylacetate-d_2 (D_2O) indicated no α hydrogens in the τ 6.3–6.8 region.

Phenylacetic anhydride-d_4 was then prepared as follows.[31] To a suspension of 10.0 g (0.063 mol) of sodium phenylacetate-d_2, 40 ml of acetonitrile (refluxed over calcium hydride overnight and distilled at 80.5°), and 5 g of activated 3 Å molecular sieves was added dropwise and with stirring a solution of 5.96 g (0.031 mol) of pure[32] *p*-toluenesulfonyl chloride in 20 ml of acetonitrile. The reaction mixture was heated at reflux (81°) for 2 hr. Evaporation of the solvent left a white solid which was added to 150 ml of anhydrous ether. The suspension was filtered and the filtrate cooled in powdered dry ice to give a white, crystalline solid which was collected in a Büchner funnel and dried in a vacuum desiccator ($CaSO_4$) to yield 6.7 g (84%) of pure product, mp 72.5–73.0°. An integrated ^1H NMR spectrum of the phenylacetic anhydride-d_4 indicated 97% deuteration in the α position at τ 6.4.

General Procedure for the Reaction of Phenylacetic Anhydride with 2-Picoline *N*-Oxide in Benzene. In the first series of reactions approximately 3.5 g of 2-picoline *N*-oxide (bp 104–108, 0.3 mm) or its labeled derivative was transferred within a drybox to the reaction flask. Anhydrous benzene (25 ml) and sufficient labeled or unlabeled phenylacetic anhydride (about 2.0 g) to give a 4:1 mole ratio of *N*-oxide to anhydride were added. The solution was heated at reflux (80°) for 24 hr under an atmosphere of dry nitrogen. Quantitative analysis of the yields of benzaldehyde (15% Carbowax 20M column at 130°, 14 min) and picolyl phenylacetates (3% OV-17 column at 200°, 20–28 min) in an aliquot were determined directly by VPC (FID). Durene (9.3 min) and triphenylmethane (42 min), respectively, were employed as internal standards.

In the second series of reactions approximately 34 ml of 1.0 *M* 2-picoline *N*-oxide in anhydrous benzene was added to phenylacetic anhydride (mole ratio 4:1). After heating the solution at reflux for 24 hr under nitrogen, an aliquot was analyzed by VPC (TC, 3% OV-17) for yields of 2-picoline (7.2 min at 90°) and picolyl phenylacetates (23–26 min at 240°). Triphenylmethane (30 min at 240°) was used as an internal standard. Benzaldehyde, 2-picoline, and esters were identified by comparison of retention times with those of authentic samples. A summary of the yield data in both series of labeled and unlabeled runs is presented in Tables I and II.

The benzaldehyde product in reactions II and III (Table I) was analyzed for deuterium content. Respectively, 3 and 74% deuterium enrichments were found.

Product Yields at an Earlier Stage of the Reaction. A mixture of 3.37 g (29.8 mmol) of 2-picoline *N*-oxide-d_4 and 1.88 g (7.4 mmol) of phenylacetic anhydride in 25 ml of dry benzene was heated at reflux under nitrogen for 30 min to yield 27.3% benzaldehyde and 7.90% picolyl phenylacetates, i.e., $k_2/k_1' \simeq 3.46$.

Similarly, a mixture of 3.80 g (33.6 mmol) of 2-picoline *N*-oxide-d_4, 2.16 g (8.4 mmol) of phenylacetic anhydride-d_4, and ca. 6 g of activated 3 Å molecular sieves in 25 ml of dry benzene heated at reflux for 5 min gave 16.8% benzaldehyde and 3.40% esters, i.e., $k_2'/k_1' = 4.95$.

Reaction of Anhydride with N-Oxide in Solvents Other than Benzene. By the general procedure outlined above 2-picoline *N*-oxide and phenylacetic anhydride (mole ratio 4:1) were heated at 80° in *o*-dichlorobenzene, benzonitrile (aniline free), and sulfolane. The yields of benzaldehyde and esters are recorded in Table III.

Comparison of retention times with those of an authentic sample[33] enabled the identification of 2-(β-phenylethyl)pyridine (3% OV-17 at 150°, 42.5 min). A relative yield was obtained by assuming an arbitrary response factor (area ratio of sample to standard vs. weight ratio of sample to standard) of 2.00. Aliquots from the reactions run in benzene, benzonitrile, and sulfolane were analyzed, using triphenylmethane (60 min) as an internal standard. The yields are given in Table III.

Reaction of Anhydride with *N*-Oxide and Added Base. A mixture of 2.85 g (26.2 mmol) of 2-picoline *N*-oxide, 1.66 g (6.52 mmol) of phenylacetic anhydride, and 0.712 g (6.65 mmol) of freshly distilled 2,6-lutidine in 25 ml of dry benzene heated at reflux for 24 hr under nitrogen gave 22.7% benzaldehyde and 27.6% picolyl phenylacetates. In a duplicate run in benzene the corresponding yields were 23.6 and 29.7%. A mixture of 2.80 g (25.7 mmol) of 2-picoline *N*-oxide, 1.64 g (6.46 mmol) of phenylacetic anhydride, and 0.691 g (6.46 mmol) of 2,6-lutidine in 25 ml of dry sulfolane yielded 31.7% benzaldehyde and 20.1% picolyl phenylacetates after heating at 80° for 24 hr.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—2-Picoline *N*-oxide-d_4, 56783-17-6; deuterium oxide, 7789-20-2; 2-picoline *N*-oxide, 931-19-1; phenylacetic anhydride, 1555-80-2; phenylacetic anhydride-d_4, 56783-18-7; phenylacetonitrile, 140-29-4.

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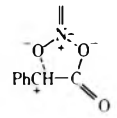
(15) The secondary effects exerted by the benzylic deuterium atoms are indeed long range and may be considered to be negligible here.
(16) R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967).
(17) The absolute yields of benzylpicolines were not determined in these experiments since they would be expected to vary in direct proportion to the yields of esters. Unlike reaction II, the relative rates of heterolytic and homolytic fragmentation in reaction III (see below) may be somewhat affected by a secondary isotope effect at the benzylic position. However, assuming a maximum effect of 1.1[18] and a ratio of esters to benzylpicolines of ca. 2.0,[9] the magnitude of error in the resulting calculation is only 4%. Hence, the yields of benzylpicolines were ignored and the rate of rearrangement was assumed to be directly proportional to the yields of esters.
(18) T. Koenig and R. Wolf, *J. Am. Chem. Soc.*, **91**, 2574 (1969).
(19) Since measuring yield variations in either benzaldehyde or 2-picoline gives similar results, changes in the destruction of benzaldehyde by Perkin condensation must be rather minimal. This is confirmed by the small differences (1–5%) between the yields of 2-picoline and benzaldehyde (Tables I and II).
(20) D. R. Coulson and N. C. Yang, *J. Am. Chem. Soc.*, **88**, 4511 (1966); A. Padwa and R. Gruber, *ibid.*, **90**, 4456 (1968); R. C. Fahey and H.-J. Schneider, *ibid.*, **92**, 6885 (1970).
(21) S. Smith, A. Fainberg, and S. Winstein, *J. Am. Chem. Soc.*, **83**, 618 (1961).
(22) Although the possibility of ion pairing may at first seem remote in sulfolane, it must be remembered that in dipolar aprotic solvents the anion is poorly solvated because it cannot form a hydrogen bond with the solvent. In fact, SN1-like ionization is not common in such solvents.[23]
(23) A. Parker, *Q. Rev., Chem. Soc.*, **16**, 163 (1962).
(24) S. Oae, Y. Kitaoka, and T. Kitao, *Tetrahedron*, **20**, 2685 (1964).
(25) It is also possible that the α-carboxybenzylcarbenium ion **3**, being very acidic, could lose a proton to the phenylacetate anion rather than form a CO bond to it.
(26) The high selectivity of the electrophilic intermediate for pyridine *N*-oxide[8a] might be explained by a 1,3-dipolar interaction of **10** with the *N*-oxide.



(27) Because of an impurity which eluted with either 2-methyl-3-benzylpyridine or 2-methyl-5-benzylpyridine, the yields of those isomers, which represent ca. 20% of the total yield of the three benzylpicoline isomers, were not determined on the VPC. However, it could be estimated from the chromatogram that the yields of the two isomers varied in direct proportion to the yield of the third isomer, 2-(β-phenylethyl)pyridine (**7**). Therefore, the yield of the latter is proportional to the rate of homolysis.
(28) Melting points were determined on a Thomas-Kofler micro hot stage utilizing a stage-calibrated thermometer and are thus corrected. Boiling points are uncorrected. Infrared spectra were determined on Beckman IR-8 or Perkin-Elmer 467 spectrophotometers. Proton magnetic resonance spectra were determined on Varian A-60 or 360 instruments; chemical shifts are relative to internal tetramethylsilane for samples prepared in organic solvents and to the sodium salt of 3-(trimethylsilyl)-1-propanesulfonic acid for samples in aqueous solution. Analytical gas chromatography was performed on Varian 1860-3 (FID) or 920 (TC) instruments equipped with Disc 204 integrators. For determining yields, the responses of authentic samples were calibrated against those of various standards. Isomers were assumed to have identical responses. Isotopic analyses were performed at 20 eV on an LKB 9000 combined gas chromatograph–mass spectrometer equipped with an accelerating voltage alternator.
(29) Sodium phenylacetate slowly exchanges α protons in the presence of 0.05 *M* deuteroxide ion and deuterium oxide.[30] Therefore, to the extent that any sodium deuteroxide remains in the reaction mixture under discussion, redissolving the sodium phenylacetate-d_2 salt in water and washing with ether would dilute the deuterium atom content of the salt.
(30) J. G. Atkinson, J. J. Csakvary, G. T. Herbert, and R. S. Stuart, *J. Am. Chem. Soc.*, **90**, 498 (1968).
(31) It was found that phenylacetic anhydride-d_4 readily exchanges α deuterons in the presence of acidic protons. Therefore, in order to prepare a highly enriched anhydride, all glassware used was oven dried, and the weighings and reagent transfers were performed in a drybox containing phosphorus pentoxide as desiccant. The anhydrous conditions prevent hydrolysis of tosyl chloride to tosyl acid.
(32) D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, "Purification of Laboratory Chemicals", Pergamon Press, Oxford, 1966, p 268.
(33) We are grateful to Dr. J. H. Fager for providing us with an authentic sample of 2-(β-phenylethyl)pyridine.

Cleavage of Cyclic Ethers by Magnesium Bromide–Acetic Anhydride. SN2 Substitution at a Secondary Site

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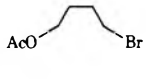
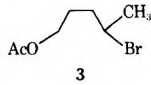
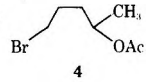
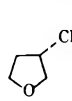
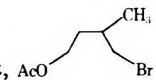
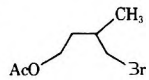
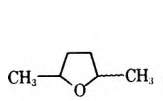
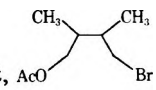
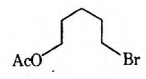
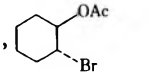
Cyclic ethers are cleaved by magnesium bromide and acetic anhydride in acetonitrile to yield bromoacetates. The reaction occurs readily at room temperature with tetrahydrofuran and substituted tetrahydrofurans. Tetrahydropyrans require higher temperature for cleavage. When *cis*- and *trans*-2,5-dimethyltetrahydrofuran are individually subjected to cleavage conditions a single diastereoisomeric bromoacetate is produced from each. The bromoacetates in turn when exposed to sodium hydroxide in warm ethylene glycol are converted to the specific isomers from which they were formed. Since the reclosure reaction must occur with inversion, the cleavage reaction must also be an inversion process. The mechanism of cyclic ether cleavage with magnesium bromide–acetic anhydride is thus shown to be exclusively an SN2 process.

The ability of Lewis acids and acid anhydrides to cleave ethers has been known since the early part of this century. The reactions have been extensively studied from the standpoints of product composition, mechanism, and stereochemistry, and the subject has been reviewed in detail.[1,2] Despite the "textbook" nature of the process, the search for methods for the formation and cleavage of ethers remains of interest. Ethers serve as effective stable blocking groups for hydroxyl functions and their use in this regard is ubiquitous in organic synthesis. Recently reports of the development of two ether cleavage reagent systems using acid anhydrides have appeared.[3,4]

Table I

Ether	Temp, time, hr	Products	Yield (ratio)
	Ambient, 12		97
 2	Ambient, 15	 3  4	70 (4.1:1)
	Ambient, 15	 	85 (2.7:1)
	Ambient, 15		88
	85°, 15		50
	Ambient, 12		80

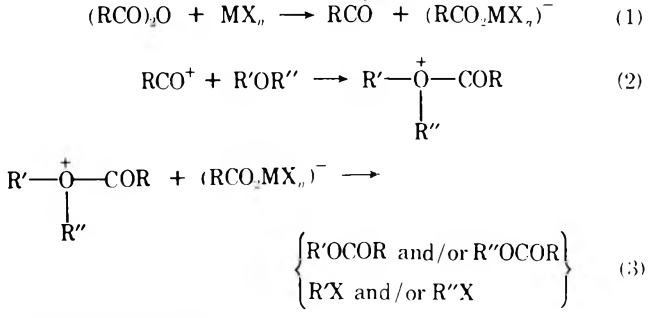
Karger and Mazur[3] have described the cleavage of both cyclic and noncyclic ethers with the mixed anhydride acetyl *p*-toluenesulfonate. In the second recent report, Ganem and Small, using a system originally reported by Knoevenagel, investigated the scope of ether cleavage affected by acetic anhydride and ferric chloride. Both reports also describe efforts to specify the mechanistic aspects of these reactions, whether the cleavage of a specific type of ether with a given reagent is an SN1 or an SN2 reaction or some combination of the two. Unfortunately the results in many of these cases cannot be interpreted unambiguously with regard to a specific mechanism. We wish to describe here a Lewis acid–acid anhydride cleavage reagent for cyclic ethers, and the results of an experiment which clearly define the stereochemical aspect of the mechanism for cleavage of a substituted tetrahydrofuran.

Cyclic ethers, particularly tetrahydrofuran and alkyl-substituted tetrahydrofurans, are cleaved by acetic anhydride in the presence of zinc chloride.[5] Such reactions have been almost invariably carried out at elevated temperatures, 190–250°C. The yields of cleavage products rarely exceed 60–70%, and other Lewis acids have not been employed to any great extent. In contrast both cyclic and acyclic ethers have been cleaved in the presence of a variety of Lewis acids in conjunction with acetyl chloride[1,2] (a more effective cleavage agent than acetic anhydride). Magnesium salts, however, have been reported to be singularly ineffective as cleavage catalysts.[6] On the basis of previous work, one would expect that the combination of acetic anhydride and magnesium bromide at moderate temperature would be among the least efficacious methods for the cleavage of a cyclic ether. It was surprising, therefore, to find that such a melange provides a mild and effective means of converting tetrahydrofurans and other cyclic ethers to the corresponding ω-bromoacetates.

Treatment of tetrahydrofuran at room temperature with 1 molar equiv of magnesium bromide and 2 equiv of acetic anhydride in acetonitrile affords 4-bromobutyl acetate (1) in 97% yield. Methyl-substituted tetrahydrofurans are similarly cleaved in yields ranging from 70 to 88% as shown in Table I. In contrast to its reactivity with acetic anhydride–zinc chloride, 2-methyltetrahydrofuran (2) affords 70% of the substitution products 3 and 4 when treated with acetic anhydride–magnesium bromide. Under the former conditions a 70% yield of olefinic acetate elimination product is obtained.[7] The finding that the major cleavage product of 2-methyltetrahydrofuran is the secondary bromide 3 suggests that the ring opening reaction is largely an SN1 process. Such a conclusion would be commensurate with the findings of Burwell and coworkers[8] for the cleavage methyl *sec*-butyl ether. The latter affords 2-chlorobutane, the product of displacement at the most substituted carbon, 50% racemized, when exposed to acetyl chloride and zinc chloride, a result suggested to be in accord with a carbonium ion process. We shall show, however, for the case of a methyl tetrahydrofuran, that cleavage of the ring and substitution of a nucleophile at the most substituted carbon is, at least stereochemically, an SN2 process.

As shown in Table I, acetic anhydride–magnesium bromide also cleaves tetrahydropyrans and epoxides. As expected,[1,2] the rate of tetrahydropyran opening is considerably slower than that of the five-membered cyclic ether. Elevated temperature is necessary to affect cleavage in a reasonable time, and a considerable portion of the product from an attempted cleavage of 2-methyltetrahydropyran was unsaturated acetate. The opening of the epoxide ring is relatively unexceptional but for the fact that magnesium bromide alone is known to rearrange epoxides under a variety of conditions.[9] We should also note that simple saturated acyclic ethers are not appreciably cleaved by magnesium bromide–acetic anhydride at room temperature, and that neither reagent by itself affects tetrahydrofuran under the described reaction conditions.

Mechanism and Stereochemistry. The commonly accepted mechanism[1,2] for the cleavage of ethers by acid anhydrides and Lewis acids is illustrated in eq 1–3. A similar



$$(RCO)_2O + MX_n \longrightarrow RC\overset{+}{O} + (RCO_2MX_n)^- \quad (1)$$

$$RCO^+ + R'OR'' \longrightarrow R'-\overset{+}{O}(R'')-COR \quad (2)$$

$$R'-\overset{+}{O}(R'')-COR + (RCO_2MX_n)^- \longrightarrow \begin{Bmatrix} R'OCOR \text{ and/or } R''OCOR \\ R'X \text{ and/or } R''X \end{Bmatrix} \quad (3)$$

sequence may be written for reactions involving acid halides.

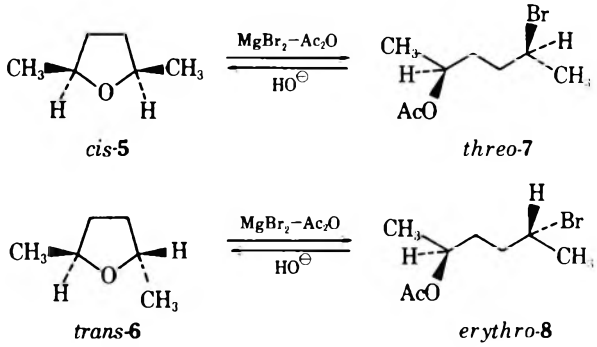
Most investigations of the details of this sequence have focused on step 3, the actual substitution reaction, in order to determine if concerted displacement or stepwise formation of a cation followed by attack of a nucleophile occurs. In their recent work on cleavages promoted by acetic anhydride–ferric chloride Ganem and Small[4] followed the stereochemical course of the reaction of optically active methyl and benzyl 2-octyl ethers. Since ferric chloride is used in these reactions in only catalytic amount, all of the products are acetates. As a consequence the position of substitution (primary vs. secondary) cannot be specified on the basis of product structure. They did observe that the resulting 2-octyl acetate was largely racemized: 96% for the methyl compound and 85% for the benzyl case. Net inversion was also found in the cleavage of the methyl ether and net retention of configuration for the benzyl compound. A variety of pathways for the substitution step of the mechanism (eq 3) may be envisioned to explain such results. For example, in the case of benzyl 2-octyl ether, racemization could result from a relatively equal mix of SN2 substitution occurring at both oxygen-bearing carbons, from SN1 reaction

at the secondary position, or from some combination of both types. Net retention would only require some excess of cleavage at the benzyl position, either concertedly or nonconcertedly. Ganem and Small quite reasonably concluded that the cleavage step occurred by SN1 and/or SN2.

In the case of the cleavage of 2-methyltetrahydrofuran with acetic anhydride–magnesium bromide it is clear that, regardless of specific mechanism, the preferred position for substitution is the secondary carbon. Further insight into the details of the substitution step may be gained from an examination of the stereochemical outcome of the cleavage. One may employ, however, as a substrate, not the optically active material, but the epimerically different compounds, *cis*- and *trans*-2,5-dimethyltetrahydrofuran. Loss of configurational integrity in the cleavage of either of these ethers can be observed as a diastereoisomeric change rather than as an enantiomeric one. To whatever extent either of these ethers yields a mixture of diastereoisomeric products one may invoke the intermediacy of a planar cationic intermediate.

The isomeric ethers *cis*- and *trans*-2,5-tetrahydrofuran were separated from a commercial mixture by spinning band distillation. As little as 10% of one isomer could be detected in the presence of the other by GLC analysis on either an SE-30 or Carbowax 20M liquid phase. The ^{13}C chemical shifts of the methyl and methine carbons of each ether are also readily distinguished and both analytical methods showed that the lower boiling cis compound used for subsequent experiments contained less than 10% of the trans isomer. Each isomer when exposed to anhydrous magnesium bromide–acetic anhydride in acetonitrile produced a *single* bromoacetate. The latter compounds, though undistinguishable by normal spectroscopic methods, are readily separable by GLC.

The production of a single bromoacetate from each of the isomeric dimethyltetrahydrofurans demands that the cleavage reactions occur with either complete retention or complete inversion of configuration. Thus *cis*-**5** must open either with inversion to give *threo*-**7** or with retention to yield *erythro*-**8**. Similarly *trans*-**6** must yield *erythro*-**8** by inversion or *threo*-**7** by retention. The identification of the

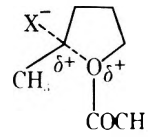


cis-**5** *threo*-**7**

trans-**6** *erythro*-**8**

configurations of the bromoacetates was made by reconstituting the original ethers from the cleavage products. Each of the isomeric bromoacetates was treated with potassium hydroxide in ethylene glycol. The resulting 2,5-dimethyltetrahydrofurans (ca. 40% yield in each case) were isolated by distillation. The bromoacetate from *cis*-**5** gave only *cis*-**5** again after base treatment, and the one obtained from *trans*-**6** similarly afforded only *trans*-**6**. Since re-formation of the ethers from the bromoacetates must be a simple SN2 inversion reaction, *the initial cleavage reaction must also occur cleanly with inversion*. If, for example, *cis*-**5** had undergone either SN1 cleavage or some combination of concerted and nonconcerted opening a mixture of both *cis*-**5** and *trans*-**6** would have been obtained on reclosure. In the event that cleavage had occurred with retention of configuration *trans*-**6** would have been the ultimate product from the opening and reclosure of *cis*-**5**. Our results show therefore that the cleavage of a *secondary* cyclic ether is stereochemically an SN2 process.

The finding that 2-methyltetrahydrofurans are opened at a secondary position with clean inversion of retention cannot necessarily be extended to the cleavage reactions of other ethers. Five-membered heterocycles are in general more easily opened than their higher homologues. Harley-Mason[10] has found, for example, that substituted pyrrolidines are cleaved by anhydrides under conditions where the corresponding piperidines are inert. Tetrahydrofuran cleavage may more closely resemble epoxide opening than the cleavage of an acyclic ether. As a consequence the transition state for opening of the ring of the intermediate acyl oxonium ion in a concerted displacement may display considerable positive character at carbon. Bond breakage may to a large extent precede bond cleavage but without the actual formation of a symmetric intermediate. The finding that concerted displacement occurs preferentially at a secondary site is compatible with such a pathway.[11]



Experimental Section

Gas chromatographic analyses were performed on an F & M 720 chromatograph. Infrared spectra were determined with Perkin-Elmer spectrometers, Models 137-B and 257. Proton NMR spectra were recorded in the indicated solvent with either a Varian T-60 or a Jeol 100-MHz spectrometer and ^{13}C spectra on a Varian CFT-20 instrument. Tetramethylsilane was used as internal reference for both nuclei. Chemical shifts are given in parts per million downfield from Me_4Si. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Solvents were purified according to standard procedures.[12]

4-Bromobutyl Acetate (1). General Procedure for the Cleavage of Tetrahydrofurans. Anhydrous magnesium bromide was prepared by the addition, under an argon atmosphere, of 2.16 ml (26 mmol) of 1,2-dibromoethane to 0.63 g (26 mmol) of magnesium turnings suspended with stirring in 25 ml of dry ether. When formation of the salt was complete the ether was removed under vacuum and replaced with 25 ml of dry acetonitrile. To this stirred suspension, cooled in an ice–water bath, was added 2.05 ml (26 mmol) of dry tetrahydrofuran and 5.2 ml (52 mmol) of acetic anhydride. The reaction mixture was brought to room temperature and stirred for 12 hr. Saturated sodium bicarbonate solution was then added and the mixture was stirred to destroy excess acetic anhydride. Ether extraction followed by drying of the extract over sodium sulfate and evaporation of the solvent under reduced pressure afforded a dark brown oil. Evaporative distillation of the oil yielded 4.89 g (96.5%) of 4-bromobutyl acetate: bp 85–87° (1.8 mm) [lit.[13] 92–93° (12 mm)]; ir ($CHCl_3$) 1742 cm^{-1}; ^1H NMR (CCl_4) 1.6–2.2 (m, 4 H, CH_2), 2.02 (s, 3 H, $COCH_3$), 3.46 (t, 2 H, CH_2Br, J = 6 Hz), 4.08 ppm (t, 2 H, CH_2O–, J = 6 Hz).

Anal. Calcd for $C_6H_{11}BrO_2$: C, 36.95; H, 5.69; Br, 40.97. Found: C, 36.95; H, 5.68; Br, 40.89.

Cleavage of 2-Methyltetrahydrofuran. 4-Bromopentyl Acetate (3) and 5-Bromo-2-pentyl Acetate (4). Cleavage of 2.6 ml (26 mmol) of 2-methyltetrahydrofuran under the previously described conditions gave, after distillation, 3.79 g (70% yield) of a mixture of **3** and **4**. Analysis of the mixture by GLC on a 10 ft × 0.25 in, 10% diisodecyl phthalate column at 145° showed the ratio **3** to **4** to be 4.1:1: ir (mixture) (CCl_4) 1730 cm^{-1}; ^1H NMR (mixture) (CCl_4) 1.22 (d, 3 H, CH_3CHOAc, J = 6 Hz), 1.74 (d, 3 H, CH_3CHBr, J = 7 Hz), 1.7–2.0 (m, 4 H, CH_2CH_2), 2.02 (s, 3 H, $OCOCH_3$), 3.42 (t, 2 H, CH_2Br, J = 6 Hz), 3.98–4.30 (m, 3 H, BrCHC– and $-CH_2O$), 4.96 ppm (m, 1 M, –CCHOAc).

Anal. Calcd for $C_7H_{13}BrO_2$: C, 40.21; H, 6.27; Br, 38.22. Found: C, 40.35; H, 6.28; Br, 38.14.

Cleavage of 3-Methyltetrahydrofuran. The title compound exposed to the standard reaction conditions afforded, after distil-

lation, 4.63 g (85%) of a mixture of 3-methyl-4-bromobutyl acetate and 2-methyl-4-bromobutyl acetate in a ratio of 2.7:1. The proportions of the isomers were obtained from the integrated intensities of the NMR signals for the methylene protons of the acetate-bearing carbons in the two compounds; ir ($CHCl_3$) 1730 cm^{-1}; NMR (CCl_4) 0.98 (d, 3 H, CH_3, J = 6 Hz), 1.07 (d, 3 H, CH_3, J = 7 Hz), 1.5–2.2 (m, 3 H, –CH and CCH_2C), 2.04 (s, 3 H, $OCOCH_3$), 3.35–3.6 (t, 2 H, CH_2CH_2Br and d, 2 H, $-CHCH_2Br$), 3.96 (d, 2 H, $-CHCH_2O$, J = 6 Hz), 4.12 ppm (t, 2 H, CH_2CH_2O-, J = 7 Hz).

Anal. Calcd for $C_7H_{13}BrO_2$: C, 40.21; H, 6.27; Br, 38.22. Found: C, 40.31; H, 6.31; Br, 38.16.

Cleavage of 2,5-Dimethyltetrahydrofuran. A mixture of *cis*- and *trans*-2,5-dimethylfuran (2.6 g, 26 mmol) under the standard conditions afforded 5.22 g (88%) of the diastereoisomeric 2-methyl-4-bromopentyl acetates: ir ($CHCl_3$) 1730 cm^{-1}; NMR (CCl_4) 1.20 (d, 3 H, CH_3CH-O, J = 6 Hz), 1.60–1.95 (m, 4 H, CH_2), 1.69 (d, 3 H, CH_3CHBr, J = 7 Hz), 2.00 (s, 3 H, CH_3CO_2-), 4.13 (m, 1 H, CHBr), 4.9 ppm (m, 1 H, –CHO).

Anal. Calcd for $C_8H_{15}BrO_2$: C, 43.07; H, 6.77; Br, 35.82. Found: C, 43.10; H, 6.78; Br, 35.85.

Cleavage of Tetrahydropyran. Application of the usual conditions with the exception of the reaction temperature, 85° in the present case, to tetrahydropyran (2.53 ml, 26 mmol) yielded 3.32 g (50%) of 5-bromopentyl acetate:[13] ^1H NMR (CCl_4) 1.4–1.8 (m, 6 H, CH_2) 2.0 (s, 3 H, $OCOCH_3$), 3.45 (t, 2 H, CH_2Br, J = 6 Hz), 4.08 ppm (t, 2 H, CH_2O, J = 7 Hz).

Cleavage of Cyclohexene Oxide. The title compound (2.55 g, 26 mmol) after treatment with magnesium bromide–acetic anhydride and subsequent distillation gave 4.58 g (80%) of *trans*-2-bromocyclohexyl acetate:[14] ^1H NMR (CCl_4) 1.15–2 (m, 8 H), 2.05 (s, 3 H), 3.87–4.16 (m, 1 H, CHBr), 4.74–5.0 ppm (m, 1 H, CHOAc).

***cis*-2,5-Dimethyltetrahydrofuran (*cis*-5).** Distillation of commercial 2,5-dimethyltetrahydrofuran at atmospheric pressure through a Nester–Faust annular Teflon spinning band column operating at a reflux ratio of 30:1 afforded *cis*-2,5-dimethyltetrahydrofuran: bp 90–91° (lit.[15] 90–91°); ^1H NMR (CCl_4) 1.15 (d, 3 H, CH_3, J = 6 Hz), 1.28–2.24 (m, 4 H, CH_2), 3.81–4.41 (m, 2 H, CH); ^{13}C NMR ($CDCl_3$) 21.60 (CH_3), 33.38 (CH_2), 75.36 ppm (CH). Both GLC analysis on SE-30 silicone rubber and Carbowax 20M and peak height measurements of the ^{13}C NMR spectrum of the cis compound indicated the presence of no more than 10% of the trans isomer *trans*-2,5-dimethyltetrahydrofuran (*trans*-6).

***trans*-2,5-Dimethyltetrahydrofuran (*trans*-6).** The higher boiling fraction from spinning band distillation afforded the title compound: bp 91–92° (lit.[15] 92–94°); ^1H NMR (CCl_4) 1.13 (d, 3 H, CH_3, J = 6 Hz), 1.28–2.41 (m, 4 H, CH_2), 3.81–4.41 (m, 2 H, CH); ^{13}C NMR ($CDCl_3$) 21.48 (CH_3), 34.31 (CH_2), 74.55 ppm (CH).

Cleavage and Reconstitution of the Isomeric 2,5-Dimethyltetrahydrofurans. Each of the above isomers was subjected to the cleavage conditions described previously. The distilled products were analyzed on a Carbowax 20M column at a programmed temperature rate increase of 2°/min from an initial temperature of 110°. The retention time for *threo*-7 (from *cis*-5) was 10.3 min and that for *erythro*-8 (from *trans*-6) was 11.5 min. Analysis of mixtures of the isomers indicated that 10% of one isomer was detectable in the presence of the other. The bromoacetate *threo*-7 (2.26 g, 10 mmol) was dissolved in 25 ml of ethylene glycol containing 0.7 g of potassium hydroxide. The solution was heated at 60° for 6 hr. Distillation through a Vigreaux column at 92° and atmospheric pressure followed by separation of water and drying yielded *cis*-5 (0.44 g, 44%). Gas chromatographic and spectroscopic analysis as described above indicated the presence of 10% or less of the trans isomer. Application of the same procedure to *erythro*-8 (2.26 g, 10 mmol) afforded pure *trans*-6 (0.42 g, 42%).

Registry No.—1, 4753-59-7; 2, 96-47-9; 3, 26923-92-2; 4, 26923-93-3; 5, 2144-41-4; 6, 2390-94-5; 7, 56761-56-9; 8, 56761-57-0; tetrahydrofuran, 109-99-9; 3-methyltetrahydrofuran, 13423-15-9; 3-methyl-4-bromobutyl acetate, 56761-58-1; 2-methyl-4-bromobutyl acetate, 56761-59-2; 5-bromopentyl acetate, 15848-22-3; tetrahydropyran, 142-68-7; cyclohexene oxide, 286-20-4; *trans*-2-bromocyclohexyl acetate, 5837-71-8.

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An Unusual Rate Law for Vinyl Ether Hydrolysis. Observation of H_3PO_4 Catalysis at High pH

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An unusual rate law has been observed for hydrolysis of several vinyl ethers in phosphate buffers in the pH range 5.5–7.6. In addition to the expected terms in $[H^+]$ and $[H_2PO_4^-]$ alone, a term in $[H^+][H_2PO_4^-]$ was also observed. After determination of the pK'_a of H_3PO_4 (1.62 ± 0.06) in the 5% dioxane, μ = 1.0 M (KCl), solvent system used for the kinetics, and evaluation from a Brønsted correlation of the contribution expected from H_3PO_4 catalysis, it has been shown that the unusual rate law does not represent a new mechanism, but rather direct observation of H_3PO_4 catalysis at pH values *more than four units higher than its* pK'_a. The consequences of this observation are listed.

In the study of the hydrolysis of vinyl ethers to their corresponding ketones, we[1,2] and others[3a] have shown repeatedly that these species undergo hydrolysis by the rate law

$$k_\psi = k_H[H^+] + \sum_i k_{HA_i}[HA_i] \quad (1)$$

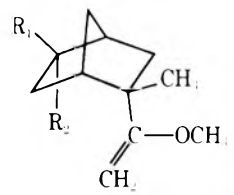
where k_ψ is the observed, pseudo-first-order rate constant, and HA_i is a general acid catalyst. We were therefore rather surprised when, while studying the hydrolysis of compounds 1 and 2 in phosphate buffers,[4] we observed apparent conformity to the rate law

$$k_\psi = k_H[H^+] + k_{H_2PO_4}[H_2PO_4^-] + k_{H_2PO_4,H}[H^+][H_2PO_4^-] \quad (2)$$

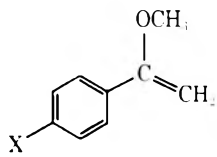
The cross term in eq 2 in $[H^+]$ and $[H_2PO_4^-]$ is hitherto unprecedented, and it presented the possibility that an unusual mechanism was operating in these hydrolyses which had previously not been observed. Another explanation of this term in eq 2 is that catalysis by undissociated H_3PO_4 was being observed at pH values *more than four units higher than its* pK_a. In this paper, we demonstrate that the rate law of eq 2 is rigorously followed, and then resolve these two kinetically equivalent possibilities, with the result that one may evaluate H_3PO_4 catalysis in buffers of $H_2PO_4^-$–$HPO_4^=$ in vinyl ether hydrolysis.

Results

The hydrolysis of all compounds was carried out in either 5% ethanol, 25° (1 and 2), or 5% dioxane, 29.9° (3 and 4), with the ionic strength maintained at 1.0 *M* with KCl;



1. $R_1 = CH_3$; $R_2 = CO_2^-$
2. $R_1 = CO_2^-$; $R_2 = H$



3. X = H
4. X = OCH

excellent pseudo-first-order kinetics were observed. In Table I are summarized the hydrolysis data for these compounds. As we have observed before, plots of the observed pseudo-first-order rate constant, k_ψ, vs. total phosphate, $[P_T]$, at a constant pH were strictly linear over the concentration range examined (0.05–0.20 *M*). Because of the strong buffer catalysis, the intercepts of such plots, which are extrapolated quantities, are a very small fraction of the observed rate constants, and the percent error in these intercepts is therefore quite large. We shall, however, make no use of these intercepts in this work. The slopes of such plots are the quantities of interest here, and they are determined with excellent precision. For a single acid, eq 1 may be rewritten

$$k_\psi = k_H[H^+] + k_{HA}f_{HA}[P_T] \quad (3)$$

in which f_{HA} is the fraction of the buffer in the acid form. If $\bar{k}_{cat}$ is the observed slope of the k_ψ vs. $[P_T]$ plot, then $\bar{k}_{cat}$ is given by

$$\bar{k}_{cat} = k_{HA}f_{HA} \quad (4)$$

and a plot of $\bar{k}_{cat}$ vs. f_{HA} should be linear through the origin. It is clear from Figure 1 that this behavior is not observed for compounds 1–4 when HA = $H_2PO_4^-$. Although the plots appear to emanate from the origin, evidently significant positive deviations from linearity are observed at $f_{HA} > 0.5$. In contrast, we have previously shown that eq 4 is followed by α-methoxystyrenes when the catalyzing acid is monprotic.[1,2] The data in Figure 1 may be fit, however by the equation

$$\bar{k}_{cat} = (k_{H_2PO_4} + k_{H_2PO_4,H}[H^+])f_{HA} \quad (5)$$

with the parameters given in Table II; this equation is equivalent to eq 2. It should be noted that fitting the data in Figure 1 with a simple linear equation gives a severely deteriorated correlation with a substantially negative intercept at $f_{HA} = 0$; such an intercept is physically meaningless since it has been shown that hydrolysis of these vinyl ethers is not accompanied by a salt effect[2] over the range of buffer concentrations used in this work.

Table I
Summary of Hydrolysis Data for Vinyl Ethers 1–4[f]

pH	f_{HA}[a]	$\bar{k}_{cat}$,[b] M^{-1} min^{-1}	k_0,[c] min^{-1}
		Hydrolysis of 1, Phosphate Buffers[d]	
5.49	0.932	10.2 ± 0.9	2.48 ± 0.01
5.78	0.876	10.0 ± 0.1	1.46 ± 0.01
6.08	0.780	8.15 ± 0.44	(7.50 ± 0.66) × 10^{-1}
6.30	0.681	6.26 ± 0.16	(5.96 ± 0.20) × 10^{-1}
6.44	0.608	5.33 ± 0.61	(4.69 ± 0.78) × 10^{-1}
6.63	0.500	4.61 ± 0.19	(2.67 ± 0.19) × 10^{-1}
6.83	0.387	3.43 ± 0.26	(1.97 ± 0.28) × 10^{-1}
7.05	0.275	2.11 ± 0.14	(1.43 ± 0.13) × 10^{-1}
7.37	0.154	1.37 ± 0.06	(5.44 ± 0.49) × 10^{-1}
7.70	0.078	0.810 ± 0.048	(2.01 ± 0.34) × 10^{-2}
		Hydrolysis of 2, Phosphate Buffers[d]	
5.37	0.948	7.20 ± 0.60	(3.65 ± 0.80) × 10^{-1}
5.43	0.941	7.50 ± 0.06	(2.41 ± 0.05) × 10^{-1}
5.59	0.916	6.48 ± 0.06	(1.91 ± 0.05) × 10^{-1}
5.76	0.881	5.83 ± 0.04	(1.30 ± 0.05) × 10^{-1}
6.06	0.788	4.39 ± 0.16	(9.72 ± 0.24) × 10^{-2}
6.32	0.671	3.49 ± 0.13	(7.20 ± 0.24) × 10^{-2}
6.47	0.591	2.86 ± 0.07	(6.36 ± 0.84) × 10^{-2}
6.65	0.489	2.38 ± 0.02	(4.61 ± 0.27) × 10^{-2}
6.83	0.387	1.88 ± 0.06	(2.70 ± 0.06) × 10^{-2}
7.01	0.294	1.42 ± 0.01	(1.87 ± 0.02) × 10^{-2}
7.32	0.170	0.888 ± 0.006	(5.72 ± 0.99) × 10^{-3}
7.51	0.119	0.618 ± 0.006	(2.39 ± 0.01) × 10^{-3}
		Hydrolysis of 3, Phosphate Buffers[e]	
5.54	0.900	1.74 ± 0.18	(1.49 ± 1.24) × 10^{-2}
5.94	0.800	1.30 ± 0.02	(9.30 ± 1.16) × 10^{-3}
6.24	0.700	1.07 ± 0.07	(5.70 ± 4.81) × 10^{-3}
6.49	0.600	(9.02 ± 0.48) × 10^{-1}	(4.18 ± 2.04) × 10^{-3}
6.61	0.500	(7.10 ± 0.19) × 10^{-1}	(3.60 ± 1.29) × 10^{-3}
6.82	0.400	(5.14 ± 0.12) × 10^{-1}	(2.95 ± 0.81) × 10^{-3}
7.02	0.300	(3.75 ± 0.14) × 10^{-1}	(2.45 ± 0.96) × 10^{-3}
7.30	0.200	(2.59 ± 0.01) × 10^{-1}	(4.03 ± 0.93) × 10^{-4}
7.63	0.100	(1.28 ± 0.01) × 10^{-1}	(5.00 ± 9.96) × 10^{-5}
		Hydrolysis of 3, Other Buffers[e]	
Acetate,			
4.70	0.500	4.27 ± 0.08	(2.01 ± 0.10) × 10^{-1}
Formate,			
3.62	0.500	80.1 ± 4.4	1.72 ± 0.15
		Hydrolysis of 4, Phosphate Buffers[e]	
5.54	0.900	20.1 ± 2.8	(3.11 ± 1.93) × 10^{-1}
5.94	0.800	17.9 ± 1.0	(1.08 ± 0.66) × 10^{-1}
6.24	0.700	14.5 ± 0.7	(7.75 ± 5.18) × 10^{-1}
6.49	0.600	12.2 ± 0.2	(6.20 ± 1.30) × 10^{-1}
6.61	0.500	9.39 ± 0.36	(4.73 ± 2.44) × 10^{-1}
6.82	0.400	7.65 ± 0.11	(2.34 ± 0.78) × 10^{-2}
7.02	0.300	4.86 ± 0.18	(4.90 ± 1.26) × 10^{-2}
7.30	0.200	3.39 ± 0.16	(7.09 ± 10.9) × 10^{-3}
7.63	0.100	1.77 ± 0.03	(5.85 ± 1.94) × 10^{-3}

[a] Equation 3. [b] Equation 4. [c] $k_0 = k_H[H^+]$; eq 1, 2, or 3. The values of k_0 are generally of very low precision, especially at the higher pH values. This fact is due to the very strong buffer catalysis, which means that k_0, an extrapolated number, is a very small percent of the values of k_ψ actually observed, whereas the error in k_0 is of the same order as the errors in k_ψ. [d] 25°, 5% ethanol, μ = 1.0 *M* (KCl). [e] 29.9°, 5% dioxane, μ = 1.0 *M* (KCl). [f] In each case, the parameters k_{cat} and k_0 (see note c) were determined by a plot of k_ψ vs. $[P_T]$ at constant pH, varying the value of $[P_T]$ from 0.05 to 0.20 *M*. The concentrations of the individual buffer species $H_2PO_4^-$ and HPO_4^{2-} can be calculated from the mass action law and the pK_a' of $H_2PO_4^-$.

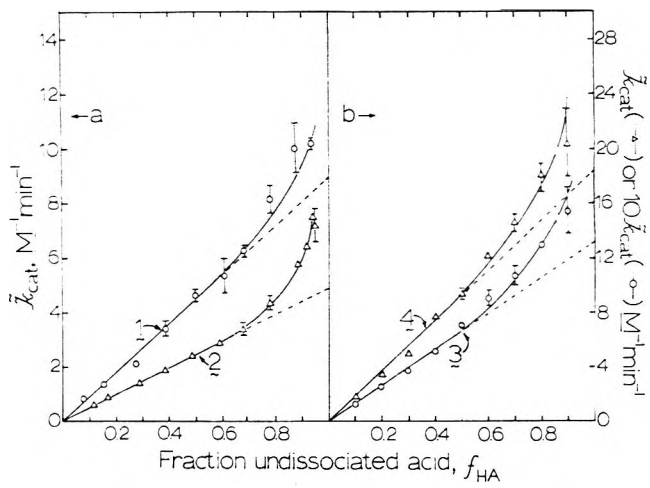


Figure 1. Slopes of buffer plots (eq 5) plotted vs. the fraction of the buffer in the $H_2PO_4^-$ form. The points are experimental, and the lines are calculated from eq 5 and the parameters in Table II. The parameters were determined by a weighted, nonlinear least-squares fit of the points using eq 5.

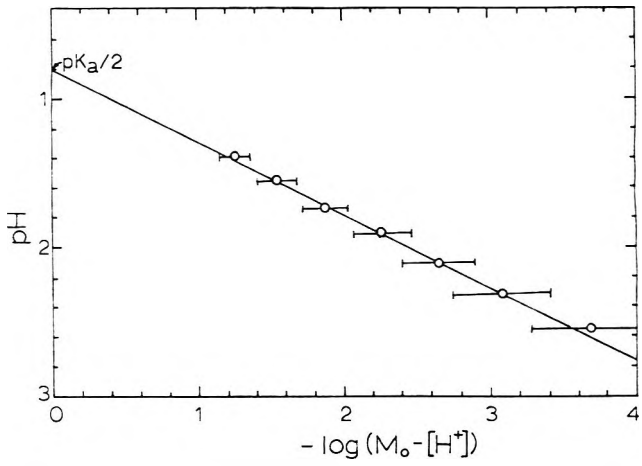


Figure 2. Dilution plot for determination of the pK'_a of H_3PO_4 in 5% dioxane, μ = 1.0 M (KCl). The error bars are standard deviations in log (M_0 − [H^+]), assuming a constant data. error of 0.03 in pH. The line is calculated for a slope of 0.49 and intercept of pK'_a/2 = 0.81, determined by a weighted least-squares fit of the data.

Table II
Parameters of Equation 5 for Hydrolysis of Vinyl Ethers 1-4

Compd[a]	$k_{H_2PO_4}$, M^{-1} min^{-1}	$k_{H_2PO_4,H^+}$, M^{-1} min^{-1}
1	(1.44 ± 0.06) × 10^{-1}	(1.14 ± 0.17) × 10^4
2	(7.58 ± 0.20) × 10^{-2}	(1.57 ± 0.08) × 10^4
3	1.33 ± 0.04	(2.53 ± 0.47) × 10^5
4	18.6 ± 0.6	(2.62 ± 1.00) × 10^6

[a] 1 and 2 in 5% ethanol. μ = 1.0 M (KCl); 3 and 4 in 5% dioxane. μ = 1.0 M (KCl).

To evaluate the possible contribution of catalysis by H_3PO_4 it was necessary to determine its operational pK_a in the solvent systems used here. Whereas operational pK_a values may be determined for weak acids by half-neutralization, this procedure is not satisfactory for stronger acids because of "buffer failure".[3] For H_3PO_4, we used a variant of the Ostwald dilution procedure, as follows, to determine the pK_a of H_3PO_4 in the 5% dioxane, μ = 1.0 M (KCl), system. When an acid HA is present in solution at M_0 mol/l. stoichiometric concentration, the mass action law becomes

$$K'_a = \left(\frac{x^2}{M_0 - x}\right)\left(\frac{\gamma_H\gamma_A}{\gamma_{HA}}\right) \quad (6)$$

where x/M_0 is the degree of dissociation of the acid, and γ_i is the activity coefficient of species i referred to 1 M infinitely dilute solution *in the 5% dioxane, μ = 1.0 M solvent system used for the kinetics.* In logarithmic form, recognizing that x = [H^+], we have

$$p[H^+] = pK'_a/2 - \tfrac{1}{2}\log(M_0 - [H^+]) + \tfrac{1}{2}\log\frac{(\gamma_H\gamma_A)}{\gamma_{HA}} \quad (7)$$

We have previously determined the relationship in this solvent system between pH meter reading and p[H^+], namely, that the two are by coincidence equal;[1] thus, we have a method for determining [H^+]. A plot of pH vs. −log (M_0 − [H^+]) should have slope 0.5 and intercept $\frac{1}{2}pK'_a + \frac{1}{2}\log(\gamma_H\gamma_A/\gamma_{HA})$. If we assume that HA makes a small perturbation in the nature of the medium (e.g. the change in ionic strength over the entire range of H_3PO_4 concentration used was found to be about 4%), then the activity coefficient term may be ignored. The linearity and slope of a plot of the data according to eq 7 are tests of this assumption, or of the less restrictive but operationally equivalent assumption that variations in the various activity coefficients are self-compensating. This is, of course, the advantage of using a high ionic strength medium: contributions of buffer components at low concentration cause only a negligible change in the nature of the solvent. Figure 2 is a dilution plot constructed from eq 7; the slope is 0.49 ± 0.01, at the theoretical prediction; the intercept of 0.81 ± 0.03 translates into a pK'_a of 1.62 ± 0.06 for H_3PO_4 in the 5% dioxane solvent system.

Discussion

It is clear from Figure 1 that the observation of the rate law of eq 2 for vinyl ether hydrolysis, first observed for **1** and **2**, is not unique to a particular structure, and is probably general for this reaction. The curves presented in Figure 1, which were adequately reproduced by eq 2 or 5, may equally well be represented by eq 8.

$$k_\psi = k_H[H^+] + k_{H_2PO_4}[H_2PO_4^-] + k_{H_3PO_4}[H_3PO_4] \quad (8)$$

The equivalency between the two expressions is given by the relation

$$k_{H_2PO_4,H}K'_{H_3PO_4} = k_{H_3PO_4} \quad (9)$$

in which $K'_{H_3PO_4}$ is the dissociation constant of H_3PO_4 determined above. In deciding between the two kinetically equivalent alternatives of eq 2 and 8, we were required to have a reasonable estimate of what to expect for catalysis by H_3PO_4. A direct measurement of $k_{H_3PO_4}$ is precluded by the fact that the observed rate constants at pH values such that [H_3PO_4] would be present in measurable concentration would be immeasurably fast (ca. 10^3 min^{-1}) by the method used here. A Brønsted α determined for α-methoxystyrene hydrolysis is 0.62 (acetate and formate buffers); this value differs from that previously given[1,2] because the previous value of 0.46 was based on the difference between acetate and phosphate; in fact, $H_2PO_4^-$ catalysis is faster by nearly a factor of 10 than that predicted from Brønsted plots of carboxylate buffers, in accord with Kresge's[3] and our[1,4] observation of positive electrostatic assistance of vinyl ether hydrolysis by negatively charged acids. Kresge and coworkers[5] have found that the hydrolysis of ethyl cyclopentenyl ether and ethyl isopropenyl ether, two vinyl ethers only slightly less reactive than α-methoxystyrene, shows α = 0.63 ± 0.03 and 0.64 ± 0.04, respectively, for catalysis by carboxylic acids, in excellent agreement with

the value of 0.62 found above. Extrapolation of the Brønsted correlation (with statistical corrections) to the pK'_a of H_3PO_4, determined as discussed in the Results section, gives an expected value for $k_{H_3PO_4}$ of $1.07 \times 10^3\ M^{-1}\ min^{-1}$; the observed value (Table II, eq 9) is $6.25 \times 10^3\ M^{-1}\ min^{-1}$, a factor of 5.8 larger than predicted. Since it has been shown by direct measurement of $k_{H_3PO_4}$ for ethyl vinyl ether that this catalytic constant lies about 0.5 log unit (a factor of 3) above the Brønsted prediction *based on carboxylate buffers*, our observed $k_{H_3PO_4}$ is thus within a factor of 2 of the expected value. The significance of the remaining difference is questionable in view of the assumptions and approximations made in this and other[3] work. The calculated values of $k_{H_3PO_4}$ for **1**, **2**, and **4** show similar agreement with observed values when we assume that the pK'_a of H_3PO_4 in the 5% ethanol, $\mu = 1.0\ M$ (KCl) system is the same as that in the dioxane system. This last assumption is quite reasonable, since a number of acids of diverse types show such an identity in pK'_a in the two solvents.

Several conclusions result from this work. (1) Kresge's caution,[3,6] that one should construct Brønsted plots from the same type of catalysts, is further underscored. (2) H_3PO_4 is confirmed to be an unusually active catalyst in vinyl ether hydrolysis, and probably in similar reactions as well. (3) Catalytic constants determined for components of polyprotic acids should be based on an exploration of the full range of pH covered by the buffer, because (4) strong acids, even if present in miniscule amounts, may have detectable catalytic activity. (5) In favorable cases such as this, catalytic constants for the stronger acids in a polyprotic array may be evaluated without direct measurement at pH values at which the strong acid dominates, at which the reaction under consideration may be too fast to measure, and at which buffer failure leads to troublesome complications in measuring buffer catalysis. (6) Finally, effects similar to those observed here might be anticipated for polybasic amines in reactions during which negative charge is present in the rate-determining step.

Experimental Section

The synthesis of all compounds, product analyses, and kinetic methods have been previously described.[1,4]

To determine the pK'_a of H_3PO_4, standard 0.1 *M* phosphoric acid was established by potentiometric titration with standard KOH. Known molarities, M_0, of H_3PO_4 were formulated in the 5% dioxane, $\mu = 1.0\ M$ (KCl) solvent system, and the pH was determined on a Radiometer Model 26 instrument using a combination electrode standardized at several pH values. The hydrogen ion concentration was determined from the pH meter reading (see Results section for a justification of this procedure) and a dilution plot, Figure 2, constructed according to eq 7. A weighted, linear least-squares analysis[7] was carried out to obtain the parameters of fit.

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Registry No.—**1**, 56650-73-8; **2**, 56650-74-9; **3**, 4747-13-1; **4**, 51440-56-3.

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The Oxidation of Terminal Olefins to Methyl Ketones by Jones Reagent Is Catalyzed by Mercury(II)[1]

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The oxidation of terminal olefins by Jones reagent in the presence of a catalytic quantity of mercury(II) affords good yields (>70%) of the corresponding methyl ketones. Similar oxidations of 1,2-disubstituted olefins gives fair (20–70%) yields; in the case of unsymmetrically substituted olefins, mixtures of ketones are produced.

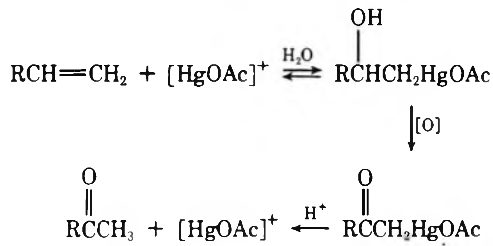
The Wacker process for oxidation of olefins to ketones has three mechanistically distinct parts:[3] first, activation of the olefinic double bond toward nucleophilic attack by coordination with Pd(II) and addition of a hydroxide moiety to this electrophilic double bond; second, conversion of the resulting 2-hydroxyethylpalladium(II) compound to ketone and a (formally) Pd(0) atom by a series of palladium(II) hydride addition–eliminations involving vinylic alcohol intermediates; third, reoxidation of the palladium(0) to palladium(II) by copper(II). Wacker oxidation is an extremely useful and general reaction. It is, nonetheless, worthwhile to try to develop procedures for oxidizing olefins that use as catalysts metals less expensive than palladium, and which involve reactions (and possibly generate products) different from those of the Wacker oxidation. Mercury(II) is an obvious candidate for the catalyst for new oxidation reactions: it resembles palladium(II) in its ability to activate olefins for nucleophilic attack,[4] but differs in that decomposition of the oxymercuration products normally generates cations by loss of mercury(0) rather than olefins by loss of mercury hydride.[5] Unfortunately, neither we nor others[6] have been able to discover a satisfactory solution to the principal problem in developing a mercury(II)-catalyzed analog of the Wacker oxidation: viz., an efficient regeneration of mercury(II) from mercury(0). In the absence of a solution to this problem, there are, however, ways of involving mercury(II) in catalytic oxidation of olefins other than in a direct analog of a Wacker oxidation.

Table I
Oxidation of Terminal Olefins by Jones Reagent Catalyzed by Mercury(II)

Olefin	Registry no.	Product	Registry no.	Isolated yield, %
1-Octene	111-66-0	2-Octanone	111-13-7	82
Undecylenic acid	112-38-9	10-Oxoundecanoic acid	676-00-6	83
3,3-Dimethyl-1-butene	558-37-2	3,3-Dimethyl-2-butanone	75-97-8	86
2-Allylcyclododecanone	32539-89-2	β-Oxo-2-propylcyclododecanone[a]	56666-10-5	70
Styrene	100-42-5	Acetophenone[b]	98-86-2	26
1,3-Hexadiene	592-48-3	Polymer		

[a] In addition, a 7% yield of 2-allyl-2-hydroxycyclododecanone was obtained. [b] Benzoic acid (16%) was also isolated, together with polymer.

One, explored in this paper, utilizes mercury(II) in oxymercuration of an olefin, oxidizes the hydroxyl moiety of the resulting 2-hydroxyalkylmercury(II) compound to an acid-labile 2-ketoalkylmercury(II) derivative, and regenerates mercury(II) by proteolysis of the carbon–mercury bond of this substance (eq 1). Thus, the mercury(II) performs the



(1)

essential function of olefin activation, but is regenerated without leaving the mercury(II) oxidation level. This cycle is, in a sense, one in which mercury(II) catalyzes the hydration of the double bond, and in which the reaction is driven in the direction of the thermodynamically less stable hydrated form by trapping this form by oxidation to ketone.

Results and Discussion

Jones reagent (CrO_3–H_2SO_4–H_2O) oxidizes alcohols to ketones efficiently, and is relatively unreactive toward olefins.[7] When Jones reagent is added to an acetone solution of an olefin at 20°, a slow, nonselective oxidation takes place. Addition of mercuric acetate or mercuric propionate (20 mol % based on olefin) to the solution results in a rapid consumption of the oxidant. Terminal olefins are converted to methyl ketones in yields of 80–90% (Table I); 1,2-disubstituted olefins react readily, but give low yields of ketones under these conditions. The yield of methyl ketones resulting from the catalyzed Jones oxidation of terminal olefins is relatively insensitive to the amount of mercuric salt added (Figure 1). The catalyzed oxidation of terminal olefins by sodium dichromate–trifluoroacetic acid solution showed similar insensitivity to the amount of mercuric salt added; the yields were, however, substantially lower than those obtained using Jones reagent (Figure 1). Note that the plots in Figure 1 are based on data collected under roughly comparable conditions, but that these conditions are not necessarily those that generated the highest yield of product. In particular, in plot A of Figure 1, the maximum detected yield of 2-octanone was approximately 50%, while the best yield isolated under optimized synthetic conditions was 82% (see the Experimental Section for details). The major function of the plots in Figure 1 is to establish the relative sensitivities of primary and secondary olefins to catalysis by mercury(II) and to provide a qualitative estimation of the absolute activity of mercury(II) as a catalyst in reactions based on Jones reagent and dichromate ion as oxidants.

The yield of ketones from 1,2-disubstituted olefins can

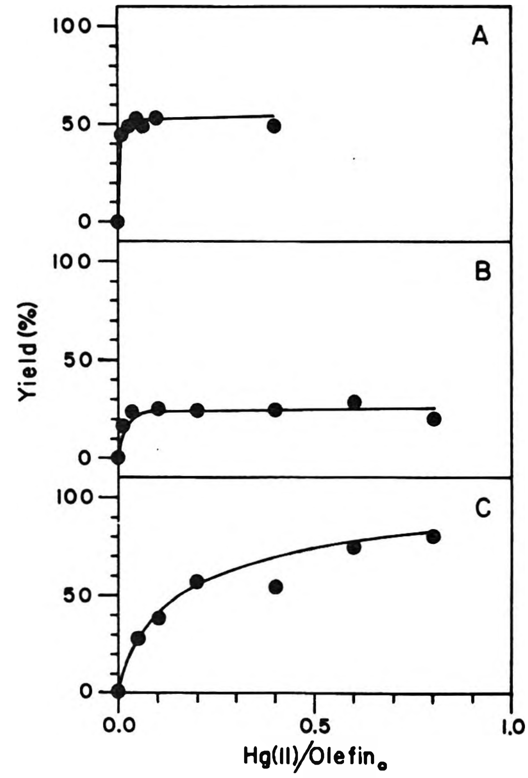


Figure 1. The yield of ketone depends on the ratio of equivalents of mercury(II) to olefin present at the start of the reaction: A, $(EtCO_2)_2Hg$-catalyzed oxidation of 1-octene to 2-octanone (25°, acetone, Jones reagent, 18 hr); B, $(EtCO_2)_2Hg$-catalyzed oxidation of 1-octene to 2-octanone (25°, dioxane, $Na_2Cr_2O_7 \cdot 2H_2O$–CF_3CO_2H, 18 hr); C, $(EtCO_2)_2Hg$-catalyzed oxidation of a mixture of *cis*- and *trans*-2-octene to a mixture of 2- and 3-octanone (25°, dioxane, $Na_2Cr_2O_7 \cdot 2H_2O$–CF_3CO_2H, 18 hr). Note that the maximum yield shown in A does not correspond to an optimized yield (see the text for a discussion of this point).

be improved using different reaction conditions (Table II); however, each 1,2-disubstituted olefin required different optimum conditions. Mercuric acetate oxymercurates olefins efficiently in aqueous tetrahydrofuran or dioxane[4,8] and these solvents also proved useful as oxidation media. Experiments in these solvents were carried out using sodium dichromate as oxidant, and making the solution acidic with trifluoroacetic acid. The yields of ketones from the oxidation of 1,2-disubstituted olefins were significantly poorer when other chromate salts, Jones reagent, hydrogen peroxide, or hypochlorite ion were used as oxidants. Yields were also poorer when mercury(II) chloride, nitrate, and tosylate were used in place of mercury(II) propionate.

Several metal ions other than mercury(II) were explored briefly, and found to be unsatisfactory as catalysts. No reaction took place on treating 2-octene with sodium dichromate–trifluoroacetic acid solution in the presence of thalli-

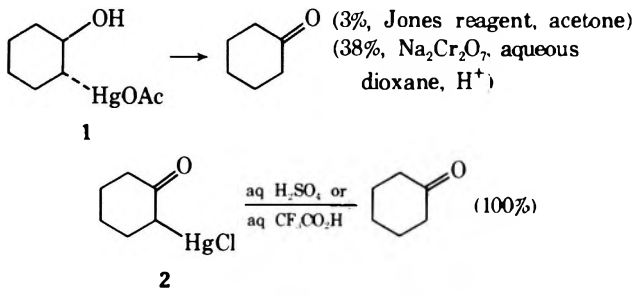
Table II
Oxidation of 1,2-Disubstituted Olefins by Sodium Dichromate-Trifluoroacetic Acid Solution Catalyzed by Mercury(II)

Olefin	Registry no.	Product	Registry no.	Isolated yield, %
cis-2-Octene	7642-04-8	2-Octanone (64%) + 3-octanone (36%)	106-68-3	56[a]
trans-2-Octene	13389-42-9	2-Octanone (63%) + 3-octanone (37%)		54[a]
Cyclohexene	110-83-8	Cyclohexanone	108-94-1	41[b]
Cyclododecene[c]	1501-82-2	Cyclododecanone	830-13-7	36[b]
Norbornene	498-66-8	Norcamphor[d]	497-38-1	20[a]
$\Delta^{2,3}$-Cholestene	15910-23-3	No reaction		

[a] Oxidation was carried out in the presence of 0.2 equiv of mercuric propionate. [b] Oxidation was carried out in the presence of 0.5 equiv of mercuric propionate. [c] A mixture of cis and trans isomers. [d] The product was isolated as the 2,4-dinitrophenylhydrazone.

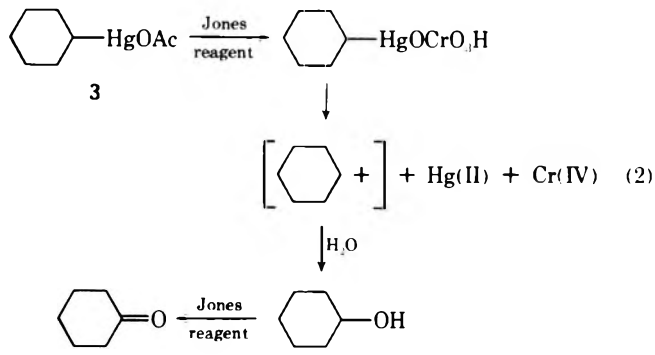
um(I), suggesting that olefin activation was slow. Similar treatment of 2-octene in the presence of gold(III), palladium(II), and rhodium(III) afforded mixtures of 2- and 3-octanone in yields of 30, 10, and 2%, respectively. Gold(0) and palladium(0) deposited on the walls of the reaction vessel in substantial amounts during the oxidation.

Evidence for the mechanism of the mercury(II)-catalyzed oxidations (eq 1) is inferential. Treatment of cyclohexene with aqueous mercury(II) acetate gives *trans*-2-hydroxycyclohexylmercuric acetate[9] (**1**), which is oxidized to cyclohexanone in yields very similar to those obtained from cyclohexene under the same reaction conditions. Similarly, 2-(chloromercuri)cyclohexanone (**2**) is converted rapidly and in high yield to cyclohexanone by aqueous sulfuric or trifluoroacetic acid. Compound **1** is itself relatively



1 **2**

stable toward the acid conditions encountered in the oxidation. Oxidation products arising directly from the β-hydroxyalkylmercury(II) cation therefore seem unlikely. Mercury(0) has been observed to form in small amounts only at elevated temperatures; no Hg(0) was observed under the conditions described. The β-hydroxymercury(II) cations have previously been shown to be stable in acid solution.[10] The difference in the yields of ketones from 1- and 1,2-disubstituted olefins under strongly acidic (Jones reagent) or weakly acidic ($Na_2Cr_2O_7$–CF_3CO_2H) conditions is reasonably attributed to differences in the oxidative and/or solvolytic[11] stabilities of primary and secondary carbon–mercury bonds. We have tested these stabilities under the conditions of these reactions by examining the behavior of cyclohexylmercuric acetate (**3**) and *n*-hexylmercuric acetate (**4**) toward Jones reagent in acetone. Compound **3** reacts rapidly; oxidation is complete in 30 min at 20°, yielding cyclohexanone in 65% yield. Under the same conditions, the carbon–mercury bond of **4** does not react appreciably: *n*-hexylmercuric sulfate can be recovered in good yield. Compound **1** does not solvolyze appreciably when treated with the components of the Jones reagent *without* the chromium trioxide (that is, acetone, water, and sulfuric acid): a small quantity of 2-hydroxycyclohexylmercuric sulfate precipitates, but no metallic mercury is formed and no organic solvolysis products can be detected. Thus, it appears that the rapid disappearance of **1** when treated with Jones reagent may be an oxidative reaction (eq 2). Cyclohexanol can be detected in ca. 5% yield after 5 min reaction time.



Conclusions

Jones reagent or trifluoroacetic acid–sodium dichromate solution oxidizes olefins to ketones in the presence of catalytic quantities of mercury(II); of the various metals tried as catalysts for the oxidation—thallium(I), gold(III), palladium(II), rhodium(III), and mercury(II)—mercury(II) gives the best yields. Qualitative evidence described above suggests that these transformations occur by the sequence of reactions outlined in eq 1. This oxidation provides a useful alternative to several of the procedures presently used to convert olefins to ketones. It is less complex than Wacker oxidation: the problems that arise in applying Wacker oxidation to high molecular weight, water-insoluble substances do not seem to be important, and it is unnecessary to have present the large excess of copper salts normally used to make the Wacker oxidation catalytic. It can be applied to unprotected olefinic carboxylic acids, where diborane–chromic acid results in destruction of the carboxylic acid moiety. It is more direct and more economical than the several procedures (oxymercuration–reduction, epoxidation–reduction) that generate an alcohol preliminary to a Jones oxidation.

Experimental Section

General. Melting points, determined on a Thomas-Hoover capillary melting point apparatus, are not corrected. GLC analysis was performed using a 10 ft × 0.125 in. 15% Carbowax 20M column on a F & M Model 810 gas chromatograph equipped with a hydrogen flame detector and a Hewlett-Packard Model 3373B electronic integrator. All solvents were reagent grade and were used without further purification. 1-Octene, 2-octene (a mixture of cis and trans isomers), *cis*-2-octene, and *trans*-2-octene (Chemical Samples Co.) were used as supplied. Norbornene, cyclohexene, styrene, cyclodo-

decene (a mixture of cis and trans isomers), 3,3-dimethyl-1-butene, and undecylenic acid (Aldrich) were used as supplied. Mercuric acetate and sodium dichromate dihydrate (Mallinckrodt), trifluoroacetic acid (Matheson Coleman and Bell), gold(III) chloride, palladium(II) chloride, and thallium(I) acetate (Fisher Scientific), and rhodium(III) chloride (Alfa) were used without further purification. Elemental analyses were performed by Robertson Laboratory, Florham Park, N.J.

Mercuric Propionate. Red mercuric oxide (108 g) was added in 10-g portions to 100 ml of hot propionic acid. The oxide dissolved, giving a slightly yellowish solution which was filtered and allowed to cool to room temperature. The resulting crystals were recrystallized from propionic acid, washed with cold, dry acetone, and dried under vacuum (0.04 mm) at room temperature for 24 hr. The yield of product was 168.7 g (97%) as white needles having mp 114–116°.

General Procedure for the Mercury(II)-Catalyzed Oxidation of Olefins. Method A. To a 500-ml erlenmeyer flask was added 22.0 g (74 mmol) of sodium dichromate dihydrate, 50 ml of water, and 300 ml of dioxane. With stirring, 6.8 g (20 mmol) of mercuric propionate and 35 ml of trifluoroacetic acid were added. The dark orange-red solution was stirred until the salts had dissolved (ca 10 min), and the flask was placed in a water bath. With continued stirring, 100 mmol of olefin was added. The solution became dark and warm; ice was added as necessary to maintain the temperature at 25 ± 5°. The solution was stirred for 18 hr, poured into water (300 ml), and extracted with hexane (3 × 75 ml). The combined extracts were washed with water (3 × 50 ml), saturated sodium chloride solution (1 × 50 ml), and water (1 × 50 ml) and dried ($MgSO_4$).

General Procedure for the Mercury(II)-Catalyzed Oxidation of Olefins. Method B. To a 500-ml erlenmeyer flask was added 200 ml of acetone, 5 ml of water, and 6.8 g (20 mmol) of mercuric propionate. The flask was placed in a water bath and, with stirring, 100 mmol of olefin was added to the bright yellow solution. Jones reagent[7] (2*M*, 75 ml) was added dropwise during 4 hr. Ice was added as necessary to maintain the temperature at 25 ± 5°. The dark greenish-brown solution was stirred for an additional 4 hr and then poured into water (200 ml) and extracted with diethyl ether (3 × 75 ml). The combined extracts were washed with water (3 × 50 ml), saturated sodium chloride solution (1 × 50 ml), and water (1 × 50 ml) and dried ($MgSO_4$).

References and Notes

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Intramolecular van der Waals–London Cohesions and Chemical Properties. Acid Weakening by Halogens and Related Effects.

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Substituent effects arising from intramolecular van der Waals–London attractions are examined. For substituents adjacent to reaction centers at which a single bond is converted into a double bond, or close to a site acquiring a charge, order-of-magnitude calculations (using London's formula) show appreciable stabilization of the new unsaturated species, or the species that has gained a negative charge, or lost a positive one, and increasing in the sequence F < Cl < Br ≃ H < I < Me.

Stabilization of anions, and destabilization of cations, by halogen substituents bound to sp^2-hybridized C atoms, which increases in the order F < H < Cl < Br < I (or roughly this order), has long been known for aromatic compounds in aqueous media.[1-3] This order is prominent in the acidities, in water, of some α-halogeno nitroalkanes[4-6] forming anions $X-C(Y)=NO_2^-$ (see Table I); i.e., effects opposing the normal inductive effect (acid strengthening by X: H ≪ I < Br < Cl < F) are important here. The (exceptionally) large anion destabilization by F (relative to H) in $F-C(Y)=NO_2^-$ [4,5] has been attributed[4] to (a) an increase in the order I < Br < Cl < F in the sum of mesomeric electron donation by Hal and Hal *p*-electron–π-electron repulsions (both are zero for H), (b) a weakening of the C–F bond on changing from sp^3 to sp^2 hybridization, (c) double bond–no bond resonance effects. However, much evidence militates, in turn, against each of these explanations: (a)[7] e.g.[2a,d] the ionization potentials[8] of compounds $Hal-CH=CH_2$ and $Hal-C_6H_5$ [IP lowest for iodides; i.e. electron donation plus repulsion greatest with I; $ICH(NO_2)_2$ should be the weakest $HalCH(NO_2)_2$ acid]; (b) C–F bond lengths,[2a,d] $r(F-C_{sp^2}) < r(F-C_{sp^3})$; (c) numerous instances where F is greatly acid strengthening despite[2a,d] similar possibilities of double bond–no bond resonance.

In addition, in compounds $Me-CHYNO_2$, Me is acid *weakening*[9] unless Y is strongly electron withdrawing—a very rare situation for Me attached to an sp^2-hybridized atom.

This article deals with a relevant and neglected nonpolar substituent effect, viz., intramolecular van der Waals–Lon-

Table I
Ionization Constants of Nitroalkanes

Nitroalkane[a]	pK_a[a] Obsd[b]	Corr	Nitroalkane[c]	pK_a[a] Obsd[b]	Corr
HCH_2NO_2	10.21	10.7	$HCH(NO_2)_2$	3.6_3	3.9_3
F_2CHNO_2[c]	12.4		$FCH(NO_2)_2$	7.70	
$ClCH_2NO_2$	7.2_2	7.5_2	$ClCH(NO_2)_2$	3.80	
$BrCH_2NO_2$	8.2	8.5	$BrCH(NO_2)_2$	3.58	
$MeCHBrNO_2$[c]	7.3		$ICH(NO_2)_2$	3.19	
$MeCH_2NO_2$	8.5	8.8	$MeCH(NO_2)_2$	5.30	
Me_2CHNO_2	7.7				
$FCHClNO_2$	10.14				
$MeCHClNO_2$	6.8				

[a] If the number of ionizable hydrogen atoms (n) exceeds one, a statistical correction ($\log n$) has to be added. [b] Data from ref 4, 5, 6, and 9. [c] No data available for FCH_2NO_2 or ICH_2NO_2. [d] Registry no. are, respectively, 75-52-5, 1493-05-6, 1794-84-9, 563-70-2, 563-97-3, 79-24-3, 79-46-9, 2375-33-9, 598-92-5. [e] Registry no. are, respectively, 625-76-3, 7182-87-8, 921-13-1, 996-67-8, 29610-14-8, 600-40-8.

don attraction. The stabilizations produced by this are proportional to the products of the polarizabilities of the interacting units, and inversely proportional to about the sixth power of the separations between them (see eq 1). Order-of-magnitude calculations for various substituents X in systems such as $XCH{=}NO_2^-$ give an increase in stabilization in the order F < Cl < Br ≃ H < I < Me.

Qualitatively, the relevant rules are: (*1*) *any chemical change in which a molecular moiety becomes more polarizable is facilitated increasingly as the polarizability of the substituent*[10] *increases.* Loss of a positive charge or acquisition of a negative one raises the polarizability (denoted by α) by[11] ca. 0.5 Å^3 per atom or molecule [principally at the charge center, but in part also for other nearby electrons (as these, too, are held less firmly after loss of a proton; and on account of the Silberstein[12b] effect—normally mutual exaltation of polarizability)]. Also, conversion of a pair of CH bonding electrons into a CC π-electron pair raises α by ca. 0.5 Å^3 (from 0.65 Å^3 to 1.15 Å^3).[2a,d] Hence, *an increase in the polarizability of a substituent* (*2*) *obstructs cation formation,* (*3*) *assists anion formation, and* (*4*) *results in an increased preference by the substituent for attachment to an sp^2- rather than an sp^3-hybridized atom.*

Quantitative treatment is difficult, but a basis for semiquantitative calculations is provided by London's formula (eq 1)[12] for the cohesion energy E_L for a pair of interacting units (A and B), where h is Planck's constant, I_A, I_B, α_A, and α_B are respectively the ionization potentials and polarizabilities of A and B, and R is the distance between the centers of their oscillating dipoles.

$$E_L = -\frac{3}{2} h \frac{I_A I_B}{I_A + I_B} \frac{\alpha_A \alpha_B}{R^6} \quad (1)$$

Interactions at close range, within molecules with many (and different) units, present numerous problems. Chiefly, formula 1 is good, and the dependence on $1/R^6$ holds accurately only at long distances R. At short distances R, an appreciable interelectronic repulsion which also depends on α_A, α_B, and R, and which is difficult to estimate, is not allowed for by formula 1. It is proposed to overcome this by use of a net cohesion energy E_L^* (E_L minus the repulsion energy). A reasonable value[2c] for E_L^* is ca. $\frac{1}{2}E_L$ if $0.507(\alpha_A^{1/4} + \alpha_B^{1/4})/R$ is in the range of ca. 0.6–0.7 [but if this quantity > ca. 0.7, the ratio E_L^*/E_L diminishes rapidly; $0.507\alpha^{1/4}$ is the approximate (average) zero-point electronic oscillation amplitude[2e] in London's simplified oscillator[12a]]. Further, α_A and α_B will ordinarily be orientation dependent,[11b] and the complexity of the orientation averaging required, and the absence of strict pairwise additivity, precludes accurate calculations of intramolecular interactions. In the present work only the principal interaction of interest within a molecule, and its change in the reaction concerned, has been calculated, and anisotropy in α was neglected.[2c]

The units, normally, are electron pairs, and the interactions of importance, usually, are those between *adjacent* electron pairs; e.g. in the π-electron–CF interaction in $FCH{=}CH_2$ the C–F bonding electrons make the main contribution, and the nonbonding electrons on F are too far away to have much effect.

The values of I and α per electron pair here used were estimated from those observed for simple model compounds, and some assumptions,[2d] but the uncertainties introduced are expected to be relatively minor. The estimation of R can be difficult. The centers of the *oscillating* dipoles, taken to be the centroids of the electron pair clouds (not nuclear positions!), are given (or roughly given) by[2c] by symmetry for C=C and C–C bonds, and known from X-ray diffraction results[13] for C–H bonds. However, for C–Hal bonds their locations had to be estimated from dipole moment data.[2c] There is thus a sizable uncertainty in the numerical values of R^6 used, in addition to that about the analytic dependence of E_L^* on R. The size of the total margin of error in the absolute magnitude of E_L^* is not known.

The chemical changes treated were

$$XCH_2NO_2 \rightleftharpoons XCH{=}N^+(-O^-)_2 + H^+ \quad X = H, Hal, or Me \quad (I)$$

$$p\text{-}XC_6H_4N^+H_3 \text{ (or } p\text{-}XC_6H_4OH) \rightleftharpoons p\text{-}XC_6H_4NH_2 \text{ (or } p\text{-}XC_6H_4O^-) + H^+ \quad (II)$$

For α and I for the π electrons in $CH_2{=}NO_2^-$ the $CH_2{=}CH_2$ values were taken, approximate cancellation of the effect of the positive charge on N and of the two (more distant) negative ones on O being assumed (giving rise also to approximately central positioning of the C=N π electrons); the internuclear distance r(C=N) used was 1.29 Å.[3,2a,c] The change in E_L (ΔE_L) was calculated for the interaction between the C–X bonding electrons and the electrons which, in the dissociation reaction (I), are converted from C–H into π electrons. The reduction in (the relevant) R^6 on dissociation was ignored to avoid overestimating of ΔE_L.

For reaction II the approach was different. The interactions (by X) of importance were taken to be those between the C–X bonding and four adjacent C–C σ *as well as* two adjacent π electrons. Acquisition of a positive charge by NH_2, or loss of a negative one by O^-, by protonation, pulls the latter six electrons away from C–X, and is estimated[2a,c]

Table II
Main Components of Cohesion Energies E_L, and Changes Therein on Ionization ΔE_L (Kilocalories/Mole)

Group X	H	F	Cl	Br	I	Me
α_B[a,b]	0.65	0.16	0.65	0.91	1.41	0.56
r(C–cCX)[a,c,d]	0.95	0.37[i]	1.05	1.05	1.05	0.75
Values for Nitronate Ions,[a,e] and ΔE_L for Deprotonation Reaction (I)						
$hI_AI_B/(I_A + I_B)$[a,f]	5.81	6.02	5.62	5.52	5.42	5.51
R[a,d]	1.39	1.31	1.48	1.48	1.48	1.21
$0.507(\alpha_A^{1/4} + \alpha_B^{1/4})/R$[g]	0.71	0.64	0.66	0.70	0.73	0.79
$-E_L$[g]	21.1	7.4[i]	13.9	19.0	28.9	39.7
$-E_L$*[g]	10.5	3.7	7.0	8.5	13	14?
$-\Delta E_L$*[g]	4.6	1.6[i]	3.0	4.1	5.7	6?
ΔE_L for Deprotonation Reaction (II)[a,h]						
$-\Delta E_L$[g]	1.13	0.47	0.81	1.11	1.7	2.6
$-\Delta E_L$*[g]	0.56	0.23	0.40	0.55	0.8	0.9

[a] See ref 2b. [b] In Å^3 per (bonding) electron pair. [c] Distance from charge centroid of C–X bonding electrons to C nucleus. [d] In Å. [e] α_A for π electrons, taken as 1.15 Å^3. [f] In electron volts. [g] E_L and ΔE_L by formula 1; E_L* and ΔE_L* estimated from these,[h] having special regard where necessary to the index of repulsion $0.507(\alpha_A^{1/4} + \alpha_B^{1/4})/R$; the minus sign denotes attraction, or gain therein. [h] See text. [i] A reduction by ¼ in the assessed CF bond moment gives r(C–cCX) = 0.82 Å, E_L = −9.2, and ΔE_L* = 2.0 kcal/mol.

to *raise* (the mean) R for these interactions by about 0.01 Å; i.e., a change of R, rather than that in α, is used in the calculation of ΔE_L.

The results obtained with eq 1[14] are shown in Table II (as are some of the quantities used in the calculation[2b]). These cohesion energies E_L*, and the substituent effect on E_L*, are substantial. The substituent effects on the changes ΔE_L* on (de)protonation are appreciable when compared with the substituent effects on the free energies (ΔG) of (de)protonation observed in aqueous medium, for both reaction I and II.[1,2a]

Put in the simplest qualitative terms, as far as E_L* is concerned F is acid weakening relative to H because the polarizability of the C–F bonding electrons is only about a quarter of that of the C–H electrons, and Me is acid strengthening because the C–C (σ) bonding electrons are much closer to the nucleus of the sp^2-hybridized C atom (and hence to the π electrons) than are the CH electrons (see values for electron centroid–nucleus separations, and for R, in Table II).

Meaningful quantitative comparisons of calculated substituent effects on E_L* with inductive effects (e.g., monopole–permanent dipole interactions) or inductomeric effects [e.g., monopole–induced (permanent) dipole interactions] are hardly practicable at present.[15] The absolute values of E_L* are too uncertain, and the *uni*directional polarizabilities required for the calculation of induction effects in unsymmetrical bonds are not available. However, in the ionization (I), the N$^+$ atom moves closer to X while a negative charge is acquired farther away; this partial cancellation of charge fields experienced by X reduces the importance of polar effects, e.g., inductive and inductomeric, and substituent effects on ΔE_L* are brought more to the fore.[17]

Intramolecular van der Waals–London attraction should have appreciable effects on many other properties,[2] e.g., in the acid strengthening and base weakening (relative to H) produced by unsaturated groups, and by many ortho substituents in benzene rings; also on bond lengths and heats of formation.

Comparisons of heats of formation of alkenes $C_2H_{4-n}X_n$ with those of their hydrogenation products $C_2H_{6-n}X_n$ give a measure of the preference by X for attachment to an sp^2 rather than an sp^3 C atom. The relevant quantity, $n^{-1} \times \{[\Delta H_f$(parent alkene) − ΔH_f(substituted alkene)] − [ΔH_f(parent alkane) − ΔH_f(substituted alkane)]}, while varying somewhat with n (and relative group dispositions, in cases of multiple substitution), appears to increase in the order F < Cl < H < Br < Me. This quantity (zero by definition for X = H) is always negative for F and positive for Me; the data,[18] unfortunately, are unsystematic, and in the range Cl, H, Br, where the differences are small, of uncertain reliability. Substituent effects on E_L* are probably the main factor in producing this sequence of preference for sp^2 attachment.

Supplementary Material Available. A fuller treatment will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3580.

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(15) E.g., it is not practicable to estimate by calculation the extent to which the inductomeric effect of Hal and the effect of Hal on ΔE_L^* contribute to the gas-phase acid strength sequence[16] $H\text{-}CH_2CO_2H \ll F\text{-}CH_2CO_2H < Cl\text{-}CH_2CO_2H < Br\text{-}CH_2CO_2H$ (in principle, both contribute to the observed halogen order, even though the inductomeric effect is expected to be the more important here). (NB The "anti-inductive" order is less prominent in $HalCH_2COOH$ than in $HalC_6H_4OH$ acidities.)
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Resonance Theory. VIII. Reactivities of Benzenoid Hydrocarbons

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An algorithm, logarithm of the number of Kekulé structures, gives resonance energies for benzenoid hydrocarbons that are equivalent to results of highly parameterized SCF–LCAO–MO calculations. The relationship also holds for odd alternant cationic and anionic species. Reactivity indices based on the structure count algorithm correlate with various types of experimental reactivity data.

A simple parameterized structure–resonance theory has recently been developed[1,2] that allows one to calculate resonance energies for many types of π-molecular systems that correlate precisely with the results of semiempirical SCF–MO (Dewar[3]) calculations, or with those obtained from open chain reference structure modified Hückel MO (Hess and Schaad[4]) procedures. During the course of that development an exponential relationship between the Kekulé structure count (SC) and the Dewar resonance energy was noted.[5] The purpose of this paper is to show that this relationship extends to cations and anions postulated as intermediates in reactions of benzenoid aromatic hydrocarbons. Consequently, accurate correlations and predictions of reactivities are quickly and precisely obtainable.

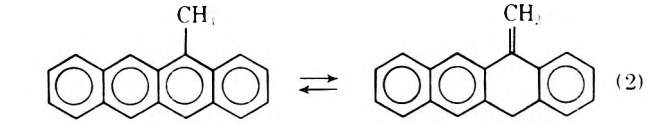
No attempt will be made here to give a quantum mechanical interpretation of the relationships described. A sufficient justification is the excellent quantitative agreement of experimental and theoretical data with the empirical SC function. However, it should be noted that the high correlative accuracy cannot arise from accidental or mathematical congruities[6] of resonance theory with the HMO formulation. HMO reactivity indices have been shown in most cases to yield poor correlations of reactivity data in comparison to the results of SCF calculations. Some illustrations of this fact will be given in tables to follow.

Resonance Energies of Benzenoid Hydrocarbons. The variable β and bond length SCF calculations, parameterized with thermochemical data, of Dewar and coworkers[3] can be taken to provide a reliable reference set of resonance energies. As shown previously,[5] there is an exact linear relationship between the logarithm of the SC and the Dewar[3b] resonance energy (RE) given in eq 1. Alternant and nonalternant benzenoid hydrocarbons, including compounds with essential single bonds, are included in the correlation.

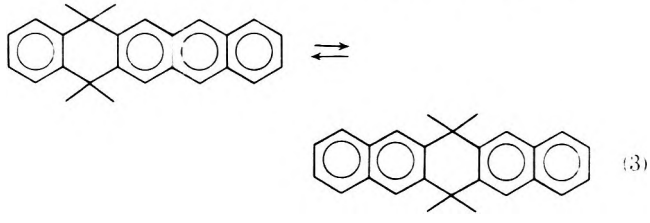
$$\text{RE (eV)} = 1.185 \ln \text{SC} \quad (1)$$

Their structures were enumerated using the graph-theoretical methods described previously.[7] The correlation coefficient of the calculated resonance energies is 0.998, and the average deviation of the SC algorithm from the SCF result is ±0.042 eV, less than 1 kcal.

The calculations for acene derivatives summarized in Table I provide a stringent test of the SC algorithm. The SCF results were obtained by Herr[8] in an attempt to understand tautomeric equilibria of the types shown in eq 2 and 3. Assuming that the enthalpy differences between



(2)


(3)

pairs of molecules are constant except for π energy differences, the energy of reaction, ΔE_π, should be a linear function of the logarithm of the ratio, SC of product P to SC of reactant R; cf. eq 4.

$$E = a(\ln \text{SC}_P - \ln \text{SC}_R) + b = a \ln (\text{SC}_P/\text{SC}_R) + b \quad (4)$$

The structure count function parallels the calculated SCF energy differences very closely as evidenced by the correlation coefficients for the two groups of reactions, 1.000 and 0.990, respectively.

Some kinetic data suitable for testing eq 1 and 4 have been published by Dewar and Pyron.[9] They determined the rate of Diels–Alder addition of maleic anhydride to the aromatic compounds listed in Table II. The logarithm of the SC ratio is obviously a paralocalization energy and is highly correlated with the logarithm of the second-order rate constant, supporting the postulation of a cyclic transition state for the cycloaddition reaction. A calculation based on the assumption of rate-determining formation of a biradical intermediate (see next section) only gives a correlation coefficient of 0.738, in complete agreement with the prior SCF calculations and conclusions.[9]

Aromatic Substitution Reactions. Electrophilic Sub-

Table I
π Energy Differences for Acene Derivatives

Registry no.	Compd	SC	$\Delta H_a(R)-\Delta H_a(P)$, eV[a]	ln (SC_P/SC_R)
108-88-3	Toluene[b]	2	−1.400	−0.693
3217-87-6	3-Methylene-1,4-cyclohexadiene	1		
90-12-0	1-Methylnaphthalene	3	−0.998	−0.405
40476-27-5	1,1-Dihydro-4-methylenenaphthalene	2		
610-48-0	1-Methylanthracene	4	−0.821	−0.288
40476-28-6	1,1-Dihydro-4-methyleneanthracene	3		
779-02-0	9-Methylanthracene	4	−0.428	0.0
40476-29-7	9,9-Dihydro-10-methyleneanthracene	4		
40476-21-9	1-Methylnaphthacene	5	−0.745	−0.223
40476-30-0	1,1-Dihydro-4-methylenenaphthacene	4		
14214-56-3	5-Methylnaphthacene	5	−0.179	+0.182
40476-31-1	5,5-Dihydro-12-methylenenaphthacene	6		
40476-23-1	1-Methylpentacene	6	−0.702	−0.182
40476-32-2	1,1-Dihydro-4-methylenepentacene	5		
40476-24-2	5-Methylpentacene	6	−0.061	+0.288
40476-33-3	5,5-Dihydro-14-methylenepentacene	8		
40476-25-3	6-Methylpentacene	6	+0.111	+0.405
40476-34-4	6,6-Dihydro-13-methylenepentacene	9		
		corr coeff 1.000		
20244-36-4	5,14-Dihydropentacene[c]	8	+0.165	+0.118
13574-08-3	6,13-Dihydropentacene	9		
40476-37-7	5,16-Dihydrohexacene	10	−0.237	+0.182
40476-38-8	6,15-Dihydrohexacene	12		
40476-39-9	5,18-Dihydroheptacene	12	+0.276	+0.223
40476-40-2	6,17-Dihydroheptacene	15		
	6,17-Dihydroheptacene	15	+0.072	−0.065
40476-41-3	7,16-Dihydroheptacene	16		
40476-42-4	6,19-Dihydrooctacene	18	−0.110	−0.105
40476-43-5	7,18-Dihydrooctacene	20		
40476-44-6	7,20-Dihydrononacene	24	−0.039	−0.041
40476-45-7	8,19-Dihydrononacene	25		
		corr coeff 0.990		

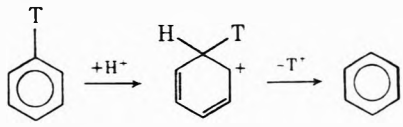
[a] Reference 8. [b] Reactions analogous to eq 2. The second compound in each pair is taken to be the product of the reaction. [c] Reactions analogous to eq 3.

Table II
Diels-Alder Reactions of Aromatic Compounds[a]

Registry no.	Reactant	SC_P/SC_R	ln (SC_P/SC_R)	ln ($k \times 10^4$)[b]
120-12-7	Anthracene	4/4	0.0	4.324
56-55-3	Benz[*a*]anthracene	6/7	−0.154	1.934
92-24-0	Naphthacene	6/5	+0.182	7.230
215-58-7	Dibenz[*a*,*c*]anthracene	10/13	−0.262	1.275
53-70-3	Dibenz[*a*,*h*]anthracene	9/12	−0.287	−0.293
224-41-9	Dibenz[*a*,*j*]anthracene	9/12	−0.287	−0.393
			corr coeff 0.989	

[a] Reference 9. Reaction with maleic anhydride, diethyl succinate solution at 129.7°C. [b] Rate constant k in l. mol^{-1} sec^{-1}.

stitution. A set of σ^+ constants that are generally applicable to electrophilic aromatic substitution reactions have been derived from extensive studies of rates of protodetritiation of polycyclic aromatic hydrocarbons.[10] These data have also been used to test various types of MO calculations,[11-13] with the assumption that the reaction involves the formation of a symmetrical Wheland transition intermediate; cf. eq 5.



(5)

Table III lists σ^+ values and several types of calculated localization energies, i.e., the π energy differences between cationic intermediates and the neutral reactant aromatic molecule. Some of the σ^+ values are estimated from older reactivity data.[10c] The most reliable HMO reactivity indices are the localization energy, L_r^+,[14] and Dewar's perturbational MO reactivity number, N_R.[14,15] They do not correlate with the σ^+ values as well as do the calculations that use SCF-MO procedures. The CNDO/2 calculations of Streitwieser et al.[12] are highly correlative but only 18 of the 26 listed compounds have been investigated. It should be pointed out that the CNDO/2 method also handles some substituted and nonalternant aromatic hydrocarbons in a satisfactory manner.[12]

The SC ratio in Table III is simply the ratio of Kekulé structures for the postulated cation and the neutral reactant. The structures for the cations were enumerated by

Table III
Localization Energies and σ^+

Registry no.	Compd (position of substitution)	σ^+	SC ratio[a]	ln (SC ratio)	L_r^+ (HMO)[b]	N_R (Dewar)[c]	ΔE (CNDO/2)[d]	ΔE^e (PPP)
71-43-2	Benzene	0.00	3/2	0.405	2.54	2.31	12.141	0.00
92-52-4	Biphenyl (2)	0.24	9/4	0.811	2.40	2.07		0.199
	Biphenyl (4)	0.24	9/4	0.811	2.45	2.07		0.198
91-20-3	Naphthalene (1)	0.35	7/3	0.847	2.30	1.81	13.115	0.907
	Naphthalene (2)	0.25	6/3	0.693	2.48	2.12	12.698	0.498
	Anthracene (1)	0.41	12/4	1.099	2.25	1.57	13.577	1.304
	Anthracene (2)	0.36	10/4	0.916	2.40	1.89	13.101	0.832
	Anthracene (9)	0.72	16/4	1.386	2.01	1.26	14.410	1.870
85-01-8	Phenanthrene (1)	0.34	13/5	0.956	2.32	1.86	13.222	1.057
	Phenanthrene (2)	0.25	11/5	0.788	2.50	2.18	12.884	0.653
	Phenanthrene (3)	0.29	12/5	0.875	2.45	2.04	13.003	0.831
	Phenanthrene (4)	0.33	12/5	0.875	2.37	1.96	13.070	0.881
	Phenanthrene (9)	0.37	13/5	0.956	2.30	1.80	13.320	1.060
217-59-4	Triphenylene (1)	0.32	23/9	0.938	2.38	2.00	13.136	0.962
	Triphenylene (2)	0.26	22/9	0.894	2.48	2.12	13.040	0.849
129-00-0	Pyrene (1)	0.67	21/6	1.253	2.19	1.51	14.093	1.465
	Pyrene (2)	0.22	13/6	0.773	2.55	2.31	12.695	
	Pyrene (4)	0.36	17/6	1.041	2.28	1.68	13.438	
	Tetracene (5)	0.80	27/5	1.686	1.93	1.02		
213-01-9	Chrysene (6)	0.46	26/8	1.179	2.25	1.67	13.714	1.451
198-55-0	Perylene (3)	0.74	40/9	1.492	2.14	1.33	14.487	1.886
191-07-1	Coronene (1)	0.44	68/28	1.224	2.31	1.80		1.430
	Benz[*a*]anthracene (7 or 12)	0.64	29/7,27/7	1.386[f]	2.10	1.43		
	Dibenz[*a*,*h*]anthracene (7)	0.65	48/12	1.386	2.13	1.51		
50-32-8	Benzo[*a*]pyrene (9)	0.86	45/2	1.609	1.96	1.51		2.273
191-26-4	Anthanthrene (7)	0.81	58/10	1.758	1.93	1.03		2.453
			corr coeff	0.977	−0.873	−0.900	0.987	0.932

[a] See text. [b] Units of β, ref 14. [c] Reference 15. [d] eV, ref 12. [e] eV relative to benzene, ref 11. [f] Average value.

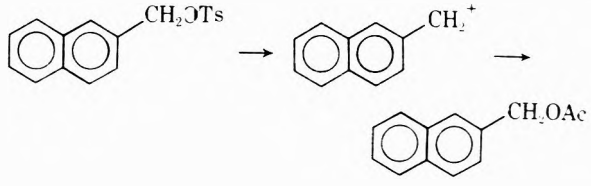
summing the absolute values of the unnormalized coefficients of eigenvectors of the nonbonding orbital for each cation.[6,7] The ln (SC ratio) is a really excellent reactivity index for electrophilic substitution as indicated by the correlation coefficient with σ^+ of 0.977. A comparison of the ln (SC ratio) with the SCF-MO calculations gives the following correlation coefficients: CNDO/2,[12] 0.989, and PPP,[11] 0.993.

Additional tables detailing the congruence of ln SC functions with theoretical and experimental results for many types of chemical reactions could be given. However, the same molecular π systems are repeatedly used in most investigations, so I have chosen to summarize results by giving only the reaction type, correlations, number of compounds considered, and brief comments. In each case the ln (SC ratio) function compared is the same as that given in Table III, or, for arylmethyl systems, is calculated in an analogous manner.

Nucleophilic Substitution. Rates of deuterium exchange with lithium cyclohexylamide in cyclohexylamine at 50°C,[16] polycylic aromatic reactants, carbanion intermediates. Expt: CNDO/2, nine compounds, corr coeff 0.930. Expt: PPP,[17] 0.844. Expt: ln (Sc ratio), 0.863. CNDO/2: ln (SC ratio), 0.980. PPP: ln (SC ratio), 21 compounds,[11] 0.992.

None of the experimental–theoretical correlations are outstandingly good. The SCF-MO calculations again show almost perfect correlations with the SC algorithm. The Dewar–Thompson[11] variable β PPP results exhibit the best correlations with ln (SC ratio) as in the previous calculations on electrophilic substitution.

Solvolytic Reactions, Arylmethyl Systems. σ^+ constants derived from rates of acetolysis of polycyclic arylmethyl tosylates and other derivatives,[18-20] arylmethyl carbonium ion intermediate; cf. eq 6. σ^+: CNDO/2,[19] nine



(6)

compounds, corr coeff 0.930. σ^+: PPP,[11] 13 compounds, 0.919. σ^+: ln (SC ratio), 14 compounds, 0.937. CNDO/2:[19] ln (SC ratio), nine compounds, 0.986. PPP:[11] ln (SC ratio), 16 compounds, 0.993. The remarks regarding the correlations for aryl carbanions in the previous paragraph also apply to this series.

Acidities of Methylarenes. Rates of hydrogen isotope exchange, catalyzed by lithium or cesium cyclohexylamide in cyclohexylamine, arylmethyl carbanion intermediate.[17,21] Expt: CNDO/2,[17] nine compounds, corr coeff 0.940. Expt: PPP,[11] 0.988. Expt: ln (SC ratio), 0.976. Expt: HMO,[21] 0.757. CNDO/2:[17] ln (SC ratio), ten compounds, 0.954. PPP:[11] ln (SC ratio), 12 compounds, 0.996. The lower correlation of CNDO/2 calculations with the SC function, coupled with the excellent agreement of PPP results, the SC function, and the experimental data, may indicate some error in the CNDO/2 calculations.

Summary

An extended discussion is not warranted in view of the empirical nature of the algorithm that has been tested in this work. The most significant results are the astonishingly precise agreements of sophisticated semiempirical MO calculations with the SC algorithms. The high correlation coefficients, from 1.000 to as low as 0.980 (for exception see previous paragraph), should not be accidently obtainable. In any event, a quantitative relationship between numbers

of structures and SCF–MO calculations has now been established, and a theoretical explanation is desirable.

The failures of the HMO method to correlate the data reviewed were attributed[12,17] to the lack of consideration of electron repulsion effects in the HMO treatment. If the SC algorithm is justified in future theoretical work, that previous conclusion may require modification. No explicit electronic charge effects are included in a structure–resonance theory that only includes Kekulé resonance structures.

At present, the efficacy of the SC approach has only been demonstrated for alternant π systems, and this may constitute a limit to use of this idea. The extension to nonalternant systems is under investigation.

Acknowledgment. The financial support of the Robert A. Welch Foundation is gratefully acknowledged.

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Synthesis of Arylphosphonous Dichlorides, Diarylphosphinous Chlorides, and 1,6-Diphosphatriptycene from Elemental Phosphorus

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Reaction of elemental white phosphorus with aryl halides at temperatures ranging from 280 to 350°C in the presence of Lewis acid catalysts gave arylphosphonous dichlorides and diarylphosphinous chlorides. Reaction of white phosphorus with *o*-dichlorobenzene in the presence of $FeCl_3$–$TiCl_4$ produced in addition to *o*-chlorophenylphosphonous and di(*o*-chlorophenyl)phosphinous chloride 1,6-diphosphatriptycene, a novel, phosphorus-containing heterocyclic compound.

The preparation of phenylphosphonous dichloride (**1a**) and diphenylphosphinous chloride (**1b**) has been investigated earlier by several research groups. One of the best routes to **1a** developed previously involved the reaction of benzene with phosphorus trichloride in the presence of aluminum chloride in stoichiometric quantities.[1]

$$C_6H_6 + PCl_3 \xrightarrow{AlCl_3} \underset{\textbf{1a}}{C_6H_5PCl_2} + HCl$$

The resulting phenylphosphonous dichloride (**1a**) forms strong complexes with the aluminum chloride catalyst. The extraction of the product is therefore difficult. An improvement of the isolation procedure was introduced by adding phosphorus oxychloride in stoichiometric quantities as a complexing agent to remove the aluminum chloride.[2,3]

Since phenylphosphonous dichloride (**1a**) disproportionates in the presence of aluminum chloride to yield diphenylphosphinous chloride (**1b**) and phosphorus trichloride[4–6]

$$2C_6H_5PCl_2 \xrightarrow{AlCl_3} \underset{\textbf{1a}}{} (C_6H_5)_2PCl + PCl_3 \quad \underset{\textbf{1b}}{}$$

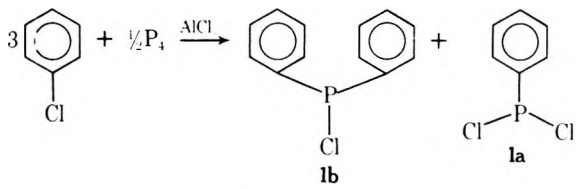
the reaction of benzene with phosphorus trichloride and aluminum chloride may be used to produce diphenylphosphinous chloride directly without isolating phenylphosphonous dichloride. The complex of diphenylphosphinous chloride with aluminum chloride formed during the disproportionation may be split by addition of potassium chloride.[4]

In this paper we wish to report the synthesis of phenylphosphonous dichloride and diphenylphosphinous chloride in high yield by a new and simple method from chlorobenzene and elemental white phosphorus.[7]

Results and Discussion

The subject reaction is carried out by heating elemental phosphorus in an excess of the chlorobenzene in a sealed

glass tube at 350°C for several hours. The reaction is catalyzed by small quantities of aluminum chloride or bromide or the corresponding ferric halides.



This method may be employed also for the preparation of substituted arylphosphonous dichlorides and diarylphosphinous chlorides from elemental phosphorus and substituted aryl chlorides.

In a typical experiment the aryl halide (4.0 mol) was heated with elemental white phosphorus (2.2 g-atoms) in the presence of 0.05 mol of anhydrous ferric or aluminum chloride at elevated temperatures for 8 hr. Reactions with *o*- or *p*-dichlorobenzene, *o*-, *m*-, or *p*-chlorotoluene, 1,2,4-trichlorobenzene, or 1-chloronaphthalene gave satisfactory yields when heated at 325°C. The reaction with chlorobenzene required higher temperatures (350°C).

In addition to ferric chloride and aluminum chloride we have found also titanium tetrachloride to be an effective catalyst. The results of these reactions are summarized in Table I.

If the catalyst was allowed to stand in the reaction mixture for several days before the heating was started it became inactive. It seemed that the metal chloride had reacted with the white phosphorus forming a new product (possibly a metal phosphide) which is inactive as catalyst.

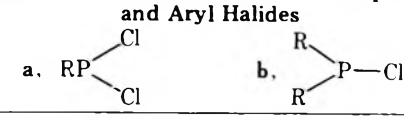
In the absence of any catalyst the main reaction taking place under identical conditions was the conversion of white phosphorus into its red modification. In some cases the formation of arylphosphonous dichlorides or diarylphosphinous chlorides occurred, but at a much slower rate than in the presence of a catalyst. In general, only traces of these reaction products were formed.

The reaction of elemental white phosphorus with aryl halides containing nitro groups such as 1-chloro-2-nitrobenzene led to violent reactions which caused the tubes to break. This was probably due to a sudden deoxygenation of the nitro group involving the interaction with phosphorus.

Synthesis of 1,6-Diphosphatriptycene. In an effort to optimize the conditions for the formation of some of these arylphosphonous and arylphosphinic halides we observed that in the reaction of *o*-dichlorobenzene with white phosphorus the composition of the reaction product mixture was strongly influenced by the type of catalyst, reaction time, and temperature. The reaction proceeded smoothly at 325°C in the presence of a small quantity of ferric chloride. In a typical experiment 70 g of white phosphorus, 8 g of ferric chloride, and 585 g of *o*-dichlorobenzene were heated for 7 hr at 325°C in a sealed tube. The resulting reaction mixture was a clear dark liquid which, on distillation, gave 76 g of *o*-chlorophenylphosphonous dichloride (**2a**) and 80 g of di(*o*-chlorophenyl)phosphinous chloride (**2b**).

If ferric chloride was replaced by titanium tetrachloride (see Table II) a much higher yield of compounds **2a** and **2b** was produced. This points out the much greater reactivity of titanium tetrachloride vs. ferric chloride. In addition the formation of a small quantity of crystalline material in the reaction mixture was observed. A combined catalyst of ferric chloride and titanium tetrachloride produced a large quantity of this crystalline substance (**10**) and some liquid material. The liquid material comprised a mixture of the above mentioned *o*-chlorophenylphosphonous dichloride,

Table I[p]
Arylphosphonous Dichlorides and Diarylphosphinous Chlorides from Elemental White Phosphorus and Aryl Halides



Compd	R	Bp, °C (mm)	Mp, °C	% yld
1a	Phenyl	48–51 (0.7)[a]		49.5
1b	Phenyl	124–126 (0.6)[b]		35.3
2a	o-Chlorophenyl	70–71 (0.7)[c]		30.0
2b	o-Chlorophenyl	148–153 (0.3)[b]	92–94	16.4
3a	p-Chlorophenyl	67–69 (0.3)[d]		20.2
3b	p-Chlorophenyl	143–146 (0.3)[e]	52–53	16.0
4a	o-Methylphenyl	67–68 (0.4)[f]		27.1
4b	o-Methylphenyl	146–147 (1.1)[h]		13.6
5a	m-Methylphenyl	58–60 (0.5)[i,j]		16.5
5b	m-Methylphenyl	135–138 (0.9)		16.1
6a	p-Methylphenyl	70–71 (0.7)		16.3
6b	p-Methylphenyl	129–130 (0.6)		16.1
7a	3-Chloro-4-methylphenyl	84–89 (0.8)[g]		19.3
7b	3-Chloro-4-methylphenyl	176–182 (1.1)		21.5
8a	2,4-Dichlorophenyl	88–91 (0.2)		17.6
8b	2,4-Dichlorophenyl	176–179 (0.3)		15.2
9a	1-Naphthyl	130–131 (0.8)[m,n]	51–54	9.7
9b	1-Naphthyl	227–229 (0.6)[o]	130–132	40.2

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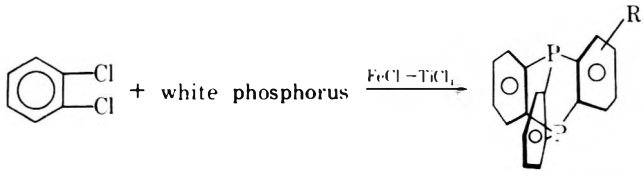
Table II
Reaction of 540 g of *o*-Dichlorobenzene with 70 g of White Phosphorus

Expt	Lewis acid catalyst	Temp, °C	Reaction time, hr	Products
A	8 g $FeCl_3$	325	7	76 g 2a 80 g 2b no 10
B	1.3 g $TiCl_4$	300	7	141 g 2a 134 g 2b 1 g 10
C	1.3 g $TiCl_4$ + 7 g $FeCl_3$	325	4	116 g 2a 64 g 2b 45 g 10

di(o-chlorophenyl)phosphinous chloride, some phosphorus trichloride, and unreacted *o*-dichlorobenzene.

The crystalline substance was separated from the liquid by filtration and recrystallized from tetrachloroethylene. The purified material melted at 313–315°C (corrected). Gas chromatographic analysis revealed that in addition to the main product an impurity (about 6%) was present which was removed by further recrystallization from tetrachloroethylene.

The results of the elemental analyses suggested that the new compound had the empirical formula $C_{18}H_{12}P_2$. This was confirmed by the mass spectrum of **10**, which showed a strong parent peak at *m/e* 290. On the basis of these data structure **10** was proposed for this substance. **10** is a novel bicyclic 5,10-*o*-benzeno-5,10-dihydrophosphanthrene which we named 1,6-diphosphatriptycene.



10, R = H
11, R = Cl

In agreement with the structure proposed for **10**, its NMR spectrum showed two groups of aromatic protons,

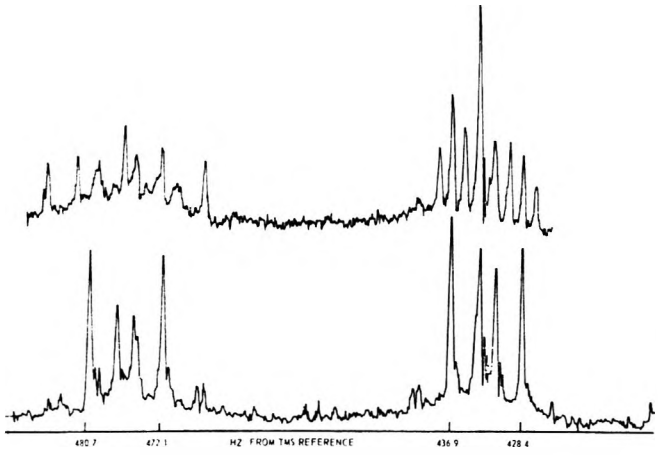
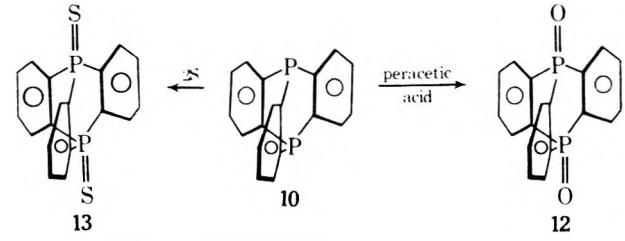


Figure 1. Top: NMR spectrum of diphosphatriptycene (ν_0 (Me_4Si) = 5994716 Hz). Bottom: ^1H spectrum with ^{31}P decoupled (ν_1 = 24285265 Hz).

one in the area from 481 to 470 Hz and the other one in the area from 437 to 427 Hz. Furthermore, the areas under the peaks indicated that both groups of protons are present in equal numbers. The one group belongs to the protons in ortho position to each of the P atoms, the other group to the corresponding protons in meta position to the P atoms. The splitting in this spectrum is very complex, since the molecule has 14 nuclei with spins of ½ (12 ^1H and 2 ^{31}P). The coupling of protons in different rings to the ^{31}P nuclei makes them interdependent. This interdependence, however, may be removed by spin decoupling the ^{31}P. Assuming that structure **10** is correct and that protons in different rings are not coupled, the expected spectrum then should show independent sets of only four spins grouped into two symmetrically equivalent pairs. The spectrum obtained in this spin-decoupling experiment was exactly identical with that expected for structure **10** and provided final proof for the correctness of this structure.[7]

The impurity accompanying the 1,6-diphosphatriptycene before recrystallization from tetrachloroethylene is according to its mass spectrum a monochloro 1,6-diphosphatriptycene (parent peak in mass spectrum *m/e* 324) which has structure **11**.

Oxidation of 1,6-diphosphatriptycene (**10**) with peracetic acid produced 1-6-diphosphatriptycene dioxide (**12**), while treatment of **10** in warm carbon disulfide with sulfur gave 1,6-diphosphatriptycene disulfide (**13**).



Effect of Catalyst on Formation of 1,6-Diphosphatriptycene. In a preliminary communication[8] we had reported the synthesis of 1,6-diphosphatriptycene (**10**) at 281°C using ferric chloride alone as catalyst. Since then, we have experienced very little success in repeating this synthesis. We believe, therefore, that the initial success in preparing **10** with ferric chloride alone at 281°C has been due to some unusual activity of the ferric chloride used in those early experiments (possibly because it contained traces of titanium tetrachloride).

Experimental Section

The elemental phosphorus (N.F. yellow sticks) used was purchased from Fisher Scientific Co., Fair Lawn, N.J. The melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were recorded on a Beckman IR 4 infrared spectrophotometer. Mass spectra were taken on an AEI MS-12. The microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Clark Microanalytical Laboratory, Urbana, Ill.

General Remarks. All reactions were carried out in a Pyrex glass tube of 20 in. length, 2.25 in. o.d., and 3/16 in. wall thickness. The charging of the tube with the catalyst, phosphorus, and the aryl halide was done under argon or nitrogen. Before sealing the tube it was cooled in dry ice–acetone. After sealing the tube was wrapped with asbestos paper and inserted into a 3-l. rocking autoclave. About 360 ml of hexane was added to the autoclave as a heat exchange medium and to provide an outside pressure on the glass. Then the autoclave was pressurized with 500 psi of nitrogen and heated to the reaction temperature.

After the reaction was completed the tube was cooled in liquid nitrogen and opened.

Phenylphosphonous Dichloride (1a) and Diphenylphosphinous Chloride (1b). A mixture of 62 g (2 g-atoms) of elemental white phosphorus, 450 g (4 mol) of chlorobenzene, and 7.5 g (0.053 mol) of anhydrous aluminum chloride was heated for 8 hr at 350°C (see general remarks) in a sealed tube. After cooling, the reaction product was distilled in vacuo, yielding 180 g of phenylphosphonous dichloride (**1a**), bp 48–51°C (0.7 mm) (49.6% of theory based on phosphorus), and 155 g of diphenylphosphinous chloride (**1b**), bp 124–126° (0.6 mm) (34.7% of theory based on phosphorus).

***o*-Chlorophenylphosphonous Dichloride (2a), Di(o-chloro-**

phenyl)phosphinous Chloride (2b), and 1,6-Diphosphatriptycene (10). A mixture of 68.2 g (2.2 g-atoms) of elemental phosphorus, 588 g (4 mol) of *o*-dichlorobenzene, 7 g (0.043 mol) of anhydrous ferric chloride, and 1.3 g (0.0068 mol) of titanium tetrachloride was heated for 4 hr at 325°C (see general remarks) in a sealed tube. After cooling the reaction product was filtered through a coarse fritted glass filter funnel. The crystalline 1,6-diphosphatriptycene (**10**, 45 g) was washed with methanol and recrystallized from tetrachloroethylene. It melted at 313–315°C; ir spectrum (KBr) bands at 3050, 1431, 1258, 1230, 1160, 1102, 1085, 1050, 940, 745 and 725 cm^{-1}.

The filtrate was distilled in vacuo, yielding 50 g of phosphorus trichloride, 116 g of o-chlorophenylphosphonous dichloride (**2a**), and 64 g of di(*o*-chlorophenyl)phosphinous chloride (**2b**).

1,6-Diphosphatriptycene Dioxide (12). In a three-neck 500-ml flask, fitted with a stirrer, condenser, and dropping funnel, a clear, hot solution of 12 g of 1,6-diphosphatriptycene (**10**) in 250 ml of tetrachloroethylene was placed. Then 28 ml of a 25% peracetic acid solution in ethyl acetate was added slowly at about 90°C. The reaction was exothermic and the temperature rose to about 120°C while a white, crystalline precipitate separated. Stirring was continued with gentle heating for another 1 hr. After cooling to room temperature the crystalline material was filtered off and recrystallized from 1-propanol: mp 488–490°C; ir spectrum (in chloroform) bands at 3020, 2375, 1450 m, 1240, and 1120 cm^{-1}.

Anal. Calcd for $C_{18}H_{12}P_2O_2$: C, 67.08; H, 3.72; P, 19.25. Found: C, 67.35; H, 3.73; P, 19.18.

1,6-Diphosphatriptycene Disulfide (13). To a solution of 2.9 g of 1,6-diphosphatriptycene in 70 ml of carbon disulfide was added a slurry of 0.64 g of sulfur in 50 ml of carbon disulfide. The mixture was refluxed for 4 hr. After standing overnight at room temperature the reaction mixture was filtered and the filtrate evaporated to dryness at reduced pressure. The crude material (4.2 g) melts at 400–402°C and was recrystallized from 300 ml of hot ethyl acetate: melting point of recrystallized product 396–399°C; ir spectrum (in chloroform) bands at 3010, 2375, 1450, 1268, 1235, 1110, and 1055 cm^{-1}.

Anal. Calcd for $C_{18}H_{12}P_2S_2$: C, 61.02; H, 3.38; P, 17.51; S, 18.07. Found: C, 61.30; H, 3.45; P, 17.30; S, 17.79.

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Registry No.—**1a**, 644-97-3; **1b**, 1079-66-9; **2a**, 1004-78-0; **2b**, 32186-89-3; **5b**, 13685-23-9; **6a**, 1005-32-9; **6b**, 1019-71-2; **7b**, 36024-98-5; **8a**, 56783-19-8; **8b**, 56783-20-1; **10**, 31634-70-5; **12**, 31634-72-7; **13**, 56783-21-2; phosphorus, 7723-14-0; chlorobenzene, 108-90-7; *o*-dichlorobenzene, 95-50-1.

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Comparative Stereochemistry of Catalytic and Diimide Reductions of Alkenes[1ab]

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The stereochemistry of the reduction of alkenes by diimide is compared with the stereochemistry of catalytic hydrogenation. Within selected groups of alkenes, mainly alkylidenecycloalkanes, the relation between the structure of the alkene and the ratio of saturated stereoisomers formed with diimide parallels that obtained on a platinum catalyst at high hydrogen pressures. This kind of correlation is not general; however, the comparisons afford a qualitative estimate of the importance and manner in which intramolecular, nonbonded interactions affect the stereochemistry of these reductions and help reveal the occurrence of exceptional catalytic mechanisms. The cis and trans 1-alkyl-4-*tert*-butylcyclohexanes which were obtained are separable by GLC (300 ft capillary coated with Apiezon L); the more stable trans isomer precedes the cis if the 1-alkyl group is methyl or ethyl but the elution order is reversed if the substituent is 2-propyl or *tert*-butyl.

The mechanism for the transfer of hydrogen from diimide (diimine or diazene)[2] to a carbon–carbon double bond is believed to consist of a single elementary process, the two hydrogen atoms being transferred simultaneously from nitrogen to carbon.[3] The apparent simplicity of the reaction commends it as a reference for the study of the stereochemistry of other cis addition reactions, and indeed van Tamelen and Timmons have compared the proportions of geometrical isomers obtained on the reduction of several olefins by diimide with the proportions obtained from catalytic hydrogenation, but the treatment was cursory.[4] In this paper we extend this comparison to learn how it may assist the disentanglement of the complex mechanisms of catalytic hydrogenation.

Substituted cyclo- or semicyclic alkenes, which yield a pair of geometrical isomers via cis addition to the opposite faces of the double bond, are suitable objects of this study. The ratio of isomers (cis/trans), which is obtained from a particular alkene upon reduction with diimide, is a measure of the difference in conformational energy of the diastereomeric transition states of the product controlling reaction, one leading to the cis isomer, the other to the trans. Because diimide is a small molecule, nonbonding interactions between it and the alkene at the transition state are likely to be small and virtually the same for both approaches.[3] Apparently, there are a few exceptions to this expectation.[4,5]

If other reducing agents are used, the ratio may be different because in comparison to the transition state for reduction by diimide, (1) the reaction centers have a completely

Table I
Comparative Stereochemistry of the Reduction of Exocyclic Alkenes (% Cis)

Alkene	(No.)	Catalytic[a] Low pressure[b]	Catalytic[a] High pressure[c]	Diimide
4-*tert*-Butylmethylenecyclohexane	(1)	87[d]	61[d]	49 (49)[e]
4-*tert*-Butylethylidenecyclohexane	(2)	32	17	46
4-*tert*-Butylisopropylidenecyclohexane	(3)	21	11	30
2-Methylmethylenecyclohexane	(4)	70[d]	67[d]	61 (61)[e]
β-Pinene	(5)	85[f]	90[f]	96[e]
2-Methylcyclopentylidenecyclopentane	(6)		21[g]	24[g]

[a] Catalyst is PtO_2 in acetic acid. Temperature ca. 27°. [b] 0.25–1 atm. [c] 80–100 atm. [d] Reference 1a. [e] Reference 4; temperature of reduction was 55°. [f] J. Sellick, M. S. Thesis, University of Arkansas, 1965. [g] Reference 6.

different arrangement, (2) the geometry of the reaction centers is similar (e.g., coplanar) but the degree of advancement through the product controlling step is different, i.e., the transition state may be relatively more product- (or reactant-) like, and (3) the preferred geometry of the reaction centers is similar but the effective size of the reagent introduces a steric effect which favors the formation of one of the stereoisomers.

If the application of these principles of comparative stereochemistry to the mechanisms of catalytic hydrogenation is to be fruitful, one needs an adequate description of the transition state of the reference reaction, some notion of the elementary processes which occur in catalytic hydrogenation, and the knowledge of the circumstances under which a particular process is likely to be product controlling. This is the order in which our subject will be discussed.

Stereochemistry of Reductions by Diimide. In their detailed analysis of the structural factors which govern the relative reactivity of olefins toward diimide, Garbisch et al. assumed a structure for the activated complex in which the "reaction orbitals" are coplanar.[3] The π-bond order of the olefinic double bond was assumed to be large so that rotation about this bond was not expected to be significant. Accordingly, for the cis cycloalkenes no appreciable ring conformation change between the starting and transition states was expected. Similar considerations lead them to conclude that, in general, changes in nonbonded repulsive energies could be neglected. They predicted that the reduction of bicyclo[2.2.1]heptene, cyclopentene, and cycloheptene through cyclononene should be stereoselective. In these compounds, differences in the torsional energy of the diastereomeric transition states arise from the opposite approaches to the double bond. The stereoselectivity observed in the reduction of 4-*tert*-butyl-1-methylcyclohexene, however, was not anticipated. This failure was attributed to the approximate manner in which the torsional potential for the activated complex was treated. It was noted that of the alternative approaches of diimide to the double bond (Figure 1) approach a, leading to the trans isomer, causes the dihedral angle $\Phi_{1,6}$ to increase and $\Phi_{2,3}$ to decrease whereas in the b approach the change is reversed. The a approach is favored because eclipsing a C–H bond with C–R results in a larger torsional strain than eclipsing C–H bonds. These effects might also be called changes in nonbonded interactions due to changes in conformation, and although small enough to be neglected in the calculations of the relative reactivities of alkenes whose structure differs markedly, they are significant factors in the determination of the stereochemistry of a particular alkene.

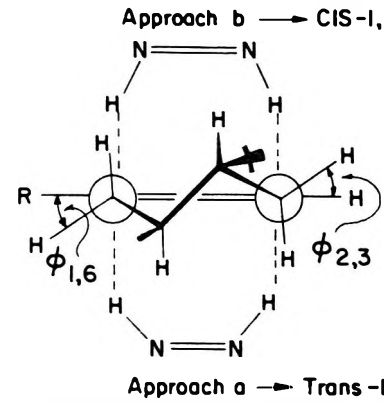


Figure 1. Model of the transition state for the transfer of hydrogen from diimide to an alkene according to Garbisch et al., ref 3.

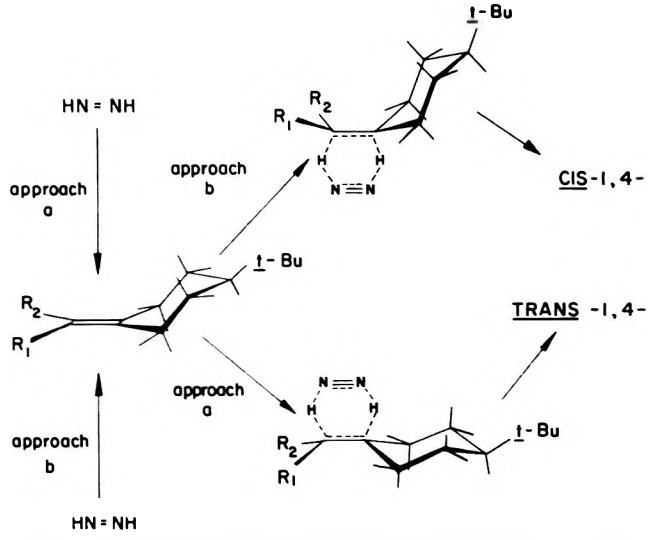


Figure 2. Change in geometry of an alkene from the ground to the diastereomeric transition states in its acceptance of hydrogen from diimide.

Results and Discussion of Diimide Reductions. The reduction of a series of exocyclic alkenes, 4-*tert*-butylmethylenecyclohexane (1), 4-*tert*-butylethylidenecyclohexane (2), and 4-*tert*-butylisopropylidenecyclohexane (3) yield increasingly larger proportions of the trans isomer (Table I). The result is in accord with the model of the transition state (Figure 2) which, according to Garbisch et al., occurs at about one-third of the "distance" along the reaction coordinate (χ) of this elementary step.[3] Apparently, the change in conformation of the alkene has introduced repulsive interactions between the vinyl substituents and the axial hydrogens at C-3 and C-5. If the conformation of the alkene did not change, all three compounds should yield the same cis/trans ratio with possibly some preference for the cis isomer if the diimide molecule exerted a steric effect. A small steric contribution may account for the excess cis isomer from 2-methylmethylenecyclohexane (4) and a larger contribution for β-pinene (5). Compounds obtained by replacing the methylene groups of either 4 or 5 by isopropylidene groups should give proportionally greater amounts of the trans isomer. Accordingly, we were not surprised to find that 2-methylcyclopentylidenecyclopentane (6) gives 76% *trans*-2-methyl-1-cyclopentylcyclopentane.[6,7]

Similarly, conformational effects are noted in compounds with endocyclic double bonds (Table II). In both 2,3-dimethylcyclopentene (7) and 2,3-dimethylcyclohexene

Table II
Comparative Stereochemistry of the Reduction of Endocyclic Alkenes (% Cis)

Alkene	(No.)	Catalytic[a] Low pressure[b]	Catalytic[a] High pressure[c]	Diimide
2,3-Dimethylcyclopentene	(7)	48[d]	37[d]	31
2,3-Dimethylcyclohexene	(8)	81[d]	70[d]	29 (24)[e]
1,4-Dimethylcyclohexene	(9)	55[d]	65[d]	45
1-methyl-4-*tert*-butylcyclohexene	(10)	35[d]	47[d]	30[f]
1,4-Di-*tert*-butylcyclohexene	(11)[g]	90 (Rh)	88 (Rh)	38
4-Methyl-1-*tert*-butylcyclohexene	(12)			49[f]
2,4-Di-*tert*-butylcyclohexene	(13)	45 (Rh)[g]		48[f]

[a] Catalyst is PtO_2 with the exception of 11 and 13, for which 5% Rh/Al_2O_3 (Rh) was used. Temperature ca. 27°. [b] 0.25–1 atm. [c] 80–100 atm. [d] Reference 1a. [e] Reference 4. [f] Reference 3. [g] Reference 21.

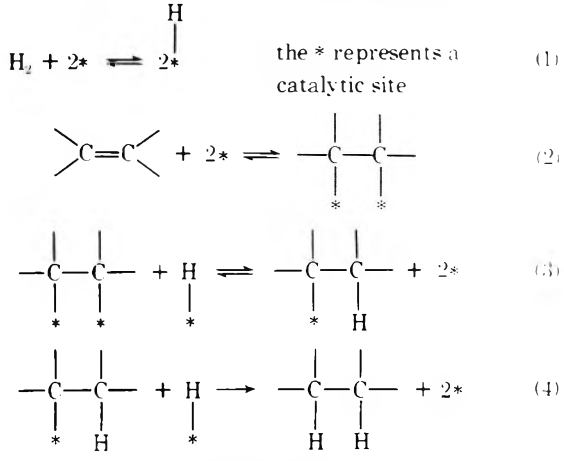
(8), the predominance of the trans isomer corresponds to a preferred approach of diimide to the double bond which permits the methyl groups to move away from one another. Garbisch's explanation for the stereoselective reduction of 4-*tert*-butyl-1-methylcyclohexene (**10**)[3] can be applied unaltered to the reduction of 1,4-di-*tert*-butylcyclohexene (**11**); however, the stereoselectivity of 1,4-dimethylcyclohexene (**9**) and 4-methyl-1-*tert*-butylcyclohexene (**12**)[3] is virtually nil. In Garbisch's model for the reduction of **10**, the *tert*-butyl group is restricted to a pseudoequatorial position; a methyl group would not be as restricted because the difference in energy of a pseudoequatorial–pseudoaxial methyl group is certain to be much less, less than the 1.6 kcal/mol difference between axial and equatorial methylcyclohexane.[8] Accordingly, a lower stereoselectivity is to be expected for compounds **9** and **12** relative to **10** and **11**. We have nothing to add to the previous speculations concerning the low stereoselectivity in the reduction of **13**.[3]

Effect upon the Rate of Reaction with Diimide of Substituting a Methyl Group for a Vinyl Hydrogen Atom. The relative rates of reduction by diimide at 80° of methylenecyclohexane (**14**) and the 4-*tert*-butylalkylidenecyclohexanes (**1**, **2**, and **3**) are (3.3), 3.4, 0.59, and 0.21, respectively, the scale being normalized to cyclohexene by assuming that the relative rate constant for **14** is the value previously reported.[3] To compare the effect of substituting a methyl group for a vinyl hydrogen in this series with previous work, the relative rates are corrected to the rate of attack at the favored face of the double bond; the corrected values are 3.5, 0.64, and 0.29, respectively, for **1**, **2**, and **3**. Substituting one vinyl hydrogen of **1** by a methyl group reduces the rate by a factor of 0.19 (compare with 0.14 ± 0.03 reported)[3] and the second substitution reduces the rate by only 0.45. In both instances the substitution has introduced a strain which is associated with cis-dialkyl substituents and this counters the expected stabilizing hyperconjugative interaction of the methyl and vinyl groups.[9] The only part of the observed relative reactivity in this series which can be attributed to changes in conformation is the change in stereospecificity with the change in vinyl substituents.

Conformational changes between the ground and transition state appear to affect the relative reactivity of certain groups of alkenes. For example, Garbisch et al. found that 1-substituted cyclohexenes are about 50% more reactive than the corresponding 4,4-dimethylcyclohexene whether the substituent is methyl, *tert*-butyl, or phenyl and they suggested that it is due, in part, to a hindered approach of diimide past the axial C-4 methyl group. We suggest, however, that the changes in geometry on proceeding through the transition state engender a repulsive interaction between the emerging axial hydrogen at C-2 and an axial methyl group at C-4, the effect being independent of the 1 substituent. The relative rate of about 1.5 at 80° corresponds to a $\Delta\Delta G^{\ddagger}$ of 0.3 kcal/mol, which is approximately one-third of the value of a single butanelike gauche interaction, one-third being the fraction of change effected on attaining the transition state.[3]

The above discussion illustrates the rationale employed to account for the stereochemistry of diimide reductions. Catalytic hydrogenations are more complex reactions but a similar analysis should apply to a series of compounds if the product-controlling step is the same for each compound. The correspondence with the ratio of isomers obtained from diimide will be the greater, the closer the transition states in the reaction series resemble the transition states of the reference reaction.

Comparison of the Stereochemistry of Catalytic Hydrogenation with Reductions by Diimide. The mechanism of the addition of hydrogen to alkenes catalyzed by various group 8 elements, in the form of films or small crystallites supported upon finely divided inert solids, is generally thought to proceed via the Horiuti–Polanyi mechanism, which is represented conventionally as follows.[10]

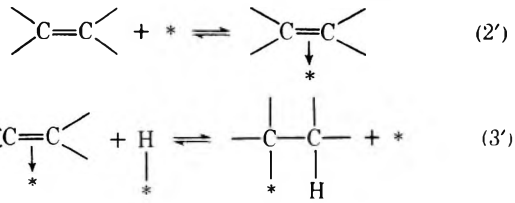


The stereoselectivity (cis/trans ratio) found in the reduction of a compound such as 4-*tert*-butylmethylenecyclohexane (**1**) should depend, therefore, on which of the reactions (2, 3, or 4) is product controlling.[1a,13] For example, **1** is hydrogenated over reduced platinum oxide, one of the more stereoselective catalysts, to give a ratio of cis/trans products which changes with increasing pressure from 6.7 at 0.25 atm to 1.6 at 100 atm. The possibility that reaction 4 is product controlling can be excluded because isomerization of **1** to 4-*tert*-butyl-1-methylcyclohexene (**10**), the more stable and less reactive alkene, is not observed. The results can be understood if one assumes that increasing the pressure has changed the product controlling reaction from (3) the formation of the "half hydrogenated" state to (2) the formation of the (α,β-diadsorbed) alkane. Similar results are obtained with various other cyclic and semicyclic alkenes.

The geometry of the transition state for reaction 2 is likely to be closely related to the geometry of the transition state for the reduction of an olefin with diimide.[1a,13b] In both reactions, the carbon atoms of the double bond be-

come attached to a pair of atoms located to one side of the molecule, and if the transition state is to conserve the combined symmetry of the reactants, the new bonds will be formed in an eclipsed conformation. The transition states of these two reactions are unlikely to lie at the same degree of advancement along the reaction coordinate (defined as χ)[3] but the similarity in the required geometry of the reaction centers in the transition states should affect similar changes in the conformational energy associated with the rest of the olefin structure. Consequently the differences in the ratio of saturated epimers which are produced from these two reactions will reflect differences in χ as well as differences in nonbonded interactions between reagent and unsaturated substrate, the classical steric effect. The degree of advancement, χ, should be greater for reaction 2 than for the transfer of hydrogen from diimide because the enthalpy of adsorption of an alkene on the catalyst is certain to be less than the heat of reduction by diimide; accordingly, the change in intramolecular compressions also will be greater. On the other hand, the catalyst would be expected to exhibit the larger "classical steric effect" which affects the cis/trans ratio in the opposite sense.

As a variation of the above mechanism, the adsorbed alkene might be represented as a π complex.[1b,12,13b,14] The transition state for reaction 2′ could have the geometry as-



(2′)

(3′)

cribed above to the transition state of reaction 2 because the geometry of the alkene in the π complex corresponds to that of an intermediate stage in the conversion of the alkene to the eclipsed conformation of the α,β-diadsorbed alkane postulated by Burwell.[12] The interactions enumerated for the transition state of reactions 2 or 2′ will be intensified in the transition state for 3 or 3′ because, in the later, the alkene is more tightly bound to the catalyst. The π-complex model is appropriate for hydrogenations catalyzed by soluble complexes of transition elements in which both hydrogen and alkene are associated with a single metal atom prior to the transfer of hydrogen to the alkene carbon atom and may be the better description for the surface catalyzed reaction too.[15-18]

Results and Discussion of Stereochemistry of Catalytic Hydrogenations Relative to Reduction by Diimide. If reaction 2 (or 2′) is product controlling as it appears to be for **1** and **10** over reduced platinum oxide at high hydrogen pressure,[13b] then the ratio of stereoisomers obtained under these conditions should parallel the ratio obtained with diimide. The data in columns 2 and 3 (Table I) shows the anticipated parallelism, and with one exception, **5**, the differences in the ratios are those to be expected if the platinum catalyst exerts a greater steric effect than diimide, the cis isomer being favored.

The data in column 1 also parallel that in column 3 but the difference is somewhat greater than in the preceding comparison. The model for the transition state for reaction 3 (or 3′) conforms to these results; however, the conclusion that the product-controlling reaction is the same for this series (low hydrogen pressure on platinum) must be accepted with caution.

Isomerization may occur undetected (except by tracer experiments) if the isomeric product is hydrogenated more rapidly than its precursor, a situation common among highly alkylated ethylenes, particularly if the pressure of hydrogen is low.[11,12]

The data in Table II are not so easily rationalized. In each instance, diimide yields less of the cis isomer than does catalytic hydrogenation on platinum. However, there is no obvious parallelism for the data in the several columns. This implies that the structures of the transition states are not generally related, perhaps because the catalyst causes the alkene to adopt a conformation which is quite different from that attained in the transition state for reductions by diimide or because the mechanism is not constant within the series.[1a,19]

Some comparisons seem useful. For example, 2,3-dimethylcyclopentene (**7**) yields with diimide about the same fraction of the cis isomer (31%) as does 2,3-dimethylcyclohexene (**8**). At high pressure on platinum, **8** yields much more of the cis isomer (70%) than does **7** (37%).[20] The explanation for the stereochemistry of the diimide reductions is the same as that for **10**; the repulsive interaction between the adjacent methyl groups is less in the transition state which leads to the trans isomer. The proportion of geometrical isomers obtained upon catalytic hydrogenation of 2,3-dimethylcyclohexene (**8**) is opposite to that given by diimide, i.e., mainly cis, but the proportion of cis isomer obtained from 2,3-dimethylcyclopentene (**7**) differs only slightly. We attribute this difference in behavior of **8** and **7** to the greater flexibility of the six-membered cycle which can *relieve* the methyl group interactions more easily than can the five-membered ring. The driving forces for the above change in stereochemistry are the nonbonded interactions between the olefin and the catalyst, the corresponding interactions with diimide being small.

The strikingly different results given by 1,4-di-*tert*-butylcyclohexene (**11**) when hydrogenated over a rhodium catalyst, ~90% cis, compared with the 38% cis obtained with diimide, indicates important differences in the geometry of the transition states of the product-controlling steps of these reactions. The high proportion of the cis isomer appears inconsistent with the ratio of isomers obtained catalytically from **9** and **10**, albeit on a platinum catalyst, and indicates that it is the mechanism on rhodium which is exceptional. The dissociative mechanism discussed by Smith and Burwell, may permit **11** to isomerize preferentially (steric effect?) to *cis*-3,6-di-*tert*-butylcyclohexene (**14**) which would yield only *cis*-1,4-di-*tert*-butylcyclohexane upon the addition of hydrogen.[21]

Equilibration and Chromatographic Separation of *cis*- and *trans*-1-Alkyl-4-*tert*-butylcyclohexanes. Following known procedures, the 1,4-disubstituted cyclohexanes were characterized as cis or trans by equilibrating a mixture of the epimers obtained by hydrogenating a particular alkylidenecyclohexane over Pt/C. The equilibration was accomplished at 250° by heating the resulting mixture and 5% Pd/C in a sealed tube.[3] From the measured ratio of epimers the difference in free energy, $\Delta G°$, was calculated to be 1.8, 2.1, and 2.3 kcal/mol for the products obtained from **1**, **2**, and **3**, respectively. These results agree satisfactorily with previous estimates of the free energy difference between axial and equatorial methyl, ethyl, and 2-propyl groups.[8]

The GLC analysis of mixtures of these pairs of epimers varies in difficulty in part because the order of elution is apparently a function of the shape or size of the alkyl substituent. The more stable, trans isomer precedes the cis if the 1-alkyl group (1-alkyl-4-*tert*-butylcyclohexane) is methyl or ethyl but the order is reversed if the substituent is 2-propyl or *tert*-butyl. For such hydrocarbons, the order of elution can be expected to follow the order of increasing

boiling point. In their critical review of the Auwers–Skita rule, van Bekkum, van Veen, Verkade, and Wepster have noted that, although generally the isomer of lower enthalpy has the lower boiling point, the reverse relationship applies to the epimers of 1,4-diisopropylcyclohexane and 1,4-di-*tert*-butylcyclohexane.[22] We found that of the epimeric pairs encountered the *cis*- and *trans*-1-ethyl-4-*tert*-butyl- and 1,4-di-*tert*-butylcyclohexanes were the most difficult to separate by GLC.[21,23]

Conclusions

Changes in conformation between the ground and transition state affect the relative rates of reduction of alkenes by diimide through changes in repulsive nonbonded interactions. Although the effects are small in comparison to the range of effects caused by other structural factors, they are important in determining the stereospecificity of the reaction.

Comparisons between the stereochemistry of reductions by diimide and hydrogenations conducted on a platinum catalyst at high pressure indicate similarities in their product-controlling transition states. However, complications resulting from competing reactions, or differences in the nature of the product-controlling step as a function of the catalyst or the conditions, probably account for the lack of any general correlation between the stereochemistry of these catalytic hydrogenations and reductions by diimide. Nevertheless, a comparison may furnish an indicator of unusual or exceptional catalytic behavior.

Nishimura et al. have shown that a supported iridium catalyst is exceptionally stereospecific for the addition of hydrogen to alkenes such as 1,2-dimethylcyclohexene.[24] The catalyst has relatively little tendency to cause alkene isomerization. Accordingly we expect that the use of such catalysts to saturate the alkenes given in Table I and II at any pressure of hydrogen will yield ratios of stereoisomers similar to those obtained with platinum catalysts at high pressures of hydrogen. This conclusion is based upon our belief that the high stereospecificity and low isomerization activity of the iridium catalysts indicate that the adsorption of alkene on these catalysts is virtually irreversible and accordingly product controlling.

Experimental Section

Alkenes. With the exception of 2-methylcyclopentylidenecyclopentane (**6**), whose preparation and properties are described in the following paper,[6] all of the alkenes have been reported previously. As judged by GLC analysis, the samples used were >99% pure. When necessary, the alkenes were purified by preparative chromatography. The assigned structures were consistent with their ir and NMR spectra.[23] β-Pinene was obtained through the generosity of Hercules Inc., Wilmington, Del. Compound **3** was prepared initially by Keulks via the Reformatsky reaction of 4-*tert*-butylcyclohexanone with ethyl α-isobutyrate and zinc.[25] It has been more recently prepared by Corey and Kwiatkowski.[26]

Hydrogenations and Reductions by Diimide. The hydrogenation procedures have been described previously.[1a,13] Except where noted, the diimide reductions, including the competitive reactions, followed the procedure of Garbisch et al., in which benzenesulfonylhydrazide is decomposed at 80° in diglyme containing triethylamine. In the alternative procedure, diimide was generated at 5° by the acid-catalyzed decomposition of potassium azodicarboxylate dissolved in methanol.[5]

Analytical Procedures. Mixtures were analyzed by GLC using either the Perkin-Elmer Model 881 gas chromatograph fitted with a flame ionization detector or an instrument equipped with a Beckman Hydrogen Flame Detector. For most analyses a column 50 ft × 0.125 in., 2% polyethylene glycol 1000 distearate supported on 80/100 mesh Chromosorb W, acid washed, was used. To separate the *cis*- and *trans*-4-*tert*-butyl-1-ethylcyclohexanes the column used was 45 ft × 0.125 in., 2.5% Carbowax 750 on Chromosorb W, acid washed. The separation of the *cis*- and *trans*-1,4-di-*tert*-butyl cyclohexanes required a capillary column, 300 ft × 0.02 in., coated with purified Apiezon L.[21] The analysis of a mixture containing **6** and its reduction products is given in the following paper.[6]

Equilibration Experiments. Following the procedure of Garbisch et al., the 1,4-disubstituted cyclohexanes were characterized as cis or trans by the equilibration of the hydrocarbon mixtures obtained from the complete reduction of 0.15 ml of the olefin (**1**, **2**, and **3**) at 4 atm over 0.02 g of 5% Pt/C in 5 ml of cyclohexane.[3] One milliliter of the resulting mixture was placed with 0.05 g of 5% Pd/C in 8 mm × ca. 15 cm Pyrex tubes which were sealed and heated at 250° in a steel bomb. After 72 hr, the tubes were removed from the bomb, cooled in a Dry Ice–2-propanol bath, and carefully opened. The reaction mixtures were analyzed by GLC.

Registry No.—**1**, 13294-73-0; **2**, 14033-64-8; **3**, 14033-75-1; **4**, 2808-75-5; **5**, 127-91-3; **6**, 56761-48-9; **7**, 16491-15-9; **8**, 1759-64-4; **9**, 2808-79-9; **10**, 3419-74-7; **11**, 5009-02-9; **12**, 3419-69-0; **13**, 3419-75-8.

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Stereochemistry of Catalytic Hydrogenation of Alkenes Contrary to the Classical Model of Adsorption[1]

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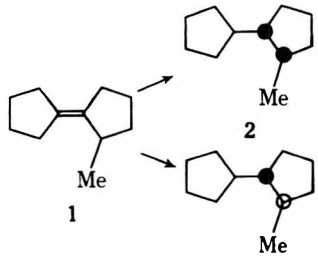
The stereochemistry of hydrogenation of 2-methylcyclopentylidenecyclopentane (1) on PtO_2, is examined to test the hypothesis that in the process of adsorption on a catalyst, an alkene experiences a change in geometry which is appreciable at the transition state for adsorption. The theory is supported by the formation of more *trans*- than *cis*-1-methyl-2-cyclopentylcyclopentane from 1 at high hydrogen pressures, a result which is contrary to expectation based upon traditional views of adsorption on surfaces. The stereochemistry of hydrogenating several isomers of 1 is determined to assess their possible role in the hydrogenation of 1. At low pressures, the hydrogenation of tetrasubstituted ethylenes which have not been rigorously purified gives erratic stereochemical results; alkenyl peroxides or their decomposition products are implicated.

The classical interpretation of the stereochemistry of catalytic hydrogenation focuses attention upon the manner in which an unsaturated molecule can be fitted best to the catalyst's surface which is assumed to be flat (catalyst hindrance).[3,4] The transfer of hydrogen from the surface to the underside of the adsorbed molecule yields the product. According to current theory, the preceding view must be an oversimplification not only because the adsorption of the unsaturated species need not be the product-controlling step but even if it is, the geometry of the unsaturated molecule is altered upon adsorption.[2,5] The resulting change in torsional strain and intramolecular nonbonding interactions will depend upon which face of the double bond becomes attached to the catalytic site.[2] Because these effects can oppose "catalyst hindrance", the relative amount of the saturated stereoisomers which is obtained from a particular alkene can be the inverse of that predicted from classical theory. This kind of argument furnished an explanation for the fact that upon hydrogenation at high pressures over reduced platinum oxide, one of the more stereoselective catalysts, 2,3-dimethylcyclopentene, yields more *trans*- than *cis*-1,2-dimethylcyclopentane.[6] The observed effect in this instance is small; however, larger deviations from the classical norm can be anticipated.

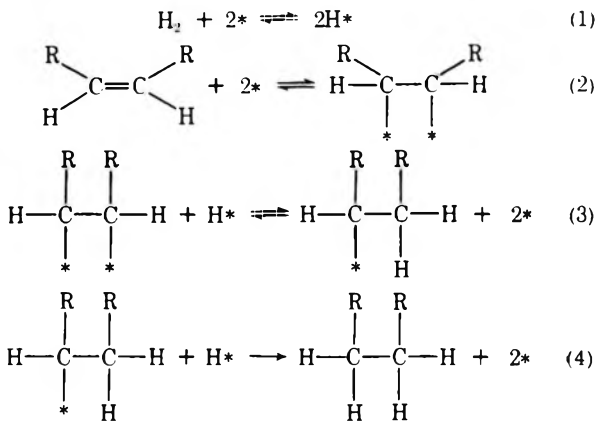
To test the above ideas, we selected 2-methyl-1-cyclopentylidenecyclopentane (1) for this study because clearly, the prediction based on classical theory is that more *cis*- (2) than *trans*-2-methyl-1-cyclopentylcyclopentane (3) will be formed.



1 2 3

We anticipated that the change in geometry of 1 on adsorption, however, would introduce repulsive interactions between the 2,2′ and 5,5′ ring positions which are much greater in the transition state which leads to the cis isomer than the transition state which leads to the trans isomer. Furthermore, the change in geometry would also tend to reduce "catalyst hindrance" involving the 2-methyl group. Our predictions drew support from the inspection of space filling models of the α,β-diadsorbed alkane which are represented in eclipsed conformations by the perspective diagrams in Figure 1.[2,5] Because they are not compressible the models overemphasize intramolecular steric hindrance; however, their use alerted us to the possible operation of the effects noted above. The hydrogenation of 2-cyclopentylidenecyclopentanol over a nickel catalyst gives mainly *trans*-2-cyclopentylcyclopentanol, but this result has been said to demonstrate the directive effect of the hydroxyl group.[7]

The preceding argument applies if adsorption of the alkene is virtually irreversible; however, other elementary processes may be product controlling. For example, if the addition of hydrogen proceeds via the Horiuti–Polanyi mechanism or one of its variations,[8,9,10] then the product-controlling reaction may be chemisorption (reaction 2), the formation of the "half-hydrogenated state" (reaction 3), or the combination of the latter with hydrogen to produce alkane (reaction 4).[2,5] Whether reaction 2 or 3 is product con-



trolling, the change in intramolecular interactions, from alkene to the respective transition states, will affect the product ratios in the same direction, although not identically.[2,5] If reaction 4 is product controlling, however, alkene isomerization should be faster than the addition of hydrogen and the distribution of saturated products should approach the equilibrium value.[5,11]

The reduction of a tetrasubstituted alkene may proceed via isomerization to one which is less substituted so that the stereochemistry observed is characteristic of the hydrogenation of the products of isomerization rather than of the initial alkene.[12] Increasing the pressure of hydrogen, however, causes more of the tetrasubstituted alkene to be hydrogenated directly.[5,13] Accordingly, the stereochemistry of the hydrogenation of alkenes which might be formed by the double-bond isomerization of 1 and the effect of hydrogen

pressure on the ratio of saturated stereoisomers which form also were examined.

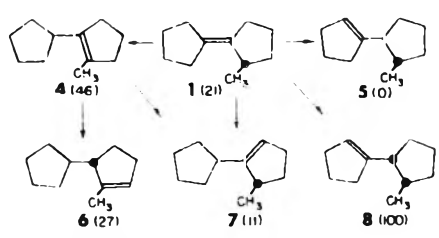
Although not anticipated from our previous experience, the ratio of stereoisomers obtained from 1 on hydrogenation over platinum oxide, particularly in the lower pressure range, seemed to be a function of the history of the alkene. Apparently, the effect is connected to the ease of peroxidation of the alkene because experiments conducted so as to mitigate exposure of the alkene to oxygen and with care to remove traces of peroxide, which might be present, lead to reproducible results.[14] In retrospect, the presence in alkenes of variable amounts of hydroperoxides or their decomposition products may account for some of the stereochemical anomalies which have been reported.[6,13,15]

Results and Discussion

Platinum Oxide. In accord with our expectations, 2-methyl-1-cyclopentylidenecyclopentane (1) yields mainly the trans dialkylcyclopentane, 3, when hydrogenated over reduced platinum oxide, a catalyst which ordinarily exhibits a relatively high stereospecificity. However, several factors tend to limit the significance of this result. At pressures near atmospheric, the stereochemistry is sensitive to the history of the alkene, that is, samples of 1 which had been kept in the laboratory for several days yielded larger percentages of the trans isomer than the freshly prepared material. Generally, the older samples also hydrogenated more slowly. Apparently the effect is due to peroxides formed on exposure of the cycloalkene to the atmosphere because after the alkene was percolated through alumina in the manner recommended by Hussey, Kuelks, Nowak, and Baker, the ratio of saturated stereoisomers was the same as that given by a fresh sample.[14] Likewise, 2-methyl-1-cyclopentylcyclopentene (4) gave erratic results at low pressures of hydrogen; the more slowly reacting samples produced the *larger proportion* of the cis isomer 2 (Figure 2). Uncontrolled variations in stereochemistry have been reported for 1,2-dimethylcyclopentene and 9,10-octalin but without comment about the likely cause of the irregular behavior.[6,12]

At low pressures, the platinum-catalyzed hydrogenation of tetrasubstituted alkenes proceeds mainly via isomerization to more easily hydrogenated and generally less substituted alkenes.[5,12] The hydrogenation of 1 was always accompanied by the appearance of 4 although the concentration of the latter remained small, less than 2%. In competition, 4 reacts about twice as rapidly as 1. Chart I indicates

Chart I
Isomers of 1 and the Percentage of *cis*-2-Methyl-1-cyclopentylcyclopentane (2) Formed from Each at 1 Atm (PtO_2)[a]



[a] Structural formulas 1, 5, 6, and 7 represent one of the epimeric forms of each compound designated.

the isomers to which 1 is most likely to be converted and the percentage of the cis isomer, 2, each produces when hydrogenated on platinum oxide at 1 atm of hydrogen.

With the exception of 6, each of the isomers could be formed from 1 via a 1,3-hydrogen shift.[16] If the mechanism

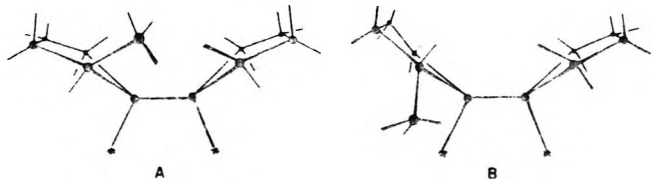


Figure 1. Diastereoisomeric adsorbed species of 1 represented as α,β-diadsorbed alkanes. A proceeds to give cis (2) and B to trans (3).

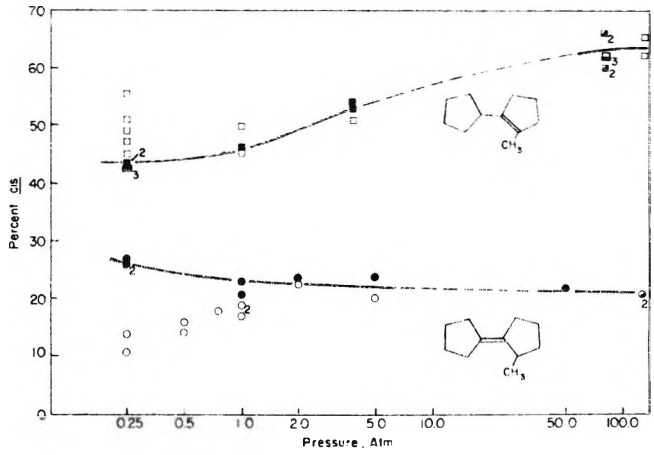


Figure 2. Percentage of cis isomer (2) which is formed over PtO_2 from 2-methyl-1-cyclopentylcyclopentene (4) or 2-methylcyclopentylidenecyclopentane (1) as a function of the hydrogen pressure. Darkened symbols represent experiments with freshly purified alkenes (see discussion): 4, □, ■; 1, ○, ●. The subscripts indicate the number of separate experiments which yielded the same result; symbols which lack a subscript represent the result of a single experiment.

of isomerization involved an allylic intermediate as suggested by Smith and Burwell,[12] then the principal product of isomerization is likely to be 4 because it would be formed through the breaking and subsequent re-formation of a tertiary hydrogen to carbon bond. The intermediate adsorbed π-allylic structure could retain the planarity of the groups about the double bond in 1 and would include the 2-methyl group in the same plane. Adsorption of the alkene with this same orientation would also allow the formation of 7 and 8 by an analogous dissociative mechanism or lead to *cis*-2-methyl-1-cyclopentylcyclopentane (2) through the acceptance of hydrogen from the catalyst. Adsorption of 1 on its opposite face would permit the formation of 7 and 5 by a dissociative mechanism or the trans saturated isomer, 3, by the simple abstraction of hydrogen from the catalyst. Because 1 yields more trans (3) than does 4, the latter cannot be the only intermediate even though it is the only isomer of 1 which is observed to form. If any of the other isomers were produced as intermediates they would escape detection because being less substituted alkenes, in competition, they are hydrogenated more rapidly than 1 or 4. Clearly the observed product distribution obtained from 1 at low pressures can be accounted for as arising via isomerization to some combination of the alkenes 4, 5, 7, and 8.[16] In the section on catalysis by palladium on carbon, we shall return to this question.

More definite conclusions regarding the stereochemistry of the direct addition of hydrogen to 1 can be inferred from experiments conducted at high pressure. Evidently, increasing the pressure of hydrogen increases the fraction of an alkene, including tetrasubstituted alkenes, which add hydrogen directly without prior isomerization.[5,12,13] Thus, 4 gives 43% cis at 0.25 atm and 62% at 80–100 atm. In this

instance, direct addition should yield only the cis isomer, **2**; the proportion of trans (**3**) actually formed is an indicator of the fraction of **4** which isomerizes to more easily hydrogenated alkenes such as **6** and **7**. Increasing the pressure causes **1** to yield more of the trans dialkylcyclopentane, **3**, and accordingly, **3** must be the principal direct reduction product of **1**. The product-limiting step at very high pressure is likely to be the adsorption of the alkene, reaction 1.

Some support for the preceding interpretation of stereochemistry may be gained from a comparison of catalytic hydrogenation at high pressure with reduction by diimide.[2] An alkene probably adopts a geometry in the transition state for adsorption on a catalyst which is quite similar to that attained in the transition state for the transfer of hydrogen from diimide to the carbon–carbon double bond. Differences in the ratios of geometrical isomers formed by these procedures can be attributed to the expected larger interactions between the catalyst and the alkene at the transition state for adsorption. The cis to trans ratios obtained from **1**, **6**, and **7** by catalytic hydrogenation at high pressure are remarkably like those obtained from diimide (Table I), indicating that intramolecular forces largely determine the ratio of stereoisomers under these conditions.[2] Not surprisingly, **5** yields only trans, **3**, with either reagent.

Table I
Comparative Stereochemistry of Catalytic (PtO_2) and Diimide Reductions of 1 and Its Isomers

	% cis (2)		
Compd	PtO_2 (1 atm)	PtO_2 (80 atm)	Diimide
1	23	21	24
4	46	62	100
6	27	20	24
7	11	12	26
5	0.0	0.0	0.0

Effect of Impurities. Apparently the impurities in the alkene affect the stereochemistry as well as the rate of hydrogenation of **1** and **4**, the effect being to *decrease* the ratio of cis (**2**) to trans (**3**) isomers obtained from **1** and *increase* the ratio of these products formed from **4**. At least for the latter, the effect is in the direction expected for an increase in the ratio of simple addition to isomerization–addition.[17] If the same explanation applied to the effect of impurities on **1**, then the simple addition of hydrogen to **1** at low pressures is more stereospecific [greater proportion of trans (**3**)] than addition at high pressures of hydrogen. This result would be expected if the mechanism were the same as that which we have postulated and supported with evidence obtained with less substituted alkenes, i.e., that the product-controlling step for the addition of hydrogen at low pressures is the formation of the "half-hydrogenated state" while the addition at high pressures is the adsorption of the alkene.[5,6] However, the fraction of saturated products which are formed via this mechanism cannot be determined from the stereochemical evidence alone. The dominant reaction path apparently involves isomerization to less substituted and more reactive alkenes.

Samples of **4** which had not been percolated through alumina prior to use gave a ratio of cis to trans isomers which decreased with conversion, from 51% cis at 6% reduction to 38% cis at 37% reduction. Rigorously purified samples did not show this effect. This trend in stereochemistry corresponds to a decrease in the relative rates of addition to isomerization resulting from a progressive change in the catalyst, as if the impurities, which had tended to favor simple addition–hydrogenation, were being destroyed.[17] Tetrasubstituted alkenes appear to be more easily affected in this way by adventitious impurities, presumably peroxides, than are less substituted alkenes.

Reduction over Palladium. Alkene isomerization characteristically accompanies hydrogenation on palladium catalysts and the hydrogenation of **1** is unexceptional in this regard.[18] Isomerization yields mainly 2-methyl-1-cyclopentylcyclopentene (**4**) and *trans*-2-methyl-1-(1-cyclopentenyl)cyclopentane (**5**). The latter is more easily hydrogenated than either **1** or **4** and consequently the amount detected after less than 60% of **1** remains (Table II) must represent only a fraction of that actually formed initially. Smaller amounts of **7** and an unidentified product, possibly *cis*-2-methyl-1-(1-cyclopentenyl)cyclopentane, are also present at this stage of the reduction. Knowledge of the distribution of the product as a function of the fraction of **1** converted would have afforded a better measure of the initial distribution of products. Although this information is lacking, the principal alkene formed appears to be **5** rather than **4**, although the latter is likely to be an initial product too. Whether the mechanism of formation of **5** is dissociative or associative, the first step would require the adsorption of **1** on the face which, ordinarily, would be thought to be the more hindered side of the molecule.[19]

Table II
Survey Hydrogenations of 1 and 4[a]

Compd	Catalyst	P, atm	% redn	% cis[b]	% other products
1	5% Pt/C	0.25	29	15	1.6 (**4**)
		1.0	100	11	
		135	66	13	2.1 (**4**)
1	5% Pd/C	0.25	36	11	10 (**4**), 13 (**5**)
		1.0	47	10	11 (**4**), 9 (**5**)
		133	100	13	
1	5% Rh/C	134	100	45	
1	5% Ru/Al_2O_3	67	45	45	0.2 (**4**)
4	5% Pd/C	0.25	7	32	0.7 (**7**)
4	5% Rh/C	134	100	94	

[a] Temperature 27 ± 2°. [b] Percent of saturated product

In comparison, the initial product of isomerization of **4** appears to be **7** rather than **6**. Although **1** is not formed initially, it would undoubtedly appear later as the reaction proceeded, since isomerization is a dominant feature of the hydrogenations of alkenes on palladium catalysts. Usually the more stable isomers predominate in the products of hydrogenation when palladium catalysts are used, and in this respect the results in Table II are not unexpected.

Other Catalysts. Several other catalysts were used in a few experiments and the results are shown in Table II. With ruthenium and rhodium catalysts, **1** yields larger proportions of the cis product than is given by platinum at the same pressure. The fact that **1** gives 55% cis at high pressure may simply reflect the fact that **4**, a principal product of the isomerization of **1**, yields the cis isomer almost exclusively (94% cis) under the same conditions. The ratio of saturated isomers obtained with platinum on carbon is similar to the ratio obtained on reduced platinum oxide; however, too few experiments were done to warrant much comment. For comparison we note that Weitkamp reports that the hydrogenation of $\Delta^{9,10}$-octalin at 25°C and 25 atm of hydrogen gives 67, 95, and 85% *cis*-decalin with platinum, ruthenium, and rhodium catalysts, respectively; the metals were supported on charcoal.[13b]

Experimental Section[20]

2-Methyl-1-(1-cyclopentenyl)cyclopentene (9). The alkenes **1** and **4** were separated from a mixture obtained by hydrogenating

the diene, 2-methyl-1-(1-cyclopentyl)cyclopentene (**9**), until the equivalent of 1 mol of hydrogen per mole of **9** had been adsorbed. The diene was prepared as follows.

To a solution of methylmagnesium iodide (0.8 mol in 250 ml of ether) was added dropwise an equal volume of an ethereal solution of 2-cyclopentylidenecyclopentanone (120 g, 0.80 mol) which had been prepared by the self-condensation of cyclopentanone.[21] The solution was refluxed on a hot water bath for 20 min. The flask was cooled; the contents were poured over 800 g of ice and 120 ml of concentrated hydrochloric acid was added. The ether layer, containing the product, was separated from the water layer, washed with a sodium bicarbonate solution until neutral, and dried over magnesium sulfate. The ether was removed by distillation and the remainder was distilled through a short fractionating column, bp 73–74° (2 mm), 226–227° (730 mm). The product consisted of three hydrocarbons from which 2-methyl-1-(1-cyclopentenyl)cyclopentene (**9**) was separated by preparative chromatography using a 15 ft × 0.375 in. o.d. column filled with 20% Carbowax 20M on 30/60 mesh Chromosorb P at 165 or 130°. The yield of **9** was 47 g (40%): n^{25}D 1.5351; d^{25} 0.9264; λ_{max} (C_2H_5OH) 238 nm (ϵ 27000) (conjugated double bond); ^{1}H NMR τ 4.58 (s, 1 H, vinylic), 7.65 (m, 8 H, allylic, 8.20) (m, 7 H, ring hydrogen plus terminal allylic methyl); ir (neat) 3040 (m, vinylic C–H stretch) 2590, 2840, (s, C–H stretch), 1640 and 1595 (w and very w, C–C stretch, conjugated diene), 1440, 1380, 1315, 1295, 1025, 960 (C–H bending), 800 (trisubstituted double bond C–H bending), and 565 cm^{-1}.[22,23]

Anal. Calcd for $C_{11}H_{16}$: C, 89.11; H, 10.98. Found: C, 88.70; H, 10.98.

The above data do not exclude unequivocally 2-methyl-3-cyclopentylidenecyclopentene (**10**); however, when the diene is half reduced with diimide, the alkene remaining is **4**. Diimide selectively reduces trisubstituted double bonds in preference to tetrasubstituted;[24] if the diene were **10**, reduction of the trisubstituted double bond would leave alkene **1**.

2-Methyl-1-cyclopentylidenecyclopentane (1). Diene **9** was selectively hydrogenated in glacial acetic acid at 1 atm hydrogen over 5% Pd/C. The isomers were separated on a 30 ft × 0.375 in. o.d. column containing 20% Carbowax 20M on 45/60 mesh Chromosorb P (Wilkens Instrument Co.) or a 35 ft × 0.375 in. o.d. column containing 30% Carbowax 20M on the same support. The product was approximately 45% 2-methyl-1-cyclopentylidenecyclopentane (**1**): bp 202° (721 mm); n^{25}D 1.4944; d^{25} 0.8817; ^{1}H NMR τ 9.02 (d, J = 7 Hz, 3 H, methyl), 8.35 (m, 8 H, ring hydrogens), and 7.86 (m, 7 H, allylic hydrogens).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.68; H, 12.11.

The remainder was the endo isomer, 2-methyl-1-cyclopentylcyclopentene (**4**): bp 199.5° (721 mm); n^{25}D 1.4925; d^{25} 0.8906; ^{1}H NMR τ 8.42 (m, 13 H, ring hydrogens plus terminal allylic methyl) and 7.78 (m, 5 H, allylic hydrogens).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.93; H, 12.19.

The exo olefin (**1**) used for hydrogenation experiments was a minimum of 98.2% pure, although, for most reductions, the purity was 99.4% or better, the main impurity being 2-methyl-1-cyclopentylcyclopentene. The 2-methyl-1-cyclopentylcyclopentene (**4**) was at least 98.5% pure.

2-Methyl-3-cyclopentylcyclopentene (6), 3-Methyl-2-cyclopentylcyclopentene (7), and *trans*-2-Methyl-1-(1-cyclopentyl-)cyclopentane (5). 2-Cyclopentylidenecyclopentanone was hydrogenated over 5% palladium on carbon (without solvent) to 2-cyclopentylcyclopentanone,[25] which was then combined with methylmagnesium bromide to give 2-cyclopentyl-1-methylcyclopentanol (**11**), bp 105° (8 mm). When heated with 85% phosphoric acid, the alcohol gave a mixture, bp 105–107° (45 mm), consisting of **4**, **5**, **6**, **7**, and unidentified alkenes in the proportion 56:13:11:5:15.[26] If **11** is converted to the chloride[27] which, in turn, is heated with potassium *tert*-butoxide,[28] the alkenes **4**, **5**, **6**, and **7** are obtained in the proportion 61:5:12:17 with 5% unidentified material. Chromatography of either mixture of alkenes through a 20 mm × 950 mm column containing 25% silver nitrate supported on basic alumina (Woelm activity grade 1) using a 95:5 volume mixture of 30–60° petroleum ether–benzene as eluent, gave pure **4** and **7** and a mixture of **5** and **6**. The order of elution was **4**, **6**, and **5**, followed by **7**. Alkenes **5** and **6** were separated by preparative GLC at 175° on a 35 ft × 0.375 in. column containing 30% Carbowax 30M on 45/60 mesh Chromosorb P. On analytical columns of either Carbowax 1000 or Apiezon L, the order of elution was **5**, **7**, **4**, and **6**, although **4** and **6** were not resolved. Compounds **6**, **7**, and **5** were characterized and their structures assigned as follows.

2-Methyl-3-cyclopentylcyclopentene (6) is a clear liquid: ir (10% in CCl_4) 3030 (=CH), 2960, 2870, 1740 (C=C), 1450, 1370, 1280, 1240, 1150, 1120, 1065, 1015, and 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) τ 8.0–9.0 (m, 14 H, ring and allylic methyl), 7.25–8.0 (m, 3 H, allylic), 4.76 (m, 1 H, vinylic); mass spectrum (70 eV) *m/e* (rel intensity) 150 (6, M$^+$), 81 (100), 80 (30).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.98; H, 11.93.

3-Methyl-2-cyclopentylcyclopentene (7) is a clear liquid: ir (10% in CCl_4) 3050 (=CH), 2960, 2780, 1740 (C=C), 1450, 1370, 1115, and 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$) τ 8.99 (d, 3 H, J = 7 Hz, methyl), 8.0–8.99 (m, 9–10 H, ring), 7.3–7.9 (m, 4–5 H, allylic), 4.80 (m, 1 H, vinylic); mass spectrum (70 eV) *m/e* (rel intensity) 150 (30, M$^+$), 135 (43), 82 (32), 81 (100), 80 (22), 79 (33), 67 (53).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.89; H, 11.94.

***trans*-2-Methyl-1(cyclopentyl)cyclopentane (5)** is a clear liquid: ir (10% in CCl_4) 3050 (–CH), 2950, 2870, 1740, (C=C), 1455, 1380, 1115, 1065, 1080, 945 cm^{-1}; ^{1}H NMR ($CDCl_3$) τ 9.08 (d, 3 H, J = 5.5 Hz, methyl), 8.0–8.5 (m, 9–10 H, ring), 7.6–8.0 (m, 4–5 H, allylic), 4.78 (m, 1 H, vinylic); mass spectrum (70 eV) *m/e* (rel intensity) 150 (39, M$^+$), 135 (44), 83 (22), 82 (100), 81 (36), 80 (21), 79 (82), 77 (27), 68 (29), 67 (91).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.08. Found: C, 88.00; H, 11.93.

***cis*- (2) and *trans*-2-Methyl-1-cyclopentylcyclopentane (3).** When saturated with hydrogen (Adams' PtO_2 in acetic acid), each of the above cyclopentenes, other than 5, yielded a mixture of two hydrocarbons which were separated by GLC on 35 ft × 0.375 in. 30% Carbowax 20M on 45/60 mesh Chromosorb P at 130°. Samples of each isomer (0.15 ml in 0.5 ml of cyclohexane) were placed with 0.02 g of 5% palladium on carbon in separate 8 mm × 15 cm Pyrex tubes and sealed. The tubes were heated at 250° for 180 hr, cooled to room temperature, and opened, and the contents were analyzed by GLC.[29] The proportion of the isomers present in each tube was identical: 86.6% of the compound with the shorter retention time. The more stable isomer was assumed to be *trans*-2-methyl-1-cyclopentylcyclopentane (**3**): ir (neat) 2950, 2870, 1450, 1370, 905 w, 890 cm^{-1} w; ^{1}H NMR ($CDCl_3$) τ 9.02 (d, 3 H, J = 9 Hz, methyl), 8.1–8.9 (m, 17 H, ring); mass spectrum (70 eV) *m/e* (rel intensity) 152 (41, M$^+$), 83 (50), 82 (100), 81 (44), 69 (28), 68 (40), 67 (88).

Anal. Calcd for $C_{11}H_{20}$: C, 86.76; H, 13.24. Found: C, 86.97; H, 12.92.

The less stable isomer (longer retention time) is the only product of the reduction of **4** by diimide and is accordingly *cis*-2-methyl-1-cyclopentylcyclopentane (**2**): ir (neat) 2950, 2870, 1455, 1370, 905 cm^{-1} w; ^{1}H NMR ($CDCl_3$) τ 9.29 (d, 3 H, J = 8 Hz, methyl), 8.1–8.9 (m, 17 H, ring); mass spectrum (70 eV) *m/e* (rel intensity) 152 (28, M$^+$), 83 (53), 82 (100), 81 (47), 69 (28), 68 (41), 67 (90).

Anal. Calcd for $C_{11}H_{20}$: C, 86.76; H, 13.24. Found: C, 87.15; H, 13.19.

Reagents. Reagent grade acetic acid, cyclohexane (99.8% pure Phillips Petroleum Co.), and triethylamine (Matheson Coleman and Bell) were used as obtained. Diglyme, bis(2-methoxyethyl) ether (Matheson Coleman and Bell), was distilled over lithium aluminum hydride before use as solvent in diimide reductions.

Platinum oxide (Adams' catalyst) and 5% palladium on powdered charcoal (batch no. 6457) were purchased from Matheson Coleman and Bell. Rhodium, 5% on calcium carbonate (batch no. C2200), was purchased from Englehard Industries, Inc. The catalysts were used as obtained.

Procedures. With the exception of the additional attention given to the condition of the alkene prior to its use in an experiment (see below) the hydrogenations were performed in the manner previously described;[5b] the acidic solvent was extracted from the hydrocarbon mixture before the latter was analyzed. Mixtures obtained from hydrogenations in other solvents were analyzed directly. On a 19 ft × 0.25 in. column packed with 20% Carbowax 1000 on 60/80 mesh Chromosorb P, the relative retention times at 130° were 1.00 (**3**), 1.08 (**5**), 1.13 (**2**), 1.43 (**7**), 1.55 (**4**), 1.56 (**6**), 1.72 (**1**).

Reductions by diimide generated in diglyme by the action of triethylamine on benzenesulfonylhydrazide followed the procedure of Garbisch, Schildcrout, Patterson, and Sprecher.[30]

Because the first series of hydrogenations of **1** and **4** gave inconsistent results the experiments were repeated with alkenes which were chromatographed over basic alumina (Woelm's activity grade 1), using pentane as eluent, immediately before it was

used.[17] The solution of alkene in pentane under a nitrogen atmosphere was concentrated to a volume of about 0.5 ml (approximately 10% alkene by volume) and added to the reaction chamber containing the reduced catalyst (1.5 mg) and the acetic acid (5 ml).

Registry No.—**1**, 56761-48-9; **2**, 935-80-8; **3**, 935-81-9; **4**, 51874-03-4; **5**, 56761-49-0; **6**, 51874-04-5; **7**, 56761-50-3; **9**, 56761-51-4; 2-cyclopentylidenecyclopentanone, 825-25-2; methyl iodide, 74-88-4.

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Structure and Reactivity in the Reduction of Conjugated Dienes by Diimide[1a]

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The reduction of unsaturated groups by the use of hydrazine, or certain of its derivatives, is thought to proceed via the formation of diimide, a reactive intermediate which apparently transfers its two hydrogen atoms to the unsaturated group in a concerted process.[2,3] For simple alkenes and nonconjugated dienes,[4] the relative rate of reduction is a function of the degree of substitution of the double bond attacked but the effect of structure on the reactivity of conjugated dienes is unreported.[5] Such information, we believed, would assist us in identifying a diene whose structure was not resolved on the basis of the spectral evidence available to us.[6] To be valid, the argument required that the possibility of the 1,4 addition of hydrogen be excluded and, although this assumption can be justified by arguments based upon the Woodward–Hoffmann rules, some experimental support seemed in order.[7]

Accordingly three readily available dienes, isoprene (**4**), 2,3-dimethyl-1,3-butadiene (**5**), and 2,5-dimethyl-2,4-hexadiene (**6**), were selected as test compounds which might show marked variations in the rate of the possible 1,4 relative to the 1,2 addition of hydrogen. Thus 1,4 addition to **6** yields an alkene which is less substituted than the product of 1,2 addition while the converse is true for **5**. Further, the 1,4 attack on **6** would be at the more highly substituted carbon atoms whereas the 1,4 attack on **5** would be at the least substituted vinyl carbons. Isoprene (**4**) represents an intermediate situation. 1,3-Cyclohexadiene (**7**) was reduced with dideuteriodiimide to determine whether the cyclic structure had any influence on the orientation of the transfer of hydrogen.

The relative reactivity of these dienes and 1,4-cyclohexadiene (**8**) toward diimide, generated at 80° from benzenesulfonylhydrazide, was determined to extend the structure–reactivity relationships observed by Garbisch et al.[3] Also measured were the relative reactivity of 1,3-cyclopentadiene (**9**), cyclopentene (**10**), and dienes **7** and **8** with diimide which was generated at 25° in methanol from the thermal decomposition of azodicarboxylic acid.[8]

Results and Discussion

There was no evidence of the 1,4 addition of hydrogen to any of the dienes examined. Table I summarizes the results of competitive experiments by listing the average relative rate constant computed from the composition of the reaction mixtures which were sampled at arbitrary intervals of time.[3] For convenience in comparing the results with previous data, the relative reactivity *per double bond*, referred to cyclohexene (**1**) or methylenecyclohexane (**2**), is listed in column 2 of Table II; the k_{rel} for **2** was assumed to be the value given by Garbisch et al.[3] The relative reactivities obtained through our competitive experiments are with reference to either **1**, denoted by A, or to **2**, by B. In the adjacent columns are listed the name and relative reactivity of the

Table I
Results of Competitive Diimide Reductions of Dienes and Reference Compounds[a]

A	B	k_A/k_B
Methylenecyclohexane (2)	4-*tert*-Butylmethylenecyclohexane (3)	0.95 ± 0.05
2,3-Dimethyl-1,3-butadiene (5)	Cyclohexene (1)	6.2 ± 0.2
Isoprene (4)	2,3-Dimethyl-1,3-butadiene (5)	2.2 ± 0.2
2,3-Dimethyl-1,3-butadiene (5)	2,5-Dimethyl-2,4-hexadiene (6)	6.1 ± 0.8
1,3-Cyclohexadiene (7)	4-*tert*-Butylmethylenecyclohexane (3)	8.5 ± 0.2
Methylenecyclohexane (2)	1,4-Cyclohexadiene (8)	1.85 ± 0.08
1,3-Cyclohexadiene (7)	1,4-Cyclohexadiene (8)	13.7 ± 2.1 25[b]
1,3-Cyclohexadiene (7)	Cyclopentadiene (9)	2.0[b]

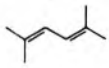
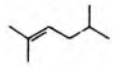
[a] Diimide generated from benzenesulfonylhydrazide in diglyme at 80° except where noted. [b] Diimide from the decomposition of azodicarboxylic acid at 25°.

Table II
Relative Reactivity of Dienes toward Diimide from Competitive Reductions at 80°. Relative Reactivity per Double Bond (k_{rel}) Is Referred to Either Cyclohexene (A) or Methylenecyclohexane (B)[a]

Diene or monoene	k_{rel}	Monoene	k_{rel}
Cyclohexene (1)	(1.00)	1	(1.00)
Methylenecyclohexane (2)	(3.27)	2	3.27
4-*tert*-Butylmethylenecyclohexane (3)	3.43 (B)		
2-Methyl-1,3-butadiene (4)	13.6 (A)	1-Pentene	20
2,3-Dimethyl-1,3-butadiene (5)	3.1 (A)	2-Methyl-1-pentene	2.04
2,5-Dimethyl-2,4-hexadiene (6)	0.5 (A)	2-Methyl-2-pentene	0.28
1,3-Cyclohexadiene (7)	14.5 (B)	1	(1.00)
1,4-Cyclohexadiene (8)	0.86 (B)	1	(1.00)

[a] Garbisch et al. (ref 3) report k_{rel} for **2** as 3.27. We used two reference compounds, **2** and **1**, and assume that their relative rate is 3.27 in order to place the two sets of measured relative reactivities on the same scale. The letter A or B indicates that one can compute the rate relative to **1** or **2**, respectively, from the data in Table I.

Table III
Relative Reactivities of Dienes and Product Alkenes Computed from the Distribution of Products as a Function of the Fraction of Diene Transformed[a]

Diene	Product alkene	k_2/k_1[b]
 (5)	 (11)	0.45 ± 0.04
 (6)	 (12)	1.4 ± 0.1
 (7)	 (1)	0.04[c]
 (8)	1	0.45 ± 0.05
 (9)	 (10)	1.75[c,d]

[a] Diimide generated at 80° from benzenesulfonylhydrazide. [b] These are the relative rate constants of eq 1. The rate of reduction *per double bond* of the diene relative to the rate of reduction of its product monoene is 1.1, 0.36, 13., 1.1, and 0.29 for dienes **5**, **6**, **7**, **8**, and **9**. [c] The result of a single experiment. The precision of the measurement is probably comparable to that reported for the other dienes. [d] Diimide generated at 25° from decomposition of azodicarboxylic acid.

reported alkene which has the same number of alkyl substituents per double bond as the diene in the column to the left. Apparently, the substitution of an alkyl group for a vinyl hydrogen has about the same effect upon the relative reactivity of dienes as it does upon monoenes.

Although the comparison between columns 2 and 4 of Table II indicates that isoprene (**4**) is less reactive than 1-pentene (presumably the less substituted double bond in **4** is the more reactive), dienes **5** and **6** appear to be more reactive than the equally substituted monoenes 2-methyl-1-pentene and 2-methyl-2-pentene, respectively. However, a direct and more appropriate measure of the effect of conjugation upon the relative reactivity can be obtained from the reductions of the symmetrical dienes. The method employs eq 2, which was derived by Frost and Pearson for consecutive first-order irreversible reactions.[9] The symbols α_1 and α_2 represent the fractions $[A]/[A]_0$ and $[B]/[A]_0$ where $[A]_0$ is the initial concentration of A and κ equals k_2/k_1. Ciola and Burwell have shown that the equation is equally applicable if the transformation of both A and B is the same function of any of the other reaction variables.[10] The results from this method of analysis of the data obtained from dienes **5**, **6**, **7**, **8**, and **9** are listed in descending order in Table III; the rate of reduction *per double bond* of each diene relative to the rate of reduction of its product monoene ($k_1/2k_2$) is 1.1, 0.36, 13, 1.1, and 0.29.

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C \quad (1)$$

$$\alpha_2 = \frac{1}{\kappa - 1}(\alpha_1 - \alpha_1^{\kappa}) \quad (2)$$

With the exception of 1,3-cyclohexadiene (**7**) and possibly **5**, each conjugated diene is less reactive *per double bond* than the monoene produced from it. These direct comparisons are undoubtedly more significant than those determined indirectly through competitive experiments by different investigators. However, the relative reactivities of 1,3- and 1,4-cyclohexadiene against cyclohexene recorded in Table III compare well with the directly measured relative reactivity of these compounds given in Table I and to the values assigned through the indirect comparison (via **2**) with Garbisch's standard, cyclohexene.

A recent paper reports the relative rates of reaction of *cis*-diimide in the gas phase with the alkenes as ethylene (1.0), *trans*-2-butene (0.33), *cis*-2-butene (0.11), 1,3-butadiene (0.065), 1,3-cyclohexadiene (~0.05), and 2,3-dimethyl-2-butene (~0.02).[5] The effect of structure upon reactivity thus displayed compares well with the results of competitive experiments in solution.[3] One should note that 1,3-butadiene is less reactive than either *cis*- or *trans*-2-butene, which, judged by the results of Garbisch (in the liquid phase),[3] are likely to be less reactive than 1-butene. Clearly conjugation reduces the reactivity of a double bond toward diimide.

The exceptional reactivity of 1,3-cyclohexadiene (**7**) compared to the other conjugated dienes illustrates the importance of the release of torsional strain as a driving force for this reaction.[3,11] The lack of planarity in the ground state of **7** results from the partial relief of bond angle and eclipsing strain involving the 5,6-methylene groups which opposes the π-conjugative interaction; the later is at a maximum for the planar molecule.[11] The stabilizing influence of conjugation which exists in the ground state will be partially lost at the transition state (rate retarding) and some of the torsional strain is released (rate enhancing); apparently the latter change is overriding. In comparison 1,3-cyclopentadiene (**9**) may owe its appreciably lower reactivity than cyclopentene to its greater energy of conjugation, although its torsional strain also would be relieved in part on reduction.[11] Similarly, acyclic dienes are stabilized through conjugation, but to a lesser extent than in **9**, and indeed the effect may be reduced markedly if rotation about the central bond is required to relieve torsional strain as in **5**, where nonbonding interactions involving the 2- and 3-methyl groups would increase the potential energy of the planar conformation about the central bond (compare **5** and **6**, Table III).[12]

The apparent equal reactivity per double bond of 1,4-cyclohexadiene and cyclohexene seems curious when one recalls that 1,4- and 1,3-cyclohexadienes have almost the same heats of formation.[11,13] If correct, it implies that the 1,4-diene derives stability from some interaction which involves the double bonds[14] and because this interaction must be lost upon reduction, the effect should retard this reaction. Experimental evidence and theory indicate that the molecules of the 1,4-diene are planar, oscillating between boatlike conformations.[15,16] Apparently, the transition state is attained with a smaller increase in torsional strain than for cyclohexene and this compensates for the stabilizing effect noted. Thus the almost equal reactivity per double bond of **1** and **8** results from different proportions of the opposing effects of changes of homoconjugation (not present in **1**) and torsional or bond angle bending strain.

From this qualitative argument it seems clear that the general approach of Garbisch et al. for estimating the contributions of resonance, torsional strain, and bond angle strain to the relative reactivities of alkenes may be extended to the dienes by an appropriate estimate of the conjugation energy as a function of the nonplanarity of the conjugated system.[16] A further advance in developing these structure–reactivity relationships into a more quantitative theory probably will require the incorporation of more accurate measures of changes in torsional and bond angle bending strain, from ground to transition state, perhaps through the use of calculations based upon molecular mechanics.[11,17]

Experimental Section

Dienes and Alkenes. Isoprene (**4**), 2,3-dimethyl-1,3-butadiene (**5**), and 2,5-dimethyl-2,4-hexadiene (**6**) were used as obtained

from Aldrich Chemical Co. Cyclohexene (1), methylenecyclohexane (2), 1,3-cyclohexadiene (7), and 1,4-cyclohexadiene (8) were purchased from Chemical Samples Co. Each of the preceding materials was at least 99% pure by GLC. 4-*tert*-Butylmethylenecyclohexane (3) was prepared from 4-*tert*-butylcyclohexanone via the Wittig reaction.[18] Cyclopentadiene (9), obtained from the dedimerization of dicyclopentadiene, was redistilled before use (99.8% by GLC).

Other alkenes which were used as authentic reference compounds for GLC analyses were obtained from Chemical Samples Co.

Other Materials. Benzenesulfonylhydrazide (from Aldrich Chemical Co.) and triethylamine and diglyme (from Matheson Coleman and Bell) were used in diimide reductions as obtained. Potassium azodicarboxylate was prepared by the hydrolysis of azodicarbonamide (Aldrich Chemical Co.).[4] Deuteriomethanol and deuterioacetic acid (99% *O-D*) were obtained from Diaprep Inc.

Reductions with Diimide. The procedure for generating diimide from benzenesulfonylhydrazide was similar to that described by Garbisch et al.[3] Solutions consisting of benzenesulfonylhydrazide (ca. 1.0 g), diglyme (10 ml), triethylamine (ca. 10 g), and either one or two of the unsaturated hydrocarbons (ca. 0.20 g each) were prepared. Eight 1-ml aliquots of the reaction solution were sealed in 8 mm × ca. 15 cm Pyrex tubes. The tubes were kept at 80° by suspending them in either a constant-temperature oil bath or refluxing reagent grade benzene. At appropriate times a tube was removed from the constant-temperature apparatus, cooled in dry ice–2-propanol, and carefully opened. The contents were poured into ca. 1.0 ml of pentane and the pentane extracts were washed twice with 1-ml portions of 5% sulfuric acid, 5% sodium hydroxide, and finally with water. The extracts were dried over magnesium sulfate, sodium sulfate, or Linde 3A molecular sieve and stored in a freezer until analysis by GLC. In those instances where pentane interfered with the product analysis, other solvents such as benzene, toluene, or xylene were used.

Competitive reductions with diimide generated from the decarboxylation of azodicarboxylic acid in methanol at 25° followed the procedure of Baird, Franzus, and Surridge.[4] Reaction solutions consisting of 50 ml of methanol, ca. 1.0 g of a mixture of the two unsaturated hydrocarbons and the internal standard (benzene or toluene), and ca. 3.5 g of potassium azodicarboxylate was stirred in a three-necked flask equipped with a vibrating stirrer (Vibro Mischer), a pressure equalizing addition funnel, and a outlet through which a positive pressure of nitrogen was maintained. A solution of 1.2 g of glacial acetic acid in methanol (15 ml) was added dropwise to the bright yellow reaction mixture. For analysis, a 1-ml portion of the mixture was removed, added to 1 ml of xylene, and washed with small portions of 5% sodium hydroxide and water. The xylene extracts were dried over Linde 3A molecular sieve and analyzed by GLC.

Analytical Procedure. The mixtures were analyzed by GLC (flame ionization detector) on either a 45 ft × 0.125 in. column of 2.5% Carbowax 600 and 2.5% Carbowax 750 on Chromosorb W (AW) 60/80 mesh (for the cyclic dienes and products) or a 25 ft × 0.25 in. column of 30% silver nitrate in triethylene glycol on 60/80 mesh Chromosorb P, which was used for the separations of the alicyclic dienes and products. All peaks were identified by comparison with synthetic mixtures of authentic standards and the molar response factor of each component was determined.[19] The columns were not able to separate 2-methyl-1-butene from 3-methyl-1-butene; however, this did not impair the ability to distinguish 1,2 and 1,4 addition to isoprene (4) because in the analysis on the $AgNO_3$ column 2-methyl-2-butene, the result of 1,4 addition, is cleanly separated from the other components of the reaction mixture.

Reduction of 1,3-Cyclohexadiene with N_2D_2. The deuteriodiimide was generated at 10° in CH_3OD (50 ml) containing the diene (0.4 g) from potassium azodicarboxylate (3.5 g) and deuterioacetic acid (1.2 g) as described by Baird et al.[4] Upon completion of the reaction, the mixture was diluted with water (100 ml) and extracted with three 40-ml portions of pentane. The solution was concentrated to a volume of ca. 5 ml and the concentrate was subjected to preparative chromatography. The ^1H NMR spectrum (Varian A-60) of the cyclohexene which was isolated was integrated and gave a ratio of 2.0:3.1:3.1 for the relative areas of the signals for the vinyl, allyl, and homoallyl protons. The ratio compares well with the value 2:3:3 expected for the product of 1,2 addition and not with the value 2:2:4 expected for 1,4 addition.

Calculations of Relative Rate Constants. A. Competitive Reductions. With the exceptions noted in Table I, the composition of the mixtures from three to six different conversions of the alkenes or dienes were used to compute the relative reactivities, k_A/k_B, from the equation $k_A/k_B = (\log [A]_0 - \log [A])/(\log [B]_0 - \log [B])$ where $[A]_0$ and $[B]_0$ represent the initial mole fractions of A and B, respectively, and [A] and [B] are the fractions when the mixture was sampled.[3]

B. Consecutive Reactions of a Diene. The value of k_2/k_1 (κ), the relative rate constants of the consecutive reactions of a diene → ene → ane, was computed using eq 2 in the form of $(\kappa - 1)\alpha_2 = \alpha_1[1 - \alpha_1^{\kappa-1}]$.[9,10] The value of κ was obtained through successive approximations using a hand-held calculator; the number reported is that for which the ratio of the right- to the left-hand side of the above equation is 1.000 ± 0.002. The precision of the values obtained for different conversions (average deviations) is indicated in Table III.

Registry No.—1, 110-83-8; 2, 1192-37-6; 3, 13294-73-0; 4, 78-79-5; 5, 513-81-5; 6, 764-13-6; 7, 592-57-4; 8, 628-41-1; 9, 542-92-7; 10, 142-29-0; 11, 563-78-0; 12, 3404-78-2.

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(1) (a) The support of this research by the National Science Foundation is gratefully acknowledged (NSF GP-15719 and NSF GP-3619X). (b) R. P. Fisher and S. E. Johnson were undergraduate research participants (NSF GY-53 and NSF GY-10017).
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Direct Dehydrogenation of Aporphine Alkaloids

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The dehydrogenation of aporphines to the corresponding dehydroaporphines, some of which are naturally occurring alkaloids, has been accomplished by the use of various chemical oxidants, including permanganate, DDQ, mercuric salts, and iodine.[1]

We now report the direct catalytic dehydrogenation of a number of aporphines to dehydroaporphines in high yield and under remarkably mild conditions. The reaction proceeds particularly well in refluxing acetonitrile, using 10% palladium on charcoal catalyst. Under these conditions, nuciferine (1) afforded dehydronuciferine (4) in 90% yield after 15 min reaction time. Other examples of this reaction

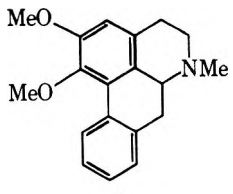
Table I
Dehydrogenation of Some Aporphines to Dehydroaporphines[a]

Aporphine used	(wt, mg)	10% Pd/C, mg	Product	Reaction time, min	Yield,[b] %
Nuciferine (1)	(100)	100	(4)	15	90
Dicentrine (2)	(140)	140	(5)	15	85
Ocopodine (3)	(150)	150	(6)	15	80
Thalicarpine (7)	(140)	140	(8)	60	55

[a] Acetonitrile solvent (10 ml) in all cases. [b] Yields of crystalline products, identical with authentic samples (melting point, ir).[1]

are indicated in Table I. The selective dehydrogenation of the aporphine moiety of thalicarpine (7) is worthy of note. In accord with this result, the simple benzylisoquinoline base laudanosine (9) was recovered unchanged after being subjected to the general dehydrogenation procedure.

The method described here would appear to displace chemical oxidations as the method of choice for the conversion of a nonphenolic aporphine to the corresponding dehydroaporphine. Preliminary dehydrogenation experiments using noraporphines or phenolic aporphines indicate the formation of products which are rapidly attacked by air during work-up, as might be expected from the results of chemical oxidation of similar substrates.[1]



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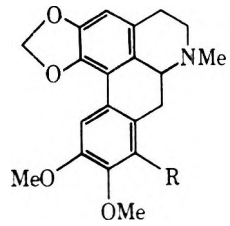

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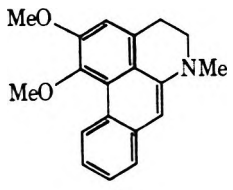
3, R = OMe



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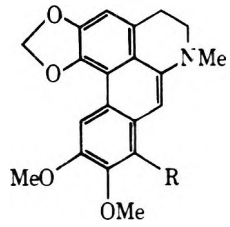
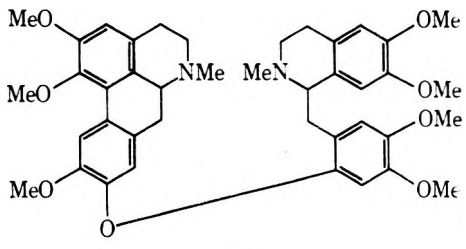


5, R = H
6, R = OMe



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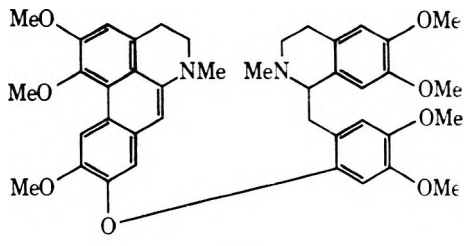

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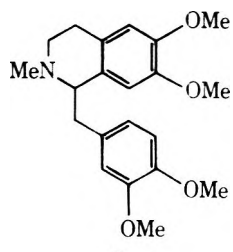

9

Experimental Section

In a typical experiment, a mixture of the aporphine (see Table I) and 10% Pd/C in acetonitrile was refluxed under nitrogen for 15 min. The catalyst was filtered off and the solvent was removed in vacuo. The yellow-green residue was crystallized from acetone or methanol. Dehydrothalicarpine (8) was isolated by PLC (silica gel plates, $CHCl_3$ + 10% MeOH), followed by crystallization.

Acknowledgment. We thank the National Institutes of Health for a grant (CA-11445) in support of this work, and also the Fundación Juan March for a fellowship to one of us (José M. Saá).

Registry No.—**1**, 475-83-2; **2**, 517-66-8; **3**, 19893-95-9; **4**, 7630-74-2; **5**, 19843-03-9; **6**, 33117-76-9; **7**, 5373-42-2; **8**, 7224-94-4.

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Novel Rearrangements of Morphanthridines

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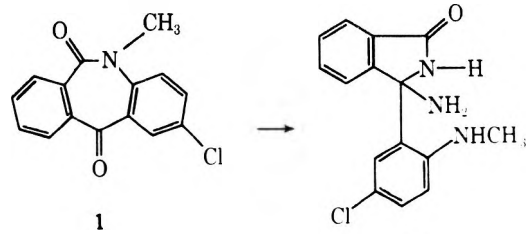
During the course of our investigations toward the synthesis of 9,13b-dihydroisoindolo[2,1-*d*][1,4]benzodiazepin-6-one[1] it was reported that 2-chloro-5-methylmorphanthridine-6,11(5*H*)-dione (1), in the presence of ammonia and NH_4Cl, rearranged in good yield to 3-amino-3-(5-chloro-2-methylaminophenyl)isoindolin-1-one (2). This observation

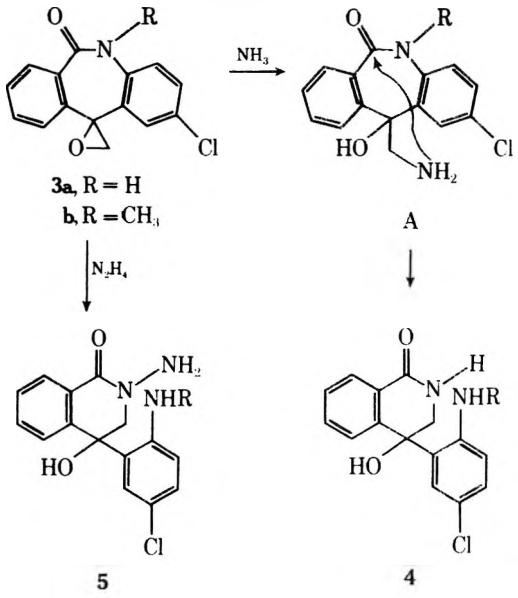


1 2

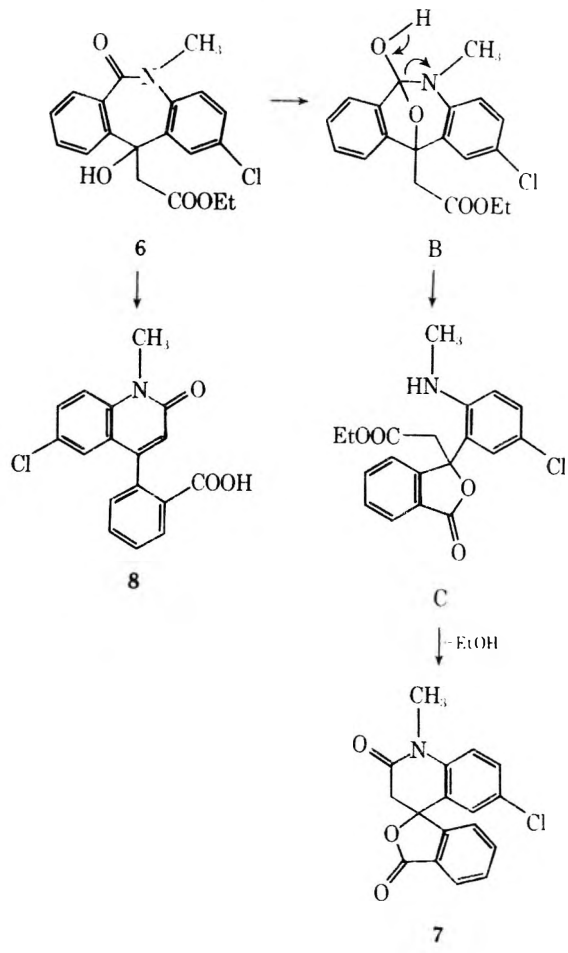
prompted further investigations into the possible rearrangements of other morphanthridines functionalized at the 11 position. We now wish to report several successful examples of such rearrangements.

When 2-chlorospiro[morphanthridine-11,2′-oxirane]-6-one (**3a**) was allowed to react with ammonia in a steel vessel at 120°, it rearranged to form 4-(2-amino-5-chlorophenyl)-3,4-dihydro-4-hydroxyisocarbostyril (**4a**) in 30% yield (Scheme I). If the morphanthridine was substituted on the nitrogen, e.g., **3b**, the reaction proceeded in much higher yield to **4b**. Similarly, the treatment of **3a** with hydrazine afforded 4-(2-amino-5-chlorophenyl)-3,4-dihydro-4-hydroxy-(2-amino)isocarbostyril (**5a**) in 50% yield.

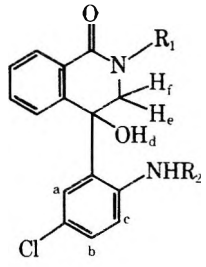
Scheme I



Scheme II



The structures of **4** and **5** were established by their characteristic NMR spectra. The aromatic proton b in the angular phenyl group of **4a** appears as a multiplet at δ 7.00, proton c, a doublet, appears at δ 6.74, but proton a, also a doublet, is strongly shifted upfield to δ 6.08. This shift is caused partly by the influence of the nuclear substituents but mainly it is due to the geometry of the molecule. Models indicate that the phenyl group is aligned almost 90° to the plane of the isoquinoline nucleus and the proximity of the a proton to the shielding cone of the condensed aromatic ring causes the shift. When $R_1 = NH_2$ in formula D, the



D

methylene protons H_e and H_f, which are magnetically nonequivalent owing to the asymmetric center at carbon 4, appear as an AB quartet and their chemical shifts are δ 4.36 and 3.42. When R_1 = H and R_2 = H or CH_3 it is observed that further coupling of the farther downfield geminal proton (H_e or H_f) to the amide proton occurs and, instead of the doublet, a multiplet is seen.

It is believed that the rearrangement proceeds by attack of ammonia (or hydrazine) on the epoxide ring to form the intermediate amino alcohol A followed by a nucleophilic attack of the amine on the amide carbonyl at the 6 position with concomitant ring opening.

We observed further that at 180°, **6** rearranged to form spiro compound **7** in 47% yield. The structure of **7** was confirmed based on the following spectral evidence. In the infrared two carbonyl absorptions at 1772 (lactone) and 1680 cm^{-1} (cyclic lactam) were observed. In the NMR spectrum, two separate aromatic regions were observed. The phthalan protons appeared between δ 8.10 and 7.60 while the quinoline protons were shifted slightly upfield, probably owing to the shielding effect of the other aromatic ring. Two methylene protons appeared as a singlet at δ 3.16.

The rearrangement (Scheme II) is believed to proceed by a nucleophilic attack of the hydroxy on the amide carbonyl possibly forming the bridged intermediate B which then opens to the intermediate C. This in turn spontaneously cyclizes with loss of ethanol to form product **7**.

Treatment of **6** with hydrazine leads to the carbostyril **8** isolated as the hydrazine salt.[2] The assignment of structure **8** was based on comparison of its NMR spectrum with that of 1-methyl-4-phenylcarbostyril[3] (**9**).

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. All pure materials were run as Nujol or halocarbon mulls. Nuclear magnetic resonance spectra were determined on Varian A-60 and T-60 spectrophotometers using tetramethylsilane as an internal reference. Mass spectra were determined on an LKB 9000 spectrometer. All elemental analyses were performed by Mr. William Bonkoski and associates at Sandoz, Inc.

2-Chlorospiro[morphanthridine-11,2'-oxirane]-6-one (3a). A mixture of 10.0 g (0.039 mol) of 2-chloromorphanthridine-6,11(5*H*)-dione[1] and 5.1 g (0.120 mol) of 57% sodium hydride in 150 ml of Me_2SO was stirred at room temperature for 30 min. To the resulting red solution was added 12.0 g (0.059 mol) of trimethylsulfonium iodide in two equal portions after which the mixture was stirred at room temperature for 4 hr. The reaction mixture was poured onto 1500 ml of cold water and the resulting precipitate was filtered, washed twice with water, and dried, yielding 6.2 g of **3a** (60%). The material was found pure enough for further use. A sample was recrystallized from methylene chloride–ether: mp 204–207°; ir ($CHCl_3$) 3480, 3180, 1660, 1370 cm^{-1}; NMR ($CDCl_3$ + Me_2SO) δ 10.43 (s, broad, 1), 8.20–7.20 (m, 7), 3.06 (s, 2).

4-(2-Amino-5-chlorophenyl)-3,4-dihydro-4-hydroxyisocarbostyril (4a). The spirooxirane **3a** (4.0 g, 0.015 mol) was added to 15 ml of anhydrous liquid ammonia containing 0.1 ml of methanol. The mixture was heated in a steel cylinder at 120° for 24 hr. The

cylinder was cooled to room temperature and the ammonia was evaporated. The resulting solid was crystallized from methanol, yielding 1.3 g of **4a** (30%): mp 271–274°; ir (Nujol) 3440, 3390, 3360, 3210 (broad), 1670, 1650 cm^{-1}; NMR (Me_2SO) δ 8.10–7.30 (m, 4), 7.80 (s, 1), 7.00 (m, 1), 6.74 (d, 1), 6.54 (s, 1), 6.08 (d, 1), 5.42 (s, 2), 4.10 (m, 1), 3.48 (d, 1).

Anal. Calcd for $C_{15}H_{13}N_2O_2Cl$: C, 62.4; H, 4.5; N, 9.7; Cl, 12.3. Found: C, 62.5; H, 4.4; N, 9.8; Cl, 12.5.

4-(2-Methylamino-5-chlorophenyl)-3,4-dihydro-4-hydroxyisocarbostyril (4b). The reaction was performed as in the previous example (**3b**) and **4b** was isolated in 71% yield: mp 238–240°; ir (Nujol) 3380, 3190 (broad), 1670, 1460 cm^{-1}; NMR (Me_2SO) δ 8.10–7.30 (m, 4), 7.82 (s, 1), 7.15 (m, 1), 6.75 (s, 1), 6.64 (d, 1), 6.02 (q, 1), 5.98 (d, 1), 4.20 (m, 1), 3.46 (d, 1), 2.75 (d, 3).

Anal. Calcd for $C_{16}H_{15}N_2O_2Cl$: C, 63.5; H, 5.0; N, 9.3; Cl, 11.7. Found: C, 63.3; H, 5.3; N, 9.0; Cl, 11.5.

4-(2-Amino-5-chlorophenyl)-3,4-dihydro-4-hydroxy-(2-amino)isocarbostyril (5a). A suspension of 0.4 g of **3a** in 5 ml of anhydrous hydrazine was refluxed for 2.5 hr. The resulting solution was poured onto 150 ml of cold water. The mixture was extracted into ethyl acetate and the organic phase dried over sodium sulfate. The solvent was removed under reduced pressure to yield 300 mg of solid which was successively washed with methylene chloride, methanol, and ether to yield 225 mg of **5a** (50%): mp 266–268°; ir (Nujol) 3440, 3360, 3295 (broad), 1650, 1625, 1465 cm^{-1}; NMR (Me_2SO) δ 8.08 (m, 1), 7.80–7.30 (m, 3), 7.01 (m, 1), 6.74 (d, 1), 6.58 (s, 1), 6.36 (d, 1), 5.26 (s, 2), 5.03 (s, 2), 4.36 (d, 1), 3.42 (d, 1).

Anal. Calcd for $C_{15}H_{14}N_3O_2Cl$: C, 59.3; H, 4.7; N, 13.8; Cl, 11.7. Found: C, 59.0; H, 4.8; N, 14.0; Cl, 11.7.

2-Chloro-5-methyl-5,6-dihydro-11-hydroxy-6-oxomorphanthridine-11-acetic Acid Ethyl Ester (6). To a suspension of 14.0 g (0.215 mol) of zinc (activated, 10 mesh) in 75 ml of benzene was added a solution of 10.0 g (0.06 mol) of ethyl bromoacetate and 11.0 g (0.041 mol) of **1** in 75 ml of benzene. When the reaction started, the mixture was refluxed for 5 hr and then poured onto 400 ml of 20% acetic acid and extracted with ethyl acetate. The organic phase was washed twice with water and dried over sodium sulfate. The solvent was removed under reduced pressure to yield 10.4 g of **6** (72%): mp 151–154°, recrystallization from ether raised the melting point to 162–165°; ir ($CHCl_3$) 3450 (broad), 1705, 1630 cm^{-1}; NMR ($CDCl_3$) δ 8.10–7.10 (m, 7), 5.46 (s, 1), 4.04 (q, 2), 3.64 (s, 3), 3.26 (d, 1), 3.02 (d, 1), 1.04 (t, 3).

Anal. Calcd for $C_{19}H_{18}NO_4Cl$: C, 63.4; H, 5.0; N, 3.9; Cl, 9.9. Found: C, 63.5; H, 4.9; N, 3.8; Cl, 10.3.

6′-Chloro-1′-methylspiro[phthalan-1,4′(3*H*)-quinoline]-2′,3(1′*H*)-dione (7). Twelve grams of **6** was heated at 140°. The temperature was then raised to 180° over a period of 20 min and kept there for 1 hr, during which time the material was constantly stirred. The resulting solid was extracted in a Soxhlet apparatus using ether as the solvent. After 5 days, the ether was removed under reduced pressure to afford a solid which was crystallized from methylene chloride–ether to yield 5.0 g of **7** (47%): mp 234–235°; ir ($CHCl_3$) 1775, 1680 cm^{-1}; NMR ($CDCl_3$ + Me_2SO) δ 8.20–7.50 (m, 4), 7.40 (m, 1), 7.10 (d, 1), 6.75 (d, 1), 3.48 (s, 3), 3.16 (s, 2).

Anal. Calcd for $C_{17}H_{12}NO_3Cl$: C, 65.1; H, 3.9; N, 4.5. Found: C, 65.2; H, 3.8; N, 4.5.

6-Chloro-1-methyl-4-(2-carboxyphenyl)carbostyril Hydrazine Salt (8). A mixture of 1.0 g of **6** and 0.5 ml of anhydrous hydrazine in 10 ml of ethanol was refluxed for 4 hr. The solvent was removed under reduced pressure and the resulting foam was dissolved in 25 ml of methylene chloride. After the solution is formed, immediate crystallization occurs yielding 0.65 g of **8** (68%): the material has no definite melting point; ir (KBr) 1640 (broad), 1580 cm^{-1} (broad); NMR (Me_2SO) δ 8.20–7.00 (m, 12), 6.42 (s, 1), 3.68 (s, 3).

Anal. Calcd for $C_{17}H_{16}N_3O_3Cl$: C, 59.0; H, 4.7; N, 12.2. Found: C, 58.8; H, 4.6; N, 11.9.

The free acid of **8** was isolated by dissolving the hydrazine salt in 2 *N* sodium hydroxide followed by acidification with 2 *N* hydrochloric acid: mp >300°; ir (KBr) 1710, 1635, 1570 cm^{-1}; NMR (Me_2SO) δ 8.05 (m, 1), 7.76 (m, 4), 7.44 (m, 1), 6.96 (m, 1), 6.51 (s, 1), 3.69 (s, 3), exchangeable acid proton falls in with the water peak of the solvent.

Anal. Calcd for $C_{17}H_{12}NO_3Cl$: C, 65.2 ; H, 3.8; N, 4.5. Found: C, 65.0; H, 4.2; N, 4.3.

Tne values for the *N*-methyl protons and the proton in the 3 position of **9** were δ 3.68 and 6.49, respectively. These chemical shifts were in close accord with those of the free acid of **8** (see above).

Acknowledgment. The authors wish to thank Dr. Sandor Barcza and his associates for ir and NMR spectra, Mr. Robert Clark for mass spectra, and Dr. Renate Coombs for interpreting the mass spectra.

Registry No.—**1**, 16219-18-4; **3a**, 56761-60-5; **3b**, 56761-61-6; **4a**, 56761-62-7; **4b**, 56761-63-8; **5a**, 56761-64-9; **6**, 56761-65-0; **7**, 56761-66-1; **8**, 56761-68-3; **8** free acid, 56761-67-2; 2-chloromorphanthridine-6,11(5*H*)-dione, 786-87-8; ethyl bromoacetate, 105-36-2; hydrazine, 302-01-2.

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Preparation of Diketoheptadecanolides and Cyclohexadecanediones by Thermolysis of a Cyclic Diperoxide

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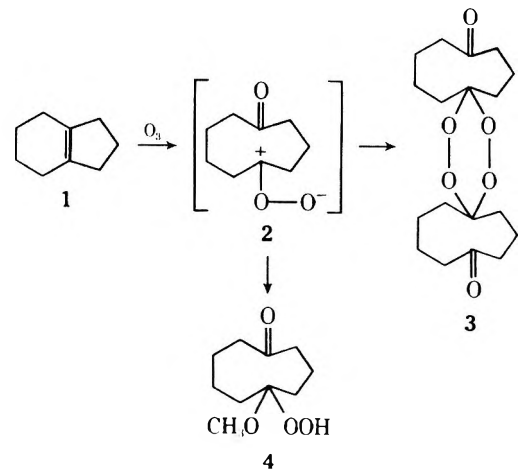
We wish to report the first preparation of four diketoheptadecanolides (**10**). Two known cyclohexadecanediones (**8** and **9**) are also obtained as products of the reaction employed. The method involves the thermolysis of the cyclic diperoxide **3** which is prepared by the reaction of **1** with ozone. The preparation of the diperoxide **3** will first be outlined and then the thermolysis reaction to yield the large-ring products will be discussed.

Criegee first reported[1] the isolation of a solid (<10% yield) upon ozonolysis of 4,5,6,7-tetrahydroindan (**1**) in petroleum ether and proposed that this compound was the cyclic diperoxide **3**, formed by dimerization of the intermediate Criegee zwitterion **2**[2] (Scheme I). In a previous paper[3]

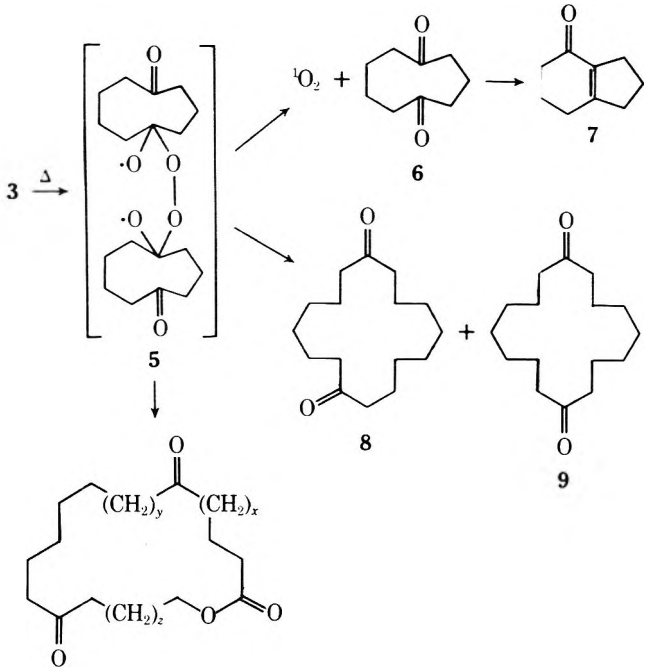
Scheme I



1 2 3 4

we reported that ozonolysis of **1** in methylene chloride gave, in addition to the expected diketone **6**, a 17% yield of **3**. This product was not formed when the ozonolysis reaction was conducted in methanol, as **2** was converted to the hydroperoxide **4** before it had an opportunity to dimerize. Although our analytical data for diperoxide **3** differ somewhat from that reported by Criegee,[1] our spectral data (ir, NMR, and mass[4]) and molecular weight determination (see

Scheme II



10a. $x = 1$; $y = 3$; $z = 1$
b, $x = 1$; $y = 2$; $z = 2$
c, $x = 2$; $y = 2$; $z = 1$
d, $x = 2$; $y = 1$; $z = 2$

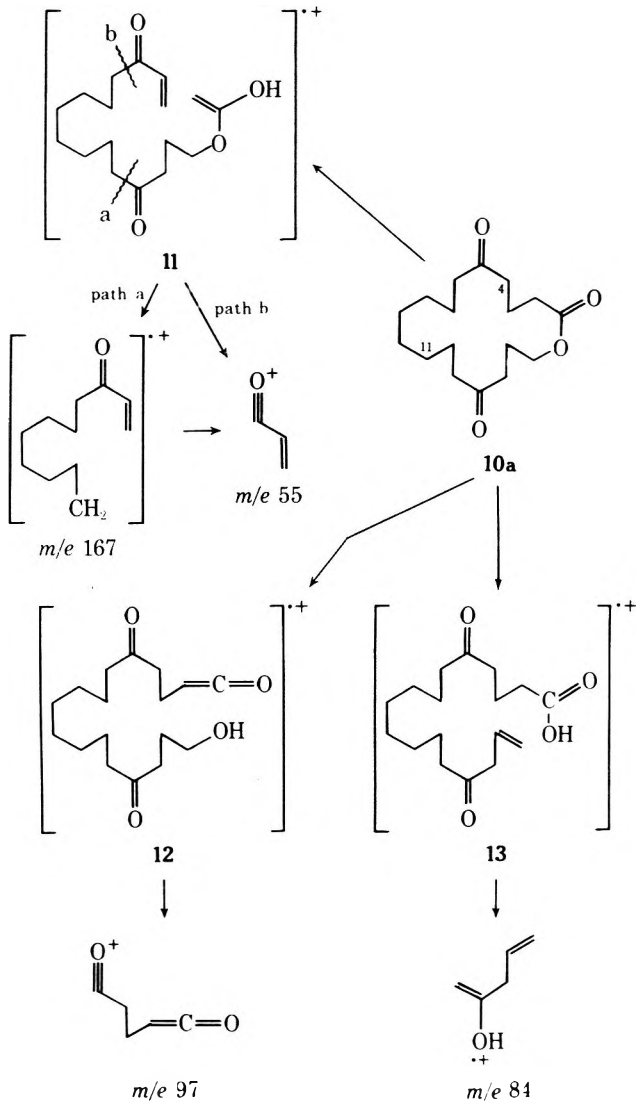
Experimental Section) are entirely consistent with the structure proposed. Criegee also reported[2] the formation of a cyclic diperoxide upon ozonolysis of 9,10-octalin and Overton[5] isolated the same type of compound upon ozonolysis of β-pinene.

Story reported[6] that thermolysis of dicyclohexylidene diperoxide yielded cyclodecane, undecalactone, and cyclohexanone. Later, he published a review[7] on the thermolysis of related di- and triperoxides as well as kinetic studies[8-10] on the decomposition of these compounds. We wish to report that thermolysis of diperoxide **3** in refluxing decane (174°) yielded three types of products: (i) 1,5-cyclononanedione (**6**), which was isolated as the cyclized product,[3] bicyclo[4.3.0]-1(6)-nonen-2-one (**7**, 18%), (ii) 1,8- (**8**) and 1,9-cyclohexadecanediones (**9**, 50%), and (iii) four diketoheptadecanolides (**10**, 16%) (Scheme II).

The formation of these three types of products may be explained in the following way. Homolysis of an oxygen–oxygen bond in **3** gives **5** which after a double β-scission[6] yields dione **6** and a molecule of singlet oxygen.[8] Loss of two molecules of carbon dioxide from **5** and recombination of the resulting radicals[6] gives diones **8** and **9**. Both of these diones have been prepared[11] previously by another method and comparison of the spectral properties, particularly the mass spectra, confirmed the identity of these compounds. The diones, which are formed in equal amounts, are the major products of the thermolysis reaction and as they may be separated by GC this is an alternative method[11] for the preparation of either **8** or **9**.

Finally, rearrangement of diradical **5** to the three possible acyl peroxides followed by loss of a molecule of carbon dioxide[6,9] leads to the four possible macrolides (**10**). Using a polar silicone phase (OV-210) for the GC separation, it was possible to isolate **10a** and **10d** as crystalline solids while the other two, **10b** and **10c**, were not resolved. The structures proposed for these macrolides are supported by microanalysis, ir, and mass spectrometry, with the latter being most useful for differentiating the isomers. Mass spectrometry has previously been shown[12,13] to be of considerable value in elucidating the structures of naturally occurring macrolides. In the present case, the major peaks in the mass spectrum of **10a** were *m/e* 167, 97, 84, and 55. Scheme III outlines a possible mode of formation of each of these peaks. McLafferty rearrangement of the parent ion of **10a** by transfer of a C-4 hydrogen atom yields **11**, which upon α-cleavage (path a or b) yields either ion *m/e* 167 or *m/e* 55, respectively. Formation of ketene **12**[14] followed by α-cleavage gives fragment *m/e* 97 and formation of carboxylic acid **13**[13] followed by a McLafferty rearrangement involving transfer of a C-11 hydrogen atom yields ion *m/e* 84. Similar fragmentation patterns account for the mass spectra of **10d** as well as the mixture of **10b** and **10c**. The $M^+ - H_2O$ (*m/e* 278) ion is a significant peak in the spectra of all these macrolides and the same peak has been reported previously in the mass spectra of large-ring lactones.[15]

Scheme III



Many macrolides are known to possess antibiotic activity[16] and several approaches to the synthesis of these structures have been reported.[17] Conformational aspects of these compounds have also received attention.[18] In this report we have outlined the facile synthesis of a number of diketoheptadecanolides[19] by an approach which should be suitable to the preparation of other diketomacrolides of different ring sizes.

Experimental Section[20]

Preparation of 10,11,21,22-tetraoxadispiro[8.2.8.2]docosane-4,16-dione (3). A solution of 10.0 g (81 mmol) of 4,5,6,7-tetrahy-

droindan (1)[21] in 50 ml of methylene chloride was stirred rapidly at −70° while a stream of ozone from a Welsbach generator (200 W) was bubbled through the solution for 45 min. An aqueous solution of 5 g of potassium iodide was added and the reaction mixture was allowed to warm to room temperature The iodine color was discharged with an aqueous solution of sodium thiosulfate and the organic phase was separated, washed with water, and dried ($MgSO_4$). The methylene chloride was removed and ethanol was added to precipitate 2.34 g (17%) of a white solid (**3**), which was recrystallized from ethanol: mp 186–187°; ir ($CHCl_3$) 1700, 1470, 1450, 1075 cm^{-1}; NMR ($CDCl_3$) τ 7.3–7.6 (8 H, m), 7.8–8.5 (20 H, m); mass spectrum *m/e* (rel intensity) 154 (14), 126 (40), 112 (46), 98 (89), 55 (100); mol wt (osmometric) calcd 340, found 347.

Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.47; H, 8.48.

Thermolysis of 3. A sample of 0.30 g (0.88 mmol) of diperoxide **3** was added in portions to 3 ml of refluxing *n*-decane and the resultant solution was refluxed for 1.5 hr. The cooled reaction solution was chromatographed on silica gel (60–200 mesh) using pentane to elute the *n*-decane and 3% ethyl acetate–chloroform to elute the 0.22 g of thermolysis products. GC analysis (190–270°) of these products indicated 18% of **7**, 50% of diones **8** and **9**, 16% of macrolides **10**, and smaller amounts of several other components.

Identification of Thermolysis Products from 3. A. Product **7**, the first major GC peak, was collected and found to be identical with a sample of bicyclo[4.3.0]-1(6)-nonen-2-one prepared previously.[3]

B. Compounds **8** and **9** analyzed as two partially resolved GC peaks of equal area. The first peak was collected, recrystallized from petroleum ether (bp 60–80°), and shown to be 1,8-cyclohexadecanedione (**8**) on the basis of the following data and comparison of this data with that published previously:[11] mp 68–69°; ir (CCl_4) 2940, 2870, 1712, 1460, 1370, 1125 cm^{-1}; mass spectrum *m/e* (rel intensity) 252 (M^+, 14), 234 (13), 195 (21), 140 (17), 125 (18), 112 (37), 97 (41), 84 (74), 55 (100). Similarly, the second peak of the doublet was collected, recrystallized from petroleum ether, and shown to be 1,9-cyclohexadecanedione (**9**) by comparison of the following data with that published previously:[11] mp 80–81° (lit.[11] 78–79°); ir (CCl_4) 2940, 2870, 1719, 1465, 1370, 1115, 1025 cm^{-1}; mass spectrum *m/e* (rel intensity) 252 (M^+, 23), 195 (13), 169 (14), 126 (46), 111 (30), 98 (88), 83 (56), 55 (100).

C. The lactones **10** upon GC analysis (266°) showed three peaks in a ratio of 1:2:1. These peaks were collected by preparative GC and the following data were found for each peak (in order of GC elution). **5,14-Diketoheptadecanolide (10a):** mp 50.5–51.0° (recrystallized as plates from petroleum ether, bp 60–80°) ir (CCl_4) 2930, 2855, 1736, 1716, 1158, 1128 cm^{-1}; mass spectrum *m/e* (rel intensity) 296 (M^+, 14), 278 (19), 167 (56), 97 (100), 84 (86), 55 (62).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.73; H, 9.46.

Mixture of 5,13-Diketoheptadecanolide (10b) and 6,14-Diketoheptadecanolide (10c). This GC fraction was an oil: ir (CCl_4) 2930, 2860, 1734, 1714, 1160 cm^{-1}; mass spectrum *m/e* (rel intensity) 296 (M^+, 12), 278 (9), 167 (19), 153 (28), 111 (56), 98 (80), 97 (65), 84 (61), 55 (100). **6,13-Diketoheptadecanolide (10d).** This last GC peak was recrystallized from petroleum ether (bp 60–80°): mp 59.0–59.5°; ir (CCl_4) 2935, 2860, 1738, 1718, 1135 cm^{-1}; mass spectrum *m/e* (rel intensity) 296 (M^+, 7), 278 (8), 153 (33), 111 (70), 98 (100), 55 (90).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.85; H, 9.75.

Acknowledgment. The authors acknowledge the financial assistance of the National Research Council of Canada.

Registry No.—**1**, 695-90-9; **3**, 56678-87-6; **7**, 22118-01-0; **8**, 17853-46-2; **9**, 31067-25-1; **10a**, 56678-88-7; **10b**, 56678-89-8; **10c**, 56678-90-1; **10d**, 56678-91-2; ozone, 10028-15-6.

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The Pyridine Route to α-Substituted Cyclohexenones

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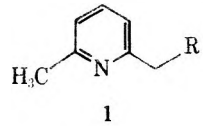
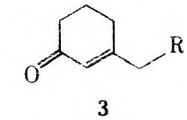
In the pyridine route to steroids,[1,2] it has been shown that 6-substituted α-picolines (**1**) may be converted to 3-substituted cyclohexenones of the type **3**. Fortunately, in the most relevant cases (i.e., where R represents a cycloalkanone ketal substituted at its α position), the 2,6-diketone intermediate **2** suffers aldolization to give **3** rather than its isomer, **4**. System **4** is, in fact, the predominant product



1



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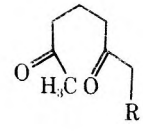

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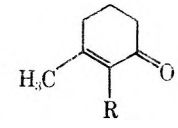
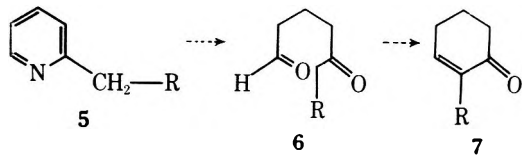


4

where R in diketone **2** represents a straight-chain alkyl group.[3,4] The structural factors which are decisive in promoting one mode of cyclization over the other are being investigated.[5] The issue of isomeric possibilities in the aldolization process does not arise for 4-acylbutyraldehydes (**6**). Such systems should be derived by reductive hydrolysis of 2-substituted pyridines (**5**). Below are described some ap-

plications of this concept to the synthesis of the α-substituted cyclohexenones (7). We believe that the pyridine

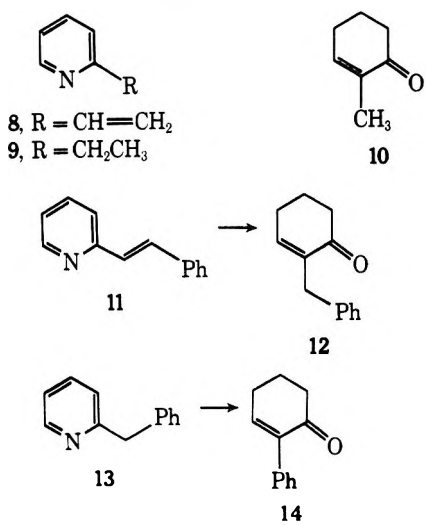


route to such systems offers advantages in terms of simplicity of operations and accessibility of starting materials.

Catalytic reduction of 2-vinylpyridine (8) affords 2-ethylpyridine (9). Compound 9 was treated with 1.1 equiv of sodium in ammonia containing 10 equiv of ethanol. The residue, upon evaporation of the ammonia, was treated with 2% aqueous ethanolic sodium hydroxide. A 57% yield of 2-methylcyclohexenone (10) was obtained. *Efforts to optimize the yield of this conversion were not persued when it was found that 2-vinylpyridine itself could be converted to 2-methylcyclohexenone in 56% yield.* For this purpose, a 6:1 molar ratio (i.e., 1.50 equiv) of sodium:2-vinylpyridine was employed. The yield for the direct conversion of 8 → 10 was increased to 63% by the use of lithium rather than sodium.

The feasibility of consolidating the reduction of a conjugated double bond with the reduction of a pyridine to the dihydro level was demonstrated with the readily available *trans*-2-stilbazole (11) (prepared by condensation of α-picoline with benzaldehyde).[6] Compound 11 was converted to 2-benzylcyclohexenone (12) in 52% yield. The feasibility of reducing the pyridine ring in the presence of the benzene ring is thus also established.

In the light of the *trans*-2-stilbazole result, it was not surprising to find that 2-benzylpyridine (13) could be converted in good yield to 2-phenylcyclohexenone (14) by reductive hydrolytic cyclization.



Previous methodology for obtaining compound 10 involves (1) selective functionalization of 2-methylcyclohexanone[7] or (2) manipulations which start with 2-methylcyclohexane-1,3-dione.[8] Similarly, compound 12 has been prepared[9] from the relatively inaccessible 2-phenylcyclohexanone,[5] 2-phenylcyclohexane-1,3-dione,[10] and 1-phenylcyclohexene.[11] Compound 14 has been obtained by equilibration of 2-benzylidenecyclohexanone[12] or through oxidative manipulations starting with 1-benzylcyclohexene.[13,14] The pyridine route, which produces such systems in one step from readily available starting materials, is the most convenient and efficient.

The inability to achieve higher yields was apparently due to different factors in the various cases. In the reduction of 9 and 11, substantial amounts of basic material were recovered. NMR analysis of this material indicated the absence of pyridine absorption. In the case of 13, the basic extract, ca. 40%, was largely starting material.

It was surprising to find, even after many attempts, that 2,5-lutidine did not produce any recognizable amounts of 4-methylcyclohexenone. The bulk (87%) of the material was obtained as a basic fraction which was largely starting material. Mass spectral analysis of some minor products, partially purified by preparative GLC, indicated the presence of reductively dimerized materials (*m/e* 216 and 218) in the reaction mixture.

Similarly, attempted conversion of 3-methyl-2-stilbazole[15] to 2-benzyl-6-methylcyclohexenone was not successful. The reasons for the nonextendability of this reduction method to systems with substitution in the 3 or the 5 positions are not clear, particularly in the light of the applicability of the reaction to 4-substituted systems.[16a,b]

Experimental Section[17]

Conversion of 2-Vinylpyridine (8) to 2-Methylcyclohexenone (10). To a solution prepared from the dissolution of lithium metal (3.45 g, 0.496 mol) in 1000 ml of dry NH_3 was quickly added a solution containing 2-vinylpyridine (10.5 g, 0.1 mol) and absolute ethanol (36.8 g, 0.8 mol) in 300 ml of anhydrous ether. After the disappearance of the blue color, the ammonia was evaporated in a stream of nitrogen, and the residue was dissolved in 480 ml of ethanol. A solution of sodium hydroxide (12.0 g, 0.3 mol) in 240 ml of H_2O was then added, and the resulting system was stirred at room temperature under an atmosphere of nitrogen for 2.5 hr. The solution was acidified by the addition of 10% HCl. The resulting solution was extracted four times with 200-ml portions of ether. The combined ether layers were washed twice with saturated $NaHCO_3$ and then once with saturated brine. The organic solution was dried over anhydrous sodium sulfate. Evaporation of the solvents followed by distillation of the residue afforded 6.97 g (63%) of **10**: bp 61–62° (10 mm); $\bar{\nu}$ ($CHCl_3$) 2920, 1667 cm^{-1}; δ ($CDCl_3$) 1.73 (m, 3 H), 1.9–2.6 (m, 6 H), 6.65 (m, 1 H); λ_{max} (95% ethanol) 236 nm (ε 9600); *m/e* 110; 2,4-DNP mp 207.5–209° (lit.[7] 207–208°).

Neutralization of the aqueous acidic layer with $NaHCO_3$ followed by extraction with three 150-ml portions of ether afforded a residue of 3.01 g whose NMR spectrum showed essentially no absorption in the region of δ 6–9 ppm.

Conversion of *trans*-2-Stilbazole (11) to 2-Benzylcyclohexenone (12). To a solution prepared from the dissolution of sodium metal (3.8 g, 0.165 mol) in 500 ml of ammonia (freshly distilled from sodium) was quickly added a solution comprised of *trans*-2-stilbazole (5.0 g, 0.0276 mol) and absolute ethanol (10.5 g, 0.229 mol) in 200 ml of absolute ether. After disappearance of the blue color, the ammonia was evaporated under a stream of nitrogen. The residue was dissolved in 120 ml of ethanol and the resulting solution was worked up as before to give 3.17 g of crude neutral material which was chromatographed on 60 g of silica gel. Elution with benzene afforded 2.61 g (52%) of 2-benzylcyclohexenone (**12**): $\bar{\nu}$ ($CHCl_3$) 2899, 1667, 1600, 1488 cm^{-1}; NMR ($CDCl_3$) δ 1.8–2.6 (m, 6 H), 3.43 (d, J = 1 Hz, 2 H), 6.63 (t, 1 H), 7.06 (s, 5 H); *m/e* 186; 2,4-DNP mp 152–153.5° (lit.[14] 153°).

The acidic aqueous layer was neutralized with solid $NaHCO_3$ and extracted with three 25-ml portions of ether. After the combined organic layers were dried over anhydrous sodium sulfate, removal of the solvents afforded a residue of 1.87 g. The NMR of this material contains essentially no absorption in the region δ 6–9 ppm.

Conversion of 2-Benzylpyridine (13) to 2-Phenylcyclohexenone (14). To a solution prepared by the dissolution of lithium (621 mg, 0.09 mol) in 300 ml of ammonia (freshly distilled from sodium) was quickly added a solution of 2-benzylpyridine (2.53 g, 0.015 0.015 mol) and absolute ethanol (6.9 g, 0.150 mol) in 100 ml of anhydrous ether. After the disappearance of the blue color, the ammonia was evaporated under a stream of nitrogen. The residue was dissolved in 50 ml of ethanol and the resulting solution was worked up in the manner described above to give 1.81 g of crude, crystalline 2-phenylcyclohexenone (**14**). Recrystallization from hexane–ethyl acetate gave pure **14**: mp 93–94° (lit.[11] 96–97°); $\bar{\nu}$ ($CHCl_3$) 2976, 1680 cm^{-1}; δ ($CDCl_3$) 1.9–2.8 (m, 6 H), 6.93 (t, 1 H), 7.32 (s, 5 H); *m/e* 172.

The aqueous acidic layer was neutralized with solid $NaHCO_3$ and extracted with three 50-ml portions of ether. After the combined organic layers were dried over anhydrous sodium sulfate, evaporation of the solvents afforded a residue of 637 mg whose NMR spectrum was very similar to that of starting **13**.

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Registry No.—**8,** 100-69-6; **10,** 1121-18-2; **11,** 538-49-8; **12,** 13694-36-5; **13,** 101-82-6; **14,** 4556-09-6.

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Purine *N*-Oxides. LXII. 2,4-Dioxopyrido[2,3-*d*]pyrimidine *N*-Oxides[1]

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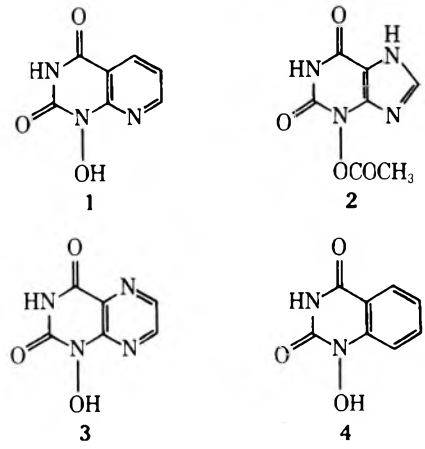
Our interest in analogs of the oncogenic 3-hydroxyxanthine,[2] the recent synthesis of 3-hydroxy-2,4-dioxopyrido[2,3-*d*]pyrimidine,[3] and the antitumor activity reported[4] for the parent compound 2,4-dioxopyrido[2,3-*d*]pyrimidine[5] against Walker muscle carcinosarcoma in rats, prompted us to synthesize the two other possible *N*-oxides, **1** and **15.**

Chemical[6-10] and biochemical[11,12] studies have shown that the oncogenicity of 3-hydroxyxanthine and some of its derivatives are paralleled by unique chemical reactivities of their esters.[2] Thus 3-acetoxyxanthine (**2**) (Chart I) undergoes, under mild conditions, an SN1′ reaction with nucleophiles to yield 8-substituted xanthines.[6-9] A series of ring analogs of 3-hydroxyxanthines are being investigated to determine the structural features of the ring system which permit the facile SN1′ reaction, and eventually the pertinence of that reactivity to oncogenicity. Our initial studies showed that the esters of ring systems with electron-rich π

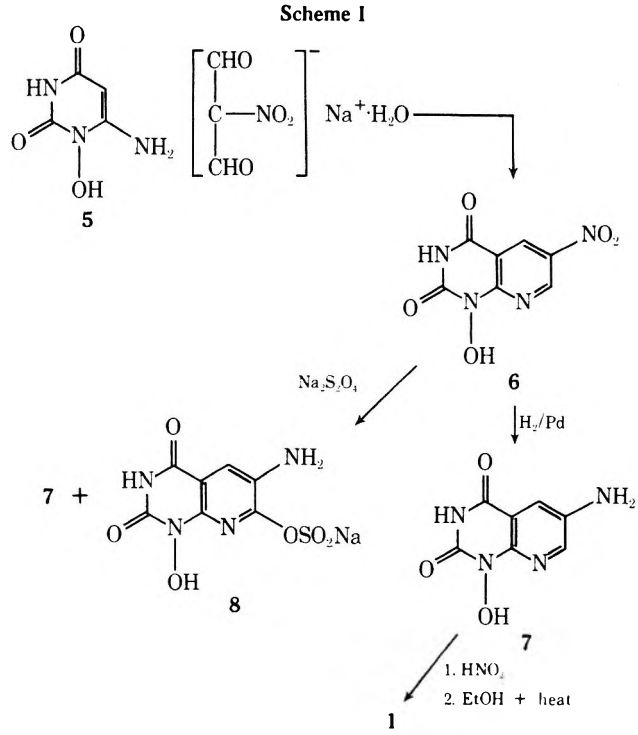
Chart I



systems are more likely to undergo an elimination–substitution reaction similar to that of the esters of 3-hydroxyxanthine. Thus the esters of the pyrrolo[2,3-*d*]pyrimidine analog of 3-hydroxyxanthine,[13] a ring system with our electron-rich π system, undergo a reaction similar to that of the esters of 3-hydroxyxanthine, whereas esters of the electron-deficient pteridine analogs,[14] **3,** do not undergo a similar reaction, and the esters of quinazoline analogs,[15] **4,** undergo a similar reaction only under very vigorous conditions. The pyridopyrimidine analog is a slight modification of **3** or **4** and its reactivity is, as expected, intermediate between them.

The starting material for the synthesis of 1-hydroxy-2,4-dioxopyrido[2,3-*d*]pyrimidine (**1**) was 1-hydroxy-2,4-dioxo-6-aminopyrimidine[16] (**5**), which was condensed with nitromalonaldehyde[17,18] by heating under reflux with dilute sodium hydroxide to yield 1-hydroxy-6-nitropyrido[2,3-*d*]pyrimidine (**6**) in 73% yield (Scheme I). This method[16] was chosen because the mild conditions do not affect the sensitive N–OH bond. Hydrogenation of **6** in the presence of Pd/C gave **7** in 40% yield. Deamination of **7** was achieved by refluxing its diazonium salt in ethanol to give **1** in 89% yield. The structure of each compound (**6, 7, 1**) was confirmed by its NMR spectrum. When **6** was reduced with so-

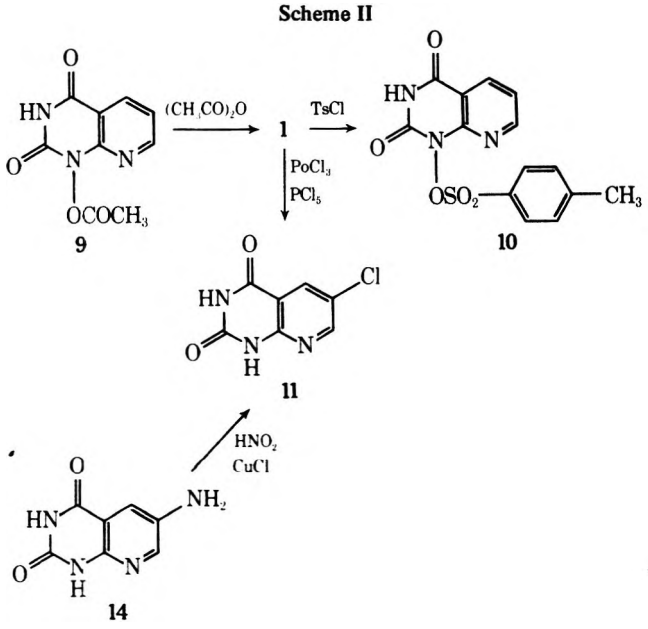
Scheme I



dium dithionite, two products were isolated, the expected amino compound 7 in 40% yield, and a second compound which analyzed as a hemihydrate of $C_7H_5N_4O_6SNa$. The structure was assigned as sodium 1-hydroxy-2,4-dioxo-6-aminopyrido[2,3-*d*]pyrimidine-7-sulfonate (8) based on the distinctive ir[19] and NMR spectra, its water solubility, and its strong $FeCl_3$ test. That structure was substantiated by hydrolysis and deamination to 2,4-dioxo-7-hydroxypyridopyrimidine, the structure of which was confirmed by NMR that give a pair of doublets in the aromatic proton region with a large 5–6 proton spin–spin coupling constant (9 Hz).[20] A similar observation was reported[21] in reduction of 2,4-dioxo-5-nitropyrimidine with sodium dithionite to give some 2,4-dioxo-5-aminopyrimidine-6-sulfonic acid. When 7 was treated with sodium bisulfite under conditions similar to those for the addition of sulfite to cytosine or uracil and its derivatives,[22,23] the starting material was recovered unchanged (Scheme I).

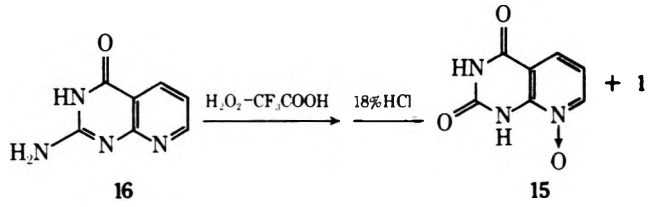
When 1 was refluxed in acetic anhydride only the acetoxy derivative 9 was obtained. Boiling in water hydrolyzed 9 to 1. No products comparable to those from 3-hydroxyxanthine results. Treatment of 1 with tosyl chloride in boiling pyridine resulted in a stable 1-sulfonyloxy derivative 10, in contrast to the substitution product, 8-sulfonyloxyquinazoline,[15] obtainable from 4. When 1 was refluxed with phosphorus oxychloride and phosphorus pentachloride, a substitution with elimination of the *N*-hydroxy group did occur, and 2,4-dioxo-6-chloropyrido[2,3-*d*]pyrimidine (11) was obtained. A similar result was obtained with the 1-hydroxyquinazoline 4 under the same conditions.[15] The mechanism of the reaction must be similar to that of the formation of 6-chloro-2,4-dioxoquinazoline from 4. The chlorine of 11 is assigned to the 6 position from the NMR spectrum. That structure was also established by unambiguous synthesis from 2,4-dioxo-6-aminopyrimidine (12) condensed with sodium nitromalonaldehyde to afford the nitro compound, 13. That was hydrogenated to the amino compound 14, and subsequent treatment of its diazonium salt with cuprous chloride yielded authentic 11 (Scheme II).

Scheme II



2,4-Dioxopyrido[2,3-*d*]pyrimidine 8-oxide (15), the third *N*-oxide isomer, was obtained in 42% yield by direct oxidation of 2-amino-4-oxopyrido[2,3-*d*]pyrimidine (16)[18] with 30% H_2O_2 in CF_3COOH, followed by refluxing with 18% HCl to deaminate the *N*-oxide of 16 to 15. Only a trace, 1.3%, of the 1 isomer, 1, was produced during the oxidation. Thus the nitrogen of the pyridine ring in 16 is more susceptible to N-oxidation than nitrogen 1 of pyrimidine ring despite the activation of the latter by an ortho amino substituent. The structure of 15 was established by comparison of its NMR spectrum with those of the two other isomers (Scheme III).

Scheme III



The 1-hydroxypyrido[2,3-*d*]pyrimidine (1) can undergo an elimination–substitution reaction to yield 11 only when it is treated with phosphorus oxychloride and phosphorus pentachloride. As expected an ester of 1 is found to be more reactive than the corresponding ester of the pteridine analog, 3,[13] and less than that of the quinazoline analog, 4.[14] In view of this relatively mild reactivity, it is improbable that 1 should be an oncogen. On the other hand, 1 might exhibit an antitumor activity such as that found for its parent compound.[4]

Experimental Section

1-Hydroxy-2,4-dioxo-6-nitropyrido[2,3-*d*]pyrimidine (6). A mixture of 1-hydroxy-2,4-dioxo-6-aminopyrimidine[16] (0.43 g, 0.003 mol) and sodium nitromalonaldehyde monohydrate (0.529 g, 0.0033 mol) in 15 ml of 1% NaOH was refluxed for 2.25 hr. The solution was cooled, acidified with glacial acetic acid to pH 5, and filtered to yield 0.49 g (73%) as a yellow solid, mp >300° dec. A $FeCl_3$ test was positive. An analytical sample was obtained by recrystallization from acetic acid: NMR (Me_2SO-d_6) δ 8.76 (d, H-5), 9.45 (d, H-7), 11.68 [broad singlet, OH + NH, exchangeable with D_2O ($J_{5,7}$ = 2.5 Hz)]; uv max (~pH) 318 nm (1), 318 (5), 280, 415 (12).

Anal. Calcd for $C_7H_4N_4O_5$: C, 37.51; H, 1.79; N, 24.99. Found: C, 37.42; H, 1.90; N, 24.81.

1-Hydroxy-2,4-dioxo-6-aminopyrido[2,3-*d*]pyrimidine (7). A. 6 (1.46 g, 0.0065 mol) was dissolved in H_2O (250 ml) by adding sufficient NH_4OH and 10% palladium on charcoal (0.4 g) was added. The theoretical amount of H_2 was absorbed during 1.5 hr. The reaction mixture was heated to 60° and filtered, and the filtrate was evaporated in vacuo nearly to dryness. The precipitate was collected to yield 0.5 g (40%), mp >300° dec. A $FeCl_3$ test was positive. An analytical sample was obtained by recrystallization from H_2O: NMR (Me_2SO-d_6) δ 5.50 (s, NH_2, exchangeable with D_2O), 7.55 (d, H-5), 8.20 (d, H-7) [two exchangeable protons (D_2O) in the offset: OH, NH] ($J_{5,7}$ = 3 Hz); uv max (~pH) 256 nm, 333 (1), 266, 362 (5), 281, 398 (12).

Anal. Calcd for $C_7H_6N_4O_3$: C, 43.30; H, 3.11; N, 28.85. Found: C, 43.15; H, 3.21; N, 28.60.

B. Sodium dithionite (0.79 g, 0.0045 mol) was added in small portions, at room temperature, to a stirred solution of 6 (0.29 g, 0.0013 mol) in H_2O (20 ml) and 1 *N* NaOH (5.5 ml). The color of the solution changed from red to yellow. After 2 hr the reaction mixture was acidified to pH 5 with glacial acetic acid and evaporated in vacuo to half of its original volume. The precipitate of 7 thus formed was collected, yield 0.1 g (40%). Concentration of the filtrate almost to dryness gave sodium 1-hydroxy-2,4-dioxo-6-aminopyrido[2,3-*d*]pyrimidine-7-sulfonate, 0.1 g, yellow solid. A $FeCl_3$ test was positive. An analytical sample was prepared by recrystallization from H_2O: NMR (Me_2SO-d_6) δ 5.92 (broad singlet, NH_2 exchangeable with D_2O), 7.70 (s, H-5); uv max (~pH) 227 nm, 269, 383 (2, 5), 229, 250 s, 289, 416 (12); ir showed characteristic sulfonic group absorptions,[19] 1240, 1198, 1055, and 731 cm^{-1}.

Anal. Calcd for $C_7H_5H_4O_6S_1Na_1 \cdot \frac{1}{2}H_2O$: C, 27.54; H, 1.97; N, 18.36; S, 10.49. Found: C, 27.41; H, 2.32; N, 18.08; S, 10.20.

1-Hydroxy-2,4-dioxopyrido[2,3-*d*]pyrimidine (1). Sodium nitrite solution (0.81 g, 0.012 mol, in 16 ml of H_2O) was added dropwise to a cooled (0–5°) and stirred solution of 7 (1.62 g, 0.0083 mol) in 18% HCl (35 ml). Stirring was continued for 15 min and H_2O was added (150 ml). The supernatant liquor was decanted, and the

ethanol (500 ml) was added to the residue. This mixture was then refluxed for 3 hr. Carbon black was added to the hot solution; filtration and evaporation in vacuo to 30 ml yielded, after filtration, 1 (1.33 g, 89%, mp 310–311° dec). An analytical sample was obtained by recrystallization from methanol: NMR (Me_2SO-d_6) δ 7.33 (dd, H-6), 8.35 (dd, H-5), 8.75 (dd, H-7), two exchangeable protons (D_2O) in the offset, OH, NH ($J_{5,6}$ = 8.0, $J_{6,7}$ = 5.0, $J_{5,7}$ = 1.8 Hz); uv max (~pH) 251 nm, 313 (1, 5), 259, 291, 368 (12).

Anal. Calcd for $C_7H_5N_3O_3$: C, 46.93; H, 2.81; N, 23.45 Found: C, 46.79; H, 2.71; N, 23.28.

1-Acetoxy-2,4-dioxopyrido[2,3-*d*]pyrimidine (9). 1 (0.09 g, 0.005 mol) was refluxed with acetic anhydride (3 ml) for 2.5 hr. After cooling, ether was added and the precipitate was collected and washed with ether to yield 9 (0.051 g, 46%). At room temperature 9 hydrolyzes in H_2O very slowly to 1. In boiling H_2O or in NaOH (pH 13) 9 is hydrolyzed very rapidly to 1: NMR (Me_2SO-d_6) δ 7.43 (dd, H-6), 8.41 (dd, H-5), 8.71 (dd, H-7), 12.2 (NH, exchangeable with D_2O).

Anal. Calcd for $C_9H_7N_3O_4$: C, 48.87; H, 3.19; N, 18.99. Found: C, 48.96; H, 3.28; N, 18.94.

1-Tosyloxy-2,4-dioxopyrido[2,3-*d*]pyrimidine (10). To a stirred solution of 1 (0.090 g, 0.0005 mol) in dry pyridine (10 ml), tosyl chloride (0.105 g, 0.00055 mol) was added in small portion at room temperature. The solution was heated at 90° for 2.5 hr. Most of the pyridine was evaporated in vacuo, H_2O was added, and the precipitate was collected and recrystallized from methanol to yield 10 (0.069, 36%): colorless needles; mp 221–222° dec; NMR (Me_2SO-d_6) δ 2.45 (s, CH_3), 8.50 (m, H-6, H′-3, H′-5), 7.93 (d, H′-2 + H′-6), 8.36 (dd, H-5), 8.50 (dd, H-7), 12.08 (s, NH) ($J_{5,6}$ = 8.0, $J_{6,7}$ = 5.0, $J_{5,7}$ = 2 Hz); uv max (~pH) 303 nm (1), 306 (12).

Anal. Calcd for $C_{14}H_{11}N_3O_5S_1$: C, 50.44; H, 3.32; N, 12.60; S, 9.62. Found: C, 50.34; H, 3.26; N, 12.54; S, 9.78.

2,4-Dioxo-6-chloropyrido[2,3-*d*]pyrimidine (11). A. A solution of 1 (0.09 g, 0.005 mol) and phosphorus pentachloride (0.329 g) in phosphorus oxychloride (5 ml) was refluxed for 3.5 hr. The cooled solution was poured into ice water $NaHCO_3$ was added to pH 5, the solution was extracted with ether (3 × 100 ml), and the ether was dried over Na_2SO_4 and evaporated to dryness. Concentrated HCl (4 ml) was added to the residue and the solution was heated under reflux for 3 hr. After evaporation of the solution to dryness, H_2O was added to the residue (3 ml). The 11 was precipitated by adjusting the acidity of the solution to pH 5 with $NaHCO_3$ to yield 14 mg (14%): mp 307° dec; NMR (Me_2SO-d_6) δ 8.20 (d, H-5), 8.61 (d, H-7), 11.56 (s, NH, exchangeable with D_2O), 11.80 (s, NH, exchangeable with D_2O) ($J_{5,7}$ = 2.5 Hz); uv max (~pH) 248 nm, 321 (1), 247, 319 (5), 240 (s), 271, 333, 364 (s) (12).

Anal. Calcd for $C_7H_4N_3O_2Cl$·½H_2O: C, 40.66; H, 2.42 N, 20.33; Cl, 17.18. Found: C, 40.74; H, 2.45; N, 20.33; Cl, 17.10.

B. To a stirred solution of 14 (0.4 g, 0.0022 mol) in 18% HCl (10 ml) at 0° was added dropwise a solution of sodium nitrite (0.225 g, 0.0032 mol) in water (5 ml). After 10 min the cold diazonium chloride solution was slowly poured with stirring into a cold cuprous chloride solution in concentrated HCl (25 ml) prepared from 0.78 g of $CuSO_4$·$5H_2O$. The thick mixture was allowed to warm at room temperature, then warmed at 60° for 1 hr. The reaction mixture was cooled, $NaHCO_3$ was added to ~pH 6, and the precipitate was collected to yield 11, 0.360 g (83%), mp 307° dec. Recrystallization from 50% CH_3COOH gave light yellow needles: uv max (~pH) 249 nm, 323 (1, 5), 240 (s), 272, 335, 364 (s) (12).

Anal. Calcd for $C_7H_4N_3O_2Cl$: C, 42.55; H, 2.04; N, 21.26; Cl, 17.94. Found: C, 42.67; H, 1.96; N, 21.40; Cl, 17.89.

2,4-Dioxo-6-nitropyrido[2,3-*d*]pyrimidine (13). A mixture of 2,4-dioxo-6-aminopyrimidine (12, 3.81 g, 0.03 mol) and sodium nitromalonaldehyde monohydrate (5.18 g, 0.033 mol) in 50 ml of 1% NaOH was refluxed for 5 hr. A precipitate started to form in a few minutes after refluxing. After cooling the precipitate was filtered to yield 13 (4.6 g, 73.7%) as light yellow crystals, mp 346° dec.

The analytical sample was prepared by recrystallization from 50% acetic acid: NMR (Me_2SO-d_6) δ 8.76 (d, H-5), 9.38 (d, H-7), 10.53 (s, broad, N^1H, N^3H, exchangeable with D_2O) ($J_{5,7}$ = 2.8 Hz); uv max (~pH) 292 nm (s), 313 (1, 5), 370 (12).

Anal. Calcd for $C_7H_4N_4O_4$: C, 40.39; H, 1.93; N, 26.92. Found: C, 40.57; H, 1.90; N, 26.83.

2,4-Dioxo-6-aminopyrido[2,3-*d*]pyrimidiee (14). To 13 (1.0 g, 0.0048 mol) in H_2O (200 ml) NH_4OH was added until it all dissolved. This was hydrogenated with 10% palladium on charcoal (0.25 g) until 360 ml of H_2 was absorbed. The palladium on charcoal was removed by filtering the boiling hot reaction mixture. Concentration of the filtrate in vacuo to ~50 ml yielded 14 (0.480 g, 56%), mp >360°. The analytical sample was obtained by recrystallization from H_2O: uv max (~pH) 243 nm, 312 (1), 260, 354 (5), 266, 360 (12).

Anal. Calcd for $C_7H_6N_4O_2$: C, 47.19; H, 3.39; N, 31.44. Found: C, 46.33; H, 31.5; N, 30.43.

1,7-Dihydroxy-2,4-dioxopyrido[2,4-*d*]pyrimidine. The above sodium sulfonate compound, 8 (41.57 mg) was dissolved in 0.1 *N* NaOH (7 ml) and stirred on a steam bath for 3 hr. The solution was acidified to pH 5.5 with acetic acid, and the solution was vaporized to dryness in vacuo. The residue was diazotized with 2 ml of 4 *N* HCl and sodium nitrite (50 ml) at 0°. After stirring at the same temperature for 15 min the mixture was added with water (25 ml). The precipitate thus formed was collected by centrifuging and was then heated under reflux for 4 hr in ethanol (25 ml). The resulting product was absorbed on a Dowex-50 [H^+] column. Elution with water gave the title compound (16 mg) in a first fraction, mp 225° dec. Further elution with water gave some 1: NMR (Me_2SO-d_6) δ 7.70, 6.17 ppm ($J_{5,6}$ = 9 Hz).

Anal. Calcd for $C_7H_5N_3O_4$·H_2O: C, 39.45; H, 3.31; N, 19.71. Found: C, 39.35; H, 3.40; N, 19.61.

2,4-Dioxopyrido[2,3-*d*]pyrimidine 8-Oxide (15). To a stirred solution of 2-amino-4-oxopyrido[2,3-*d*]pyrimidine (16, 2.1 g, 0.013 mol) in CF_3COOH (32 ml) was added 30% H_2O_2 (1.6 ml). After 4 days at room temperature the solution was evaporated to dryness in vacuo, and 18% HCl (140 ml) was added to the residue which was refluxed for 15 hr. The solution was evaporated in vacuo, and H_2O (50 ml) and a few drops of NH_3 were added to the residue, which was heated to boiling, and chromatographed on a Dowex-50 [H^+] (200–400 mesh) column (2.5 × 25 cm) that was eluted with hot H_2O. Fraction 1 (1–253 ml) contained decomposition products. Fraction 2 (299–828 ml) was evaporated to yield 15 (0.97 g, 42%), mp 338° dec. Fraction 3 (897–1265 ml) was evaporated to yield 1 (0.031 g, 1.3%), mp 310–311° dec. 15 was recrystallized from H_2O for analysis: NMR (CF_3COOH) δ 7.71 (dd, H-6), 8.88 (2 superimposed dd, H-5, H-7) ($J_{5,6}$ = 8.0, $J_{6,7}$ = 7.0, $J_{5,7}$ = 1 Hz); uv max (~pH) 266 nm s, 338 (1, 5), 280, 372 (12).

Anal. Calcd for $C_7H_3N_3O_3$: C, 46.93; H, 2.81; N, 23.45. Found: C, 47.07; H, 2.80; N, 23.12.

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Registry No.—1, 56783-76-7; 5, 56783-77-8; 6, 56783-78-9; 7, 56783-79-0; 8, 56783-80-3; 9, 56783-81-4; 10, 56783-82-5; 11, 56783-83-6; 12, 873-83-6; 13, 56783-84-7; 14, 56783-85-8; 15, 56783-86-9; 16, 7255-87-0; sodium nitromalonaldehyde, 34461-00-2; tosyl chloride, 98-59-9; 1,7-dihydroxy-2,4-dioxopyrido[2,3-*d*]pyrimidine, 56783-87-0.

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Investigation of Some Methylated Products Obtained by Reaction of β-3,4-Dihydroxyphenylalanine (Dopa) with Diazomethane in Methanol–Ether

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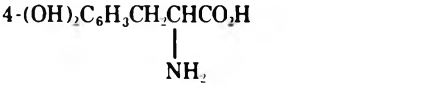
β-(3,4-Dihydroxyphenyl)alanine (**1**), usually referred to as Dopa, is a primary precursor in both catecholamine[1] and melanin biosynthesis.[2] The levo isomer of **1** is also current-

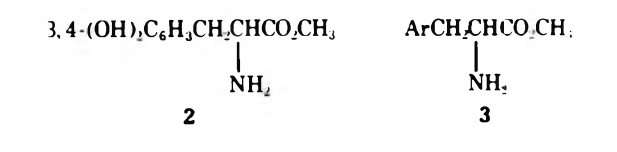


1

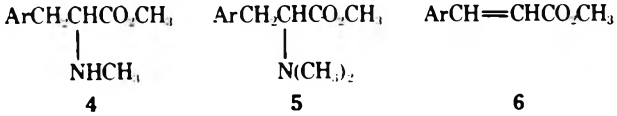
ly therapeutically useful in treating Parkinson's disease.[3] As a result of other studies in our laboratory, and because of the potential physiological significance of methylated analogs of **1**, a study of the alkylation of Dopa with diazomethane was undertaken. Previous studies of the reactions of some amino acids with diazomethane were conducted in moist ether, absolute ethanol, or ethanol–water.[4] In the present study, reactions were conducted in methanol–ether (1:1). Such a common solvent mixture slightly enhances solubility of the amino acid (relative to ether alone) and enables a study of the reactions of three functional groups in a nonaqueous medium.

Reactions were performed by suspending 0.05 mmol (10 mg) of **1** in 5 ml of methanol and adding 5 ml of a 0.2 *M* solution of diazomethane (20 molar excess) in ether. Dopa was initially relatively insoluble in the solvent system, but solution was effected between 4 and 8 hr. In order to maintain a constant temperature, to minimize loss of reagent and solvent, and to avoid artifacts due to light, the reactions were carried out at 4°C, in a glass stoppered flask, in the dark. The reaction times varied from 5 min to 24 hr and the reaction products were studied by comparison of both TLC and VPC with known synthetic products. In several reactions, analyses of products were confirmed by ir spectra and GC–MS data.

The treatment of Dopa with diazomethane led to eventual alkylation of each functional group present, i.e., carboxyl, phenolic, and amino. With respect to time, the appearance of each compound was in the order of increased methylation, i.e., **2** was detected before **3**, **3** before **4**, and **4** prior to **5**. Interestingly, traces of the trans cinnamate methyl ester (**6**) appeared at 24 hr. At the end of 24 hr, the reaction solution was clear and almost colorless, and at times longer than 24 hr, no further change was observed in the reaction products, an indication that all of the diazomethane reacted and/or evaporated. Essentially all of the reacted Dopa could be accounted for by compounds **3**–**6** at the 24-hr time period.



2 **3**



4 **5** **6**

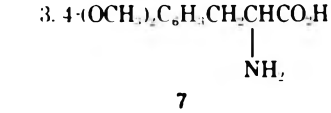
Ar = 3,4-dimethoxyphenyl

Although Dopa is quite insoluble in methanol–ether, esterification commenced instantaneously as evidenced by the formation of **2** within 5 min. After 8 hr, essentially all of **1** had reacted. The phenolic groups were rapidly methylated and small amounts of **3** were detected at 5 min. At the end of 16 hr, all traces of catechol (**2**) had disappeared. The insolubility of **1** is apparently the prime cause for the slow rate of esterification and methyl ether formation, since both carboxyl and phenolic methylation of solubilized substrates are usually quite rapid.

In the TLC observations, at least three additional spots appeared at R_f values between that of **2** and **3**. These spots were observed as early at 5–10 min, reached maximum intensity at 30–60 min, noticeably decreased after 2 hr, and completely disappeared at the end of 16 hr. Attempts to isolate the compounds causing these spots after a large-scale reaction were fruitless. These substances could be unstable intermediates or other products which may have also interfered with VPC analysis. Attempts to determine which of the phenolic groups was first methylated were also precluded by the fact that the methyl esters of 3-*O*-methyl-Dopa and 4-*O*-methyl-Dopa appeared at R_f values very close to that of the unidentified spots mentioned above.[5]

The amino group was the slowest to react and N-methylation occurred only after the carboxyl and phenolic functions had begun to react. However, N-alkylation was observed before complete esterification was achieved. The monomethyl analog **4** was detected within 1 hr and traces of the *N*,*N*-dimethyl derivative **5** were observed at the 2-hr time period. That the reaction pathway does not involve a continuous direct methylation of the amino esters was demonstrated by the fact that no reaction occurred at the end of 24 hr when methanolic solutions of **3** or **4** were treated with ethereal diazomethane. These results could be explained by assuming small amounts of the dipolar ions continuously generated from Dopa and which can be slowly alkylated to the N-methylated zwitterions. In the present study, the intermediate dipolar N-methylated amino acids were not detected by TLC methods when the reaction was conducted in the absence of water. However, when the reaction was conducted in moist ether, the amino acids of **3**, **4**, and **5** were readily detectable. These observations are also consistent with that of Kuhn and co-workers, who demonstrated that when water was present in ether solutions of diazomethane, N-methylated dipolar ions were formed.[4] In absolute ethanol using dry diazomethane, the esters were not converted into dipolar ions.[4b] With increasing amounts of water, greater quantities of the dipolar ions were formed, partly owing to the hydrolysis of the amino methyl esters.

The cinnamate ester (**6**), however, was not obtained from the uncharged amino methyl esters. To ensure that loss of ammonia from **3** or dimethylamine from **5** to give **6** was not base catalyzed, a mixture of **3** and **5** in MeOH–Et_2O for 24 hr also gave no reaction. When the free acid form, **7**, was

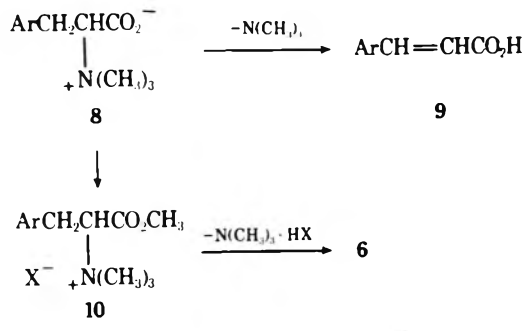


7

treated with diazomethane, the formation of **3**, **4**, **5**, and **6** was observed.

Two plausible pathways leading to the formation of the cinnamate ester (**6**) may be envisaged. Elimination of trimethylamine from **8** gives the unsaturated acid **9**, which upon additional methylation may produce **6**. Similarly, Hofmann elimination of the permethylated analogue **10** would furnish **6** directly.[6]

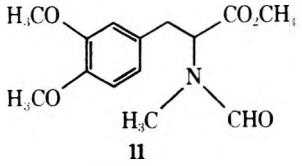
In no case could the trimethyl betaine (**8**) be isolated. Even when water was used in place of methanol, the betaine could not be obtained. Several different methods of



Ar = 3,4-dimethoxyphenyl

alkylation, including the use of dimethyl sulfate and methyl iodide, failed to produce the betaine from **1**. Kuhn had isolated the trimethyl betaine of phenylalanine in 39% yield (plus a 50% yield of amino ester)[4a] but no mention of a betaine was made when tyrosine was made to react with diazomethane.[7] The presence of alkoxy groups on the aromatic nucleus may enhance the formation of the conjugated cinnamyl system.

The syntheses of compounds **2**–**6** were achieved without much difficulty, but provided some interesting observations. The formamide **11** was utilized in the preparation of



11

4. In the NMR of **11**, the methyl protons of the carbomethoxy group and the proton of the formyl group each appeared as two peaks of approximately equal height, with the former at δ 3.73 and 3.75 and the latter at δ 7.84 and 8.00, respectively. These results may be explained by assuming two different configurations, i.e., the cis and trans rotamers of **11**, which are quite common in N-substituted formamides.[8] Similar observations in the NMR have been previously reported for esters of substituted formamides.[9] Thus, the protons giving rise to two peaks exist in different chemical environments having a population of approximately 50% each. One might also expect to observe two peaks for the *N*-methyl protons as well. Although two distinct peaks were not observed, the NCH_3 peak at δ 2.86 had a break in it and was not as sharp as the NCH_3 peaks of **4** and **5**. Addition of deuteriobenzene clearly separated the *N*-methyl peaks, resulting in a significant upfield shift of the methyl trans to the amide carbonyl.[8b]

The *N,N*-dimethyl analogue **5** could be prepared in quantitative yield by catalytic reductive alkylation of **3**.[10] It was essential that the free base was used, since the hydrochloride of **3** apparently gave the isoquinoline derivative, the NMR of which was similar to that of analogous compounds previously reported.[11]

Finally, the hydrochlorides of **3**, **4**, and **5** were converted to analytical samples of the free amines by passing methanolic solutions of the hydrochlorides through an anion (OH^-) exchange column and elution with methanol. Very little ester hydrolysis was observed in this very useful but apparently seldom used procedure[12] for conversion of the amine salt to the free amino ester.

Experimental Section

Ir spectra were obtained with $CHCl_3$ solutions recorded on a Perkin-Elmer Infracord Model 137B. NMR spectra were obtained from a Varian 60-MHz instrument with $CDCl_3$ solutions (except where noted otherwise) using Me_4Si as an internal standard. Reported NMR data are expressed in δ units. Mass spectra were obtained using a LKB Model 9000 gas chromatograph–mass spectrometer. VPC was performed employing a Varian Model 1860 unit in the fid mode; column conditions 6 ft × 0.125 in. stainless steel 3% OV-1 on Supelcoport, 160°, 30 ml/min He flow. Recorded R_f values are the averages of at least five runs on silica gel GF plates (250 μm thick, Analtech) with C_6H_6–CH_3OH (6:1) as a solvent. Prior to use, the plates were dried at 120°C for 2 hr, then transferred immediately to a desiccator containing Drierite. For comparison on TLC the amino acids of **3**, **4**, and **5** were obtained by hydrolysis of the related esters. Melting points were observed in capillaries in a Thomas-Hoover apparatus and are uncorrected. Purified compounds gave one spot on TLC, and one peak on VPC. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Dopa was purchased from Nutritional Biochemical Corp. and was found to be chromatographically (TLC) pure.

General Procedure for the Reactions of Dopa with Diazomethane. An ethereal solution of diazomethane was prepared from *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalamide.[13] Titration with benzoic acid[14] indicated the diazomethane solution to be 0.2 *M*. To a 50-ml round-bottom flask containing a Teflon-coated magnetic stirring bar and a suspension of finely powdered **1** (10 mg, 5.1×10^{-2} mmol) in absolute methanol (5.0 ml) was added 0.2 *M* diazomethane–ether (5.0 ml, 20-fold excess). The reaction flask was stoppered lightly and placed in the cold room at 4° in the dark. Single reaction runs were made at 5, 10, 15, 20, 30, and 45 min. Duplicate studies were made at 1, 2, 4, 8, 16, and 24 hr. The solvent was removed at the rotary evaporator at 25° or less and the reaction residue was treated with 1.0 ml of absolute methanol. Both TLC and VPC results were compared with standard solutions prepared from the synthetic compounds. Identification of the amino acid methyl esters was also confirmed in a few reactions by gas chromatography–mass spectrometry, and by observing the decrease of ir absorbance of the N–H bond (ca. 3300–3400 cm^{-1}) as time progressed.

***dl*-β-(3,4-Dihydroxyphenyl)alanine Methyl Ester (2).** The methyl ester hydrochloride of **1** was prepared in greater than 95% yield by either of two methods: (a) refluxing in CH_3OH saturated with HCl gas for several hours or (b) gentle refluxing for 1–2 hr in $SOCl_2$–CH_3OH. The free amine was liberated from the hydrochloride using the method of O'Neill et al.[15] Recrystallization from $CHCl_3$–petroleum ether (bp 30–60°) gave white crystals, mp 124–126° (lit.[15] 126°), R_f 0.32.

***dl*-β-(3,4-Dimethoxyphenyl)alanine Methyl Ester (3).** Using the procedure of Schrecker and Hartwell,[16] *N*-formyl-β-(3,4-dimethoxyphenyl)alanine was refluxed in CH_3OH saturated with gaseous HCl to give **3** HCl in 97% yield. Recrystallization from CH_3OH–Et_2O gave white crystals, mp 183.5–184° dec (lit.[16] 185–186° dec). A solution of the hydrochloride (551 mg, 2.0 mmol) in a minimum amount of methanol was placed on a chromatography column (1 × 30 cm) containing Bio-Rad Dowex Ag-1X-8 (200–400 mesh, OH^- form) and eluted with CH_3OH.[12] After 1 ml of forerun, 2-ml fractions were collected and monitored by TLC. Fractions 5–13 were combined to yield 393 mg (82%) of the free amine **4** as a straw-colored oil: R_f 0.47; ir 3400, 3340 (NH_2), 1735 cm^{-1} (C=O); NMR δ 1.50 (broad, NH_2), 2.98 (d, 2, CH_2), 3.2–2.4 (m, 1, CH), 3.71 (s, 3, CO_2CH_3), 3.86 (s, 6, $ArOCH_3$), 7.73–7.80 (m, 3, ArH); *m/e* 239 (M^+), 180 ($M^+ - CO_2CH_3$), 151 ($M^+ - H_2NCHCO_2CH_3$). Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 59.78; H, 7.03; N, 5.60.

***dl*-*N*-Formyl-*N*-methyl-β-(3,4-dimethoxyphenyl)alanine Methyl Ester (11).** The preparation of **11** was conducted similar to a procedure described by Olsen.[17] To a solution of *N*-formyl-β-(3,4-dimethoxyphenyl)alanine[16] (1.012 g, 4.0 mmol) in 20 ml of freshly distilled anhydrous DMF was added 1.2 ml (19.6 mmol) of CH_3I, followed by freshly prepared Ag_2O (2.784 g, 12.0 mmol). The reaction mixture was stirred for 12 hr at room temperature and filtered, and the solid was washed twice with 1–2 ml of DMF. $CHCl_3$ (100 ml) was added to the filtrate and a slight precipitate formed. The filtrate was transferred to a separatory funnel and washed with 5% aqueous KCN (2 × 20 ml) and distilled H_2O (4 × 20 ml or until neutral to pH paper), then dried ($MgSO_4$) overnight. The solution was decanted and evaporated (under 40°) to an oil. Last traces of solvent were removed at 35° (0.5 mm), giving 760 mg of yellow-brown oil. White crystals could be obtained from the oil in either of two ways: (a) addition of EtOAc to about twice the volume of oil and storage of the solution in the refrigerator for several days, or (b) chromatography on silicic acid, eluting with CH_2Cl_2 and then CH_2Cl_2–CH_3OH (9:1). Recrystallization from EtOAc gave mp 92.5–105°.[18] Attempts to recrystallize from at least 13 different solvent systems either failed to give crystals or did not fur-

ther affect the melting point range: ir 1735 (ester C=O), 1665 cm^{-1} (amide C=O); NMR δ 2.86 (s, 3, NCH_3), 3.20 (d, 2, $ArCH_2$), 3.4–3.6 (m, 1, CH), 3.73 and 3.75 (s, s, 3, CO_2CH_3), 3.84 (s, 6, $ArOCH_3$), 6.67–6.83 (m, 3, ArH), 7.84 and 8.00 (s, s, 1, CHO); upon addition of C_6D_6 all peaks shifted upfield with separation of the NCH_3 and $ArOCH_3$ signals into each of two distinct peaks; *m/e* 281 (M^+), 222 ($M^+ - CO_2CH_3$), 151 [$M^+ - CH_3(CHO)NCHCO_2CH_3$, base]. Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.54; H, 6.61; N, 4.87.

***dl*-*N*-Methyl-β-(3,4-dimethoxyphenyl)alanine Methyl Ester (4).** Using the procedure above for the preparation of **3**, 155 mg (0.05 mmol) of **11** was converted to the hydrochloride of **4**. Recrystallization from C_6H_6–CH_3OH gave 92 mg (58%) of **4** HCl as a white solid (one spot on TLC). Utilizing the ion-exchange procedure described above, 66 mg of free amine was obtained as a clear oil: R_f 0.50; ir 3300 (NH), 1725 cm^{-1} (C=O); NMR δ 1.60 (broad, NH), 2.35 (s, 3, NCH_3), 2.90 (d, 2, CH_2), 3.28–3.50 (m, 1, CH), 3.67 (s, 3, CO_2CH_3), 3.87 (s, 6, $ArOCH_3$), 6.70 (m, 3, ArH); *m/e* 253 (M^+), 194 ($M^+ - CO_2CH_3$), 151 ($M^+ - H_3CNHCHCO_2CH_3$), 102 ($H_3C^+NH{=}CHCO_2CH_3$, base). Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.67; H, 6.99; N, 5.45.

***dl*-*N*,*N*-Dimethyl-β-(3,4-dimethoxyphenyl)alanine Methyl Ester (5).** To a solution of **3** (95.6 mg, 0.4 mmol) in 2 ml of CH_3OH were added paraformaldehyde (85 mg), 10% Pd/C (50 mg), and anhydrous $MgSO_4$ (50 mg). The mixture was subjected to a reductive alkylation at 45° similar to the procedure of Bowman and Stroud[10] to give **5** (107 mg, 100%) as a colorless, clear oil. An analytical sample of the free amine was prepared by making the solid hydrochloride, and recrystallization, followed by the ion-exchange procedure described above: R_f 0.60; ir 1725 cm^{-1} (C=O); NMR δ 2.38 (s, 6, NCH_3), 2.94 (dd, 2, CH_2), 3.28–3.47 (m, 1, CH), 3.59 (s, 3, CO_2CH_3), 3.84 (s, 6, $ArOCH_3$), 6.75 (s, 3, ArH); *m/e* 267 (M^+), 151 [$M^+ - (H_3C)_2N{=}CHCO_2CH_3$], 116 [$(H_3C)_2{}^+N{=}CHCO_2CH_3$, base]. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.81; H, 7.86; N, 5.15.

When the hydrochloride of **3** was treated under identical conditions stated above, the major product appeared to be the isoquinoline analogue. Ion exchange produced an oil: NMR δ 2.53 (s, 3, NCH_3), 3.04 (d, J = 6 Hz, 2, $ArCH_2CHCO_2$–), 3.54 (t, J = 6 Hz, 1, CH), 3.72 (s, 3, CO_2CH_3), 3.83 (s, 8, two $ArOCH_3$ + $ArCH_2N$), 6.54 (s, 1, ArH), 6.60 (s, 1, ArH).

3,4-Dimethoxycinnamic Acid Methyl Ester (6). The cinnamate ester was prepared from the free acid by gentle refluxing in $SOCl_2$–CH_3OH, mp 60–62° (lit.[19] 68–69°), R_f 0.88.

Acknowledgments. This investigation was supported in part by NIH Grant CA-11959. Mass spectra were obtained by Mr. John Naworal on an LKB-9000 supported by NIH RR-00273. Appreciation is also extended to James Ramsey (supported by ACS Project Seed) and Donald Evans for some technical assistance. 3-*O*-Methyl-Dopa and 4-*O*-methyl-Dopa were kindly provided by Dr. Sidney Teitel of Hoffmann-La Roche, Inc.

Registry No.—**1**, 63-84-3; **3**, 56771-16-5; **3** HCl, 56771-17-6; **4**, 56771-18-7; **5**, 56771-19-8; **5** HCl, 56771-20-1; **11**, 56771-21-2; *N*-formyl-β-(3,4-dimethoxyphenyl)alanine, 53053-93-3; 2-methyl-3-carbomethoxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 56771-22-3; diazomethane, 334-88-3.

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(5) With the aid of three different spray reagents, the unidentified substances appearing at R_f values between that of **2** and **3** afforded different colors than that observed by spraying samples of 3-*O*-methyl-Dopa and 4-*O*-methyl-Dopa. Based on the overall observations, it appears that very small amounts, if any, of the monomethoxy methyl esters are present during the reaction.
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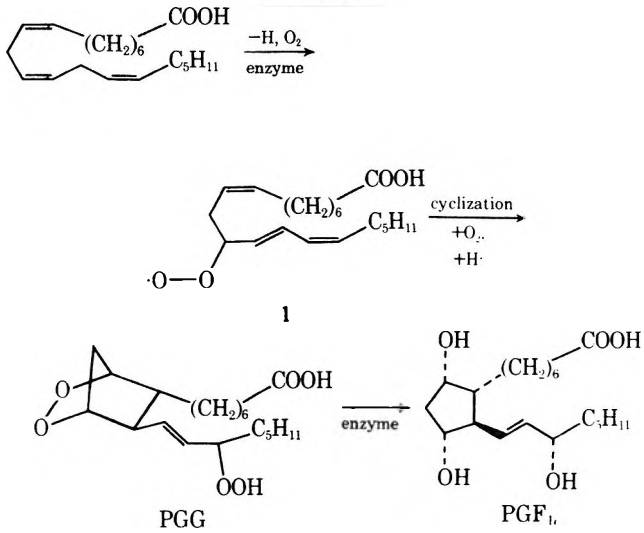
Peroxy Radical Cyclization as a Model for Prostaglandin Biosynthesis

Summary: Unsaturated lipid hydroperoxides are converted into prostaglandin analogs by free-radical initiators.

Sir: The biosynthesis of prostaglandins has been the focus of extensive investigation over the past several years.[1] A peroxy radical cyclization mechanism leading to intermediate endoperoxides has been proposed for this biosynthesis (Scheme I). The intermediacy of endoperoxides has, in

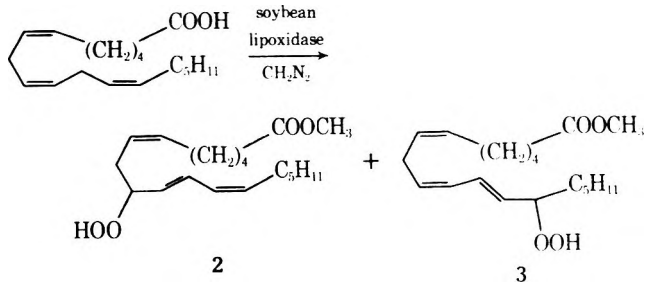
Scheme I



fact, been concretely established by the isolation of two such compounds, PGG and PGH, from tissue homogenates which were actively engaged in the production of prostaglandins.[2]

Recently, we reported a method for generating specific peroxy radicals from the corresponding hydroperoxide.[3] This method is based on the fact that hydroperoxy hydrogens are readily abstracted by free radicals. Thus, hydroperoxides act as a source of the corresponding peroxy radical when treated with appropriate free radical initiators. We report here the application of this method to a hydroperoxide which should lead to a peroxy radical analogous to **1**.

Polyunsaturated fatty acids are converted into hydroperoxides by a class of enzymes known as lipoxygenases (fatty acid: oxygen oxidoreductase). These enzymes have been identified in extracts from a variety of plant sources including soybeans,[4] potato tubers,[5] and wheat flour.[6] With the soybean enzyme,[7] γ-linolenic acid (*all-cis*-6,9,12-octadecatrienoic acid) could be converted into a 1:1 mixture of the ω-10 and ω-6 hydroperoxides **2** and **3**. The reaction was carried out on the ammonium salt of the fatty acid at pH 7 for 2 min.[8] The crude hydroperoxide fatty acids were then converted into the hydroperoxide methyl esters **2** and **3** by reaction with diazomethane. **2** and **3** could be separated by high performance liquid chromatography (HPLC) with 6 ft × ⅛ in. of Corasil II and 0.24% isopropyl alcohol in hexane solvent. Thus, pure **2** could be isolated in an overall 15–20% yield based on starting fatty acid. The structures of **2** and **3**



were assigned by conversion to the ketostearates followed by mass spectral analysis.[4b]

Incubation of **2** (10.8 mg, .0333 mmol) with di-*tert*-butyl peroxyoxalate (DBPO; 3.22 mg, 0.014 mmol) in O_2-saturated benzene at 25° for 16 hr led to complete consumption of **2**. The products of the reaction, all of which were more polar than starting hydroperoxide, were reduced with $NaBH_4$ (25 mg, 0.661 mmol in 10 ml of CH_3OH) and then converted into the trimethylsilyl ethers for analysis by gas chromatography (GLC). Chromatography of the reduced and silylated product mixture on a 1% OV-17 column at 220° revealed at least four volatile products with retention times expected for PGF-type products from a C-18 fatty acid.[9]

Combined GLC–MS analysis of the product mixture indicates that two of these four compounds (retention times 9.5 and 10.5 min) are structurally analogous to authentic $PGF_{1\alpha}$. Prominent fragments of one of these compounds and $PGF_{1\alpha}$ analyzed under identical GLC–MS conditions are presented in Table I.

Table I
Mass Spectral Data (I.P. = 70 eV) of Trimethysilyl Ethers and Methyl Esters of $PFG_{1\alpha}$ and Synthetic C-18 PGF (Retention Time 9.5 min)

$PGF_{1\alpha}$			C-18 PGF		
Fragment[a]	*m/e*	%	Fragment[a]	*m/e*	%
M − 90	496	2	M − 90	468	2
	355	24		355	48
M − 233	353	100	M − 233	325	72
M − 251	335	72	M − 251	307	61
M − 277	309	80	M − 277	281	75
M − 289	297	62	M − 289	269	100
	295	50		295	22

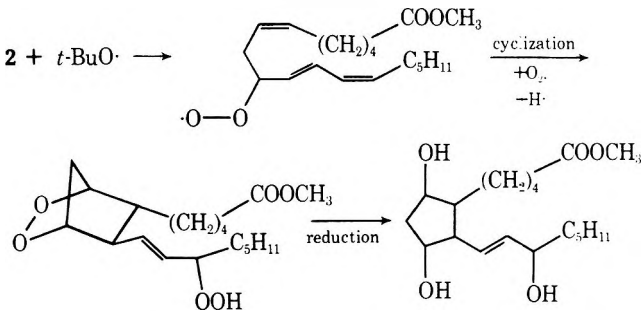
[a] Fragments between 200 and 500 *m/e* are shown and referred to the largest peak in this region as base.

The mass spectra of the synthetic PGF's (which have carboxyl side chains smaller than $PGF_{1\alpha}$ by C_2H_4, 28 *m/e*) are strikingly similar to $PGF_{1\alpha}$.[10] Every fragment from the synthetic PGF's between 200 and 500 *m/e* with a relative intensity greater than 20% of base corresponds either to a fragment of the same mass (loss of the carboxyl side chain) or to a fragment of *m/e* − 28 (retention of carboxyl side chain) from $PGF_{1\alpha}$.[11]

A mechanism consistent with our observations is presented in Scheme II. *tert*-butoxy radicals generated by de-

composition of DBPO abstract the labile hydroperoxide hydrogen[3] from **2** giving the peroxy radical. Cyclization of this radical to the endoperoxide followed by reduction[12] leads to PGF-type products.

Scheme II



4

The work reported here lends support to the notion that prostaglandin biosynthesis is a controlled free-radical reaction.[1] Other workers have noted the formation of prostaglandins in autoxidizing lipid.[11,13] The method reported here has the advantage of producing specific peroxy radicals for study as compared to the rather random autoxidation format.

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(11) (a) Our mass spectra were compared to those of compounds obtained by autoxidation of methyl α-linolenate (W. A. Pryor and J. P. Stanley). Fragmentation patterns were generally similar with some exceptions that may be explicable by differences in the proposed structures. We thank Professor Pryor for this information before publication. (b) W. A. Pryor and J. P. Stanley, Abstracts of Papers, American Chemical Society Meeting, Chicago, Ill., Aug 25–29, 1975, paper ORGN-50.
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A Suggested Mechanism for the Production of Malonaldehyde during the Autoxidation of Polyunsaturated Fatty Acids. Nonenzymatic Production of Prostaglandin Endoperoxides during Autoxidation

Summary: Autoxidation of methyl linolenate is shown to yield materials which give positive tests for both prostaglandin E and malonaldehyde, and it is suggested that both tests respond to prostaglandin-like endoperoxides which can be formed by autoxidation.

Sir: When polyunsaturated fatty acids (PUFA) or esters containing three or more double bonds undergo autoxidation, a material is produced which develops color in a sensitive test with thiobarbituric acid (TBA).[1-9] This TBA test is the most frequently used index of lipid peroxidation both in vitro and in vivo. Although the TBA-reactive material is frequently referred to as malonaldehyde,[5,6,9,10] it has been known for some time[3,4] that this material is predominantly nonvolatile; therefore, it is not malonaldehyde, but rather is a nonvolatile precursor of malonaldehyde.

In 1962, Holman et al.[4] suggested that a five-membered monocyclic peroxide is the nonvolatile malonaldehyde precursor. However, their mechanism does not appear to accommodate all the known facts of TBA-color production during PUFA autoxidation.[1] A more attractive mechanism, in our view, is one in which the nonvolatile malonaldehyde precursor is a bicyclic endoperoxide analogous to that which is formed in the biosynthesis of prostaglandins.[11-20] Figure 1 shows this mechanism as applied to methyl linolenate (18:3). Abstraction of an "internal" allylic hydrogen followed by reaction with O_2 leads to peroxy radicals **4** and **5**. Radical **4** has a structure which allows cyclization to endoperoxide radicals **9**, which are allylic, probably via the oxy-bridged radicals **6**. Radicals **9**, then, can become converted into endoperoxides **10** or **11**.[21-23] Radicals **4** and **5** also can lead to the conjugated hydroperoxides **7** and **8** which are known products of autoxidations.

Our first indication that the nonvolatile malonaldehyde precursor is an endoperoxide came from comparisons of the responses of autoxidized solutions of 18:3 to the TBA test and a test developed for prostaglandin E (PGE).[19,24,25] The PGE test, which involves rapid formation of absorption at 278 nm upon addition of alcoholic base,[19,24,25] probably is relatively unspecific, but it is believed to convert PGE compounds into conjugated dienones such as PGB.[24] Since base is known to rapidly decompose secondary dialkyl peroxides to form ketones and alcohols,[26-28] we expected that endoperoxides, if produced in our autoxidations, would be converted by base into PGE-type compounds. The PGE-type compounds would then react further with base to give PGB-type chromophores and a positive PGE test. It appeared reasonable a priori that endoperoxides could be formed nonenzymatically by autoxidation in our system since the suggested mechanism for their biosynthesis involves a radical cyclization;[11-20] furthermore, Nugteren et al.[29a] have shown that autoxidation of 8,11,14-eicosatrienoic acid gives prostaglandins. Thus, we hypothesized that endoperoxides are produced on autoxidation of 18:3 and are the precursors of malonaldehyde under TBA-test conditions and PGB under conditions for the PGE test. (Note that **10** and **11** should give malonaldehyde but only **11** should give a PGE test.)

Indeed, autoxidized 18:3 does give a PGE test. This is true regardless of whether the oxidation is spontaneous (i.e., effected by pure air), or is initiated[1,2] by ozone or NO_2. On the other hand, 18:2, autoxidized under the same condi-

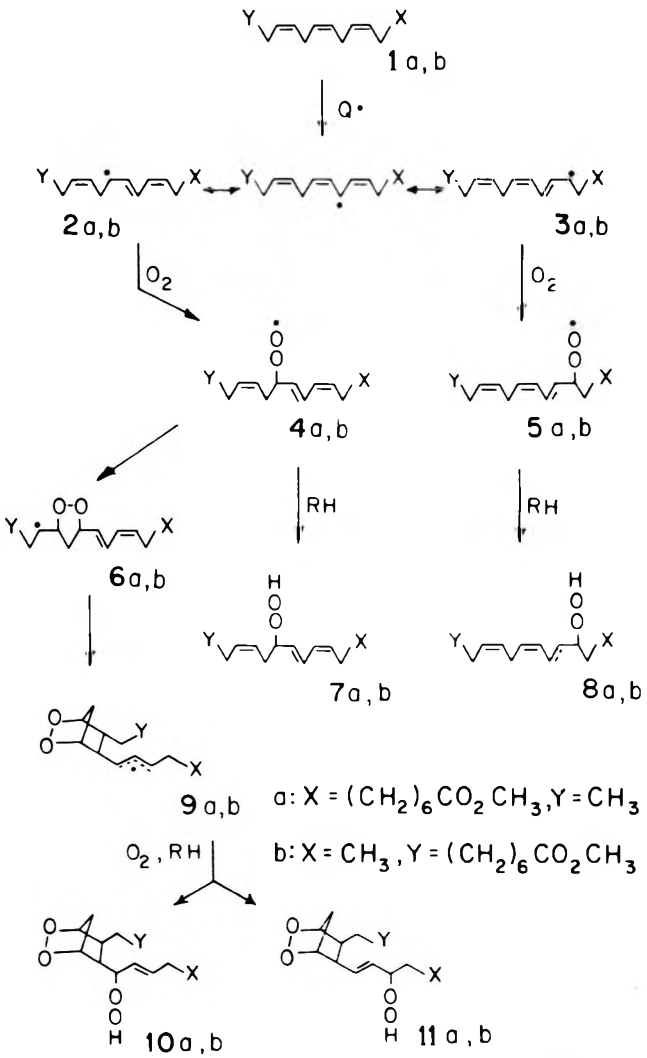

Figure 1. Mechanism for conversion of methyl linolenate to conjugated hydroperoxides and to prostaglandin-like endoperoxides.

tions and to the same degree of reaction, gives either no response or a much lower response to both the PGE and TBA tests.[29b]

When the formation of total peroxidic material, conjugated dienes, and TBA- and PGE-test reactive material is followed as a function of time for autoxidizing 18:3, with added α-tocopherol to produce a significant induction period,[1,2] curves such as shown in Figure 2 are obtained. It can be seen that during the induction period the rates of formation of both TBA- and PGE-test reactive material are very much smaller than the rates of appearance of total peroxide and conjugated diene. These data suggest that the TBA-test and the PGE-test reactive materials have common precursors, namely endoperoxides, which are different from the conjugated hydroperoxide products. [The amounts of PGE material in Figure 2 were calibrated by adding authentic PGE (generously supplied by Upjohn Co.) to our runs.]

The malonaldehyde precursor is a labile peroxide. Shaking an ether solution of autoxidized 18:3 with aqueous $SnCl_2$ not only destroys the peroxidic material (determined iodometrically), but also destroys both the TBA- and the PGE-test reactive material. Partial reduction indicates that the malonaldehyde precursor is reduced faster than is the total peroxidic material. We also have followed the rates of disappearance, during heating under an inert gas, of the total peroxidic materials and the TBA- and PGE-test reactive materials in a sample of autoxodized 18:3.

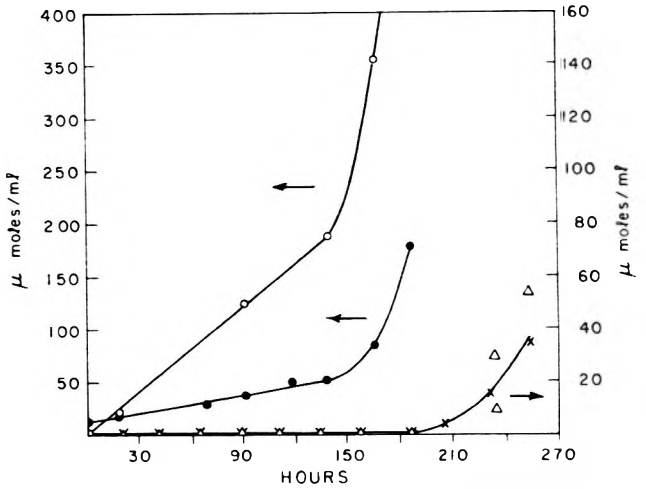

Figure 2. Formation of total peroxide (○), conjugated dienes (●), TBA-test reactive material (×), and PGE-test reactive material (△) with time, during the autoxidation of methyl linolenate containing 1 mg of vitamin E/ml of ester, exposed to 0.25-l./min flow of air containing 1.5 ppm O_3. Left ordinate is for peroxide and conjugated dienes; right ordinate is for TBA-reactive material and PGE-reactive material.

Each of these materials is found to disappear at 80° by a first-order process, with the following rate constants ($\times 10^5$ in reciprocal seconds): total peroxide, 3.4 ± 0.6; TBA, 5.5 ± 2; and PGE, 5.8 ± 1.[30] Although the reproducibility of the rate constants is, for unknown reasons, less than we would have wished, it appears likely that the TBA- and PGE-test reactive materials disappear faster than do conjugated hydroperoxides like 7 and 8. Thus, the former materials cannot be identical with the type of conjugated hydroperoxides, such as 7 and 8, which are the principle hydroperoxides produced.

Although VPC indicates the presence of a large number of product fractions, we have isolated one which appears to contain the reduced and derivatized endoperoxides.[30a] The product mixture from autoxidation of 18:3 was reduced with $SnCl_2$, which converts hydroperoxide into alcohol and endoperoxide into diol,[11,14] and separated into five fractions by silica gel chromatography using cyclohexane as solvent (to remove unreacted 18:3) followed by preparative thin layer chromatography (TLC) using ethyl acetate–isooctane–water, 1:1:2 as solvent. Fraction 1 was subjected to further TLC (50:50 $CHCl_3$–ethyl acetate) into five fractions. The second of these, 1B (R_f 0.22), which represents 81% of fraction 1 and 20% of the total isolated product, was investigated by uv, ir, and NMR spectroscopy. This fraction showed no significant absorbance below 220 nm, indicating that it does not contain a conjugated diene. The ir spectrum reveals very strong alcohol OH stretching, very little if any vinyl hydrogen stretch, and a slightly broadened carbonyl peak. The NMR spectrum indicates that the material is a mixture but is consistent with PGF_1-type compounds being a major component.

Trimethylsilyl and acetate derivatives[14,15,31] were prepared from fraction 1B and the mixture was subjected to gas chromatography–mass spectroscopic analysis. The mass spectra are similar to spectra obtained for similar derivates of $PGF_{1\alpha}$[14,15,32] and to spectra obtained by Porter from cyclization of 6,9,12-octadecatrienoic acid.[33]

There are two major conclusions from the work reported here. The first is that autoxidation of methyl linolenate, and, by extension, other PUFA esters containing three or more double bonds, produces endoperoxides. This finding complements that of Nugteren et al.[29] who found that autoxidation of a trienoic acid gave prostaglandins.[34] It is one

of the basic tenets of free-radical biology that autoxidation of PUFA in vivo, and particularly lipids in membranes, is responsible for important biological consequences.[34,35] The extent to which cyclic peroxides, endoperoxides, and PG analogues, with either natural (i.e., enzymatically produced) or unnatural structures, may be involved in free-radical biology obviously warrants considerable further research effort. The second hypothesis suggested by our work is that PG-like endoperoxides decompose both thermally and under the mild acid catalysis of the TBA test to produce malonaldehyde, and that endoperoxides are the principal nonvolatile precursor of malonaldehyde under our conditions.

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(23) (a) A total of 128 isomeric endoperoxides are possible, of which one (**11b**) has a structure analogous to the enzymatically produced isomer. We estimate ~1% yield of this isomer in the autoxidation. No particular stereochemistry is meant to be implied by the structures in Figure 1. (b) Note that a diunsaturated PUFA would give a radical analogous to **6** that had just one unsaturation; thus dienes would not give an allylic radical on cyclization to **9**.
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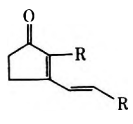

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(30) (a) It is worth stressing that our suggestion that an endoperoxide is the precursor of malonaldehyde (like the previous proposal[4]) is based solely on inferential evidence. Indeed, to date no one has ever isolated any prostaglandin-like endoperoxide from either natural or synthetic sources, although solutions rich in endoperoxides have been prepared.[11,17,22b] All workers, including ourselves, have reduced the endoperoxide in situ before chromatography. (b) The rate constants for the disappearance of the TBA- and PGE-reactive materials (which presumably are those for the decomposition of the endoperoxide under the acidic or basic conditions of these two tests to produce malonaldehyde or PGE) indicate the endoperoxide in our system is more stable than is that from enzymatic preparations. The inherent thermal stability of the 2,3-dioxanorbornane ring system is probably substantial; the biochemical preparations likely contain impurities which catalyze the decomposition.
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(32) After correcting for the two-carbon difference in 8,11,14-eicosatrienoic rather than 9,12,15-octatrienoic as substrate.
(33) Professor N. A. Porter, private communication, Aug 8, 1975. See ref 22.
(34) Endoperoxides apparently can be produced from either acids or esters of PUFA by autoxidation, in contrast with prostaglandin synthetase which operates on acids.
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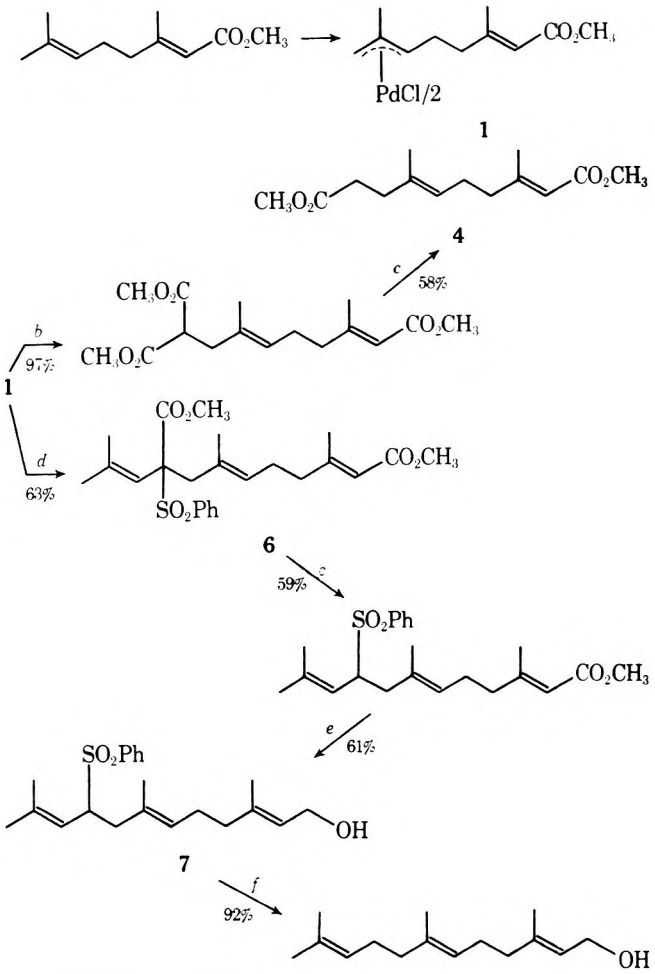
A New Approach for the Stereocontrolled Synthesis of Acyclic Terpenes

Summary: A short stereoselective approach to farnesol, geranylgeraniol, and dimethyl 3,7-dimethyl-(*E*,*E*)-2,6-decadiene-1,10-dioate based upon the regioselectivity and stereospecificity of allylic alkylation via π-allylpalladium complexes is reported.

Sir: The problems of synthesizing trisubstituted double bonds of defined geometry came to the fore in the squalene problem.[1a] Renewed interest developed as a result of the structural elucidation of the juvenile hormone.[1b] The acyclic polyisoprenoids in general represent an important class of natural products because of their myriad of applications as well as their importance as biosynthetic intermediates. We wish to report (1) an unusual chemospecificity in the formation of π-allylpalladium complexes, (2) a stereoselective approach to acyclic terpenoids[2] involving a direct homologation of simpler building blocks, (3) a new approach to prenylation, and (4) the first application of π-allylpalladium complexes in natural products synthesis.[3]

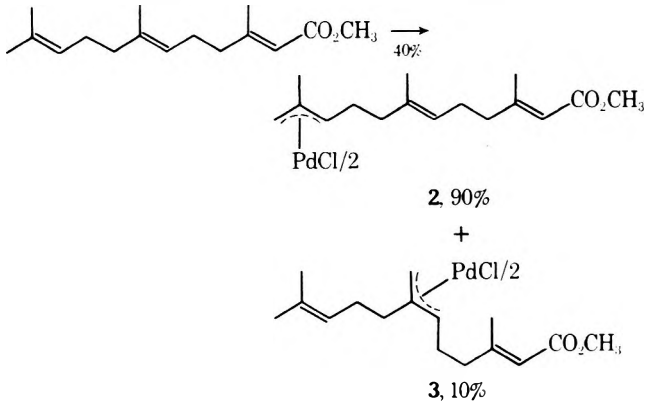
Treatment of methyl geraniate with palladium chloride under standard conditions[4] (PdCl, NaCl, $CuCl_2$, NaOAc, HOAc, 95°, 68%) gave a single π-allylpalladium complex, mp 117–118°, assigned structure **1**[5] (see Scheme I). The NMR spectrum indicated that the *E*-α,β-unsaturated system was intact [δ 5.74 (s, 1 H, 2.18 (s, 3 H)] and the stereochemistry of the π-allyl unit was syn [δ 3.75 (s), 3.50 (t, J = 7 Hz), 2.70 (s), each 1 H]. The preference for the nonconjugated double bond is somewhat surprising in light of the importance of the acidity of the abstracted hydrogen on the rate of formation of π-allyl complexes[6] and by consideration of the usual factors affecting stability of the initial olefin–palladium π complex.[7] Thus, π basicity of the olefin appears to be the predominant factor determining this chemospecificity.

Scheme I
η^3-1-[1′-(3′-Methyl-4′-carbomethoxy-(*E*)-3′-butenyl)]-2-methyl-π-allylpalladium Chloride Dimer as a Synthon[a]



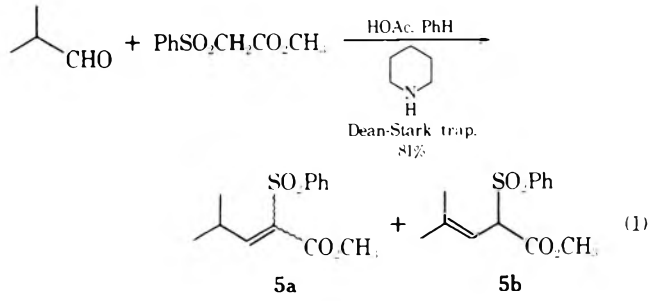
[a] All yields are for compounds purified by chromatography or distillation and are not optimized. [b] $NaCH(CO_2CH_3)_2$, diphos, THF, 25°, 18 hr. [c] LiI, $3H_2O$, NaCN, DMF, 120°, 17 hr. [d] $(CH_3)_2C{-}CH{-}C(SO_2Ph)CO_2CH_3\ Na^+$, diphos, THF, 25°, 24 hr. [e] Dibal, $PhCH_3$–hexane, −40° to 0°. [f] $Li/C_2H_5NH_2$, −78°.

Formation[4] of the π-allyl complexes from methyl farnesoate also involve only the nonconjugated double bonds with a preference for the sterically less crowded terminal olefin (**2:3**, 9:1).[8] The enoate system of **2**[9] [δ 5.63 (1 H, s), 2.15 (3H, s)] and the central trisubstituted double bond [δ 5.12 (1 H, m), 1.61 (3 H, brs)] are unaffected. The π-allyl system is syn [δ 3.69 (s), 3.54 (m), 2.65 (s), each 1 H, 2.06 (3 H, s)].



Activation of complex **1** by adding 1,2-bis(diphenylphosphino)ethane allows smooth condensation with dimethyl malonate with complete regioselectivity and stereospecificity. Decarbomethoxylation[10] completes this short stereoselective synthesis of the dimethyl ester of a pheromone of the Monarch butterfly (**4**).[11]

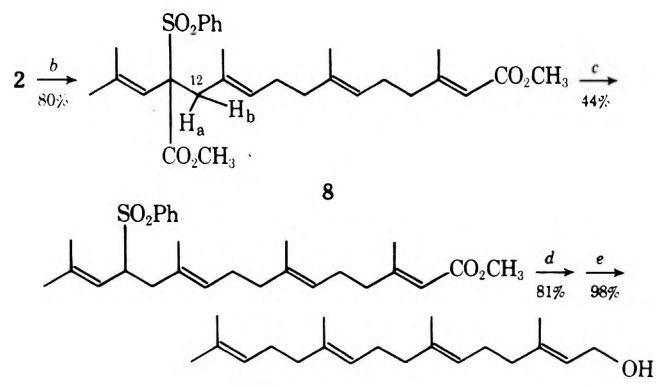
Prenylation was accomplished using the anion derived from the sulfone ester **5**, mp 60–70°, available as shown in eq 1. NMR analysis indicates this material to be a 1.8:1



mixture of the conjugated and unconjugated isomers **5a** [δ 7.18 (d, J = 11 Hz), 3.10 (m), 1.12 (d, J = 7 Hz)] and **5b** [δ 5.12 (d, J = 11 Hz), 4.62 (d, J = 11 Hz), 1.76 (s), 1.58 (s)]. Since both give the same anion, their separation is obviated. Conversion to their anion (NaH, THF, room temperature) and alkylation with **1** produced **6** [δ 5.64 (1 H, s), 5.35 (1 H, s), 5.19 (1 H, m), 3.12 (1 H, d, J = 15 Hz), 2.94 (1 H, d, J = 15 Hz)] as the sole product. The stereochemistry of the 6,7 double bond as *E* was indicated by the NMR spectrum (δ 1.60, 3 H, s) and the subsequent conversion to *all-trans*-farnesol. Decarbomethoxylation and reduction of the ester produced the hydroxy sulfone **7** which was reductively cleaved to *all-trans*-farnesol, identical with an authentic sample.[12] Spectroscopic[13] and chromatographic analysis did not reveal the presence of other geometric isomers.

The utility of this approach is further illustrated by the prenylation of methyl farnesoate to geranylgeraniol (see Scheme II) using the same sequence as above. Alkylation proceeded without any detectable (by NMR) formation of alternative isomers. The alkylation product **8** showed five olefinic methyl groups [δ 2.13 (3 H), 1.76 (3 H), 1.56 (6 H), and 1.44 (3 H)], four vinyl protons [δ 5.58 (s, 1 H), 5.28 (s, 1 H), 5.16 (m, 2 H)], and a clean AB (J = 15 Hz) pattern (δ 3.10 and 2.76) for the C-12 methylene group. The standard methods of decarbomethoxylation and reduction completed the synthesis of geranylgeraniol.

Scheme II
Synthesis of Geranylgeraniol[a]



[a] All yields are for product after purification by chromatography or distillation and have not been optimized. [b] $(CH_3)_2C{-}CH{-}C(SO_2Ph)CO_2CH_3\ Na^+$, Ph_3P, THF, 25°, 20 hr. [c] LiI, $3H_2O$, NaCN, DMF, 120°, 17 hr. [d] Dibal, $PhCH_3$, −40°. [e] $Li/C_2H_5NH_2$, −78°.

The direct and chemospecific prenylation of simpler terpenes to more complex terpenes should prove to be a useful approach to such compounds. The fact that trisubstituted double bonds can be created with complete stereochemical control enhances the utility of this scheme for such a purpose.

Acknowledgment. We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for their generous support of our programs. L.W. expresses his gratitude to the Deutsches Forschungs Gemeinschaft for a fellowship for part of his stay in these laboratories.

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(1) (a) For an early elegant solution to the squalene problem, see J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 2539 (1959). (b) For a review see B. M. Trost, *Acc. Chem. Res.*, **3**, 120 (1970); also B. M. Trost in "Insect Juvenile Hormones", J. J. Menn and M. Beroza, Ed., Academic Press, New York, N.Y., 1972, pp 217–236.
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(3) B. M. Trost and P. E. Strege, *J. Am. Chem. Soc.*, **97**, 2534 (1975); B. M. Trost and L. Weber, *ibid.*, **97**, 1611 (1975), and earlier references therein.
(4) B. M. Trost and P. E. Strege, *Tetrahedron Lett.*, 2603 (1974).
(5) All new compounds have been characterized by ir, NMR, and mass spectroscopy as well as elemental composition.
(6) H. C. Volger, *Recl. Trav. Chim. Pay-Bas*, **87**, 225 (1968).
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(8) A higher chemospecificity was observed with methyl farnesoate compared to geranylacetone: B. M. Trost, T. J. Dietsche, and T. J. Fullerton, *J. Org. Chem.*, **39**, 737 (1974). Conformation of the molecules in solution and/or neighboring-group participation provide possible rationalizations.
(9) This compound crystallized only at low temperature and was a yellow oil at room temperature. Nevertheless a satisfactory elementary analysis was obtained on the oil and NMR gave no indication of the presence of any isomers.
(10) J. McMurry and G. B. Wong, *Synth. Commun.*, **2**, 389 (1972).
(11) For alternative approaches see J. Meinwald, A. M. Chalmers, T. E. Pliske, and T. Eisner, *Chem. Commun.*, 86 (1969); D. H. Miles, P. Loe, W. S. Johnson, A. F. Kluge, and J. Meinwald, *Tetrahedron Lett.*, 3019 (1972).
(12) We thank Professor C. J. Sih for this sample.
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(14) Camille and Henry Dreyfus Teacher Scholar Grant Recipient, 1970–1975.

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Reductions with Copper Hydride. New Preparative and Mechanistic Aspects

Summary: Simple copper hydride reagents are described which reduce conjugated carbonyl compounds to the saturated derivatives; a special effect of added *sec*-butyl alcohol allows reduction of acrylates and labeling experiments establish the sources of the added hydrogens.

Sir: Since the first suggestions of unique reduction reactions promoted by complex copper hydrides,[1] related reagents have been shown to be of general utility for conversion of organic halides and sulfonate esters to hydrocarbons,[2–4] and for conversion of α,β-unsaturated ketones into saturated ketones.[4,5] The reagents suggested to be most effective are obtained by generation of CuH at −50°, solubilization with a second ligand, and filtration at low temperature.[4,5] No general procedures for reduction of α,β-unsaturated esters have been reported.

Using the general technique of earlier workers,[1,2] we have developed simple preparations of effective copper-based reagents which provide efficient 1,4 reduction of both conjugated ketones *and* esters, including two examples of acetylenic esters. The reductions show features associated with electron-transfer processes, including a dramatic increase in efficiency in difficult cases with 2-butanol in the medium. In contrast to reduction of halides to hydrocarbons,[2] these reactions involve transfer of a hydrogen atom from the copper hydride to carbon, specifically the β carbon of the unsaturated carbonyl system.

The complex hydrido–metallic species are prepared according to eq 1 and 2. The species involving the lithium cation (eq 1, here referred to as Li complex) and the parallel species with the sodium cation (eq 2, Na complex) are obtained as brown-black suspensions in tetrahydrofuran by simply mixing the reagents at 0° under argon and stirring for 30 min. A series of unsaturated ketones and esters were studied in reaction with both the Li complex and the Na complex; the more efficient conversions are displayed in Table I. Cyclic enones are best reduced with the Li complex, as the Na complex gives lower yields (60–70%). With chalcone and the ester examples, the Na complex gives better results, especially in the presence of excess 2-butanol. In the examples of entries 6, 7, 9, and 10, high molecular weight products were the main products with the Li complex and with the Na complex in the absence of added alcohol.

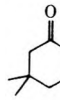
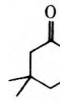
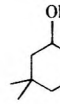
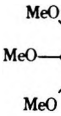
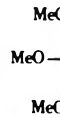
$$2LiAlH(OCH_3)_3 + CuBr \xrightarrow[THF]{0^\circ} \text{“Li complex”} \quad (1)$$

$$NaAlH_2(OCH_2CH_2OCH_3)_2 + CuBr \xrightarrow[THF]{0^\circ} \text{“Na complex”} \quad (2)$$

The procedure is exemplified by the reduction of methyl 3,4,5-trimethoxycinnamate. Vitride[6] (70% in benzene, 2.24 ml, 16.0 mmol of hydride) was added dropwise to a suspension of cuprous bromide[7] (1.44 g, 8.0 mmol) in 15 ml of THF at 0°. After 30 min, the mixture was cooled to −78° and 2-butanol (1.6 ml, 18.0 mmol) was added, followed by a solution of methyl 3,4,5-trimethoxycinnamate (252 mg, 1.0 mmol) in 4 ml of THF. The mixture was stirred at −20° for 2 hr, quenched with 4 ml of water, and poured into saturated aqueous ammonium chloride. After dilution with ether, the organic layer was washed successively with water and aqueous ammonium chloride solution and concentrated to afford a residue of essentially pure methyl (3,4,5-trimethoxyphenyl)propionate. Short-path distillation [90° (0.01 Torr)] gave a pure sample,[8] 242 mg, 93% yield.

The reductions of 2,2,6,6-tetramethylhept-4-en-3-one and methyl cinnamate were studied in some detail. Both Li complex and Na complex give high yields and selective 1,4 reduction with the ketone. Neither reagent gives high yields of methyl 3-phenylpropionate when allowed to react with methyl cinnamate in THF. In this case, a major product (isolated in 20–28% yield) is dimethyl *meso*-3,4-diphenyladipate (**1**).[9] The formation of **1**, an example of hydrodimerization characteristic of electrolytic reduction,[10] and the tendency to form higher molecular weight products

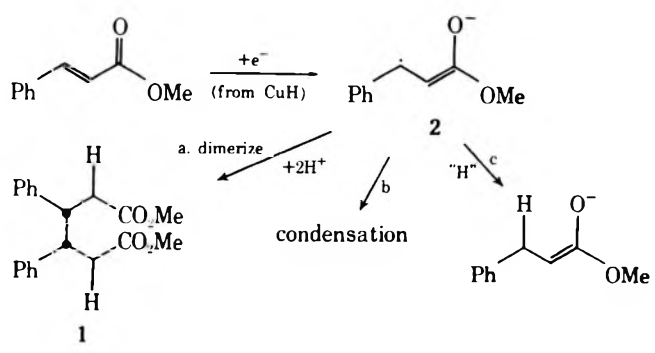
Table I
Reductions with Copper Hydride[a]

Entry	Substrate	CuH complex[b]	Products (% yield)	
1		Li	 (84)	 (3)
2		Li	 (92)	 (6)
3		Li	 (98)[c]	 (2)
4		Li	 (87)	 (12)
5		Na	 (98)[c]	 (1)
6	$PhCOCH{=}CHPh$	Na[d]	$PhCOCH_2CH_2Ph$ (65)[e]	$PHCH(OH)CH{=}CHPh$ (0)
7		Na[d]	(84)	
8		Na	 (92)	
9		Na[d]	 (82)[c]	
10		Na[d]	 (92)[c]	
11	$CH_3C{\equiv}CCO_2Me$	Na[f]	 (29)	
			 (25)	
			 (18)	
12	$PhC{\equiv}CCO_2Me$	Na[f]	 (56)	
			 (21)	
			 (6)	

[a] All reactions were run for 1 hr at −20° according to the general procedure detailed in the text without added 2-butanol unless otherwise noted. The yields were determined by quantitative GPC analysis, after isolation of the crude organic product mixture, using internal standards and pure samples of each of the products for calibration. All reactions were complete unless otherwise noted. [b] Li refers to the Li Complex of eq 1. Na refers to the Na Complex of eq 2. [c] The yield is based on pure material isolated by distillation. [d] The medium contained 15 mol equiv of 2-butanol. [e] The yield is based on starting material not recovered (85% conversion). [f] This reaction was quenched after 15 min at −20°.

may be rationalized by means of an initial electron-transfer step to give an intermediate radical anion, 2. This transient intermediate could account for oligomeric products through preferential coupling (path a) or condensation with the starting ester (path b), instead of the hydrogen transfer (path c) that leads to the desired monomeric reduction product. Consistent with this scheme and previous studies of electron-transfer reactions of enones,[11] addition of 2-butanol (~15 mol equiv) to the reaction mixture tends to favor the simple reduction product.

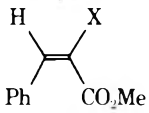
The source of "H" in step c is clearly the hydride originating from the aluminum hydride species in eq 1. For ex-



ample, when the Li complex was prepared from LiAl-$D(OCH_3)_3$[12] and allowed to react with methyl cinnamate, methyl 3-deuterio-3-phenylpropionate was obtained in 20% yield.[13] With same reagent, 2,2,6,6-tetramethylheptenone gave 2,2,6,6-tetramethyl-5-deuterio-3-heptanone in 87% yield.[14] With the Li complex under the usual conditions, but with D_2O being added instead of water during isolation, methyl cinnamate led to 3-phenylpropionate with deuterium only in the α position.[15] These results suggest that the hydrogen added in the β position arises from the copper hydride, while the hydrogen added in the α position results from protons in the medium or added during isolation.

That the 2-butanol acts as a proton donor (and not a hydrogen atom donor, from C-2) was shown by the formation of unlabeled methyl phenylpropionate (82% yield) from reduction of methyl cinnamate in the presence of 2-deuterio-2-butanol.[16] On the other hand, 2-butanol-*O-d* leads to methyl phenylpropionate with 24% deuterium at the α position (~50% labeling of one proton) and <1% deuterium in the β position. The effectiveness of 2-butanol appears to result from selective proton transfer—slow toward the copper hydride but rapid enough toward an intermediate (e.g., 2) to inhibit oligomerization reactions.[17]

Two acetylenic esters undergo successful reduction. The reaction with methyl phenylpropiolate is highly selective for single stage reduction, giving predominately the cis-unsaturated ester upon proteolytic isolation. Consistent with an α-carboxyvinyl metal intermediate (e.g., 4), the yield and geometry of the products depend on temperature and duration of reaction before quenching.[18] Longer reaction times give lower yields and more trans isomer. Quenching with D_2O provides a mixture of *cis*- and *trans*-cinnamates with >98% α deuterium (i.e., 5) from methyl phenylpropiolate and the Na complex.[19,20]



4. X = Cu
5. X = D

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(8) The purity and identity of this compound were established by spectral (^{1}H NMR, ir, mass) and chromatographic (GPC) means.
(9) Compound **1** was identified by interpretation of ^{1}H NMR and mass spectra and by comparison of melting point with the literature value: found mp 174–175°; literature mp 174–175° [D. Y. Curtin and S. Dayagi, *Can. J. Chem.*, **42**, 867 (1964)].
(10) Cf., K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger, J. P. Kaplan, and J. F. Simcone, *J. Am. Chem. Soc.*, **92**, 2800 (1970).
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(12) This compound was prepared from lithium aluminum deuteride and methyl alcohol in tetrahydrofuran. A filtered, titrated solution of lithium aluminum deuteride was employed.
(13) The deuterium was ascertained to be specifically at the β position by ^{1}H NMR analysis, using rare earth shift reagents to separate and simplify the multiplets due to the α- and β-hydrogen atoms. Integration of the NMR signals and abundances of peaks in the molecular ion region of the mass spectrum suggested replacement of one hydrogen by deuterium to the extent of ~85%.
(14) The position of the deuterium in the 2,2,6,6-tetramethyl-5-deuterio-3-heptanone was obvious from the ^{1}H NMR spectrum ($CDCl_3$). The multiplet which appears as a triplet (J = 7.8 Hz) of area 2 at δ 1.50 in 2,2,6,6-tetramethylheptan-3-one now appears as triplet of triplets at δ 1.50, of area 1 1 ($J_{H_\alpha-H_\beta}$ = 7.8 Hz, $J_{H_\beta-D_\beta}$ = 1.0 Hz). The area of the signals (doublet of triplets) due to the α hydrogens is 2.0 (no deuterium incorporation). The relative abundances of ions in the parent ion region of the mass spectrum also indicated the presence of one deuterium in ~90% of the molecules.
(15) The extent of incorporation was low (45% of one hydrogen in the β position), perhaps owing to exchange with aqueous solutions during isolation. The experiment was designed to show the absence of proton (deuteron) delivery to the β position.
(16) The labeled alcohol was prepared by reduction of acetone with lithium aluminum deuteride and contained >96% deuterium at C-2 by NMR analysis.
(17) On the other hand, methyl alcohol is too reactive toward the copper hydride species and drastically decreases the reducing ability, while *tert*-butyl alcohol has no significant effect on the reactions.
(18) Maximum yield is obtained after 15 min at −20° (cis, 55%; trans, 21%) but drops if the reaction is quenched after 30 min at 0° (cis, 14%; trans, 13%).
(19) The extent of deuterium incorporation was determined by NMR spectral analysis, using integration of the signal appearing at δ 5.90 (d, α H, J = 13 Hz, cis isomer), and δ 6.38 (d, α H, J = 16 Hz, trans isomer). Cf., K. Brocklehurst, H. S. Price, and K. Williamson, *Chem. Commun.*, 884 (1968).

(20) We are pleased to acknowledge financial support for this work from the National Institutes of Health (AI-08687).
(21) Recipient of a Camille and Henry Dreyfus Teacher-Scholar Grant (1973–1978).
(22) NIH Postdoctoral Trainee, 1972–1973.

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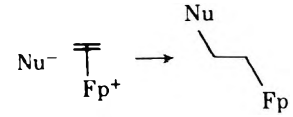
Metal Assisted C—C Bond Formation. Use of a Methyl Vinyl Ketone Complex in Michael Condensations

Summary: Methyl vinyl ketone complexed by $C_5H_5Fe(CO)_2^+$ is shown to be a powerful acceptor of nucleophiles in Michael-type reactions.

Sir: The addition of kinetically generated enolates to vinyl ketones is generally complicated by polymerization of the acceptor component under the aprotic conditions required to minimize proton transfer and consequent equilibration of the donor enolate.[1]

It has recently been shown[2] that the polymerization problem may be resolved through the use of α-silylated vinyl ketones, and a number of such reagents have been successfully employed with regiospecifically generated lithium enolates in ring annelation reactions.[2,3]

Since we had previously reported[4] that enolates of β-dicarbonyls could be condensed with isolated olefins activated by coordination with η^5-$C_5H_5Fe(CO)_2^+$ (eq 1), we were



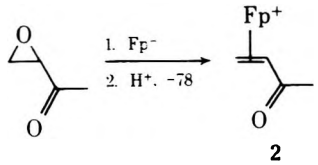
(1)

Fp ≡ η^5-$C_5H_5Fe(CO)_2$

led to consider extension of these reactions to Michael condensations. Moreover, the powerful activating influence exerted upon an olefin by metal complexation left open the possibility that such reactions might also be effected with regiospecifically generated enol derivatives.

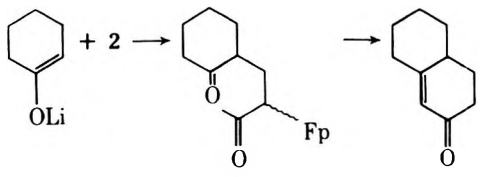
The present paper describes the use of a novel methyl vinyl ketone acceptor component (2) in both electroneutral and cationic Michael-type condensations.

Complex 2, which is readily obtained in high yield from methyl vinyl ketone epoxide[5] following a procedure previously reported[6] may be stored at 0° for prolonged periods. A brief description of its preparation follows. Methyl vinyl ketone epoxide (1.3 g, 15 mmol) was added to an equivalent of $C_5H_5Fe(CO)_2Na$[7] in 30 ml of THF cooled to 0°. After 30 min at 0°, the reaction mixture was cooled to −78° and 30 mmol of HBF_4-Et_2O was added dropwise. The resulting yellow solid was collected and recrystallized from acetone–ether at 0° to give 4.87 g (97%) of 2: ir (KBr) 2092, 2049, 1704 cm^{-1}; NMR (acetone-d_6) τ 3.93 (s, 5, Cp), 4.73 (dd, 1, J = 8, 14 Hz, CH=), 5.32 (d, 1, J = 8 Hz, *cis*-CH_2=), 5.92 (d, 1, J = 14 Hz, *trans*-CH_2=).



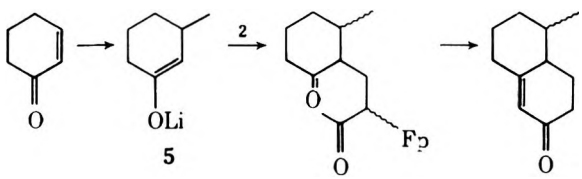
2

The complex cation is an effective and powerful acceptor of nucleophiles. Thus, when acetonitrile solutions of 2 are treated at −78° with cyclohexanone lithium enolate, the adduct (3) is obtained in 45% yield. This substance may be cyclized, with concurrent loss of the Fp group, to the octalones (4,[8] 76%) on refluxing in methylene chloride solutions for 19 hr in the presence of activity I basic alumina. The facile loss of the organometallic group under these relatively mild conditions suggests that cleavage of the metal–carbon bond may be promoted by the acyl group through base attack on the organometallic group and release of an enolate ion.



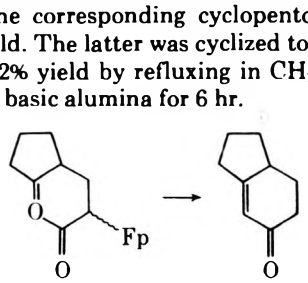
3 4

The regiospecifically generated enolate (5), formed by $LiCuMe_2$ addition to cyclohexenone[10,3a] similarly gave the adduct (6, 70%), as a mixture of diastereomers.[11] Cyclization with 2% KOH in methanol led, as before, to concurrent removal of the Fp group and to the formation of methyl octalones (7,[12] 70%).



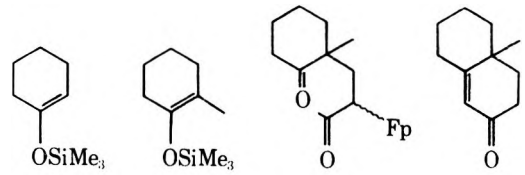
5 6 7

Significantly, complex 2 may serve as an acceptor component with uncharged donors as well. Both cyclohexanone and cyclopentanone enamines react rapidly at 0° with 2 affording 3 or the corresponding cyclopentone adduct (8), both in 85% yield. The latter was cyclized to the hydroindanone (9)[14] in 72% yield by refluxing in CH_2Cl_2 solution in the presence of basic alumina for 6 hr.



8 9

Except in terms of the mildness of reaction conditions, these reactions provide no synthetic advantage over the use of the nonactivated acceptor component in a normal enamine reaction. However, the use of silyl enol ethers as reaction partners with 2 provides a means for carrying out Michael condensations under mild conditions with regiospecifically generated enol derivatives.[16] Thus, cyclohexanone enol silyl ether (10) was found to react at 0° in 2 hr with 2 in acetonitrile solution. Cyclization of the crude adduct (3) in the presence of basic alumina gave 4 in 65% overall yield. The regioisomeric enol silyl ether (11), also added within 1 hr at 0° to 2, affording the methyloctalone (13)[17] in 58% yield, after cyclization of 12 in the presence of basic alumina.



10 11 12 13

Our experience with Fp(olefin) complexes of simple monosubstituted olefins suggests that similar cationic complexes of other vinyl ketones should prove as accessible at 2. The use of these components as well as cationic complexes of cyclic enones and of substituted vinyl ketones as components in metal-assisted Michael reactions is being examined.

Acknowledgment. This work was supported by grants from the National Institutes of Health (GM-16395) and by the National Science Foundation (GP-27991) which are gratefully acknowledged.

References and Notes

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(2) G. Stork and B. Ganem, *J. Am. Chem. Soc.*, **95**, 6152 (1973).
(3) (a) R. K. Boeckman, *J. Am. Chem. Soc.*, **95**, 6867 (1973); **96**, 6179 (1974). (b) G. Stork and J. Singh, *ibid.*, **96**, 6181 (1974).
(4) A. Rosan, M. Rosenblum, and J. Tancrede, *J. Am. Chem. Soc.*, **95**, 3062 (1973).
(5) Prepared in 67% yield, from methyl vinyl ketone and 30% hydrogen peroxide, following the procedure used for the preparation of isophorone oxide [R. L. Wasson and H. O. House, *Org. Synth.*, **37**, 58 (1957)], except that only 20% as much sodium hydroxide solution was used and the product was extracted with $CHCl_3$ rather than ether.
(6) W. P. Giering, M. Rosenblum, and J. Tancrede, *J. Am. Chem. Soc.*, **94**, 7170 (1972).
(7) J. J. Eisch and R. B. King, "Organometallic Syntheses", Vol. 1, Academic Press, New York, N.Y., 1965, p 151.
(8) Obtained as a mixture of $\Delta^{1,9}$ and $\Delta^{9,10}$ isomers, λ_{max}^{EtOH} 239 nm (lit.[10] 239 nm), 2,4-dinitrophenylhydrazone mp 165–167° (lit.[10] mp 168–170°).
(9) G. Stork, A. Brizzolara, H. Landesman, J. Szuskovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
(10) G. H. Posner, *Org. React.*, **19**, 1 (1972).
(11) At least three and possibly all four stereoisomers of 6 are formed, as is indicated by the presence of three cyclopentadienyl proton signals ($CDCl_3$) at τ 5.15, 5.19, and 5.23 in a ratio of 1:1:2.
(12) This material crystallizes on standing to give colorless needles, mp 33.5–34.5°. A 2,4-dinitrophenylhydrazone had mp 181–183 (lit.[13] mp 188–189°).
(13) R. A. Kretchmer and W. M. Schafer, *J. Org. Chem.*, **38**, 95 (1973).
(14) This material showed λ_{max}^{EtOH} 234 nm (lit.[9] 233 nm). Its semicarbazone had mp 214–219° (lit.[15] mp 220°).
(15) V. Prelog and M. Zimmermann, *Helv. Chim. Acta*, **32**, 2360 (1949).
(16) The addition of enol silyl ether to enones in the presence of $TiCl_4$ has recently been reported by K. Narasaka, K. Soai, and T. Mukaiyama, *Chem. Lett.*, 1223 (1974), but the preservation of regiospecificity in these reactions has not been demonstrated.
(17) Semicarbazone mp 198–200° (lit.[18] mp 200–202°).
(18) F. Sondheimer and D. Rosenthal, *J. Am. Chem. Soc.*, **80**, 3995 (1958).

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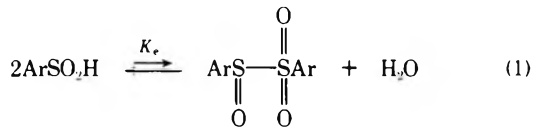
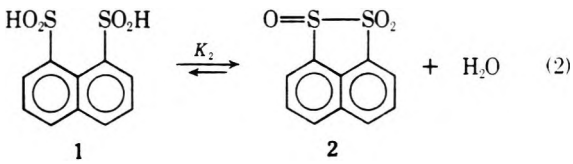
The Naphthalene-1,8-disulfinic Acid–Naphtho[1,8-*cd*]-1,2-dithiole 1,1,2-Trioxide Equilibrium. A Sulfinic Acid–Sulfinyl Sulfone Equilibrium Where the Sulfinyl Sulfone is Strongly Favored Even in Aqueous Solution

Summary: In aqueous dioxane the equilibrium between the cyclic sulfinyl sulfone, naphtho[1,8-*cd*]-1,2-dithiole 1,1,2-trioxide, and naphthalene-1,8-disulfinic acid strongly favors the sulfinyl sulfone; this is in dramatic contrast to the usual situation in aqueous media, where no detectable amount of sulfinyl sulfone can be found in equilibrium with the corresponding sulfinic acid.

Sir: Aryl sulfinyl sulfones, $ArS(O)SO_2Ar$, are the anhydrides of aromatic sulfinic acids.[1] The equilibrium constant for their formation (eq 1) is normally so small that in a medium containing an appreciable amount of water, such as 60% dioxane, the concentration of sulfinyl sulfone present at equilibrium is <0.01% of the concentration of the sulfinic acid.[2] We have now found, however, that in this same solvent in the case of naphthalene-1,8-disulfinic acid (**1**) and the cyclic sulfinyl sulfone **2**, naphtho[1,8-*cd*]-1,2-dithiole 1,1,2-trioxide, the equilibrium (eq 2) strongly favors the sulfinyl sulfone, the equilibrium concentration of **2** being almost three times that of **1**. The evidence for this is outlined in the following paragraphs.



(1)



(2)

1 **2**

A concentrated aqueous solution of sodium naphthalene-1,8-disulfinate (**3**)[5] (synthesized by reaction of hydrogen peroxide anion with the known[7] cyclic thiolsulfonate, naphtho[1,8-*cd*]-1,2-dithiole 1,1-dioxide) was acidified with hydrochloric acid in the expectation that **1** would precipitate. Instead of **1** the sulfinyl sulfone **2** precipitated in ~35% yield.[8] That the isolation of **2** rather than **1** was not the result of a solubility phenomenon but rather because of **2** being favored over **1** at equilibrium was demonstrated in the following way.

Treatment of a very dilute (1.7×10^{-4} *M*) solution of **2** with excess standard sodium hydroxide in 60% dioxane resulted in immediate hydrolysis of **2** to **3**, as evidenced by a change in the uv spectrum from that associated with **2** (curve A, Figure 1) to that for sodium naphthalene-1,8-disulfinate (curve B). This solution of the disulfinate was then acidified with sufficient concentrated perchloric acid to give a solution with $[H^+]$ = 0.01–0.10 *M*. Immediately after acidification, the spectrum of the solution was as shown in curve C. (This is presumably the spectrum associated with naphthalene-1,8-disulfinic acid, **1**.) Upon standing the spectrum of the acid solution initially changed quite rapidly, but after ~60 min at room temperature one observed a final spectrum (curve D) that did not change further with time. This spectrum is very similar to, but not identical with, the spectrum of **2**, and is consistent with that expected for an equilibrium mixture of **1** and **2** in which the majority of the material is present as **2**. The same change was observed when solutions of the disulfinate were added to trifluoroacetate buffers having a pH from 2.81 to 3.81. Kinetic measurements showed that the experimental first-order rate constant for the approach to equilibrium, k_{exptl}, was independent of pH and equal to $2.5 \pm 0.2 \times 10^{-3}$ sec^{-1} at 25°.

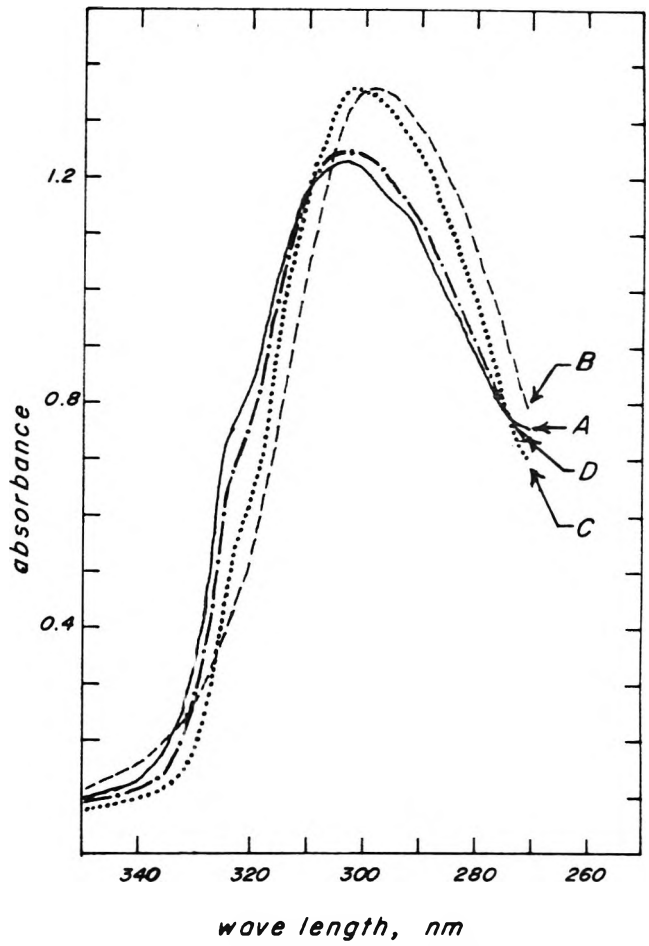
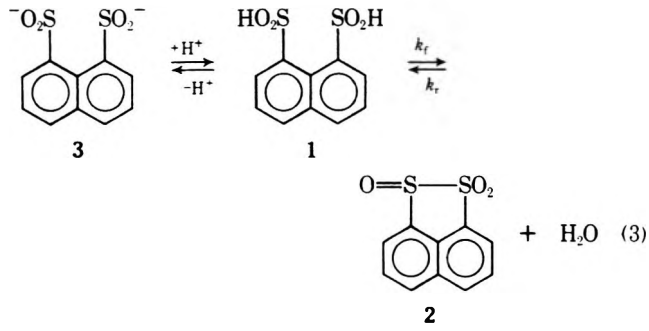


Figure 1. Curve A (——): **2**, 1.7×10^{-4} *M* in dioxane. Curve B (- - - -): **2**, 1.7×10^{-4} *M* in 60% dioxane after addition of sodium hydroxide to hydrolyze **2** to **3**. Curve C (· · · · ·): solution of curve B immediately after addition of sufficient concentrated perchloric acid to give final $[H^+]$ = 0.1 *M*. Curve D (– · – · –): solution of curve C after standing for 60 min at 25°.

When the disulfinate was added to a chloroacetate buffer having a pH of 5.18, there was *no* spectral change indicating the formation of **2**. On the other hand, when **2** was added to this buffer or to more alkaline chloroacetate or formate buffers having pH's from 5.48 to 6.8 a spectral change occurred that indicated that **2** was undergoing irreversible hydrolysis. Its rate of hydrolysis under these conditions contains both a pH-independent term and one whose rate is proportional to the concentration of the buffer anion. The pH-independent term, which is presumably equal to the rate of spontaneous hydrolysis of **2** under these conditions, has a value of $0.7 \pm 0.1 \times 10^{-3}$ sec^{-1}.

These various results are all accommodated by the scheme shown in eq 3. In reasonably acid solutions (pH ≤3.8) **3** is protonated to **1**, and **1** is in equilibrium with **2**, with **2** being markedly favored at equilibrium. The measured rate constant for approach to equilibrium, k_{exptl}, will be equal[9] to $k_f + k_r$. At pH ≥5.2 the hydrolysis of **2** is irreversible because **1** is deprotonated as soon as it is formed. The pH-independent rate of hydrolysis under these conditions should be equal to k_r. From the measured values of $(k_f + k_r)$ and k_r, K_2 (eq 2) is estimated to be 2.6 ± 0.4, indi-



cating that at equilibrium in 60% dioxane the concentration of **2** will be about three times that of **1**.

As noted earlier, a sulfinyl sulfone is the anhydride of the corresponding sulfinic acid. Given the thermodynamics associated with other acid–anhydride equilibria,[10] it is most remarkable, even allowing for the intramolecular nature of sulfinyl sulfone formation in eq 2, that **2** should actually be favored over **1** at equilibrium in aqueous dioxane. It becomes even more striking when one recalls the marked thermal instability of aryl sulfinyl sulfones.[11]

The behavior of the **1** ⇌ **2** equilibrium suggests that the enthalpy difference between $ArSO_2H$ and $ArS(O)SO_2Ar$ in sulfinic acid–sulfinyl sulfone equilibria generally must be considerably less than in usual acid–anhydride equilibria, such as those involving carboxylic acids and their anhydrides. We have confirmed that this is indeed the case by measuring $\Delta H°$ for the reaction $PhS(O)SO_2Ph + H_2O \rightarrow 2PhSO_2H$ in 60% dioxane. This turns out to be only -0.3 ± 2.0 kcal/mol, *far less* than $\Delta H°$ of -14.0 kcal/mol for the hydrolysis of acetic anhydride[10a] or the $\Delta H°$ of -16.3 ± 2.0 kcal/mol that we find for the hydrolysis of phenyl α-disulfone ($PhSO_2SO_2Ph + H_2O \rightarrow PhSO_3H + PhSO_2H$) in 60% dioxane.[12]

These various results and conclusions have a number of important consequences for the chemistry of mono- and disulfinic acids. Reports in the literature of inability to isolate certain disulfinic acids[14a,b] or of their exhibiting peculiar behavior[14c] could well be due to a favorable equilibrium constant for formation of the cyclic sulfinyl sulfone and subsequent decomposition reactions of the sulfinyl sulfone. These points are under further investigation and will be reported in detail in subsequent publications.

Acknowledgment. This research was supported by the National Science Foundation, Grant GP 35927X.

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(2) For a 0.1 *M* solution of *p*-toluenesulfinic acid in acetic acid–5% water containing 0.4 *M* H_2SO_4 the equilibrium concentration of sulfinyl sulfone is 0.08% that of the sulfinic acid.[3] In 60% aqueous dioxane containing 0.10 *M* $HClO_4$ the equilibrium concentration must be at least a factor of 10 lower than this since the sulfinyl sulfone is not detectable spectrophotometrically at equilibrium.[4].
(3) J. L. Kice, G. Guaraldi, and C. G. Venier, *J. Org. Chem.*, **31**, 3561 (1966).
(4) J. L. Kice and G. Guaraldi, *J. Am. Chem. Soc.*, **89**, 4113 (1967).
(5) The identity of this salt was established by oxidation with standard sodium hypochlorite, exactly 2.0 mol required/mol of **3**, to the known[6] compound, sodium naphthalene-1,8-disulfonate.
(6) This has been synthesized (H. Margolis, unpublished results) from 8,8′-dithiodinaphthalene-1-sulfonate[7] by oxidation with potassium permanganate according to the procedure given for the preparation of sodium naphthalene-1,4-disulfonate in *Methoden Org. Chem.* (*Houben-Weyl*), **9**, 245 (1955).
(7) A. Zweig and A. K. Hoffman, *J. Org. Chem.*, **30**, 3997 (1965).
(8) The ir spectrum of **2** showed bands due to the sulfonyl group, at 1320, 1175 and 1140 cm^{-1}, and due to the sulfinyl group, at 1085 cm^{-1}. The presence of the strong sulfonyl group absorption rules out the alternate sulfinic anhydride structure, –S(O)OS(O)–, for **2**. Anal. Calcd: C, 50.42; H, 2.53; S, 26.87. Found: C, 50.29; H, 2.79; S, 26.52.
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(11) J. L. Kice and N. E. Pawlowski, *J. Am. Chem. Soc.*, **86**, 4898 (1964).
(12) The enthalpy changes associated with each of the following reactions were measured in an LKB 8700-1 precision calorimetry system using standard procedures:[13] (1) $PhS(O)SO_2Ph + 2OH^- \rightarrow 2PhSO_2^- + H_2O$; (2) $PhSO_2SO_2Ph + 2OH^- \rightarrow PhSO_3^- + PhSO_2^- + H_2O$; (3) $PhSO_2H + OH^- \rightarrow PhSO_2^- + H_2O$; (4) $PhSO_3H + OH^- \rightarrow PhSO_3^- + H_2O$. The value of $\Delta H°$ for the reaction $PhS(O)SO_2Ph + H_2O \rightarrow 2PhSO_2H$ is equal to $\Delta H_1 - 2\Delta H_3$ and that for $PhSO_2SO_2Ph + H_2O \rightarrow PhSO_3H + PhSO_2H$ is equal to $\Delta H_2 - \Delta H_3 - \Delta H_4$.
(13) We acknowledge helpful assistance from Mr. Wiltshire Johnson and Dr. C. A. Wulff in carrying out the calorimetric measurements.
(14) (a) H. J. Barber and S. Smiles, *J. Chem. Soc.*, 1141 (1928); (b) W. L. F. Armarego and E. E. Turner, *ibid.*, 3668 (1956); (c) *ibid.*, 13 (1957).
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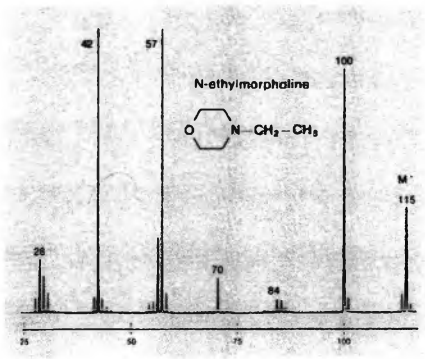

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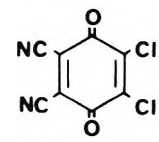
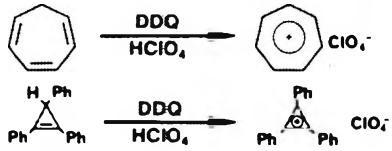
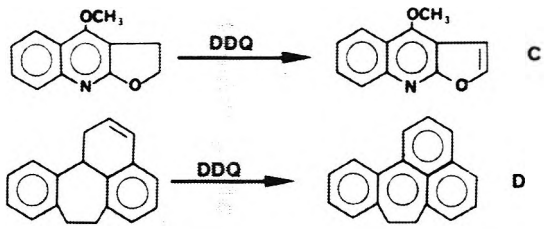


DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), a quinone of high oxidation potential, is often the reagent of choice for dehydrogenation and selective oxidation in organic synthesis. Thus, **DDQ** effects the dehydrogenation of the methano-bridged **A** to give the novel 10π-electron annulene **B** in excellent yield.[1]

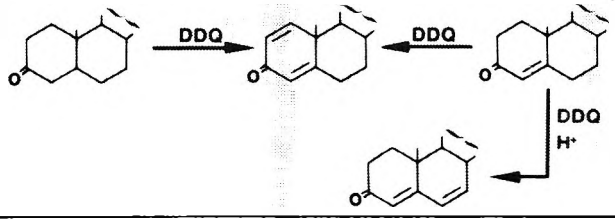
DDQ has been used to prepare salts of stable aromatic cations by oxidation of the parent hydrocarbons [2]



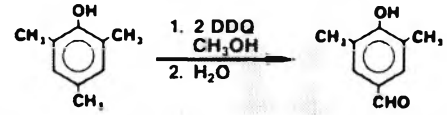
The use of **DDQ** in extending aromatic systems is exemplified by the preparation of dictamnine[3] (**C**) and the hydrocarbon **D**.[4]



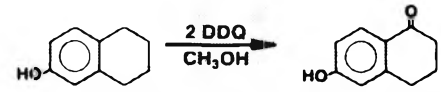
The dehydrogenation of 3-ketosteroids is one example of the extensive use of **DDQ** in the steroid field (for a review, see ref 5). Saturated 3-keto steroids give the corresponding $\Delta^{1,4}$-3-keto derivative,[6,8] while Δ^4-3-ketosteroids yield the same $\Delta^{1,4}$ product under aprotic conditions, and the $\Delta^{4,6}$ diene in the presence of hydrogen chloride[7] or *p*-toluenesulfonic acid.[8]



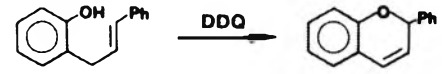
The oxidation of appropriately substituted phenols to quinone methides leads to many useful synthetic applications of **DDQ**. Thus, mesitol is oxidized in methanol to the corresponding *p*-carboxaldehyde by two equivalents of **DDQ**.[9]



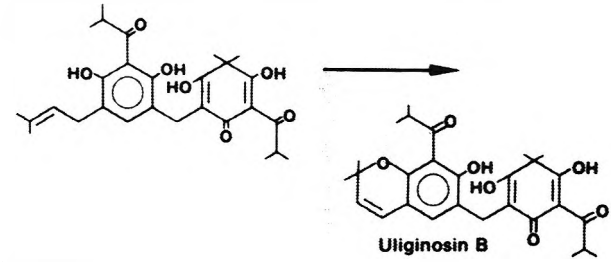
Similarly, 6-hydroxytetralin gives the corresponding tetralone.[10]



o-Alkenylphenols undergo oxidative cyclization to the corresponding ethers.[11]



This cyclodehydrogenation procedure has been applied to the synthesis of uliginosin B.[12]



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1) E. Vogel, W. Klug, and A. Breuer, *Org. Syn.*, **54**, 11 (1974).
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