VOLUME 41 JULY 23, 1976 NUMBER 15 JOCEAH

THE JOURNAL OF Organic Chemistry

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How a letter and a one-word approval in 1918 changed the picture of American chemistry.

In 1918, Dr. C.E.K. Mees, Kodak's first director of research, wrote a letter to George Eastman about a critical situation facing American chemistry.

War had shut off Germany as a supplier of synthetic organic reagents. And the only other American source was a small lab at the University of Illinois.

Dr. Mees said: "The continuance of effective research in pure organic chemistry in this country is largely dependent upon the establishment of a satisfactory source of synthetic reagents. No such source is at present in sight. . . . Unless something is done immediately, organic research will languish . . ."

He proposed establishing a nonprofit Department of Synthetic Chemistry as part of the Eastman Kodak Research Laboratory. George Eastman simply wrote "approved."

After considering the American Chemical Society's first 100 years, we can only repeat the one word that put us in the picture:

"Approved."

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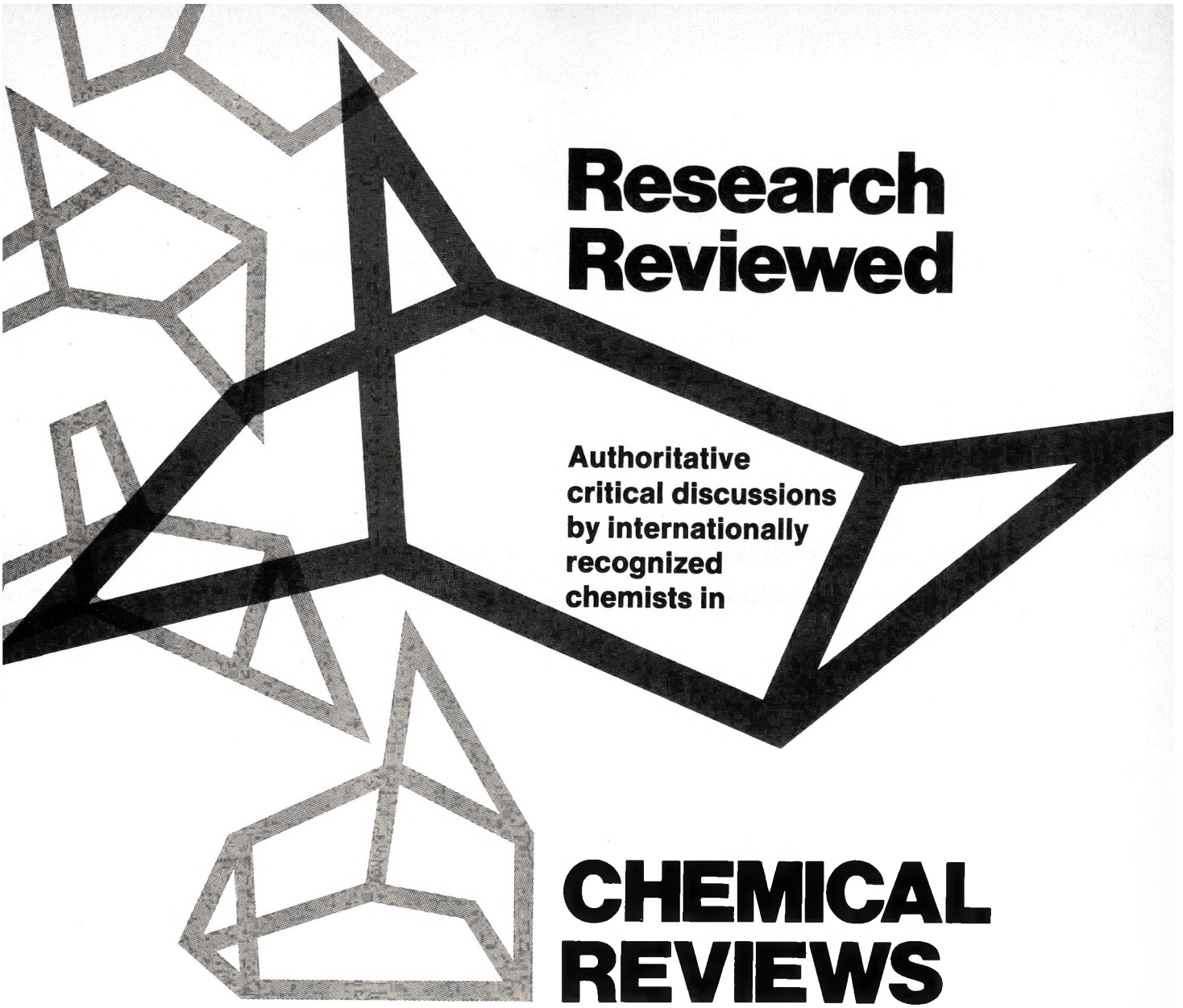

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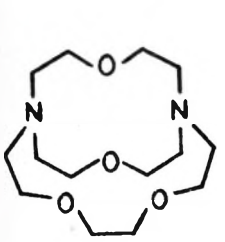

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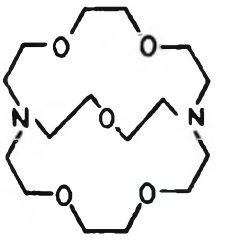

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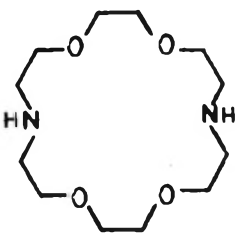

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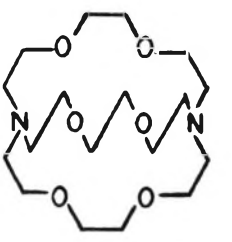

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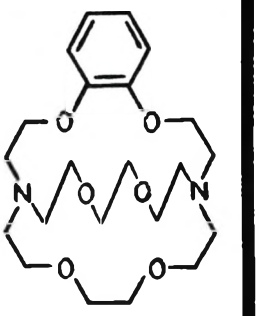


V
Kryptofix® 222B

A GRAVE SUBJECT

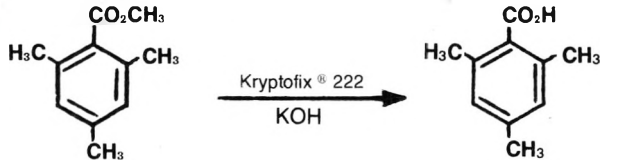
Imagine a chemical tomb; a repository or resting place for ions and small molecules; a sort of molecular vault. What a fascinating idea! In 1969 Dietrich, Lehn, and Sauvage at the Universite Louis Pasteur in Strassbourg, France reported just such a class of compounds. These were the macrobicyclic diamine crown ether crypts I, II and IV. [1,2]

The crypts form stable complexes (cryptates) with alkali and alkaline earth cations[1-7] much like the planar crown ether complexes extensively investigated by Pedersen.[3] X-ray crystallographic studies indicate 1:1 stoichiometry with the metal ion positioned in the center of the ligand cavity and bound to nitrogen as well as the oxygen hetero atoms.[5-7] The rigic three dimensional crypts form much more stable complexes than the crowns as well as giving much greater selectivity between various cations. Table I lists stability constants of various cations with selected crypts[4] and crowns[9] in water at 25°.

TABLE I

Ligand	Log 10 Ks for Cations								
	Li	Na	K	Rb	Cs	Mg	Ca	Sr	Ba
Kryptofix® 222	< 2	3.0	5.3	4.3	< 2	< 2	4.4	8.0	9.5
Kryptofix® 221	2.5	5.3	3.9	2.5	< 2	< 2	6.9	7.3	6.3
Kryptofix® 211	4.3	2.8	< 2	< 2	< 2	-	2.8	< 2	< 2
18 crown 6		0.80	2.03	1.56	0.99	-	0.50	2.72	3.87
15 crown 5		0.70	0.74	0.62	0.8	-	1.95	1.71	
Dicyclohexyl 18 crown 6									
cis syn cis	0.6	1.21	2.02	1.52	0.96				
cis anti cis		0.69	1.63	0.87	0.9				

The cryptates like the crown ether complexes have found synthetic utility as catalysts for promoting reactions which would otherwise be impractical or impossible. For example the hydrolysis of sterically hindered esters is greatly accelerated in the presence of the appropriate crypt or cryptate.

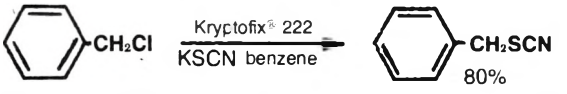


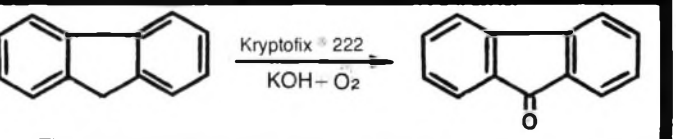
Data for the hydrolysis of methyl mesitoate are illustrated in table II.

TABLE II

Ligand	Solvent	Time	Temp	Yield
none	1-propanol	5 hrs.	75°	0%
dicyclohexyl 18 crown 6	toulene	31 hrs.	74°	58%
Kryptofix® 222	toluene	12 hrs.	25°	80%
Kryptofix® 222	DMSO	2 min.	25°	50%

Although the crown ethers are also effective in catalyzing the reaction it is quite evident that the crypts allow higher yields with shorter reaction times and milder conditions. The reaction of benzyl chloride with potassium thiocyanate in the presence of 0.0001 mole of Kryptofix® 222 in chloroform for 6 days at room temperature gives an 80% yield of benzyl thiocyanate.





The same system without Kryptofix® 222 gives little or no reaction even after 10 days. Fluorene in the presence of potassium hydroxide and catalytic amounts of Kryptofix® 222 (0.0005 moles) in tetrahydrofuran is converted to the fluorenyl anion which may then be converted to fluorenone with oxygen.[10]

The remarkable selective complexing properties of the crypts render them suitable for a wide variety of interesting applications. The crypts are particularly useful in the concentration and separation of lead, silver, thallium, transition metals, actinides, uranium, and platinum.[10] The metals may be resurrected from the concentrated or purified crypt complex by treatment with a proton acid, lewis acid, quarternization of the amine or oxidation to the N-oxide with peracids. Other interesting applications are the selective decorporation of radioactive strontium, biological ion transport studies, and ion selective membrane electrodes. Interesting pharmacological activity has also been reported. For example N-alkylated Kryptofix® 22 compounds reportedly show antitiviral activity against A^2 influenza virus in the Hermann chick fibroblast tissue culture screen.[10] Kryptofix® 222 reportedly inhibits catechol amine induced free fatty acid mobilization which suggests utility in the treatment of diabetes and hyperlipemia.[10]

A host of interesting new developments almost certainly lies ahead. If you can't wait to get started on the next one drop us a line and we will forward a booklet containing additional information to help you along.

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10. J. M. Lehn U. S. Patent 3,888,877 June 10, 1975.

NOTES

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JULY 23, 1976

Synthesis of 4,4,9,17-Tetramethyl-2,6-dithia[7.1]paracyclophane and Isolation of Atropisomeric Forms of the Tetraoxide

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Research Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, New Jersey 07901

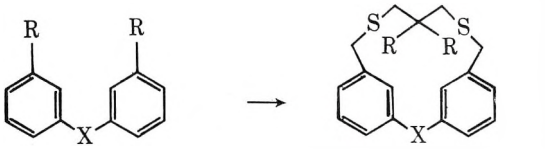
Received February 2, 1976

Unsuccessful attempts were made to synthesize a [5.1]metacyclophane by the Stevens rearrangement of the bissulfonium salts derived from the 2,6-dithia[7.1]metacyclophanes **9, 10, 11,** and **12.** Compound **15b** preferentially underwent a double Sommelet rearrangement in good yield to provide 4,4,9,17-tetramethyl-2,6-dithia[7.1]paracyclophane. The bissulfone derived by oxidation was shown to exist in atropisomeric forms **20** and **19.** These atropisomers, designated *syn*-**20** and *anti*-**19,** were isolated by preparative high-pressure liquid chromatography, and the activation energy of their interconversion to the 50:50 equilibrium mixture determined by the appropriate kinetic measurements.

The chemistry of [2.2]metacyclophanes has been greatly extended using the ready synthetic access provided by the sulfur extrusion procedures of Boekelheide[1-3] and others.[4-6]

When our work commenced these procedures had been used exclusively to prepare [2.2]cyclophanes. It was not evident to us at that time whether they were more generally applicable. Only recently has the sulfone pyrolysis procedure of Vogtle[4] been shown to work well for the preparation of cyclophanes with bridges other than ethano between the aromatic rings.[7]

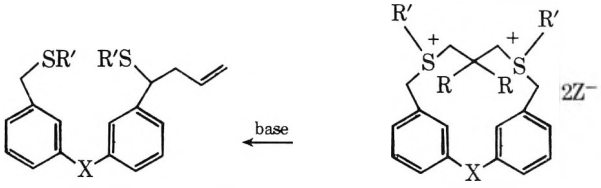
We chose to investigate whether the Stevens rearrangement procedure[1] could be used to prepare other metacyclophanes. In particular, we were interested in [5.1]metacyclophanes, whose aromatic rings are able to adopt the same relationship to one another as those of the dibenzsuberane system. The spatial relationship of the aromatic rings to one another in such bridged diarylmethanes is considered important in the design of antidepressant drugs.[8] A suitable starting material to explore this possibility, the diacid **1,** was readily available from the reaction of benzoic acid, paraformaldehyde, and concentrated sulfuric acid, using the procedure of Schöpff.[9,10] The diacid **1** was esterified, and the dimethyl ester **2** reduced with $LiAlH_4$ to give the known carbinol **3.**[11] This carbinol **3** was in turn converted to the dichloro compound **4.** When this dichloro compound **4** was treated with 1,3-propanedithiol in refluxing ethanolic sodium hydroxide under conditions designed to favor intramolecular reaction, a good yield (83%) of the 2,6-dithia[7.1]metacyclophane **9** was obtained. Chromic acid oxidation of the dichloro compound **4** yielded the corresponding benzophenone **5** which, on reaction with 1,3-propanedithiol under analogous conditions, yielded 2,6-dithia[7.1]metacyclophan-14-one (**10**). Conversion of both these metacyclophane derivatives **9** and **10** to their bissulfonium salts was effected by reaction with Meerwein's salt. Reaction of these sulfonium salts, under conditions described by Boekelheide[1] to favor the Stevens rearrangement, gave products **14a** and **14b,** respectively, based on their NMR spectra. These compounds **14a** and **14b** appeared to be derived from an initial Saytzeff elimination followed by the orbital



1, R = CO_2H; X = CH_2
2, R = CO_2CH_3; X = CH_2
3, R = CH_2OH; X = CH_2
4, R = CH_2Cl; X = CH_2
5, R = CH_2Cl; X = CO
6, R = CH_2SH; X = CO
7, R = CH_2SCN; X = CH_2
8, R = CH_2SH; X = CH_2

9, R = H; X = CH_2
10, R = H; X = CO
11, R = CH_3; X = CO
12, R = CH_3; X = CH_2

R′Z



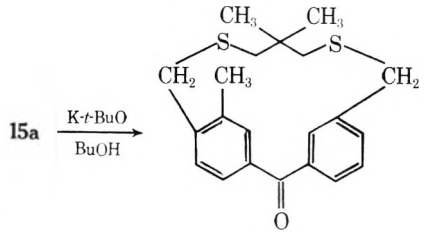
14a, R′ = CH_2CH_3; X = CH_2
14b, R′ = CH_2CH_3; X = CO

13, R = H; R′ = CH_2CH_3; X = CH_2; Z = BF_4
15a, R = R′ = CH_3; X = CO; Z = FSO_3
15b, R = R′ = CH_3; X = CH_2; Z = FSO_3

symmetry allowed rearrangement of the resulting allyl sulfonium ylide.[12]

The dichloro compounds **4** and **5** were converted by standard procedures to the dithiols **8** and **6**. Reaction of these dithiols **8** and **6** with 2,2-dimethyl-1,3-dibromopropane in 2-methoxyethanol containing sodium hydroxide provided the 4,4-dimethylmetacyclophanes **12** and **11** in moderate yields (55 and 48%, respectively). Conversion of these compounds **12** and **11** to the bissulfonium salts **15b** and **15a** was effected by magic methyl.

When the metacyclophanone bissulfonium salt **15a** was allowed to react under Stevens rearrangement conditions a multiplicity of products was obtained. With potassium *tert*-butoxide in *tert*-butyl alcohol a small amount of one crystalline product **16** was isolated and characterized. This compound **16** was derived from two further competing processes,



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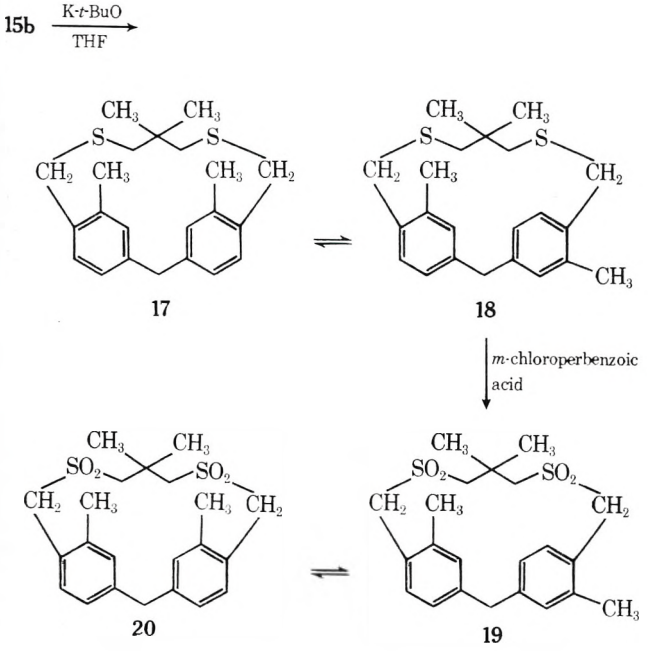
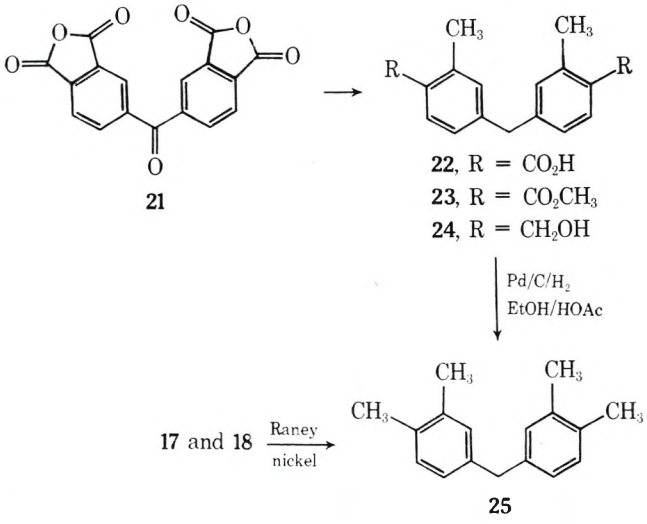


17 18 20 19

i.e., Sommelet rearrangement and transmethylation. On the other hand, reaction of the metacyclophane bissulfonium salt **15b** with potassium *tert*-butoxide in THF provided a good yield (85%) of an oil which was essentially homogeneous, based on TLC evidence. One product was obtained from this oil by direct crystallization. It was evident from the analytical and spectral data that this product was the paracyclophane derivative **18**, derived from a double Sommelet rearrangement of the bissulfonium salt **15b**. Of especial interest was the time-dependent nature of the NMR spectrum of compound **18**. On being allowed to remain in the NMR probe, the intensity of the singlet at δ 0.30 assigned to the *gem*-dimethyl group dropped, and two new singlets appeared, one at δ 0.52 and one above the Me_4Si signal at δ −0.22. Other changes also occurred in the low-field part of the spectrum. Examination of models and inspection of their symmetry properties suggested that the crystalline Sommelet product was the anti atropisomer **18** which, on solution, slowly equilibrated via bond rotation to a syn/anti mixture. The syn atropisomer **17**, in which the *gem*-dimethyl group is no longer symmetrical with respect to the aromatic rings, presumably favors a conformation with one of the methyl groups oriented within the ring. Such a conformation would permit shielding of this methyl group by the aromatic rings and thus account for a chemical shift above Me_4Si signal. Furthermore, it was then evident, based on the NMR spectrum, that the original oil from the reaction of the bissulfonium salt **15b** with potassium *tert*-butoxide was essentially a mixture of the syn and anti atropisomers **17** and **18**.

It seemed surprising that the bissulfonium salt **15b**, instead of undergoing a double Stevens rearrangement which would have given the relatively strain-free [5.1]metacyclophane, gave instead the highly rigid 4,4,9,17-tetramethyl-2,6-dithia[7.1]-paracyclophane **17/18**. Additional proof for the structural assignment was therefore sought. Desulfurization of the product mixture **17/18** using Raney nickel yielded a crystalline hydrocarbon whose melting point was essentially identical with that reported in the literature for 1,1′-methylenebis(3,4-dimethylbenzene) (**25**).[13] Unfortunately, the method of synthesis previously used to prepare this compound **25** was ambiguous. We therefore chose to synthesize the hydrocarbon **25** from the commercially available 3,3′,4,4′-benzophenone tetracarboxylic anhydride (**21**), which has the appropriate



21 25

carbon skeleton. High-pressure hydrogenation gave, surprisingly, a single diacid **22** whose structure was assigned from the NMR spectrum. The spectrum indicated that the molecule was symmetrical about the methylene group and the low-field aromatic proton, i.e., next to the carboxyl group, had an ortho coupling. The carboxyl groups of the diacid **22** were converted by standard procedures to methyl groups. The resulting crystalline hydrocarbon **25** was identical in all respects with that derived from the desulfurization of the dithia[7.1]-paracyclophanes **17** and **18**.

We made several attempts to obtain a pure sample of the syn paracyclophane **17** but the low energy barrier to interconversion of **17** and **18** created experimental problems. We therefore oxidized the mixture of atropisomers **17** and **18** to the corresponding bissulfones **20** and **19**. In a somewhat analogous case of the 3,13-dioxa-8-thia-2,14-dioxo[15]paracyclophane, oxidation to the sulfone increased the activation energy to internal rotation of the aromatic ring by nearly 3 kcal/mol.[14] In our case the increase in conformational stability now permitted separation of the syn and anti atropisomers **20** and **19** by means of preparative high-pressure liquid chromatography and their complete characterization. Assignment of the anti structure **19** to the higher melting atro-

Table I. Eyring/Arrhenius Plot Data

Temp, °C	$1/T$, K × 10^{-3}	k, s^{-1} × 10^{-4}	Ln k/T
70	2.914	0.740	−1.535
80	2.832	1.934	−1.442
90	2.754	5.673	−1.337

Table II. Thermodynamic Parameters for the Equilibration

E_a	25.2 ± 1.2 kcal/mol
$\Delta H^{\ddagger}$	24.5 ± 1.2 kcal/mol
$\Delta S^{\ddagger}$	−6.4 ± 3.5 eu

pisomer was possible from the NMR spectrum. The *gem*-dimethyl group was a singlet in contrast to the lower melting syn atropisomer **20** where it was a doublet. In neither case, though, were the chemical shifts of the methyl groups anomalous, and therefore the methyl groups are presumably oriented away from the center of the ring. Interrelationship between the sulfides and sulfones was obtained directly by oxidation of the crystalline *anti*-dithia[7.1]paracyclophane **18** to the higher melting anti bissulfone **19.**

With the separate crystalline atropisomers **20** and **19** in hand, an estimate of the barrier to their interconversion, i.e., the internal rotation of one aromatic ring, was obtained from kinetic data. A preliminary estimate was made by studying the rate of convergence of the NMR spectra of compounds **19** and **20** when heated at 100 °C in DMF. The position of equilibrium was also established by this experiment as being, not surprisingly, 50:50. It is evident from models that whether the aromatic methyl groups are on the same or opposite sides of the ring there are no serious steric interactions. A more precise estimate of the activation energy to interconversion of compounds **19** and **20** was obtained by use of analytical high-pressure liquid chromatography to measure the rate of conversion of the higher melting anti atropisomer **19** to the equilibrium mixture at 70, 80, and 90 °C. From an Arrhenius and Eyring plot the appropriate activation parameters were obtained (Table II).

This type of isomerism, designated atropisomerism,[15] has long been known for hindered diphenyl derivatives.[16] In these cases, though, as in other cases of restricted rotation in diphenyls, the barrier to interconversion appears to be due to ortho/ortho′ substituent interaction.[17] In our case of the interconversion of compounds **19** and **20,** it appears to be, based on models, due to the transannular interaction of the ortho H atom with the methylene group between the sulfone and the *gem*-dimethyl group. Whatever the reason, the 2,6-dithia[7.1]paracyclophane ring system does appear to be capable of an unusual type of isomerism which permits isolation and characterization of stable atropisomers. Recently, several other examples of stable atropisomers have been provided by the work of Oki.[18]

The very elegant work of Mislow[19] may also be regarded as a logical extension of the stereochemical possibilities created by restricted rotation about carbon–carbon single bonds.

The failure of the Sevens rearrangement to provide the [1.5]metacyclophane[20] is understandable in the light of the radical pair mechanism proposed for the Stevens rearrangement.[21] This mechanism requires a homolytic cleavage in the ylide as the rate-determining step. Thus, both carbons of the new bond to be formed must be attached to stabilizing functionality, i.e., to facilitate ylide formation in one direction and homolysis in the other. The Stevens rearrangement is therefore well suited to the preparation of [2.2]cyclophanes where both carbon atoms of the new bond are benzylic. Its use in other situations seems extremely limited in view of these structural requirements and the other reaction pathways open to sulfonium salts on treatement with base, as is evident from our work.

Experimental Section[22]

3,3′-Methylenedi(benzyl alcohol) (3). This substance, mp 42–43 °C, was prepared by the $LiAlH_4$ reduction, by the procedure of LeBlanc,[11] of the dimethyl ester **2** of the diacid **1** obtained by the concentrated H_2SO_4 catalyzed condensation of paraformaldehyde and benzoic acid by the procedure of Schöpff.[9,10,23]

1,1′-Methylenebis(3-chloromethylbenzene) (4). Thionyl chloride (19 g, 0.16 mol) was added to benzene (100 ml) containing 3 drops of pyridine. 3,3′-Methylenedi(benzyl alcohol) (**3,** 15 g, 0.066 mol) dissolved in benzene was added slowly with stirring. The mixture was refluxed for 2 h. The benzene was removed. The residue was redissolved in ether. The ether solution was washed (10% aqueous $KHCO_3$, brine), dried ($MgSO_4$), and concentrated to dryness. The residue was distilled in vacuo. The main fraction was the bis(chloromethyl) compound **4** (11.65 g, 67% yield): bp 157–162 °C (0.2 mm); NMR δ 7.22 (s, 8), 4.50 (s, 4), 3.98 (s, 2); ir (film) 1604 (m), 1590 (m), 1488 (m), 1444 (s), 1264 (s), 700 cm^{-1} (s).

Anal. Calcd for $C_{15}H_{14}Cl_2$: C, 67.93; H, 5.32. Found: C, 68.05; H, 5.60.

2,6-Dithia[7.1]metacyclophane (9). 1,1′-Methylenebis(3-chloromethylbenzene) (**4,** 6.35 g, 24 mmol) was dissolved in an ethanol/benzene mixture (200 ml of a 4:1 mixture). Propane-1,3-dithiol (2.87 g, 26 mmol) and NaOH (2 g, 50 mmol) were dissolved in 95% ethanol (200 ml). Both solutions were added simultaneously and dropwise to refluxing ethanol (600 ml) under N_2. The addition took 2 h. The mixture was refluxed for a further 1 h. The solvents were removed in vacuo. The residue was dissolved in chloroform and water. The chloroform layer was separated, washed (brine), dried ($MgSO_4$), and concentrated to dryness. The waxy solid was recrystallized from 2-propanol/ether to give 2,6-dithia[7.1]metacyclophane (**9**): mp 92–94 °C (6.0 g, 83% yield); NMR δ 7.28–6.88 (m, 8), 3.94 (s, 2), 3.58 (s, 4), 2.12 (t, 4), 1.56–1.06 (m, 2); ir (Nujol) 1600 (m), 1580 (m), 1232 (m), 714 cm^{-1} (s); MS *m/e* 300 (M^+).

Anal. Calcd for $C_{18}H_{20}S_2$: C, 71.98; H, 6.71. Found: C, 72.42; H, 6.96.

2,6-Dimethyldithia[7.1]metacyclophane-2,6-bis(thiaonium tetrafluoroborate) (13). The dithia[7.1]metacyclophane **9** (1 g, 3.3 mmol) was dissolved in methylene chloride (5 ml). Triethyloxonium tetrafluoroborate (1.4 g, 7.3 mmol) was added as a solid with stirring. After 2 h at room temperature the methylene chloride was decanted from an insoluble gum which had separated. The gum was crystallized from ethanol to give the bissulfonium salt **13,** mp 168 °C dec (1.7 g, 97% yield).

Anal. Calcd for $C_{22}H_{30}B_2F_8S_2$: C, 49.64; H, 5.68. Found: C, 49.73; H, 5.85.

Reaction of the Bissulfonium Salt 13 with NaH. The bissulfonium salt **13** (1.6 g, 3 mmol) was added to a slurry of sodium hydride (derived from washing 1.26 g of 57% NaH in oil, 30 mmol) under N_2. The mixture was stirred at room temperature for 24 h. Ice was added to decompose excess NaH. The mixture was partially concentrated in vacuo, and then extracted (ether). The combined extracts were washed (brine) and dried ($MgSO_4$). Removal of the ether gave a yellow oil [0.9 g, NMR δ 5.90–4.70 (m, ~2), 3.28 (d, <1)]. This material consisted mainly of compound **14a.**

3,3′-Bis(chloromethyl)benzophenone (5). 1,1′-Methylenebis(3-chloromethylbenzene) (**4,** 2.65 g, 0.01 mol) was dissolved in a 1:1 mixture of acetic anhydride and CCl_4 (40 ml). Chromic anhydride (2 g, 0.02 mol) was added with stirring at room temperature. After 3 h water (350 ml) was added. The mixture was extracted (ether). The ethereal extract was washed (10% aqueous $KHCO_3$, brine) and dried ($MgSO_4$). Removal of the ether gave a solid which was recrystallized from ether to give 3,3′-bis(chloromethyl)benzophenone (**5,** 1.8 g, 64% yield): mp 114–116 °C; ir (Nujol) 1660 (s), 1604 (m), 1310 (m), 1262 (m), 1186 (m), 702 cm^{-1} (s); uv (MeOH) 253 nm (ε 17 900).

Anal. Calcd for $C_{15}H_{12}Cl_2O$: C, 64.53; H, 4.33. Found: C, 64.45; H, 4.23.

3,3′-Bis(mercaptomethyl)benzophenone (6). 3,3′-Bis(chloromethyl)benzophenone (**5,** 10 g, 35.8 mmol) was dissolved in ethanol (200 ml). Thiourea (6.2 g, 81.5 mmol) was added and the mixture refluxed for 16 h. The reaction mixture was concentrated to half volume in vacuo and then diluted with ether. On standing a solid separated, which was collected. This solid (13.6 g, mp 163–8 °C) was refluxed in 10% aqueous NaOH (100 ml) for 3 h under N_2. The cooled solution was extracted (ether), made acid (2 N HCl), and reextracted (ether). The latter ethereal extracts were combined, washed (brine), and dried

($MgSO_4$). Removal of the ether yielded a solid which was recrystallized from ether to give 3,3′-bis(mercaptomethyl)benzophenone (**6**, 6.9 g, 70% yield): mp 95–96 °C; NMR δ 7.84–7.24 (m, 8), 3.78 (d, 4, J = 8 Hz), 1.82 (t, 2); ir (Nujol) 1644 (s), 1600 (s), 1580 (m), 1302 (s), 1290 (s), 1180 (m), 700 cm^{-1} (m); uv (MeOH λ_{max} 225 nm (ε 15 790).

Anal. Calcd for $C_{15}H_{14}OS_2$: C, 65.69; H, 5.15. Found: C, 65.75; H, 5.47.

2,6-Dithia[7.1]metacyclophan-14-one (10). 3,3′-Bis(chloromethyl)benzophenone (**5**, 1.6 g, 5.8 mmol) was dissolved in a 3:1 ethanol/benzene mixture (180 ml). This solution was added dropwise to refluxing ethanol (400 ml) to which was being added dropwise a solution of 1,3-propanedithiol (0.626 g, 6.0 mmol) and NaOH (0.48 g, 11.6 mmol) in 95% ethanol (180 ml). Addition of the two solutions took 1 h. The mixture was refluxed for a further 4 h. The solvents were removed in vacuo and the residue redissolved in methylene chloride. This solution was washed (2 N HCl, brine), dried ($MgSO_4$), and concentrated to dryness. The residue (1.6 g) was recrystallized from ethanol to give 2,6-dithia[7.1]metacyclophan-14-one (**10**, 1.41 g, 77% yield): mp 87–89 °C; NMR δ 8.0–7.20 (m, 8), 3.70 (s, 4), 2.56 (t, 4), 2.02–1.48 (quintet, 2); ir (Nujol) 1656 (s), 1600 (m), 1580 (m), 1314 (s), 1284 (s), 976 (m), 730 cm^{-1} (s); uv (MeOH) λ_{max} 253 nm (ε 14 120).

Anal. Calcd for $C_{18}H_{18}OS_2$: C, 68.78, H, 5.77. Found: C, 68.47; H, 6.00.

Attempted Stevens Rearrangement on 2,6-Dithia[7.1]metacyclophan-14-one (10). 2,6-Dithia[7.1]metacyclophan-14-one (**10**, 1 g, 2.2 mmol) was dissolved in methylene chloride (20 ml). With stirring at room temperature triethyloxonium fluoroborate (1.3 g, 6.8 mmol) was added. A thick gum slowly separated. The methylene chloride was removed. Tetrahydrofuran and NaH (0.72 g, 30 mmol) were added. The mixture was stirred for 16 h and concentrated to dryness and the residue was partitioned between methylene chloride and water. The methylene chloride layer was washed (water), dried ($MgSO_4$), and concentrated to dryness. The residue (1.2 g) was put onto an alumina column (neutral III) made up in hexane. A major fraction (360 mg) was eluted by benzene. This was concluded to be principally the rearranged Saytzeff elimination product **14b** based on spectral data: MS m/e 370 (M^+) 329 ($M - CH_2CH{=}CH_2$); NMR δ 7.75–6.9 (m, 8), 5.95–5.30 (m, 1), 5.17–4.72 (d of m, 2), 4.05–3.65 (m, 1), 3.72 (s, 2), 2.80–2.06 (sextet, 6), 1.38–0.95 (sextet, 6).

4,4-Dimethyl-2,6-dithia[7.1]metacyclophan-14-one (11). 3,3′-Bis(mercaptomethyl)benzophenone (**6**, 3 g, 11 mmol) was dissolved in 2-methoxyethanol (100 ml). This solution was added during 1.5 h to refluxing 2-methoxyethanol (800 ml), to which was being added at the same time a solution of sodium hydroxide (0.9 g, 22 mmol) and 2,2-dimethyl-1,3-dibromopropane (2.53 g, 11 mmol) in 2-methoxyethanol (100 ml). After completion of the addition refluxing was continued for a further 1.5 h. The 2-methoxyethanol was removed in vacuo and the residue partitioned between ether and water. The ethereal layer was washed (brine), dried ($MgSO_4$), and concentrated to dryness. The resulting oil (3.5 g) crystallized slowly and was recrystallized from ether to give 4,4-dimethyl-2,6-dithia[7.1]metacyclophan-14-one (**11**, 2.17 g, 58% yield): mp 103–105 °C; NMR δ 8.00–7.25 (m, 8), 3.70 (s, 4), 2.66 (s, 4), 1.00 (s, 6); ir (Nujol) 1672 (s), 1586 (m), 1320 (s), 746 cm^{-1} (s); uv (MeOH) 249 nm (ε 14 730).

Anal. Calcd for $C_{20}H_{22}OS_2$: C, 70.16; H, 6.48. Found: C, 70.39; H, 6.60.

Attempted Stevens Rearrangement of 4,4-Dimethyl-2,6-dithia[7.1]metacyclophan-14-one (11). 4,4-Dimethyl-2,6-dithia[7.1]metacyclophan-14-one (**11**, 0.8 g, 2.34 mmol) was dissolved in methylene chloride (30 ml) and cooled to −60 °C. Methyl fluorosulfonate (0.6 g, 5.15 mmol) in methylene chloride (5 ml) was added with stirring and the mixture allowed to warm to room temperature. Ethyl acetate (30 ml) was added. A solid **15a** (1.1 g, mp 125–127 °C) separated and was collected. The bulk of this precipitate (0.98 g, 1.7 mmol) was added to a solution of potassium *tert*-butoxide (1 g, 8.9 mmol) in *tert*-butyl alcohol (40 ml). The mixture was stirred at room temperature for 66 h. The *tert*-butyl alcohol was removed in vacuo, and the residue partitioned between water and ether. The ether was washed (brine), dried ($MgSO_4$), and removed. The residue (0.45 g) was subjected to preparative TLC (silica GF/benzene). The major band (200 mg) was eluted as a crystalline compound. This material was recrystallized to give compound **16**: mp 137–138 °C; NMR δ 7.92 (pr of t, J = 7 Hz), 7.52–6.90 (m, 7), 3.78 (q, 2, J = 13 Hz), 3.62 (s, 2), 2.44 (s, 3), 2.30 (q, 4, J = 13 Hz), 0.90 (s, 3), 0.82 (s, 3); ir (Nujol) 1680 (s), 1576 (m), 1276 (s), 1172 (m), 712 cm^{-1} (m); uv λ_{max} (MeOH) 251 nm (ε 12 800); MS m/e 356 (M^+).

Anal. Calcd for $C_{21}H_{24}OS_2$: C, 70.76; H, 6.79. Found: C, 70.59; H, 6.49.

1,1′-Methylenebis(3-thiocyanomethylbenzene) (7). 1,1′-Methylenebis(3-chloromethylbenzene) (**4**, 10.6 g, 0.04 mol) was added along with potassium thiocyanate (8.8 g, 0.088 mol) to 95% ethanol (200 ml). The mixture was refluxed for 4 h. A solid slowly separated. The ethanol was removed. The residue was dissolved in methylene chloride. The methylene chloride solution was washed (water), dried ($MgSO_4$), and removed in vacuo. The resulting solid was recrystallized from methanol to give 1,1′-methylenebis(3-thiocyanomethylbenzene) (**7**, 9.6 g, 77% yield): mp 60–62 °C; NMR δ 7.35–7.00 (m, 8), 4.02 (s, 4), 3.94 (s, 2); ir (Nujol) 2148 (s), 1600 (m), 1586 (m), 1254 (m), 708 (s), 700 cm^{-1} (s).

Anal. Calcd for $C_{17}H_{14}N_2S_2$: C, 65.80; H, 4.55; N, 9.03. Found: C, 66.02; H, 4.75; N, 8.73.

4,4-Dimethyl-2,6-dithia[7.1]metacyclophane (12). 1,1′-Methylenebis(3-thiocyanomethylbenzene) (**7**, 21.1 g, 0.068 mol) was dissolved in ether and added to ether containing $LiAlH_4$ (5.0 g, 0.135 mol). The mixture was refluxed for 2 h and added to excess saturated potassium sodium tartrate solution. The resulting solids were removed by filtration and washed with ether. The ethereal layer was separated, washed (brine), dried ($MgSO_4$), and concentrated to dryness. The resulting oil (17.7 g, 0.068 mol, 100% yield) crystallized slowly in the refrigerator: NMR δ 7.08 (s, 8), 3.88 (s, 2), 3.62 (d, 4, J = 7 Hz), 1.66 (t, 2, J = 7 Hz). The crude dithiol 8 was dissolved in 2-methoxyethanol (100 ml) and added to a solution of NaOH (5.4 g, 0.136 mol) in 2-methoxyethanol (200 ml). This solution was added dropwise to refluxing 2-methoxyethanol (1500 ml) to which 1,3-dibromo-2,2-dimethylpropane (15.64 g, 0.068 mol) dissolved in 2-methoxyethanol (250 ml) was being added at the same rate. After addition was completed (5 h), the mixture was refluxed for a further 4 h and allowed to stand overnight. 2-Methoxyethanol was removed in vacuo. The residue was partitioned between ether and water. The ethereal layer was separated, washed (brine), dried ($MgSO_4$), and concentrated to dryness. The residue was recrystallized from ether to give 4,4-dimethyl-2,6-dithia[7.1]metacyclophane (**12**, 10.8 g, 48% yield): mp 100–102 °C; NMR δ 7.40–6.90 (m, 8), 3.94 (s, 2), 3.56 (s, 4), 2.18 (s, 4), 0.88 (s, 6); ir (Nujol) 1602 (m), 1590 (m), 1282 (m), 1224 (m), 920 (m), 716 (s), 704 cm^{-1} (s).

Anal. Calcd for $C_{20}H_{24}S_2$: C, 73.14; H, 7.37. Found: C, 73.32; H, 7.23.

2,4,4,6-Tetramethyl[7.1]metacyclophane-2,6-bis(thiaonium fluorosulfonate) (15b). 4,4-Dimethyl-2,6-dithia[7.1]metacyclophane (**12**, 410 mg, 1.25 mmol) was dissolved in methylene chloride (2 ml) and the solution cooled to −50 °C. Methyl fluorosulfonate (330 mg, 2.75 mmol) in cooled methylene chloride (3 ml) was added dropwise with stirring. After stirring for 1 h to room temperature, ethyl acetate (3 ml) was added. The crystalline precipitate (607 mg, 87% yield) of the bissulfonium salt **15b**, mp 190 °C dec, was collected.

Anal. Calcd for $C_{22}H_{30}F_2O_6S_4$: C, 47.46; H, 5.43. Found: C, 47.50; H, 5.55.

4,4,9,17-Tetramethyl-2,6-dithia[7.1]paracyclophane (17/18). The bissulfonium salt **15** (460 mg, 0.83 mmol) was added to a solution of potassium *tert*-butoxide (250 mg, 1.66 mmol) in dry tetrahydrofuran (60 ml) with stirring. Stirring was continued for 30 min at room temperature. The tetrahydrofuran was removed in vacuo. The residue was dissolved in methylene chloride. The solution was washed (water, brine), dried ($MgSO_4$), and concentrated to dryness. The residue (253 mg, 85% recovery) partially crystallized. Recrystallization from ethanol/benzene gave *anti*-4,4,9,17-tetramethyl-2,6-dithia[7.1]paracyclophane (**18**, 80 mg, 27% yield): mp 150–151 °C; NMR δ 7.10–6.76 (m, 6), 3.74 (s, 2), 3.62 (q, 4, J = 14 Hz), 2.24 (s, 6), 1.36 (q, 4, J = 13 Hz), 0.30 (s, 6); ir (Nujol) 1602 (m), 1156 (s), 816 (m), 740 (m), 718 cm^{-1} (s); uv λ_{max} (MeOH) 248 nm (ε 680); MS m/e 356 (M^+).

Anal. Calcd for $C_{22}H_{28}S_2$: C, 70.73; H, 7.92. Found: C, 71.07; H, 7.53.

On warming the NMR solution (45–50 °C), the most striking change is the diminution of the signal at δ 0.30 and the appearance of two new singlets at δ 0.52 and −0.22. Other more complex changes take place in the lower field part of the spectrum.

Desulfurization of 4,4,9,17-Tetramethyl-2,6-dithia[7.1]paracyclophane (17/18). The dithia[7.1]paracyclophane **17/18** (188 mg, 0.53 mmol) was refluxed in ethanol (180 ml) with Raney nickel suspension (20 ml) for 18 h. The Raney nickel was removed and the filtrate concentrated to dryness. The residue (72 mg, 61% recovery) was analyzed by VPC on a Chromosorb (AW-DMCS) column with a UCW-98 coating. Three peaks were obtained, retention time 2.6 (8.2%), 3.9 (86.6%), 7.1 min (5.2%). The retention time 3.9 min material was identified by comparison with authentic 1,1′-methylenebis(3,4-dimethylbenzene). The residue was distilled in a short tube in a hot block at 0.2 mm. The bulk of the material distilled to give a colorless liquid (42 mg) which slowly crystallized on cooling. This was recrystallized from petroleum ether (40–60 °C)/ethanol to give 1,1′-methylenebis(3,4-dimethylbenzene) (12 mg, **25**): mp (34–35 °C (lit.[13] 35–36 °C); no depression of melting point on admixture with material prepared by unambiguous synthesis (see below); identical NMR and mass

spectra.

Synthesis of Authentic 1,1′-Methylenebis(3,4-dimethylbenzene) (25). 3,3′,4,4′-Benzophenone tetracarboxylic dianhydride (**21**, Aldrich, 6 g, 18.6 mmol) was dissolved in a 1:1 mixture of ethanol and acetic acid (120 ml). Pd/C catalyst (7 g, 10%) was added and the mixture hydrogenated in a Parr apparatus at 55 °C for 3 h at 45 psi. A fall in pressure was observed. The catalyst was removed and the filtrate concentrated to dryness. The residue was dissolved in ether and extracted with 10% aqueous $KHCO_3$ solution (three times). The bicarbonate washings were acidified and reextracted (ether). Removal of the ether gave a solid (4.7 g), mp 236–239 °C. This solid was suspended in methanol (50 ml), concentrated H_2SO_4 (3 ml) was added, and the mixture was refluxed for 4 h. The methanol was removed. The residue was dissolved in ether, washed (water, 10% $KHCO_3$, and brine), dried ($MgSO_4$), and concentrated to dryness. The residue (4.2 g) was distilled. The main fraction was dimethyl 4,4′-methylenebis(*o*-toluate) (**23**): bp 173 °C (0.2 mm) (3.8 g, 65% yield, based on the bis anhydride); NMR δ 7.80 (d, 2, J = 9 Hz), 7.20–6.90 (m, 4), 3.92 (s, 2), 3.84 (s, 6), 2.55 (s, 6); ir (film) 1724 (s), 1612 (m), 1572 (m), 1440 (s), 1260 (s), 1200 (s), 1082 (s), 780 cm^{-1} (m); uv (MeOH) λ_{max} 237 nm (ϵ 20 370), 284 (2790).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.07; H, 6.71.

The dimethyl ester **23** (3.8 g, 12.2 mmol) was dissolved in ether (20 ml) and added to a slurry of $LiAlH_4$ (1.5 g) in ether (100 ml). The mixture was refluxed for 2 h. The excess $LiAlH_4$ decomposed with saturated potassium sodium tartrate. The mixture was filtered through Celite. The Celite was washed with ether. The ethereal filtrate was dried ($MgSO_4$) and concentrated to dryness. The residue (3.03 g, 97% yield) crystallized on standing. A portion (~⅓) was recrystallized from 2-propanol to give 1,1′-methylenebis(3-methyl-4-hydroxymethylbenzene) (**24**): 0.91 g; mp 93–95 °C; NMR δ 7.25–6.80 (m, 6), 4.44 (s, 4), 3.80 (s, 2), 2.50 (s, 2 exch), 2.16 (s, 6); ir (Nujol) 3350–3250 (s), 1040 (s), 1020 (s), 846 (m), 822 (m), 750 cm^{-1} (m).

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.69; H, 8.02.

The dibenzyl alcohol **24** (3 g, 11.7 mmol) was dissolved in a 1:1 mixture of ethanol/acetic acid (80 ml). Pd/C (3 g, 10%) was added and the mixture hydrogenated in a Parr apparatus at 55 °C and 42 psi for 5 h. The mixture was passed through Celite. The filtrate was concentrated to dryness and the residue (1.8 g, 69%) distilled in a short-path apparatus. The principal fraction, bp 108 °C (0.2 mm), was 1,1′-methylenebis(3,4-dimethylbenzene) (**25**): mp 34–35.5 °C (petroleum ether/ethanol) (lit.[13] mp 35–36 °C); NMR δ 6.94 (s, 6), 3.84 (s, 2), 2.20 (s, 12); ir (film) 1612 (m), 1576 (m), 1502 (s), 1452 (s), 1384 (m), 1018 (m), 998 (m), 826 (m), 802 (s), 750 cm^{-1} (s).

Anal. Calcd for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 91.25; H, 9.10.

***anti*-4,4,9,17-Tetramethyl-2,6-dithia[7.1]paracyclophane 2,2,6,6-Tetraoxide (19).** The crystalline *anti*-dithia[7.1]paracyclophane **18** (100 mg, 0.28 mmol) was dissolved in methylene chloride (50 ml). *m*-Chloroperbenzoic acid (260 mg of 85%, i.e., 1.33 mmol) was added with stirring at room temperature. The mixture was stored overnight at −7 °C. The precipitated *m*-chlorobenzoic acid was removed. The filtrate was washed (10% aqueous $KHCO_3$ solution, water), dried ($MgSO_4$), and concentrated to dryness. The solid residue (118 mg) was rapidly recrystallized from ethanol to give the *anti*-dithia[7.1]paracyclophane tetraoxide **19**: mp 256–257 °C; NMR (DMF) δ 7.36–6.96 (m, 6), 4.28 (q, 4, J = 14 Hz), 3.91 (s, 2), 2.36 (s, 6), 2.27 (s, 4), 1.28 (s, 6); ir (Nujol) 1608 (w), 1308 (s), 1292 (s), 1134 (s), 850 cm^{-1} (m); uv λ_{max} (MeOH) 251 nm (ϵ 7 200); MS *m/e* 420 (M^+).

Anal. Calcd for $C_{22}H_{28}O_4S_2$: C, 62.82; H, 6.71. Found: C, 62.92; H, 6.63.

***syn*-4,4,9,17-Tetramethyl-2,6-dithia[7.1]paracyclophane 2,2,6,6-Tetraoxide (20).** The crystalline *anti*-dithia[7.1]paracyclophane **18** (1 g, 2.8 mmol) was equilibrated to a syn/anti mixture by refluxing overnight in chloroform. The chloroform was removed and the residue oxidized by *m*-chloroperbenzoic acid as described above for the anti isomer. The resulting residue (1.1 g) of a mixture of syn and anti isomers of the tetraoxide was separated by preparative high-pressure liquid chromatography on a Waters Model ALC 100 with a Model 6000 pump. An 8 ft × 0.375 in. column of Woelm neutral III alumina N 18 with a 75:25 mixture of 25% water saturated isooctane and THF as the mobile phase. Portions (100 mg) of the syn/anti mixture were injected with a 2-ml loop injector. Separation and isolation required five recycles at a flow rate of 4 ml/min (~22 h total). Detection was by means of uv absorption (254 nm). From several such portions, fractions containing the pure fast and slow isomers were combined. The fast isomer was recrystallized from ethanol to give the *anti*-4,4,9,17-tetramethyl-2,6-dithia[7.1]paracyclophane 2,2,6,6-tetraoxide, mp 256–257 °C, identical with the material prepared from the crystalline *anti*-dithia[7.1]paracyclophane by mixture melting point, NMR, and retention time in high-pressure liquid chromatography. The slower moving isomer was recrystallized from ethanol to give *syn*-4,4,9,17-tetramethyl-2,6-dithia[7.1]paracyclophane 2,2,6,6-tetraoxide (**20**): mp 230–232 °C; NMR (DMF) δ 7.20 (s, 6), 4.39 (q, 4, J = 14 Hz), 3.94 (s, 2), 2.30 (q, 4, J = 14 Hz), 1.33 (s, 3), 1.28 (s, 3); ir (Nujol) 1608 (w), 1308 (s), 1288 (s), 1122 (s), 846 cm^{-1} (m); uv (MeOH) λ_{max} 252 nm (ϵ 7310); MS *m/e* 420 (M^+).

Anal. Calcd for $C_{22}H_{28}O_4S_2$: C, 62.82; H, 6.71. Found: C, 62.45; H, 6.59.

Equilibration of the *syn*- and *anti*-Dithia[7.1]paracyclophane Tetraoxides 19/20. The deuterated DMF solution of both syn and anti isomers was heated overnight at 100 °C. The spectra resulted from either isomer were identical and consisted of a 1:1 mixture. Solutions (0.5%) in dioxane of the pure syn and anti isomers were prepared. These solutions were heated overnight in vials in temperature-controlled silicone oil baths at 70, 80, and 90 °C. After freezing aliquots of these solutions, their composition was determined by high-pressure liquid chromatography under conditions employed for the kinetic studies below. Peak area was estimated as the peak height times width at half height. Within the limits of error of this procedure (±1%) each of the six vials contained a 1:1 syn/anti mixture. Thus, neglecting the small differences in ϵ in the uv spectrum, the equilibrium constant K can be assumed to be unity over this temperature range.

Kinetic Measurements. A Waters Model 202/401 liquid chromatograph, equipped with a Model 6000 pump and uv detector for 254 nm, was employed. A 6 ft × 0.125 in. column was packed with HC-Pellumina (Reeve Angel) and eluted with 25% water saturated isooctane/tetrahydrofuran (75:25). The flow rate was maintained at 1.5 ml/min at 1500 psi. Septum injection was used. The anti isomer had a retention time of 18 min, the syn isomer a retention time of 26 min. Baseline separation was achieved at 20-μg levels. Solutions (0.5%) of the anti isomer in *p*-dioxane were heated in reaction vials, equipped with Teflon septa, in constant-temperature silicone oil baths at 70, 80, and 90 ± 0.5 °C. Aliquots were removed at appropriate times and frozen immediately in a dry ice bath. Samples (4 μl) of these aliquots were analyzed. Peak areas were estimated by multiplying peak height by the width at half height. The shapes of the curves obtained from both isomers were similar. A plot of log [1 − 2 (% of syn)/(% of anti)] vs. time was made for each temperature. The linear regression equations were estimated by the least-squares method. The validity of the equations were checked by testing the significance of the slopes. In all cases the probability (p <0.001) indicated that the relation could be expressed as linear. The resulting data (Table I) were used via Eyring and Arrhenius plots to derive the thermodynamic parameters for the process (Table II).[24]

Acknowledgments. We wish to acknowledge the support and encouragement of Dr. Max Wilhelm, and helpful discussions with Professors Paul Gassman and Peter Yates. We thank Mr. Louis Dorfman's staff for microanalysis and spectra.

Registry No. —**3**, 59054-28-3; **4**, 59054-29-4; **5**, 59054-30-7; **6**, 59054-31-8; **7**, 59054-32-9; **8**, 59054-33-0; **9**, 59054-34-1; **10**, 59054-35-2; **11**, 59054-36-3; **12**, 59054-37-4; **13**, 59054-39-6; **14a**, 59054-40-9; **14b**, 59054-41-0; **15a**, 59054-43-2; **15b**, 59054-45-4; **16**, 59070-05-2; **17**, 59054-46-5; **18**, 59121-41-4; **19**, 59054-47-6; **20**, 59121-42-5; **21**, 2421-28-5; **23**, 59054-48-7; **24**, 59054-49-8; **25**, 726-05-6; thionyl chloride, 7719-09-7; propane-1,3-dithiol, 109-80-8; triethyloxonium tetrafluoroborate, 368-39-9; thiourea, 62-56-6; 2,2-dimethyl-1,3-dibromopropane, 5434-27-5; methyl fluorosulfonate, 421-20-5; potassium thiocyanate, 333-20-0.

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(23) We wish to acknowledge the help of the late Mr. A. Wajngurt and Mr. M. Loo with large-scale preparations of the dimethyl ester.
(24) We wish to acknowledge the computer handling of our data by Mr. John Schaffhausen of Professor Paul Gassman's group at the University of Minnesota.

Indolizidines, α-Arylthiohemiaminals, and α-Arylsulfonylhemiaminals from a Quinolizidine Enamine and an Arenesulfonyl Chloride[1]

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The treatment of the quinolizidine enamine 6-dehydrodeoxynupharidine (**1**) with *p*-toluenesulfonyl chloride in benzene solution produces the following compounds: *p*-tolyl disulfone (**2**); *p*-tolyl disulfide (**3**); 7β-(*p*-tolylthio)-deoxynupharidin-6-ol (**4**); 7α-(*p*-tolylthio)-7-epideoxynupharidin-6-ol (**5**); 7β-(*p*-toluenesulfonyl)deoxynupharidin-6-ol (**6**); 7α-(*p*-toluenesulfonyl)-7-epideoxynupharidin-6-ol (**7**); and two epimeric indolizidinecarboxaldehydes, **8** and **9**, which arise by skeletal rearrangement. All of the products are isolated except for one of the epimeric indolizidines, **8**. Gross structures assigned are consistent with spectral evidence and elemental analyses. The C-7 configuration in the α-thiohemiaminals **4** and **5** is determined by circular dichroism and the configuration at the same center in the α-sulfonylhemiaminals **6** and **7** is established by chemical correlation with **4** and **5**. The C-3 configuration and the stereochemistry of the ring fusion in the isolated indolizidinecarboxaldehyde, 5α-(3-furyl)-3β,10β-dimethylindolizidine-3α-carboxaldehyde (**9**), is ascertained through infrared studies of the primary alcohol, **14**, obtained from **9** by reduction. Primary alcohol **14** gives Bohlmann infrared bands, indicating the trans-fused indolizidine ring system, and infrared bands revealing the intramolecular hydrogen bonding of the primary alcohol to the nitrogen. The rationale for product formation is based on *p*-toluenesulfonyl chloride acting as an ambident electrophile.

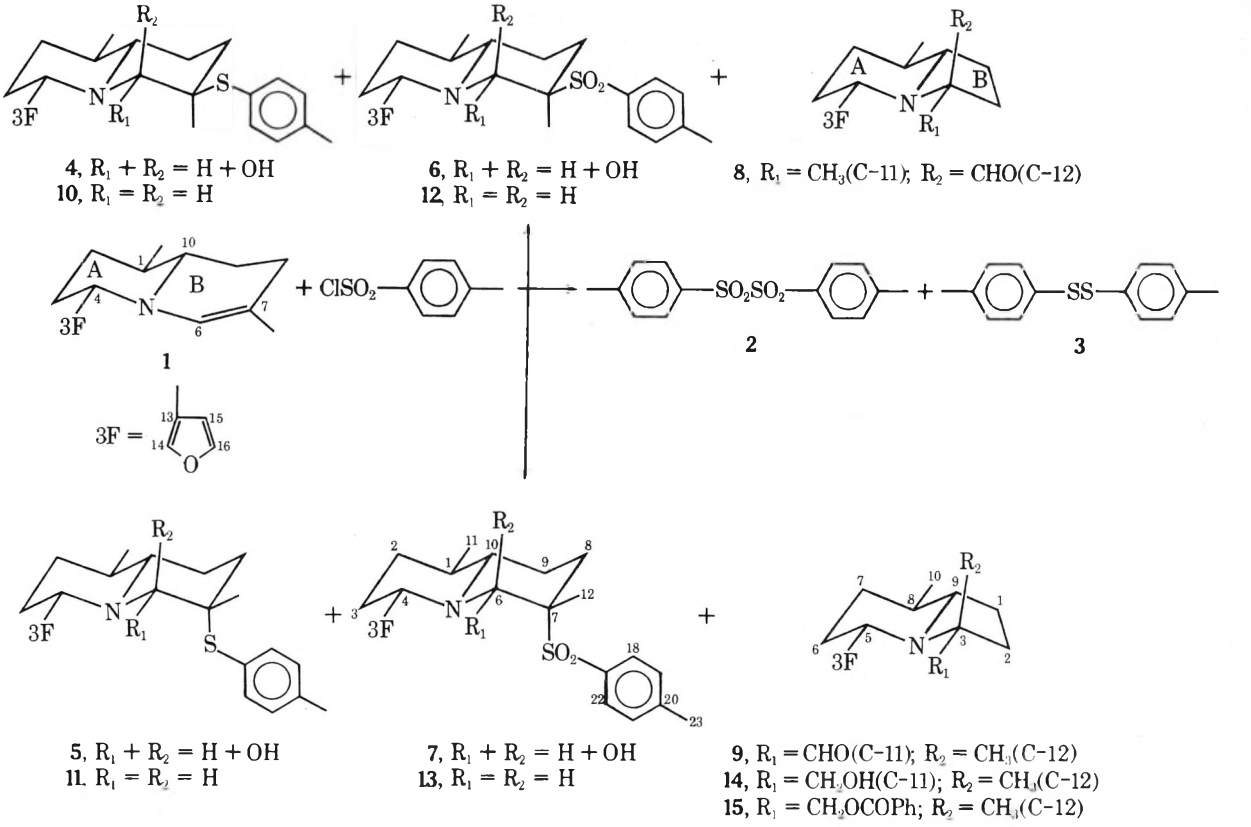
We wished to prepare a group of α-arenesulfonylhemiaminals for the purpose of comparing their metal hydride reductions with those of α-arylthiohemiaminals. Therefore we carried out the reaction of *p*-toluenesulfonyl chloride with 6-dehydrodeoxynupharidine (**1**). No less than eight products, including *p*-tolyl disulfone (**2**), *p*-tolyl disulfide (**3**), and three pairs of diastereomers, result from this reaction which takes the unusual course, outlined in Scheme I, in producing the rearranged indolizidines **8** and **9** and the α-thiohemiaminals **4** and **5** in addition to affording the desired and expected α-sulfonylhemiaminals **6** and **7**. Because of the unusual course of this reaction we wish to present the evidence for the formation of the six compounds **4–9**; the procedures for the isolation of five of them (**4–7** and **9**); and the structure determination of **4–7** and **9** as the principal topics of this paper. *p*-Tolyl disulfone (**2**)[2,3,4] and *p*-tolyl disulfide (**3**)[5,6] have long been known and their identification needs no further treatment beyond what is given in the Experimental Section. Finally a brief discussion regarding product formation is presented. The features of α-sulfonyl- and α-thiohemiaminal reductions will be treated in a separate paper at a later date.

The Indolizidines. Although only one of the two indolizidine aldehydes, **9**, could be isolated for study, there was evidence that both diastereomers **8** and **9** were formed. Thus the ^1H NMR of a chromatographic fraction showing two spots on TLC revealed a pair of singlets at δ 0.92 and 1.07, the lower field signal being the more intense. These signals were attributed to C-11, the methyl group attached to C-3 of **8** or **9**. Moreover the same spectrum exhibited a pair of aldehyde protons at δ 9.04 and 9.79 whose integrated intensities were in the ratio of 8:1.

Chromatographic refinement of this same fraction gave the pure diastereomer **9** but failed to separate the minor diastereomer **8** in a state completely free of **9**. The ^1H NMR of **9** revealed the C-8 methyl (C-10) doublet at δ 0.91, the C-5 proton double doublet at δ 3.36, and the 3-furyl multiplets at δ 6.36 and 7.26, the last two signals representing three protons. Consequently neither the furan ring nor ring A of the starting enamine had been altered since these ^1H NMR characteristics agree with those of the corresponding protons[7,8] in deoxynupharidine and 7-epideoxynupharidine (**1**, 6,7β- and 6,7α-dihydro, respectively). This conclusion was supported by the ^{13}C NMR spectrum, which exhibited the C-10 quartet at 18.5 ppm, the C-8 doublet at 37.0 ppm, and the C-9 doublet at 67.5 ppm in addition to the normal 3-furyl signals at 109.8, 127.0, 140.0, and 142.9 ppm, all in accord with the ^{13}C chemical shifts of corresponding carbons in deoxynupharidine and 7-epideoxynupharidine.[9]

The appearance of the ir absorption at 5.79 μm and the ^1H NMR singlet at δ 9.04 indicated the presence of the aldehyde function. The aldehyde group must be attached to a quaternary carbon which also bears the second methyl group since the latter appears at δ 1.07 as a singlet. The quaternary carbon was linked to the nitrogen since the higher field singlet in the ^{13}C NMR appeared at 70.5 ppm. The second carbon attached to nitrogen gave the 67.5-ppm doublet as already mentioned above. The third carbon attached to nitrogen, as yet unaccounted for, appeared as a doublet at 52.9 ppm and was assigned to C-5. Therefore, of the total 15 carbons indicated by

Scheme I. Products from the Reaction of *p*-Toluenesulfonyl Chloride and 6-Dehydrodeoxynupharidine and Subsequent Transformations



the mass spectrum and the elemental analysis of the corresponding primary alcohol (see the Experimental Section), the two remaining carbons were incorporated into the structure as C-1 and C-2 to complete a five-membered B ring as shown in **8** and **9**. The remaining features of the ^{13}C NMR are consistent with the structure; the 28.6-ppm triplet corresponds to the C-9 chemical shift in deoxynupharidine and one of the triplets at 34.6, 33.2, or 31.6 ppm agrees with the 30.6-ppm chemical shift of C-8 in deoxynupharidine. Therefore two of the three signals at 34.6, 33.2, and 31.6 ppm remain for C-6 and C-7.

The mass spectrum is consistent with the indolizidine aldehyde structure. In addition to the molecular ion, of special significance is the appearance of the base peak at *m/e* 218, corresponding to the loss of CHO, and *m/e* 110, accounted for by the loss of all carbon, hydrogen, and oxygen comprising the original six-membered ring and the transfer of a single hydrogen from the remaining five-membered ring, which carries the charge.

Reduction of the indolizidine aldehyde afforded a primary alcohol as indicated by the appearance of the hydroxyl group at 2.92 μm in the ir, a two-proton AB quartet at δ 2.62 in the ^1H NMR, and a triplet at 67.2 ppm in the ^{13}C NMR. The base peak at *m/e* 218 in the MS corresponds to the loss of CH_2OH from the parent ion. The ir revealed the presence of Bohlmann bands in the region of 3.62 μm showing that the indolizidine was trans fused.[10] A cis-fused indolizidine would possess no α hydrogens which are anti diaxial to the nitrogen lone pair and therefore Bohlmann bands would not be expected in such a case. Infrared spectral examination of the indolizidine alcohol in carbon tetrachloride solutions as dilute as 1.4×10^{-2}M revealed the presence of an intramolecular hydrogen bonded hydroxyl at 3438 cm^{-1} but no free hydroxyl was observed in the region of 3500–3650 cm^{-1}. Therefore the simultaneous occurrence of Bohlmann bands and intramolecular hydrogen bonding is evidence for assigning the structure **14** to the indolizidine alcohol and structure **9** to the corresponding aldehyde. A recent x-ray crystallographic study of the benzoate, **15**, hydrobromide confirms the structure of **14**.[11]

The α-Arylthiohemiaminals. The spectral data indicated that no skeletal alteration had occurred in the transformation of enamine **1** to hemiaminals **4** and **5**. For example, the MS peaks at *m/e* 248, 246, 231, 228, 218, 216, and 214 showed that the entire carbon, nitrogen, and oxygen skeleton of the enamine had been preserved in **4** and **5**. The unaltered ring A and attached 3-furyl group were confirmed in the presence of peaks at *m/e* 136, 107, 94, and 81. Both series of peaks have been observed in the MS of other α-thiohemiaminals derived from the enamine **1**.[12,13] Also, the unaltered presence of the C-1 methyl and 3-furyl group attached to the quinolizidine system at C-4 was confirmed by the ^1H NMR; the C-1 methyls appeared as doublets in the δ 0.93 region while the 3-furyl groups gave rise to the resonance of three of the seven protons observed in the δ 6.4–7.4 region and resulted in the C-4 protons appearing as a double doublet at δ 3.6–3.8.

The presence of the hemiaminal function in **4** and **5** was indicated by the appearance of the hydroxyl absorption in the 2.8–2.9-μm region of the ir and the carbinyl (C-6) proton in the region of δ 4.2–4.3 in the ^1H NMR. Conversion with perchloric acid of **4** to a crystalline immonium perchlorate exhibiting absorption at 6.05 μm supported the hemiaminal presence in **4**.

The incorporation of sulfur as aryl sulfide, rather than aryl sulfone, was first revealed in the parent ions at *m/e* 371 in the MS but was supported later in a number of ways, most interesting among them being the acidic solution uv which revealed several new absorption bands in the 260–280-nm region not observed in the neutral solution uv nor in the neutral nor acidic solution uv of the sulfone hemiaminals, **6** and **7**. Moreover, the acidic solution CD of **4** exhibited a positive CD band at 282 nm while the CD of **5** gave a negative band at 289 nm as illustrated in Figure 1. The appearance of these bands is generally characteristic of acidic solutions of hemiaminals possessing sulfide substituents at α or β carbons.[14,15] A specific

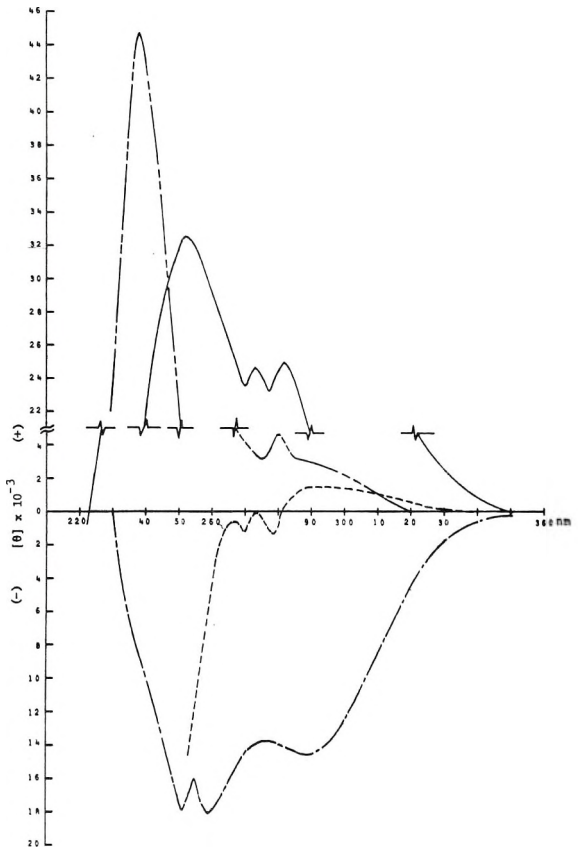


Figure 1. The circular dichroism of 7β-*p*-tolylthiodeoxynupharidin-6-ol, **4** (—); 7α-*p*-tolylthio-7-epideoxynupharidin-6-ol, **5** (— - —); 7β-*p*-toluenesulfonyldeoxynupharidin-6-ol, **6** (— - - —); 7α-*p*-toluenesulfonyl-7-epideoxynupharidin-6-ol, **7** (- - - -), in EtOH with added $HClO_4$.

case in point is the pair 7β-phenylthiodeoxynupharidin-6-ol and 7α-phenylthio-7-epideoxynupharidin-6-ol; in neutral solution both have low-intensity bands in the 240–280-nm region but in acidic solution both show high-intensity bands ($[\theta] > 4000$) at 295 nm, the 7β isomer giving a positive band and a 7α isomer a negative band.[16] Therefore the positive negative bands exhibited by **4** and **5**, respectively, establish the configuration of C-7 in **4** and **5** when these results are compared to those of earlier studies.[14]

Reduction of the hemiaminal function with sodium borohydride in methanol converted **4** and **5**, respectively, to **10** and **11** whose spectral data and elemental analyses are consistent with C-7 substituted aryl sulfide derivatives, but not sulfones. Oxidation of **10** and **11**, in acidic solution, with hydrogen peroxide gave the sulfones **12** and **13**, respectively, which were employed to correlate the C-7 configuration of α-thiohemiaminals **4** and **5** with the same center in α-sulfonylhemiaminals **6** and **7**.

The α-Arenesulfonylhemiaminals. The detailed spectral properties of **6** and **7** presented in the Experimental Section generally are similar to those of the α-thiohemiaminals **4** and **5** already discussed and demonstrate the preservation of the unaltered skeleton of the starting enamine and the hemiaminal character. However, the MS of **6** and **7** showed parent ions at *m/e* 403 indicating the incorporation of two additional oxygens not possessed by the sulfides and the ir exhibited strong bands in the regions 8.6–8.9 and 7.4–7.7 μm characteristic of sulfones.[17] Another significant property difference was observed in the acidic solution CD which are included for comparison in Figure 1. The CD bands in the 280–300-nm region for the α-sulfonylhemiaminals were much less intense than those of the α-thiohemiaminals.

Attempts to correlate the α-sulfonylhemiaminals with the α-thiohemiaminals by reduction of **12** and **13** to sulfides with lithium aluminum hydride in refluxing ether were unsuccessful; only unconverted starting sulfones were recovered. However, reduction of **6** with sodium borohydride in methanol gave the sulfone **12** which was identical with the sulfone obtained from the α-thiohemiaminal **4** through the latter's reduction followed by sulfide to sulfone oxidation, as discussed above. In a similar manner **7** gave **13** identical with the sulfone obtained from **5**. These correlations establish the configurations of **6** and **7** at C-7.

Interestingly, the ir of **12** and **13** in solution both show Bohlmann bands, the intensity of the absorptions being slightly greater for **13** than **12**. Furthermore, the ^{13}C NMR of **12** reveals the C-7 methyl (C-12) at 17.1 ppm which appears at 4–5 ppm higher field than the chemical shift of the C-7 methyl in **13**. These results, in conjunction with those from earlier ^{13}C studies of methyl decalins[18] and quinolizidines,[19] and the known stereochemical requirements needed for Bohlmann band appearance,[10] define the stereochemistry of ring fusion and conformation of the quinolizidine B ring. Thus in both **12** and **13** ring B is trans fused to ring A and possesses a chair conformation. The C-7 methyl is axial in **12** but equatorial in **13**.

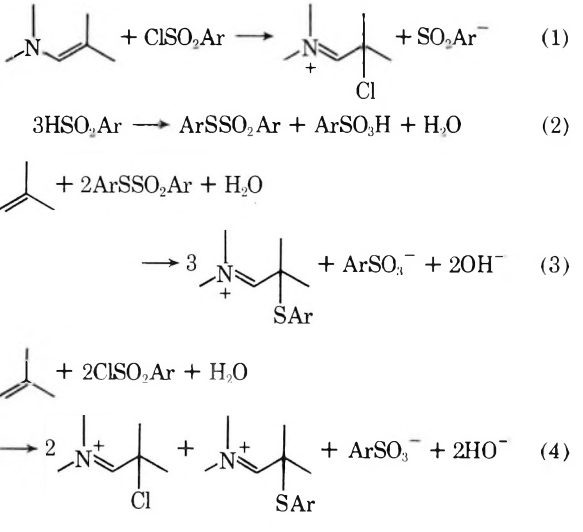
The above conclusion regarding ring B stereochemistry in **13** was not clearly predictable since the larger free-energy difference ($\Delta G° = -2.5$ kcal/mol) between an axial and equatorial sulfonyl group,[20] relative to that of the methyl group, might have forced the arylsulfonyl group into an equatorial conformation with the consequent development of a trans-fused twist boat or a cis-fused chair ring B, a prediction inconsistent with results. Presently no completely satisfactory explanation can be offered for the axial conformational preference of the bulky sulfonyl group in **13**.

Discussion

Since the purpose of this paper is to point out the exceptional products resulting from treatment of an enamine with a sulfonyl chloride, some attention should be given to the manner in which these products are formed.

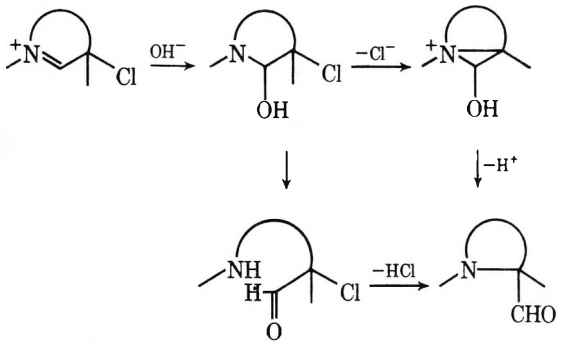
The action of arenesulfonyl halides on enamines is reported[21] to generate sulfones in the straightforward manner expected for the reaction of an electrophilic sulfur derivative on a nucleophilic enamine. However, among one of these reports there is mentioned[22] in a footnote that in addition to the predominating sulfone a sulfide also results and that the latter was observed even when analytically pure arenesulfonyl chloride was used. In our studies no *p*-toluenesulfenyl chloride nor *p*-tolyl *p*-toluenethiosulfonate could be detected in the sulfonyl chloride employed.

For the moment, we suggest that the exceptional products



result from the processes in eq 1–4. Attack of enamine on chlorine rather than sulfur of the sulfonyl chloride leads to the α-chloroimmonium ion and the formation of sulfinate anion as indicated in eq 1. In turn, the arenesulfinate anion becomes protonated giving the arenesulfonic acid, a weak acid, which undergoes disproportionation to arenesulfonic acid and aryl arenethiosulfonate, according to eq 2. The aryl arenethiosulfonate serves as an electrophilic thiating agent which competes for enamine and converts it to an α-thioimmonium ion that subsequently gives α-thiohemiaminal. Such electrophilic attack of thiosulfonate produces additional arenesulfinate whose fate is also disproportionation. Equation 3 sums up both the reaction of enamine with aryl arenethiosulfonate and the disproportionation of arenesulfonic acid. The indolizidine aldehydes likely result, at least in part, from the chlorine-containing immonium ion (eq 1) through routes depicted in Scheme II.

Scheme II. Possible Routes from the Chlorine-Containing Immonium Ion to Aldehyde



There is close analogy or precedent for each of the steps indicated by eq 1–3. The behavior of arenesulfonyl chlorides as ambident electrophiles capable of furnishing positive chlorine, as required in eq 1, is demonstrated in reactions with the sodium enolates of β-keto esters.[23] The disproportionation of sulfinic acids to thiosulfonates and sulfonic acids, eq 2, is well known[24] and there is ample precedent for the electrophilic thiating capability of aryl and alkyl arenethiosulfonates on enamines[12,22,25] and aromatic amines[26] as required by eq 3.

Combining eq 1–3 and including a trivial equation for the conversion of sulfinate anion to sulfinic acid with water gives eq 4 which clearly indicates the overall requirement for water in order that the enamine be oxidized and the sulfur reduced. In our experimental procedure, water was not added. But in all but one of the several experiments, no precaution was taken to dry the solvents nor to exclude water from the reaction mixtures. In one experiment the solvents were dried and still the same quinolizidine and indolizidine derivatives were obtained. However, all product mixtures were separated on columns of hydrated alumina. Therefore the hydration of α-chloro- and α-arenesulfonyl immonium salts and sulfinate ion and the subsequent rearrangement very likely have taken place to some extent on columns of hydrated alumina in addition to that which might have occurred in wet benzene solution.

Regarding the formation of the disulfide, the hydrolysis of an unstable arenesulfinic acid is known to yield disulfide and arenesulfonic acid.[27] The generation of *p*-tolyl disulfide may take place by a similar process. As for *p*-tolyl disulfone, its generation most likely comes from the reaction of *p*-toluenesulfinate anion with *p*-toluenesulfonyl chloride.

This proposal for the formation of the unexpected products resulting from the action of *p*-toluenesulfonyl chloride with an enamine is not intended to be the last word on the subject but rather a working hypothesis to be tested by further study.

Experimental Section

Spectra were determined as follows. ^1H NMR at 60 MHz in $CDCl_3$, 2% Me_4Si (δ 0.0) on a Varian A-60 spectrometer unless otherwise indicated, symbols, br, s, d, and m refer to broad, singlet, doublet, and multiplet, respectively; ^{13}C NMR at 25.16 MHz and ^1H NMR at 100 MHz in $CDCl_3$, both relative to Me_4Si (δ 0.0) on a Varian XL100 spectrometer operating in the pulsed Fourier mode. Fourier transformations were based on 8192 data points and employed the absorption spectrum; field/frequency lock was established on deuterium of $CDCl_3$, between 1 and 5K transients were used for fully decoupled ^{13}C spectra and three–four times that many for off-resonance decoupled spectra used to assist the assignment of ^{13}C resonance lines. Ir spectra were determined in the phase indicated on Perkin-Elmer 137 and 621 spectrometers, w, m, s refer to weak, medium, and strong, respectively; mass spectra were determined on a Hitachi Perkin-Elmer RMU6E using a direct inlet probe at 110 °C, unless indicated otherwise, and at 70 eV. High-resolution mass spectra were run on an AEI MS-9. Melting points were determined on a Köfler micro hot stage and/or a Mel-Temp apparatus and are uncorrected. The circular dichroism was determined on a Jasco Model 5 spectropolarimeter in solution at the concentrations indicated. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Thin layer chromatography was performed on microscope slides uniformly coated with Al_2O_3 (GF_{254}) using the solvent systems indicated; the spots were developed with Dragendorff reagent.

The *p*-tosyl chloride was freshly recrystallized[28] and its mass spectra, run prior to use, showed no peaks corresponding to the presence of the sulfenyl chloride (M^+, *m/e* 190) nor *p*-tolyl *p*-toluenethiosulfonate (M^+, *m/e* 278).

Reaction of 6-Dehydrodeoxynupharidine (1) with *p*-Toluenesulfonyl Chloride and the Isolation of *p*-Tolyl Disulfone and *p*-Tolyl Disulfide. The following is typical of several reactions carried out between the title reactants. A solution of 1072 mg (4.64 mmol) of **1** and 885 mg (4.64 mmol) of *p*-tosyl chloride in 20 ml of C_6H_6 was kept under N_2 at 0 °C for 1.5 h and thereafter a −20 °C for 4 days.[29] The frozen contents were warmed to 25 °C, and the persisting solid filtered and washed with CH_2Cl_2–C_6H_6, yielding 53 mg of *p*-tolyl disulfone (**2**): mp 204 °C dec (lit. 212 °C dec[2]); ir 6.05 (w), 6.27 (m), 7.48 (s), 7.71 (m), 8.82 (s), 9.41 (m), 12.43 (m), 14.46 μm (m); MS (110 °C) *m/e* (rel intensity) 310 (7) (M^+), 262 (9), 155 (73), 139 (100), 92 (53).

The filtrate was concentrated and then chromatographed on 75 g of Al_2O_3 (activity 3). The chromatography was monitored by TLC on Al_2O_3 (GF_{254}). The column was eluted with 350 ml of C_6H_6, 360 ml of 8:1 C_6H_6–Et_2O, 200 ml of 5:3 C_6H_6–Et_2O, 100 ml of 1:1 C_6H_6–Et_2O, 60 ml of 1:3 C_6H_6–Et_2O, 100 ml of CH_2Cl_2, 100 ml of 17:3 CH_2Cl_2–MeOH, and 100 ml of MeOH in the order given in 37 30–40-ml fractions (A1–A37). According to TLC, mixtures of unconverted enamine (**1**), indolizidine aldehydes (**8** and **9**), 7β-*p*-tolylthiodeynupharidin-6-ol (**4**), and *p*-tolyl disulfide (**3**) emerged in the C_6H_6 fractions A1–A5, the indolizidine aldehydes in the C_6H_6 fractions A6–A8, and a mixture of indolizidine aldehydes and 7α-(*p*-tolylthio)-7-epideoxynupharidin-6-ol (**5**) in 8:1 C_6H_6–Et_2O fractions A9–A15. Mixtures of **6** and **7** emerged in fractions A22–A26, fractions eluted at the end of the 8:1 C_6H_6–Et_2O elution and with later eluents richer in Et_2O.

Fractions A1 and A2, eluted with C_6H_6, yielded a total of 95 mg of material showing on TLC two spots, one Dragendorff active and uv inactive and the other Dragendorff inactive but uv active. The former corresponded to unconverted **1**. Rechromatography of this two-component mixture on 15 g of Al_2O_3 (activity 2) with 150 ml of hexane afforded 17 mg of *p*-tolyl disulfide: mp 47–48 °C (lit. 41,[5] 47–48 °C[6]); TLC uv active; MS *m/e* 246 (M^+).

7α-(*p*-Tolylthio)-7-epideoxynupharidin-6-ol (5). Fractions A10–A15 were recombined (73 mg) and chromatographed on 15 g of Al_2O_3 (activity 3) with 100 ml of 19:1 C_6H_6–Et_2O, 100 ml of 9:1 C_6H_6–Et_2O, 100 ml of 3:2 C_6H_6–Et_2O, and 60 ml of MeOH. Ten 20-ml fractions, B1–B10, and then five 30–35 ml fractions, B11–B15, were collected. Fractions B8–B10 combined consisted of 13 mg of **5** (0.035 mmol, 0.76%), an oil: TLC (C_6H_6) R_f 0.125; TLC (8:1 C_6H_6–Et_2O) R_f 0.33; TLC (8:3 C_6H_6–Et_2O) R_f 0.55; ^1H NMR δ 0.93 (s superposed on d, 6 H, C-1 and C-7 CH_3), 2.29 (s, 3 H, $ArCH_3$), 3.60 (d of d, J = 4 and 8 Hz, 1 H, C-4 H), 4.30 (m, 1 H, C-6 H), 6.45 (m, 1 H, 3-furyl β H), 6.83–7.37 (m, 6 H, 3-furyl α H and ArH); ir (liquid film) 2.86 (m), 5.82 (w), 6.04 (w), 6.23 (w), 6.70 (m), 6.89 (m), 7.28 (m), 11.47 (s), 12.3 (s), 12.6 μm (m); uv (neutral 95% EtOH) λ_{sh} 268 nm (ε 2050), λ_{max1} 262 nm (ε 2800), λ_{max2} 254 nm (ε 2940), λ_{max3} 248 nm (ε 2510), λ_{max4} 242 nm (ε 2270); uv (95% EtOH, $HClO_4$ added) λ_{sh1} 275 nm (ε 2800), λ_{sh2} 267 nm (ε 2570), λ_{sh3} 254 nm (ε 3260), λ_{sh4} 247 nm (ε 3850), λ_{sh5} 242 nm (ε 4420), λ_{sh6} 237 nm (ε 4670); CD (*c* 0.18 mg/ml, neutral 95% EtOH, *l* = 0.1 dm) $[\theta]_{330}$ +74°, $[\theta]_{320}$ + 144°, $[\theta]_{312}$ +186°, $[\theta]_{310}$ +

173°, $[\theta]_{300}$ +82°, $[\theta]_{295}$ 0°, $[\theta]_{293}$ −21°, $[\theta]_{290}$ +21°, $[\theta]_{275}$ + 907°, $[\theta]_{258}$ −12°, $[\theta]_{250}$ +194°, $[\theta]_{240}$ + 1030°, $[\theta]_{235}$ + 3960°; CD (*c* 0.18 mg/ml, 95% EtOH, $HClO_4$ added, *l* = 0.1 dm) $[\theta]_{360}$ 0°, $[\theta]_{290}$ −14 500°, $[\theta]_{288}$ −14 500°, $[\theta]_{275}$ − 13 800°, $[\theta]_{259}$ −18 100°, $[\theta]_{255}$ −15 900°, $[\theta]_{251}$ −17 900°, $[\theta]_{240}$ −9690°; MS *m/e* (rel intensity) 371 (7) (M^+), 353 (20), 342 (2), 248 (21), 246 (73), 231 (100), 230 (51), 229 (47), 228 (22), 218 (74), 216 (33), 214 (27), 202 (12), 200 (12), 192 (10), 188 (12), 186 (10), 176 (21), 174 (14), 164 (15), 136 (21), 124 (79), 123 (67), 107 (39), 96 (68), 95 (46), 94 (81), 91 (94), 82 (29), 81 (20).

7β-(*p*-Toluenesulfonyl)deoxynupharidin-6-ol (6). The A series chromatography yielded, in fractions A23–A26, a 102-mg mixture of 7α-(*p*-toluenesulfonyl)-7-epideoxynupharidin-6-ol (**7**) and 7β-(*p*-toluenesulfonyl)deoxynupharidin-6-ol (**6**), 45 mg of which was chromatographed on 15 g of SiO_2 (activity 2) with 100 ml of C_6H_6, 330 ml of 10:1 C_6H_6–Et_2O, 270 ml of 8:1 C_6H_6–Et_2O, 140 ml of 6:1 C_6H_6–Et_2O, 200 ml of 3:2 C_6H_6–Et_2O, 100 ml of 1:1 C_6H_6–Et_2O, and 50 ml of EtOH in the order given in 39 35-ml fractions (C1–C39). Combined fractions C1–C6 contained 9 mg of **6** (0.0223 mmol, 0.48%), an oil: TLC (3:2 C_6H_6–Et_2O) R_f 0.30; mp 114–118 °C; ^1H NMR δ 0.97 (m, 3 H, C-1 CH_3), 1.19 (s, 3 H, C-7 CH_3), 2.45 (s, 3 H, Ar CH_3), 3.67 (m, C-4 H), 3.80 (br s, OH), 4.26 (br s, 1 H, C-6 H), 6.31 (m, 1 H, 3-furyl β H), 7.09–7.46 (ArH and 3-furyl α H), 7.54 (ArH), 7.68 (ArH); ir (KBr) 2.88 (m), 6.24 (m), 6.69 (m), 6.89 (m), 6.97 (m), 7.16 (w), 7.30 (w), 7.86 (s), 8.76 (s), 11.44 (m), 12.27 (m), 12.56 (m), 12.92 μm (m); MS *m/e* (rel intensity) 403 (6) (M^+), 385 (2), 374 (1), 248 (6), 229 (100), 228 (24), 214 (46), 200 (16), 107 (19), 96 (20), 94 (30), 91 (46), 81 (14); CD (*c* 0.58 mg/ml, neutral 95% EtOH, *l* = 0.1 dm) $[\theta]_{285}$ +69°, $[\theta]_{277}$ +919°, $[\theta]_{272}$ +503°, $[\theta]_{270}$ +694°, $[\theta]_{265}$ +381°, $[\theta]_{263}$ +503°, $[\theta]_{260}$ +381°, $[\theta]_{250}$ −139°; CD (*c* 0.58 mg/ml, 95% EtOH, $HClO_4$ added, *l* = 0.1 dm) $[\theta]_{320}$ +208°, $[\theta]_{290}$ +3120°, $[\theta]_{285}$ +3120°, $[\theta]_{280}$ +4570°, $[\theta]_{275}$ +3120°, $[\theta]_{260}$ +6240°, $[\theta]_{238}$ +44 720°, $[\theta]_{220}$ −13 520°, $[\theta]_{213}$ +4160°.

7α-(*p*-Toluenesulfonyl)-7-epideoxynupharidin-6-ol (7). Fractions C37–C39 were combined (24 mg) and chromatographed on 15 g of Al_2O_3 (activity 2) with 100 ml of C_6H_6, 90 ml of 8:1 C_6H_6–Et_2O, 220 ml of 8:3 C_6H_6–Et_2O, 150 ml of 2:1 C_6H_6–Et_2O, 150 ml of 2:1 C_6H_6–Et_2O containing 4% MeOH in the order given in 27 35-ml fractions (D1–D27). Fractions D16–D27 (13 mg) were combined with fractions C26–C36 (14 mg) and chromatographed on 10 g of SiO_2 (activity 2) with 455 ml of CH_2Cl_2 in 13 35-ml fractions and then with 10% MeOH in CH_2Cl_2 in a single fraction which yielded 15 mg of material which was applied to a 20 × 20 cm plate coated with 0.25 mm of SiO_2. This was developed twice with 3:2 C_6H_6–Et_2O and the R_f 0.44 band was removed to obtain 12 mg of **7** (0.0298 mmol, 0.64%), an oil: ^1H NMR δ 0.88 (m, 6 H with δ 0.90 s, C-1 CH_3), 0.90 (s superposed on δ 0.88 m, 6 H with 0.88 m, C-7 CH_3), 2.45 (s, 3 H, Ar CH_3), 3.53–3.95 (m, 2 H, 1 H on addition of D_2O, C-4 H and C-6 OH), 5.03 (br s becoming narrow on addition of D_2O, 1 H, C-6 H), 6.74 (m, 1 H, 3-furyl β H), 7.2–7.8 (m, 6 H, 3 furyl α H and Ar H); ir (CCl_4) 2.85 (w), 5.79 (w), 6.00 (w), 6.24 (m), 6.68 (m), 6.87 (s), 6.27 (m), 7.64 (s), 7.71 (s), 8.66 (s), 8.77 (s), 8.93 (s), 11.48 μm (s); MS (130 °C) *m/e* (rel intensity) 403 (4), 385 (12), 374 (0.4), 370 (0.6), 357 (5), 321 (6), 248 (6), 229 (100), 228 (41), 214 (40), 200 (21), 107 (36.3), 94 (53), 91 (34), 81 (25); CD (*c* 0.46 mg/ml, neutral 95% EtOH, *l* = 0.1 dm) $[\theta]_{298}$ 0°, $[\theta]_{287}$ −386°, $[\theta]_{280}$ −2280°, $[\theta]_{277}$ −2630°, $[\theta]_{275}$ −2720°, $[\theta]_{274}$ −2630°, $[\theta]_{270}$ −3160°, $[\theta]_{265}$ −2630°, $[\theta]_{262}$ −2670°, $[\theta]_{252}$ −1400°, $[\theta]_{250}$ −1580°, $[\theta]_{244}$ −2630°, $[\theta]_{240}$ −4120°; CD (*c* 0.26 mg/ml, 95% EtOH, $HClO_4$ added, *l* = 0.1 dm) $[\theta]_{340}$ 0°, $[\theta]_{324}$ +307°, $[\theta]_{310}$ +843°, $[\theta]_{297}$ +1530°, $[\theta]_{287}$ +1380°, $[\theta]_{281}$ 0°, $[\theta]_{279}$ −1380°, $[\theta]_{274}$ 0°, $[\theta]_{270}$ −1230°, $[\theta]_{268}$ −613°, $[\theta]_{264}$ −1070°, $[\theta]_{258}$ −7820°, $[\theta]_{253}$ −14 600°; CD (*c* 0.13 mg/ml, 95% EtOH, $HClO_4$ added, *l* = 0.1 dm) $[\theta]_{238}$ −61 300°; high-resolution mass spectrum (70 eV, 110 °C) obsd/calcd mass (formula) 385.1709/385.1712 and 385.1740/385.1712 ($C_{22}H_{27}NO_3$, $[M - H_2O]^+$).

Indolizidine Aldehyde 9. The initial chromatography (A′ series) of a reaction mixture from 685 mg of enamine (2.96 mmol) and 546 mg of *p*-tosyl chloride (2.96 mmol) yielded 673 mg of a mixture of unconverted enamine, 7β-(*p*-tolylthio)deoxynupharidin-6-ol (**4**), and indolizidine aldehydes (**8** and **9**) in the C_6H_6 eluent comprising the second through ninth 40-ml fractions (A′2–A′9). This 673-mg mixture was chromatographed (B′ series) on 30 g of Al_2O_3 (activity 2). Elution with C_6H_6 resulted in fractions B′1–B′11 (10 ml each) of which fractions B′9–B′11 yielded 38 mg of a mixture of the indolizidine aldehyde **8** (0.154 mmol, 5.2%) and its C-3 epimer, **9**: TLC (C_6H_6) R_f 0.33; TLC (3:2 C_6H_6–Et_2O) R_f 0.55; ^1H NMR δ 0.92 (s, C-3 CH_3), 1.07 (s, C-3 CH_3), 9.04 (s, C-3 CHO), 9.79 (s, C-3 CHO, δ 9.04:9.79 8:1), ^1H NMR (C_6D_6) δ 0.90 (s, C-3 CH_3), 1.00 (s, C-3 CH_3), 9.14 (s, C-3 CHO), 9.64 (s, C-3 CHO). Repeated chromatography of earlier and later fractions yielded an additional 28 mg of material which when combined with the 38 mg (0.267 mmol total, 9.0%) and thereafter chromatographed yielded pure indolizidine aldehyde **9**, an oil: TLC (C_6H_6) R_f 0.33; ^1H NMR δ 0.91 (d, *J* = 5 Hz, C-8 CH_3), 1.07 (s, 3 H, C-3 CH_3), 3.36 (d of d, *J* = 5 and 9 Hz, 1 H, C-5 H), 6.36 (m, 1 H, 3-furyl β H), 7.26 (m, 2 H, 3-furyl α H), 9.04 (s, 1 H, CHO); ^1H NMR (C_6D_6) δ 0.75 (d, *J* = 5 Hz, C-8 CH_3), 1.00 (s, 3 H, C-3 CH_3), 3.06 (d of d, *J* = 5 and 9 Hz, 1 H, C-5 H), 6.14 (m, 1 H, 3-furyl β H), 7.02 (m, 2 H, 3-furyl α H), 9.14 (s, 1 H, CHO); ^{13}C NMR δ 12.5 (C-11), 18.5 (C-10), 28.6 (C-1), 33.2 (C-6, C-7, or C-2), 34.6 (C-6, C-7, or C-2), 31.6 (C-6, C-7, or C-2), 37.0 (C-8), 52.9 (C-5), 70.5 (C-3), 67.5 (C-9), 109.8 (C-15), 127.0 (C-13), 140.4 (C-14), 142.9 (C-16); ir (liquid film) 3.57 (m), 5.79 (s), 7.30 (m), 11.45 μm (m); MS *m/e* (rel intensity) 247 (24) (M^+), 232 (27), 218 (100), 204 (35), 110 (62), 82 (63).

7β-(*p*-Tolylthio)deoxynupharidin-6-ol (4). Continuing the B′ series chromatography by eluting with benzene gave fractions B′12–15 (20 ml each) and B′16–20 (35 ml each). Fractions B′12–19 recombined consisted of a mixture of indolizidine aldehydes (**8** and **9**), the title hemiaminal (**4**), and the 7β-tolysulfone hemiaminal, **6**, according to TLC. This mixture was rechromatographed (C′ series, 10 g of Al_2O_3, activity 2) using first benzene and collecting four 20-ml fractions (C′1–C′4) and six 35-ml fractions (C′5–C′10). Fractions C′4–C′8 contained a total of 90 mg of the pure title compound, **4** (0.242 mmol, 8.2%), an oil: TLC (C_6H_6) R_f 0.25; ^1H NMR δ 0.92 (d, *J* = 5 Hz, 3 H, C-1 CH_3), 1.14 (s, C-7 CH_3), 2.33 (s, 3 H, $ArCH_3$), 3.12 (br s, 1 H, C-6 OH), 3.75 (d of d, *J* = 4 and 8 Hz, 1 H, C-4 H), 4.03 (br s, 1 H, C-6 H), 6.29 (m, 1 H, 3-furyl β H), 6.93–7.53 (m, 6 H, 3-furyl α H and ArH); ir (liquid film) 2.86 (m), 6.23 (w), 6.72 (m), 6.94 (m), 7.20 (m), 7.34 (m), 11.48 (s), 12.34 (m), 12.72 μm (m); uv (neutral 95% EtOH) λ_{max} 264 nm (ε 452); uv (95% EtOH, $HClO_4$ added) λ_{max1} 283 nm (ε 3270), λ_{max2} 274 nm (3350), λ_{max3} 242 nm (5900); CD (*c* 0.43 mg/ml, neutral 95% EtOH, l = 0.1 dm) $[\theta]_{310}$ +128°, $[\theta]_{262}$ + 3600°, $[\theta]_{240}$ +940°, $[\theta]_{232}$ +2830°, $[\theta]_{230}$ +2310°, $[\theta]_{225}$ +3770°; CD (*c* 0.086 mg/ml, 95% EtOH, $HClO_4$ added, *l* = 0.1 dm) $[\theta]_{340}$ +860°, $[\theta]_{282}$ +24 830°, $[\theta]_{277}$ +23 120°, $[\theta]_{273}$ +24 620°, $[\theta]_{270}$ +23 540°, $[\beta]_{252}$ +32 530°, $[\theta]_{225}$ +300°; MS *m/e* (rel intensity) 371 (43) (M^+), 355 (7), 342 (8), 248 (100), 246 (4), 231 (4), 228 (30), 218 (10), 216 (10), 214 (20), 192 (19), 176 (7), 164 (19), 124 (17), 123 (19). 107 (42), 96 (25), 94 (31), 91 (35), 81 (25).

Conversion of 7β-(*p*-Tolylthio)deoxynupharidin-6-ol (4) to Its Immonium Perchlorate. A solution of 27 mg of the title hemiaminal in 2 ml of absolute EtOH was treated with 0.36 ml of 0.2 M aqueous $HClO_4$. The bulk of the solvent was vacuum evaporated, and the solid was separated by filtration and then recrystallized from $(CH_3)_2CO$–Et_2O to obtain 18 mg of white needles: mp 222.5–225 °C; ir (KBr) 3.21 (w), 6.05 (m), 6.26 (w), 6.74 (m), 6.94 (m), 7.30 (m), 9.2–9.5 (s), 11.46 (s), 12.38 μm (s).

Anal. Calcd for $C_{22}H_{30}NO_6SCl$: C, 58.21; H, 6.22; N, 3.09; S, 7.06. Found: C, 58.03; H, 6.30; N, 2.96, S, 7.06.

7β-(*p*-Tolylthio)deoxynupharidine (10). A gentle stream of CO_2 was bubbled through a solution of 40 mg of 7β-(*p*-tolylthio)deoxynupharidin-6-ol in MeOH. Thereafter 90 mg of $NaBH_4$ was added and the resulting mixture was kept at 25 °C for 48 h, at the end of which time TLC indicated that greater than 90% of the starting hemiaminal had been consumed. Thereafter the MeOH was vacuum evaporated, the residue mixed with C_6H_6, the solids removed by filtration, and the filtrate concentrated and added to a column of 15 g of Al_2O_3 (activity 2) which was eluted successively with 100 ml of C_6H_6, 50 ml of 9:1 C_6H_6–Et_2O, and 50 ml of 3:2 C_6H_6–Et_2O in 20-ml fractions. Fraction 1 yielded 26 mg of **10**: mp 88–89 °C; TLC (8:2 C_6H_6–Et_2O) R_f 0.9; ^1H NMR δ 0.84 (br s, 3 H, C-1 CH_3), 1.22 (s, 3 H, C-7 CH_3), 1.77 (d, *J* = 11 Hz, C-6 ax H), 2.29 (s, 3 H, $ArCH_3$), 2.75 (d, *J* = 11 Hz, 2 H with δ 2.88 d of d, C-6 eq H), 2.88 (d of d, *J* = 4 and 8 Hz, 2 H with δ 2.75, C-4 H), 6.17 (m, 1 H, 3-furyl β H), 6.78–7.37 (m, 6 H, 3-furyl α H and ArH); ir (liquid film) 3.66 (m), 6.26 (w), 6.68 (m), 6.72 (m), 7.24 (m), 7.28 (m), 11.42 μm (s); MS *m/e* (rel intensity) 355 (17) (M^+), 267 (12), 232 (92), 231 (43), 220 (16), 178 (20), 136 (34), 107 (23), 96 (49), 94 (100), 84 (56), 81 (22).

Anal. Calcd for $C_{22}H_{29}NOS$: C, 74.32; H, 8.23; N, 3.94; S, 9.02. Found: C, 74.56; H, 8.15; N, 3.95; S, 8.85.

7α-(*p*-Tolylthio)-7-epideoxynupharidine (11). A solution of 4 mg 7α-(*p*-tolylthio)-7-epideoxynupharidin 6-ol in 5 ml of MeOH was treated with 19 mg of $NaBH_4$ at 25 °C for 10 days. The reaction mixture was concentrated and chromatographed on 7 g of Al_2O_3 (activity 2) which was eluted successively with 30 ml of C_6H_6, 100 ml of 9:1 C_6H_6–Et_2O, and 100 ml of 4:1 C_6H_6–Et_2O in seven 30–35-ml fractions. Fraction 1 yielded 3 mg of **11**: mp 170–172 °C; TLC (7:3 C_6H_6-Et_2O) R_f 0.8; ^1H NMR (100 MHz) δ 0.96 (d, *J* = 5 Hz, 6 H with δ 0.97 s, C-1 CH_3), 0.97 (s superposed on δ 0.96 d, 6 H with 0.96 d, C-7 CH_3), 1.75 (d, *J* = 12.4 Hz, C-6 ax H), 2.35 (s, 3 H, $ArCH_3$), 2.90 (d, *J* = 12.4 Hz, 2 H with δ 2.94, d of d, C-6 eq H), 2.94 (d of d, *J* = 3 and 8 Hz, C-4 H), 6.54 (m, 3-furyl β H), 6.95–7.25 (m, 3-furyl α H and Ar H); ir (liquid film) 3.62 (w), 6.00 (w), 6.23 (w), 6.69 (m), 6.90 (m), 7.29 (m), 11.42 (s), 12.28 (s), 12.69 μm (s); MS *m/e* (rel intensity) 355 (6)

(M+), 233 (74), 232 (38), 231 (45), 220 (15), 178 (30), 136 (30), 107 (34), 96 (100), 94 (61), 81 (45).

Anal. Calcd for $C_{22}H_{29}NOS$: C, 74.32; H, 8.23; N, 3.94. Found: C, 74.07; H, 8.12; N, 3.76.

7β-(p-Toluenesulfonyl)deoxynupharidine (12). A solution of 13 mg of 7β-(p-toluenesulfonyl)deoxynupharidin-6-ol (6) in MeOH was acidified to pH 4 with a gentle stream of gaseous HCl and then treated portionwise with a total of 50 mg of $NaBH_3CN$. Periodically HCl was bubbled into the solution to maintain the pH between 4 and 6. When TLC indicated that >90% hemiaminal had been consumed, the solution was concentrated under vacuum and the residue was treated with aqueous KOH and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), concentrated under vacuum, and chromatographed on 10 g of Al_2O_3 (activity 2) with 50 ml of C_6H_6, 150 ml of 19:1 C_6H_6–Et_2O, 150 ml of 9:1 C_6H_6–Et_2O, and 50 ml of 3:1 Et_2O–MeOH in 20-ml fractions for fractions 1–6 and 35-ml fractions for fractions 7–11. Fractions 2–4 combined yielded 7 mg of **12** in white needles: mp 170–172.3 °C; TLC (developed three times with 19:1 C_6H_6–Et_2O) R_f 0.65; ^1H NMR (100 MHz) δ 0.88 (d, J = 5.8 Hz, 3 H, C-1 CH_3), 1.28 (s, 3 H, C-7 CH_3), 2.08 (d, J = 11.8 Hz, C-6 ax H), 2.42 (s, 3 H, Ar CH_3), 2.80 (d of d, J = 11.8 and 2.4 Hz, 2 H with 2.98 d of d, C-6 eq H), 2.98 d of d, J = 2 and 8 Hz, C-4 H), 6.23 (m, 1 H, 3-furyl β H), 7.15–7.40 (m, 4 H, ArH), 7.63 (m, 2 H, 3-furyl α H); ir (KBr) 3.62 (w), 6.26 (m), 6.69 (m), 6.84 (m), 6.89 (m), 7.22 (m), 7.28 (m), 7.79 (s), 8.72 (s), 8.89 (m), 9.08 (m), 9.32 (s), 9.38 (m), 9.66 (m), 9.79 (m), 11.43 (s), 12.26 (s), 12.34 μm (s); ^{13}C NMR δ 17.1 (C-12), 19.1 (C-11), 21.7 (C-23), 26.6 (C-9), 29.0 (C-8), 33.6 (C-2), 35.4 (C-3), 36.6 (C-1), 55.7 (C-6), 60.2 (C-4), 62.8 (C-7), 68.7 (C-10), 109.2 (C-15), 129.6 (C-18 and C-22 or C-19 and C-21), 130.7 (C-18 and C-22 or C-19 and C-21), 139.8 (C-14), 143.5 (C-16); MS m/e (rel intensity) 387 (6) (M+), 252 (11), 232 (51), 231 (100), 216 (5), 136 (15), 107 (9), 96 (26), 94 (37), 91 (11), 81 (12).

Anal. Calcd for $C_{22}H_{29}NO_3S$: C, 68.18; H, 7.54; N, 3.62. Found: C, 68.33; H, 7.59; N, 3.50.

7α-(p-Toluenesulfonyl)-7-epideoxynupharidine (13). A solution of 32 mg of 7α-(p-toluenesulfonyl)-7-epideoxynupharidin-6-ol (7) in MeOH was treated with one portion of 39 mg of $NaBH_4$ at 25 °C for 12 h. The solution was concentrated and thereafter chromatographed on 10 g of Al_2O_3 (activity II) which was eluted with 50 ml of C_6H_6, 40 ml of 3:1 C_6H_6–Et_2O, 50 ml of 3:2 C_6H_6–Et_2O, and 30 ml of Et_2O. Fractions 1–6 consisted respectively of 20, 10, 25, 30, 30, and 60 ml portions of eluent. Fractions 5 and 6 were predominantly unconverted hemiaminal sulfone but fractions 3 and 4 combined yielded 17 mg of pure title sulfone **13**: mp 136–137 °C; TLC (7:3 C_6H_6–Et_2O) R_f 0.7; ^1H NMR (100 MHz) (d, J = 5.6 Hz, 3 H, C-1 CH_3), 1.10 (s, 3 H, C-7 CH_3), 2.42 (s, 3 H, $ArCH_3$), 3.12 (d of d, J = 2 and 10 Hz, 1 H, C-4 H), 3.41 (d, J = 12 Hz, 1 H, C-6 eq H), 6.50 (m, 1 H, 3-furyl β H), 7.15–7.50 (m, 4 H, ArH), 7.70 (m, 2 H, 3-furyl α H); ^1H NMR (C_6D_6) δ 0.70 (d, J = 5 Hz, 3 H, C-1 CH_3), 0.99 (s, 3 H, C-7 CH_3), 1.74 (d, J = 12 Hz, C-6 ax H), 1.90 (s, 3 H, $ArCH_3$), 2.92 (d of d, J = 4 and 10 Hz, 1 H, C-4 H), 3.59 (d, J = 12 Hz, 1 H, C-6 eq H), 6.55, 6.70, 6.82 (3 H, Ar H and 3-furyl H), 7.64, 7.89 (2 H, ArH and 3-furyl H); ^{13}C NMR δ 19.0 (C-11), 21.6 (C-12 or C-23), 22.7 (C-23 or C-12), 25.2 (C-9), 29.3 (C-8 or C-3), 31.5 (C-3 or C-8), 31.8 (C-1), 34.1 (C-2), 58.8 (C-6), 60.3 (C-4), 62.3 (C-7), 67.2 (C-10), 110.6 (C-15), 128.3 (C-13), 129.4 (C-17 or C-20), 130.7 (C-20 or C-17), 140.1 (C-14), 143.2 (C-16), 144.0 (C-18 and C-22 or C-19 and C-21), 144.5 (C-18 and C-22 or C-19 and C-21); ir (CCl_4) 3.69 (w), 6.29 (m), 6.71 (m), 6.96 (m), 7.02 (m), 7.35 (m), 7.71 (s), 7.80 (s), 8.76 (s), 8.87 (s), 11.60 μm (s); MS m/e (rel intensity) 387 (5) (M+), 252 (12), 232 (46), 231 (100), 216 (5), 136 (16), 107 (8), 96 (29), 94 (40), 91 (7), 81 (10).

Anal. Calcd for $C_{22}H_{29}NO_3S$: C, 68.18; H, 7.54; N, 3.62; S, 8.27. Found: C, 67.93; H, 7.29; N, 3.58; S, 7.94.

Reduction of Indolizidine Aldehyde 9 to Primary Alcohol 14. A solution of 68 mg of **9** in 5 ml of MeOH was treated with 80 mg of $NaBH_4$ at 25 °C for 5 min at which time TLC (Al_2O_3, C_6H_6) indicated the complete consumption of aldehyde (R_f 0.33). The solution was concentrated and chromatographed on 10 g of Al_2O_3 (activity 3) which was eluted with 50 ml of C_6H_6. Vacuum evaporation of the C_6H_6 gave 78 mg of alcohol **14**, an oil: TLC (7.5:2.5 C_6H_6–Et_2O) R_f 0.42; ^1H NMR (100 MHz) δ 0.96 (d, J = 6.2 Hz, 3 H, C-8 CH_3), 1.02 (s, 3 H, C-3 CH_3), 2.62 (A or B of AB q, J = 10 Hz, 1 H, CH_2OH), 2.91 (B or A of AB q, J = 10 Hz, 1 H, CH_2OH), 3.52 (d of d, J = 6 and 8 Hz, 1 H, C-4 H), 6.52 (m, 1 H, 3-furyl β H), 7.28–7.52 (m, 3-furyl α H); ^{13}C NMR δ 18.4 (C-10 or C-12), 18.5 (C-12 or C-10), 28.8 (C-1), 33.1 (C-6, C-7, or C-2), 36.7 (C-6, C-7, or C-2), 36.8 (C-6, C-7, or C-2), 37.1 (C-8), 52.9 (C-5), 65.0 (C-3), 67.2 (C-11), 69.3 (C-9), 109.5 (C-15), 127.9 (C-13), 139.3 (C-14), 142.8 (C-16); ir (liquid film) 2.92 (m), 3.62 (w), 6.72 (m), 6.92 (m), 7.20 (m), 7.33 (m), 11.48 μm (s); ir (6.5, 4.8, 3.0, 2.2, 1.7, 1.4 × 10^{-2} M in CCl_4) 3438 (intramolecular bonded OH), 3500–3650 cm^{-1} (free OH) absent; MS m/e (rel intensity) 249 (1), 248 (2), 247 (2), 246 (1), 234 (4), 218 (100), 164 (11), 136 (6), 107 (16), 96 (9), 94 (36), 91 (6), 82 (21), 81 (26).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.47; H, 9.17; N, 5.44.

Conversion of the Primary Alcohol 14 to Its Benzoate 15. A solution of 29 mg of **13** in 0.5 ml of CH_2Cl_2 was treated at 25 °C for 1 h with 9 drops of benzoyl chloride and 12 drops of pyridine. Thereafter the resulting solution was kept at 0 °C for 14 h at the end of which TLC (7.5:2.5 C_6H_6–Et_2O) showed **14** (R_f 0.42) had been consumed and **15** (R_f 0.75) present. The solvent was evaporated at reduced pressure and the residual oil was taken up in 5 ml of Et_2O. The Et_2O solution was shaken with 5 ml of 0.5% aqueous HCl, separated, and washed with H_2O. The combined aqueous and aqueous HCl washings were basified (pH 14) with MeOH, saturated with NaCl, and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried (Na_2SO_4) and the solvent was evaporated at reduced pressure. The resulting residue was chromatographed on 5 g of Al_2O_3 (activity 2) by eluting with 5% Et_2O–hexane. The first fraction (1 ml), containing no Dragendorff active material, was discarded. Fraction 2 (40 ml) yielded 18 mg of pure **15**, an oil: TLC (7.5:2.5 C_6H_6–Et_2O) R_f 0.75; ir (CCl_4) 3.60 (w), 5.80 (s), 11.45 μm (s); ^1H NMR δ 0.93 (d, J = 5.5 Hz, 3 H, C-8 CH_3), 1.14 (s, 3 H, C-3 CH_3), 3.56 (m, 1 H, C-5 H), 3.71 (s, 2 H, C-3 CH_2O), 6.48 (m, 1 H, 3-furyl β H), 7.3–7.65 (m, 5 H, 3-furyl α H and benzoyl ArH), 8.03 (q, 2 H, J = 2 and 7 Hz, benzoyl ortho Ar H); ^1H NMR (C_6D_6) δ 0.83 (d, J = 5.5 Hz, 3 H, C-8 CH_3), 1.02 (s, 3 H, C-6 CH_3), 3.86 (s, 2 H, C-3 CH_2O).

Conversion of the Benzoate Ester 15 to Its Hydrobromide Salt. A solution of 18 mg of the benzoate **15** (0.05 mmol) in 0.5 ml of MeOH was treated with 0.6 ml of 0.1 M aqueous HBr (0.06 mmol). The solvent was evaporated under vacuum and the solid residue was recrystallized over the course of several weeks from MeOH at 0 °C. One-half of the resulting prism-shaped crystals (14 mg) was recrystallized from C_6H_6 to obtain needles: mp 212–213 °C; MS (130 °C) m/e (rel intensity) 353 (0.6) (M+), 338 (1.1), 231 (6), 218 (100), 203 (0.6), 187 (0.7), 176 (0.6), 174 (0.6), 161 (1.1), 136 (1.9), 122 (1.6), 107 (2.7), 105 (89), 94 (7). The remaining half of the original crystals was recrystallized from wet MeOH to obtain prisms: mp partially 94–110 °C and completely 208–219 °C.

TLC of the base liberated from the salt showed R_f 0.75 (7.5:2.5 C_6H_6–Et_2O).

Transformation of 7β-(p-Tolylthio)deoxynupharidine (10) to 7β-(p-Toluenesulfonyl)deoxynupharidine (12). A solution of 5 mg of **10** in 0.45 ml of acetic acid was treated with 0.05 ml of 30% H_2O_2 at 25 °C. After 1 h TLC (7:3 C_6H_6–Et_2O) exhibited the starting sulfide spot (R_f 0.82) and a new spot (R_f 0.53). After 20 h both R_f 0.82 and R_f 0.53 spots disappeared and a second new spot at R_f 0.71 appeared. After 21 h the reaction mixture was evaporated to dryness under vacuum and a drop of pyridine was added. The excess pyridine was removed at reduced pressure and the residue was chromatographed on 1 g of Al_2O_3 (activity 3) with C_6H_6, the first 20 ml of which yielded 1.6 mg of **12**: TLC (7:3 C_6H_6–Et_2O) R_f 0.71; ir (CCl_4) identical with that of **12** isolated from the reaction of p-toluenesulfonyl chloride and 6-dehydrodeoxynupharidine as described elsewhere above.

Transformation of 7α-(p-Tolylthio)deoxynupharidine (11) to 7α-(p-Toluenesulfonyl)deoxynupharidine (13). A solution of 3.6 mg of **11** in 0.45 ml of acetic acid was treated with 0.05 ml of 30% H_2O_2 at 25 °C for 25 h. The solvent was removed at reduced pressure and the residue basified with a drop of pyridine. Excess pyridine was removed at reduced pressure and the residue was chromatographed on 1 g of Al_2O_3 with C_6H_6, the first 5 ml of which was discarded. Continued elution with 20 ml of CH_2Cl_2 yielded 2.2 mg of **13**: TLC (7:3 C_6H_6–Et_2O) R_f 0.69; ir ($CHCl_3$ or CCl_4) identical with those of **13** obtained in the reaction of 6-dehydrodeoxynupharidine with p-toluenesulfonyl chloride as described elsewhere above.

Registry No.—**1**, 32468-93-4; **2**, 10409-07-1; **3**, 103-19-5; **4**, 59187-39-2; **4** perchlorate, 59187-40-5; **6**, 59187-41-6; **8**, 59187-42-7; **9**, 59246-19-4; **10**, 59187-43-8; **11**, 59187-44-9; **12**, 59187-45-0; **13**, 59187-46-1; **14**, 59187-47-2; **15**, 59187-48-3; **15** HBr, 59246-20-7; p-toluenesulfonyl chloride, 98-59-9.

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(29) When the reaction solution was kept at 25 °C in benzene, conditions previously used to good advantage in the reaction of **1** with arylthiosulfonates (see ref 16), dark-colored intractable material resulted. Therefore the typical procedure consisted in mixing the reactant at 25 °C and cooling immediately thereafter.

Reactions of Activated Arenesulfonates with Oxygen and Nitrogen Nucleophiles. Hydroxide Ion and Micellar Catalysis

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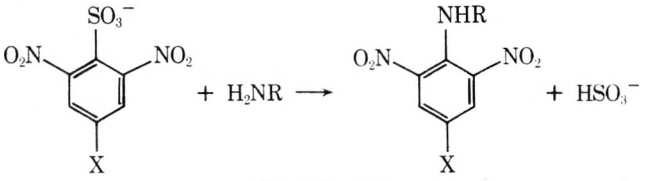
The reactions of 2,4,6-trinitrobenzenesulfonate ion (TNBS) and 2,6-dinitro-4-trifluoromethylbenzenesulfonate ion (TFBS) with OH^- are catalyzed by OH^- as are the reactions with aniline and glycinate ion, and the kinetic parameters have been evaluated in terms of a mechanism in which a tetrahedral intermediate decomposes to products spontaneously or with hydroxide ion catalysis. Decomposition of the tetrahedral intermediate can be followed spectrophotometrically for reaction of TNBS with OH^- in aqueous Me_2SO. At relatively low pH (<10.5), cationic micelles of cetyltrimethylammonium bromide (CTABr) catalyze the reactions of TNBS by the following factors: glycinate, 6; leucinate, 38; phenylglycinate, 174; aniline, 30. The reaction of glycineamide is slightly inhibited by CTABr. In CTABr the hydroxide ion catalysis of reactions of TNBS with aniline or OH^- is considerably less than at relatively low pH. The reaction of phenoxide ion with TNBS is catalyzed by a factor of 2000 by CTABr.

Activated arenesulfonates, e.g., 2,4,6-trinitrobenzenesulfonate ion (TNBS) and 2,6-dinitro-4-trifluorobenzenesulfonate ion (TFBS), react readily with primary and secondary amines and are useful protein modifying agents.[1] The reaction of TNBS with amino acid anions is reportedly cleanly second order.[1a,b] Aromatic nucleophilic substitution by uncharged



(X = NO_2, CF_3)

and anionic nucleophiles is catalyzed by cationic micelles,[2–5] which also speed formation of the tetrahedral intermediate.[6,7] Addition to give the tetrahedral intermediate is generally rate limiting for reactions of halonitrobenzenes in polar hydroxylic solvents.[13,14]

The polarities of micellar surfaces are similar to those of many proteins,[10] so that nucleophilic aromatic substitution catalyzed by a micelle should be a better model for protein modification than reaction in water, and the effects of cationic micelles of cetyltrimethylammonium bromide (CTABr) upon reactions of TFBS and 2,4-dinitrofluorobenzene were examined.[15] For both reagents micellar catalysis increases with increasing hydrophobicity of the nucleophile, as is generally found,[8–12] but the effect is much more marked for reactions of TFBS.

In this paper we extend the investigation to reactions of TNBS and we show that for reactions with hydroxide and glycinate ion and aniline there is a base-catalyzed reaction suggesting that the breakdown of the tetrahedral intermediate can become rate limiting, which complicates discussion of the micellar catalysis. However, reaction of phenoxide ion with TNBS is very strongly catalyzed by CTABr, showing the role of substrate hydrophobicity in a non-base-catalyzed nucleophilic aromatic substitution.

Experimental Section

Materials. The preparation of the surfactants and most of the reagents followed methods already described.[4,5,15] The tertiary amines were treated with tosyl chloride to remove secondary or primary amines and then distilled.

Kinetics. All the reactions were followed spectrophotometrically in water, at 25.0 °C, using Gilford spectrophotometers[15] at the following wavelengths: amino acid derivatives, 420 nm; phenoxide ion, 446 nm; OH^-, 430 nm; aniline, 435 nm.

The nucleophile was in large excess over the arenesulfonate, which was $1–4 \times 10^{-5}$ M, and the integrated first-order rate constants, k_ψ, are in s^{-1}, and the second-order rate constants, k_2^{obsd}, $M^{-1}\,s^{-1}$, were calculated by dividing k_ψ by the reagent concentration. It was necessary to use low concentrations of TNBS because otherwise there was precipitation during reactions with aniline in the absence of surfactant. The rate constants for reactions with amines in water were unaffected, within experimental error, by up to threefold changes in reagent concentration or for reaction with aniline by increases in pH from 7.5 to 10.

The pH was such that the amino acids were wholly in the reactive anionic form, and 0.027 M carbonate buffer was used, except for re-

Table I. Reactions of Amines in the Absence of Surfactant[a]

Reagent	k_2, M^{-1} s^{-1} TNBS	TFBS
Glycinate	6.41	0.15[b]
Leucinate	4.86	0.029[b]
Phenylglycinate	8.47	0.061[b]
Glycineamide	1.45	0.037[b]
Aniline[c]	2.99	0.00105

[a] At 25.0 °C in aqueous solution. [b] Reference 15. [c] pH 7.5.

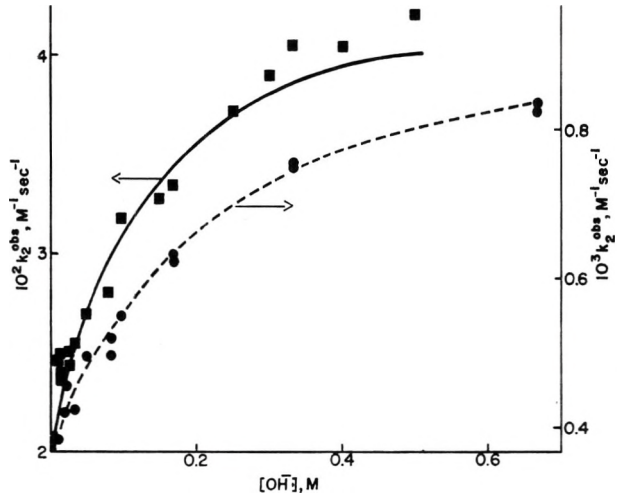


Figure 1. Effect of OH^- upon the second-order rate constants of OH^- with TNBS (solid line) and TFBS (broken line). The lines are calculated.

actions with tertiary amine buffers. Redistilled, deionized, CO_2-free water was used for the kinetic solutions.

The amines and phenoxide ion are so much more reactive than hydroxide ion that its reaction can be neglected. The reaction of phenoxide ion with TNBS was shown to give the phenoxy ether initially, by comparison of the spectra obtained by repetitive scanning of the reaction mixture with authentic material prepared from picryl chloride.[16] The phenoxy ether readily hydrolyzes under the reaction conditions,[13] so reaction was followed at 446 nm, which is an isosbestic point. There was a small change in the spectra of the products of reaction with the amines, but it was so much slower than attack of the amines on TNBS that it did not complicate the rate measurements.

Results and Discussion

Reactions of amino acid anions with TNBS are cleanly second order, and are not catalyzed by weak bases,[1a,b] but the reaction of TFBS with hydroxide ion is of greater than first order with respect to hydroxide ion,[15] suggesting that attack of hydroxide ion is assisted by a second hydroxide ion. We subsequently found that reactions of aniline and glycinate anion are catalyzed by added hydroxide ion, suggesting that an initially formed tetrahedral intermediate decomposes spontaneously at low pH (pH <10) but with hydroxide ion catalysis at high pH. Most of our experiments with amines were at pH such that there was no hydroxide ion catalysis, and these will be considered first.

Reactions of Amines in the Absence of Surfactants. The second-order rate constants for reactions of amines with TNBS and TFBS at relatively low pH are in Table I. TFBS and 2,4-dinitrofluorobenzene have similar reactivities toward amines,[15] but TNBS is much more reactive because of powerful electron withdrawal by the *p*-nitro group. Hydroxide ion catalysis of amine reactions will be discussed after consideration of the reactions of TNBS and TFBS with hydroxide ion.

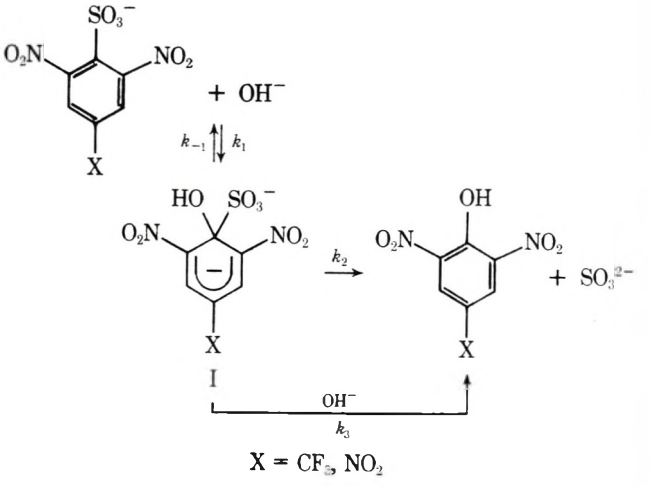
Reactions with Hydroxide Ion. The second-order rate constants for reactions of TNBS and TFBS with hydroxide ion increase with increasing hydroxide ion concentration, but tend to level off at relatively high concentrations of hydroxide ion (Figure 1). These results were unexpected because in polar hydroxylic solvents nucleophilic aromatic substitutions with oxygen nucleophiles are typically second-order reactions,[13] but reactions with amines are often base catalyzed,[13,14,17] suggesting that the high order with respect to hydroxide ion in reactions of these activated arenesulfonates is due to intervention of a base-catalyzed reaction (Scheme I).

Table II. Analysis of the Rate Constants for Reactions with Hydroxide Ion[a]

Substrate	k_1, M^{-1} s^{-1}	k_2/k_{-1}	k_3/k_2, M^{-1} s^{-1}	k_3/k_{-1}, M^{-1} s^{-1}
TNBS	4.5×10^{-2}	0.8	19	15 (15)
TFBS	1.0×10^{-3}	0.6	11	6.4 (6.9)

[a] The values in parentheses are estimated from the initial slopes of plots of k_2^{obsd} against $[OH^-]$.

Scheme I



X = CF_3, NO_2

Applying the steady-state approximation gives

$$k_2^{obsd} = k_1(k_2 + k_3[OH^-])/(k_{-1} + k_2 + k_3[OH^-]) \quad (1)$$

where k_2^{obsd} is the second-order rate constant with respect to OH^- and the arenesulfonate, and neglecting electrolyte effects of NaOH upon the individual rate constants.

Equation 1 can be rearranged to

$$k_2^{obsd}/(k_1 - k_2^{obsd}) = (k_2/k_{-1}) + (k_3[OH^-]/k_{-1}) \quad (2)$$

which should give a linear relation between the left-hand term and $[OH^-]$ if the correct value of k_1 is used. We chose arbitrary values of k_1 and selected that which gave the best linear fit, and thus calculated k_2/k_{-1} and k_3/k_{-1} (Table II).

Equation 1 reduces to eq 3 when $[OH^-] \to 0$

$$k_2^{obsd} = k_1k_2/(k_{-1} + k_2) \quad (3)$$

and the extrapolated values of k_2^{obsd} (Figure 1) agree reasonably well with the predicted values.

Another test of equation is to use the initial slope of a plot of k_2^{obsd} against $[OH^-]$. Differentiation of eq 1 gives

$$\frac{k_3}{k_1k_{-1}}\frac{dk_2^{obsd}}{d[OH^-]} = \frac{k_3}{k_{-1} + k_2 + k_3[OH^-]} \quad (4)$$

From the experimental value of $dk_2^{obsd}/d[OH^-]$ (Figure 1) and the estimated values of k_1 and k_2/k_{-1} (Table II) we calculate the values of k_3/k_{-1}, given in parentheses in Table II, which are in satisfactory agreement with the values obtained using eq 2.

Added salts increase k_2^{obsd}, and NaCl has a larger effect

Table III. Salt Effects upon Reaction of TNBS with Hydroxide Ion

	Salt[a]	
[OH⁻], M	NaCl	$NaClO_4$
0.005	2.08	3.68
0.025	2.48	3.81 3.22
0.167	3.39	4.29 3.68
0.333	3.69	4.26

[a] Reactions with added salt are at $I = 1$.

Table IV. Reaction of TNBS in Tertiary Amines[a]

$[Et_3N]$, M	[NMP], M	10^2 [OH⁻], M[b]	10^4 k_ψ, s^{-1}	10^2 $k_\psi/[OH^-]$, M^{-1} s^{-1}
0.0497		0.45	1.26	2.8 (2.1)
0.249		1.04	3.08	3.0 (2.4)
0.489		1.46	4.12	2.8 (2.4)
	0.0521	0.37	0.80	2.1 (2.1)
	0.267	0.85	1.91	2.3 (2.3)
	0.512	1.20	2.52	2.1 (2.4)

[a] At 25.0 °C and [TNBS] = 3.9×10^{-5} M; the values of $k_\psi/[OH^-]$ in parentheses are interpolated for reaction with NaOH. [b] Calculated from pK_a of the amines.

Table V. Reaction of TNBS in Tertiary Amine Buffers[a]

R_3N	$[R_3N]/[R_3\overset{+}{N}H]$	$[R_3N]$, M	10^4 k_ψ, s^{-1}
Et_3N	4	0.032	2.09
		0.064	2.65
		0.128	3.01
NMP	2	0.032	0.77
		0.064	0.81
		0.128	0.92
NMP	4	0.032	1.19
		0.064	1.39
		0.128	1.65

[a] At 25.0 °C and [TNBS] = 3.9×10^{-5} M at $I = 1$ (NaCl).

than $NaClO_4$, but carrying out the reaction at an ionic strength of 1 does not eliminate the dependence of k_2^{obsd} on hydroxide ion (Table III).

The decomposition of the intermediate (I) to products probably requires loss of a proton from the hydroxyl group, and this ionization should be subject to a positive salt effect. Because NaCl and $NaClO_4$ have different salt effects, we see no simple way of allowing for the effects of NaOH as an electrolyte,[18] because it has to be present in relatively high concentration, and the rate constants in Table I may include a contribution due to an (undetermined) electrolyte effect. However, the high order with respect to hydroxide ion is not eliminated by working at constant ionic strength.

The decomposition of the intermediate (I) could be general base or specific hydroxide ion catalyzed. The usual test of carrying out the reaction in buffers of a given pH is not readily applicable at these high concentrations of hydroxide ion, but we used triethylamine and *N*-methylpyrrolidine (NMP) as sources of hydroxide ion, and found no catalysis by the tertiary amine.

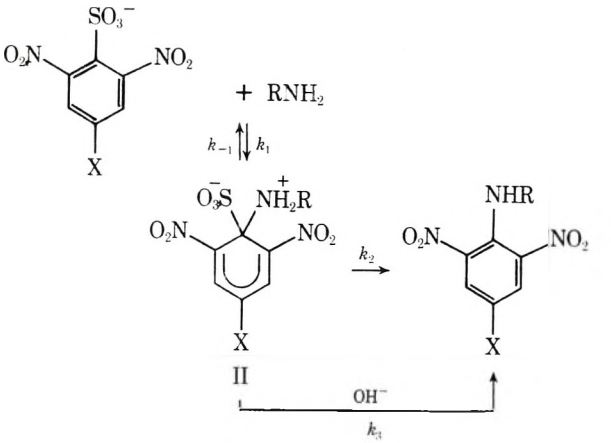
The reaction of TNBS was followed using a range of concentrations of tertiary amine (Table IV), and the concentrations of hydroxide ion were calculated from the values of pK_a of 10.65 and 10.46 for triethylamine and *N*-methylpyrrolidine, respectively,[23] neglecting activity effects. (This neglect is probably not too serious because the ionic strengths of the solutions are low.) The second-order rate constants, $k_\psi/[OH^-]$, calculated in this way, agree reasonably well with the second-order rate constants, k_2^{obsd}, determined from reaction in sodium hydroxide (Figure 1). When reaction was carried out using fixed buffer ratios and ionic strength of 1 (with NaCl), the first-order rate constants increased, but not markedly, with amine concentration (Table V). The variations in k_ψ with buffer concentration could well be due to the different concentrations of ammonium ions because there is no reason to believe that sodium and trialkylammonium ions will have the same salt effects; in fact there is evidence which suggests the opposite because the bulky anionic transition states could interact favorably with the bulky ammonium ions.[3b,19-22] It is difficult to carry out buffer dilution experiments if high buffer concentrations have to be used.

These experiments with tertiary amines suggest that the reaction is not general base catalyzed, but this conclusion is tentative because kinetic salt effects could complicate the situation and if the Bronsted coefficient, β, is close to unity the tertiary amines may not be basic enough to contribute to the catalysis by hydroxide ion, although often hydroxide ion is less basic kinetically than expected from its formal pK value,[24] so that proton loss from I could be concerted with product formation.

These hydroxide ion reactions involve dianionic tetrahedral intermediates, and dianionic Meisenheimer complexes have been observed in addition of hydroxide ion to 1,3,5-trinitrobenzene.[25]

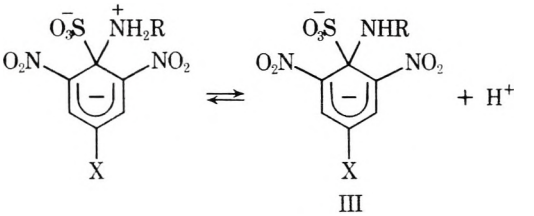
Hydroxide Ion Catalysis of Reactions with Amines. Both TNBS and TFBS react much more rapidly with primary amines than with hydroxide ion, but the attack of amines is catalyzed by hydroxide ion (Tables VI and VII). The reaction is formulated in Scheme II, which is similar to Scheme I for reaction with hydroxide ion.

Scheme II



X = CF_3, NO_2
R = C_6H_5, $CH_2CO_2^-$

In the above scheme it is possible that decomposition of the intermediate (II) to products involves the ionization



III

followed by slow decomposition of the dianion (III), or a concerted process (cf. ref 13, 14, 17).

The kinetics can be treated using the method outlined for reaction with hydroxide ion, with the simplification that the amines, which are in relatively low concentration, do not act as base catalysts.

Rearrangement of eq 1 gives

Table VI. Hydroxide Ion Catalysis of Reactions of TNBS and TFBS with Aniline[a]

	k_2^{obsd}, M^{-1} s^{-1}	
[NaOH], M	TNBS[b]	TFBS[c]
0	2.99 (3.00)	0.00105 (0.00105)
0.010	5.87 (5.82)	
0.015	6.92 (7.05)	
0.020		0.0035 (0.0034)
0.025	9.18 (9.18)	0.0040 (0.0040)
0.033	10.5 (10.7)	0.0047 (0.0050)
0.040		0.0056 (0.0058)
0.050	13.7 (13.7)	0.0077 (0.0070)
0.084		0.0115 (0.0108)
0.100	18.7 (19.2)	
0.150	24.2 (21.6)	
0.167		0.0227 (0.0195)
0.333		0.0420 (0.0355)

[a] At 25.0 °C the values in parentheses are calculated (Table VIII). [b] 0.01 M $PhNH_2$. [c] 0.0333 M $PhNH_2$.

Table VII. Hydroxide Ion Catalysis of Reactions of TNBS with Glycinate Ion[a]

[NaOH], M	k_2^{obsd}, M^{-1} s^{-1}
0	6.41 (6.41)
0.015	8.35 (8.34)
0.023	9.16 (9.24)
0.040	11.0 (10.8)
0.090	14.3 (14.1)
0.140	15.8 (16.4)

[a] At 25.0°C with 0.01 M glycinate ion; the values in parentheses are calculated (Table VIII).

$$\frac{1}{k_2^{obsd}} = \frac{1}{k_1} + \frac{k_{-1}}{k_1(k_2 + k_3[OH^-])} \quad (5)$$

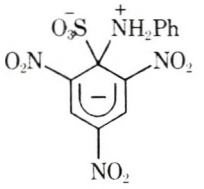
If k_2^{OH} and k_2^0 designate the values of the observed second-order rate constant, k_2^{obsd}, in the presence and absence of hydroxide ion, we obtain

$$\frac{k_2^{OH}}{k_2^{OH} - k_2^0} = \frac{k_1 k_2}{k_{-1} k_2^0}\left(1 + \frac{k_2}{k_3[OH^-]}\right) \quad (6)$$

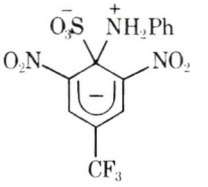
[In this formulation the observed rate constants are corrected for the minor contribution from a direct reaction of OH^- with the substrate (Figure 1)].

Plots of $k_2^{OH}/k_2^{OH} - k_2^0$) against $1/[OH^-]$ are linear for reactions of aniline with TNBS and TFBS (Figure 2), and from the slope and the intercept we estimate k_2/k_3, and insertion of these values into eq 5 then gives k_1 and k_{-1}/k_2. The values of the various kinetic parameters are given in Table VIII, and the calculated values of k_2^{obsd} agree reasonably well with the observed values (Tables VI and VII).

These results suggest that in the absence of added strong base the intermediates return to starting material much more readily than go to product, and the various kinetic parameters depend markedly on the structure of the reagents. Considering first the reactions with aniline, the values of k_2/k_{-1} and k_3/k_{-1} are much larger for the reaction with TNBS than with TFBS, probably because the strong electron withdrawal by the 4-nitro group allows easier proton loss from IV than from V, but the values of k_3/k_2 are very similar.



IV



V

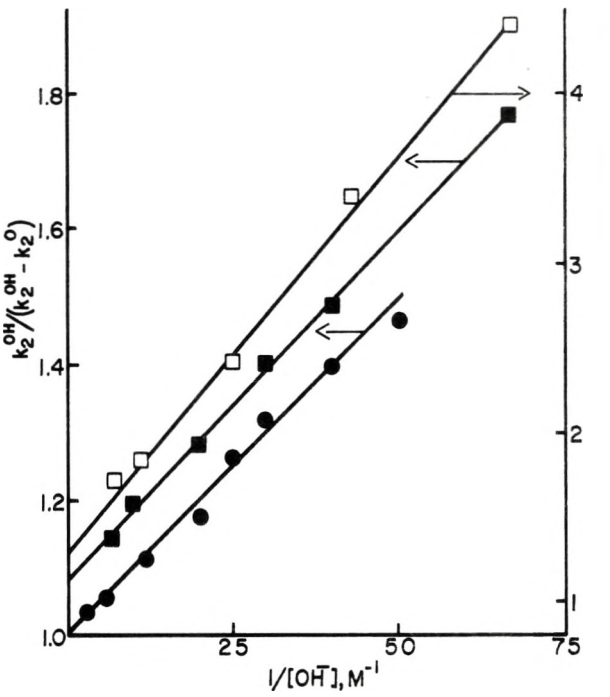
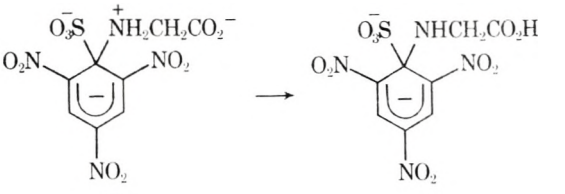


Figure 2. Analysis of the hydroxide ion catalyzed reactions of aniline (solid points) and glycinate ion (open points) with TNBS (■, □) and TFBS (●).

The pattern is different again for reaction with glycinate ion, where k_2/k_{-1} is larger than for reaction with aniline. This difference was unexpected because the −I effect of the phenyl group should make IV a stronger acid than VI. The difference could be due to an intramolecular proton transfer to the carboxylate moiety of VI, because although the carboxylate ion



VI

is a weak base it is in a favorable position to accept a proton from the ammonium ion, and this intramolecular proton transfer could occur more readily than an intermolecular transfer to water.[26] This suggestion is consistent with the observation that k_3/k_{-1} is similar for reactions of TNBS with aniline and glycinate ion (Table VIII), because k_3 involves proton transfer to OH^-.

This explanation suggests that the proton loss from the ammonium ion in the intermediate (VI) is part of the rate-limiting step of product formation and, by implication, that this is also true for reaction with aniline. The values of k_3/k_2 for reaction with aniline are smaller than expected if they were controlled by the equilibrium basicities of water and hydroxide ion (assuming that proton loss is a prerequisite for decomposition of the intermediates to products). Intramolecular proton transfer from an ammonium ion moiety to an o-nitro group has been considered as a route to the decomposition of tetrahedral intermediates, especially for reactions in nonpolar solvents.[14] Consistently, TNBS is more reactive than TFBS, but the difference is most marked for the reactions with aniline, not because the rates of nucleophilic attack are so different, but because the values of k_2/k_{-1} and k_3/k_{-1} are much lower for reaction of TFBS (Table VIII).

Formation of Tetrahedral Intermediates. The difference between the kinetic forms of the reactions of halobenzenes and

Table VIII. Analysis of the Base-Catalyzed Reactions with Amines

Substrate	Amine	k_2^0, M^{-1} s^{-1}	k_1, M^{-1} s^{-1}	k_2/k_{-1}	k_3/k_{-1}, M^{-1} s^{-1}	k_3/k_2, M^{-1} s^{-1}
TNBS	Aniline	2.99	32.7	0.10	11.4	113
TFBS	Aniline	0.00105	0.123	0.01	1.05	105
TNBS	Glycinate	6.41	24.8	0.35	10.0	29

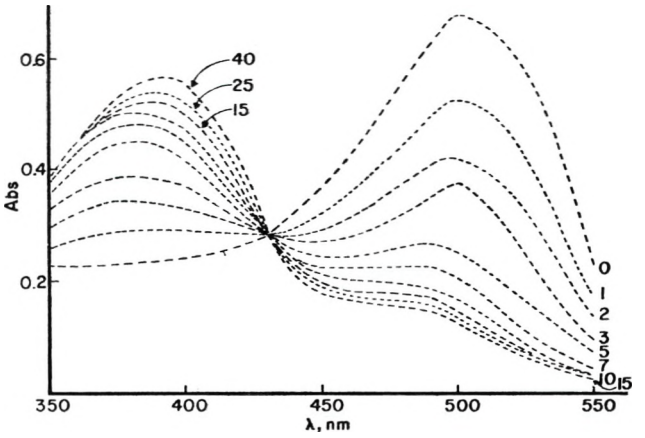


Figure 3. Repetitive scans of the spectrum of TNBS (3.9×10^{-5} M) and 0.333 M NaOH in DMSO-H_2O (65:35 v/v) at 25 °C. The times are in minutes.

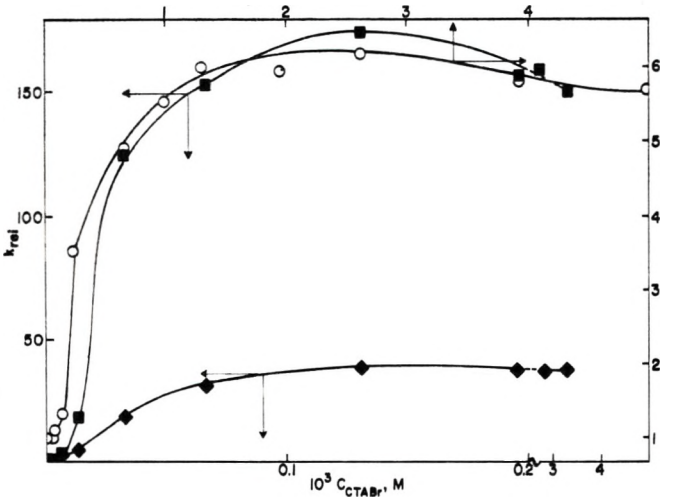


Figure 4. Micellar catalysis by CTABr of the reactions of 8.08×10^{-4} M leucinate (♦), 1.44×10^{-4} M phenylglycinate (■), and 10^{-3} M glycinate ion (○).

these activated arenesulfonates arises because the sulfite dianion should be a poorer leaving group than a halide ion and the strong electron withdrawal by the substituents in TNBS and TFBS should stabilize a tetrahedral intermediate.

Repetitive scans of the reaction mixtures in water gave no evidence for buildup of an intermediate, but we saw spectral evidence for intermediate formation between TNBS and OH^- in aqueous DMSO.

In the reaction of TNBS with 0.333 M NaOH in Me_2SO-H_2O 65:35 (v/v) at 25 °C there was an immediate appearance of a peak with λ_{max} at 505 nm which gradually disappeared giving picrate ion, λ_{max} 390 nm (Figure 3).

These observations show that activated arenesulfonates are useful substrates for dissection of the various steps of aromatic substitution, even for reagents such as OH^- and solvents such as water, which generally give (rate limiting) nucleophilic addition.

Micellar Effects on Reactions with Amino Acids. Most of the amine reactions were followed at pH <10.5 where catalysis by hydroxide ion should be very small and with such low concentration of amine that its contribution as a base should be negligible. Most of the work was done using amino acid anions (Figure 4), and the pattern of micellar catalysis was similar to that observed earlier for reactions with TFBS,[15] but different from that with fluoro- or chloro-2,4-dinitrobenzene, where catalysis increased with increasing hydrophobicity of the amino acid, but not markedly so.[24] The micellar rate enhancements are summarized in Table IX. Cationic micelles of CTABr inhibit the reaction of glycineamide with TNBS (Table X), and the inhibition is more marked than with TFBS.[15] The micellar catalysis by CTABr tends to be larger for reactions of TFBS than for TNBS (ref 15 and Table IX), in line with the greater hydrophobicity of TFBS.

Table IX. Second-Order Rate Constants for Reactions of TNBS and TFBS in CTABr[a]

Reagent	TNBS, k_2^{obsd}	TFBS,[b] k_2^{obsd}
Glycinate	44 (6)	8.7 (5.8)
Phenylglycinate	1470 (174)	14.8 (247)
Leucinate	186 (38)	2.7 (93)
Glycineamide	(<1)	(<1)

[a] At 25.0 °C, the values in parentheses are rate enhancements by the micelle. [b] Reference 15.

Table X. Reaction of TNBS with Glycineamide in CTABr[a]

10^3 [CTABr], M	k_2, M^{-1} s^{-1}
	1.45
0.65	0.78
1.30	0.86
2.61	0.81
3.26	0.79
4.56	0.86

[a] At 25.0°C with 0.0185 M Glycineamide at pH 9.5 (0.027 M carbonate).

All the kinetic evidence suggests that nucleophilic addition is the slow step for reaction with the halodinitrobenzenes in water,[13] whereas for reactions of the arenesulfonate, it is decomposition of a tetrahedral intermediate, and one can explain the different patterns of micellar catalysis in these terms. Increasing the hydrophobicity of the amine will increase the micellar catalysis of the formation of the tetrahedral intermediate by nucleophilic attack upon either the fluorobenzene or the arenesulfonate. But reaction of the arenesulfonate involves a partitioning of the intermediate which can go on to products or revert to reactants, and drawing the intermediate more deeply into the Stern layer of the micelle should assist decomposition to product by increasing the rate of ionization of the ammonium ion,[29] because of unfavorable coulombic interactions between it and the cationic head groups of the micelle (Scheme III). Thus the bulkier the group R the more

Scheme III

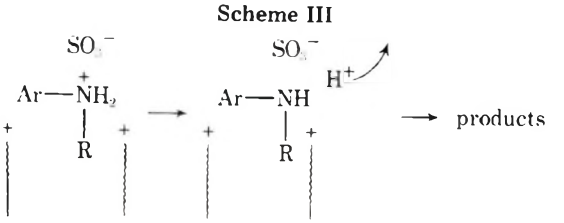


Table XI. Micellar Catalysis of the Reaction of TNBS with Aniline[a]

10^4 [CTABr], M	k_2^{obsd}, M^{-1} s^{-1}	10^4 [CTABr], M	k_2^{obsd}, M^{-1} s^{-1}
	3.21	10.0	94.0[c] (30)
	2.97[b]	10.0	87.4[c,e] (28)
	3.15[c]	10.0	92.2[d] (29)
	3.21[d]	20	88.9 (28)
2.0	23.5 (7.3)	20	98.2[b] (32)
4.0	86.8[b] (29)	40	87.1 (27)
5.0	96.7 (30)	40	86.8[b] (29)
9.0	106 (33)	40	86.2[d] (27)

[a] At 25.0°C with 1.3×10^{-5} M substrate and 3.33×10^{-3} M aniline in 0.027 M carbonate buffer at pH 8.5 unless specified; the values in parentheses are rate enhancement. [b] 1.67×10^{-3} M aniline. [c] pH 7.5. [d] pH 10.1. [e] 4×10^{-5} M substrate.

Table XII. Micellar Catalysis of the Reaction of TFBS with Aniline[a]

10^4 [CTABr], M	pH 8.5	pH 10.1
	0.11	0.11
6.67	9.74 (87)	10.4 (93)
10.0	9.79 (87)	10.8 (96)
20.0	9.79 (87)	10.4 (93)
30.0	9.50 (85)	
40.0	9.10 (82)	9.40 (84)

[a] Second-order rate constants, 10^2 k_2^{obsd}, M^{-1} s^{-1} at 25.0 °C with 10^{-5} M substrate and 3.33×10^{-2} M aniline. The values in parentheses are rate enhancements by the micelle.

Table XIII. Effects of Hydroxide Ion on Reactions of Aniline in CTABr[a]

[NaOH], M[b]	k_2^{obsd}, M^{-1} s^{-1} TFBS[c]	TNBS[d]
(7.5)		94.0[d]
(10.1)	0.11	92.2[d]
0.005		120
0.010	0.32	136
0.010		146[e]
0.010		127[f]
0.020		151
0.025	0.43	
0.025	0.44[g]	
0.025	0.34[e]	
0.025	0.34[h]	
0.033		165
0.050	0.50	181
0.100		199
0.167	0.61	

[a] At 25.0 °C with 10^{-3} M CTABr unless specified. [b] The values in parentheses are pH in 0.027 M carbonate buffer. [c] In 0.033 M aniline. [d] In 1.67×10^{-3} M aniline unless specified. [e] In 2×10^{-3} M CTABr. [f] In 4×10^{-3} M CTABr. [g] In 0.67×10^{-3} M CTABr. [h] In 3×10^{-3} M CTABr.

readily should the tetrahedral intermediate go on to products, so that hydrophobicity of the amine assists both steps of the reaction with the arenesulfonates, but only the initial addition to the halobenzenes, because then the second step is fast.

Micellar Effects on Reaction with Aniline. At low pH the reactions of TNBS and TFBS with aniline are catalyzed effectively by micellized CTABr (Tables XI and XII), and the catalysis is larger than that of approximately tenfold for reaction with 2,4-dinitrofluorobenzene.[4] The micellar catalysis is not affected by small changes in reactant concentration or pH, and as expected in terms of reagent hydrophobicity the catalysis is greater for TFBS than for TNBS.

Table XIV. Micellar Effects upon the Reaction of TNBS with Hydroxide Ion[a]

[OH⁻]M	10^3 [CTABr], M 0.65	2.61	3.26	4.56
0.0132	33.9 (15)	43.2 (23)	50.4 (22)	50.7 (22)
0.159			14.1 (4.3)	
0.238			11.2 (3.3)	

[a] Values of 10^2 k_2^{obsd}, M^{-1} s^{-1} at 25.0°C; the values in parentheses are relative to reaction in the absence of CTABr.

The reactions with aniline in water are strongly catalyzed by hydroxide ion (Table VI), but surprisingly this base catalysis is smaller when reaction is carried out in sufficient CTABr to incorporate the substrate (Table XIII). Because incorporation of reactants into the Stern layer of a micelle can markedly increase their concentration in that layer and so speed reaction, a reaction in which three reagents generate the transition state should be catalyzed more by a micelle than an otherwise similar bimolecular reaction. For example, micellar catalysis of a two-proton benzidine rearrangement is much greater than that of a one-proton benzidine rearrangement.[31]

These reactions of the arenesulfonates in the presence of hydroxide ion are an exception to this generalization, probably because the unfavorable coulombic interactions between the first formed tetrahedral intermediate and the cationic head groups speed decomposition of the intermediate through assisting spontaneous proton loss from the ammonium ion (Scheme III).

The rate increase with added hydroxide ion is greater for the reaction of TFBS with aniline than for that of TNBS (Tables VI and XIII), whether reaction is carried out in water or CTABr, but for both arenesulfonates the base catalysis is markedly reduced by CTABr, and the effect of hydroxide ion changes little with small variations in the concentration of CTABr. We did not attempt to estimate the various kinetic parameters for these reactions in CTABr (cf. Table VIII), because the overall effect of hydroxide ion is relatively small, and there is also a problem because of uncertainties in the distribution of OH^- between the micelles and bulk solvent.

Micellar Effects upon Reactions with Hydroxide Ion. Although micellized CTABr strongly catalyzes the reaction of hydroxide ion with 2,4-dinitrofluorobenzene,[3b] it is less effective for the reactions with TNBS and TNFS even in dilute alkali, and the catalysis decreases markedly as the hydroxide ion concentration is increased (Tables XIV and XV and ref 15). This behavior is unusual; for example, the catalysis by CTABr of the reactions of hydroxide ion with 2,4-dinitrofluoro- and chlorobenzene decreases only slightly as the concentration of hydroxide ion is increased.[3]

Micellar catalysis is generally larger for reactions of higher order, but this is not the case for these arenesulfonate reactions with either aniline or hydroxide ion (cf. Table XIII).

These differences between reactions in water and in CTABr could arise because (1) the micelle speeds the spontaneous decomposition of the dianionic intermediate, Scheme I, so that the hydroxide ion catalyzed decomposition competes less effectively, or (2) the micelle suppresses the hydroxide ion catalyzed decomposition of the intermediate (I). Insofar as cationic micelles increase acid ionization, the first explanation seems the more probable, but it is difficult to give a quantitative discussion because we do not know how the distribution of hydroxide ion between water and micelles depends on hydroxide ion concentration. (For discussions of this general problem of reagent distribution in kinetic and other studies see ref 1, 12, 32, and 33.)

Table XV. Micellar Effects upon the Reaction of TFBS with Hydroxide Ion[a]

[OH⁻], M	10³ [CTABr], M	0.65	1.30	3.04[b]	3.26	4.56
0.0264		6.89 (15)	6.67 (15)		6.10 (13)	5.01 (11)
0.0833				3.70 (7.3)		
0.167				2.94 (4.7)		
0.333				1.63 (2.2)		

[a] Values of $10^3\ k_2^{obsd}$, $M^{-1}\ s^{-1}$ at 25.0 °C; the values in parentheses are relative to reaction in the absence of CTABr. [b] From ref 15.

Table XVI. Micellar Catalysis of the Reaction of Phenoxide Ion with TNBS[a]

10³ [CTABr], M	k_2^{obsd}, $M^{-1}\ s^{-1}$	k_{rel}
	0.0059	
0.333	6.00	1020
0.400	8.57	1450
0.467	11.2	1900
0.533	11.7	1980
0.600	10.9	1850
0.667	9.85	1670
0.800	9.06	1540
1.00	7.96	1350
1.34	6.69	1130
2.00	4.63	790

[a] At pH 10 (0.01 M borate) at 25.0 °C with 2×10^{-5} M TNBS and 6.67×10^{-4} M phenol. The reaction was followed at 446 nm.

Reaction of TNBS with Phenoxide Ion. Micelles of CTABr are very effective catalysts of the attack of phenoxide ion upon 2,4-dinitrofluorobenzene,[5] and a similar, but much larger, catalysis was found with TNBS (Table XVI). Phenol is partially ionized under the experimental conditions, and the second-order rate constants are calculated in terms of the phenoxide ion concentration, allowing for the micellar effect upon the apparent dissociation constant.[5]

The rate maximum is found at a relatively low concentration of CTABr, pointing to strong interactions between the reactants and micelles of CTABr, and the rate enhancement is approximately tenfold larger than that found with 2,4-dinitrofluorobenzene.[5] These observations are as expected for micellar catalysis of a reaction between two relatively hydrophobic reagents.[8-12]

Micellar Catalysis of Reactions of Arenesulfonates and Halobenzenes. These reactions of activated arenesulfonates with amines or hydroxide ion are two-step reactions in which decomposition of a tetrahedral intermediate appears to be rate limiting, and is base catalyzed, whereas nucleophilic addition on halodinitrobenzenes appears to be rate limiting. It is therefore difficult to compare the origins of the micellar catalyses; for example, the catalysis of the reactions of the halobenzenes increases with increasing hydrophobicity of the nucleophile, but not markedly so, but the dependence of the catalysis on hydrophobicity of the nucleophile is much more striking for reactions of the activated arenesulfonates.[2-5,15] For reactions of the arenesulfonates, the more hydrophobic the nucleophile the more deeply it is drawn into the Stern layer, and the more readily the tetrahedral intermediate, e.g., IV or V, loses a proton and goes on to product, but only the first effect is important for reactions of the halobenzenes.

However, we can compare micellar effects upon non-base-catalyzed nucleophilic aromatic substitutions by using a nucleophile such as phenoxide ion. The reaction of 2,4-dinitrofluorobenzene with phenoxide ion is catalyzed 230-fold by micelles of CTABr,[5] whereas for this reaction of TNBS the catalysis is by a factor of 2000 (Table XV), showing the high sensitivity of the micellar catalyzed reactions of the arenesulfonates to hydrophobicity of the nucleophile.

Acknowledgments. Support of this work by the National Science Foundation and the Arthritis and Metabolic Diseases Institute of the U.S. Public Health Service is gratefully acknowledged.

Registry No.—Glycinate, 23297-34-9; leucinate, 17332-93-3; phenylglycinate, 58013-93-7; glycineamide, 598-41-4; aniline, 62-53-3; TNBS, 16655-63-3; TFBS, 59016-58-9; hydroxide ion, 14280-30-9; NaCl, 7647-14-5; $NaClO_4$, 7775-09-9; Et_3N, 121-44-8; NMP, 120-94-5; CTABr, 57-09-0; phenoxide ion, 3229-70-7; 2,4-dinitrofluorobenzene, 70-34-8.

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Catalytic Ring Opening of Substituted 2-Oxetanones

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Salts or complexes of Pd(II) promote the cleavage of the *C*-alkyl–oxygen bond (1–4 bond) of substituted 2-oxetanones **1** (β-lactones). In aprotic medium, 4-vinylic substituted **1** are isomerized to butadiene carboxylic acids **2** whereas in alcohol the addition of one molecule of solvent takes place. The overall process represents an easy synthetic route to unsaturated ether acids **3** or ether esters **4**. The addition of ligands has a major effect both on the nature of the products formed and on the rate of the reactions. A mechanism involving the formation of unstable η^3 allylic intermediates is proposed to account for the observed results.

The versatility of 2-oxetanones (β-lactones) is considerable and has made them an attractive class of synthetic intermediates[1] as well as a thoroughly investigated family of monomers yielding, under the influence of a wide variety of catalysts, high molecular weight polyesters,[2] some of which are biodegradable.[3]

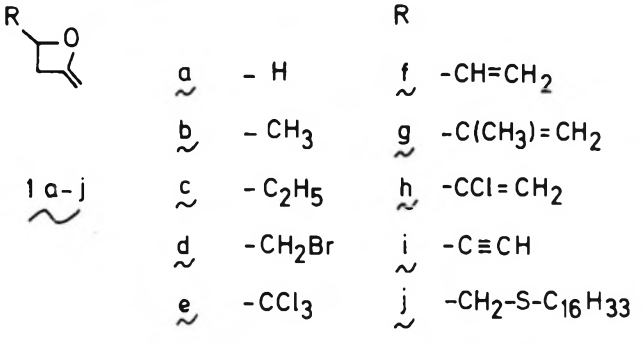
From a mechanistic point of view, the most distinctive feature of these strained cycles is a duality of ring opening; indeed, they can undergo either a classical *C*-acyl–oxygen cleavage or *C*-alkyl–oxygen bond breaking.[4]

The latter type of ring opening has interesting theoretical and synthetic potentialities; we have already reported the catalyzed isomerization of some substituted β-lactones[5] and the goal of this paper is to sum up additional results obtained in this field and to propose a mechanism for the described reactions.

Results

Most of the substituted lactones **1a–i** (Chart I) were synthesized by the addition of ketene to the appropriate aldehyde

Chart I. 4-Substituted 2-Oxetanones Submitted to Catalytic Ring-Opening Conditions



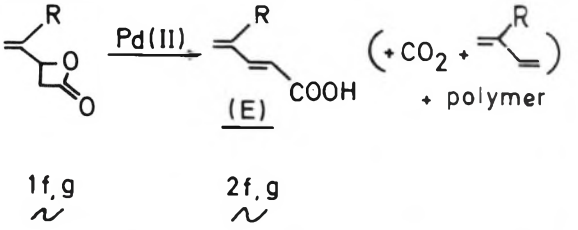
(see Experimental Section) and the resulting lactones **1** treated with catalytic amounts of group 1B, 6B, and 8 metal complexes.

It appeared that, in general, a large majority of the metals used favor polymerization pathways. Carbonyls of Ni, Co, Fe, W, and Cr(0) show no particular activity. However, mostly with some d^6 or d^8 metals such as Ir(III), Rh(III), Pt(II), and Pd(II), monomeric isomerization compounds **2** are obtained with very variable yields but, except for the palladium-catalyzed reactions, the yield of **2** is always poor (below 35%).

The most specific catalysts are Pd(II) derivatives: $PdCl_2$, $Pd(OAc)_2$, and $PdCl_2 \cdot 2PhCN$. Although some η^3-allylic species such as η^3-allylpalladium triethyl phosphite chloride (prepared in situ by a 2:1 addition of triethyl phosphite to the dimeric η^3-allyl chloride) also show some catalytic activity, they are in no way superior to the salts, so we concentrate here on the results obtained with the latter in protic and aprotic solvents. Because of its superior activity and solubility, and unless stated otherwise, Pd(II) acetate is used as the standard catalyst throughout this work.

1. Reactions in Aprotic Medium (C_6H_6, $CHCl_3$, CH_2Cl_2 . . .). At room temperature, the vinyl lactones **1f** (VPL) and **1g** are isomerized to the corresponding butadiene carboxylic acids **2f** and **2g** (Scheme I) under the influence of catalytic amounts of Pd(II) salts. Molar ratios of Pd(II) to

Scheme I



lactones were kept in between 0.01 and 0.05, depending on solubilities.

The yield of **2** (50–80%) depends on the selected conditions and the reaction rates increase with the solvent polarity. The addition of small amounts of sodium borohydride to the reaction mixture (in benzene or pure, with a ratio of palladium to borohydride varying from 0.1 to 1) did not show any major effects on the reaction rate, as it could be expected to if hydrido complexes were implicated in a slow step of the catalytic process.

Saturated lactones (**1a–e** and **1j**) under the same conditions are slowly polymerized to oligomers seemingly identical with those described by Saegusa,[6] i.e., polyesters with unsaturated acid termini, as shown by ir spectroscopy. On the other hand, **1h** and **1i** are surprisingly stable and have to be heated at 50 °C for several hours to be oligomerized, with almost no unsaturated acid formed. The deactivation of the vinyl group, or its substitution by an acetylenic function, is thus sufficient to prevent any carbon–oxygen bond cleavage. Unsaturated five-membered isomers of **1f,** α- and β-angelica lactones, remain also unaffected under the same catalytic conditions.

The addition of higher or stoichiometric amounts of metal salts is impossible because of their poor solubility; moreover, side reactions, mostly oligomerizations of **2,** become important when such noncatalytic conditions are used.

With the object of unambiguously checking the position of the migrating hydrogen in the isomerizing cycle, the α,α-dideuterated lactone **1k** has been synthesized from ketene-d_2 and acrolein and submitted to a catalytic ring opening (Scheme II).

The reaction is clean and shows that the migrating atom is a proton α to the carbonyl; H_β in the *non*deuterated acid appears as a doublet of doublet[7] centered at 7.30 ppm (100 MHz) whereas in **2k** the coupling with H_γ (doublet centered at 7.30 ppm, ^3J = 10 Hz) is exclusively observed. Besides, neither is

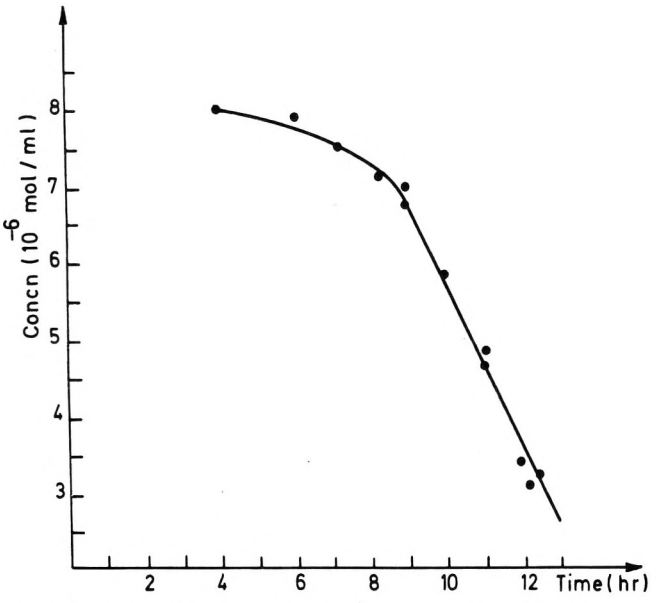


Figure 1. Rate of VPL ring opening as a function of time. Conditions: 25 °C in CH_2Cl_2 with a ratio $Pd(OAc)_2$: VPL 0.02.

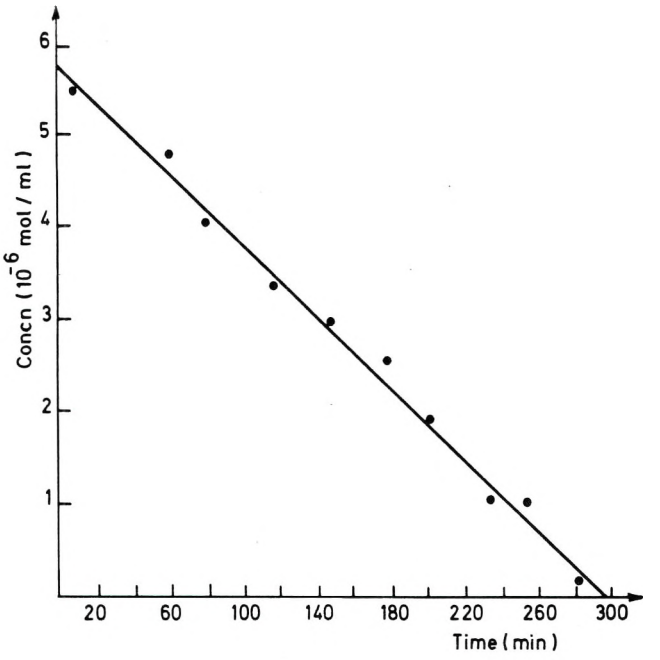
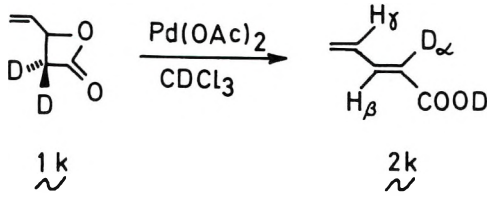


Figure 2. Same as Figure 1 but after addition of trimethyl phosphite (TMP). Conditions: 0 °C in CH_2Cl_2, ratio $Pd(OAc)_2$: VPL 0.02 and TMP: Pd(II) 4.

Scheme II



1k 2k

H_α (doublet in the protonated molecule, δ 5.91 ppm, ^3J = 15.8 Hz) nor any acidic proton present. After the addition of a drop of water, the last one shows up at about 11.5 ppm.

No isotopic effect was observed when equimolecular mixtures of **1f** and **1k** were submitted to ring-opening conditions.

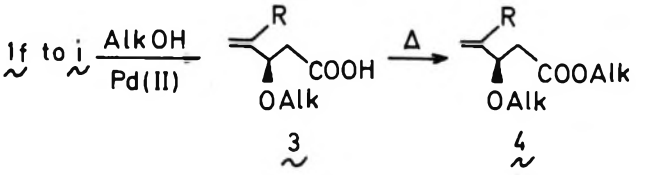
2. Effects of Ligands on the Catalysis. The addition of tertiary phosphines or phosphites to the system causes a significant increase in the reaction rate (see kinetics) as well as major changes in the nature of the compounds formed.

For instance, if r represents the molar ratio of the added ligand to $Pd(OAC)_2$, the addition of n-Bu_3P, with $r = 1$, to a methylene chloride solution of VPL leads to an important evolution of CO_2 with formation of polymers (≈50%) whereas polymerization prevails (>80%) when $2 < r < 4$. It is of definite preparative interest that the addition of trimethyl phosphite (TMP) leads to an almost quantitative isomerization into **2f** when $3 < r < 4$; when $r < 3$, the loss of CO_2 remains important (20–50%).

Other ligands (triphenylphosphine, phosphite, or -arsine) gave intermediate results of those described above, although no straightforward correlation appears between basicity or bulkiness of the ligands and the products formed. **2f** and a catalytic amount of triphenyl phosphite do not appreciably react in methylene chloride, as checked by VPC. However, a further addition of palladium acetate to the mixture yields reaction products whose concentration is proportional to the amount of added salt. The relatively high ratio of phosphite to metal is thus probably due to a partial neutralization of the former by the acid formed from the catalyst.

3. Reactions in Protic Solvents. At room temperature in methanol or ethanol, in the presence of a catalytic amount of $PdCl_2$, the ring opening of the unsaturated lactones **1f–i** smoothly takes place with the formation of ether acids **3** (Scheme III). The yield of **3** is above 80%. If the crude mixture of **3** is refluxed for a few hours, a quantitative esterification

Scheme III



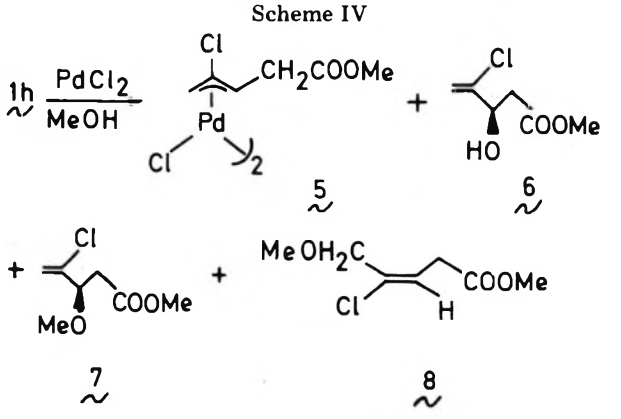
3 4

takes place and the overall process constitutes an easy synthetic route to the polyfunctional molecules **4.**

Isolation of the acid **3** renders a further esterification noncatalytic in palladium and a precipitation of Pd(0) is then observed. Thus it seems that metal complexation is different in the crude mixture and in a solution of previously isolated **3**, where a competition between esterification and formation of η^3-allylic species probably occurs. It was checked that under the same catalytic conditions, neither was **3** nor **4** formed when **2f** was reacted with methanol at 25 or at 60 °C. In the latter case, **2f** methyl ester is formed (as identified by comparison with an authentic sample). That allows the ruling out of **2f** as being an intermediate in the formation of **3.**

Deactivation of the vinyl function in **1h** is reflected by a poor reactivity at room temperature and by a competitive ring opening with breaking of either *C*-alkyl or *C*-acyl–oxygen bonds and formation of **6** and **7** in about 35 and 45% yields, respectively, at 50 °C (Scheme IV).

Scheme IV



In addition, about half of the metal is recovered as a η^3-allylic species **5**, and an estimated 7–10% of **8** is identified as a product of the reaction.

In the same conditions, no alcohol ester corresponding to **6** is ever observed with **1f** or **1g**; that rules out a possible formation of **6** by a reaction of **1h** with the water resulting from esterification of the acid. It was checked that under the conditions used, **6** was neither transformed into **7** nor was **7** into **8** in an appreciable amount. Moreover, **5** is not a catalyst for the ring opening of β-lactones.

4. Kinetics of the Reaction. The rate of the VPL ring opening in CH_2Cl_2 under the influence of $Pd(OAC)_2$ has been studied at 25 °C with no added ligand (Figure 1), and at 0 °C after the addition of TMP, $r = 4$ (Figure 2). In both experiments the ratio of Pd(II) to VPL was 0.02. An induction period of several hours is observed when the Pd(II) salt alone is used but *not* if any TMP is added to the sample.

In both cases (but only after an induction time of about 7 h at 25 °C), the disappearance of the lactone is independent of its concentration in the solution. Such an observation is characteristic of a process with a rate-controlling active catalytic species. Any determination of the reaction order with respect to the metal was hampered by solubility problems. Nevertheless, the above results also show that the reaction is not autocatalytic in the sense that the products formed have little influence on the reaction rate. Furthermore, the initially added **2** (alone, with $PdCl_2$ or as a Pd(II) salt) has no influence on the induction time and thus **2** is not a co-catalyst. After consumption of the initial lactone, isomerization of some freshly added monomer immediately starts again although at a slightly different rate.

Discussion

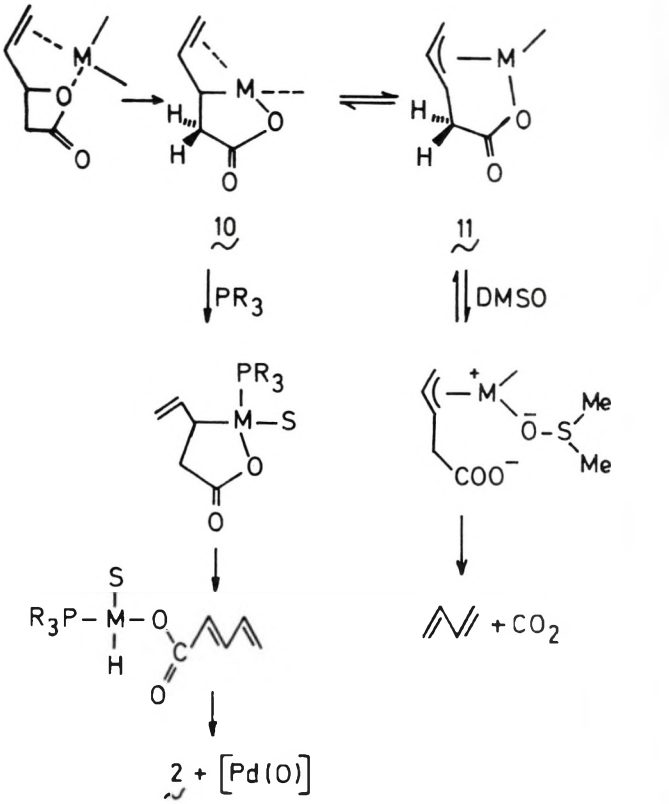
The experimental data indicate that we are dealing with a true catalytic process and that an unsaturated vinyl group β to the carbonyl is necessary for its observation. Its replacement by a chain containing an heteroatom susceptible to assist the ring opening[8] such as in **1j** leads to an inert compound as far as our catalytic system is concerned.

On the other hand, it is well known that palladium derivatives form reactive π complexes with olefins.[9] The examination of molecular models of VPL (**1f**) strongly favors a bidentate type of complexation with the endocyclic oxygen acting as the second site of coordination. The complexation of the endocyclic oxygen is also substantiated by the finding that ring opening of β-lactones on aluminum alkoxide catalysts takes place through coordination of the same oxygen to the Lewis acid site.[10] Thus, it is reasonable to propose on the basis of favorable steric factors a bidentate type of complexation of the monomer.

The induction period observed could be explained by a slow reduction of the catalyst by the olefinic lactone to a palladium(0) complex which then reacts with another lactone molecule by oxidative addition to give **10** or **11**. The latter quickly stabilize to either an unsaturated acid **2** or a polymer or loses CO_2, depending upon the experimental conditions (Scheme V).

Examples are known where π-allyls possessing an α activated methylene are easily transformed into conjugated molecules when bases (e.g., amines) are added to the system.[11] Not only does the opening of the lactone cycle ipso facto generate a base (the carboxylate anion) but it does so close to the activated methylene. The abstraction of one hydrogen liberates an acyldiene which obviously, if the reaction is to proceed catalytically, does not effectively compete with the pure lactone for coordination to the metal. We have indeed confirmed that **2f** reacts more slowly than the lactone itself

Scheme V



with the catalysts and mostly forms insoluble oligomers after several days.

The proposed mechanism is supported by the stability to our catalysts of the otherwise reactive acetylenic lactone **1i**; the spatial factors for a favorable coordination (bidentate) and the possibility of formation of π-allylic derivatives both lack in this case. The deep red color immediately observed after the addition of the highly reactive 1,5-cyclooctadienenickel(0) to a benzene solution of VPL is also characteristic of a π-allyl path. Although then another reactional pathway (mostly polymerization) is favored over the formation of **2f** ($\approx$10%), it clearly hints that the ability to form such species could be determinant.

Moreover, the precipitation in some frozen-out samples of a highly unstable black compound which quickly evolves CO_2 upon handling is consistent with a structure such as **10**. Since no isotopic effect was observed, the insertion step with the breaking of the lactone cycle and the formation of **10** is probably rate determining.

The quantitative evolution of CO_2, observed in good coordinating aprotic solvents (DMF, Me_2SO) is explained by a poor solvation of the carboxylate anion, and that promotes reaction through the carboxylate (evolution of CO_2).

Alcohols, which stabilize the developing positive charge when the cycle opens up, predominantly give nucleophilic substitution products (ether acids **3**). The influence of phosphites or phosphines is less clear. They surely compete for coordination, as indicated by the various colorations observed with different ratios of metal to ligands, and significantly reduce the induction time; such an effect has previously been noted.[12] However, the competition for coordination (e.g., between an olefinic bond and the phosphorus atom) should also promote rearrangement through the σ-allyl and/or stabilize some metal hydride intermediate. The formation of allylic cations such as those previously proposed as reactive intermediates in nucleophilic substitutions[13] of η^3-allyl enhances the electrophilic character of the species; that would favor an attack of the carboxylate ion on a methylenic proton[14] and thus cannot be ruled out.

Experimental Section

NMR spectra were recorded on Varian T-60 or HA-100 spectrometers with chemical shifts measured in parts per million (δ) downfield from Me_4Si or HMDS. The abbreviations for multiplicity employed are s = singlet, d = doublet, a = quartet, pt = pseudotriplet, m = multiplet.

Ir spectra were obtained neat (NaCl disks) on Perkin-Elmer 21 or 125 instruments.

VPC were carried out on a Varian 1700 (analytical) or on a Varian 2800 (preparative) instrument equipped with thermal conductivity detectors. The analytical columns used were 6 × 0.25 in., 15% SE-30 on Chromosorb W 30–60 and the preparative columns 16 × 0.75 in., 15% Carbowax on Cellite 30–60.

Boiling points are uncorrected.

Kinetic Runs. The disappearance of the C=O stretching vibration of VPL (1825 cm^{-1}) is plotted against a calibration curve and against the appearance of the absorption of the conjugated acid (1695 cm^{-1}) and of the polyester (1735 cm^{-1}).

Preparation of Lactones. 2-Oxetanone (**1a**) was purchased from Fluka AG and used as such. 4-Bromomethyl-2-oxetanone (**1d**) was prepared according to ref 15. 4-Trichloromethyl-2-oxetanone (**1e**) was prepared according to ref 16. For 4-vinyl-2-oxetanone (**1f**, VPL), see ref 17. For γ-(*n*-hexadecylthio)-β-butyrolactone (**1j**), see ref 9.

The other lactones (**1b**, **1c**, **1g**, **1h**, and **1i**) were prepared by cycloaddition of ketene to the appropriate aldehyde with boron trifluoride etherate as catalyst according to the following general description.

A 2% solution of the catalyst in dry diethyl ether was kept under nitrogen at −20 to −40 °C. Ketene was then bubbled in and the aldehyde added at approximately equimolecular rate via a perfusor.

Every hour, some fresh catalyst was added, usually half the initial amount, and after all the aldehyde was in, the flow of ketene was continued for about 15 min, and finally the solution was flushed with nitrogen. Enough triethylamine to neutralize the catalyst was then slowly introduced into the cooled solution and after removal of the solvent, the mixture quickly distilled under vacuum. A second distillation on toluene 2,4-diisocyanate (drying agent) gave the pure lactone.

4-Methyl-2-oxetanone (1b) from acetaldehyde, 80%: bp 55–57 °C (18 mm); ir (neat) 1828 cm^{-1} (C=O); NMR (neat, 60 MHz, HMDS) δ 1.40, d, 3 H, ^3J = 5.5 Hz (CH_3); (AB) H_A 2.90, H_B 3.48, ^2J = 16.4 Hz (CH_2); (X) 4.30–4.80, m, 1 H.

4-Ethyl-2-oxetanone (1c) from propionaldehyde, 75%: bp 53–55 °C (15 mm); ir (neat) 1824 cm^{-1} (CO); NMR (neat, 100 MHz, Me_4Si) δ 1.0, t, 3 H, ^3J = 7.2 Hz; 1.76, m, 2 H (CH_2); (AB) H_A 3.16, H_B 3.61, ^2J = 16.5 Hz; (X) 4.50, m, 1 H.

4-Isopropenyl-2-oxetanone (1g) from methacrolein, 70%: bp 36–38 °C (3 mm); ir (neat) 1825 (CO), 1660 cm^{-1} (C=C); NMR (neat, 100 MHz, Me_4Si) δ 1.77, weakly coupled d, 3 H; (AB) H_A 3.24, H_B 3.66, ^2J = 16.5 Hz; (X) 4.9 pt, 1 H, J = 5.5 Hz; 5.0–5.2, 2 H, olefinic protons, J = 1.2 Hz (=CH_2).

4-(α-Chlorovinyl)-2-oxetanone (1h) from α-chloroacrolein, 45%: bp 53–56 °C (5 mm); ir (neat) 1845 (CO) and 1624 cm^{-1} (C=C); NMR (neat, 60 MHz, HMDS) δ (AB) 3.5, 2 H, ^2J = 16.2 Hz (CH_2); (X) 5.0, pt, 1 H, J = 5.0 Hz; 5.46–5.62, ^2J = 2.4 Hz (=CH_2).

4-Ethynyl-2-oxetanone (1i) from propynal was prepared according to ref 18.

The catalyst was not destroyed by the addition of triethylamine, which leads to an almost explosive polymerization of the monomer, but instead, after removal of the solvent, the cooled reaction mixture was quickly washed twice with cold water, dried on Drierite, and distilled: bp 34–36 °C (3 mm); 40%; ir (neat) 3330 (≡CH), 2145 (C≡C), and 1830 cm^{-1} (CO); NMR ($CDCl_3$, 100 MHz, HMDS) δ 2.97, d, 1 H, ^3J = 2.0 Hz (≡CH); (AB) 3.71, H_A = 3.54, H_B = 3.87, ^2J = 16.7 Hz; (X) 5.0–5.14, m, 1 H. Irradiation on the acetylenic proton gives the pure H_x system, four sharp lines.

4-Vinyl-2-oxetanone-3-d_2 (1k). The deuterated ketene was prepared by cracking of acetone-d_6. By comparison with its nondeuterated analogue, the complete disappearance of the CH_2 AB system is observed whereas CH X appears as a large doublet at 4.84 ppm, ^3J = 6.5 Hz. The vinylic part of the molecule remains unchanged.

Catalysis. The reactions were performed under a nitrogen atmosphere; the solvents used were dried and kept under an inert atmosphere to ensure reproducible results, although no major differences were observed when no such precautions were taken. The lactones were added to the catalyst solution through a septum (catalytic ratio of 0.01–0.05) and the reaction followed as described, by VPC, ir, and NMR.

Ring-Opening Catalysis of 1. The conditions used for the isomerization of **1f** are typical.

A. With the Palladium Salt Alone (No TMP Added). $Pd(OAc)_2$ (15 mg) was added to a solution of 1 ml of VPL in 2 ml of methylene chloride. The mixture was stirred overnight at room temperature under a nitrogen atmosphere, and after complete disappearance of the lactone (ir), the solvent was removed under vacuum and the residue extracted three times with 5 ml of hot pentane or hexane. Upon cooling, needles of **2** precipitate, isolated yield 50%. The acid can be further sublimed under vacuum for analytical purpose, mp 72 °C, NMR as described in ref 17.

B. With Trimethyl Phosphite–Pd(OAc)$_2$, r = 3.5. The overall procedure is the same as described above; 28 μl of TMP was added to the lactone solution through a septum and after 0.5 h, the solution worked up as described, isolated yield 80–90%.

(*E*)-3-Methyl-1,3-butadiene-1-carboxylic Acid (2g): NMR ($CDCl_3$, 100 MHz, Me_4Si) δ 12.50, s, 1 H (COOH); 1.90, t, 3 H, ^4J = 2.2 Hz (CH_3); 5.40, m, 2 H (=CH_2); 7.45, d, 1 H, ^3J = 15.8 Hz (H_2); 5.89, d, 1 H, ^3J = 15.8 Hz (H_1).

3-Ethoxy-4-pentenoic Acid (3f), R = H; Alk = C_2H_5. See ref 5.

3-Methoxy-4-pentenoic Acid Methyl Ester (4f, R = H; Alk = CH_3), bp 68–70 °C (15 mm), 85%.

Anal. Calcd for $C_7H_{12}O_3$: C, 58.33; H, 8.33. Found: C, 58.2; H, 8.2.

Ir (neat) 1747 (CO_2CH_3) and 1645 cm^{-1} (C=C); NMR ($CDCl_3$, 60 MHz, HMDS) δ 3.60, s, 3 H ($COOCH_3$); 3.80, s, 3 H (OCH_3); 2.5, 2 H, ^2J = 12.5 Hz (CH_2AB); 3.78–4.13, m, 1 H (CH X); 5.06–6.0, m, 2 H (=CH_2 ABC).

3-Methoxy-4-methyl-4-pentenoic Acid Methyl Ester (4g, R = CH_3): ir (neat) 1742 (COOMe) and 1650 cm^{-1} (C=C); NMR, see **4f** except for the olefinic part, 1.60, d, 3 H, J = 1 Hz (=C-CH_3); 4.91, m, 2 H (=CH_2).

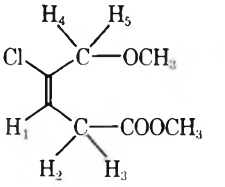
3-Methoxy-4-chloro-4-pentenoic Acid Methyl Ester (7). Anal. Calcd for $C_7H_{11}ClO_3$: C, 47.05; H, 6.16. Found: C, 47.1; H, 6.3.

Ir (neat) 1632 (C=C) and 1743 cm^{-1} ($COOCH_3$); NMR ($CDCl_3$, 60 MHz, HMDS) δ 3.58, s, 3 H ($COOCH_3$); 3.20, s, 3 H (OCH_3); 2.56, 2 H, ^3J = 6.5 Hz (isochronous protons) (CH_2 A_2); 4.13, pt, 1 H (CH X); 5.3–5.5, m, 2 H (=CH_2).

3-Hydroxy-4-chloro-4-pentenoic Acid Methyl Ester (6). Anal. Calcd for $C_6H_9O_3Cl$: C, 43.77; H, 5.47. Found: C, 43.5; H, 5.2.

Ir (neat) 3500 (OH), 1740 ($COOCH_3$), and 1640 cm^{-1} (C=C); NMR ($CDCl_3$, 60 MHz, Me_4Si) δ 3.63, s, 3 H ($COOCH_3$); 4.20, s, 1 H (disappears after addition of D_2O) (OH); 2.63, 2 H, ^2J = 16.0 Hz (CH_2 AB); 4.45–4.70, m, 1 H (CH X); 5.51–5.21, m, 2 H (=CH_2).

4-Chloro-5-methoxy-3-pentenoic Acid Methyl Ester (8): bp 68–72 °C (1 mm), purified by GLC; ir (neat) 1740 (CO_2Me) and 1665 cm^{-1} (C=C); mass spectrum (70 eV) m/e 178–180, 143 (M − Cl) base peak, 147 (M − OMe), 119 (M − CO_2Me), 118 [M − CH_2=C(OH) OMe], 105–107 (M − CH_2 − COOMe); NMR (C_6D_6, 100 MHz,



HMDS) δ 3.25, s, 3 H ($COOCH_3$); 2.95, s, 3 H (OCH_3); 5.85, t of t, ^3J = 6.8, ^4J = 1.1 Hz (H_1); 3.00, d of t, ^3J = 6.8, ^5J = 1.75 Hz (H_2, H_3); 3.64, m, 2 H ($H_{4,5}$). The stereochemistry at the double bond is proposed on mechanistic ground.

3-Methoxy-4-pentynoic Acid Methyl Ester (4i): ir (neat) 2300 (C≡C) 1750 cm^{-1} (COOMe); NMR (C_6D_6, 60 MHz, HMDS) δ 3.22, s, 3 H ($COOCH_3$); 2.95, s, 3 H (OCH_3); 2.41, d, 2 H, ^3J = 5.5 Hz (CH_2 A_2); 3.68, t, 1 H, ^3J = 5.5 Hz (CH X); ≡CH masked by the OMe.

Bis(1-methylenemethoxycarbonyl)-2-chloro-η^3-allylpalladium Chloride (5). Anal. Calcd for $C_6H_8ClO_2Pd$: C, 24.88; H, 2.76. Found: C, 25.1; H, 3.0.

Ir (KBr) 1731 cm^{-1} ($COOCH_3$), no double bond; NMR (C_6D_6, 100 MHz, Me_4Si) δ 3.74, s, 3 H ($COOCH_3$); 2.86, d, 2 H, ^3J = 6.74 Hz (CH_2); 2.87, d, 1 H, ^2J = 2.93 Hz (H anti); 4.07, t, 1 H, ^3J = 6.74 Hz (H anti); 4.20, d, 1 H, ^2J = 2.93 Hz (H syn).

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for many helpful comments concerning the NMR analysis and P. Lefebvre for his help in the kinetic runs.

Registry No.—**1b**, 3068-88-0; **1c**, 15890-55-8; **1f**, 7379-74-0; **1g**, 43084-06-6; **1h**, 59092-50-1; **1i**, 59092-51-2; **2g**, 4941-92-8; **4f**, 59092-52-3; **4g**, 59092-53-4; **4i**, 59092-54-5; **5**, 59109-99-8; **6**, 59092-55-6; **7**, 59092-56-7; **8**, 59092-57-8; ketene, 463-51-4; acetaldehyde, 75-07-0; propionaldehyde, 123-38-6; methacrolein, 78-85-3; α-chloracrolein, 683-51-2; propynal, 624-67-9.

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Heterocyclic *N*-Oxides as Synthetic Intermediates. 4. Reaction of Benzyne with 1,3,4-Oxadiazin-6-one 4-Oxides and Related Compounds[1]

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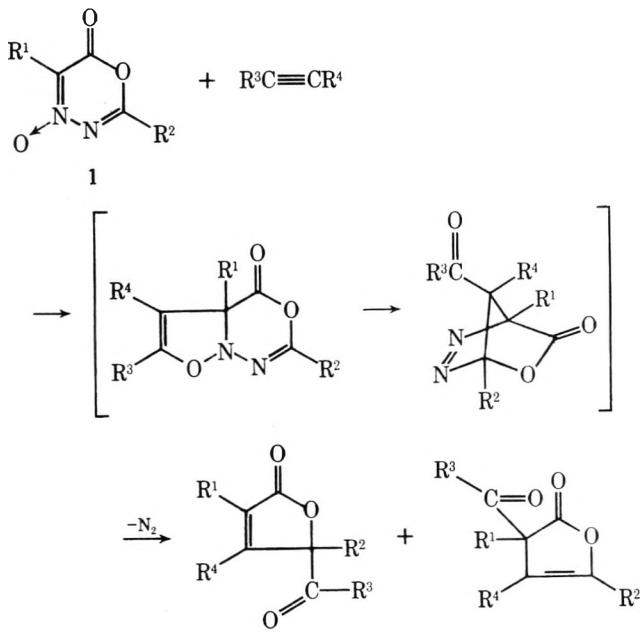
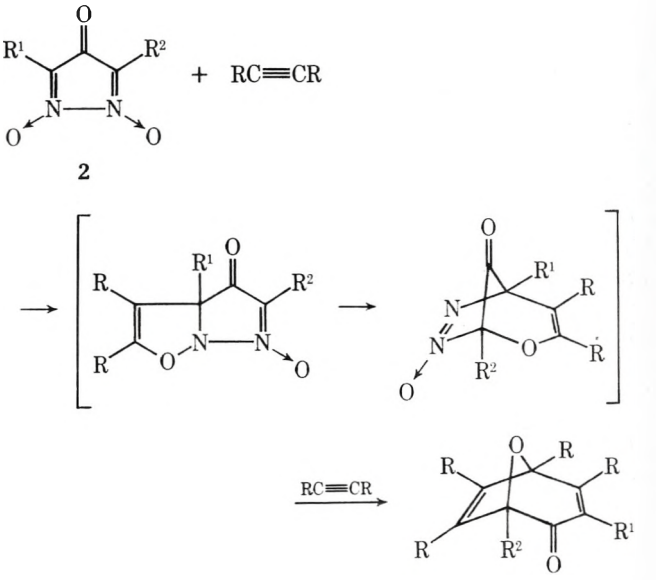
Received February 3, 1976

Benzyne, generated from benzenediazonium 2-carboxylate, condenses with 1,3,4-oxadiazin-6-one 4-oxides (**1**) to yield mixtures of substituted benzofurans (**3**) and acylbenzofuranones (**4**). A side product of this reaction, a diaryl homophthalic anhydride (**5**), apparently results from trapping of the benzyne precursor by an intermediate from the primary reaction. A mechanism to rationalize these products is presented and is substantiated in part by isolation of a 1:1 adduct (**10**) from benzyne and 2-methyl-5-phenyl-3,4-diazacyclopentadienone 3,4-dioxide.

It has been shown recently that 1,3,4-oxadiazin-6-one 4-oxides (**1**) react with a variety of acetylenes to produce acylbutenolides.[3] It was proposed that this transformation resulted from a hetero-Cope (3,3) rearrangement within a first-formed 1,3-cycloadduct. A related reaction involving a

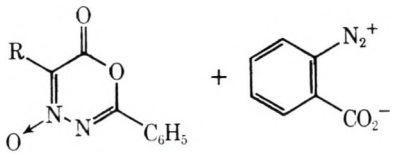


1,3 rearrangement had also been investigated between acetylenes and 2,5-disubstituted 3,4-diazacyclopentadienone 3,4-dioxides (**2**).[4] Spurred by these results and those of

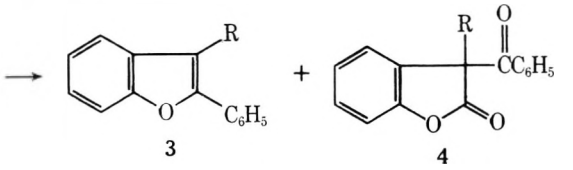


Abramovitch and co-workers concerning the reactions of other heterocyclic *N*-oxides with benzyne,[5] we now have examined the reactions of this reactive "acetylene" with these two novel heterocyclic systems.

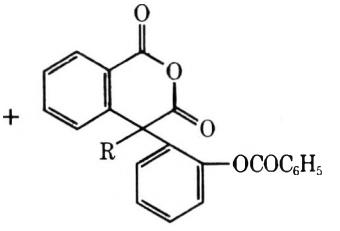
The oxadiazinone reactions proved to be complex and three main products could be isolated and identified when that heterocycle was heated with benzenediazonium 2-carboxylate as the benzyne precursor. In addition a fourth product was sometimes detected but has not been positively identified. (See Experimental Section.)



1a, R = CH_3
b, R = C_2H_5
c, R = C_6H_5

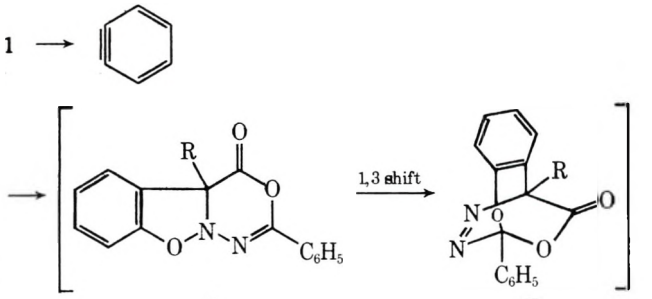


3 **4**

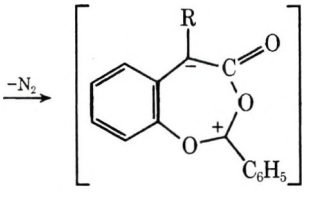


5

The structures of the furans and furanones were established by spectral methods, degradation, and independent synthesis (Experimental Section). The structure of the anhydrides is somewhat less securely established, but the evidence accumulated will be presented in a later section. Mechanistically one can account for these products by schemes similar to those already proposed for the other acetylene reactions.



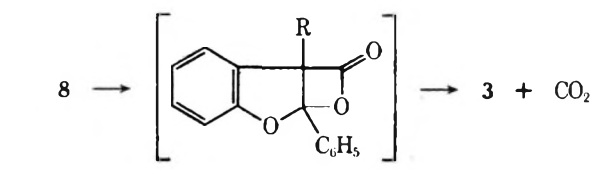
6 **7**



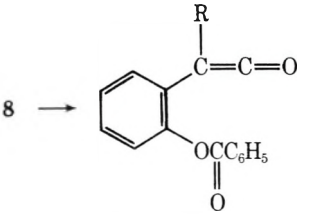
8

In this case a 1,3 rather than a 3,3 rearrangement occurs to preserve the benzene ring. Loss of nitrogen from **7** leads to a dipolar intermediate **8** analogous to that proposed earlier.[4] However, this seven-membered ring does not possess the resonance stabilization of the earlier pyrylium oxide[4] and as a result is a high-energy intermediate for which many decomposition paths may be envisioned.

Collapse to a β-lactone followed by loss of carbon dioxide furnishes the benzofurans.

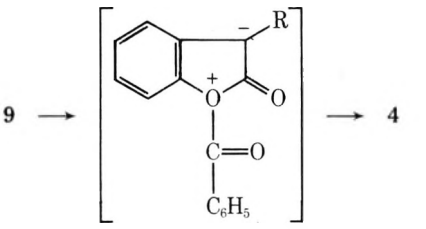


There is ample precedent in the literature for such a "[2 + 2]" cycloreversion.[6] However, a more accessible path involves ring opening to a ketene **9** and the major product-forming path apparently involves just such an intermediate.



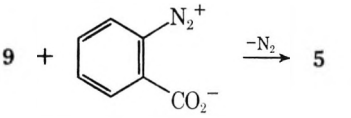
9a, R = CH_3
b, R = C_2H_5
c, R = C_6H_5

It is suggested that intramolecular closure of **9** can generate the benzofuranones.



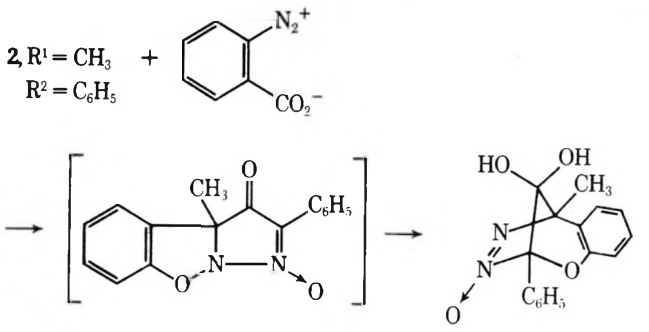
To establish this point *o*-benzoyloxydiphenylacetyl chloride was treated with a tertiary amine, Dabco, to generate ketene **9c**. From this reaction a mixture of **3c** and **4c** was isolated. (It is assumed that **3c** arises by ring closure of the ketene to **8** followed by intramolecular collapse to furan.) This reaction has yet to be explored in depth but at least it has been established that benzofurans and benzofuranones can be obtained from precursors suggested by this benzyne reaction.

Finally, the homophthalic anhydride **5** can be envisioned as arising from the reaction of the ketene with the benzyne precursor either before or after loss of nitrogen but before loss of carbon dioxide. (The existence of benzopropiolactone or its open-chain form has been suggested to account for other reactions.[7]) The interception of such a reactive intermediate demands that the ketene have a reasonable lifetime and it is probably significant that the yield of **5** is best when R = phenyl. (The experimental method employed whereby benzenediazonium 2-carboxylate was continually added to the reaction mixture over a period of time rather than having all reactants mixed at the beginning also helps to account for this result; see Experimental Section.)



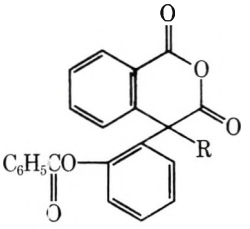
To test this mechanism the reaction of benzenediazonium 2-carboxylate with diphenylketene was examined and diphenylhomophthalic anhydride was isolated in 20% yield.

Some evidence that the proposed cycloaddition mechanism is correct was obtained by treating ketonitrone **2**, $R^1 = CH_3$, $R^2 = C_6H_5$, with benzenediazonium 2-carboxylate; a 1:1 adduct could be isolated as the hydrate **10**. The structure of **10** was surmised from its elemental analysis, spectral properties (see Experimental Section), and the similarity of its ir and NMR spectra to those of a similar adduct of **2** with acetylenedicarboxylic ester.[4] Since it is known that thermal loss of nitrous oxide is more difficult than that of nitrogen, the relative stability of **10** is not too surprising. However, the base peak (*m/e* 236) in the mass spectrum of **10** corresponded to the molecular ion less the elements of water and nitrous oxide (298 − 18 − 44 = 236).

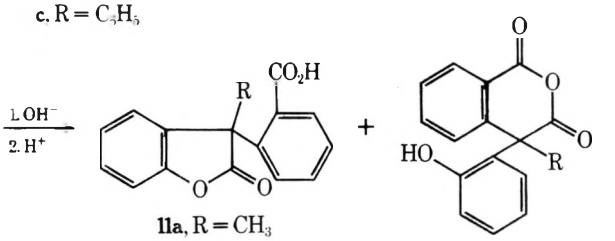


10

Reactions of the Homophthalic Anhydrides. The structure of **5** was suggested by elemental analyses and spectral properties. Attempts to degrade them to simpler compounds, however, led to some unforeseen results. The anhydride could not be selectively hydrolyzed without cleaving the ester and the result of alkaline hydrolysis of **5c** was to produce a mixture of **11c** and **12c**. Hydrolysis of **5a** was cleaner, however, and only **11a** was obtained.



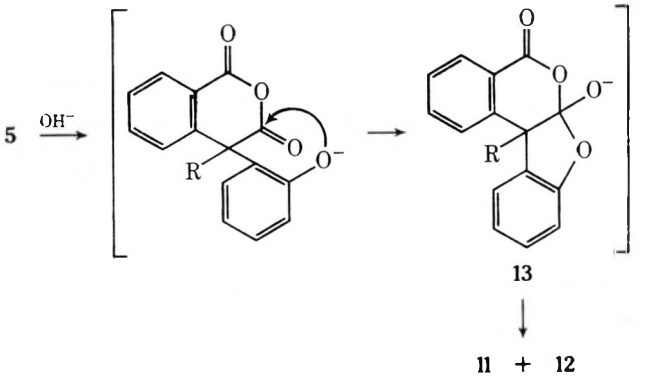
5a, R = CH_3
b, R = C_2H_5
c, R = C_6H_5



11a, R = CH_3
b, R = C_2H_5
c, R = C_6H_5

12a, R = CH_3
b, R = C_2H_5
c, R = C_6H_5

These results suggest that a common intermediate **13** is formed which may partition in different ways depending upon the substituent R. Attempts to capture an intermediate by methylation either with diazomethane or dimethyl sulfate in base produced only the methyl ester of **11**. Although it has not been possible to synthesize **5**, the reactions described seem consistent with the proposed structures.



13

11 + **12**

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer Model 137-A Infracord or a Perkin-Elmer 457. NMR spectra were measured on a Varian A-60A spectrometer; mass spectra were measured with an A.E.I. MS 902 mass spectrometer at 70 eV. We are indebted to Mr. Donald Schifferl for these measurements. The elemental analyses were done by Midwest Microlab.

J. T. Baker silica gel (60–200 mesh) was dried at 135 °C for 4 h before use and the column chromatography was monitored by TLC on Baker-flex sheets (silica gel 1B-F).

Reaction of 1,3,4-Oxadiazin-6-one 4-Oxides with Benzyne. Benzenediazonium 2-carboxylate[8] was prepared in an apparatus described by Crews.[9] In all of the following experiments, this precursor was prepared from 1 g (7.3 mmol) of anthranilic acid.

Method A. A magnetically stirred solution of the oxadiazinone oxide[3] (4 mmol) in 1,2-dichloroethane (20–35 ml) was boiled gently on a steam bath. The suspension of benzenediazonium 2-carboxylate in 20 ml of 1,2-dichloroethane was added in several portions over a period of 5 min. The darkened solution was boiled for an additional 15 min. After cooling, the solution was concentrated in vacuo, and the resulting residue was chromatographed on a silica gel column (40 g) with benzene as the eluent.

The benzofuran derivatives **3a–c** were the first products eluted from the column. These derivatives were purified further by microdistillation or recrystallization as outlined in Table I.

The benzofuranones **4a–c** were the next compounds eluted from the column. These derivatives were also purified further by distillation or recrystallization as shown in Table II.

The third component eluted from the column was dissolved in a minimal amount of hot benzene and Skellysolve B was added to precipitate a solid. Several recrystallizations from the same solvent mixture yielded the homophthalic anhydride derivatives **5a–c** as colorless, crystalline solids. The physical properties of these derivatives are tabulated in Table III.

In the case of **5a**, the filtrate from the first recrystallization was concentrated in vacuo to leave a yellow solid. This solid was purified on a neutral alumina column (1 × 10 cm) with methylene chloride as the eluent. The yellow band was collected. After two recrystallizations from anhydrous methanol, it yielded bright yellow prisms (19 mg): mp 136–137 °C; ir (KBr) 1620, 1605, 1550, 1255, 1200, 1145, 830, 824, 783, 760, 695 cm^{-1}; NMR ($CDCl_3$/Me_4Si) δ 1.68 (s, 3 H), 6.0–6.8 (m, 4 H), 7.3–7.7 (m, 9 H); MS *m/e* rel intensity) 284 (100), 256 (25), 242 (32), 241 (100), 239 (40).

Anal. Calcd for $C_{21}H_{16}O$: C, 88.73; H, 5.64; N, 0.0. Found: C, 87.81; H, 5.61; N, 0.0.

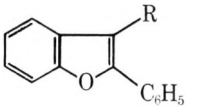
The final compounds eluted from the columns were identified as the unreacted oxadiazinone oxides **1a–c**.

Method B. The suspension of benzenediazonium 2-carboxylate in 25 ml of methylene chloride was added to an ice-cold solution of 2,5-diphenyl-1,3,4-oxadiazin-6-one 4-oxide (**1c**,[3] 4 mmol) in 35 ml of methylene chloride. This mixture was heated under reflux for 5 h and worked up as in method A. A comparison of the two methods is shown in Table IV.

3-Methyl-2-phenylbenzofuran was prepared according to Takagi and Ueda[10] with slight modification.

A mixture of 3-formyl-2-phenylbenzofuran[10] (5 mmol), 85% hydrazine hydrate (14.2 mmol), and potassium hydroxide (14.4 mmol) in 15 ml of diethylene glycol was refluxed for 1 h. The condenser was removed and the pot temperature was raised to 215 °C. The condenser was replaced and reflux was continued for an additional 3.5 h. The cooled mixture was diluted with H_2O and extracted with ether. The ether layers were washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo. By distillation of the crude product under vacuum through

Table I. Benzofuran Derivatives[a]



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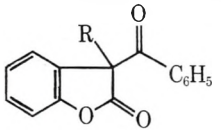
Registry no.	Compd	R	Bp (0.3 Torr) or (mp), °C	Yield,[b] %
4521-08-8	**3a**[10]	CH_3	76–78 (bath)	7.5
59092-74-9	**3b**	C_2H_5	90–92 (bath)	6
13054-95-0	**3c**	C_6H_5	(120–122)[c] (CH_3OH)	1

[a] Biphenylene appears to be an impurity in all of these derivatives and it was not possible to obtain satisfactory elemental analyses of **3b**. [b] The yields are based on reacted oxadiazinone oxide and represent purified products. [c] Lit.[11] mp 123 °C.

Table II. Benzofuranone Derivatives

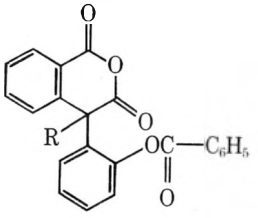


4

Registry no.	Compd	R	Bp (bath), °C (Torr)	Mp, °C	Yield,[c] %	Ir, cm^{-1}[d] Lactone C=O	Ir, cm^{-1}[d] Ketone C=O
59092-75-0	4a	CH_3[a]	106–108 (0.4)		36	1810	1680
59092-76-1	4b	C_2H_5[a,b]	148–150 (0.35)		30	1810	1680
59092-77-2	4c	C_6H_5		192–193[e]	15	1810	1675

[a] A small amount of the deacylated benzofuranone is a contaminant, as seen in the elemental analyses. This deacylation occurred on the silica gel column. [b] Calcd for $C_{17}H_{14}O_3$: C, 76.69; H, 5.26. Found: C, 75.82; H, 5.23. [c] The yields are based on reacted oxadiazinone oxide and represent purified products. [d] Measured as a KBr pellet or as a film. [e] Lit.[12] mp 186 °C.

Table III. Homophthalic Anhydrides[a]



5

Registry no.	Compd	R	Mp, °C	Yield,[b] %	Ir,[c] cm^{-1} Anhydride C=O	Ir,[c] cm^{-1} Ester C=O
59092-78-3	5a	CH_3	226–228	3	1785, 1740[d]	1740[d]
59092-79-4	5b	C_2H_5	198–200	1	1790, 1745	1745
59092-80-7	5c	C_6H_5	239–241	20	1780, 1740	1740

[a] Derivatives 5a and 5c were analyzed and gave satisfactory elemental analyses.[e] The molecular ions were present in the mass spectra but the base peak in all of them was *m/e* 105 ($C_6H_5CO^+$). [b] The yields are based on reacted oxadiazinone oxide and represent purified products. [c] Measured as KBr pellets. [d] In the case of 5a, high-resolution infrared spectroscopy resolved the two bands at 1740 cm^{-1}. [e] Calcd for $C_{23}H_{16}O_5$ (5a): C, 74.19; H, 4.30. Found: C, 73.95; H, 4.33. Calcd for $C_{28}H_{18}O_5$ (5c): C, 77.42; H, 4.15. Found: C, 77.02; H, 4.19.

Table IV

Compd	Method A (yield, %)	Method B (yield, %)
3c	1	Trace
4c	15	10
5c	20	12.5

a short path distilling head, 3-methyl-2-phenylbenzofuran (872 mg, 84%) was obtained as a colorless oil, bp 127–128 °C (0.3 Torr), mp 32–34 °C. The spectral properties of this oil were identical with those reported[10] and with those of **3a**.

3-Benzoyl-3-phenyl-2(3*H*)-benzofuranone was prepared according to Löwenbein and Simonis.[12]

Sodium (0.11 g) was added to a suspension of 3-phenyl-2(3*H*)-benzofuranone[13] (5 mmol) in 20 ml of anhydrous ether. This mixture was heated under reflux until the sodium was dispersed. Benzoyl chloride (4.7 mmol) was added to this mixture dropwise at room temperature. Then the mixture was heated under reflux for 15 min and suction filtered, and the filter cake was washed with 50 ml H_2O and air dried. Recrystallization from benzene yielded the product as white prisms (48%), mp 191–193 °C (lit.[12] mp 186 °C). Mixture melting point and spectral properties of this solid confirmed the structure of **4c**.

Deacylation of 3-Benzoyl-3-methyl-2(3*H*)-benzofuranone. A solution of 180 mg (0.7 mmol) of **4a** in benzene was placed on a silica gel column, prepared from 2 ml of H_2O and 10 g of silica gel, for 12 h. Elution of the column with 50 ml of C_6H_6 yielded a pale yellow oil (95 mg; 90%). Microdistillation of this oil under vacuum yielded 3-methyl-2(3*H*)-benzofuranone as a clear oil, bp (bath) 61–63 °C (4 Torr). Spectral properites of this oil were identical with those reported by Elix and Ferguson.[14]

Anal. Calcd for $C_9H_8O_2$: C, 72.97; H, 5.41. Found: C, 72.67; H, 5.41.

Treatment of Diphenylketene with Benzenediazonium 2-Carboxylate. Using method A above, 4 mmol of diphenylketene yielded a red semisolid after concentration in vacuo. This residue was dissolved in hot methanol and cooled in an ice bath to yield a yellow solid, from which 250 mg (19%) of 1,1-diphenylhomophthalic anhydride was obtained as white prisms (ethyl acetate): mp 230–232 °C (lit.[15] mp 228–229 °C); ir (KBr) 1790, 1750, 1295, 1250, 1150, 1025, 764, 757, 723, 702 cm^{-1}; MS *m/e* (rel intensity) 270 (100), 241 (26), 239 (22), 165 (17); no parent peak visible at 70 eV.

Anal. Calcd for $C_{21}H_{14}O_3$: C, 80.25; H, 4.46. Found: C, 80.09; H, 4.46.

Alkaline Hydrolysis of 5c. A suspension of 250 mg (0.58 mmol) of **5c** in 12 ml of 5% NaOH was refluxed for 10 h. The solution was then acidified in an ice bath with 5% HCl. The white solid isolated after suction filtration was dried in vacuo at 67 °C for 4 h. This solid (184 mg, 97%) was an admixture of **11c** and **12c**: mp 238–250 °C; ir (KBr) 1800, 1775, 1730, 1695, 1465, 1290, 1230, 1130, 1070, 760, 720, 705 cm^{-1}. The carbonyl bands at 1775 and 1730 cm^{-1} were assigned to the anhydride moiety in **12c** and the bands at 1800 and 1695 cm^{-1} were assigned to the lactone and the carboxylic acid, respectively, in **11c**.

The acidic filtrate from the hydrolysis was extracted with ether (5 × 25 ml). The dried (Na_2SO_4) ether solution was evaporated in vacuo to yield 67 mg (95%) of benzoic acid as confirmed by a mixture melting point determination with an authentic sample.

Treatment of 11c and 12c with Diazomethane. A solution of 124 mg (0.38 mmol) of the solid admixture **11c** and **12c** in 16 ml of CH_2Cl_2 and 8 ml of CH_3OH was treated dropwise with an ethereal solution of diazomethane until the yellow color persisted. Concentration in vacuo left a solid, which yielded 102 mg (79%) of 3-(o-carbomethoxyphenyl)-3-phenyl-2(3*H*)-benzofuranone as white plates (CH_3OH): mp 145–147 °C; ir (KBr) 1800, 1725, 1470, 1450, 1425, 1285, 1265, 1235, 1145, 1085, 1065, 1055, 962, 952, 775, 760, 715, 700 cm^{-1}; NMR (acetone-d_6–Me_4Si) δ 3.53 (s, 3 H), 6.9–7.9 (m, 13 H); MS *m/e*

(rel intensity) 344 (77), 284 (100), 268 (65), 257 (55), 255 (75), 251 (90).

Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.74; H, 4.65. Found: C, 76.73; H, 4.90.

Treatment of 11c and 12c with Dimethyl Sulfate. A stirred solution of 184 mg (0.56 mmol) of **11c** and **12c** in 0.7 ml of 10% Na_2CO_3 and 2 ml of absolute C_2H_5OH was cooled in an ice bath. Dimethyl sulfate (52 μl, 0.56 mmol) was added dropwise from a syringe and stirring continued for 15 min. The ice-cold mixture was treated four more times with dimethyl sulfate while the pH was kept at 8 with 10% Na_2CO_3. After the final addition, the mixture was stirred overnight at room temperature and finally heated on a steam bath for 0.5 h. The pH was again adjusted to 8 and the white solid filtered and washed with liberal amounts of H_2O. This solid was purified on a silica gel column (10 g) with $CHCl_3$ as the eluent. The isolated solid was recrystallized from CCl_4 to yield 66 mg (35%) of the methyl ester of **11c** as white plates. A mixture melting point with the product from the diazomethane reaction was not depressed.

Alkaline Hydrolysis of 5a. Using the same procedure as for **5c**, 29.8 mg (0.08 mmol) of **5a** in 2 ml of 5% NaOH yielded 19 mg (88%) of a beige solid which was recrystallized from chloroform–hexane mixtures to yield 3-(*o*-carboxyphenyl-)-3-methyl-2(3*H*)-benzofuranone (**11a**) as white needles: mp 214–215 °C; ir (KBr) 2800–2500, 1800, 1695, 1475, 1460, 1400, 1255, 1230, 1140, 1090, 1075, 1030, 904, 895, 763, 702 cm^{-1}; NMR (acetone-d_6–Me_4Si) CH_3 δ 1.87; MS *m/e* (rel intensity) 268 (73), 224 (42), 195 (84), 194 (100), 165 (58).

Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.68. Found: C, 71.07; H, 4.96.

***o*-Benzoyloxydiphenylacetic acid** was prepared according to Arventi.[11]

3-Phenyl-2(3*H*)-benzofuranone[13] (3.2 g, 15.25 mmol) in 12 ml of 5% NaOH was added to a solution of 10.5 g of Na_2CO_3 in 65 ml of H_2O. This mixture was boiled until the mixture was homogeneous. This mixture was stirred mechanically while 2.25 ml (19.4 mmol) of benzoyl chloride was added dropwise at room temperature over a period of 45 min. The resulting mixture was then diluted with 150 ml of H_2O and acidified with 10% H_2SO_4. The resulting suspension was then boiled gently for a few minutes and after cooling, the crystalline mass was suction filtered and washed with 100 ml of warm H_2O. Recrystallization of this solid from glacial acetic acid yielded 3.02 g (62%) of *o*-benzoyloxydiphenylacetic acid in two crops; mp 148–151 °C (lit.[11] mp 152 °C); ir (KBr) 2725, 2600, 1735, 1690, 1255, 1210, 1175, 1090, 1060, 1025, 763, 732, 704 cm^{-1}.

***o*-Benzoyloxydiphenylacetyl chloride** was prepared in the usual manner starting with 1 g (3 mmol) of the carboxylic acid. The resulting yellow oil was used immediately: ir (KBr) 1805, 1735 cm^{-1}.

Dehydrochlorination of o-Benzoyloxydiphenylacetyl Chloride. The acid chloride was dissolved in 15 ml of dry C_6H_6. Dabco (387 mg, 3.46 mmol) was added and the mixture was refluxed for 21 h under a $CaSO_4$ drying tube. The salts were removed by filtration and the filtrate evaporated in vacuo to yield an orange semisolid. This residue was purified on a silica gel column (40 g) with benzene as the eluent. The first fractions yielded 2,3-diphenylbenzofuran (**3c**), 592 mg (73%). The second component was identified as **4c** (27 mg, 3%) by comparison of the ir spectrum with that of an authentic sample.

Treatment of 2-Methyl-5-phenyl-3,4-diazacyclopentadienone 3,4-Dioxide[16] with Benzenediazonium 2-Carboxylate. Using method A, the ketonitrone **2** (4 mmol) yielded a red residue after evaporation of volatiles. This residue was dissolved in 10 ml of ethyl acetate and treated with 1 ml of H_2O. After stirring for 1 h at room temperature, the ethyl acetate solution was decanted through a cone of Na_2SO_4. The ethyl acetate was evaporated in vacuo and the resulting residue was slurried in hot benzene.[17] After cooling, suction filtration yielded 655 mg (55%) of a beige powder. This powder was recrystallized from ethyl acetate–hexane mixtures to yield **10** as beige plates in several crops: mp 183–185 °C dec; ir (KBr) 3400, 1510 (N=N→O), 1445, 1215, 1125, 1080, 1015, 850, 757 cm^{-1}; NMR (acetone-d_6–Me_4Si) δ 1.87 (s, 3 H), 5.82 (s, 1 H), 6.28 (s, 1 H), 7.0–7.65 (m, 7 H), 7.7–7.9 (m, 2 H); MS *m/e* (rel intensity) 236 (100), 135 (77), 208 (27), 207 (32), 105 (41), 77 (36), 44 (27), 28 (27), 18 (>100); the parent peak was faintly present at 70 eV.

Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.45; H, 4.70; N, 9.40. Found: C, 64.66; H, 4.80; N, 9.40.

Registry No.—**1a**, 28969-38-2; **1b**, 28969-39-3; **1c**, 28969-37-1; **2** (R^1 = CH_3; R^2 = C_6H_5), 16901-38-5; **10**, 59092-81-8; **11a**, 59092-82-9; **11c**, 59092-83-0; **12c**, 59092-84-1; benzyne, 462-80-6; benzenediazonium 2-carboxylate, 1608-42-0; 3-formyl-2-phenylbenzofuran, 37883-64-0; 3-methyl-2(3*H*)benzofuranone, 32267-71-3; diphenylketene, 525-06-4; 1, 1-diphenylhomophthalic anhydride, 14596-73-7; 3-(*o*-carbomethoxyphenyl)-3-phenyl-2(3*H*)-benzofuranone, 59092-85-2; *o*-benzoyloxydiphenylacetic acid, 59092-86-3; o-benzoyloxydiphenylacetyl chloride, 59092-87-4.

References and Notes

(1) This research was sponsored by the National Institutes of Health, National Cancer Institute, Grant 10742.
(2) Reilly Fellow, 1973–1974.
(3) Part 3 in this series: J. P. Freeman, J. A. Kassner, and R. C. Grabiak, *J. Org. Chem.*, **40**, 3402 (1975).
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(17) The benzene filtrate was separated on silica gel to yield a small amount of starting heterocycle and also a small amount of an unidentified orange oil.

Chemistry of Heterocyclic Compounds. 22. Condensation Reactions of 2-Substituted Pyridines[1a,b]

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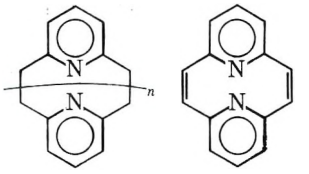
Condensation reactions of 2-substituted pyridines were investigated as model systems which would afford insight into possible synthetic routes to the 2,6-pyridino macrocyclic series **1** and **2**. While phenylacetic acid and deoxybenzoin (**15**) reacted with benzaldehyde (**8**) under Perkin and Knoevenagel conditions, respectively, to form predominantly the *E* olefin (with the desired cis-phenyl rings), ethyl 2-pyridylacetate (**7**) and α-(2-pyridyl)acetophenone (**17**) reacted with 2-pyridinecarboxaldehyde (**10**) to afford almost exclusively the *Z* isomer (with trans-pyridyl rings). A mechanism explaining the predominance of the undesired *Z* isomer in these heterocyclic systems is proposed.

As part of a continuing study of open- and closed-chain polypyridines, one of our initial goals was the construction of [2,2. . .]pyridinophanes (**1** and **2**). At the onset of this work,



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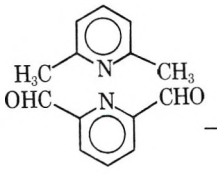

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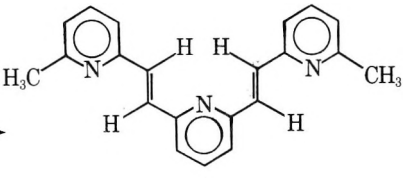

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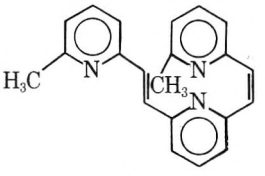

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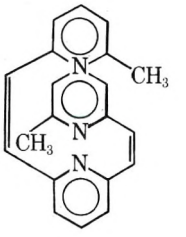

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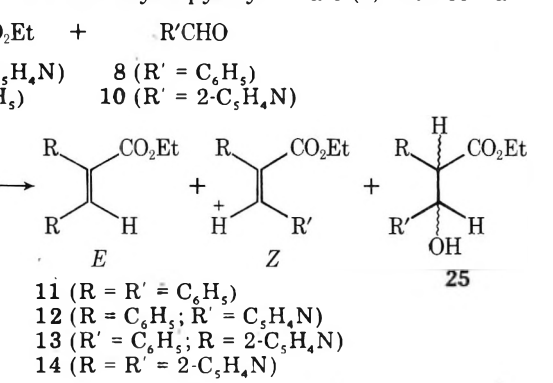
several members of **1** had been prepared albeit in low yields by means of a Wurtz coupling reaction under high dilution.[2] During the course of this investigation, Boekelheide and Lawson[3] reported the successful synthesis of **2** ($n = 1$) through a novel double ring contraction of a disulfide macrocycle. Earlier an unsuccessful attempt[2b] to prepare **2** ($n = 1$) by condensation of 2,6-dimethylpyridine with 2,6-pyridinedicarboxaldehyde (**3**) in the presence of acetic anhydride was reported; however, the open-chain trans,trans diene **4** was isolated and later confirmed to possess two trans linkages.[4] Under diverse conditions, condensations of simple 2-methylpyridines with aromatic aldehydes have been reported[5] to afford predominantly the corresponding trans olefins. Conversely, the well-known Perkin[6] and Knoevenagel[7] condensations of arylacetic acids and α-arylacetophenones, respectively, with substituted benzaldehydes have been shown to give α,β-unsaturated carbonyl compounds with the cis-phenyl orientations in excellent yields. Thus, we herein report our preliminary data on the condensation of simple heterocyclic esters and ketones with various aldehydes in order to ascertain the applicability of these condensation reactions to the construction of pyridinophanes.

Results and Discussion

Condensations of 2-methylpyridines with 2-pyridinecarboxaldehydes have afforded stilbazoles (2-styrylpyridines) which generally possess the *E* configuration. In light of our synthetic goals, we desired procedures which will permit construction of this linkage with the *Z* configuration (cis orientation of the heterocyclic rings); therefore, the utilization of either the Perkin condensation or the Knoevenagel reaction might afford a procedure to the disubstituted acrylates and 1-phenyl-2-propenones, which possess a predominance of the desired cis hetero-ring orientation.

Substituted Acrylates. Bragg and Wibberley[9] reported the condensation of ethyl 2-pyridylacetate (**7**) with benzal-



RCH_2CO_2Et + R′CHO

7 (R = 2-C_5H_4N) **8** (R′ = C_6H_5)
9 (R = C_6H_5) **10** (R′ = 2-C_5H_4N)

11 (R = R′ = C_6H_5)
12 (R = C_6H_5; R′ = C_5H_4N)
13 (R′ = C_6H_5; R = 2-C_5H_4N)
14 (R = R′ = 2-C_5H_4N)

dehyde using a catalytic amount of piperidine and isolation (46%) of cinnamate **13** containing the desired *E* orientation (cis rings) about the double bond. Those authors unfortunately subjected the reaction mixture to rigorous distillation conditions, then reported the isolation of a single picrate derivative in an unspecified yield and no confirmatory spectral data. Repetition of their original procedure, as best possible, was carried out until the purification stage; in order to prevent thermal degradation, a combination of both thin and thick layer chromatography was used to isolate the products. Although two products, *E*- and *Z*-**12**, were isolated in 20 and 10%, respectively, the major component (43%) was the unreacted ester **7**. NMR analysis of the initial reaction mixture substantiated this product distribution (see Table III) and supported the slight predominance of the *E* isomer, thus partially confirming the previous results.[8]

Similarly, ethyl 2-pyridylacetate was condensed with the more reactive 2-pyridinecarboxaldehyde (**10**) in the presence of piperidine to afford (~70%) **14** in less than half of the time required for the reaction with benzaldehyde. However, in this case the *Z* isomer was isolated in a 2:1 predominance over the corresponding *E* isomer. Small amounts (2%) of the intermediate alcohols **25** as well as starting ester (**7**) were also recovered. Reaction of **7** and **10** under standard Perkin condi-

Table I. Selected Spectral and Physical Data for the Substituted Ethyl Acrylates[a]

Registry no.	Compd	Mp or bp, °C (mm)	Ir, cm^{-1} [b] >C=O	Ir, cm^{-1} [b] >C=C<	Uv, nm (ε × 10^3)[c]		NMR, δ, ppm[d] >=<^{H}	NMR, δ, ppm[d] -OCH$_2$-	NMR, δ, ppm[d] -CH$_3$
7042-31-1	*E*-11	30–31[e]	1710	1625	219 (16.4)	284 (14.8)	7.79	4.15	1.14
59169-48-1	*E*-12	195–203 (4)	1713	1644	250 (10.1)	292 (11.7)	7.93	4.26	1.24
24832-45-9	*E*-13	179–186 (2.5)[f]	1712	1630		281 (15.8)	7.93	4.28	1.26
59169-51-6	*E*-14	145–150 (3.5)	1714	1591	257 (10.9)	291 (11.3)	7.97	4.27	1.26
2048-32-0	*Z*-11	135–140 (0.1)[g]	1723	1604	222 (14.3)	287 (20.8)	6.99	4.24	1.14
59169-49-2	*Z*-12	69.5–71.5	1722[h]	1620	223 (10.9)	304 (16.7)	6.91	4.41	1.29
59169-50-5	*Z*-13	150–160 (0.15)	1723	1586	220 (11.6)	299 (18.5)	7.67	4.33	1.18
59169-52-7	*Z*-14	77.5–79	1723[h]	1587	263 (12.4)	311 (23.6)	7.67	4.46	1.35

[a] Satisfactory analytical data (±0.4% for C, H, and N) were obtained for all new compounds in this table. [b] Thin films, except where noted. [c] Methanol solvent. [d] Deuteriochloroform solvent, ca. 10% w/v. [e] Lit.[13] mp 31–32 °C. [f] Lit.[9] bp 160–161 °C (1 mm). [g] Lit.[13] bp 130 °C (0.01 mm). [h] Chloroform solvent.

Table II. Selected Spectral and Physical Data for the Substituted Benzoylethylenes[a]

Registry no.	Compd	Mp, °C	Ir, cm^{-1} [b] >C=O	Ir, cm^{-1} [b] C-O	Uv, nm (ε × 10^3)[c]	
7474-65-9	*E*-19	100.5–101.5[d]	1645	1250	255 (16.5)	295 (14.4)
59169-53-8	*E*-20					
34236-72-1	*E*-21	155–157[e]	1668[f]		257 (16.3)[g]	318 (16.4)[g]
59169-55-0	*E*-22	86.5–88.5	1644	1265	268 (13.5)	297 (15.9)
59169-57-2	*E*-23	185.5–186.5[h]	1645	1265	266 (18.2)	289 (18.2)
59169-59-4	*E*-24	Oil	1659	1259	259 (14.2)	293 (12.2)
7512-67-6	*Z*-19	86–87.5[i]	1659	1225	254 (23.5)	282 (21.1)
59169-54-9	*Z*-20	157.5–158.5	1670	1232	256 (21.9)	303 (18.9)
3423-64-1	*Z*-21	168–168.5[j]	1672[f]		251 (21.6)[g]	328 (20.4)[g]
59169-56-1	*Z*-22	115–116	1682	1240	258 (21.5)	297 (21.5)
59169-58-3	*Z*-23	135–136[k]	1689	1225	251 (22.4)	327 (22.4)
59169-60-7	*Z*-24	154–155.5	1687	1243	254 (21.7)	310 (21.2)

[a] Satisfactory analytical data (±0.4% for C, H, N) were obtained for all new compounds in this table. [b] Nujol mulls. [c] Methanol solvent. [d] Lit.[20] mp 99–101 °C. [e] Lit.[20] mp 155–157 °C. [f] In carbon tetrachloride.[20] [g] In ethanol (95%).[20] [h] Lit.[7a] mp 188–189.5 °C. [i] Lit.[20] mp 85–87 °C. [j] Lit.[20] mp 167–168 °C. [k] Lit.[7a] mp 135–136 °C.

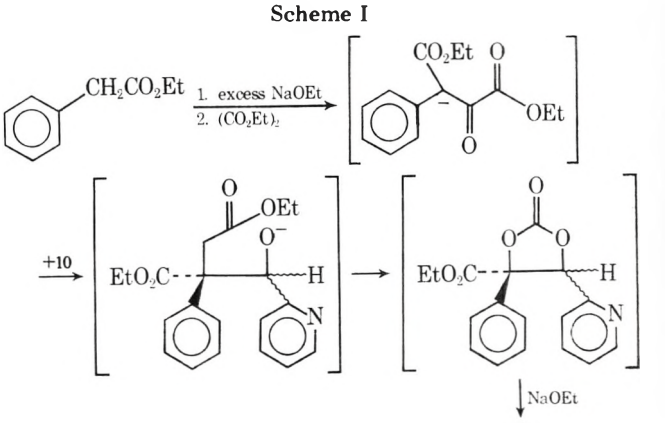
tions, i.e., triethylamine and acetic anhydride at room temperature, gave a similar 2:1 ratio of *Z* to *E* isomer distribution along with the acetate of **25**. This latter product resulted from use of the mild reaction conditions. In all of the reactions in which acetic anhydride was used, 3-substituted propenoic acids were detected but not isolated. In the absence of acetic anhydride, triethylamine in absolute ethanol affected the condensation of **7** and **10** resulting in an increased predominance (3:1) of the *Z* isomer. The intermediary alcohol **25** was also detected but not isolated. The NMR analysis as well as actual product isolation (Table III) showed a similar *Z* to *E* product distribution (ca. 2–3 to 1), thus indicating no distinct advantage to any of these procedures.

Numerous attempts to condense ethyl phenylacetate (**9**) with **10** under varied reaction conditions failed. Others have reported similar results.[9] In order to complete this series as well as by-pass the low acidity of the α proton of **9**, acrylates *E*- and *Z*-**12** were synthesized by a procedure described by Shahak[10] (Scheme I). Although both isomers of **12** were isolated in low yield, the *E* isomer was isolated in predominance. This product distribution probably results from steric approach control of the intermediate carbanion on **10**; the intermediates were not isolated.

For comparative purposes, the α-phenylcinnamates **11** were prepared by various literature procedures.[11-14] Selected physical and spectral data for **11**–**14** are given in Table I.

Disubstituted Benzoylethylenes. Deoxybenzoin (**15**), α-(4-nitrophenyl)acetophenone (**16**), and α-(2-pyridyl)acetophenone (**17**) were each condensed with either **8** or **10**; the

Scheme I



12

physical and spectral data for the resultant products are listed in Table II. In general, these α-substituted acetophenones were reacted with a slight excess of the appropriate aldehyde in the presence of a catalytic amount of piperidine. Benzene was used as solvent, rather than ethanol, which permitted the azeotropic removal of water. The product distribution for the various reactions is summarized in Table III.

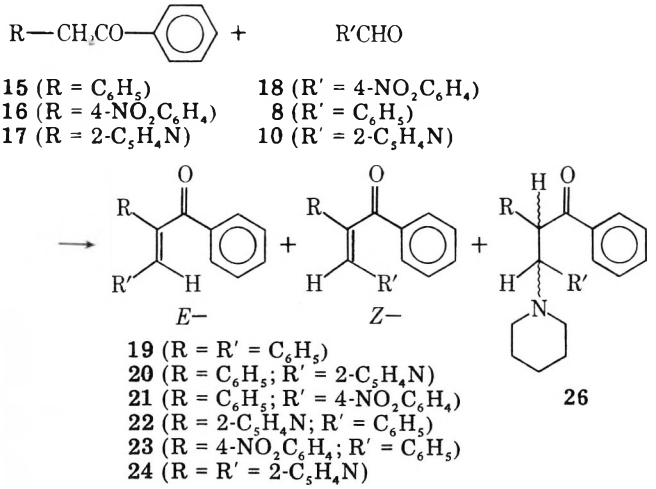
When benzaldehyde is used, these condensation reactions proceed smoothly with a catalytic amount of piperidine; however, with 2-pyridinecarboxaldehyde, an equivalent amount of piperidine was necessary to realize the theoretical amount of water and to ensure completion of the reaction. In these cases, the piperidine underwent a Michael addition with

Table III. Summary of Product Distribution

Reaction prepn of	Method	Yield, % Isolated E-	Isolated Z-	Isolated Other components	Estimates from NMR data E-	Estimates from NMR data Z-	Estimates from NMR data Other components
11[a]		60	11		78	22	
12	A, B			**9** (>95)			
	D	16	9	**9** (>70)	*b*	*b*	*b*
13	A	20	10	**7** (43)	30	12	**7** (~50)
14	A	20	45	**7** (13), **25** (2)	24	50	**7** (16), **25** (4)
	B		46		23	50	**7** (<10), **25** acetate (18)
	C		49		~17	60	**7** (10), **25** (18)
19	E	74	26				
20	E	0	67	**26** (27)	<5	~70	**26** (~30)
	F	0		**27a** (71), **27b** (15)			
22	E	0	74	**26** (traces)	<5	>90	**26** (traces)
23	E[c]	25	62		29	70	
	E[d]	9	64	**15** (5)	13	69	**15** (6)
24	E	0	30	**26** (15)	<5	~50	**26** (~20)[e]

[a] Values cited were derived from condensation of the corresponding acid. [b] Not available. [c] With crude benzaldehyde, traces of benzoic acid. [d] With freshly distilled benzaldehyde. [e] Other components were detected but not characterized.

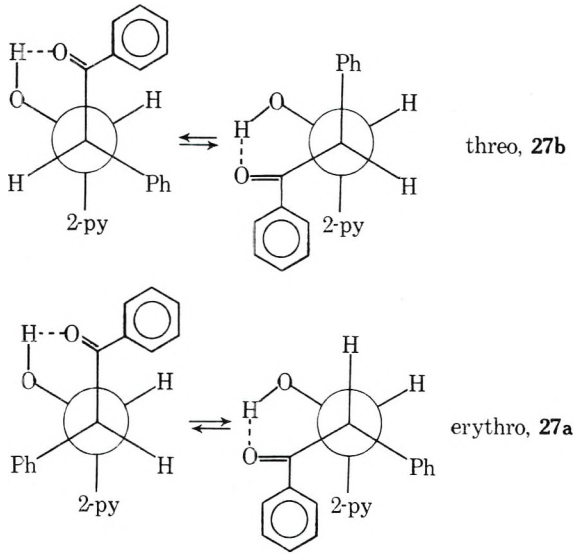
the condensation product; therefore, the adduct had to be refluxed with dilute mineral acid to effect elimination of piperidine and generate the desired olefin. For example, when deoxybenzoin (**15**) and **10** were condensed in the presence of



an equivalent amount of piperidine, the piperidine adduct **26** was isolated in 27% yield. This compound apparently decomposes to the *Z* isomer on extended heating, since *Z*-**20** was isolated in 67% yield by refluxing the reaction mixture. Adduct **26** smoothly underwent β-elimination of piperidine in refluxing 5% hydrochloric acid to generate exclusively (91%) *Z*-**20**.

In order to assign the structure to this initial piperidine adduct **26**, a sample was partially isomerized (26%) at elevated temperatures. The erythro and threo isomers of **26** were separated. Since the vicinal methine coupling constant in the NMR spectrum of the initial adduct is 11.5 Hz compared with 10.5 Hz for the thermally derived isomer the structures were at best tentatively assigned to the threo and erythro isomers, respectively.

To circumvent this addition product, **15** and **10** were condensed in the presence of a tertiary or highly hindered secondary amine catalysis. The intermediate alcohols **27a** and **27b** were isolated in 72 and 15% yield, respectively. The NMR spectrum of the major alcohol showed a methine coupling constant of 5 Hz, while for the minor isomer the coupling constant was 7.5 Hz. This methine–hydrogen coupling can be



rationalized using the Newman projections of the most stable conformations of **27a** and **27b**, noting the repulsion of the largest groups as well as hydrogen bonding. With the aid of these drawings, the isomer with the larger coupling constant would be the threo isomer. Thus, the major alcohol (**27a**) isolated in this condensation reaction has the smaller coupling constant and is probably the erythro isomer. Indeed, the erythro isomer was expected to predominate.[7b,15] Further substantiation of the structural assignment is available by comparison to similar systems.[16] Also, **27a** was heated to 150 °C for several hours and upon cooling **27b** was isolated as the major thermodynamic product.

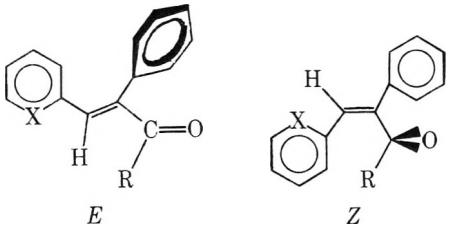
Photochemical Isomerization. The *E* isomers in Table II were prepared in more suitable quantities by mild photoisomerization of the readily available corresponding *Z* isomer. A 0.01 M benzene solution of the respective *Z* isomer under an argon atmosphere in Pyrex was allowed to stand in sunlight for approximately 6 h.[7a] In this way, *E*-**22** and *E*-**24** were prepared and isolated in 30% yield. The photolysis mixture containing *E*- and *Z*-**20** could not be separated. From preliminary experiments, it was found that more dilute solutions irradiated for longer periods of time resulted in increased photoisomerization. For example, *E*-**13** was obtained from the corresponding *Z* ester in 88% yield by photolysis of a 0.001 M

solution for 72 h. Alternate procedures for photoisomerization of substituted (*Z*)-2-stilbazoles are well documented.[5e,17]

The olefinic lability of the *E* isomers which possess a β-2-pyridyl group is supported by the fact that neither **20** or **24** could be isolated in the pure form. Nucleophilic attack at the β position (Michael addition) is an extremely facile process. Such reactions have been previously reported during attempted isolation of 3- and/or 4-(2′-pyridyl)cyclopentadienones[18] and 2-aryl-3-(2′-pyridyl)acrylonitriles.[19] During attempted molecular distillation, *E*-**24** underwent a thermal decomposition; however, spectral data were obtained on a freshly chromatographed sample.

Isomeric Relationships of the Acrylates and Disubstituted Benzoylethylenes. Structural assignments of the α,β-unsaturated esters and ketones in Tables I and II, respectively, were based on NMR, ir, and uv spectral data as well as by comparison of the spectral data of several well-known analogues, e.g., **21** and **23.** Although each spectral method might enable distinction between the *E* and *Z* isomers, these tabular combinations provide unequivocal structural assignments. Black and Lutz[7a] have discussed the reactivity and uv spectral data for the related α-phenylchalcones; further confirmation of their assignments was provided by ir and uv data.[20] Likewise, the configuration of the acid precursors to **11** was well established.[12]

The carbonyl absorption for the nonconjugated *Z* esters and ketones generally appeared at a higher frequency than that of the corresponding *E* isomer, approximately 10 and 25–40 cm^{-1}, respectively. The C–O stretching frequency of the *E* ketones and the carbon–carbon double bond stretching frequency both absorb at a higher frequency owing to increased conjugation expected in the *E* isomer.



(1)

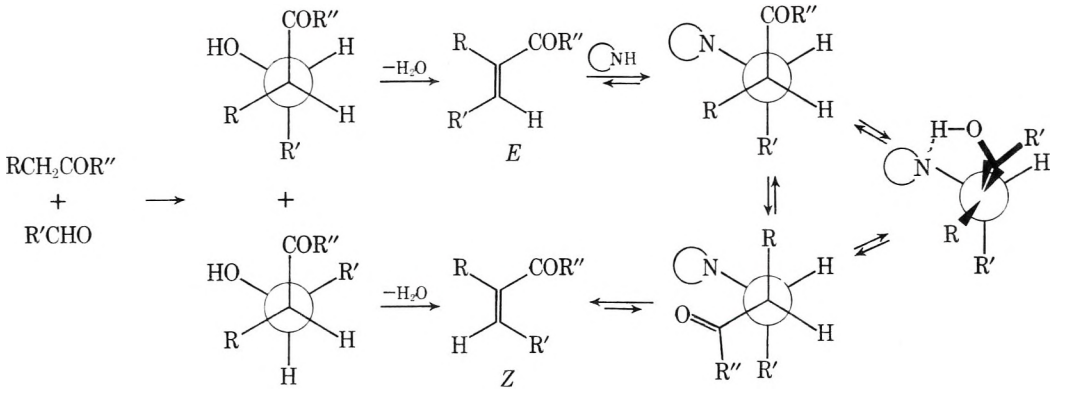
X = N or CH
R = Ph or OEt

With the exception of **13,** the uv data in Tables I and II exhibited a higher λ_{max} for each *Z* isomer as well as a larger molar extinction coefficient. This general effect was more pronounced at the longer wavelength absorption band. The exception of **13** is attributed to the difficulty in isolation and purifying the samples; this spectral method is less useful in these heterocyclic systems owing to the sensitivity to trace impurities.[22]

The NMR spectrum of the α,β-unsaturated ketones exhibited only a broad aromatic region in which the vinylic hydrogen resonance was superimposed and indistinguishable. Isomeric differentiation was possible for the esters (see Table I). Although the methyl group of the ester exhibited no difference in chemical shifts which could be related to olefinic stereochemistry, the methylene function exhibited an isomeric distinction in $CDCl_3$ solvent.[21] Since the *Z* isomer carbonyl group is less effectively conjugated (eq 1), the methylene resonance was shifted downfield by 5–18 Hz compared to the *E* isomer. The vinylic proton resonance can be easily characterized as a sharp spike. The cis relationship between the carbonyl group and vinylic proton in the *E* isomer resulted in the appearance of a more deshielded vinylic resonance (δ 7.0–7.7). The vinylic hydrogens of *Z*-**13** and *Z*-**14,** which have the 2-pyridyl group cis to the vinylic proton, were also more deshielded (ca. 0.7 ppm) than the corresponding *Z*-**11** and *Z*-**12,** which possess a cis phenyl–vinylic hydrogen relationship. The pyridine nitrogen lone pair has been shown to effect this magnitude of deshielding within a range of 0.5–0.7 ppm.[24]

Conclusions

Table III shows both the percentages of actual products and NMR spectral percentages of the initial reaction mixture. Although acrylates **12** and **13** give a slight preference for the desired *E* isomer, the 1:2 (*E* to *Z*) distribution shown for **14** indicates that the increased electron withdrawal of the 2-pyridyl moiety causes an isomerization in the later stages of the reaction via either (1) abstraction–equilibration of the α proton of an intermediate, or (2) Michael addition, followed by isomerization, and elimination. A better insight into the mechanistic course can be shown for the benzoylethylenes. The alcohol intermediate **27** (**a** and/or **b**) loses water with "stereoelectronic overlap" control[6a] to initially generate the *E* isomer. Since the *E* olefin is effectively conjugated through the coplanar carbonyl, verified by the spectral data, a facile Michael addition at the β carbon of the α,β-unsaturated carbonyl system occurs.[7a] Furthermore, piperidine undergoes such addition to the *E* isomer,[18,19] whereas no addition products are derived from the *Z* isomer. A similar facile nucleophilic 1,4 addition ($NaBH_4$) has been recently reported[23] for methyl (*E*)-α-(*p*-nitrophenyl)cinnamate (reaction time 10 min), whereas the *Z* isomer required about 8 h for complete reduction. Subsequently, the piperidine adduct can undergo equilibration to the more stable isomer, followed by β-elimination resulting in formation of the *Z* isomer. Thus, Michael addition and subsequent elimination equilibrates the *E* and *Z* isomer. However, if such an equilibrium exists under these conditions, it is dramatically shifted toward the *Z* isomer in **20, 22,** and **24,** and to a lesser extent with the 2-pyridyl acrylates. Since the *Z* olefin resembles a trans stilbene, nucleophilic addition would be greatly diminished. Indeed, both *E*- and *Z*-**19** can be equilibrated with a 10 molar excess of piperidine at 80 °C for 24 h to afford the same 72:28 ratio of *Z*- to *E*-**19;** a ratio which is closely aligned to ours.



Thus, in both the Perkin and Knoevenagel reactions in which products possess a 2-pyridyl moiety, an increased *Z* to *E* ratio is experienced over the corresponding model compounds.

We are currently attempting multiple-sequential condensation reactions of 2,6-pyridinedicarboxylates and 2,6-pyridinedicarboxaldehydes in order to gain access to systems **1** and **2**.

Experimental Section

Melting points were measured in capillary tubes with a Thomas-Hoover Unimelt and are reported uncorrected. NMR (60 MHz) spectra were measured in deuteriochloroform solvent and recorded on either a Varian Associates A-60A or a Perkin-Elmer R12-B spectrometer. All chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (~1%) as the internal standard. Ir spectra were recorded on either a Perkin-Elmer 137 or a Perkin-Elmer 621 grating spectrophotometer. Uv spectra were determined in absolute methanol on a Cary 14 recording spectrophotometer; absorbance values were reported in wavelength (nm) followed by molar extinction coefficient (ϵ). Elemental analyses were performed by either Mr. R. Seab in these laboratories or by Galbraith Laboratories, Inc., Knoxville, Tenn.

Preparative thick layer chromatography (THLC) utilized Brinkmann PF-254+366 silica gel of 2-mm thickness. Reported frontal retention (R_f) values were obtained from thin layer chromatography utilizing Brinkmann HF-254+366 silica gel of 0.25-mm thickness; the solvent system for both thin and thick layer methods was identical. Dry column chromatography used nylon tubing and Waters Associates dry column grade silica gel, activity III. All solvents and reagents were dried and either distilled or recrystallized by standard procedures.

Substituted Ethyl Acrylates. Selected spectral data for these acrylates are compiled in Table I.

Ethyl (*Z*)- and (*E*)-2,3-Di(2'-pyridyl)acrylates (14). Method A. Piperidine–Ethanol. A mixture of ethyl 2-pyridylacetate[25] (2.66 g, 16.1 mmol), 2-pyridinecarboxaldehyde (1.72 g, 16.1 mmol), and piperidine (1 ml) in 25 ml of absolute ethanol was refluxed for 12 h. The solvent and excess volatile reagents were removed in vacuo affording an oil, which was dissolved in ether–petroleum ether (bp 30–60 °C), decolorized, and allowed to crystallize, giving 980 mg (25%) of *Z*-**14**, mp 77.5–79 °C.

Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.50; H, 5.30; N, 10.95.

The mother liquor (3 g) was chromatographed on a column of silica gel with cyclohexane–ethyl acetate (3:1) and using gradient elution to pure ethyl acetate. Combined fractions afforded an additional 820 mg of *Z*-**14**, 350 mg of ethyl 2-pyridylacetate, 800 mg (20%) of *E*-**14** [bp 145–150 °C (3.5 mm)], and 86 mg (2%) of the intermediary alcohols.

Anal. Calcd for $C_{15}H_{14}N_2O_2$ (*E*-**14**): C, 70.85; H, 5.55. Found: C, 70.73; H, 5.60.

Method B. Acetic Anhydride–Triethylamine. A solution of ethyl 2-pyridylacetate (3.31 g, 20 mmol), 2-pyridinecarboxaldehyde (2.15 g, 20 mmol), triethylamine (25 ml), and acetic anhydride (25 ml) was stirred at 25 °C under nitrogen for 15 h. The mixture was poured into ice water, basified with solid sodium carbonate, and extracted with ether. The ether layer was dried over anhydrous sodium sulfate and concentrated. NMR analysis of the residue indicated <23% of *E*-**14**, 50% of *Z*-**14**, and traces of acetylated intermediary compounds (ca. 18%). The residue was dissolved in dichloromethane, conveniently decolorized through a small silica gel column, and recrystallized from cold ether–petroleum ether to give 2.32 g (46%) of *Z*-**14**, mp 77–78 °C.

Method C. Triethylamine–Ethanol. An ethanol solution of ethyl 2-pyridylacetate (3.31 g, 20 mmol), 2-pyridinecarboxaldehyde (2.14 g, 20 mmol), and triethylamine (20 ml) was refluxed under nitrogen for 16 h. The solvents and volatile reactants were removed in vacuo and NMR analysis of the residue indicated 18% of alcoholic intermediates, 17% of *E*-**14**, 60% of *Z*-**14**, and ~10% starting ester. Recrystallization of the decolorized residue gave 2.5 g (50%) of *Z*-**14**, mp 77.5–79 °C.

Ethyl (*Z*)- and (*E*)-2-(2'-pyridyl)cinnamate (13) were prepared from ethyl 2-pyridylacetate (505 mg, 3.06 mmol) and redistilled benzaldehyde (358 mg, 3.38 mmol) via method A. After removal of the solvents and excess volatile reagents, the residue was chromatographed (THLC) with cyclohexane–ethyl acetate (2:1), affording *Z*-**13** [78 mg, 10%; bp 150–160 °C (0.15 mm); R_f 0.63; methiodide mp 223–225 °C (dec), lit.[8] mp 227–228 °C (dec)], *E*-**13** [(154 mg, 20%; bp 179–186 °C (2.5 mm), lit.[8] bp 160–161 °C (1 mm)], unreacted starting ester (216 mg; 43%; R_f 0.41), and several trace unidentified compounds.

Ethyl (*Z*)- and (*E*)-2-Phenyl-3-(2'-pyridyl)acrylate (12). Method A. Piperidine–Ethanol. A mixture of ethyl phenylacetate (3.0 g, 20 mmol), 2-pyridinecarboxaldehyde (2.1 g, 20 mmol), and piperidine (1 ml) in 25 ml of absolute ethanol was refluxed for 12 h. After standard workup procedures, the unreacted starting materials were recovered (>95%).

Method B. Acetic Anhydride–Triethylamine. The above procedure was followed except for the substitution of acetic anhydride (15 ml) and triethylamine (15 ml) for the base and solvent. After standard workup the starting ester and aldehyde were recovered (>95%).

Method D.[10] A mixture of ethyl phenylacetate (1.64 g, 10 mmol), diethyl oxalate (1.46 g, 10 mmol), and sodium hydride (270 mg, 11.2 mmol) in 50 ml of di(*n*-butyl) ether was warmed at 65–70 °C for 1 h. The ethanol was removed in vacuo; then after cooling to less than 50 °C, 2-pyridinecarboxaldehyde (1.09 g, 10 mmol) was added and the mixture was refluxed under nitrogen for 1 h. The reaction mixture was cooled, poured into ice water, extracted with chloroform, washed successively with a 10% sodium carbonate solution, water, and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed (THLC) with cyclohexane–ethyl acetate (2:1) affording *Z*-**12** (145 mg; 9%; mp 69.5–71.5 °C; R_f 0.60), *E*-**12** [253 mg; 16%; bp 195–203 °C (4 mm); R_f 0.54], unreacted ethyl phenylacetate (70%), and several minor unidentified compounds.

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found (*Z* isomer): C, 75.76; H, 5.82; N, 5.71. Found (*E* isomer): C, 75.68; H, 5.82; N, 5.46.

(*Z*)- and (*E*)-2-phenylcinnamic acids were prepared by standard Perkin procedures[11] from phenylacetic acid and benzaldehyde. The utilization of Fieser's method[12] for isomer separation afforded pure *Z* acid (11%; mp 138–139 °C, lit.[12] 138–139 °C) and *E* acid (59.5%; mp 172–173 °C, lit.[12] mp 174 °C).

Ethyl (*E*)-2-Phenylcinnamate. The *E* acid was esterified using standard acid-catalyzed conditions and workup. The residual oil was recrystallized from diethyl ether–hexane (1:1) affording pure *E*-**11**, mp 30–31 °C (lit.[13] mp 31–32 °C).

Ethyl (*Z*)-2-Phenylcinnamate. Prolonged esterification for the preparation of *Z*-11 from the acid was obviated by an adaptation of Mills' procedure.[14] A mixture of (*Z*)-2-phenylcinnamic acid (1.26 g, 5.63 mmol), ethyl iodide (870 mg, 5.60 mmol), and triethylamine (550 mg, 5.45 mmol) was refluxed under nitrogen for 7 h. After cooling, the mixture was extracted with anhydrous ether and concentrated. The residue was suspended in ethyl acetate, filtered through activated alumina, and concentrated to give 853 mg (62%) of pure *Z*-**11**, bp 135–140 °C (0.1 mm) [lit.[13] bp 130 °C (0.01 mm)].

Substituted 1,2-Diarylbenzoylethenes. Selected spectral and melting point data for these benzoylethenes are compiled in Table II.

Deoxybenzoin was prepared by the method of Kohler and Nygaard:[26] mp 54.5–55.5 °C (lit.[26] mp 55 °C); NMR δ 4.23 (s, $COCH_2$, 2 H), 7.1–7.6 (m, ArH, 10 H); ir (Nujol) 1675 cm^{-1} (C=O).

2-(4'-Nitrophenyl)acetophenone was prepared by an established procedure:[27] mp 142–143.5 °C (lit.[27] mp 144 °C); NMR δ 6.40 (s, $COCH_2$, 2 H), 7.2–7.75 (m, ArH, 5 H), 7.9–8.35 (m, *o*-BzH and 3',5'-ArH, 4 H); ir (Nujol) 1689 (C=O), 1225 and 1208 cm^{-1} (C–O).

α-(2-Pyridyl)acetophenone was prepared (69%) by an established procedure,[28] bp 149–155 °C (2 mm), mp 54–56 °C (cyclohexane) (lit.[28] mp 52.5–54 °C).

General Condensation for 1,2-Diaryl Benzoylethylenes. Method E. Piperidine–Benzene. A mixture of 2-arylacetophenone (25 mmol), arylaldehyde (29 mmol), and piperidine (0.1 ml) in 25 ml of dry benzene was refluxed under nitrogen. After 5–14 h, the theoretical amount of water had been collected utilizing a Dean-Stark separator. Solvent and excess volatile reagents were removed in vacuo. The residue was decolorized and recrystallized usually from ethanol–ether. The mother liquors were concentrated and chromatographed (THLC). Yields were essentially quantitative.

Condensation of Deoxybenzoin with 2-Pyridinecarboxaldehyde. Method E. Piperidine Catalyst. Materials were condensed by the above general procedure and after refluxing for 19 h, the NMR spectrum of the reaction mixture indicated 20% completion. Addition of 1 ml of piperidine followed by another 2 h of reflux gave an additional amount of water. Finally, addition of a slight molar excess of piperidine gave rise to the theoretical amount of water after 6 h. The solvent and excess volatile reagents were removed in vacuo and the residue was recrystallized from ether–ethanol affording 2.38 g (27%)

of 1-phenyl-2-*N*-piperidino-2-(2′-pyridyl)benzoylethane (**26**): mp 167.5–169 °C; NMR δ 0.85–1.70 (m, 3,4,5-pip-H, 6 H), 1.95–2.95 (m, 2,6-pip-**H**, 4 H), 4.72 (d, pyr-CH–, J = 11.5 Hz, 1 H), 5.84 (d, PhC**H**–, J = 11.5 Hz, 1 H), 6.80–7.65 (m, Ar**H**, 11 H), 8.00–8.25 (m, o-Bz**H**, 2 H), 8.47–8.65 (m, 6-pyr-H, 1 H); ir (Nujol) 1673 (C=O), 1592, 1219, 763, and 699 cm^{-1}.

Anal. Calcd for $C_{25}H_{26}N_2O$: C, 81.04; H, 7.08; N, 7.56. Found: C, 80.64; H, 6.97; N, 7.47.

The mother liquor was concentrated affording 4.79 g (67%) of *Z*-**20**: NMR δ 6.77–7.68 (ArH and vinyl H, m, 12 H), 7.83–8.10 (o-BzH, m, 2 H), 8.13–8.32 (6-pyr-H, m, 1 H). Other spectral data are listed in Table II.

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 84.13; H, 5.18; N, 4.89.

The piperidine adduct (1.11 g, 30 mmol) in 30 ml of 5% hydrochloric acid was refluxed overnight, poured into ice water, basified with a 10% sodium carbonate solution, extracted with chloroform, and dried with anhydrous magnesium sulfate. Concentration afforded a residue which was recrystallized from 95% ethanol providing 780 mg (91%) of pure *Z*-**20**.

All new 1,2-diarylbenzoylethenes listed in Table II were prepared via method E. NMR spectral data and pertinent microanalyses for these new compounds follow: *E*-**19** [NMR δ 7.05–7.57 (m, ArH and vinyl H, 14 H), 7.83–8.08 (m, o-BzH, 2 H)]; *Z*-**22** [NMR δ 6.95–7.75 (m, ArH, 11 H), 7.85–8.15 (m, o-BzH, 2 H), 7.92 (s, vinyl H, 1 H), 8.50–8.68 (m, 6-pyr-H, 1 H)]; *Z*-**24** [NMR δ 6.82–7.78 (m, ArH, 9 H), 7.85–8.35 (m, o-BzH, 2 H), 7.92 (s, vinyl H, 1 H), 8.65–8.75 (m, 6-pyr-H, 2 H).

Anal. Calcd for $C_{20}H_{15}NO$ (*Z*-**22**): C, 84.18; H, 5.30; N, 4.91. Found: C, 84.51; H, 5.18; N, 4.91.

Anal. Calcd for $C_{19}H_{14}N_2O$ (*Z*-**24**): C, 79.70; H, 4.93; N, 9.79. Found: C, 79.44; H, 4.75; N, 9.67.

Method F. Dicyclohexylamine Catalyst. Deoxybenzoin (1.96 g, 10.0 mmol) and 2-pyridinecarboxaldehyde (1.07 g, 10.0 mmol) in benzene (20 ml) were refluxed utilizing a Soxhlet extractor equipped with a calcium hydride filled thimble. While refluxing over 6 h, dicyclohexylamine (1.81 g, 10.0 mmol) was added slowly. Evaporation to dryness and trituation with ether gave 1.76 g (58%) of *erythro*-3-hydroxy-1,2-diphenyl-3-(2′-pyridyl)propanone (**27a**): mp 149.5–150.5 °C; NMR δ 3.50–4.38 (s, –OH, 1 H, exchangeable with D_2O), 5.24 (d, pyr-C**H**–, J = 5 Hz, 1 H), 5.59 (d, PhCH–, J = 5 Hz, 1 H), 6.90–7.56 (m, ArH, 11 H), 7.73–8.03 (o-BzH, 2 H), 8.38–8.60 (m, 6-pyr-H, 1 H); ir (Nujol) 3400–3000 (broad, OH), 1675 (C=O), 1600, 1294, 1062, and 705 cm^{-1}.

Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.25; H, 5.59; N, 4.58.

Column chromatography of the mother liquor on silica gel using cyclohexane–ethyl acetate (2:1) gave an additional 390 mg (13%) of the propanone **27a**, mp 145–148 °C, and 440 mg (14.5%) of the corresponding threo isomer (**27b**): mp ~130 °C; NMR δ 3.81–4.48 (s, –OH, 1 H), 5.18 (d, pyr-C**H**, J = 7.5 Hz, 1 H), 5.46 (d, PhCH, J = 7.5 Hz, 1 H), 6.69–7.52 (m, ArH, 11 H), 7.76–8.08 (m, o-BzH, 2 H), 8.34–8.57 (m, 6-pyr-H, 1 H). An analytical sample of the latter isomer could not be obtained.

Thermal Equilibration of 1-Phenyl-2-*N*-piperidino-2-(2′-pyridyl)benzoylethane (26). A benzene solution of **26** showed no change after 15 h at 85 °C; therefore, it was sealed in a tube and heated at 160 °C for 30 min. After cooling, the mixture was chromatographed on silica gel eluting with cyclohexane–ethyl acetate (4:1) to give predominantly starting material along with 116 mg (26%) of its stereoisomer: NMR δ 0.87–1.55 (m, 3,4,5-pip-H, 6 H), 1.73–2.93 (m, 2,6-pip-H, 4 H), 4.66 (d, pyr-C**H**, J = 10.5 Hz, 1 H), 5.83 (d, PhC**H**, J = 10.5 Hz, 1 H), 6.70–7.62 (m, ArH, 11 H), 7.77–8.11 (m, o-BzH, 2 H), 8.45–8.63 (m, 6-pyr-H, 1 H). Attempted purification of this isomer was not successful.

Condensation of 2-(4′-nitrophenyl)acetophenone with benzaldehyde followed the above general procedure via method E, except that crude benzaldehyde, which contained several percent of benzoic acid, was utilized. The theoretical amount of water was collected within 1 h. Reflux was continued for an additional 1 h, then the mixture was cooled and concentrated. The residue was recrystallized from benzene–cyclohexane to afford a mixture of both isomers. Separation of the low-melting *Z* isomer was easily achieved by recrystallization from 95% ethanol affording 2.1 g (25%) of *Z*-**23**: NMR δ 7.0–7.78 (m, ArH and vinyl H, 11 H), 7.86–8.35 (m, o-BzH and 3′,5′-ArH, 4 H); other spectral data are in Table II.

The mother liquor afforded 5.1 g (62%) of the *E* isomer: NMR δ 6.85–7.35 (m, ArH and vinyl H, 11 H), 7.35–8.10 (o-BzH, 2 H), 8.10–8.45 (m, 3′,5′-ArH, 2 H); other spectral data are in Table II.

General Photoisomerization of Substituted Benzoylethenes and Ethyl Acrylates. A 0.01 M benzene solution of either *Z*-**20**, *Z*-**22**, or *Z*-**24** was flushed well with argon and allowed to stand in direct sunlight for 4–6 h. Evaporation of the solvent and chromatography (THLC) gave 25–35% of the corresponding *E* isomer, with the exception of **20** whose isomers were inseparable under the chromatography conditions: *E*-**22** [NMR δ 6.4–7.75 (m, ArH, vinyl H, 12 H), 7.75–8.11 (m, o-BzH, 2 H), 8.55–8.84 (m, 6-pyr-H, 1 H)]; *E*-**24** [NMR δ 6.79–7.82 (m, ArH and vinyl H, 10 H), 7.82–8.13 (m, o-BzH, 2 H), 8.44–8.74 (m, 6-pyr-H, 2 H)]; other selected spectral and physical data are given in Table II.

This general procedure was conveniently applied to the ethyl acrylates. When a 4.5×10^{-3} M benzene solution of ethyl (*Z*)-2,3-di(2′-pyridyl)acrylate (**14**) was subjected to direct sunlight under an inert atmosphere for 4 days, after concentration, the residue was chromatographed (THLC) affording (88%) ethyl (*E*)-2,3-di(2′-pyridyl)acrylate, bp 129–132 °C (0.6 mm).

Prolonged exposure times increases the amount of *E* isomer; the reaction conditions were not optimized.

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Registry No.—**8**, 100-52-7; **10**, 1121-60-4; **15**, 451-40-1; **16**, 3769-82-2; **17**, 1620-53-7; **18**, 555-16-8; *erythro*-**26**, 59169-61-8; *threo*-**26**, 59169-62-9; **27a**, 59169-63-0; **27b**, 59169-64-1; ethyl 2-pyridylacetate, 2739-98-2; ethyl phenylacetate, 101-97-3; (*E*)-2-phenylcinnamic acid, 91-48-5; (*Z*)-2-phenylcinnamic acid, 91-47-4; deoxybenzoin, 451-40-1; piperidine, 110-89-4.

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Studies on the Syntheses of Heterocyclic Compounds. 657.[1a] Total Synthesis of Angustine, Naucléfine, and Gentianine[1b]

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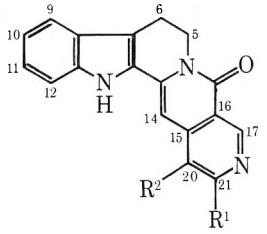
Condensation of 4-methyl-5-vinylnicotinonitrile (**7**) with ethyl oxalate, followed by acid hydrolysis, gave 3-ethoxycarbonyl-1-oxo-5-vinylpyrano[4,3-*c*]pyridine (**10**), which was heated in wet dimethylformamide to afford an unexpected product, gentianine (**6**). Gentianine (**6**) was also prepared directly from **7**. Condensation of **7** with ethyl formate yielded 3,4-dehydrogentianine (**16**). Treatment of the lactone (**10**) with tryptamine gave the 7-azaisocarbostyril (**14**), from which angustine (**1**) was synthesized by direct acid treatment or basic hydrolysis, followed by acidic cyclization. By the reaction of 3,4-dehydrogentianine (**16**) with tryptamine in acidic conditions, angustine (**1**) was also synthesized and naucléfine (**4**) was synthesized from nicotinonitrile (**17**) in a similar way.

In 1973, Cheng and his co-workers reported the isolation of angustine (**1**), angustoline (**2**), and angustidine (**3**) from *Strychnos angustiflora*.[2] Since then their distribution in species of *Mitragyna*, *Naucléa*, *Uncaria*, and *Strychnos* has been established.[3] Recently the related bases naucléfine (**4**) and nauclétine (**5**) were found in *Naucléa latifolia*.[4] Their

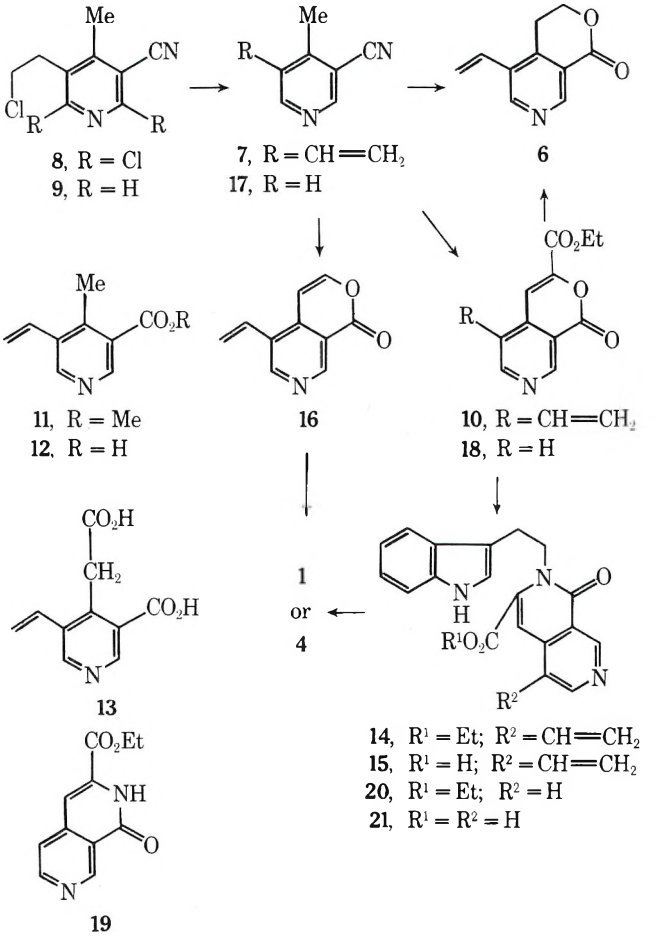


1, $R^1 = H$; $R^2 = -CH^{19}{=}CH_2^{18}$
2, $R^1 = H$; $R^2 = -CH(OH)Me$
3, $R^1 = Me$; $R^2 = H$
4, $R^1 = R^2 = H$
5, $R^1 = H$; $R^2 = COMe$

structures were assigned on the basis of spectral evidences and confirmed by the synthesis of angustoline (**2**),[5] angustidine (**3**),[6,7] and naucléfine (**4**).[4] Angustoline had been already converted into angustine (**1**).[2] It seemed worthwhile from a pharmacological point of view to investigate an effective synthesis of angustine and its derivatives. They are essentially *corynanthé* type alkaloids incorporating in their skeleton a tryptamine moiety and a secologanin monoterpene unit closely related to the alkaloid, gentianine (**6**).[2] We had therefore planned their synthesis using gentianine-like compounds and herewith describe biomimetic total syntheses of angustine (**1**) and naucléfine (**4**), and an alternative synthesis of gentianine (**6**).

According to a modified Govindachari procedure,[8] 4-methyl-5-vinylnicotinonitrile (**7**) was prepared via 2,6-dichloro-5-(2-chloroethyl)-3-cyano-4-methylpyridine (**8**) and 5-(2-chloroethyl)-4-methylnicotinonitrile (**9**). The nitrile **7** was condensed with ethyl oxalate in the presence of sodium hydride in benzene and in situ treated with diluted hydrochloric acid[9] to give the lactone **10**, mp 120 °C, in 76% yield.

Krapcho and Lovey had already carried out the decarboxylation of geminal diesters, β-keto esters, and α-cyano esters by heating in the presence of sodium chloride in wet dimethyl sulfoxide or wet dimethylformamide.[10] It was furthermore reported that even in the absence of sodium chloride, the reaction proceeded satisfactorily.[11,12] In expectation of a decarboxylation, the lactone **10** was heated with sodium chloride in wet dimethylformamide for 3 days and an unexpected product, mp 80–81 °C, *m/e* 175 (M^+), was isolated in 12% yield



after purification by column chromatography. The ir spectrum (in potassium bromide) of the product showed a carbonyl absorption at 1720 cm^{-1} and the NMR spectrum (δ in deuteriochloroform) revealed two neighboring methylene groups at 3.09 and 4.55 (each 2 H, each t, J = 6 Hz), a vinyl group at 5.59 (1 H, dd, J = 2 and 11.5 Hz), 5.76 (1 H, dd, J = 2 and 18 Hz), and 6.80 (1 H, dd, J = 11.5 and 18 Hz), and two aromatic protons at 8.80 and 9.11 ppm (each 1 H, each s). These spectral data suggested the product to be gentianine (**6**), which was also confirmed by direct comparison with an authentic sample.

When the lactone **10** was heated for 3 days in wet dimethylformamide in the absence of sodium chloride, the formation of gentianine (**6**) was also detected by gas chramotography. It is likely that decarboxylation and disproportionation occurred during the above transformation. The crude reaction product was treated directly with diazomethane and then carefully purified using silica gel column chromatography to afford methyl 4-methyl-5-vinylnicotinate (**11**) together with gentianine.

The formation of methyl 4-methyl-5-vinylnicotinate (**11**) was confirmed by a direct comparison with the authentic sample, prepared from the nitrile **7** via 4-methyl-5-vinylnicotinic acid (**12**). It was assumed that an aldehyde equivalent, formed by refluxing the dehydrolactone (**10**) in wet dimethylformamide, gave through disproportionation gentianine (**6**) and a derivative of the dicarboxylic acid (**13**), which was further decarboxylated to the nicotinic acid (**12**).

Gentianine (**6**) was furthermore synthesized by heating **7** with formalin in the presence of aqueous sodium bicarbonate solution for 19 h at 100 °C, followed by acid treatment. Govindachari and coworkers had previously prepared gentianine (**6**) by a similar reaction using the nicotinic acid analogue **12** derived from **7**.[8]

Refluxing the above lactone (**10**) with an equimolar amount of tryptamine in acetic acid for 3 h gave, in 90% yield, the azaisocarbostyril (**14**), the structure of which was confirmed by spectral evidence. The ester **14** was hydrolyzed with ethanolic potassium hydroxide at room temperature and the crude acid (**15**) obtained was then heated with a mixture (1:1 v/v) of concentrated hydrochloric acid and glacial acetic acid until no further generation of carbon dioxide could be detected. After chromatographic purification, angustine (**1**), mp >300 °C, was obtained in 23.5% overall yield from the ester **14**. Direct heating of **14** in a mixture of concentrated hydrochloric acid and acetic acid also gave angustine (**1**) in 8% yield. The uv, ir, and mass spectra of the synthetic compound were identical with those of natural angustine. The NMR spectrum (in dimethyl sulfoxide-d_6) at 110 °C was identical with that at the same temperature provided by Dr. Cheung. Taking the NMR spectra in the same solvent at room temperature and at 90 °C, some values of chemical shifts were considerably changed as predicted by Phillipson and coworkers.[3] Identity of the synthetic product with natural angustine (**1**) was further confirmed by high-pressure liquid chromatography.

Condensation of 4-methyl-5-vinylnicotinonitrile (**7**) with ethyl formate in the presence of sodium hydride in dry dimethyformamide or dry benzene at room temperature, followed by a treatment of the product with hydrochloric acid, gave dehydrogentianine (**16**). This pyrone was heated for 3 h with an equimolar amount of tryptamine in acetic acid to afford a mixture to which concentrated hydrochloric acid was added. Refluxing the resulting mixture for 10 h, followed by column chromatographic purification, afforded in 9.5% yield angustine (**1**).

Thereafter naucléfine (**4**) was synthesized according to the above sequence. 4-Methylnicotinonitrile (**17**)[13] was condensed with ethyl oxalate in the presence of potassium *tert*-butoxide in dry benzene and then treated with diluted hydrochloric acid to give the lactone **18** in addition to the naphthyridine **19**. The lactone **18** was converted into the azaisocarbostyril **20** by refluxing for 3 h with tryptamine in glacial acetic acid. After hydrolysis of **20** with ethanolic potassium hydroxide at room temperature, the crude acid **21** was heated for 7 days with a mixture of concentrated hydrochloric acid and glacial acetic acid to afford naucléfine (**4**) in 10% overall yield. Refluxing the azaisocarbostyril **20** with a mixture of concentrated hydrochloric acid and glacial acetic acid for 7 days also furnished naucléfine (**4**) in 15% yield. The uv, ir, NMR (in dimethyl sulfoxide-d_6), and mass spectra were superimposable with those of the natural product. The total syntheses of angustine (**1**) and naucléfine (**4**) have therefore been accomplished.

Experimental Section

All melting points are uncorrected. Uv spectra were measured with a Hitachi EPS-3 recording spectrometer, ir spectra with a Hitachi EPI-3 recording spectrometer, NMR spectra with a JEOL JNM-PMX-60 and JNM-PS-100 spectrometer, and mass spectra with a Hitachi RMU-7 spectrophotometer. The apparatus used for gas chromatography was a JEOL JGC-1100 equipped with a hydrogen flame ionization detector. High-pressure liquid chromatography was carried out with Waters Associated ALC-GDC 202,R401 instrument (6000 pumping system), with a 254-nm uv detector. The column (1 ft × 0.25 in.) was packed with μ-Bondapak C_{18} and elution was carried out with methanol–water (3:1 v/v) and flow rate of 1.5 ml/min.

5-(2-Chloroethyl)-4-methylnicotinonitrile (9). The trichloro compound 8 (48 g)[8] was hydrogenated for 6 h in methanol (300 ml) in the presence of sodium acetate (41 g) and 10% Pd/C (9.6 g) at room temperature under hydrogen (1 atm) until no more hydrogen had been absorbed. The resulting solution was filtered and the catalyst was washed with methanol. The combined filtrate and washings were evaporated. The residue was treated with aqueous sodium bicarbonate solution and extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated to give a syrup, whose distillation at 147–149 °C (4 mm) afforded **9** (30.8 g, 88.7%) [lit.[8] bp 144–145 °C (3 mm)]: NMR (CCl_4) δ 2.48 (3 H, s, ArMe), 3.08 (2 H. t, J = 7 Hz, CH_2CH_2Cl), 3.67 (2 H, t, J = 7 Hz, CH_2CH_2Cl), 8.42 and 8.54 ppm (each 1 H, each s, 2 ArH).

4-Methyl-5-vinylnicotinonitrile (7). A mixture of the above nitrile (**9**, 4.8 g) and potassium hydroxide (1 g) in ethanol (10 ml) was stirred for 1 h at room temperature. After addition of water, the reaction mixture was extracted with ether. The extract was dried over Na_2SO_4 and evaporated to give a syrup whose distillation at 135–143 °C (10 mm) afforded **7** (3.0 g, 78%) [lit.[8] bp 98 °C (2 mm)]: NMR ($CDCl_3$) δ 2.55 (3 H, s, ArMe), 5.55 (1 H, dd, J = 11.5 and 2 Hz, $CH{=}CH_2$), 5.74 (1 H, dd, J = 18 and 2 Hz, $CH{=}CH_2$), 6.88 (1 H, dd, J = 18 and 11.5 Hz, $CH{=}CH_2$), 8.67 and 8.71 ppm (each 1 H, each s, 2 ArH).

3,4-Dihydro-3-ethoxycarbonyl-1-oxo-5-vinylpyrano[3,4-c]pyridine (10). To a solution of the preceding nitrile (**7**, 1 g) and ethyl oxalate (20 ml) in dry benzene (10 ml), 50% sodium hydride (400 mg) was added in small portions, and the mixture was stirred for 24 h under nitrogen at room temperature. With cooling, 10% hydrochloric acid was slowly added to the above resulting mixture, which was then washed several times with ether. The aqueous layer was made basic with 10% ammonia and extracted with chloroform. The chloroform layer was washed with water, dried over Na_2SO_4, and evaporated to give a powder, the recrystallization of which from ethanol afforded **10** (1.2 g, 76%) as pale yellow needles: mp 120 °C; ir ($CHCl_3$) 1740, 1720, 1640, and 1580 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (3 H, t, J = 7 Hz, CH_2CH_3), 4.43 (2 H, q, J = 7 Hz, CH_2CH_3), 5.67 (1 H. dd, J = 11.5 and 2 Hz, $CH{=}CH_2$), 5.89 (1 H, dd, J = 18 and 2 Hz, $CH{=}CH_2$), 7.06 (1 H, dd, J = 18 and 11.5 Hz, $CH{=}CH_2$), 7.62 (1 H, s, 4-CH), 9.02 (1 H, s, 6-CH), and 9.42 ppm (1 H, s, 8-CH); mass spectrum m/e 245 (M^+).

Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.73; H, 4.65; N, 5.70.

Gentianine (6). A. A mixture of the above lactone (**10**, 70 mg), sodium chloride (50 mg), and water (2 drops) in dimethylformamide (5 ml) was refluxed for 3 days in an oil bath. After cooling, followed by an addition of water, the resulting mixture was extracted with chloroform. The extract was dried over Na_2SO_4 and evaporated to leave a gum, which was chromatographed on silica gel. Benzene–methanol (100:0.5 v/v) eluate yielded a powder, the recrystallization of which from carbon tetrachloride gave gentianine (**6**, 7 mg, 12%), as colorless needles: mp 80–81 °C (lit.[8] mp 80–81 °C); ir ($CHCl_3$) 1720 and 1621 cm^{-1}; NMR ($CDCl_3$) δ 3.09 (2 H, t, J = 6 Hz, 4-CH_2), 4.55 (2 H, t, J = 6 Hz, 3-CH_2), 5.59 (1 H, dd, J = 11.5 and 2 Hz, $CH{=}CH_2$), 5.76 (1 H, dd, J = 18 and 2 Hz, $CH{=}CH_2$), 6.80 (1 H, dd, J = 18 and 11.5 Hz, $CH{=}CH_2$), 8.80 (1 H, s, 6-CH), and 9.11 ppm (1 H, s, 8-CH); mass spectrum m/e 175 (M^+).

B. A mixture of 4-methyl-5-vinylnicotinonitrile (**7**, 0.5 g), sodium bicarbonate (0.5 g), 27% formalin (0.7 ml), and water (7 ml) was heated for 10 h at 100 °C in a sealed tube. After cooling, the excess of formalin was distilled off. The mixture was acidified with 10% hydrochloric acid, washed with ether, and then basified with 10% ammonia. The basic material was extracted with ether and the extract was washed with water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel with benzene–methanol (100:0.5 v/v) to give a powder, whose recrystallization from carbon tetrachloride afforded gentianine (**6**, 28 mg, 7.8%) as colorless needles, mp 81–82

°C. The ir (in $CHCl_3$), NMR (in $CDCl_3$), and mass spectra, and TLC and GLC (SE-30 and 1.6% OV-17) behaviors were identical with those of the product prepared by method A and authentic gentianine (**6**). A mixture melting point test with an authentic sample showed no depression.

Methyl 4-Methyl-5-vinylnicotinate (11) A. A mixture of 4-methyl-5-vinylnicotinonitrile (**7**, 1 g) and potassium hydroxide (3 g) in methanol was refluxed for 24 h. After cooling, the mixture was acidified to pH 5 with concentrated hydrochloric acid and then evaporated to dryness. The residue was extracted several times with methanol. The combined methanolic solution was saturated with hydrogen chloride gas and the mixture was refluxed for 5 h. After evaporation of the reaction mixture, the residue was extracted with chloroform, which was washed with 10% ammonia and water, dried over Na_2SO_4, and evaporated to give a brown residue, which was purified by sublimation at 80 °C (4 mm) to afford **11** (800 mg) as colorless needles: mp 46–47 °C; ir ($CHCl_3$) 1720 and 1645 cm^{-1}; NMR ($CDCl_3$) δ 2.55 (3 H, s, ArMe), 3.90 (3 H, s, OMe), 5.46 (1 H, dd, J = 11.5 and 2 Hz, CH=C**H**$_2$), 5.63 (1 H, dd, J = 18 and 2 Hz, CH=C**H**$_2$), 6.93 (1 H, dd, J = 18 and 11.5 Hz, C**H**=CH$_2$), 8.66 and 8.90 ppm (each 1 H, each s, 2 ArH); mass spectrum m/e 177 (M^+).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.27; N, 7.91. Found: C, 67.35; H, 6.36; N, 7.88.

B. A mixture of the dehydrolactone **10** (70 mg) and water (2 drops) in dimethylformamide (5 ml) was refluxed for 3 days. After distillation of the solvents under reduced pressure, the residue was dissolved in methanol. An excess of diazomethane in ether was added to the above methanolic solution and the mixture was set aside for 16 h at room temperature. After the evaporation, the residue was chromatographed on silica gel. Benzene eluate gave **11** (2.5 mg) as colorless needles, mp 46–47 °C, which was identical with the authentic sample prepared as above with comparisons of the ir, NMR, and mass [m/e 177 (M^+)] spectra and chromatographic behaviors on TLC and GLC (SE-30). Benzene–methanol (99.5:0.5 v/v) eluate gave gentianine (2 mg) as colorless needles, mp 80–81 °C, whose ir and NMR spectra and chromatographic behaviors on TLC and GLC were identical with those of the authentic sample.

3-Ethoxycarbonyl-2-(β-3-indolylethyl)-5-vinyl-7-azaisocarbostyril (14). A solution of tryptamine (320 mg) and the lactone **10** (400 mg) in glacial acetic acid (10 ml) was refluxed for 3 h. After cooling, the solvent was distilled off. The residue was taken up in chloroform. The extract was washed with 10% ammonia and water and dried over Na_2SO_4. After evaporation of the solvent, the resulting powder was recrystallized from ethanol to give **14** (700 mg, 90%) as colorless needles: mp 145 °C; uv (EtOH) 335, 290 sh, 280 sh, and 273 nm (log ϵ 2.95, 2.93, 3.01, and 3.02); ir ($CHCl_3$) 3480 (NH), 1720 and 1670 (C=O), and 1605 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz, CH_2CH_3), 3.22 (2 H, t, J = 7.5 Hz, C**H**$_2$CH$_2$N), 4.03 (2 H, q, J = 7 Hz, OC**H**$_2$CH$_3$), 4.68 (2 H, t, J = 7.5 Hz, CH$_2$C**H**$_2$N), 5.59 (1 H, dd, J = 11.5 and 2 Hz, CH=C**H**$_2$), 5.82 (1 H, dd, J = 18 and 2 Hz, CH=C**H**$_2$), 6.89 (1 H, d, J = 1.5 Hz, indole α-H), 8.00 br (1 H, s, indole NH, disappeared with D_2O), 8.56 (1 H, s, 6-CH), and 9.45 ppm (1 H, s, 8-CH); mass spectrum m/e 387 (M^+).

Anal. Calcd for $C_{23}H_{21}N_3O_3 \cdot 0.25H_2O$: C, 70.45; H, 5.55; N, 10.72. Found: C, 70.79; H, 5.43; N, 10.79.

1-Oxo-5-vinylpyrano[3,4-*c*]pyridine (16). To a solution of 4-methyl-5-vinylnicotinonitrile (**7**, 1g) and ethyl formate (10 ml), 50% sodium hydride (400 mg) was added in portions and the mixture was stirred for 24 h at room temperature under nitrogen. After acidification with 10% hydrochloric acid, the aqueous solution was washed with ether, basified with 10% ammonia, and then extracted with chloroform. The chloroform extract was washed with saturated sodium chloride aqueous solution, dried over Na_2SO_4, and evaporated to give a gum, which was chromatographed on silica gel (30 g). Benzene eluate gave the starting material (400 mg) and dehydrogentianine (**16**) as a solid, the recrystallization of which from methanol–ether afforded colorless needles (150 mg, 21%): mp 119–120 °C; ir ($CHCl_3$) 1736, 1630, and 1580 cm^{-1}; NMR ($CDCl_3$) δ 5.65 (1 H, dd, J = 11.5 and 2 Hz, CH=C**H**$_2$), 5.74 (1 H, dd, J = 18 and 2 Hz, CH=C**H**$_2$), 6.99 (1 H, dd, J = 18 and 11.5 Hz, C**H**=CH$_2$), 6.70 (1 H, d, J = 6 Hz, CH=CHO), 7.48 (1 H, d, J = 6 Hz, CH=C**H**O), 8.95 and 9.48 ppm (each 1 H, each s, 2 ArH); mass spectrum m/e 173 (M^+).

Anal. Calcd for $C_{10}H_7NO_2$: C, 69.35; H, 4.07. Found: C, 69.14; H, 4.17.

Angustine (1). A. To a solution of the azaisocarbostyril **14** (600 mg) in ethanol (30 ml) a mixture of potassium hydroxide (98 mg) in ethanol (5 ml) was added and the resulting mixture was stirred for 6 h at room temperature. After acidification with 10% hydrochloric acid, the solvent was distilled off to give a syrup, to which glacial acetic acid (10 ml) and concentrated hydrochloric acid (10 ml) were added without purification. The mixture was then refluxed for 3 days until the cease of generation of carbon dioxide. After cooling the reaction mixture was made basic with 10% sodium hydroxide solution and then extracted several times with n-butyl alcohol. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave a gum, which was chromatographed on silica gel. Benzene–methanol (99.5:0.5 v/v) eluate gave a yellow powder, the recrystallization of which from chloroform–methanol gave angustine (**1**, 114 mg, 23.5%) as yellow plates: mp >300 °C (lit.[2] mp >340 °C and lit.[3] mp 283–284 °C dec); uv (EtOH) 400, 380, 304, 292, and 255 nm (log ϵ 4.66, 4.64, 4.19, 4.17, and 4.32); ir (Nujol) 3300–3100 (NH), 1640 (C=O), 1610, 1600, 1148, 830, 815, and 740 cm^{-1}; NMR (Me_2SO-d_6 at 25 °C)[16] δ 4.38 (2 H, t, J = 7 Hz, 5-CH$_2$), 5.65 (1 H, dd, J = 11.5 and 2 Hz, 18-CH), 6.05 (1 H, dd, J = 18 and 2 Hz, 18-CH), 7.05–7.66 (6 H, m, 4 ArH, 14- and 19-CH), 8.80 (1 H, s, 21-CH) and 9.20 ppm (1 H, s, 17-CH); mass spectrum m/e 313 (M^+) (100%). The uv, ir, and mass spectra, TLC,[13] and HPLC behaviors were identical with those of natural product.

B. A mixture of the azaisocarbostyril **14** (92 mg) and concentrated hydrochloric acid (2 ml) in glacial acetic acid (2 ml) was refluxed for 3 days until the cease of generation of carbon dioxide. After cooling, 10% ammonia was added to the reaction mixture, which was extracted several times with n-butyl alcohol. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave a gum, which was purified as above to afford angustine (**1**, 3 mg, 4%) as yellow plates, mp >300 °C, which was identical with angustine prepared by method A on spectral and TLC comparisons.

C. A solution of tryptamine (20 mg) and the dehydrogentianine **16** (28 mg) in glacial acetic acid (5 ml) was refluxed for 3 h. After an addition of concentrated hydrochloric acid (5 ml), the mixture was refluxed for 5 h. After cooling, 10% sodium hydroxide solution was added to the reaction mixture, which was extracted with n-butyl alcohol. The extract was washed with saturated sodium chloride aqueous solution, dried over Na_2SO_4, and evaporated to leave a gum, which was chromatographed on silica gel (1.5 g). Benzene–methanol (99.5:0.5 v/v) eluate gave a yellow powder, the recrystallization of which afforded angustine (**1**, 4.7 mg, 9.4%) as yellow plates, mp >300 °C, which was identical with angustine prepared by method A on spectral and TLC comparisons.

3-Ethoxycarbonyl-1-oxopyrano[3,4-*c*]pyridine (18). To a solution of 4-methylnicotinonitrile (**17**,[14] 300 mg) and ethyl oxalate (5 ml) in dry benzene (10 ml), potassium *tert*-butoxide (600 mg) was added in small portions and the mixture was stirred for 24 h under nitrogen. Under cooling with ice, 10% hydrochloric acid was added dropwise to the above mixture, which was then washed with ether. The aqueous layer was made basic with 10% ammonia and extracted with chloroform. The chloroform layer was washed with water, dried over Na_2SO_4, and evaporated to give a residue which was chromatographed on silica gel. The benzene–methanol (99.7:0.3 v/v) eluate afforded a powder, which was recrystallized from ethanol to give **18** (54 mg, 10%) as colorless needles: mp 138–139 °C; ir ($CHCl_3$) 1740, 1720, 1630, and 1575 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (3 H, t, J = 7 Hz, CH_2CH_3), 4.83 (2 H, q, J = 7 Hz, C**H**$_2$CH$_3$), 7.33 (1 H, s, 4-CH), 7.36 (1 H, d, J = 6.5 Hz, 5-CH), 8.91 (1 H, d, J = 6.5 Hz, 6-CH), and 9.46 ppm (1 H, s, 8-CH).

Anal. Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.16; H, 4.24; N, 6.40.

The benzene–methanol (99.5:0.5 v/v) eluate gave a powder which was recrystallized from ethanol to afford the naphthyridine **19** (58 mg, 10%) as colorless needles: mp 232–234 °C (lit.[15] mp 229–230 °C); ir ($CHCl_3$) 3350 (NH), 1718, 1664, and 1592 cm^{-1}; NMR ($CDCl_3$) δ 1.51 (3 H, t, J = 7 Hz, CH_2CH_3), 4.46 (2 H, q, J = 7 Hz, C**H**$_2$CH$_3$), 7.02 (1 H, s, 6-CH), and 9.56 ppm (1 H, s, 8-CH).

Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.28; H, 4.83; N, 12.68.

3-Ethoxycarbonyl-2-(β-indolylethyl)-7-azaisocarbostyril (20). A solution of tryptamine (296 mg) and the above lactone **18** in glacial acetic acid (10 ml) was refluxed for 3 h. After cooling, the solvent was distilled off to give a residue, which was taken up in chloroform. The extract was washed with 10% ammonia and water, dried over Na_2SO_4, and evaporated to afford a powder, which was recrystallized from ethanol to yield **20** (550 mg, 82%) as colorless needles: mp 158–159 °C; ir ($CHCl_3$) 3460 (NH), 1720, 1650, and 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (3 H, t, J = 7 Hz, CH_2CH_3), 3.23 (2 H, t, J = 7.5 Hz, C**H**$_2$CH$_2$N), 4.00 (2 H, q, J = 7 Hz, C**H**$_2$CH$_3$), 4.70 (2 H, t, J = 7.5 Hz, CH$_2$C**H**$_2$N), 6.89 (1 H, d, J = 1.5 Hz, indole α-H), 8.68 (1 H, d, J = 5.6 Hz, 6-CH), and 9.68 ppm (1 H, s, 8-CH).

Naucléfine (4). A To a solution of the azaisocarbostyril **20** (320 mg) in ethanol (10 ml), a solution of potassium hydroxide (53 mg) in ethanol (10 ml) was added and the resulting mixture was stirred for 6 h at room temperature. After acidification with 10% hydrochloric

acid, the solvent was evaporated to leave the acid **21** as a gum to which a mixture of acetic acid (5 ml) and concentrated hydrochloric acid (5 ml) was added. The mixture was refluxed for 7 days until carbon dioxide had ceased to be evolved. After being allowed to stand overnight, crystals formed were collected by filtration and then suspended in chloroform. The chloroform suspension was shaken with 10% ammonia, washed with water, and dried over Na_2SO_4. Evaporation of the chloroform yielded a powder, which was recrystallized from methanol to give naucléfine (**4**, 26 mg, 10%) as yellow needles, mp 285–290 °C (lit.[4] mp 285–290 °C), whose uv [(EtOH) 390, 372, 300, 290, 250, and 220 nm], ir [(KBr) 3500 (NH), 1650 (C=O), 1610 and 1538 cm^{-1}], NMR [(Me_2SO-d_6) δ 4.92 (2 H, t, J = 7 Hz, 5-CH_2), 6.96–7.70 (6 H, m, indole aromatic protons and 14- and 20-CH), 8.56 (1 H, d, J = 6.5 Hz, 21-CH), and 9.25 (1 H, s, 17-CH)] spectra were superimposable on those of natural product.

B. A mixture of the azaisocarbostyril **20** (300 mg), concentrated hydrochloric acid (5 ml), and glacial acetic acid (5 ml) was refluxed for 7 days after standing overnight. Crystals formed were collected and worked up as above to give naucléfine (**4**, 28 mg, 15%) as yellow needles, mp 285–290 °C, which was identical with the above product prepared by method A.

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(16) NMR (Me_2SO-d_6 at 90 °C) δ 4.49 (2 H, t, J = 7 Hz, 5-CH_2), 5.73 (1 H, dd, J = 11.5 and 2 Hz, 18-CH), 6.90 (1 H, dd, J = 18 and 2 Hz, 18-CH), 8.87 (1 H, s, 21-H), and 9.26 (1 H, s, 17-CH).

A Novel Cleavage of Aryl Benzyl Ethers and Allyl Aryl Ethers by Sodium Bis(2-methoxyethoxy)aluminum Hydride. An Alternative Synthesis of Pentazocine

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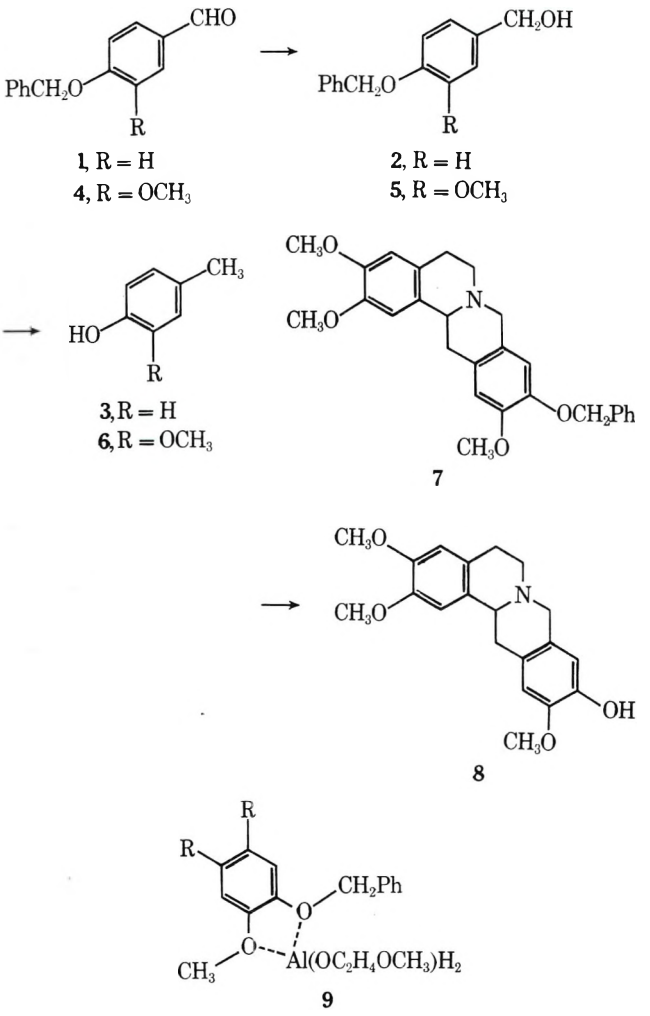
Refluxing with sodium bis(2-methoxyethoxy)aluminum hydride in xylene causes an effective cleavage of benzyl or allyl ether. Using this reaction, pentazocine (**10**) was synthesized as follows. Hydrogenolysis of 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-benzazocin-4-one (**11**) with palladium on charcoal, followed by condensation of the resulting secondary amide (**12**) with dimethylallyl bromide gave the *N,O*-bis(dimethylallyl) compound (**15**), which yielded pentazocine (**10**) on refluxing with sodium bis(2-methoxyethoxy)aluminum hydride in xylene. The conversion of 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocinium bromide (**17**) into pentazocine was examined under various conditions.

Although several examples of the hydrogenolysis of various types of organic compounds using complex metal hydrides have been reported, there are few synthetic applications.[1-3] Since sodium bis(2-methoxyethoxy)aluminum hydride, commercially available, has many advantages over other complex metal hydrides, the hydrogenolysis with sodium bis(2-methoxyethoxy)aluminum hydride have been studied. In this paper we now wish to report effective cleavages of aryl benzyl ethers or allyl aryl ethers with sodium bis(2-methoxyethoxy)aluminum hydride and alternative synthetic methods of pentazocine (**10**), a nonnarcotic analgesic, applying this reagent.

Debenzylation of the compounds having a methoxyl group at a vicinal carbon with sodium bis(2-methoxyethoxy)aluminum hydride proceeded more smoothly than that of the benzyl ether on monooxygenated aryl group. Thus, refluxing of 4-benzyloxybenzaldehyde (**1**) with an excess of the reagent in xylene for 6 h gave mainly 4-benzyloxybenzyl alcohol (**2**), and *p*-cresol (**3**) was obtained as a sole product by the same treatment as above for 60 h. On the other hand, when 4-benzyloxy-3-methoxybenzaldehyde (**4**) was refluxed with an excess of sodium bis(2-methoxyethoxy)aluminum hydride in xylene, creosol (**6**) was formed together with a small amount of 4-benzyloxy-3-methoxybenzyl alcohol (**5**) after 6 h, and creosol (**6**) was homogeneously obtained after 10 h. Treatment of 10-benzyloxy-5,6,13,13a-tetrahydro-2,3,11-trimethoxy-8*H*-dibenzo[*a,g*]quinolizine (**7**)[4] under the same conditions for 6 h caused the cleavage of the benzyl ether to afford the phenolic tetrahydroprotoberberine (**8**)[4] in an excellent yield (Scheme I).

Scheme I



Alkoxyaluminum hydride, such as $AlH_2(OC_2H_4OCH_3)$, would be reversibly formed from sodium bis(2-methoxyethoxy)aluminum hydride in solution as other complex metal hydrides.[5,6] We believe that the alkoxyaluminum hydrides play an important role as Lewis acid for the present hydrogenolysis and the debenzylation of the compounds having vicinal methoxyl group proceeded easily because of the formation of the complex as **9**.

This hydrogenolysis seemed to be useful for the debenzylation or deallylation of the compound which is labile to acid or catalytic hydrogenolysis. Recently we reported a synthetic method of producing pentazocine (**10**) from tyrosine.[7] The last stages have been further elaborated by application of this reagent.

Hydrogenolysis of the amide (**11**) in the presence of 10% palladium on charcoal under hydrogen in acetic acid at 80 °C gave the secondary amide (**12**), mp 275–277 °C, in 98% yield. Refluxing **12** with benzyl chloride in the presence of potassium carbonate in methanol afforded, in 78% yield, the *O*-benzyl ether (**13**), mp 194 °C, which reacted with dimethylallyl bromide in the presence of sodium hydride in dry dioxane to yield the *N*-dimethylallyl compound (**14**), mp 151–152 °C, in 90% yield. Refluxing **14** with sodium bis(2-methoxyethoxy)aluminum hydride in dry xylene for 60 h gave pentazocine (**10**) in 55% yield (Scheme II). All the physical properties of the synthetic pentzocine were identical with those of the authentic sample.[8]

When the above secondary amide (**12**) was heated with dimethylallyl bromide in the presence of sodium hydride in dry dioxane, the *N,O*-bis(dimethylallyl) compound (**15**), mp 129–131 °C, was obtained in 76% yield. Treatment of **15** with sodium bis(2-methoxyethoxy)aluminum hydride in hot xylene for 42 h gave pentazocine (**10**) in 62% yield. This procedure, **11** → **12** → **15** → **10**, was the best transformation of the amide (**11**) into pentazocine (**10**) (46% overall yield from **11**).

The rate of O-debenzylation or deallylation was slower than that of reaction for the amide group. Thus, refluxing the *N,O*-bis(dimethylallyl) compound (**15**) with sodium bis(2-methoxyethoxy)aluminum hydride in dry benzene for 5 h yielded mainly the amine (**16**) together with a small amount of pentazocine (**10**). Further treatment of **16** with sodium bis(2-methoxyethoxy)aluminum hydride in xylene for 42 h gave pentazocine (**10**).

Conversion of the quaternary salt (**17**), obtained from the amine (**18**) and dimethylallyl bromide, into pentazocine (**10**) had already been carried out under several conditions by one of the authors.[8-10] Refluxing **17** with sodium bis(2-methoxyethoxy)aluminum hydride in xylene for 17 h yielded pentazocine (**10**) and the amine (**18**) in 10.5 and 42.5% yield, respectively. Furthermore, heating **17** with triphenylphosphine in dry acetonitrile at 130–140 °C in a sealed tube[11] and a treatment of **17** with sodium *n*-propylmercaptide in hexamethylphosphoric triamide at 0 °C[12] also furnished pentazocine (**10**) in 18 and 8% yield, respectively, along with the amine (**18**) in 58 and 19.6% yield, respectively.

Experimental Section

All melting points were uncorrected. Ir spectra were taken with a Hitachi 215 recording spectrometer. NMR spectra were measured with JNM-PMX-60 and JNM-PS-100 spectrophotometers with tetramethylsilane as internal standard; mass spectra were taken with a Hitachi RMU-7 spectrometer. Sodium bis(2-methoxyethoxy)aluminum hydride (70%) in benzene (Wako Chemicals) was used for the following reactions.

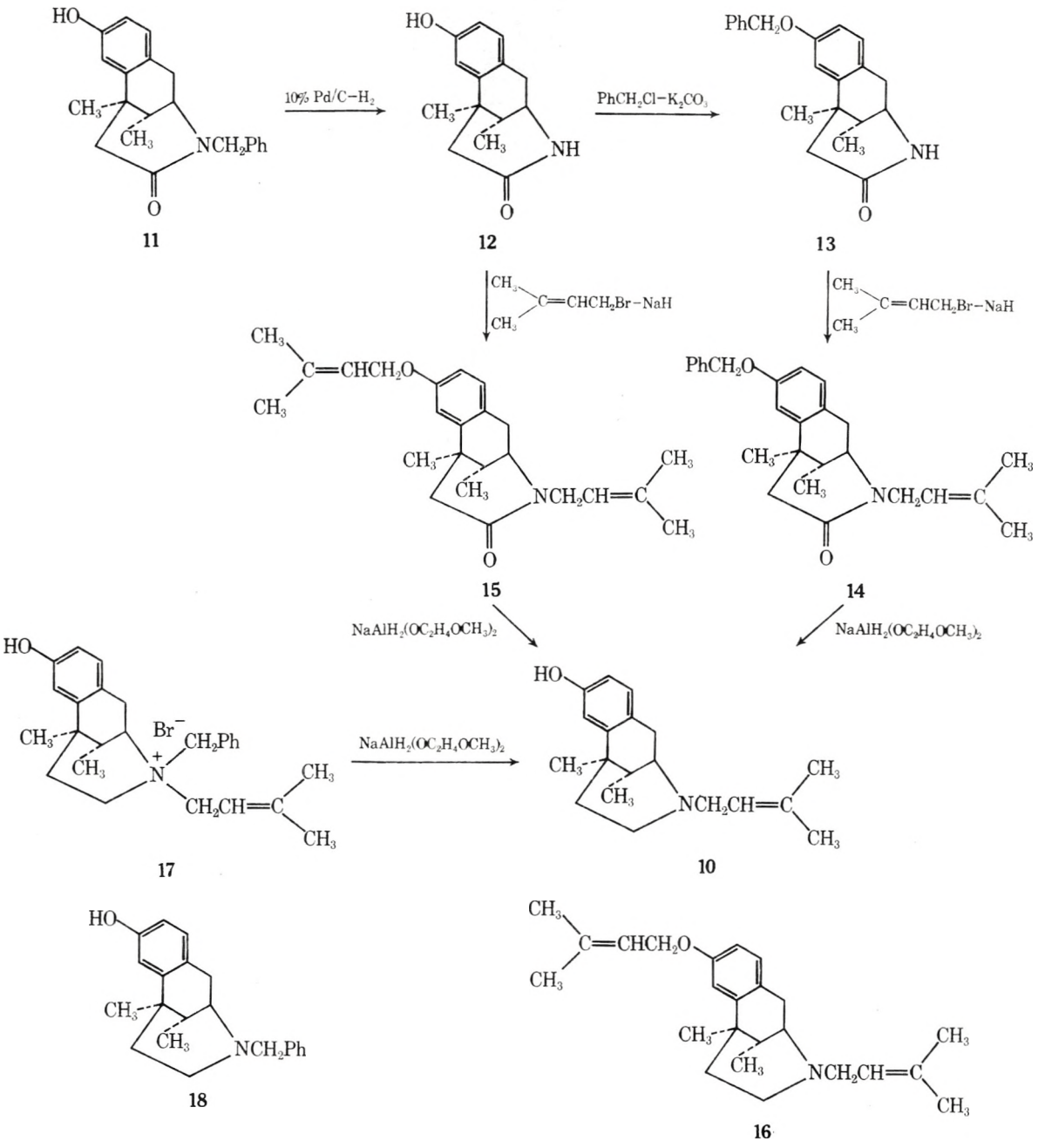
***p*-Cresol (3).** A mixture of 212 mg of 4-benzyloxybenzaldehyde (**1**) and 1.5 g of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 5 ml of dry xylene was refluxed for 60 h under stirring and protection from moisture. After an addition of an excess of 10% aqueous sodium hydroxide solution, the separated organic layer was extracted with water. The combined aqueous layers were acidified with 10% hydrochloric acid and extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried over Na_2SO_4, and evaporated to give 75 mg of *p*-cresol (**3**) as an oil, bp 76 °C (5 mmHg), which was identical with an authentic sample.

Creosol (6). A mixture of 242 mg of 4-benzyloxy-3-methoxybenzaldehyde (**4**) and 1.5 g of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 5 ml of dry xylene was refluxed for 10 h under the same conditions as above. The same workup as above gave 92 mg of creosol (**6**) as an oil, bp 79 °C (4 mmHg), which was identical with the authentic sample.

5,6,13,13a-Tetrahydro-10-hydroxy-2,3,11-trimethoxy-8*H*-dibenzo[*a*,*g*]quinolizine (8). A mixture of 80 mg of 10-benzyloxy-5,6,13,13a-tetrahydro-2,3,11-trimethoxy-8*H*-dibenzo[*a*,*g*]quinolizine (**7**) and 550 mg of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 3 ml of dry xylene was heated under reflux and stirring in an oil bath for 6 h under a current of nitrogen gas. After the reaction mixture had been decomposed with 10% sodium hydroxide, the separated aqueous layer was washed with benzene, neutralized with crystalline ammonium chloride, and extracted with chloroform. After drying over Na_2SO_4, evaporation of the solvent gave a pale yellow solid, which was recrystallized from methanol to afford 58 mg of **8** as crystals, mp 193–195 °C (lit.[4] mp 193–195 °C).

1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-benzazocin-4-one (12). A mixture of 500 mg of 3-benzyl-1,2,3,4,5,6-hexahydro-2,6-methano-6,11-dimethyl-3-benzazocin-4-one (**11**)[7] and 300 mg of 10% Pd/C in 20 ml of acetic acid was stirred at 80 °C for 21 h under a current of hydrogen. After filtration through Celite and washing with ethanol, evaporation of the combined filtrate and washings gave a pale brown caramel, which was solidified by addition of *n*-hexane. The resulting solid was collected by filtration and washed with chloroform to give a pale brown solid, whose recrystallization from ethanol afforded 354 mg of **12** as colorless crystals: mp 275–277 °C dec; ir ν_{max} ($CHCl_3$) 3600 (OH), 3400 (NH), and 1650 cm^{-1} (C=O); NMR (CF_3CO_2H) δ 1.16 (3 H, d, J = 7 Hz, C_{11} Me), 1.56 (3 H, s, C_6 Me), 2.82 (2 H, broad s, C_5 CH_2), and 6.76–7.20 (3 H, m, $C_{7,9}$ and C_{10} CH); mass spectrum m/e 231 (M^+).

Scheme II



Anal. Calcd for $C_{14}H_{17}NO_2 \cdot \frac{1}{4}H_2O$: C, 71.31; H, 7.48; N, 5.94. Found: C, 71.24; H, 7.24; N, 5.65.

1,2,3,4,5,6-Hexahydro-2,6-methano-6,11-dimethyl-3-(3-methyl-2-butenyl)-8-(3-methyl-2-butenyloxy)-3-benzazocin-4-one (15). A mixture of 475 mg of the above amide (**12**) and 495 mg of 50% sodium hydride in 200 ml of dry dioxane was refluxed for 2.5 h. After cooling, 1.55 ml of dimethylallyl bromide was added to the above mixture and the resulting mixture was further refluxed for 5 h under protection from moisture. The excess of sodium hydride was decomposed with crystalline ammonium chloride. After evaporation of the solvent, the resulting residue was dissolved in chloroform, washed with water and saturated aqueous sodium chloride solution, dried over Na_2SO_4, and evaporated to afford a solid, which was washed with *n*-haxane to give a colorless solid. Recrystallization from benzene–*n*-hexane gave 589 mg of **15** as colorless crystals: mp 129–131 °C; ir ν_{max} ($CHCl_3$) 1672 (C=C) and 1620 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.0 (3 H, d, J = 7 Hz, C_{11} Me), 1.34 (3 H, s, C_6 Me), 1.73 [12 H, s, 2 =C(Me)$_2$], 2.43 (2 H, s, C_5 CH_2), 2.87 (2 H, d, J = 7 Hz, C_1 CH_2), 5.17 (1 H, m, >C=CHCH$_2$N<), 5.49 (1 H, m, >C=CHCH$_2$O–), and 6.53–7.06 (3 H, m, $C_{7,9}$ and C_{10} CH); mass spectrum *m/e* 367 (M^+).

Anal. Calcd for $C_{24}H_{33}NO_2$: C, 78.43; H, 9.05; N, 3.81. Found: C, 78.31; H, 9.19; N, 3.65.

8-Benzyloxy-1,2,3,4,5,6-hexahydro-2,6-methano-6,11-dimethyl-3-benzazocin-4-one (13). A mixture of 140 mg of the amide (**12**), 91 mg of benzyl chloride, and 51 mg of potassium carbonate in 15 ml of dry methanol was refluxed for 3 days. The inorganic materials were filtered off and washed with methanol. Evaporation of the combined filtrate and washing gave a pale yellow solid, which was dissolved in chloroform. The chloroform layer was washed with water and saturated aqueous sodium chloride solution, dried over Na_2SO_4, and evaporated. The residue was triturated with *n*-hexane to give a colorless powder, which was recrystallized from benzene to afford 150 mg of **13** as colorless crystals: mp 194 °C; ir ν_{max} ($CHCl_3$) 3400 (NH) and 1645 cm^{-1} (C=O); NMR (CF_3CO_2H) δ 1.13 (3 H, d, J = 7 Hz, C_{11} Me), 1.50 (3 H, s, C_6 Me), 2.25 (1 H, m, C_{11} CH), 2.76 (2 H, broad s, C_5 CH_2), 5.23 (2 H, s, PhCH_2O), 7.06 (3 H, s, $C_{7,9}$ and C_{10} CH), and 7.36 (5 H, s, Ph).

Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.13; H, 7.21; N, 4.18.

8-Benzyloxy-1,2,3,4,5,6-hexahydro-2,6-methano-6,11-dimethyl-3-(3-methyl-2-butenyl)-3-benzazocin-4-one (14). A mixture of 90 mg of **13** and 90 mg of 50% sodium hydride in 6 ml of anhydrous dioxane was refluxed for 2.5 h, and then treated with 0.09 ml of dimethylallyl bromide as the case of **15**. The same workup as before gave a solid, which was washed with *n*-hexane to give a colorless

solid. Recrystallization from benzene–*n*-hexane gave 98 mg of **14** as colorless crystals: mp 151–152 °C; ir ν_{max} ($CHCl_3$) 1620 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.98 (3 H, d, J = 7 Hz, C_{11} Me), 1.33 (3 H, s, C_6 Me), 1.70 [6 H, s, =$C(Me)_2$], 2.43 (2 H, s, C_5 CH_2), 2.87 (2 H, m, C_1 CH_2), 3.53 (2 H, m, NCH_2OCH=), 4.43 (1 H, , C_2 CH), 5.02 (2 H, s, $PhCH_2O$), 6.83 (3 H, m, $C_{7,9}$ and C_{10} CH), and 7.35 (5 H, s, Ph).

Anal. Calcd for $C_{26}H_{31}NO_2$: C, 80.17; H, 8.02; N, 3.60. Found: C, 80.08; H, 8.09; N, 3.62.

1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-(3-methyl-2-butenyl)-3-benzazocine (Pentazocine, 10). A. A mixture of 450 mg of the amide (**15**) and 3.6 g of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 20 ml of dry xylene was heated under reflux and stirring in an oil bath for 42 h under a current of nitrogen. After the reaction mixture had been acidified with 10% hydrochloric acid while cooling, the organic layer separated was extracted with water. Both aqueous layers were combined and neutralized with 10% ammonia, and the separated free base was extracted with chloroform. The extract was dried over Na_2SO_4 and evaporated to give a caramel-like substance, which was purified on silica gel chromatography using benzene–methanol (98.5:1.5 v/v) to afford a caramel. Recrystallization from acetone gave 216 mg of pentazocine (**10**) as colorless crystals, mp 146–148 °C (lit.[8] mp 146–148 °C), which was identical with the authentic sample[8] from the ir and NMR spectra and TLC comparisons and mixture melting point test.

B. A mixture of 45 mg of the amide (**14**) and 350 mg of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 3 ml of dry xylene was refluxed for 60 h with stirring under a current of nitrogen. The same workup as above gave a pale brown caramel, which was purified by preparative TLC on silica gel with methanol–ethyl acetate–benzene (1:5:4 v/v) to afford 18 mg of pentazocine (**10**).

C. A solution of 100 mg of the amide (**15**) and 900 mg of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 5 ml of dry benzene was refluxed for 5 h with stirring under a current of nitrogen. The same workup as before gave 6 mg of pentazocine (**10**). The organic layer was washed with saturated aqueous sodium chloride solution, dried over Na_2SO_4, and evaporated to give a colorless caramel, which was solidified by triturating with ether. The resulting solid was recrystallized from methanol–ether to afford 70 mg of 1,2,3,4,5,6-hexahydro-2,6-methano-6,11-dimethyl-3-(3-methyl-2-butenyl)-8-(3-methyl-2-butenyloxy)-3-benzazocine (**16**) hydrochloride as colorless crystals: mp 117 °C; ir ν_{max} ($CHCl_3$) 1670 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.83 (3 H, d, J = 7 Hz, C_{11} Me), 1.34 (3 H, s, C_6 Me), 1.73 [12 H, s, 2 =$C(Me)_2$], 4.5 (2 H, d, J = 7 Hz, $ArOCH_2CH$=), and 6.78 (3 H, m, $C_{7,9}$ and C_{10} CH).

Anal. Calcd for $C_{24}H_{35}NO{\cdot}HCl{\cdot}\frac{1}{3}H_2O$: C, 72.79; H, 9.08; N, 3.54. Found: C, 72.65; H, 9.11; N, 3.29.

A mixture of 32 mg of the above amine (**16**) and 300 mg of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 2 ml of dry xylene was refluxed for 42 h. The same workup as above gave 19 mg of pentazocine (**10**).

D. To a solution of 91 mg of the quaternary ammonium salt (**17**) in 0.5 ml of hexamethylphosphoric triamide, 48 mg of 50% sodium hydride, and 76 mg of *n*-propyl mercaptan were added at 0 °C under a current of nitrogen. The reaction mixture was stirred for 15 min at 0 °C and then poured into ice–water, a mixture of which was washed with ether. The aqueous layer was neutralized with crystalline ammonium chloride and then extracted with chloroform. The extract was dried over Na_2SO_4 and evaporated. Purification of a pale brown caramel by preparative TLC on silica gel with methanol–ethyl acetate–benzene (1:5:4 v/v) gave 5 mg of pentazocine (**10**) and 12 mg of the amine (**18**), whose ir and NMR spectra and TLC behaviors were identical with those of **18**.

E. A mixture of 91 mg of the quaternary ammonium salt (**17**) and 58 mg of triphenylphosphine in 2 ml of acetonitrile was heated at 130–140 °C in a sealed tube for 12 h. After evaporation of the solvent, the residue was acidified with 10% hydrochloric acid and washed with ether. The aqueous layer was neutralized with 10% ammonia and extracted with chloroform. The extract was dried over Na_2SO_4 and evaporated to give a colorless caramel, which was purified by preparative TLC as above to give 10 mg of pentazocine (**10**) and 35 mg of the amine (**18**).

F. A mixture of 91 mg of the quaternary ammonium salt (**17**) and 576 mg of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 4 ml of dry xylene was refluxed for 17 h with stirring under a current of nitrogen. The same workup as method A, followed by purification by preparative TLC, gave 6 mg of pentazocine (**10**) and 26 mg of the amine (**18**).

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Registry No.—1, 4397-53-9; **3**, 106-44-5; **4**, 2426-87-1; **6**, 93-51-6; **7**, 59069-55-5; **8**, 39595-83-0; **10**, 359-83-1; **11**, 59122-20-2; **12**, 59069-56-6; **13**, 59069-57-7; **14**, 59069-58-8; **15**, 59069-59-9; **16**, 59069-60-2; **17**, 59122-21-3; **18**, 57573-46-3; sodium bis(2-methoxyethoxy)aluminum hydride, 21608-56-0; dimethylallyl bromide, 870-63-3; benzyl chloride, 100-44-7.

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Microbial Transformations of Natural Antitumor Agents. 2. Studies with *d*-Tetrandrine and Laudanosine

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Microbial transformation studies have been conducted on benzyltetrahydroisoquinoline and bisbenzyltetrahydroisoquinoline alkaloids. The 4′-methyl ether of laudanosine (**2**) was cleaved in high yield by *Cunninghamella blakesleeana* (ATCC 8688a) to give pseudocodamine (**2b**) as the sole product. *Streptomyces griseus* (UI 1158) was used to chemically transform the natural antitumor alkaloid, *d*-tetrandrine (**1**). The metabolite was identified as *N*(2′)-nor-*d*-tetrandrine (**1a**) on the basis of NMR and mass spectral correlations, and was obtained in 50% yield. Both reactions represent highly selective dealkylations of polyfunctional molecules.

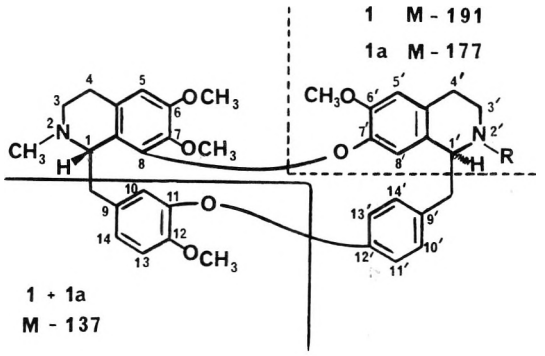
The successful application of microorganisms in the preparation of difficult-to-synthesize steroids has been well documented.[1] The use of microbial systems as tools for achieving chemical transformations of other classes of natural products has not been systematically exploited. Advantages of such microbial systems include mild reaction conditions, their se-

lectivity with polysubstituted organic compounds, and their potential for large-scale production of metabolites through routine fermentation scale-up techniques.

Many active antitumor compounds have been isolated from a variety of natural sources. These compounds are often structurally complex, and serious difficulties are encountered in the preparation of potentially active derivatives, and in the study of their metabolism. Microbial transformation systems are being developed to accomplish such goals.

This report is concerned with microbial transformation studies on the bisbenzyltetrahydroisoquinoline alkaloid, *d*-tetrandrine (1) (Chart I), a compound which has demonstrated potent antitumor[2] and cytotoxic[3,4] activity. The use of this compound may be limited by a multitude of dose dependent toxic effects[5-7] some of which may be related to the production of metabolites in mammalian systems. In this regard, the availability of N- and O-demethylated derivatives of 1 for antitumor and/or toxicity studies, and as intermediates in the synthesis of potentially less toxic derivatives would be of particular interest. De novo synthesis of such derivatives is a laborious and low-yielding process, and requires the judicious application of suitable protecting groups.[8,9]

Chart I



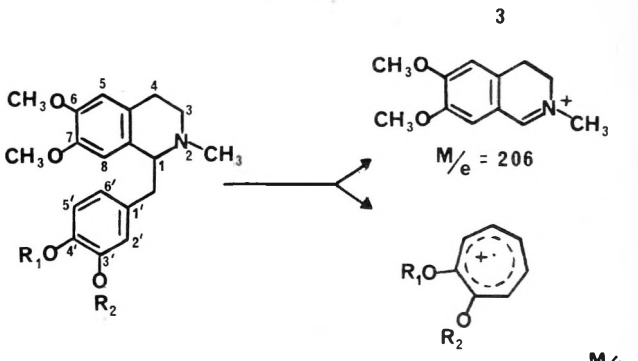
1 R=CH_3
1a R=H

d-Tetrandrine was available in limited supply for our initial work. In addition, microbial transformation studies had not been reported for monomeric or dimeric benzylisoquinoline alkaloids like 1 and laudanosine (2). Laudanosine represents one-half of the dimeric structure of 1, and it could be prepared in quantity. Thus, initial microbial transformation experiments were performed with laudanosine (2) in the hope that microorganisms metabolizing this "model" compound would also metabolize 1.

Some 60 cultures were used to conduct small-scale screening experiments with (*RS*)-laudanosine. Several of these organisms had previously achieved O- and N-dealkylations, or hydroxylations with other substrates.[10-17] (*RS*)-Laudanosine metabolites were produced by the following cultures: *Cunninghamella blakesleeana* (ATCC 8688a), *Stysanus microsporus* (UI 2833), *Aspergillus niger* (ATCC 10581), *Cunninghamella echinulata* (ATCC 9244), and *Microsporum gypseum* (ATCC 11395). Yields of metabolites obtained with *C. blakesleeana* were reproducible and were considerably higher than those obtained with other cultures. (*RS*)-Pseudocodamine (1.20 g) was obtained when *C. blakesleeana* was incubated with 2.7 g of (*RS*)-laudanosine.

The mass spectrum of the metabolite (**2b**, Chart II) was typical of benzyltetrahydroisoquinolines[18,19] and indicated that O-demethylation had occurred in the benzylic portion of laudanosine. The NMR spectrum was of limited value in distinguishing between the two possible O-dealkylation products, (*RS*)-pseudocodamine (**2b**) or (*RS*)-laundanine (**2a**), since only the 7-methoxy signal is sufficiently shielded and separated from the remaining methoxyl signals.[20] The metabolite had the same melting point as pseudocodamine,[21] some 30 °C lower than that reported for the isomeric compound (**2a**). Final proof of structure was obtained by alkaline permanganate degradation of the ethyl ether derivative of the metabolite (**2c**) to 4-ethoxy-3-methoxybenzoic acid by the method of Späth.[22]

Chart II



		M/e
2 $R_1, R_2 = CH_3$	4, $R_1, R_2 = CH_3$	151
2a $R_1 = CH_3, R_2 = H$	4a, $R_1 = H, R_2 = CH_3$	137
2b $R_1 = H, R_2 = CH_3$	4b, $R = CH_3, R = H$	137
2c $R_1 = C_2H_5, R_2 = CH_3$		

Unreacted laudanosine recovered from the fermentation was not optically active, and neither was the metabolite. Thus, the O-demethylation reaction was nonstereoselective. When the yield of **2b** is corrected for recovered starting material, (*RS*)-pseudocodamine was obtained in 89% yield.

Cultures capable of metabolizing 2 and other natural products such as dimethoxyaporphine,[11] acronycine,[17] and L-tyrosine[23] were examined for their potential to transform *d*-tetrandrine. Those yielding metabolites of 1 were *Cunninghamella blakesleeana* (ATCC 8688a), *Cunninghamella echinulata* (NRRL 3655), *Mucor mucedo* (UI4605), *Penicillium brevi-compactum* (ATCC 10418), *Streptomyces griseus* (UI 1158), *Streptomyces punipalus* (NRRL 3529), and *Streptomyces lincolnensis* (ATCC 25466). All except for *C. blakesleeana* gave high yields of a common metabolite. *S. griseus* was selected for a preparative scale fermentation.

The metabolite **1a** was obtained in 50% yield from a 2.0-g incubation of *d*-tetrandrine. Although the classical structure proof of compounds like **1a** involves Hofmann degradation, or Na/liquid ammonia cleavage of the aryl ethers to yield known benzyltetrahydroisoquinolines,[24] it is possible to characterize them by mass spectral and NMR methods. Bick et al.[25] found that all resonances due to heteroatom methyl substituents in 1 are well separated and easily distinguished in the NMR spectrum. Correlations between *d*-tetrandrine (1) and the metabolite **1a** are shown in Table I. The only signal absent in **1a** is that attributable to the *N*(2′)-methyl group of 1. The spectrum of **1a** is nearly identical with that of (*RS*)-(**1a**) obtained synthetically,[25] and of cycleanorine (*SS*)-(**1a**), a minor alkaloid isolated from *Cyclea peltata*.[26]

The elemental composition of the metabolite **1a**, 608.2938 (calcd for $C_{37}H_{40}N_2O_6$, 608.2886) indicated the loss of a single methyl group from *d*-tetrandrine. Other mass spectral fragments were consistent with the published spectrum of **1a**,[26] and that of an authentic sample of 1.

In the low-resolution spectrum, weak but diagnostic peaks occur at M − 191 and M − 137 for 1, and M − 177 and M − 137 for **1a** as illustrated in Chart I. These peaks support the NMR spectral correlation which indicated that the *N*(2′)-methyl group was selectively cleaved by the microorganism.

Table I. Chemical Shifts[a] (ppm) of the *N*- and *O*-Methyl Groups of *d*-Tetrandrine (1) and the Metabolite 1a

	C-12	C-6	C-6′	C-7	N(2)	N(2′)
d-Tetrandrine (1)	3.93	3.75	3.37	3.20	2.33	2.62
1 literature[25]	3.9	3.73	3.35	3.18	2.3	2.59
Metabolite (1a)	3.92	3.73	3.35	3.23	2.32	
(+/−)-1a[9]	3.95	3.75	3.35	3.22	2.33	
(+/+)-1a[26]	3.88	3.70	3.33	3.22	2.33	

[a] Spectra obtained in $CDCl_3$ with Me_4Si as internal standard.

This microbial reaction provides a simple and rapid route to the preparation of *N*(2′)-nor-*d*-tetrandrine (1a) which may serve as a useful intermediate in the synthesis of potentially active tetrandrine derivatives. The reaction is accomplished in high yield with no complicating side products, and may be conducted in large scale using suitable fermentation apparatus. When corrected for unreacted starting material recovered from the fermentation, the N-demethylation reaction is essentially quantitative. The identified metabolite is also produced by the *Streptomyces*, *Penicillium*, and *Mucor* species described earlier, but in somewhat lower yields as estimated by TLC. *Cunninghamella blakesleeana* gave a different and currently unidentified metabolite, but in lower yield. Efforts are being made to improve metabolite yields before preparative scale fermentations are conducted to isolate and characterize this and possibly other metabolites of 1.

We had initially thought that biotransformations observed on monomeric benzyltetrahydroisoquinolines would also occur on the dimeric molecule (1). Instead, N-demethylation, not O-demethylation, was the predominant mode of biotransformation of 1. O-Dealkylation was the major path of metabolism with (*RS*)-laudanosine (2). Microorganisms capable of metabolizing 1 did not metabolize 2 well either. Obvious differences in the two substrates which might shift dealkylation pathways are molecular size, and the bulk of the bisaryl ether couplings of 1 relative to 2. The nature of the ether substituents might also influence the mode of biotransformation of compounds like 1 and 2. Steric factors appear to be important in directing O-dealkylations with other alkaloids.[11]

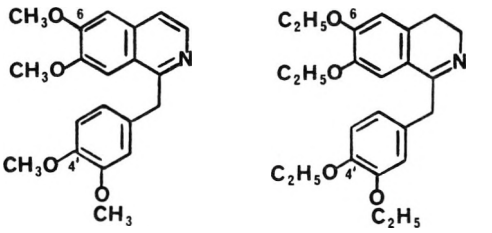
Studies on the microbial[10,30] and mammalian metabolism of papaverine (5) have been conducted. The major metabolic products obtained with this fully aromatic benzylisoquinoline alkaloid derivative (5) are the 4′- and 6-O-demethylated derivatives. Gyarmati et al.[32] found that a dihydrobenzylisoquinoline alkaloid derivative (6) also underwent O-dealkylation at the 4′ and 6 positions. It appears that O-dealkylation will occur at the 6 position of isoquinolines lacking a basic nitrogen atom, and/or an *N*-methyl substituent. Further studies are in progress to elucidate the importance of these features in directing O-dealkylation reactions with isoquinolines.

The microbial reactions observed with both laudanosine and *d*-tetrandrine were highly selective dealkylations of polyfunctional molecules, similar to those observed with microbial transformations of other natural products.[11,16,27-29] The yields of both transformations were high but they could be improved.

In an earlier report, microorganisms gave high yields of 9-hydroxyacronycine, a metabolite also produced in mammals.[17] Microorganisms may serve as useful metabolic models to predict ways in which mammals metabolize natural products like 1 and 2.[10] N- and O-dealkylation reactions are common mammalian monooxygenase reactions, and it is plausible that the metabolites identified in this work will also be obtained in mammalian systems. Other metabolites of both of the alkaloids studied have been observed with other cultures. These metabolites will be isolated and identified once conditions for their production have been optimized.

To our knowledge, this is the first report of microbial transformations of mono- or dimeric benzyltetrahydroisoquinolines.

Chart III



5 6

Experimental Section

NMR spectra were obtained with a Varian T-60 spectrometer with Me_4Si as an internal standard. Low-resolution mass spectra were taken on a Finnigan Model 3200 instrument. High-resolution mass spectral data were obtained through the services of Battelle Columbus Laboratories, Columbus, Ohio. Melting points were obtained with a Thomas-Hoover melting point apparatus and are corrected. Ir spectra were obtained with a Perkin-Elmer 267 instrument, and optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind.

Chromatographic Procedures. Thin layer chromatography (TLC) was performed on 0.25 mm thick layer plates of silica gel GF_{254} prepared with a Quickfit Industries speader. Plates were air dried for 1 h, and oven activated at 120 °C for 30 min prior to use. Solvent systems used in developing TLC plates were A, C_6H_6–MeOH–58% NH_4OH (80:30:0.1); B, C_6H_6–MeOH–58% NH_4OH (40:12:0.1); C, C_6H_6–MeOH–HOAc (40:2:1). Visualization usually involved viewing developed plates under short (254 nm) and long (365 nm) wavelength ultraviolet light, and by later spraying them with Dragendorff's reagent.[33] Column chromatography was conducted with silica gel (Baker 3405) which was slurried and wet packed in the developing solvents.

Fermentation Procedures. All cultures described in this work are maintained in the culture collection of the University of Iowa, College of Pharmacy. Those bearing the designation (UI) have been maintained in our collection for some time, while those bearing designations of (NRRL) and (ATCC) were obtained from the Northern Regional Research Laboratories of the Agriculture Research Service of the USDA in Peoria, Ill., and the American Type Culture Collection, Rockville, Md., respectively.

Fermentations were conducted using the two-stage procedure and medium previously described.[11,17] Small-scale fermentation screening experiments were conducted in 25 ml of sterile medium in 125-ml Erlenmeyer flasks shaken at 250 rpm, at 27 °C. Larger scale fermentations were done in 500-ml or 1000-ml Erlenmeyer flasks containing ⅕ of their volumes of sterile medium. The progress of microbial transformation reactions was routinely monitored by TLC as follows: 4-ml samples of incubations were withdrawn at time intervals, adjusted to pH 8.5 with saturated $NaHCO_3$, and extracted with 1.0 ml of ethyl acetate, and 30 μl of the extracts were spotted on TLC plates.

Preparation of (*RS*)-Laudanosine (2). (*RS*)-Laudanosine was prepared by $NaBH_4$ reduction of papaverine methiodide by literature procedures.[34] The product obtained was comparable in all physical properties to an authentic sample of racemic laudanosine (Sigma Chemical Co.): mp 114–116 °C (reported[34] 114–116 °C); picrate, mp 176–177 °C (reported[35] 174–176 °C).

Preparation of 3-Ethoxy-4-methoxybenzoic Acid (*O*-Ethylisovanillic Acid). *O*-Ethylisovanillic acid was prepared from isovanillic acid by the method of Späth,[22] mp 164–165 °C (reported[22] 164–165 °C). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.34; H, 6.47.

Preparation of 4-Ethoxy-3-methoxybenzoic Acid (*O*-Ethylvanillic Acid). *O*-Ethylvanillic acid was prepared from vanillic acid by the procedure of Späth.[22] mp 195–196 °C (reported[36] 195–196 °C). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.10; H, 6.40.

Microbial Conversion of (*RS*)-Laudanosine (2) to (*RS*)-Pseudocodamine (2b) with *Cunninghamella blakesleeana* (ATCC 8688a). Second-stage cultures of *C. blakesleeana* were grown in 5.1 l. of medium in 500-ml Erlenmeyer flasks. A total of 2.7 g of **2** was converted to its HCl salt with 6 N HCl, and was dissolved in 220 ml of sterile deionized water. After neutralizing the laudanosine **2** solution with 5% NaOH, it was distributed evenly among the culture flasks. Formation of the metabolite **2b** was followed by TLC using solvent system A. After 5 days of incubation, the fermentation was harvested, all cultures were pooled and adjusted to pH 8.5 with saturated $NaHCO_3$, and this mixture was extracted with ether in a continuous liquid–liquid extractor. The combined ether extracts were dried over anhydrous Na_2SO_4 and evaporated to a gold oil (4.5 g). The oil was applied to a silica gel column (400 g, 53 × 5.5 cm), and eluted with C_6H_6–MeOH–58% NH_4OH (300:20:0.1) at a rate of 2 ml/min, while 15-ml fractions were collected. Fractions 56–140 yielded 1.35 g of (*RS*)-laudanosine as unreacted starting material, mp 115 °C. Fractions 164–400 gave pure (*RS*)-pseudocodamine (**2b**), 1.20 g (46% yield): mp 132–133 °C (reported[21] 131–132 °C); mass spectrum *m/e* (rel abundance) 343 (1), 342 (1), 206 (100), 191 (9), 190 (21), 137 (7); NMR ($CDCl_3$) 2.55 (s, 3 H, NCH_3), 3.57 (s, 3 H, 7-OCH_3), 3.77 (s, 3 H, OCH_3), 5.92 (s, 1 H. OH), 6.05 (s, 1 H, Ar), 6.83 ppm (m, 4 H, Ar). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 70.47; H, 7.11; N, 4.08.

Permanganate Degradation of 2b to 4-Ethoxy-3-methoxybenzoic Acid. (*RS*)-Pseudocodamine (**2b**), 75 mg, isolated from the fermentation was suspended in 10 ml of dry dimethylformamide with 50 mg of NaH, and 17.4 μl of ethyl iodide was added to the mixture with a microsyringe over a 30-min period. Upon completion of the addition of ethyl iodide, TLC (solvent B) indicated that the reaction was complete. The product (**2c**) was identical with **2** on TLC. The reaction mixture was stirred with 10 g of ice, extracted exhaustively with ethyl acetate, and dried over anhydrous Na_2SO_4 before evaporation to an oil: NMR ($CDCl_3$) 1.43 (t, 3 H, $-CH_2CH_3$), 3.78 (s, 3 H, $-OCH_3$), 3.83 (s, 3 H, $-OCH_3$), 6.12 (s, 1 H, Ar), 6.83 ppm (m, 4H, Ar).

A solution of 450 mg of $KMnO_4$ in 25 ml of H_2O was added dropwise to a suspension of 62 mg of **2c** in 10 ml of H_2O until the reaction mixture remained purple (15 ml of $KMnO_4$ solution). TLC (solvent C) indicated that the reaction was nearly complete. Addition of 1 ml more of the permanganate solution followed by stirring for 1 h completed the reaction. The mixture was acidified with concentrated H_2SO_4 and extracted with ethyl acetate. The extract was purified by preparative TLC (1.0 mm thick layers, solvent C). Elution of the product from the silica gel with methanol, and crystallization from methanol gave 25 mg of an analytical sample (75% yield) of 4-ethoxy-3-methoxybenzoic acid, mp 192–193 °C (reported[36] 195–196 °C). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.10; H, 6.40.

Production of *N*(2′)-Nor-*d*-tetrandrine (1a) from *d*-Tetrandrine (1) by *Streptomyces griseus* (UI 1158). *S. griseus* was grown in 9 l. of medium held in 1.0-l. flasks, and 2 g of *d*-tetrandrine (1) which was converted to the HCl salt with 6 N HCl and dissolved in 40 ml of H_2O was distributed evenly among them. Fermentation monitoring with TLC (solvent A) indicated that the biotransformation was completed after 7 days. After adjusting the combined fermentation beers to pH 8.5 with saturated $NaHCO_3$, this solution was exhaustively extracted with ether in a continuous liquid–liquid extractor. Evaporation of the combined ether extracts gave a residue of 3.05 g which was subjected to column chromatography on silica gel (310 g, 5.5 × 43 cm) using C_6H_6–MeOH (20:1) as the developing solvent. Fractions of 17 ml were collected at a flow rate of 2 ml/min, and fractions 131–335 gave 1.0 g of unreacted *d*-tetrandrine, while fractions 390–1050 gave 1.0 g of the metabolite **1a** as a dry, pure glass upon evaporation of the eluting solvent. Attempts to crystallize the metabolite failed, and analytical data were obtained on the amorphous material: NMR ($CDCl_3$) 2.32 (s, 3 H, NCH_3), 2.6–4.2 (complex signals representing benzylic and other nonaromatic H, 14 H), 3.23 (s, 3 H, 7-OCH_3), 3.35 (s, 3 H, 6′-OCH_3), 3.73 (s, 3 H, 6-OCH_3), 3.92 (s, 3 H, 12-OCH_3), 6.00 (s, 1 H, Ar), 6.30 (m, 2 H, Ar), 6.50 (m, 2 H, Ar) 6.73 (d, 1 H, Ar), 6.87 (s, 2 H, Ar), 7.33 ppm (m, 2 H, Ar); mass spectrum *m/e* (rel abundance) 608 (62), 471 (6), 431 (10), 382 (67), 381 (68), 368 (48), 350 (12), 335 (8), 191 (100); elemental composition (by high-resolution mass spectroscopy) 608.2938 (calcd for $C_{37}H_{40}N_2O_6$, 608.2886).

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Registry No.—**1**, 518-34-3; **1a**, 38769-08-3; **2**, 1699-51-0; **2b**, 6391-58-8; **2c**, 59069-53-3; *O*-ethylisovanillic acid, 2651-55-0; isovanillic acid, 645-08-9; *O*-ethylvanillic acid, 3535-30-6; vanillic acid, 121-34-6.

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18-Hydroxy-11-deoxycorticosterone. Chemical Synthesis, Structure, and Circular Dichroism†

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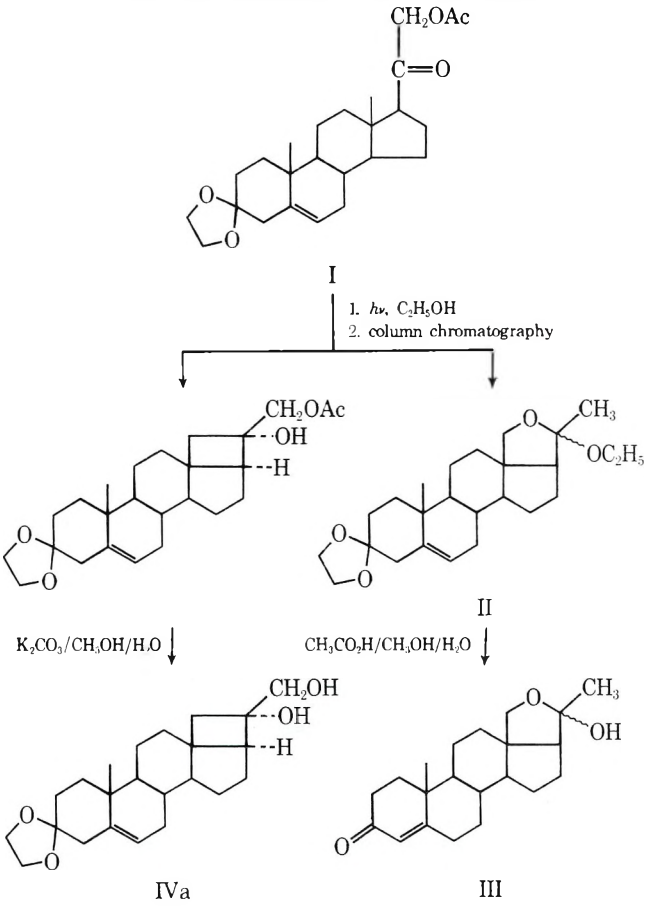
18-Hydroxy-11-deoxycorticosterone (18-OH-DOC) has been prepared in two steps from 18-hydroxyprogesterone in high yield. 18-Hydroxyprogesterone has in turn been prepared in ~20% yield by photolysis of the ethylene ketal of deoxycorticosterone 21-acetate followed by acidic and then basic hydrolysis and column chromatography. The circular dichroic spectra of 18-OH-DOC and related compounds are reported. From the induced circular dichroism of 18-OH-DOC with $Pr(dpm)_3$, it is concluded that 18-OH-DOC has the 20→18-cyclohemiketal structure with C-20 having the *R* configuration.

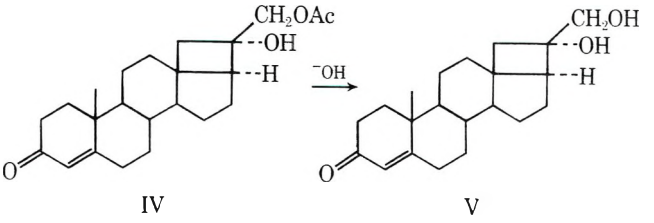
18-Hydroxy-11-deoxycorticosterone (18-OH-DOC) was first isolated and identified as a naturally occurring steroid from incubated sectioned rat adrenal by Birmingham and Ward in 1961[1] and by Péron in the same year.[2] It was characterized to be in the 20→18-cyclohemiketal form. The in vivo secretion of 18-OH-DOC in rats was demonstrated by Cortes et al.[3] The endogenous formation of 18-OH-DOC has also been demonstrated in the camel by Race and Wu in 1964,[4] and in man by Melby and collaborators,[5,6] who isolated and identified 18-OH-DOC from human adrenal vein blood. They obtained levels comparable to those of aldosterone and deoxycorticosterone in normal subjects, and elevated levels in patients suffering from various forms of hypertension, including Cushing's syndrome and essential hypertension.

Because of the possibly important role of 18-OH-DOC in the etiology of essential hypertension,[7] a careful study of the structure and the biological activities of 18-OH-DOC appears to be necessary. To this end, we embarked on a synthesis of 18-OH-DOC so that a reasonable amount of the steroid may be at hand. When we began our synthetic work, the synthesis of 18-OH-DOC had been described by Pappo in 1959 only in a preliminary communication[8] and in U.S. Patents.[9] It involves a 15-step synthesis starting from the alkaloid conessine. This ingenious but long synthesis was, however, not practical in our hands. We decided to adopt a simpler synthesis of 18-OH-DOC starting from 18-hydroxyprogesterone according to Scheme II. This route to 18-OH-DOC has been reported by us in preliminary form.[10] Recently, several groups have reported on similar preparations with varying degrees of success.[11,12] In this paper, we wish to describe in greater detail our synthesis, and some physicochemical studies on 18-OH-DOC and related compounds.

Chemical Synthesis. A. 18-Hydroxyprogesterone. As the immediate precursor for the synthesis of 18-OH-DOC, we chose the structurally similar steroid 18-OH-progesterone (III). It possesses the Δ^4-3-ketone as well as the 20→18-cyclohemiketal structure which can be modified to 18-OH-DOC by functionalizing the 21-methyl group. 18-OH-Progesterone was prepared from the readily available ethylene ketal of deoxycorticosterone 21-acetate (I) by the photochemical method developed by Jeger et al.[13,14] The advantage of this method (Scheme I) is its simplicity and convenience. However, Jeger et al.[13,14] reported a 5% overall yield of III from I, a result which was substantiated by us. We attempted to improve the yield of 18-OH-progesterone by acid hydrolysis of the photolysate directly. However, it was found that under these conditions, another product, IV, was obtained which had nearly the same polarity as 18-OH-progesterone and could only be separated with difficulties. We therefore incorporated another hydrolytic step under alkaline conditions. This resulted in the conversion of IV to the diol V, which can be separated easily from 18-OH-progesterone.

Scheme I. Jeger's Photochemical Reaction of Deoxycorticosterone Acetate Derivative (I)





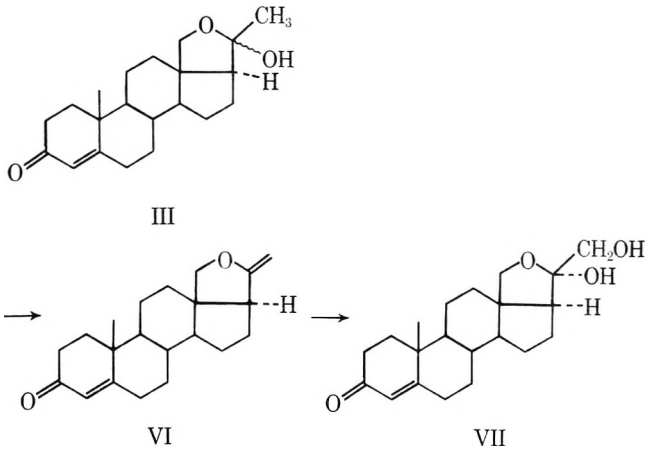
With this modified procedure, 18-OH-progesterone was obtained in 15–24% overall yield from I. The process is thus competitive with other reported syntheses of 18-OH-progesterone[15] in terms of yield.

B. Conversion of 18-Hydroxyprogesterone to 18-OH-DOC. Having prepared 18-OH-progesterone (III), the

† This paper is dedicated to Professor C. A. Winkler of McGill University on the occasion of his 65th birthday by one of his colleagues (T.H.C.).

remaining task was to convert this compound to the enol ether VI by dehydration and thence to the title compound 18-OH-DOC (VII) by hydroxylation.

Scheme II



Phosphorus oxychloride with triethylamine were found to be the reagents of choice for achieving the dehydration of III to IV in quantitative yield. The reaction conditions are extremely critical for the dehydration to be successful (see Experimental Section). It is essential that reagents used should be dried just prior to use and moisture excluded from the reaction. Dehydration of III to VI under basic condition has recently been reported.[11]

When a benzene solution of VI was treated with a solution of osmium tetroxide (1.1 molar equiv) in the presence of pyridine at 0 °C under nitrogen, a rapid reaction (complete in 1 h) occurred. Hydrolysis of the reaction mixture containing the osmate esters under mild conditions at room temperature for 1 h with a mixture of aqueous sodium sulfite and potassium carbonate gave pure, colorless, crystalline 18-OH-DOC (VII, mp 154–156 °C). An analytical sample had mp 165–168 °C, $[\alpha]^{25}D$ +110.3°. A crucial point in obtaining quality 18-OH-DOC in high yield is to evaporate the reaction mixture under reduced pressure at room temperature to total dryness followed by ether extraction of the crude residue. 18-OH-DOC (VII) so obtained was identical with an authentic sample from Pappo[8] by the following criteria: identity of the infrared spectra and the fragmentation patterns of the mass spectra; identical R_f values on TLC and paper chromatograms. 18-OH-DOC (VII) was further characterized by the mobility on paper chromatogram, positive reaction with the Porter–Silber test, negative reaction with the blue tetrazolium test, and mass spectral comparisons with the 18-OH-DOC obtained by incubation with rat adrenals.

Structure of 18-OH-DOC. The structure of 18-OH-DOC was demonstrated by Birmingham and Ward to be in the 20→18-cyclohemiketal form by near infrared.[1] In spite of this there has been confusion in the literature concerning the structure of 18-OH-DOC.[16] For example, Diminguez[17] as well as others have observed that there are two interconvertible forms of 18-OH-DOC during paper chromatography. Authentic, crystalline, and chemically synthesized 18-OH-DOC has been said to exhibit the same interconversion when dissolved in polar solvent for an extended time.[17] Dominguez argued that the possibility that the structure of the crystalline, chemically synthesized compound is the 18-OH-DOC (presumably in the keto form) and that it interconverts to the hemiketal form in solution cannot be entirely ruled out. We wish to reiterate here the known spectroscopic data as well as to present some new circular dichroic data of 18-OH-DOC which permit us to conclude that 18-OH-DOC, either in the

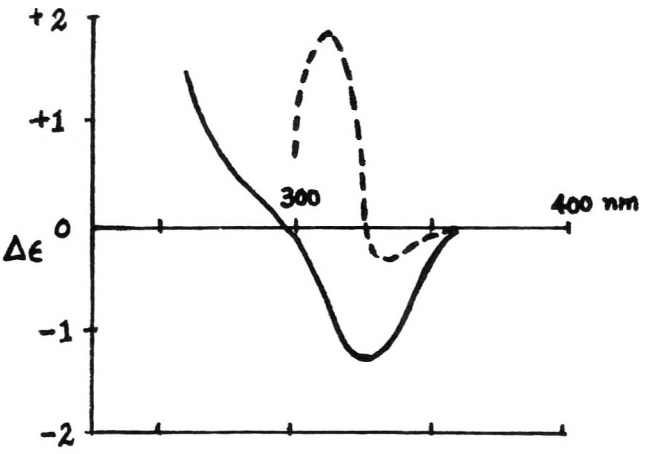
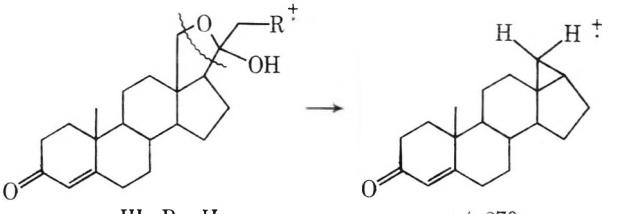


Figure 1. CD of (a) 18-OH-DOC (—); (b) a 1:1 mixture of 2.0×10^{-4} mol of 18-OH-DOC and $Pr(dpm)_3$ in $CHCl_3$ (- - - -).

crystalline state or when dissolved in nonpolar solvent, has the 20→18-cyclohemiketal structure with *R* configuration at C-20. The ir spectrum of crystalline 18-OH-DOC (in KBr) shows peaks at 1660 cm^{-1} for the α,β-unsaturated ketone moiety and absence of absorption in the 1700-cm^{-1} region which is normally expected for the C-20 carbonyl group. This argues for the hemiketal structure for 18-OH-DOC. A similar conclusion has been drawn on the basis of mass spectral fragmentation studies of 18-OH-DOC.[18] We have substantiated this conclusion by comparing the mass spectrum of 18-OH-DOC with that of 18-OH-progesterone. We found that one of the common pathways for both compounds is the cleavage indicated below, thus confirming the cyclic structure in both VII and III.[19] This leaves little room for doubt about the cyclohemiketal structure for 18-OH-DOC in the crystalline state.



III, R = H
VII, R = OH

m/e 270

The solution ir (CH_2Cl_2) spectrum of 18-OH-DOC shows absorption at 1665 cm^{-1} and no peak at 1700 cm^{-1}.[11] This indicates again that in this solvent, the keto form is not present to any significant extent.

We have examined the circular dichroism (CD) of 18-OH-DOC in chloroform (Figure 1a). Figure 1a shows that the CD curve of VII exhibits two Cotton effects: a negative one in the 330-nm region and an intensive positive one around 250 nm. Both transitions can be assigned to the Δ^4-3-keto chromophore. A noteworthy feature of Figure 1a is the absence of Cotton effect in the 290-nm region. This observation is in agreement with the absence of a $n \rightarrow \pi^*$ transition of a saturated ketone in VII. For comparative purposes, the CD curve of deoxycorticosterone acetate (Figure 4) was found to have Cotton effects at 250 nm, 330 nm and 290 nm whereas 18-OH-progesterone (Figure 2a) shows Cotton effects only at 250 and 330 nm.

Recently, Nakanishi et al. developed a method for absolute configurational studies of vicinal glycols.[20] The method consists of measuring the CD of substrate and $Pr(dpm)_3$ (dpm = dipivalomethanato; sometimes called thd = 2,2,6,6-tetramethyl-3,5-heptadionato) dissolved in a dry nonpolar solvent. The solution shows an induced Cotton effect on ca. 300 nm,

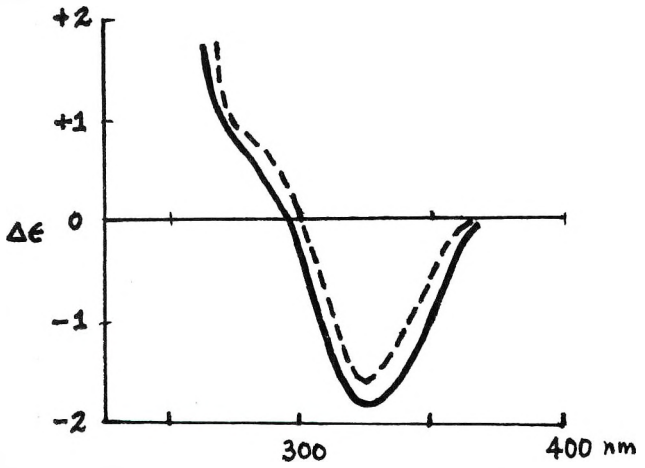


Figure 2. CD of (a) 18-hydroxyprogesterone (—); (b) a 1:1 mixture of 2.0×10^{-4} mol of 18-hydroxyprogesterone and $Pr(dpm)_3$ in $CHCl_3$ (- - - -).

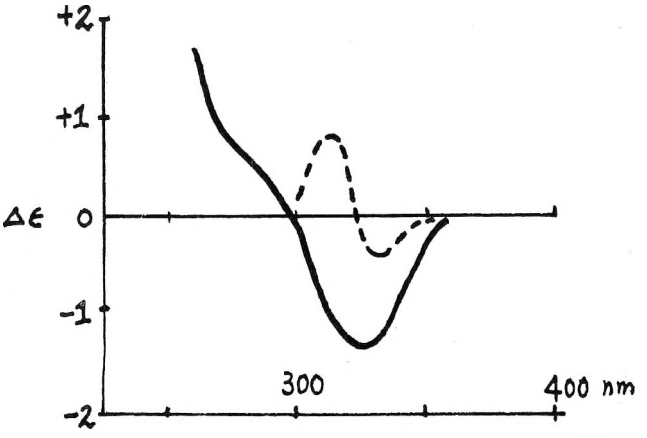
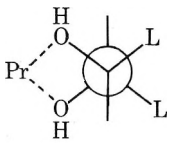


Figure 3. CD of (a) 18,20-cyclo-20,21-dihydroxy-Δ^4-pregnen-3-one (V) (—); (b) a 1:1 mixture of 2.0×10^{-4} mol of V and $Pr(dpm)_3$ in $CHCl_3$ (- - - -).

presumably due to the formation of a bidentate adduct between the glycol and $Pr(dpm)_3$. The sign of the Cotton effect can be related with the chirality of the glycol. It appears to us that the method can serve as a probe for the existence of the glycol moiety. Indeed, when the CD curve of 18-OH-DOC in $CHCl_3$ was taken in the presence of molar quantity of $Pr(dpm)_3$, a change in the Cotton effect at ca. 310 nm was observed (Figure 1b). The change cannot be due to complexation of $Pr(dpm)_3$ either with the enone chromophore or with only one of the hydroxy groups in VII. This is demonstrated by the fact that the CD curve of 18-hydroxyprogesterone is not at all affected by the addition of $Pr(dpm)_3$ (Figure 2b). This confirms therefore the hemiketal structure for 18-OH-DOC in chloroform.

In the case of an acyclic glycol, the origin of the induced CD is assumed to be due to the preferred formation of a complex between the ion Pr and one conformer of the glycol where the bulkier groups are pseudoequatorial in the complex (A). The



A

L = bulkier group

assignment of configuration to an unknown glycol is accomplished essentially by comparing its induced CD with that of

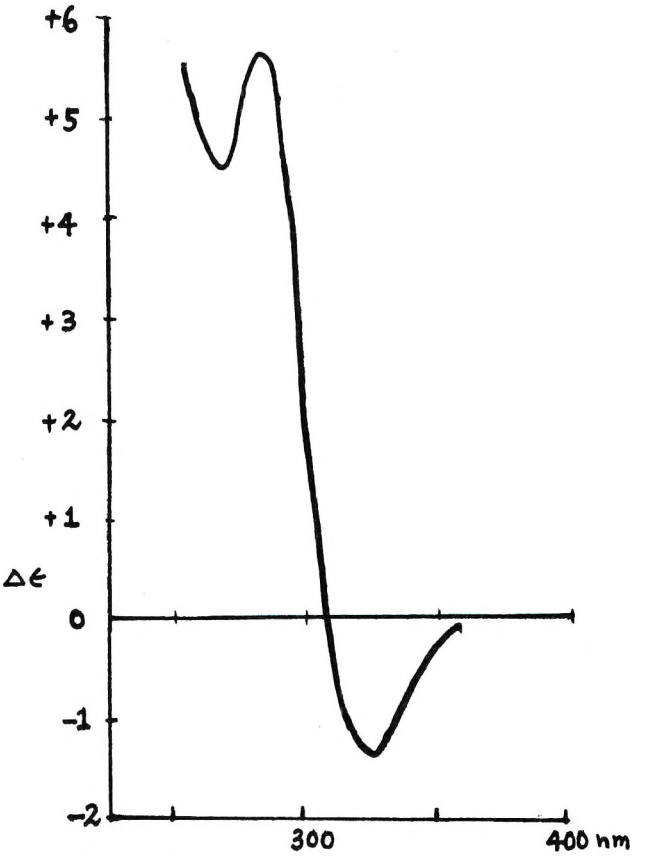
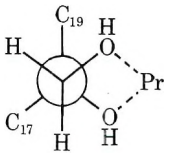


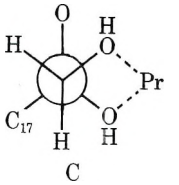
Figure 4. CD of 11-deoxycorticosterone acetate in CH_3OH.

a model compound of known configuration. The success of this method depends then on a judicious choice of model compound. In attempting to interpret the induced CD observed for VII and to derive information about the configuration at C-20, we feel that the 18,20-cyclo compound V can serve admirably as the model for VII. Compound IVa obtained from photolysis has been assigned to have the 20*S* configuration.[21] The transformation IVa → V establishes the same configuration for C20 in V. The CD curve of V shows the same general features as 18-OH-DOC (Figure 3a). When equal mole of $Pr(dpm)_3$ was added, an induced positive CD was observed (Figure 3b) of the same direction and nearly the same magnitude as that observed for VII. The preferred conformer of the complex of $Pr(dpm)_3$ with V is likely to have the more hindered C-17 pseudoequatorial (B). Since the observed in-



B

duced CD for VII is the same as that of V, it is likely therefore that the complex in VII responsible for the induced CD also has the same chirality with the bulkier C-17 pseudoequatorial (C). This renders the configuration at C-20 of VII as *R*.



C

The conclusion that the chemically synthesized 18-OH-DOC has a C-20 *R* configuration is compatible with stereo-

chemical consideration about the mode of hydroxylation of the enol ether VI. The reagent, osmium tetroxide, would most likely attack the double bond from the less hindered side. Inspection of the molecular model indicates that this is the side opposite to the D ring, thus giving rise to the *R* configuration at C-20.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Model 257 and/or Model 337 grating infrared spectrophotometer. Uv spectra were measured with a Unicam SP-800 spectrophotometer using methanol as the solvent, unless otherwise stated. Optical rotations were determined in chloroform with a Perkin-Elmer Model 141 polarimeter using a 1-dm microcell at the sodium D line. Circular dichroism curves were obtained using a Japan Spectroscopic Co. ORD/UV-5 with CD attachment. Mass spectra were obtained on an AEI MS-902 mass spectrometer by a direct probe method at minimum temperatures (165–200 °C) necessary to vaporize the sample. The ionizing energy was kept at 70 eV and the ionizing current at 500 μA. High-resolution mass measurements were made by the peak-matching method using a perfluorokerosene reference. If not otherwise stated, thin layer chromatography (TLC) was carried out routinely using neutral aluminum oxide (Woelm Co.). Column chromatography was carried out using neutral aluminum oxide (Woelm Co.). Paper chromatography was kindly performed by Mrs. H. Traikov at the Allen Memorial Institute of Psychiatry, McGill University. Proportions indicated for solvent mixtures were by volume. The microanalyses were made by Scandinavian Microanalytical Laboratories, Herlev, Denmark, and by Dr. C. Daesslé of Organic Microanalyses, Montreal.

Chemicals and Reagents. Deoxycorticosterone acetate was purchased from Searle Chemicals, Inc., Chicago, Ill. Petroleum ether refers to the fraction of boiling point 30–60 °C and was dried over sodium wire. Phosphorus oxychloride was redistilled just prior to use. Dry tetrahydrofuran, ether, and benzene were obtained by distillation over lithium aluminum hydride or sodium wire. Pyridine and triethylamine were freshly distilled from potassium hydroxide pellets. Solvents were usually removed by rotary evaporation under vacuum at a water-bath temperature of approximately 40 °C. All compounds reported were purified until no impurities could be detected by TLC analysis.

General Procedure for Photolysis and Isolation of 18-Hydroxyprogesterone. An apparatus similar to that previously described by Jeger et al. was used. The light source was a Hanovia 450-W high-pressure mercury lamp (Model 679-A-36) and was fitted with a Corex filter cylinder (1 mm thick, Hanova Model 513-27-114). The lamp was placed in a water-cooled quartz immersion apparatus which was submerged in the irradiation solution. A solution of I (2.08–2.09 g)[22] in absolute ethanol (1.85 l.) was photolyzed for 4 h. After evaporation of the solvent, the photolysate was dissolved in aqueous 70% acetic acid (25 ml) and was heated with stirring at 80–90 °C for 4 h under an atmosphere of nitrogen. The hydrolysis was followed by infrared (the appearance of a strong band near 1680 cm^{-1} for the α,β-unsaturated ketone group) and by ultraviolet (the appearance of an absorption maximum near 240 nm) spectroscopy. The solvent was evaporated under reduced pressure. The product (2.50–2.53 g) was then treated with a mixture of methanol (13 ml), potassium carbonate (1.41 g), and water (13 ml). The resulting solution was stirred under nitrogen at room temperature for 12 h. The process of hydrolysis was followed by infrared spectroscopy (the disappearance of a band near 1740 cm^{-1} for the acetate group). The solvent was removed by azeotropic distillation with benzene (15 ml × 15). The brown, gummy product was taken up in methylene chloride (250 ml), washed with water (5 ml × 4), and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was further dried under vacuum for 2–3 h at room temperature. The brown, glassy product (1.50–1.52 g) was dissolved in a minimum volume of benzene and chromatographed over a column (2.5 cm i.d.) of neutral alumina (60 g, Woelm activity I) made up with petroleum ether. Fractions of 100–150 ml each were collected and the progress of chromatography was followed by TLC and by crystallization of each fraction (see Table I).

Identification of Products. 18-Hydroxyprogesterone (III). The identity of III was confirmed by mixed TLC and comparisons of the infrared and mass spectra with those of authentic 18-OH-progesterone.

18,20-Cyclo-20-hydroxy-Δ⁴-pregnen-3-one (IX). This compound was not reported by Jeger in his photolysis experiments.[13,14]

Table I. Products Isolated by Alumina Column Chromatography of the Hydrolyzed Ethanolic Photolysate of I

Fraction	Solvent of elution	Av % yield	Mp, °C	$[\alpha]^{25}D$ ($CHCl_3$)	Structure of compd
1–11	Benzene	4	103–105	+102.9°	VIII
18–57	Benzene, benzene–ether (90:10)	2–4	195–197	+138.1°	IX
67–115	Benzene–ether (85:15), (80:20), (75:25)	15–24	150–154	+152.8°	III
122–145	Ether	17–22	183–187	+128.8°	V

The identity of this compound was secured from spectroscopic investigation as well as comparison with reported physical data. Recrystallization twice from acetone–hexane gave IX with mp 195–197 °C (lit.[23] mp 191–192 °C), $[\alpha]^{25}D$ +138.1° (*c* 0.51, $CHCl_3$) (lit.[23] $[\alpha]D$ +130°).

18,20-Cyclo-20,21-dihydroxy-Δ⁴-pregnen-3-one (V). Recrystallization twice from acetone–hexane gave V as a crystalline solid with mp 183–187 °C, $[\alpha]^{25}D$ +128.8° (*c* 0.51, $CHCl_3$). Its ir spectrum (KBr) showed absorption at 3410, 1650, and 1610 cm^{-1}. The uv spectrum (EtOH) showed λ_{max} 242 nm (ε 16 940). Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.20; H, 9.28. Molecular weight calcd, 330.2194; found, 330.2154.

17-Nor-13,17-seco-Δ⁴,¹³⁽¹⁸⁾,¹⁵-androstrien-3-one (VIII). Elution with benzene gave a colorless residue. Crystallization from acetone–hexane gave VIII with mp 103–105 °C (lit.[23] mp 109 °C), $[\alpha]^{25}D$ +102.9° (*c* 0.51, $CHCl_3$) (lit.[23] $[\alpha]D$ +110°).

Conversion of 18-OH-Progesterone to 18-OH-DOC. A. Preparation of 18,20-Epoxy-Δ⁴,²⁰-pregnadien-3-one (VI). All glassware was thoroughly cleaned, oven dried, and stored in a desiccator prior to use. Phosphorus oxychloride, triethylamine, pyridine, and benzene were freshly redistilled. In a 25-ml three-necked flask fitted with a calcium chloride tube and nitrogen-inlet tube was placed 51 mg of 18-OH-progesterone (III, 0.51 mmol), 15 ml of benzene, and 0.9 ml of triethylamine. The flask was capped with a rubber septon. The solution was stirred at room temperature and 46 mg of phosphorus oxychloride (2 molar equiv) was added with a microsyringe through the rubber septon. The addition was repeated at intervals of 1 h until the dehydration reaction was completed. The progress of the reaction was followed by TLC from the disappearance of VI to the formation of a less polar compound XI which could be hydrolyzed back to VI with aqueous 10% acetic acid in a few minutes at room temperature. The reaction was interrupted after 3.5 h (a total of 138 mg of phosphorus oxychloride had been added). The reaction mixture was immediately taken up in benzene (250 ml) containing pyridine (1.5 ml), rapidly washed with cold 10% sodium carbonate solution (5 ml × 1) and cold water (6 ml × 7), and dried over anhydrous sodium sulfate. The dried benzene solution was then carefully concentrated to a small volume (5–10 ml), but never to dryness, with a rotary evaporator under reduced pressure at room temperature. The excess of triethylamine was removed at this stage. The dehydration product XI was homogeneous and free of the starting material VI by TLC analysis.

18-OH-progesterone (III)	Enol ether (VI)	Benzene–ethyl acetate
R_f 0.13	R_f 0.57	8:2
R_f 0.52	R_f 0.70	2:8

It is essential that the enol ether (XI) obtained be osmylated without delay in the next step of synthesis.

B. Preparation of 18-OH-DOC (VII). To a solution of the enol ether (ca. 50 mg) in benzene (8 ml) was added dropwise with stirring at 0 °C under nitrogen a solution of osmium tetroxide (1.1 molar equiv, 45 mg) in benzene (1 ml) containing pyridine (5 drops). The oxidizing reagent was delivered with a syringe through the rubber septon. The reaction was completed in 1 h as indicated by TLC (the disappearance of VI and the formation of a prominent dark spot on the baseline). The mixture was stirred for an additional 1 h. The brown solution was treated with a solution of sodium sulfite (195 mg) and potassium carbonate (310 mg) in water (2 ml), and the resulting mixture stirred at room temperature for 2 h. The hydrolysis was essentially completed

in the first hour as indicated by TLC (the appearance of a single spot with the R_f of VII). The dark brown reaction mixture was evaporated at 30–40 °C under reduced pressure to total dryness with a rotary evaporator. The dark brown residue was taken up in a small volume of water (10 ml) and repeatedly extracted with ether (20 ml × 10). The ether extract was washed with cold water (5 ml × 3) and dried over anhydrous sodium sulfate. A trace of pyridine (1 drop) was added and the ether solution evaporated at 30–40 °C under reduced pressure to afford colorless crystalline 18-OH-DOC (VII, mp 154–158 °C) in 94% yield (50 mg). The crude product was homogeneous as indicated by TLC: R_f 0.23 (SiO_2 G), 0.31 (SiO_2 Eastman) in benzene–ethyl acetate (2:8). Recrystallization twice from acetone–hexane containing a trace of pyridine gave VII, mp 165–168 °C, $[\alpha]^{25}D$ +110.3° (c 0.21, $CHCl_3$) {lit.[19] $[\alpha]^{28}D$ +121° (aqueous 70% methanol)}. The infrared and mass spectra of VII were identical with those of an authentic sample of 18-OH-DOC obtained from Pappo.[8] The two samples showed identical mobility on TLC and paper chromatogram.

Pappo[8] pointed out that the melting point of 18-OH-DOC can vary depending on the solvent of crystallization.

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Registry No.—I, 13382-00-8; III, 22618-71-6; V, 59055-10-9; VI, 56896-04-9; VII, 59121-45-8; VIII, 59055-11-7; IX, 59055-12-8.

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Determination of the Configuration of the Four D-Benzylpenicilloates

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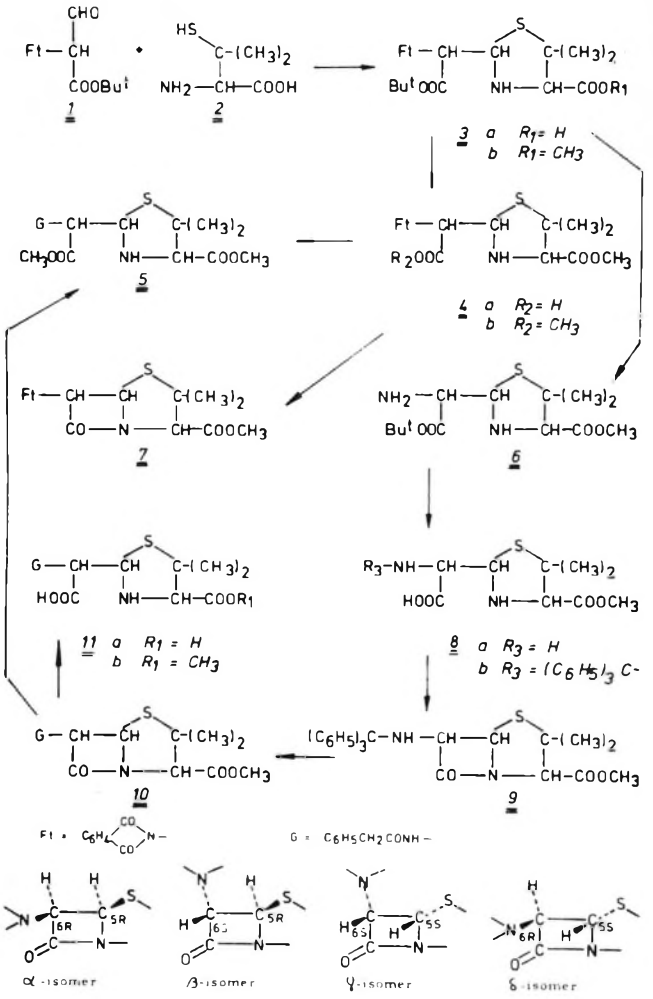
The configuration of the four dimethyl D-benzylpenicilloates was determined, and their stereochemical relationship to the dimethyl phthalimidopenicilloates, prepared according to Sheehan et al., was established, using a series of transformations and physicochemical techniques. The compounds designated as β and γ isomers in the Sheehan nomenclature were found to correspond to the γ and δ isomers of "Chemistry of Penicillin", and to have the 5*R*,6*S* and the 5*S*,6*S* configuration, respectively. In the course of this study, 5-epi-6-epibenzylpenicillin methyl ester (γ-**10**) having the 5*S*,6*S* configuration was prepared for the first time. The isomer with the 5*S*,6*R* configuration, which was consequently denoted as δ isomer, was prepared from 5-epibenzylpenicillin methyl ester, and was identical with the β isomer of "Chemistry of Penicillin". It was also established that sodium benzylpenicilloate α isomer, having the 5*R*,6*R* configuration of the natural penicillins, isomerized in aqueous solution to a mixture, containing mainly the δ isomer (5*S*,6*R*).

The first step in the Sheehan synthesis of penicillin[1] is the condensation of *tert*-butyl phthalimidomalonaldehydate (**1**) with D-penicillamine (**2**). When this reaction was performed in alcohol–water, containing sodium acetate, only two of the four possible[2] phthalimidopenicilloates,[3] called α and γ isomers, were formed,[5] the γ isomer being the major component. Using pyridine as solvent, the main product was the α isomer,[6] which has also been obtained by heating the γ isomer in the same solvent.[1] It has been shown[1,5] that the α isomer has the same configuration as the natural penicillins, namely 5*R*,6*R*,[7] whereas the stereochemistry of the γ isomer is unknown. When the *tert*-butyl group of **3b** was removed with acid at about 75 °C, another isomer of unknown configuration, designated as β isomer, was formed. It could be cyclized to a 6-phthalimidopenicillanate (**7**) by treatment with thionyl chloride.[5,8]

During the wartime research on penicillin, four benzylpenicilloates (**5**), designated by the letters α, β, γ, and δ, were obtained.[4] Their configuration, except that of the α isomer, which corresponds to the natural penicillin, is unknown and their relation to the phthalimidopenicilloates (**3**) of Sheehan has not been investigated.

In order to determine the configuration of the γ isomer of **3a**, we transformed this product into a penicillin using the second Sheehan synthesis,[9] which we had applied previously.[6] Hydrazinolysis of γ-**3b**, prepared by methylation of γ-**3a**, yielded γ-**6**, from which the *tert*-butyl group was removed with acid, to give γ-**8a**. This compound was transformed into γ-**8b**, by treatment with triphenylchloromethane, and cyclized with diisopropylcarbodiimide to methyl 6-tritylaminopenicillanate (γ-**9**). From the NMR spectrum a cis configuration of the hydrogen atoms on C-5 and C-6 could be deduced. As this compound was different from methyl (5*R*,6*R*)-tritylaminopenicillanate, prepared from natural 6-aminopenicillanic acid,[9] it can be concluded that the γ isomers have a 5*S*,6*S* stereochemistry. Detritylation of γ-**9** and phenylacetylation



led to a benzylpenicillin methyl ester (γ-**10**), whose NMR spectrum confirmed the 5*S*,6*S* configuration. To our knowledge, this is the first time that a penicillin with 5-epi-6-epi configuration is reported.

On the other hand, γ-**3b** was transformed into dimethyl benzylpenicilloate (**5**), by cleavage of the *tert*-butyl ester and esterification to γ-**4b**, followed by removal of the phthaloyl group and phenylacetylation. This benzylpenicilloate (γ-**5**) was identical with the compound obtained by methanolysis of γ-**10**, which shows that no inversion of configuration occurred during the transformation of γ-3b to γ-**10**. Methanolysis was carried out in the presence of diazomethane, a method used for the first time in this work. This procedure was also applied to natural and 6-epibenzylpenicillin methyl ester, and gave the same yield as the more tedious triethylamine-catalyzed methanolysis. However, no alcoholysis of the β lactam was observed when benzylpenicillin methyl ester was treated with ethanol and diazomethane. The physical constants of γ-**5** corresponded to those of the δ isomer of "Chemistry of Penicillin", which had been prepared by hydrolysis of benzylpenicillin in the presence of copper sulfate or by treatment of the α-penicilloate with copper sulfate, followed by reaction of the copper salt with diazomethane.[10]

The β isomer of **4a** could be obtained either from α-**3b** or γ-**3b** by treatment with anhydrous hydrogen chloride at 75 °C. Using the procedure described for the DL analogue,[8] β-**4a** was cyclized to **7** with thionyl chloride. The methyl 6-phthalimidopenicillanate (β-**7**) thus obtained had the 6-epi configuration, and was identical with the product obtained by base-catalyzed epimerization of **7** having the natural configuration.[11,12] The products of the β series consequently have the 5*R*,6*S* configuration.

In order to establish the correlation with the benzylpenicilloates described in "Chemistry of Penicillin", the methyl ester of 6-epibenzylpenicillin[13] was subjected to methanolysis. Dimethyl benzylpenicilloate (**5**), which was obtained in this way, had the same physical properties as the γ isomer, which was prepared by condensation of methyl benzylpenaldate (methyl phenylacetamidomalonaldehydate) with penicillamine, followed by esterification of the thiazolidine carboxy group with diazomethane.[14]

A possible modification of the stereochemistry of C-5 or C-6, during the conversion of β-**4a** into **7**, was excluded by transformation of β-**4a** to β-**5**. Esterification of the carboxyl group of β-**4a** with diazomethane gave β-**4b**, which by removal of the phthaloyl group and phenylacetylation yielded β-**5**. The dimethyl benzylpenicilloate (β-**5**) thus obtained was identical with the compound obtained by methanolysis of the methyl ester of 6-epibenzylpenicillin, which confirms the previously assigned 5*R*,6*S* configuration to the β series.

The fourth phthalimidopenicilloate, which we shall call the δ isomer, must have the 5*S*,6*R* configuration of the 5-epipenicillins. Methyl 6-phthalimido-5-epipenicillanate has been prepared recently[15] by opening of the thiazolidine of natural **7** with chlorine and ring closure of the methyl 2*S*-chloro-α-(1-chlorothio-1-methylethyl)-4-oxo-3-phthalimido-1-azetidineacetate thus obtained with stannous chloride.

5-Epibenzylpenicillin methyl ester (δ-**10**), which was prepared from the 5 epimer of **7**,[16] could not be transformed directly into **5** by reaction with methanol in the presence of triethylamine or diazomethane, a method which has been used for the preparation of other penicilloates, apparently because of a greater stability of the β-lactam ring. For this reason, δ-**10** was hydrolyzed with sodium hydroxide, yielding a mixture of penicilloates (**11b**), from which δ-**5** was isolated after reaction with diazomethane. This compound presented the physical properties of the β isomer of "Chemistry of Penicillin", where it has been obtained by refluxing α- or γ-**5** ("Chemistry of Penicillin" nomenclature) in toluene in the presence of some iodine.[17] Condensation of methyl benzylpenaldate with penicillamine methyl ester in boiling toluene also gave this β isomer together with the γ isomer (i.e., the δ and the β isomer in the Sheehan nomenclature).[17]

The phthalimidopenicilloate of this series (δ-**4b**) could not be prepared directly. It was detected by TLC in the reaction mixture obtained during the transformation of α-**4b** or γ-**4b** into β-**4b** by treatment with *p*-toluenesulfonic acid in nitromethane solution. The NMR spectrum of the mixture provided the data of δ-**4b**.

The most significant NMR values of the four isomers of the dimethyl penicilloates of the benzyl (**5**) and the phthalimido series (**4b**) are given in Table I. For the phthalimidopenicilloates (**4b**), the chemical shift of the C-3 proton appears at higher field in the compounds with 5*S* configuration than in the 5*R* isomers. This shielding had been observed previously in carboxythiazolidines[7] derived from D-penicillamine, when the C-3 proton was cis oriented relative to the C-5 proton, and it had led to the correct assignment of a 5*S* configuration to γ-**4b**.[18] This correlation between the chemical shift of the C-3 proton and the configuration at C-5 does not occur in the benzylpenicilloates (**5**). This difference can be explained by a difference of conformation, and/or by the greater flexibility of a phenylacetamido compared to a phthalimido group.

It has been observed[19,20] that the p*K* value of the protonated thiazolidine of benzylpenicilloate (**11a**) decreases from 5.3 to 4.7 when a neutral or alkaline solution of **11a** is kept for several hours. This change of p*K* was explained by the transformation of penicilloic acid to penamaldic acid.[19] This conversion was unlikely, because we observed that the solution even after storage for 50 h presented only the weak phenyl bands around 260 nm, and not the strong absorption at 280 nm of penamaldate. We also found[20] that there was a paral-

Table I. NMR Data[a] for Penicilloates

	Nomenclature					
	Sheehan[b]	Chem. Pen.[c]	Configuration	H-3	H-5 (J, Hz)	H-6 (J, Hz)
4b	α		5*R*,6*R*	3.78	5.31 (10)	4.93 (10)
	β		5*R*,6*S*	3.87	5.86 (9.5)	4.73 (9.5)
	γ		5*S*,6*S*	3.59	5.34 (8)	5.14 (8)
	δ[d]		5*S*,6*R*	3.66	5.58 (7)	5.15 (7)
5	α	α	5*R*,6*R*	3.31	5.09 (4)	4.61 (4)
	β[d]	γ	5*R*,6*S*	3.43	5.10 (4.3)	4.86 (4.3)
	γ[d]	δ	5*S*,6*S*	3.53	4.95	4.95
	δ[d]	β	5*S*,6*R*	3.49	5.05 (2.5)	5.15 (2.5)

[a] In parts per million using Me_4Si as internal reference. [b] Nomenclature used by Sheehan et al. [c] Nomenclature of "Chemistry of Penicillin". [d] Nomenclature used for the first time in this publication.

lelism between the change of pK and the mutarotation of the solution of benzylpenicilloate. This change of rotation had already been observed.[21] When a solution of natural (α isomer) benzylpenicilloate was kept until a constant $[\alpha]$D was obtained (about 70 h) and lyophilized, and then treated with diazomethane, we found that the four isomers were present, but that the δ isomer (5*S*,6*R*) was the main component (about 70%).

Experimental Section

Melting points were determined in open capillaries with a Büchi-Tottoli apparatus. Solvents were evaporated under reduced pressure below 30 °C. TLC was performed on silica gel F-254 plates (Merck) using the following mobile phases: I, C_6H_6–EtOAc–HCOOH, 20:10:0.25; II, C_6H_6–Me_2CO, 90:10; III, C_6H_6–Me_2CO, 80:20; IV, *n*BuOAc–*n*-BuOH–H_2O–MeOH–HOAc, 80:15:24:5:40. Spots were located by uv illumination and by exposure to iodine vapor. Column chromatography was performed on silica gel (Merck 0.06–0.2 mm). The optical rotation was measured at room temperature on a Thorn-NPL automatic polarimeter Type 243. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer. Mass spectra were recorded on an AEI MS-12 apparatus, and NMR spectra on a Hitachi Perkin-Elmer R 24 apparatus with tetramethylsilane for $CDCl_3$ solutions, and with the sodium salt of 2,2-dimethyl-2-silapentane-5-sulfonic acid (DSSA) for D_2O solutions, as internal standard.

Methyl (3-Carbomethoxy-2,2-dimethyl-5-thiazolidino)-phthalimidoacetate α Isomer (5*R*,6*R*-4b). *tert*-Butyl (3-carboxy-2,2-dimethyl-5-thiazolidino)phthalimidoacetate (α-**3a**) was prepared in 70% yield by condensing D-penicillamine (**2**) and *tert*-butyl phthalimidomalonaldehydate (**1**) in pyridine at 80 °C, as described by Hoogmartens et al.[6] This compound was dissolved in CH_2Cl_2 and esterified at 0 °C with diazomethane in ether. After evaporation of the solvent and recrystallization in absolute ethanol α-**3b** was obtained in 93% yield, mp 176–177 °C, TLC (system II) R_f 0.73, $[\alpha]^{23}$D −2.5° (*c* 2.0, dioxane), in agreement with previously reported values.[1]

Removal of the *tert*-butyl ester group of α-**3b** was performed by treatment of this compound with anhydrous hydrogen chloride in freshly distilled nitromethane at 0 °C over a period of 10 min, as described for the DL compound.[5] The resulting amino acid hydrochloride, which crystallized after addition of anhydrous ether to the cold concentrated nitromethane solution and after storage for 2 h at 0 °C (yield 70%, mp 108–110 °C dec), was suspended in anhydrous ether and treated with a slight excess of diazomethane in ether at 0 °C. Compound α-**4b** was obtained as an amorphous powder by evaporating the solvent under reduced pressure: TLC (system II) R_f 0.67; $[\alpha]^{22}$D −2° (*c* 1.0, MeOH); *m/e* 392; ir (KBr) 3340 (NH), 1780, 1715 (imide), 1740, 1215 (ester), 725 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.19 (s, CH_3), 1.64 (s, CH_3), 3.2 (br, NH), 3.71 and 3.73 (two s, OCH_3), 3.78 (s, H-3), 4.93 (d, J = 10 Hz, H-6), 5.31 (d, J = 10 Hz, H-5), 7.6–8.0 (m, C_6H_4). One of the two isomers, prepared[22] by condensation of methyl phthalimidomalonaldehydate and D-penicillamine, and esterification with diazomethane, had mp 138–139 °C, $[\alpha]^{25}$D −5° (*c* 1, MeOH).

Dimethyl Benzylpenicilloate α Isomer (5*R*,6*R*-5). A. From Sodium Benzylpenicillin. Sodium benzylpenicillin (4.2 g, 11.8 mmol) was dissolved in 250 ml of methanol containing 2.0 ml (14.3 mmol) of triethylamine. After keeping for 45 h at room temperature, the solvent was distilled off under reduced pressure and the residue was taken up in 50 ml of water and 50 ml of ether. After cooling to 0 °C, the mixture was acidified (pH 3.6) with 1 N HCl, the ethereal phase was decanted, and the aqueous phase was further extracted with four volumes of ether. The combined organic layer was dried (Na_2SO_4) and evaporated. By crystallization from methanol–ether (1:9) 1.6 g (35%) of the C-7 methyl ester of benzylpenicilloate was obtained, mp 125.5–127 °C. This product was dissolved in 30 ml of dichloromethane and 10 ml of methanol, and treated with a slight excess of diazomethane in ether. The solvent was evaporated under reduced pressure, the residue was taken up in ether, and 2.36 g (12.4 mmol) of *p*-toluenesulfonic acid monohydrate was added. After storage for 2 h, the crystals were collected. They were suspended in ether, and the suspension was shaken with 5% $NaHCO_3$ solution and water. The ether layer was dried (Na_2SO_4) and evaporated, yielding 0.99 g (64% based on the monomethyl ester) of crystalline dimethyl benzylpenicilloate α isomer: mp 85–86 °C; TLC (system III) R_f 0.52; $[\alpha]^{22}$D +82° (*c* 0.5, MeOH); *m/e* 380 (M^+ very weak), 321 ($M - COOCH_3)^+$; ir (KBr), 3350 (NH), 3270, 1640, 1530 (amide), 1730, 1230 (ester), 725, 695 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.12 (s, CH_3), 1.43 (s, CH_3), 2.94 (br, NH), 3.31 (s, H-3), 3.62 (s, CH_2), 3.71 (s, two OCH_3), 4.61 (dd, J = 4 and 9 Hz, H-6), 5.09 (d, J = 4 Hz, H-5), 6.20 (d, J = 9 Hz, NHCO), 7.34 (s, C_6H_5).

"Chemistry of Penicillin" [23] gives mp 87–89 °C, $[\alpha]^{25}$D +81.5° (*c* 1, MeOH).

B. From Benzylpenicillin Methyl Ester. Benzylpenicillin methyl ester[13,24] (2 g, 5.7 mmol) was dissolved in 5 ml of absolute methanol and 5 ml of dry ether, and 10 ml of ether containing 6 mmol of diazomethane was added. After standing overnight, the solution was evaporated under reduced pressure, and the resulting oil was dried in vacuo over P_2O_5. After addition of dry ether, 1.540 g (71%) of crystals was obtained, with the same physical constants as the product described under A.

***tert*-Butyl (3-Carboxy-2,2-dimethyl-5-thiazolidino)phthalimidoacetate γ Isomer (γ-3a).** This compound was prepared by condensing equimolecular amounts of *tert*-butyl phthalimidomalonaldehydate and D-penicillamine hydrochloride in ethanol–water containing sodium acetate, as described by Sheehan et al.[1] After storage for 16 h at room temperature a first crop of crystals was obtained, followed by a second one, obtained by partial evaporation of the filtrate. The purity of γ-**3a**, after two recrystallizations from MeOH, was checked by TLC in the system I (R_f 0.23), which allowed the distinction from α-**3a** (R_f 0.34). A certain amount (15%) of α-**3a** was isolated by heating the residue, obtained by evaporation of the filtrates, in pyridine at 80 °C. Total yield of γ-**3a** 42%; mp 155–157 °C; $[\alpha]^{22}$D −19° (*c* 1.0, dioxane), +6° (*c* 1.0, HOAc); NMR [$CDCl_3$–$(CD_3)_2SO$ (2:1)] δ 1.22 (s, CH_3), 1.41 (s, *t*-Bu), 1.60 (s, CH_3), 3.43 (s, H-3), 4.87 (d, J = 9 Hz, H-6), 5.17 (d, J = 9 Hz, H-5), 7.75 (m, C_6H_4). Sheehan et al.[1] reported a melting point of 145–146 °C and $[\alpha]^{23}$D +22° (*c* 1, HOAc), and Hoogmartens et al.[6] give $[\alpha]^{25}$D −13° (*c* 1, dioxane). The more negative rotation reported here is probably the correct one, since in those reports the γ isomer was purified by recrystallization from the more polar solvent system methanol–water. The observed difference in optical rotation may be easily explained by assuming a contamination of γ-3a with a small amount of β isomer, which in analogy with the values of the isomers of **4b**, should have a high positive $[\alpha]$D and a R_f value similar to that of the γ isomer.

***tert*-Butyl (3-Carbomethoxy-2,2-dimethyl-5-thiazolidino)-phthalimidoacetate γ Isomer (γ-3b).** Compound γ-**3a** (8.48 g, 20.2 mmol) was dissolved in 350 ml of dry dichloromethane, and treated at 0 °C with an ethereal solution of diazomethane until a yellow color persisted. By evaporation of the solvent and crystallization in absolute ethanol, 6.54 g (74.5%) of γ-**3b** was obtained: mp 126–128 °C; TLC

(system II) R_f 0.64; $[\alpha]^{22}D$ −18.5° (c 1.0, dioxane); NMR ($CDCl_3$) δ 1.17 (s, CH_3), 1.40 (s, t-Bu), 1.58 (s, CH_3), 3.30 (br, NH), 3.51 (s, H-3), 3.67 (s, OCH_3), 4.92 (d, J = 9 Hz, H-6), 5.22 (d, J = 9 Hz, H-5), 7.6–7.8 (m, C_6H_4). Upon addition of D_2O, the signal at 3.30 ppm disappeared and a sharpening of the signals at 3.51 and 5.22 ppm was observed. Melting point and [α]D are in agreement with those previously reported[1] for the same compound, prepared in 43% yield by esterification in dioxane.

***tert*-Butyl (3-Carbomethoxy-2,2-dimethyl-5-thiazolidino)-aminoacetate Hydrochloride γ Isomer (γ-6).** A solution of 4.34 g (10 mmol) of γ-**3b** in 80 ml of pure dioxane and 0.6 ml (12 mmol) of hydrazine hydrate was stored for 21 h at room temperature under a nitrogen atmosphere, as described for the DL compound.[5] The reaction mixture was freeze dried, and the residue was dried in vacuo over P_2O_5. The white powder was stirred for 2 h in 64 ml of 0.2 N HCl, and after cooling for 15 min, the precipitate of phthalhydrazide was filtered off; the filtrate was lyophilized and dried over P_2O_5 and KOH. Crystallization from MeOH–Et_2O yielded 2.62 g (77%) of γ-**6** in two fractions: mp 152–154 °C dec; TLC (system IV) R_f 0.55; ir (KBr) 3250 (NH), 2890 (NH_3^+), 1740, 1720, 1215, 1155 cm^{-1} (ester).

Methyl 6-Tritylaminopenicillanate γ Isomer (5*S*,6*S*-9). A solution of 3.7 g (10.9 mmol) of γ-**6** in 60 ml of anhydrous nitromethane was cooled to 0 °C, and a stream of dry HCl was bubbled through the stirred solution for 30 min. The reaction mixture was stored for 4 h (storage for a longer time gave a lower yield) at 0 °C, and the major part of the HCl was removed under reduced pressure. Anhydrous Et_2O (120 ml) was added gradually, and the precipitate was filtered off, washed with Et_2O, and dried for 3 h in vacuo over P_2O_5 and KOH. Recrystallized triphenylchloromethane (7.45 g, 25.5 mmol) was added to the dried precipitate (**8a** HCl), followed by a solution of 150 ml of anhydrous CH_2Cl_2 and 7.72 g (60 mmol) of *N*-ethyldiisopropylamine. The reaction mixture was immediately cooled in dry ice–butanol, stirred for 0.5 h, and stored for 20 h at −13 °C. Until this stage of the procedure contact with humidity was avoided as much as possible. The reaction mixture was poured into 150 ml of ice–water, and immediately adjusted to pH 6 with dilute H_3PO_4. The organic layer was decanted, washed twice with water, dried (Na_2SO_4), and evaporated at room temperature. The oily residue of **8b** was dissolved in 70 ml of CH_3NO_2, containing 2.81 g (22.4 mmol) of diisopropylcarbodiimide (DICI), stored overnight at room temperature, and evaporated. Rapid chromatography of the residue over silica gel (100 g) using benzene as eluent, followed by a second chromatographic purification of the collected fractions containing the desired product, yielded 1.2 g (2.55 mmol, 22%) of 5*S*,6*S*-**9** as an amorphous product: TLC (in benzene) R_f 0.1; $[\alpha]^{20}D$ −96° (c 1.0, $CHCl_3$), −96° (c 1.0, n-BuOAc); *m/e* 472; ir (KBr) 3290 (NH), 1780 (β-lactam), 1740, 1210 (ester), 745, 705 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.50 (s, two CH_3), 3.30 (br, NH), 3.60 (s, H-3), 3.78 (s, OCH_3), 4.04 (d, J = 4.5 Hz, H-5), 4.38 (br, H-6, upon addition of D_2O, d, J = 4.5 Hz), 7.35 (s, C_6H_5).

Methyl 6-tritylaminopenicillanate, prepared by reaction of triphenylchloromethane with natural 6-aminopenicillanic acid followed by esterification with diazomethane,[9] had mp 163–165 °C; $[\alpha]^{31}D$ +100° (c 1, n-BuOAc); NMR ($CDCl_3$) δ 1.22 (s, CH_3), 1.48 (s, CH_3), 3.26 (br, NH), 4.33 (s, H-3), 4.42 (m, J = 4 Hz, H-5 and H-6), 7.32 (m, C_6H_5).

Benzylpenicillin Methyl Ester γ Isomer (5*S*,6*S*-10). A solution of *p*-toluenesulfonic acid monohydrate (190 mg, 1 mmol) in 20 ml of anhydrous Me_2CO was added to a solution of γ-**9** (472 mg, 1 mmol) in Me_2CO (20 ml). The reaction mixture was stirred at room temperature for 30 min and evaporated to dryness. The resulting oil was washed twice with Et_2O, and dried in vacuo over P_2O_5 for 2 h. This tosylate salt (420 mg) was dissolved in 30 ml of a solution of dry CH_2Cl_2 and 101 mg (1 mmol) of freshly distilled triethylamine. At 0 °C, solutions of triethylamine (111 mg, 1.1 mmol) and phenylacetyl chloride (166 mg, 1.1 mmol) in CH_2Cl_2 (20 ml for each) were added gradually to the cooled and vigorously stirred solution. After stirring for 2 h, the reaction mixture was washed successively with 0.01 N HCl (2 × 10 ml), 5% $NaHCO_3$ (2 × 20 ml), and water. The organic layer was dried (Na_2SO_4), evaporated, and purified by chromatography over silica gel (15 g) using benzene–acetone (99:1) as eluent. The fractions containing the desired product were collected and evaporated, yielding 160 mg (46%) of γ-**10** as an oil: TLC (system III) R_f 0.60; $[\alpha]^{20}D$ −236° (c 0.7, acetone); *m/e* 348; ir (KBr) 3200, 1660, 1515 (amide), 1780 (β-lactam), 1740, 1210 cm^{-1} (ester); NMR ($CDCl_3$) δ 1.30 (s, CH_3), 1.58 (s, CH_3), 3.61 (s, CH_2), 3.74 (s, OCH_3), 3.78 (s, H-3), 5.21 (d, J = 4 Hz, H-5), 5.51 (dd, J = 4 and 9 Hz, H-6), 6.40 (d, J = 9 Hz, NHCO), 7.35 (s, C_6H_5).

Methyl (3-Carbomethoxy-2,2-dimethyl-5-thiazolidino)-phthalimidoacetate γ Isomer (γ-4b). The *tert*-butyl group of γ-**3b** was removed by treatment with anhydrous hydrogen chloride at 0 °C for a period of 10 min, as described for the DL compound.[5] The amino acid hydrochloride (γ-**4a**) crystallized directly in 93% yield from the cold nitromethane solution (mp 120–122 °C dec). This compound was suspended in ether and treated with a slight excess of diazomethane in ether at 0 °C. By concentration of the solution, γ-**4b** was obtained in 84% yield: mp 145–147 °C; TLC (system II) R_f 0.51; $[\alpha]^{22}D$ −28.5° (c 1.0, MeOH); *m/e* 392; ir (KBr) 3300 (NH), 1780, 1720 (imide), 1740, 1200 (ester), 710 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.21 (s, CH_3), 1.65 (s, CH_3), 3.6 (br, NH), 3.75 and 3.80 (two s, OCH_3), 3.59 (s, H-3), 5.14 (d, J = 8 Hz, H-6), 5.34 (d, J = 8 Hz, H-5), 7.6–8.0 (m, C_6H_4). One of the two isomers, prepared[22] by condensation of methyl phthalimidomalonaldehydate with D-penicillamine, and esterification with diazomethane, had mp 146–147 °C; $[\alpha]^{27}D$ −28° (c 1, MeOH).

Dimethyl Benzylpenicilloate γ Isomer (5*S*,6*S*-5). A. From γ-4b. An amount of 1.6 g (4.08 mmol) of γ-**4b** was dissolved in 40 ml of dioxane, and 0.240 g (4.8 mmol) of hydrazine hydrate was added. After keeping for 20 h at room temperature, the solvent and excess hydrazine were removed by lyophilization. The residue, after drying in vacuo over P_2O_5 for 2 h, was stirred for 2 h at room temperature in 25 ml of 0.2 N HCl. After cooling to 0 °C for 15 min, phthalhydrazide was removed by filtration and the filtrate was lyophilized. The residue (0.85 g, 2.8 mmol) was dissolved in 60 ml of CH_2Cl_2 at 0 °C, and 14.3 ml of a solution of 1.4 ml (10 mmol) of Et_3N in 49 ml of CH_2Cl_2 was added, followed by a simultaneous and dropwise addition of 15.8 ml (3.1 mmol) of the same Et_3N solution and of 4.1 g (3.1 mmol) of phenylacetyl chloride in 15 ml of CH_2Cl_2. The mixture was stirred for 2 h at 0 °C, and then extracted successively with 20 ml of 0.1 N HCl, 50 ml of 5% $NaHCO_3$ solution, and water. After drying (Na_2SO_4), the organic solvent was evaporated, and the residue was purified on a column of 10 g of silica gel using benzene–acetone (98:2) as eluent. The fractions containing the desired component were evaporated and crystallized from ether: 185 mg (12% overall yield); mp 106–108 °C; TLC (system III) R_f 0.50; $[\alpha]^{22}D$ −41° (c 0.3, MeOH); *m/e* 380 (M^+ very weak), 321 ($M - COOCH_3$)$^+$; ir (KBr) 3280 (NH), 3240, 1640, 1555 (amide), 1740, 1210 (ester), 725, 695 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.11 (s, CH_3), 1.59 (s, CH_3), 3.2 (br, NH), 3.53 (s, H-3), 3.61 (s, CH_2), 3.74 and 3.75 (two s, OCH_3), 4.95 (m, H-5 and H-6; upon irradiation of NHCO, a singlet appeared), 6.50 (m, NHCO, coupled with H-6 and virtually coupled with H-5), 7.28 (s, C_6H_5). For dimethyl benzylpenicilloate δ isomer of "Chemistry of Penicillin" a mp 116–117 °C and $[\alpha]^{23}D$ −40° (c 1, MeOH) is given.[10]

B. From Benzylpenicillin Methyl Ester γ Isomer. A quantity of 175 mg (0.5 mmol) of γ-**10** was dissolved in 0.5 ml of absolute methanol and 1.5 ml of ether containing 0.6 mmol of diazomethane, and kept overnight. After evaporation of the solvent, the oily residue was chromatographed over silica gel (5 g) using benzene–acetone (99:1) as eluent. The first fraction (35 mg) contained starting material, the second one (50 mg) consisted of a mixture of α-**5** and γ-**5** in a ratio of 2:1 (as determined by NMR), and the third one (50 mg) contained almost pure γ-**5** (5*S*,6*S*-**5**), which was identical with the product prepared by method A.

Methyl 6-Phthalimidopenicillanate β Isomer (5*R*,6*S*-7). A stream of anhydrous HCl was passed for 7 min through a solution of 3.12 g (7.2 mmol) of α-**3b** in 60 ml of redistilled nitromethane, kept at 71–76 °C in an oil bath. The solution was kept for 16 h in the refrigerator. The crystals of β-**4a** hydrochloride were filtered off, washed with CH_2Cl_2, and dried over P_2O_5 and KOH in vacuo, yielding 1.50 g (50%), mp 149–150 °C dec. This product was suspended in 22.5 ml of purified thionyl chloride and 75 ml of dry CH_2Cl_2. The mixture, which became clear after 1.5 h, was refluxed for 4 h with stirring. After evaporation of the solvent, the residue was dissolved in 30 ml of CH_2Cl_2 and washed with 5% $NaHCO_3$ solution, 3 N HCl, and water. After drying over Na_2SO_4, the solvent was evaporated. The residue was dissolved in benzene and chromatographed over 8 g of silica gel using benzene and benzene–acetone (50:1) as eluent. The eluate was monitored by TLC in the system II. The fractions, containing the component with the highest R_f value, were collected and evaporated. Treatment of the residue with ligroin yielded 130 mg (10%) of crystals. Recrystallization in acetone–ether–ligroin gave 85 mg of β-7: mp 178.5–180 °C; $[\alpha]^{20}D$ +203° (c 0.5, $CHCl_3$), +216° (c 0.5, dioxane); *m/e* 360; ir (KBr) 1785, 1728 (imide), 1770 (β-lactam), 1750, 1215 cm^{-1} (ester); NMR ($CDCl_3$) δ 1.49 (s, CH_3), 1.67 (s, CH_3), 3.81 (s, OCH_3), 4.64 (s, H-3), 5.40 (d, J = 2 Hz, H-6), 5.59 (d, J = 2 Hz, H-5), 7.6–8.1 (m, C_6H_4).

The same physical constants are described for methyl 6-epiphthalimidopenicillanate, obtained by base-catalyzed epimerization of methyl 6-phthalimidopenicillanate.[11,12]

Methyl (3-Carbomethoxy-2,2-dimethyl-5-thiazolidino)-phthalimidoacetate β Isomer (β-4b). An amount of 2.37 g (5.7 mmol) of the hydrochloride salt of β-**4a**, which has also been used as

starting product for preparing β-**7**, was suspended in 80 ml of dry dichloromethane, and treated at 0 °C with an ethereal solution of diazomethane until a yellow color persisted. After evaporation of the solvent, the oily residue was purified by chromatography over silica gel (50 g), using benzene–acetone (97:3) as eluent, and crystallized from a minimum amount of absolute MeOH, yielding 0.53 g (23%) of β-**4b**: mp 119–122 °C; TLC (system II) R_f 0.53; $[\alpha]^{22}D$ +121° (*c* 1.0, MeOH); *m/e* 392; ir (KBr) 3340 (NH), 1780, 1715 (imide), 1740, 1215 (ester), 725 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.23 (s, CH_3), 1.56 (s, CH_3), 3.7 (br, NH), 3.75 and 3.80 (two s, OCH_3), 3.87 (s, H-3), 4.72 (d, *J* = 9.5 Hz, H-6), 5.86 (d, *J* = 9.5 Hz, H-5), 7.6–8.0 (m, C_6H_4).

Dimethyl Benzylpenicilloate β Isomer (5*R*,6*S*-5). A. From 6-Epibenzylpenicillin Methyl Ester. 6-Epibenzylpenicillin methyl ester[13] (1.8 g, 5.3 mmol) was dissolved in 100 ml of absolute MeOH, and 0.76 ml (5.3 mmol) of freshly distilled NEt_3 was added. The optical rotation (0.5-dm tube) of the solution changed from 155° to a constant value of 79° after 65 h. The solvent was evaporated under reduced pressure. The residue was taken up in 50 ml of $CHCl_3$ and 50 ml of water, and acidified with 11 ml of 0.5 N HCl. The organic layer was decanted, washed with water, and dried with Na_2SO_4. After evaporation of the solvent, the residue was taken up in ether, and 1.4 g (70%) of β-**5** was obtained: mp 108–109 °C; TLC (system III) R_f 0.46; $[\alpha]^{22}D$ +120° (*c* 1.0, MeOH); *m/e* 380 (M^+, very weak), 321 ($M - COOCH_3)^+$; ir (KBr) 3360 (NH), 3310, 1645, 1530 (amide), 1730, 1215 (ester), 730, 695 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.12 (s, CH_3), 1.30 (s, CH_3), 3.20 (br, NH), 3.43 (s, H-3), 3.61 (s, CH_2), 3.66 and 3.70 (two s, OCH_3), 4.86 (dd, *J* = 4.3 and 9 Hz, H-6), 5.10 (d, *J* = 4.3 Hz, H-5), 6.25 (d, *J* = 9 Hz, NHCO), 7.30 (s, C_6H_5).

By methanolysis of 6-epibenzylpenicillin methyl ester in MeOH–Et_2O in the presence of a slight excess of diazomethane, as described for α-**5**, compound β-**5** was obtained in 72% yield. This method is more straightforward than the base-catalyzed methanolysis.

For dimethyl benzylpenicilloate γ isomer of "Chemistry of Penicillin" mp 110–110.5 °C and $[\alpha]^{22}D$ +122° (*c* 1, MeOH) are reported.[14]

B. From β-4b. Removal of the phthaloyl blocking group from β-**4b** (0.53 g, 1.3 mmol) and N-phenylacetylation of the resulting methyl (3-carbomethoxy-2,2-dimethyl-5-thiazolidino)aminoacetate hydrochloride were performed as described for the γ isomer (γ-**4b**), yielding, after column chromatographic purification and crystallization from ether, 0.20 g (40%) of β-**5**, which was identical with the product (5*R*,6*S*-**5**) prepared by method A.

Dimethyl Benzylpenicilloate δ Isomer (5*S*,6*R*-5). A. From 5-Epibenzylpenicillin Methyl Ester. A sample of 1.050 g (3 mmol) of 5-epibenzylpenicillin methyl ester[16] was dissolved in 54 ml of MeOH and 21 ml of water. To this solution was added dropwise 29 ml of 0.1 N NaOH over a period of 60 min. Methanol was distilled off in vacuo, and the residue was extracted with two 25-ml portions of ethyl acetate. The organic layer, from which 40% of starting material could be recovered, was extracted with water. The combined water layers were covered with EtOAc, cooled in ice–water, and acidified with H_3PO_4 (10%) to pH 3. The organic phase was decanted, and the water layer was extracted with two volumes of EtOAc. The combined organic layer was dried (Na_2SO_4) and evaporated. The residual oil was dissolved in 15 ml of Et_2O and 15 ml of CH_2Cl_2, cooled in ice–water, and treated with a slight excess of ethereal diazomethane. After chromatography of the mixture over silica gel, using benzene–acetone (97:3) as eluent, three fractions were collected. The first fraction, evaporated to dryness and dissolved in ether, yielded, after standing for several days, 60 mg of crystalline δ-**5**: mp 110–111 °C; TLC (system III) R_f 0.53; $[\alpha]^{22}D$ +1° (*c* 0.5, MeOH); *m/e* 380 (M^+ very weak), 321 ($M - COOCH_3)^+$; ir (KBr) 3330, 1655, 1520 (amide), 1735, 1210-(ester), 725, 695 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 0.83 (s, CH_3), 1.54 (s, CH_3), 3.49 (s, H-3), 3.68 and 3.70 (two s, OCH_3), 3.63 (s, CH_2), 5.15 (dd, *J* = 2.5 and 9.5 Hz, H-6), 5.05 (d, *J* = 2.5 Hz, H-5), 6.32 (d, *J* = 9.5 Hz, CONH), 7.30 (s, C_6H_5). From the third fraction, 80 mg of a crystalline compound was obtained, which was shown by TLC, NMR, and optical rotation to be the enantiomer of 5*R*,6*S*-**5**, and the second fraction consisted of a mixture of these two isomers together with some traces of other isomers of dimethyl benzylpenicilloate. The total yield from the methanolysis of methyl 5-epibenzylpenicillin, as determined by NMR, amounted to about 20% of 5*S*,6*R*-**5** and 20% of the enantiomer of 5*R*,6*S*-**5**, taking into account the 40% of recovered starting material. The formation of the enantiomer of 5*R*,6*S*-**5** during this transformation may be explained by assuming a partial epimerization of 5-epipenicillin methyl ester at position 3 before the hydrolysis took place.[16] By carrying out the reaction in other solvents such as dioxane–water, or by maintaining the pH during hydrolysis at a constant value of 9, 10, or 10.5, lower yields were obtained. Treatment of the 5-epipenicillin ester with diazomethane in methanol–ether for 16 h at room temperature gave only starting material. Dimethyl benzylpenicilloate β isomer of "Chemistry of Penicillin"[17] has mp 113–114 °C and $[\alpha]^{26}D$ +24.5° (*c* 0.5, MeOH). It should be noted that this isomer was obtained by refluxing in toluene the α or γ isomer ("Chemistry of Penicillin" nomenclature), which have a high $[\alpha]D$, and that the product probably was not pure.

B. From Natural Benzylpenicilloic Acid (5*R*,6*R*-11a). The $[\alpha]D$ of the monosodium salt of benzylpenicilloic acid[19–21] fell from 128° to 100° (after 5 h), 60° (after 20 h), 36° (after 40 and 65 h). Monosodium benzylpenicilloic acid (3.35 g) was dissolved in 150 ml of water, and the pH was adjusted to 7 with 2 N NaOH. After standing for 70 h, the solution was cooled in ice–water, and acidified in the presence of 100 ml of EtOAc with H_3PO_4 (20%) to pH 2.6. The EtOAc was decanted, and the water was extracted twice with EtOAc. The combined organic layer was dried (Na_2SO_4) and evaporated. The oily residue was dissolved in Et_2O–CH_2Cl_2 and esterified with diazomethane at 0 °C. The mixture, containing about 70% of the δ isomer, 15% of the α isomer, and 10% of N-methylated penicilloate (based on NMR), was separated by column chromatography over silica gel (50 g), using benzene–acetone (97:3) as eluent. Thus δ-**5** (1.6 g, 42%) was obtained. It has the same NMR spectrum as the product prepared by method A.

Isomerization of γ-4b (5*S*,6*S*-4b) in Acidic Solution. Anhydrous *p*-toluenesulfonic acid[25] (5.1 g, 30 mmol) was added to a solution of 3.9 g (10 mmol) of γ-**4b** in 120 ml of freshly distilled nitromethane. After the mixture was stirred at room temperature for 4 h, the solvent was evaporated, and the oily residue was taken up in CH_2Cl_2 and successively washed with $NaHCO_3$ (5%) and water. The organic layer was dried (Na_2SO_4) and evaporated to an oil, which was taken up in anhydrous ether. After standing for several days, 0.39 g (10%) of colorless crystals were filtered off. The physical constants of this product (melting point, TLC, and NMR) were found to be identical with those of the starting isomer γ-**4b**. Analysis of the filtrate by TLC revealed the presence of at least three different compounds (R_f 0.67, 0.52, and 0.48, system II), which were identified as isomeric dimethyl phthalimidopenicilloates, since the mass spectrum of the mixture was identical with that of pure α or γ isomer. From the NMR spectrum, it was deduced that the mixture, in addition to a small amount (5%) of α-**4b** (R_f 0.67), consisted mainly of β- and γ-**4b** (R_f 0.53 and 0.51, respectively) and of δ-**4b** (R_f 0.48): NMR ($CDCl_3$) δ 1.26 (s, CH_3), 1.55 (s, CH_3), 3.5 (br, NH), 3.75–3.80 (two s, OCH_3), 3.66 (s, H-3), 5.15 (d, *J* = 7 Hz, H-6), 5.58 (d, *J* = 7 Hz, H-5), 7.6–8.0 (m, C_6H_4). Chromatography of the filtrate over silica gel (120 g), using benzene–acetone (98:2) as eluent, yielded 1.8 g (50%) of a mixture of γ-**4b** and β-**4b** in the ratio of 2:3 (by NMR).

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Registry No.—α-**3a**, 1056-69-5; γ-**3a**, 59168-65-9; α-**3b**, 59054-13-6; γ-**3b**, 59054-14-7; β-**4a** HCl, 59121-40-3; α-**4b**, 59054-15-8; β-**4b**, 59054-16-9; γ-**4b**, 59054-17-0; δ-**4b**, 59054-18-1; α-**5**, 57628-09-8; β-**5**, 59054-19-2; γ-**5**, 59054-20-5; δ-**5**, 59054-21-6; γ-**6** HCl, 59054-22-7; β-**7**, 19788-66-0; γ-**8a** HCl, 59054-23-8; γ-**8b**, 59054-24-9; γ-**9**, 59054-25-0; α-**10**, 653-89-4; β-**10**, 21794-95-6; γ-**10**, 59054-26-1; δ-**10**, 59034-27-4; α-**11a**, 493-39-0; sodium benzylpencillin, 69-57-8; benzylpenicilloic acid C-7 methyl ester, 59054-27-2.

References and Notes

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(3) Penicilloates with a phthalimido side chain will be called phthalimidopenicilloates, whereas the compounds with a phenylacetamido side chain will be designated as benzylpenicilloates, according to the nomenclature of "Chemistry of Penicillin".[4]
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Preparation and Isomerization of 5-Epibenzylpenicillins

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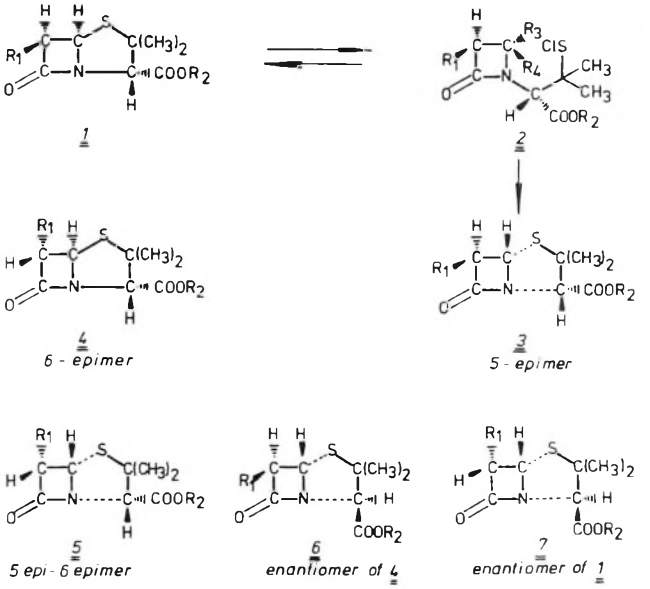
5-Epibenzylpenicillin methyl and benzyl ester were obtained by replacement of the phthalimido side chain of the corresponding 6-phthalimido-5-epipenicillanates, which were prepared from the natural isomer by the method of Kukolja. Base-catalyzed isomerization of silylated 5-epibenzylpenicillin methyl ester in the presence of triethylamine and DBN was investigated. With triethylamine, no epimerization was observed, whereas a mixture of 5 epimer and of the enantiomers of the 6 epimer and natural isomer was obtained when DBN was used as catalyst. These observations, which indicate an epimerization at position 3, are compared with the results of isomerizations of penicillanates with a different configuration and with other side chains. The general mechanism of epimerization of penicillanates is discussed. The antibiotic activity of the sodium salt of 5-epibenzylpenicillin, prepared by hydrogenolysis of the benzyl ester, is less than 0.1% of that observed for natural benzylpenicillin.

In the course of the study of the configuration of the four D-benzylpenicilloates,[1] 5-epibenzylpenicillin was needed. At that moment, only methyl and benzhydryl 6-phthalimido-5-epipenicillanate had been described.[2] Compound **3bx** was prepared by transformation of **1bx** into **2bxv** and **2bxw** by chlorinolysis of the S_1–C_5 bond, and by recyclization of **2bxw** with $SnCl_2$. This method has been applied for the preparation of several 5-epipenicillins having a cyclic or an acyclic imido side chain.[3]

The replacement of the phthalimido side chain by a phenylacetamido group seemed to be impossible in the penicillin series, because treatment with hydrazine causes cleavage of the β-lactam ring.[4] For this reason the procedure of Kukolja[2] was applied to the methyl ester of benzylpenicillin (**1ax**). Treatment of **1ax** with an equivalent amount of chlorine yielded a mixture of 25% of **2axv** and 75% of **2axw** (as determined by NMR). Attempts to cyclize this mixture with $SnCl_2$ gave several compounds of unknown structure but no 5 epimer could be detected. It should be noted that chlorinolysis of the S_1–C_5 bond in benzylpenicillin in the presence of an excess of chlorine has led to an olefinic azetidinone, which has been cyclized to a thiazabicycloheptenone.[5]

This negative result prompted an attempt to remove the phthaloyl group with hydrazine in dimethylformamide, a method which has been used successfully in the cephalosporin series.[6] Application of this procedure to **3bx** gave methyl 6-amino-5-epipenicillanate (**3cx**) in 75% yield. The success of this reaction is probably due to the greater stability of the β-lactam in the 5 epimer, because treatment of **3bx** with hydrazine in dioxane also gave **3cx**, albeit in lower yield, whereas reaction of **1bx** with hydrazine in dimethylformamide still caused cleavage of the β-lactam ring. By reaction of **3cx** with phenylacetyl chloride, 5-epibenzylpenicillin methyl ester (**3ax**) was obtained.

In order to prepare a salt of 5-epibenzylpenicillin, we applied the same scheme to the benzyl ester. Benzyl 6-phthalimidopenicillanate (**1by**), obtained by esterification of 6-phthalimidopenicillanic acid[7] with benzyl bromide in dimethylformamide, was treated with chlorine as described for the methyl ester.[2] The resulting 2-chloro-α-(1-chlorothio-1-methylethyl)-4-oxo-3-phthalimido-1-azetidineacetate was obtained in good yield but it could not be crystallized although it contained practically only the trans isomer (**2byw**). Treatment of this material with $SnCl_2$ afforded **3by** in 85% total yield. Since the presence of water greatly affects the stereoselectivity of the reductive cyclization,[2] it is necessary to perform this step with anhydrous $SnCl_2$ under strictly anhydrous conditions, in order to obtain a high yield of **3by**, because **1by** cannot be separated from the desired isomer **3by** by column chromatography. The presence of appreciable



a. R_1 = $C_6H_5CH_2CONH$ -
b. R_1 = $C_6H_4(CO)_2N$ -
c. R_1 = $Cl^{\ominus}H_3N^{\oplus}$ -
d. R_1 = $C_6H_5OCH_2CONH$ -

x. R_2 = CH_3 -
y. R_2 = $C_6H_5CH_2$ -
z. R_2 = Na

v. R_3 = H, R_4 = Cl
w. R_3 = Cl, R_4 = H

Table I. Optical Rotations and NMR Data[a] for Epimeric Penicillanates

Configuration	Product	^{1}H NMR values 3-H	5-H (J, Hz)	6-H (J, Hz)	$[\alpha]_D$ in acetone	Ref
3*S*,4*S*,5*R*,6*R*	**1ax**	4.37	5.48 (4)	5.64 (4)	+246	10
	1ay	4.40	5.50 (4)	5.61 (4)	+218	*b*
	1bx	4.68	5.60 (4.5)[c]	5.68 (4.5)[c]	+275 +279[d]	11, 12
3*S*,4*S*,5*R*,6*S*	**4ax**	4.44	5.12 (1.8)	5.01 (1.8)	+191	10
	4ay	4.49	5.13 (1.5)	5.03 (1.5)	+149	13
	4bx	4.63	5.57 (2.1)[c]	5.39 (2.1)[c]	+207 +207[d]	11, 12
3*S*,4*R*,5*S*,6*S*	**5ax**	3.78	5.21 (4)	5.51 (4)	−236	1
3*S*,4*R*,5*S*,6*R*	**3ax**	3.69	5.03 (2)	4.78 (2)	−164	*e*
	3ay	3.70	5.00 (2)	4.80 (2)	−119	*e*
	3bx	3.90	5.56 (2)[f]	5.42 (2)[f]	−192[d]	2

[a] In parts per million in $CDCl_3$. [b] E. Roets, unpublished results. [c] Assignment based on deuterium exchange.[12] [d] In chloroform. [e] This publication. [f] Assignment based on the inversion of values of chemical shifts for C-5–C-6 cis relative to C-5–C-6 trans, as observed for the pairs **1ax–4ax**, **1ay–4ay**, **1bx–4bx**, and **5ax–3ax**.

(more than 5%) quantities of **1by** causes difficulties in the next step. The phthaloyl group of **3by** was removed with hydrazine as described for the methyl ester. Benzyl 6-amino-5-epipenicillanate hydrochloride (**3cy**) could not be isolated but it was immediately phenylacetylated. 5-Epibenzylpenicillin benzyl ester (**3ay**) was obtained in a somewhat lower yield (35%) than the methyl ester (60%). Hydrogenation of **3ay** in the presence of Pd/C in methanol–water containing $NaHCO_3$ gave the sodium salt of 5-epibenzylpenicillin (**3az**). Its activity against *Staphylococcus aureus* ATCC 6538P is less than 0.1% of that observed for natural benzylpenicillin. It is not hydrolyzed by penicillinase of *Bacillus cereus*.

Chemical shift values and optical rotations of four epimeric penicillins are shown in Table I. The trans orientation of the protons on C-5 and C-6 in compounds **3** and **4** is indicated by small J values and by a large shielding of the C-6 proton, causing this proton to resonate at higher field than the C-5 proton, while the converse is true for the cis isomers (**1** and **5**). For the two isomers with 5*S* configuration (**3** and **5**) a strong diamagnetic shift of the C-3 proton was observed, which is indicative of a cis relationship between 5-H and 3-H. This effect is also observed for carboxythiazolidine derivatives[8] and for phthalimidopenicilloates.[1]

An attempt was made to calculate the contribution of the different chiral centers to the optical rotation, using a computation method analogous to that used for the isorotation rules of Hudson in the carbohydrate series.[9] The contribution of the centers N-4 and C-5 can be estimated as ±209 by the following calculation:

$$[\alpha]_D \text{ of } \mathbf{1ax} - [\alpha]_D \text{ of } \mathbf{3ax} = 2\,[\alpha]_D \text{ of } 4S,5R = +410$$

$$[\alpha]_D \text{ of } \mathbf{5ax} - [\alpha]_D \text{ of } \mathbf{4ax} = 2\,[\alpha]_D \text{ of } 4R,5S = -427$$

Similar calculations give ±32 for C-6 and ±9 for C-3. In order to check these values, it would be necessary to perform the same calculations for the benzyl esters and for the methyl phthalimidopenicillanates. Only a partial check is possible because only three isomers are available, which gives one pair of epimers. Nevertheless, rather similar values were obtained for the different chiral centers. At any rate, this calculation indicates that the chiral centers N-4 and C-5 provide a predominant contribution to the optical rotation.

In order to extend these calculations, an attempt was made to prepare the fourth isomer of the methyl phthalimidopenicillanates, i.e., **5bx**. It has been shown that penicillins with this side chain can be readily isomerized with base, and in particular, that **1bx** is transformed into **4bx**.[11,14]

Treatment of **3bx** with triethylamine gave only starting product. When **3bx** was treated with a stronger base, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), a large amount of starting material was recovered after a short reaction time, whereas a more prolonged reaction resulted in extensive decomposition. At any rate, compound **5bx** was not obtained from this isomerization, but surprisingly, **6bx**, which is the enantiomer of **4bx**, was isolated from the reaction mixture in a yield of 5–20% depending on the reaction conditions. The preparation of **5bx** was also attempted by chlorinolysis of **4bx**, and ring closure with $SnCl_2$. Again only **4bx** was recovered. All these experiments indicate that phthalimidopenicillanates with hydrogen on C-5 and C-6 in trans configuration, i.e., **3bx**, **4bx**, and **6bx**, are the most favored ones, and that an exo stereochemistry of the C-3 substituent (**6bx**) is preferred to an endo position (**3bx**).

It has also been observed that penicillins with a phenylacetamido side chain can be isomerized with base, provided that the amino group is trimethylsilylated.[10] When **3ax** was silylated with *N,O*-bis(trimethylsilyl)acetamide (BSA) and then treated with DBN for 20 min at room temperature, a mixture of **3ax**, **6ax**, and **7ax** was obtained. Prolonged reaction times (1–5 h) resulted in the disappearance of **3ax**, but also a lower yield was obtained for **6ax** and **7ax**, though they were still present in the same ratio as after a short reaction time. Using triethylamine as base, and a reaction time of up to 50 h, only starting product (**3ax**) was recovered. It should be noted that in no case formation of **5ax** or of 1,4-thiazepine (IV) was observed.

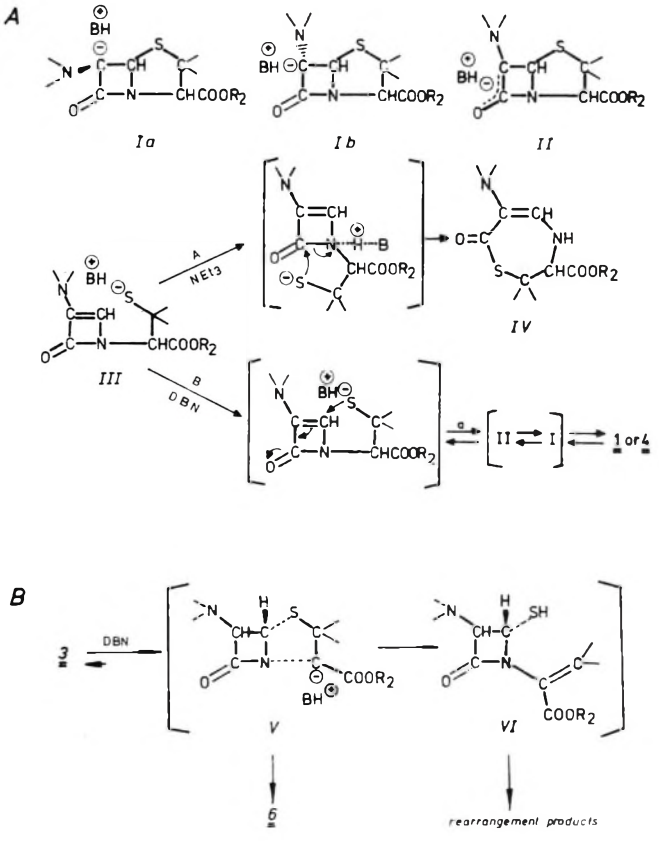
As can be seen in Table II, in which the results of our experiments together with those of other closely related isomerizations are summarized, the behavior of 5-epipenicillin upon base-catalyzed epimerization is clearly different from that of penicillanates having the natural configuration at C-5 (**1** or **4**). Using a strong base like DBN, a penicillin with a phthalimido side chain like **1bx** is transformed almost completely into the 6 epimer **4bx**, whereas a 1:3 ratio of normal to 6 epimer is obtained from a penicillin with a phenyl- (**1ax**) or a phenoxyacetamido (**1dy**) side chain. The strong base causes a fast isomerization, and almost the same equilibrium mixture can be isolated in good yield from either **1** or **4**. Prolonged treatment with DBN results, however, in substantial degradation, and in all cases lower yields of penicillanates are obtained. For these isomerizations, ion pairs Ia and Ib or the enolate II have been proposed as intermediates,[10,14,15] and the free-energy difference between **1** and **4**, which is largely dependent on the nature of the side chain, was considered as the driving force for the predominant formation of 6 epimer or trans isomer. With triethylamine as base, the epimerization

Table II. Base-Catalyzed Isomerization of Penicillanates

Product	Reagent	Reaction conditions[a]	Results	Ref
1bx	NEt_3, 3 equiv	12 h	40% **4bx**, <1% **1bx**, 28% IV	11
		12h	38% **4bx**, ±1% **1bx**, 25% IV	*b*
	DBN, 1 equiv	10 min[c]	82% **4bx**[d,e]	*b*
		1.5 h[c]	50% **4bx**[d,e]	
4bx	NEt_3, 3 equiv	72 h	Large amount **4bx**, 4% IV	11
		240 h	68% **4bx**, 12% IV	11
3bx	NEt_3, 3 equiv	50 h	**3bx** unchanged	*b*
	DBN, 1 equiv	2 min[c]	73% **3bx**, 5% **6bx**[e,f]	*b*
		10 min	14% **3bx**, 18% **6bx**[e,f]	*b*
		1 h	3% **3bx**, 16% **6bx**[e,f]	*b*
1dy	BSA; NEt_3, 5 equiv	24 h	58% (**4dy** + **1dy**) 2:1, 19% IV	10
	BSA; DBN, 1 equiv	10 min	>80% (**4dy** + **1dy**) 3:1	10
4dy	BSA; NEt_3, 5 equiv	24 h	64% (**4dy** + **1dy**) 7:3, 18% IV	10
4dx	BSA; DBN, 1 equiv	10 min	>80% (**4dx** + **1dx**) 3:1	10
1ax	BSA; NEt_3, 5 equiv	24 h	76% (**4ax** + **1ax**) 5:95, 8% IV	*b*
		48 h	60% (**4ax** + **1ax**) 1:5, 25% IV	*b*
	BSA; DBN, 1 equiv	15 min	75% (**4ax** + **1ax**) 3:1[d,e]	*b*
		5 h	20% (**4ax** + **1ax**) 4:1[d,e]	*b*
4ax	BSA; DBN, 1 equiv	10 min	89% (**4ax** + **1ax**) 3:1	10
3ax	BSA; NEt_3, 5 equiv	50 h	>90% **3ax**[e]	*b*
	BSA; DBN, 1 equiv	2 min	>90% **3ax**, ±3% **6ax**[f]	*b*
		20 min	50% **3ax**, 22% **6ax**, 5% **7ax**[e,f]	*b*
		45 min	18% **3ax**, 16% **6ax**, 4% **7ax**[e,f]	*b*
		5 h	<5% **3ax**, 8% **6ax**, 2% **7ax**[e,f]	*b*

[a] In CH_2Cl_2 solution and at room temperature. [b] Results of the present study. [c] Experiment at 0 °C. [d] No compound corresponding to **3** was detected by NMR. [e] No thiazepine IV was detected by TLC. [f] No compound corresponding to **5** was detected by NMR.

is much slower, and an additional compound, 1,4-thiazepine (IV), is formed in an amount increasing with the reaction time. Its formation has been explained by assuming an enethiolate III as a secondary intermediate, produced in a rate-determining step from the initial intermediate I or II by a β-elimination mechanism.



a) only I or II with R-configuration at C-5 are formed in this stereoselective step.

In our opinion this intermediate is probably also formed during the isomerization of **1** or **4** with DBN, although I or II are the predominant intermediate species. We suggest that III, which rearranges by nucleophilic attack on the β-lactam amide to 1,4-thiazepine IV in the presence of triethylamine (pathway A), is not transformed into IV during reaction with a strong base, but leads to degradation products or goes back to penicillanates (pathway B). In this case, the β-lactam amide is not opened by $^-SC(CH_3)_2-$, because the strong base prevents protonation of the bridgehead nitrogen, which is considered to be an essential step for the substitution reaction due to the poor leaving character of an uncharged secondary amine group. Since in no case 5 epimer (**3**) could be detected during the isomerization **1** ⇄ **4**, we also suggest that in pathway B, only penicillanates are produced with natural configuration at C-5, like **1** or **4**. The high stereoselectivity of this addition step may be due to the electrostatic repulsion between S^- and the C-3 carbomethoxy group, forcing the two groups into an anti position before the addition takes place.

In these isomerization reactions, removal of the C-6 hydrogen is considered as the first step, in accordance with the ElcB mechanism proposed by Ramsay and Stoodley.[15] Consequently, since a larger activation energy is expected for the deprotonation at the endo side of the molecule, the epimerization should occur at a slower rate for penicillins with trans-oriented azetidinone protons like **3** and **4**. It can be seen in Table II that this effect is, as anticipated, more pronounced with a weak base like triethylamine than with DBN.

Notable differences of rate of isomerization for **1bx** ⇄ **4bx**, **1dy** ⇄ **4dy**, and **1ax** ⇄ **4ax** under the influence of triethylamine are observed (Table II). They probably are related to the acidity of the C-6 hydrogen, which depends on the structure of the side chain.

We consider that the results obtained for the epimerization of **3ax** or **3bx** are not consistent with the mechanistic scheme as outlined above. In particular, the formation of compounds **6** and **7** upon treatment of **3** with DBN requires the inversion of the configuration of C-3, which, in principle, may be in-

duced by removal of the 3-H atom (V). However, epimerization at position 6 (Ia) which may result in the formation of the 5-epi-6 epimer (**5**), cannot be excluded on the basis of our results, since the absence of compound **5** in the reaction mixture can be explained either by the fact that it is unstable under the reaction conditions used, or that it is not formed as a result of a still larger free-energy difference between **3** and **5** than between **4** and **1**. Since in 5-epipenicillins 3-H has the exo stereochemistry, whereas 6-H as well as the 3 substituent are both at the endo side of the molecule, removal of the 3 hydrogen may become competitive if not preferred to the deprotonation at C-6, although this latter hydrogen is intrinsically more acidic. The negative free-energy difference between **6** and **3**, which is ascribed to the relief of compressional interaction between the C-3 substituent and the azetidinone ring in the process **3** → **6**, is considered as the driving force for the preferential formation of compound **6** upon reprotonation. This isomer, which has the 3*R*,5*S*,6*R* configuration, is the enantiomer of the 6 epimer (**4**) having the 3*S*,5*R*,6*S* stereochemistry, and it is thus expected to undergo base-catalyzed epimerization at position 6, resulting in the formation of compound **7** which is the enantiomer of **1**. In the epimerization of **3ax** with DBN, the isomers **6ax** and **7ax** are obtained in a ratio of 4:1, whereas in the epimerization of methyl 6-phthalimido-5-epipenicillanate (**3bx**) no **7bx** was formed. A similar trend was already mentioned in our discussion of the isomerization **1** ⇄ **4**, where a reduction in the bulkiness of the C-6 substituent also was accompanied with an increase of the 6β isomer in the equilibrium mixture.

Base-induced removal of the 3-H atom of penicillanoyl derivatives has been discussed recently by Stoodley.[18] The deprotonation was considered as the slow step in the formation of a series of rearrangement products involving the resulting secoceph-3-em derivative (VI). In accord with the observation[18] that there was little evidence for the secoceph-3-em → penicillanoyl transformation, we suggest that a deprotonation–reprotonation mechanism via intermediate V is operative in the epimerization of 5-epipenicillins at position 3, and that intermediate VI may account for the substantial loss of material observed during these isomerizations.

It should be noted that the formation of about 20% of the enantiomer of 5*R*,6*S*-D-benzylpenicilloate during basic hydrolysis of 5-epibenzylpenicillin methyl ester[1] may be rationalized in a similar way, by assuming partial epimerization of the 5-epipenicillanate at position 3 before the hydrolysis took place.

Experimental Section

General experimental details are given in the preceding paper.[1] For TLC, the following mobile phases were used: I, C_6H_6–Me_2CO, 80:20; II, *n*-BuOAc–*n*-BuOH–H_2O–MeOH–HOAc, 80:15:24:5:40; III, Me_2CO–HOAc, 95:5.

Benzyl 6-Phthalimidopenicillanate (1by). To a solution of 25 g (72 mmol) of 6-phthalimidopenicillanic acid[7] in 130 ml of dimethylformamide was added 10.1 ml (72 mmol) of freshly distilled triethylamine and 11 ml (90 mmol) of freshly distilled benzyl bromide. The mixture was stirred at room temperature for 4 h and then poured into 700 ml of ice–water under vigorous stirring. The aqueous suspension was extracted with two 250-ml portions of chloroform and the combined organic layer was successively washed with 200 ml of $NaHCO_3$ (1%) and H_2O, dried (Na_2SO_4), and evaporated. The yellow oil was crystallized from 200 ml of ether, yielding 34 g (77%) of **1by**, mp 133–136 °C. Recrystallization from acetone–ether raised the melting point to 138–140 °C; TLC (system I) R_f 0.84; $[\alpha]^{25}D$ +253° (*c* 1, $CHCl_3$); *m/e* 436; ir (KBr) 1780 (β-lactam), 1795, 1730 (phthalimide), 1750, 1210 cm^{-1} (ester); NMR ($CDCl_3$) δ 1.40 (s, CH_3), 1.74 (s, CH_3), 4.62 (s, 3-H), 5.10 (s, $CH_2C_6H_5$), 5.46 (d, *J* = 4 Hz, 5-H), 5.54 (d, *J* = 4 Hz, 6-H), 7.23 (s, C_6H_5), 7.63 (m, C_6H_4).

Benzyl 6-Phthalimido-5-epipenicillanate (3by). Benzyl 6-phthalimidopenicillanate (26.16 g, 60 mmol), dissolved in dry methylene chloride (400 ml) and carbon tetrachloride (200 ml), was treated at room temperature with an equimolecular amount of chlorine (60 mmol, titrated), dissolved in carbon tetrachloride, for 30 min. The solvent was evaporated, and the residual oil was dried over P_2O_5 in a vacuum desiccator for 2 h. From the NMR spectrum it could be deduced that it contained mainly **2byw** with only a small amount of **2byv**. To the dried product, dissolved in anhydrous tetrahydrofuran (200 ml), 12.02 g (62 mmol) of anhydrous[16] $SnCl_2$ was added, and the mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was dissolved in ethyl acetate, washed with three volumes of ice–water, and dried (Na_2SO_4). The product was purified on silica gel using benzene–acetone (95:5) as eluent, and the fractions containing the desired compound were dissolved in benzene and freeze dried, yielding 23.0 g (85.1%) of **3by**: mp 66–68 °C; TLC (system I) R_f 0.82; $[\alpha]^{25}D$ −104° (c 1, $CHCl_3$); *m/e* 436; ir (KBr) 1780 (broad peak, β-lactam and phthalimide), 1725 (broad peak, phthalimide and ester), 1200 cm^{-1} (ester); NMR ($CDCl_3$) δ 1.35 (s, CH_3), 1.60 (s, CH_3), 3.85 (s, 3-H), 5.16 (s, $CH_2C_6H_5$), 5.35 (d, *J* = 2 Hz, 6-H), 5.48 (d, *J* = 2 Hz, 5-H), 7.30 (s, C_6H_5), 7.75 (m, C_6H_4).

Methyl 6-Phthalimido-5-epipenicillanate (3bx). To a suspension of 18 g (50 mmol) of **1bx**[7] in 400 ml of carbon tetrachloride was added 70 ml of a solution of Cl_2 (50 mmol, titrated), in carbon tetrachloride, and the mixture was stirred for 30 min at room temperature. The resulting solution was evaporated to a yellow oil, and upon addition of anhydrous ether 12.47 g (58%) of a crystalline product was recovered. From the NMR spectrum [($CDCl_3$) δ 1.74 (s, two CH_3), 3.88 (s, OCH_3), 4.59 (s, 3-H), 5.55 (d, *J* = 2 Hz, 5-H or 6-H), 6.04 (d, *J* = 2 Hz, 6-H or 5-H), 7.85 (m, C_6H_4)], which is entirely in agreement with the published values,[2] it was established that the crystalline product was the trans isomer **2bxw**. No more crystalline product could be obtained from the residue (36%) obtained by evaporation of the filtrate and which consisted of a mixture of the trans and the cis isomer. The azetidinone **2bxw** (12.47 g, 29 mmol) was treated with anhydrous $SnCl_2$ (6.06 g, 31 mmol) in 200 ml of anhydrous tetrahydrofuran at room temperature for 2 h. Upon concentration of the mixture, a white precipitate formed, which was removed by filtration. The filtrate was evaporated to dryness and the residue crystallized from acetone–ether, yielding 7.81 g (21.7 mmol, 75%) of **3bx**. The residue, obtained before by evaporation of the filtrate, was also treated with $SnCl_2$ and the resulting mixture of **1bx** (R_f 0.79, system I) and **3bx** (R_f 0.72) was separated on silica gel using benzene–acetone (98:2) as eluent. From the fractions containing the desired compound, another 2.47 g of **3bx** was recovered. The total yield for the transformation of **1bx** into **3bx** amounted to 10.28 g (57%). Recrystallization from acetone afforded a pure sample: mp 174–176 °C; TLC (system I) R_f 0.75; $[\alpha]^{25}D$ −182° (*c* 1, $CHCl_3$); ir (KBr) 1780 (β-lactam), 1780, 1715 (phthalimide), 1745 and 1210 cm^{-1} (ester); NMR ($CDCl_3$) δ 1.50 (s, CH_3), 1.70 (s, CH_3), 3.82 (s, OCH_3), 3.90 (s, 3-H), 5.45 (d, *J* = 2 Hz, 6-H), 5.56 (d, *J* = 2 Hz, 5-H), 7.85 (m, C_6H_4). Kukolja[2,3] gives mp 174–175 °C and $[\alpha]D$ −192° ($CHCl_3$).

5-Epibenzylpenicillin Methyl Ester (3ax). To a solution of methyl 6-phthalimido-5-epipenicillanate (2.880 g, 8 mmol) in freshly distilled dimethylformamide (30 ml), cooled to −10 °C, was added 8 ml of a 1 M solution of hydrazine hydrate (0.48 ml in 10 ml) in dimethylformamide. After the mixture was stirred at room temperature for 30 min, the phthalhydrazide complex was decomposed by addition of 9.5 ml of 1 NHCl, and the solvent was evaporated under reduced pressure at 40 °C. The resulting oil was taken up in 30 ml of water under vigorous stirring, and the insoluble phthalhydrazide was removed by filtration, washed, and discarded. The combined aqueous phase was evaporated to an oil and dried over P_2O_5 under vacuum for 2 h. Crystallization from absolute methanol and ether afforded 1.600 g (75%) of the hydrochloride of methyl 6-amino-5-epipenicillanate (**3cx**): mp 157 °C dec; TLC (system II) R_f 0.38; $[\alpha]^{25}D$ −210° (*c* 0.5, MeOH); ir (KBr) 2940 (NH_3^+), 1780 (β-lactam), 1730, 1195 cm^{-1} (ester); NMR (D_2O–DSSA) δ 1.40 (s, CH_3), 1.63 (s, CH_3), 3.76 (s, OCH_3), 4.03 (s, 3-H), 4.70 (d, *J* = 2 Hz, 6-H or 5-H), 5.37 (d, *J* = 2 Hz, 5-H or 6-H). This salt was then N-phenylacetylated by treatment of an ice-cooled suspension of 1.600 g (6 mmol) of **3cx** in 45 ml of anhydrous methylene chloride with 6 ml of a solution containing 2.1 ml of triethylamine in 13 ml of methylene chloride, followed by simultaneous and dropwise addition of 7 ml of the triethylamine solution and of a phenylacetyl chloride solution (1.3 ml in 8.7 ml of methylene chloride). After the addition was complete, stirring was continued for 1 h, and the resulting methylene chloride solution was successively washed with 1 N HCl (50 ml), $NaHCO_3$ 5% (2 × 50 ml), and H_2O (3 × 60 ml). The organic layer was dried (Na_2SO_4) and purified by column chromatography on silica gel using benzene–acetone (97:3) as eluent, yielding after crystallization from ether 1.650 g (79%) of **3ax**: mp 143–145 °C; TLC (system I) R_f 0.52; $[\alpha]^{25}D$ −164° (*c* 0.5, acetone); *m/e* 348 (M^+), 274 [$M - (CH_3)_2CS]^+$;[17] ir (KBr) 3260, 1645, 1530

(amide), 1790 (β-lactam), 1740, 1205 cm^{-1} (ester); NMR ($CDCl_3$) δ 1.38 (s, CH_3), 1.55 (s, CH_3), 3.50 (s, CH_2), 3.69 (s, 3-H), 3.71 (s, OCH_3), 4.78 (dd, J = 2 and 7 Hz, 6-H), 5.03 (d, J = 2 Hz, 5-H), 7.20 (br, –CONH– and C_6H_5).

5-Epibenzylpenicillin Benzyl Ester (3ay). Benzyl 6-phthalimido-5-epipenicillanate (4.36 g, 10 mmol) in 10 ml of dimethylformamide was treated with an equimolecular amount of hydrazine hydrate as described for the methyl ester. Decomposition of the resulting phthalhydrazide complex with 1 N HCl (11 ml) could not yield crystalline **3cy.** The product was immediately transformed to the *N*-phenylacetyl derivative by reaction with phenylacetyl chloride in the presence of triethylamine. The reaction product was purified by column chromatography on silica gel using benzene–acetone (97:3) as eluent, and crystallized from CCl_4 or from benzene–ether, yielding 1.3 g (30.6%) of **3ay:** mp 90–91 °C; TLC (system I) R_f 0.68; $[\alpha]^{25}D$ −119° (c 1, acetone); *m/e* 424 (M^+), 350 $[M - (CH_3)_2CS]^+$;[17] ir (KBr) 3320, 1650, 1520 (amide), 1770 (β-lactam), 1745 and 1200 cm^{-1} (ester); NMR ($CDCl_3$) δ 1.30 (s, CH_3), 1.52 (s, CH_3), 3.50 (s, CH_2CO), 3.70 (s, 3-H), 4.80 (dd, J = 2 and 7 Hz, 6-H), 5.00 (d, J = 2 Hz, 5-H), 5.13 (s, $CH_2C_6H_5$), 6.60 (d, J = 7 Hz, NHCO), 7.20 (s, $C_6H_5CH_2CO$–), 7.25 (s, $C_6H_5CH_2O$–).

5-Epibenzylpenicillin Sodium Salt (3az). A solution of **3ay** (200 mg, 0.47 mmol) in 5 ml of distilled water and 20 ml of methanol, containing 1 equiv of $NaHCO_3$ (39.5 mg), was hydrogenated over 10% Pd/C (200 mg) for 3 h at room temperature and at a pressure of 3.5 kg/cm^2. The catalyst was filtered off, and the methanol was evaporated. After addition of water (10 ml) and ethyl acetate (20 ml), the mixture was acidified to pH 3 with 0.1 *N* HCl. The layers were separated, and the water was extracted twice with ethyl acetate. The combined organic layer was washed with H_2O (20 ml), and after addition of 40 ml of H_2O adjusted to pH 6.8 with 0.1 *N* NaOH. The aqueous layer was freeze dried, yielding 0.100 g (60%) of the sodium salt of 5-epibenzylpenicillin: mp 136–138 °C; TLC (system III) R_f 0.56; $[\alpha]^{25}D$ −108° (c 1, H_2O); ir (KBr) 3280, 1660, 1540 (amide), 1750 (β-lactam), 1390 cm^{-1} (carboxylate); NMR (D_2O–DSSA) δ 1.44 (s, CH_3), 1.57 (s, CH_3), 3.63 (s, 3 protons, 3-H and CH_2–), 4.82 (d, J = 2 Hz, 6-H or 5-H), 5.10 (d, J = 2 Hz, 5-H or 6-H), 7.31 (s, C_6H_5).

Anal. Calcd for $C_{16}H_{17}N_2O_4SNa$: C, 53.91; H, 4.80; N, 7.86. Found: C, 53.64; H, 4.75; N, 7.61.

As in the case of 6-epibenzylpenicillin,[10] no hydrolysis was observed when sodium 5-epibenzylpenicillin was treated with an aqueous penicillinase solution (Penase Leo Lot 80096) at pH 7.

Epimerization of 5-Epibenzylpenicillin Methyl Ester (3ax). A solution of **3ax** (0.696 g, 2 mmol) in anhydrous methylene chloride (5 ml) was treated with BSA (1.2 ml, 5 mmol), and stirred for 100 min at room temperature under an atmosphere of nitrogen. The reaction mixture was cooled to 0 °C, DBN (0.24 ml, 2 mmol) was added, and stirring was continued for 20 min at room temperature. The solution was then poured into a mixture of ice–water (10 ml) and 1 N HOAc (2 ml), and shaken for 5 min. The layers were separated, the aqueous phase was extracted with two volumes of methylene chloride, and the combined organic layer was washed with H_2O and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel (15 g) using benzene–acetone (97:3) as eluent. A first fraction of the eluate consisted of a mixture (50 mg) of two isomers, which were found by TLC and NMR to be identical with natural (R_f 0.64) and 6-epibenzylpenicillin methyl ester (R_f 0.62) in a ratio 7:3 (NMR). The $[\alpha]D$ of this mixture was −194°. From the second fraction of the eluate 0.140 g (20%) of 6-epibenzylpenicillin methyl ester was obtained as a crystalline product after treatment with ether. The $[\alpha]^{25}D$ −184° (c 1, acetone) indicated that this product was the enantiomer of 6-epibenzylpenicillin methyl ester with structure **6ax.** As the $[\alpha]D$ of the mixture from the first eluate is more levorotatory, it must be concluded that natural penicillin methyl ester (with $[\alpha]D$ +246°) is not present, but also must be the enantiomer with structure **7ax.** From the third fraction of the eluate 0.350 g (50%) of the starting product **3ax** (R_f 0.52) was recovered. When the reaction with DBN was carried out for 45 min, only 18% of starting material **3ax,** 16% of **6ax,** and 4% of **7ax** were recovered, and after a reaction time of 5 h, the yields of **7ax** and **6ax** were only 2 and 8%, respectively. More than 90% of **3ax** was recovered unchanged after a reaction time of 2 min with DBN, or after 50 h with 5 equiv of triethylamine as base.

Epimerization of Benzylpenicillin Methyl Ester (1ax). Solutions of **1ax**[10] (0.696 g, 2 mmol) in anhydrous methylene chloride (5 ml) were treated with BSA (1.2 ml, 5 mmol) for 2 h at room temperature. The silylated penicillanate was then isomerized with DBN (1 equiv) for 15 min and for 5 h, or with triethylamine (5 equiv) for 24 and 48 h. The reaction mixtures were worked up as described for the 5 epimer, and were analyzed by NMR after purification by column chromatography on silica gel using benzene–acetone (98:2) as eluent. The results are collected in Table II.

Epimerization of Methyl 6-Phthalimidopenicillanate (1bx) and Its 5 Epimer (3bx). Methyl 6-phthalimidopenicillanate (**1bx,** 0.360 g, 1 mmol) was dissolved in anhydrous methylene chloride (5 ml) and treated with DBN (0.12 ml, 1 mmol) at 0 °C for 10 min and for 90 min. After the mixtures were worked up, **4bx** was obtained in a crystalline state from methanol in a yield of 82 and of 50%, respectively. Similarly, methyl 6-phthalimido-5-epipenicillanate[2] (**3bx**) was isomerized with DBN and with triethylamine. The reaction mixtures were worked up and separated by column chromatography on silica gel. The results, which are collected in Table II, were based on optical rotation, TLC, and NMR spectroscopy. Compound **6bx,** which was isolated from the epimerization mixture with DBN, was identified as the enantiomeric form of the 6 epimer **4bx,** since all physical constants (TLC, NMR, ir, *m/e*) except the optical rotation, which was negative [$[\alpha]^{25}D$ −199 (c 1, acetone)], were identical with those of **4bx.**

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Registry No.—**1ax,** 653-89-4; **1bx,** 19788-65-9; **1by,** 59034-26-3; **2bxw,** 34734-72-0; **3ax,** 59034-27-4; **3ay,** 59034-28-5; **3az,** 59034-29-6; **3bx,** 34716-53-5; **3by,** 59034-30-9; **3cx,** 59034-31-0; 6-phthalimidopenicillanic acid, 20425-27-8; benzyl bromide, 100-39-0.

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Liquid Crystals. 6. Mesomorphic Phenols and Primary Amines. *p*-Phenylene Dibenzoates with Terminal Hydroxy and Amino Groups[1]

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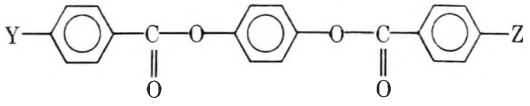
Liquid crystalline phenols and aromatic primary amines are rare, apparently because their characteristic intermolecular hydrogen bonding gives rise to melting points above the mesophase–isotropic liquid transition temperature and to nonlinear molecular associations in the liquid state. Therefore, the discovery that *p*-phenylene dibenzoates (1) with terminal OH or NH_2 groups are generally mesomorphic was unexpected. Six amines, five phenols, and the aminophenol of this molecular system were synthesized and found to exhibit nematic mesomorphism. Two of these, the diphenol and aminophenol, also form smectic mesophases. Evidence is presented to support the following explanation of this unusual behavior. Superimposed on a rigid, rod-shaped, polar molecule that is already predisposed to mesomorphism, electron donation by the terminal OH or NH_2 to the ester carbonyl with which it is conjugated produces extremely high molecular polarity. Powerful dipolar intermolecular attractive forces result, and provide a very stable mesophase when the compound melts. Within the well-ordered parallel molecular alignment of the mesophase, hydrogen bonding is no longer a detriment to mesomorphism and may, in fact, enhance it.

The molecular structural criteria for mesomorphism (liquid crystallinity)[3-6] are rigidity, rod shape, and polarity. However, most phenols and aromatic primary amines that satisfy these criteria fail to exhibit mesomorphism. An earlier communication[7] briefly described the preparation and properties of *p*-phenylene di-*p*-aminobenzoate, **1** (Y = Z = NH_2), and *p*-phenylene di-*p*-hydroxybenzoate, **1** (Y = Z = OH), both of which are mesomorphic, and claimed that these



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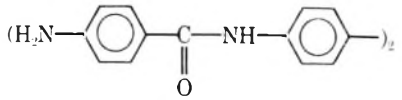
were the first examples of a liquid crystalline primary amine and phenol that are incapable of intramolecular hydrogen bonding. A more thorough literature search has since revealed this claim to be in error. At least two other such primary amines (**2**[8a] and **3**[8b]) and another such phenol (**4**[9]) have been reported. Also, the diamine, **1** (Y = Z = NH_2), believed by us



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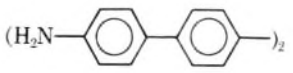

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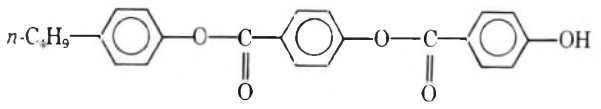

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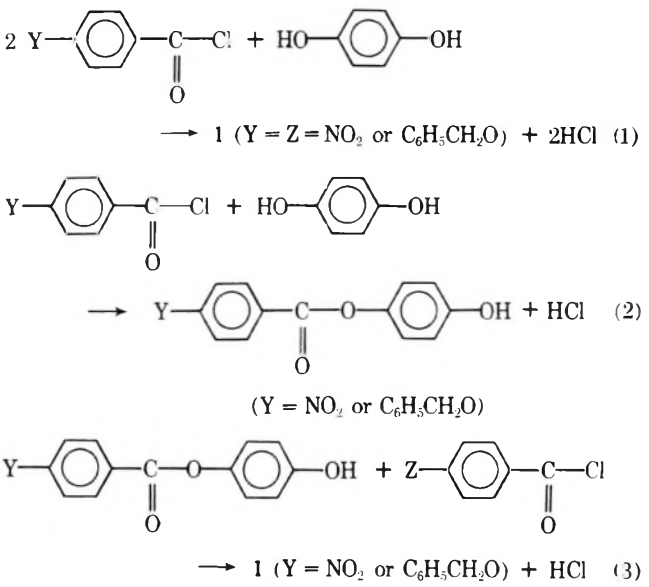
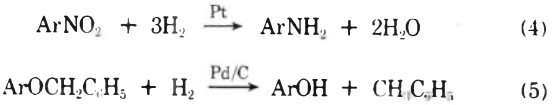
to be a new compound, had been described earlier in a patent[10] as an intermediate for the preparation of poly (ester imides). Nonetheless, the list is short, and it remains true that mesomorphism of these types of compounds is unusual. Gray[11] has proposed that this rarity is associated with intermolecular hydrogen bonding raising the melting point above the mesophase–isotropic liquid transition temperature, and perhaps also encouraging a nonlinear molecular arrangement that is incompatible with mesophase formation. Whatever the negative factors, it is clear that they are overcome in certain instances. Since we had discovered two examples of such behavior among the *p*-phenylene dibenzoates (**1**), it was decided to prepare additional phenolic and primary amino derivatives of this molecular system to see if they, too, are mesomorphic.

As intermediates, esters of type **1** with terminal nitro or benzyloxy groups were synthesized as in eq 1–3. The nitro



groups were then reduced to NH_2 and the benzyloxy groups converted to OH by hydrogenolysis as in eq 4 and 5. The intermediates and the final products were examined with a hot



stage polarizing microscope and, with only one exception, were found to be mesomorphic. These results are further evidence of the strong tendency of the *p*-phenylene dibenzoates (**1**) to be mesomorphic,[12] and show that, for this molecular system at least, there is little antagonism between the presence of a phenolic OH or an aromatic NH_2 group and the ability to form a mesophase.

Experimental Section

Para-Substituted Benzoic Acids. *p*-Benzyloxybenzoic acid was obtained in 64% yield by a Williamson type reaction of ethyl *p*-hydroxybenzoate with benzyl chloride, hydrolysis of the resulting ethyl *p*-benzyloxybenzoate in ethanolic KOH solution, and acidification with HCl,[13] mp 193 °C (from ethanol).[14] The methyl, *n*-hexyloxy, and chloro acids were purchased.

Benzoyl Chlorides. Benzoyl, *p*-anisoyl, and *p*-nitrobenzoyl chlorides were commercial products. The others were obtained from the corresponding acids by treatment with thionyl chloride.

Table I. *p*-Phenylene Dibenzoates (1)[a]

Registry no.	Y	Z	Recrystn solvent	Yield, %	Transition temp, °C Mp	N–I
59138-51-1	NO_2	H	Dioxane	98	231	(209)[b]
59138-52-2	NO_2	CH_3	Dioxane–ethanol	68	211	276
59138-53-3	NO_2	CH_3O	Dioxane	98	200[c]	300.5[c]
59138-54-4	NO_2	n-$C_6H_{13}O$	Ethanol	79	167	255.5[d]
59138-55-5	NO_2	Cl	Dioxane–ethanol	92	202	270
59138-56-6	NO_2	$C_6H_5CH_2O$	Dioxane–ethanol	41	211.5	284.5 dec
59138-57-7	$C_6H_5CH_2O$	H	Benzene	74	175	177
59138-58-8	$C_6H_5CH_2O$	CH_3	Benzene	95	197.5	247
59138-59-9	$C_6H_5CH_2O$	CH_3O	Dioxane	94	177.5	279.5
59138-60-2	$C_6H_5CH_2O$	n-$C_6H_{13}O$	Dioxane–ligroin	67	145	233
53201-63-1	$C_6H_5CH_2O$	$C_6H_5CH_2O$	Chloroform	72	233	260
59138-61-3	NH_2	H	Dioxane	89	239	*e*
59138-62-4	NH_2	CH_3	Dioxane	86	228.5	240
59138-63-5	NH_2	CH_3O	Dioxane	79	212.5	277.5
59138-64-6	NH_2	n-$C_6H_{13}O$	Dioxane	92	191	207
59138-65-7	NH_2	Cl	Ethanol	17	191	246
59138-66-8	NH_2	$C_6H_5CH_2O$	Dioxane–ligroin	70	221, 202.5, 174[f]	251
22095-98-3	NH_2	NH_2	Dioxane	94	323[g]	>360 dec
59138-67-9	OH	H	Dioxane	95	258	>355 dec
59138-68-0	OH	CH_3	Dioxane–ligroin	94	220.5	>355 dec
59138-69-1	OH	CH_3O	Dioxane	97	219	>355 dec
59138-70-4	OH	n-$C_6H_{13}O$	Ethanol–water	18	175	>310 dec
59138-71-5	OH	NH_2	Dioxane	83	304.5	>308[h]
53201-62-0	OH	OH	Dioxane	66	328 dec[i]	>360[h]

[a] Satisfactory analytical data (±0.4% for C, H, N for the amines, and Cl for the chloroamine) were reported for all new compounds listed in the table. [b] Monotropic transition observed on supercooling the isotropic melt. [c] Lit.[19] values: mp 200.2 °C, N–I transition temperature 300.2 °C. [d] There is also a Sm–N transition at 210 °C. [e] Not mesomorphic. [f] Polymorphic. [g] Lit.[10] mp 310 °C. [h] A focal-conic texture, indicating smectic mesomorphism, develops at varying temperatures on cooling the melt. The maximum temperature at which its appearance has been noted is ca. 300 °C. In other determinations, it was observed to appear (and to disappear again on heating) at much lower temperatures. [i] This melting point was reported earlier[7] to be 340 °C, but has been found to vary with heating rate. The 328 °C figure is an average from five determinations, and is in good agreement with the differential scanning calorimeter value of 327 °C at a heating rate of 20 °C/min.

***p*-Hydroxyphenyl Benzoates.** *p*-Hydroxyphenyl *p*-nitrobenzoate was prepared in 57% yield by overnight reaction of *p*-nitrobenzoyl chloride (practical grade) and a fivefold molar excess of hydroquinone in pyridine solution at room temperature,[15] followed by precipitation in water,[12] mp 199 °C (from ethanol) (lit.[16] 193.5 °C). Anal. Calcd for $C_{13}H_9NO_5$: C, 60.24; H, 3.50. Found: C, 60.14; H, 3.50.

p-Hydroxyphenyl *p*-benzyloxybenzoate was obtained in 64% yield by the same general procedure, but with *p*-benzyloxybenzoyl chloride and at reflux temperature. Reaction at room temperature gave a yield of only 21% and purification of the product was difficult, mp 210 °C (from ethanol). Anal. Calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 74.88; H, 4.95.

***p*-Phenylene Dibenzoates with Terminal Nitro and Benzyloxy Groups.** The general procedure for the preparation of *p*-hydroxyphenyl benzoates was used for synthesis of these compounds also. The symmetrically substituted esters, 1 (Y = Z = NO_2) and 1 (Y = Z = $C_6H_5CH_2O$), were obtained from the appropriate acyl chloride and hydroquinone. The former, a known compound,[10,12,17] was produced in good yield at room temperature. However, the latter required reaction at reflux, reflecting the low reactivity of *p*-benzyloxybenzoyl chloride (see previous paragraph).

Unsymmetrically substituted esters were prepared from ArCOCl and *p*-hydroxyphenyl *p*-benzyloxybenzoate or *p*-nitrobenzoate. Here again, a difference in reactivity was observed. The nitrophenol reactions proceeded satisfactorily at room temperature, whereas the benzyloxyphenol required refluxing. The ester, 1 (Y = NO_2; Z = $C_6H_5CH_2O$), could have been made either from unreactive benzyloxyphenol and nitrobenzoyl chloride or from unreactive benzyloxybenzoyl chloride and nitrophenol. This dismal choice was decided by the better availability of the nitrophenol at the time.

The esterifications were run overnight or longer, and 1.5–3 mol of ArCOCl per mole of phenolic OH was used. A high molar ratio improves yields, but also encourages the formation of by-product acid anhydride during the aqueous precipitation step.[18,19] E.g., *p*-benzyloxybenzoyl chloride (18.0 mmol) and *p*-hydroxyphenyl *p*-nitrobenzoate (6.00 mmol) in 60 ml of dry pyridine (room temperature, 42 h) gave 2.47 mmol (41%) of the desired ester, 1 (Y = $C_6H_5CH_2O$; Z = NO_2). In addition, there were recovered 4.04 mmol of *p*-benzyloxybenzoic acid, mp 193, 187.5 °C (by acidification of the aqueous pyridine filtrate), and 5.50 mmol of *p*-benzyloxybenzoic anhydride, mp 117 °C (lit.[20] 119 °C), ir (KBr) 1760 and 1719 (C=O doublet), 1057 cm^{-1} (C–O–C stretch) (from recrystallization of the crude ester). We have not found anhydride by-products to be a serious problem since they are more soluble than the esters and, therefore, are easily removed by recrystallization.

Further results are summarized in Tables I and II.

Table II. Infrared Spectra of *p*-Phenylene Dibenzoates (1)[a]

Y	Z	Absorption bands, cm^{-1} C=O stretch	N–H or O–H stretch
CH_3O	CH_3O	1723	
$C_6H_5CH_2O$	n-$C_6H_{13}O$	1730	
Cl	NO_2	1735	
NH_2	NH_2	1703	3480, 3433, 3380, 3360
NH_2	H	1699, 1732	3479, 3380
NH_2	CH_3	1701, 1733	3476, 3378
NH_2	CH_3O	1710–1730[b]	3462, 3438, 3374
NH_2	n-$C_6H_{13}O$	1698, 1728	3477, 3379
NH_2	$C_6H_5CH_2O$	1697, 1730	3458, 3364
NH_2	Cl	1702, 1738	3472, 3374
OH	NH_2	1700–1710[b]	3382
OH	OH	1700	3390
OH	H	1710, 1733	3438
OH	CH_3	1712, 1731	3420–3440[b]
OH	CH_3O	1710, 1728	3420
OH	n-$C_6H_{13}O$	1702, 1732	3421

[a] KBr pellet. [b] Broad band.

p-Phenylene Dibenzoates with Terminal Amino Groups. These were obtained by low pressure hydrogenation of the corresponding nitro esters over platinum catalyst in dioxane. Typically, 7 mmol of the nitro compound, 300 ml of dioxane that had been recently distilled from sodium metal, 0.2 g of PtO_2, and an initial H_2 pressure of 25 psig were used. The mixture was shaken at room temperature until the theoretical pressure drop occurred, and the product was recovered by filtration, distillation of dioxane from the filtrate, and recrystallization of the residue from an appropriate solvent.

In the preparation of 1 (Y = Z = NH_2), neither the starting dinitro ester nor the product was completely soluble in the dioxane, but the reaction proceeded smoothly. The insoluble portion of the product was separated from catalyst by extraction with hot dioxane.

Two of the reductions gave by-products that were difficult to separate from the desired amines. Both appear to have been the result of incomplete hydrogenation. In the synthesis of 1 (Y = Cl; Z = NH_2), the material was a solid with a metallic lustre that was insoluble in all common solvents. We have identified it as di-*p*-(*p*-chlorobenzoyloxy)phenyl *p*-azoxybenzoate (**5**): mp 315.5 °C; nematic–isotropic (N–I) transition temperature >322 °C dec (from aniline); ir (KBr) 1735 (ester C=O), 1303 (N–O in –N=NO–), 1089 cm^{-1} (ArCl). Anal. Calcd for $C_{40}H_{24}N_2O_9Cl_2$: C, 64.27; H, 3.24; N, 3.75; Cl, 9.49. Found: C, 64.25; H, 3.14; N, 3.78; Cl, 9.41. Hydrolysis in ethanolic KOH followed by acidification gave *p*-chlorobenzoic acid, mp 240.5 °C (after two vacuum sublimations) (lit. 239.7,[21] 241.5 °C[22]), and another acid that was insoluble in common organic solvents with the exception of pyridine, did not melt at 380 °C but gave an orange sublimate at ca. 280 °C. This behavior is consistent with the reported properties of *p*-azoxybenzoic acid.[23] In the preparation of 1 (Y = $C_6H_5CH_2O$; Z = NH_2), the by-product was also a relatively insoluble solid, mp 256 °C, N–I transition temperature >308 °C dec (from nitrobenzene). The compound has not been identified, but there is evidence that it, too, contains an unreduced N–O bond (C, H, and N contents are below those of the amine and the yield of by-product decreases with increasing hydrogenation time).

Other results are presented in Tables I and II.

p-Phenylene Dibenzoates with Terminal Hydroxy Groups. The phenolic esters were synthesized by low pressure hydrogenolysis of the corresponding benzyloxy compound over a palladium catalyst in dioxane.[24,25] For a typical run, 2 mmol of the benzyloxy ester, 300 ml of dioxane (freshly distilled from sodium), 0.3 g of 5% Pd on charcoal, and an initial H_2 pressure of 25 psig were used. The mixture was shaken at room temperature overnight and worked up as described above for hydrogenations of nitro esters. The only hydrogenolysis that did not go well was that of 1 (Y = $C_6H_5CH_2O$; Z = *n*-$C_6H_{13}O$), which apparently contained a catalyst-poisoning contaminant. Three runs, with spent catalyst removed and fresh catalyst added each time, served only to improve the quality of recovered starting material. The fourth run gave a low (18%) yield of the desired phenol.

1 (Y = Z = OH) was first prepared by tetrazotization of 1 (Y = Z = NH_2) followed by hydrolysis.[7] This method was abandoned when it was found that extensive hydrolysis of ester linkages occurs as a side reaction. The hydroquinone produced in the hydrolysis complexes with the desired phenolic ester. The 1:1 complex with 1 (Y = Z = OH) was isolated as rod-shaped plates: mp 249.5 °C; ir (KBr) 3470 and 3390 (aromatic OH), 3080 and 3050 (aromatic C–H), 1713 cm^{-1} (ester C=O). Anal. Calcd for $C_{26}H_{20}O_8$: C, 67.82; H, 4.38. Found: C, 67.71; H, 4.28. On heating the material above its melting point, there was heavy sublimation, leaving a residue of crude 1 (Y = Z = OH), mp 313.5 °C (to nematic liquid), appearance of focal-conic smectic texture at 235 °C.

Demethylation of 1 (Y = Z = OCH_3) with BBr_3, $AlCl_3$, or $AlBr_3$ was also explored. The first two reagents gave low-melting solids that were not mesomorphic, while $AlBr_3$ gave very poor yields of a solid: mp 333 °C; N–I transition temperature >339 °C; crystallization temperature 212 °C; ir (KBr) 3395 (aromatic OH), 2930 (aliphatic C–H), 1700 cm^{-1} (ester C=O). This product resembles 1 (Y = Z = OH) in melting behavior except that it does not display a smectic mesophase. The ir spectrum indicates that Friedel–Crafts ring methylation occurred via the CH_3Br formed in the ether cleavage and the $AlBr_3$.

The remaining results are summarized in Tables I and II.

Apparatus. Transition temperatures were determined with a Reichert Thermopan polarizing microscope equipped with a Kofler micro hot stage. Calorimetric measurements were taken with a Perkin-Elmer differential scanning calorimeter, Model DSC-1 B. Both instruments were calibrated against pure substances having known melting points. Ir spectra were measured on a Perkin-Elmer grating ir spectrophotometer, Model 457. Hydrogenations and hydrogenolyses were run in a Parr Series 3910 hydrogenation apparatus.

Analyses. Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Results and Discussion

For the most part, the syntheses of the amines and phenols went well. In the preparation of the intermediate nitro- and benzyloxy-substituted type 1 esters by reaction of an aroyl chloride and a phenol in pyridine solution (eq 1–3), it was found that a benzyloxy group on either the acid chloride or the phenol has a deactivating effect. For these compounds, good yields were obtained only by operating at reflux, whereas their nitro-substituted counterparts reacted readily at room temperature. High molar ratios of acid chloride to phenol gave improved yields, but also resulted in anhydride formation during precipitation of the reaction mixtures in water (eq 6 and 7). The anhydrides were easily removed from the desired

$$\mathrm{ArCOCl} + \mathrm{H_2O} \xrightarrow{\text{pyridine}} \mathrm{ArCOOH} + \mathrm{HCl} \quad (6)$$

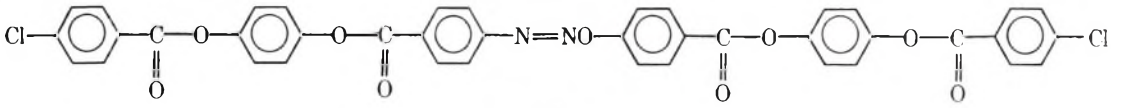
$$\mathrm{ArCOCl} + \mathrm{ArCOOH} \xrightarrow{\text{pyridine}} (\mathrm{ArCO})_2\mathrm{O} + \mathrm{HCl} \quad (7)$$

esters by recrystallization. All of the intermediate esters are mesomorphic (Table I).

The reductions of nitro esters to amino esters with hydrogen over platinum catalyst (eq 4) went smoothly with the exception of the reaction leading to 1 (Y = NH_2; Z = Cl), which gave a low yield (17%) because of great difficulty in separating a by-product that proved to be the azoxy compound **5**. An incompletely reduced by-product (unidentified) was also formed in smaller amount during the synthesis of 1 (Y = $C_6H_5CH_2O$; Z = NH_2). Catalyst selectivity was displayed in this synthesis, too, in that 1 (Y = $C_6H_5CH_2O$; Z = NO_2) was reduced to the amine in 70% yield with no apparent hydrogenolysis of the benzyloxy group.

The hydrogenolyses of benzyloxy-substituted esters to phenols over palladium on charcoal (eq 5) proceeded nicely, again with one exception. The ester 1 (Y = $C_6H_5CH_2O$; Z = *n*-$C_6H_{13}O$) stoutly resisted repeated attempts at hydrogenolysis, but finally gave a low yield of phenol on the fourth try.

Of the seven amines, five phenols, and the "hybrid" aminophenol, 1 (Y = OH; Z = NH_2), that were prepared, only 1 (Y = NH_2; Z = H) failed to exhibit mesomorphism (Table I). Furthermore, the relatively high N–I transition temperatures of the liquid crystalline amines and phenols show that their nematic mesophases are very stable. This is particularly noteworthy for the diamine and the phenols, the mesophases of which decompose thermally at temperatures over 300 °C without undergoing transition to isotropic liquid. If one uses the N–I point as a measure of "group efficiency" in promoting nematic mesomorphism in system 1,[12,19] the OH end group is unsurpassed and NH_2 is exceeded by only a few others. E.g., for 1 (Y = CH_3O; Z = variable), the N–I transition temperatures for various Z's decrease in the order OH > CN > CH_3O $\simeq$ NO_2 > NH_2 $\simeq$ Cl $\simeq$ Br > CH_3 > F > CF_3 > H. The heat of transition is a still better criterion for mesophase stability since it is a direct measure of the energy required to disrupt the ordered nematic molecular "lattice". Dewar and Griffin[19] have determined N–I transition enthalpies for esters of the type 1 (Y = CH_3O; Z = variable). From these data, they calculated ΔS_{N-I} and found a correlation between the ΔH and ΔS values which implies that molecular order in the nematic mesophase is closely related to the strength of intermolecular association for this series. Unfortunately, we could not determine ΔH_{N-I} for the hydroxy ester because it decomposes before the transition temperature is reached. However, the amino ester, 1 (Y = CH_3O; Z = NH_2), gave ΔH_{N-I} = 0.324 kcal/mol, from which was calculated ΔS_{N-I} = 0.589 eu. These values place NH_2 relative to other Z groups as follows: ΔH_{N-I} CH_3O, 0.408 > CH_3, 0.387 > NH_2, 0.324 > Cl, 0.282 > Br, 0.248 > F, 0.244 > CN, 0.228 > NO_2, 0.192 > H, 0.158; ΔS_{N-I}



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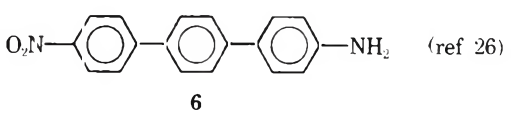
CH_3, 0.713 > CH_3O, 0.711 > NH_2, 0.589 > Cl, 0.511 > F, 0.466 > Br, 0.451 > CN, 0.383 > H, 0.355 > NO_2, 0.334. Presumably, OH would occupy a position no lower than that of NH_2 in both lists. Again, these results indicate that NH_2 (and, by inference, OH) as an end group in **1** produces highly stable, well-ordered nematic mesophases.

Since mesomorphic primary amines and phenols are rare, we sought an explanation of why system **1** is so apparently well suited to produce them. Gray's proposal[11] (mentioned in the introduction) that intermolecular H bonding is responsible for their scarcity is reasonable and has experimental support. Listed below on the left are a primary amine and several phenols that do not exhibit mesomorphism. Opposite them, on the right, are closely related mesomorphic compounds in which intermolecular H bonding through NH_2 or OH has been reduced by the opportunity for intramolecular H bonding (**9** and **10**), by substitution of aliphatic OH for phenolic OH (**11**), or has been eliminated completely by etherification of phenolic OH (**12** and **13**).

Not mesomorphic



(ref 26)

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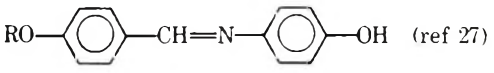

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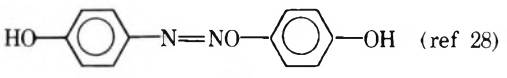

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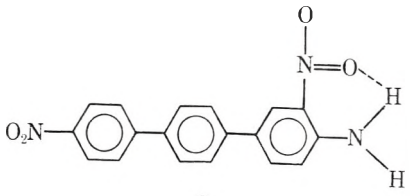
8

Mesomorphic



(ref 26)

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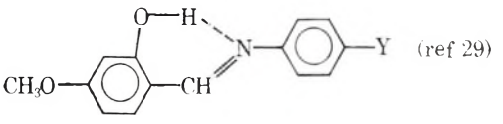
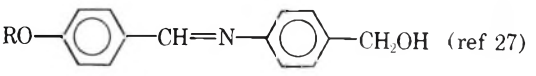


(ref 29)

10

(Y = CN, Ph, CH=CH_2, *n*-C_4H_9)



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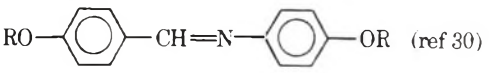
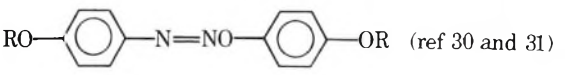


(ref 30)

12



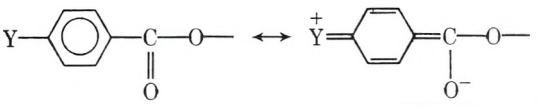
(ref 30 and 31)

13

(R = CH_3, C_2H_5, and *n*-alkyl)

The N–H and O–H stretch bands from the ir spectra of the amines and phenols of this study are presented in Table II. For the amines, with the exception of the aminophenol **1** (Y = OH; Z = NH_2), there are free (not H bonded) NH_2 bands in the 3430–3480-cm^{-1} region, but no evidence of free OH (3590–3650 cm^{-1}) in the phenols. Bands at 3360–3380 cm^{-1} for N–H and at 3380–3440 cm^{-1} for O–H show that there is H bonding in all of the compounds. It seems safe to assume that this is intermolecular in light of the high melting points (Table I) and because an extended conformation of the ester molecules, precluding intramolecular H bonding, is the only one consistent with the observed mesomorphism. Thus, if Gray's hypothesis is correct, as it appears to be, amines and phenols of type **1** must possess some special feature or features whereby they exhibit mesomorphism in spite of intermolecular H bonding.

The three rigid, polarizable phenylene rings are undoubtedly helpful, this group having been clearly demonstrated to encourage mesomorphism,[32] as are the two carbonyl groups with their dipoles crosswise to the long molecular axis, providing lateral intermolecular attractive forces.[33] However, the most important special feature appears to be conjugation of the terminal OH or NH_2 group with C=O through the intervening phenylene ring. Returning to the ir spectral data in Table II, the C=O stretch band frequencies conform very well with the views of Dewar et al. concerning the effects of end groups on this bond in system **1**.[17,19] Their suggestion is that an electron-releasing end group conjugated with the ester carbonyl results in a significant contribution by structure **14**,

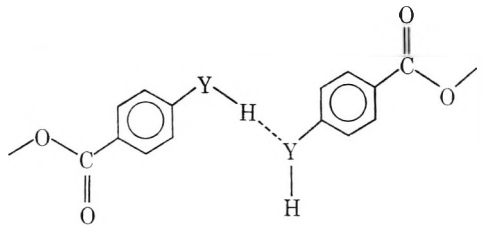


14

whereas an electron-withdrawing group has little effect on C=O. If this is correct, there should be a shift in the carbonyl absorption band to lower frequency on replacement of an electron-withdrawing by an electron-releasing end group owing to the decreased double bond character of the C–O bond. This is exactly what we observed. Starting with the electron-withdrawing end groups, Cl and NO_2, and proceeding to the moderately electron-releasing alkoxy substituents, the

band shifts from 1735 cm^{-1} to 1723–1730 cm^{-1}. For the more potent electron releasers, NH_2 and OH, the band is shifted to 1703 and 1700 cm^{-1}, respectively, in the spectra of the diamino and dihydroxy esters. For unsymmetrically substituted amines and phenols, two C=O absorption bands were usually observed, reflecting the individual effects of the dissimilar end groups on the carbonyls nearest them. Arranging these data in descending order of absorption frequency in cm^{-1}, the groups fall into the same sequence of electron-withdrawing > moderately electron-releasing > strongly electron-releasing: Cl 1738; H, CH_3 1731–1733; alkoxy 1728–1732; OH 1702–1712; NH_2 1697–1710. The polar contributing structure **14** should enhance intermolecular attraction and thus encourage mesomorphism. Since there appears to be a large contribution by **14** for the amines and phenols, their liquid crystallinity is no longer so surprising. However, the benign role of H bonding and the smectic mesomorphism observed for two of the esters remain to be explained.

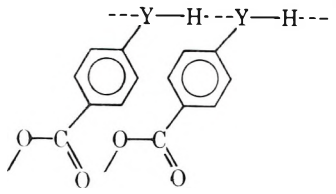
The ir spectra, high melting points, and molecular structures of the amines and phenols all indicate intermolecular H bonding, and yet these compounds exhibit very stable mesophases. Accordingly, we must conclude that H bonding is not a deterrent to mesomorphism here and, in consideration of the very high mesophase stabilities, may even encourage it. We propose that this unusual behavior is associated with the particularly strong tendency of the rod-shaped molecules in this series to assume a well-ordered parallel alignment as a result of powerful lateral dipole–dipole attractive forces. These, in turn, we ascribe to the large contribution of the polar structure **14** to the resonance hybrid. Under these circumstances, with the molecules already in a parallel array, there is no obvious reason why end-to-end H bonding (**15**) should



15 (Y = NH or O)

not occur. The resulting linear dimers (or polymers in the cases of the diamine, diphenol, and aminophenol) would not only be compatible with nematic mesomorphism, but would be expected to enhance mesophase stability by providing additional intermolecular attraction.[34]

By a similar argument, sidewise H bonding (**16**) in a preexisting parallel molecular "lattice" is also reasonable, and



16 (Y = NH or O)

would encourage smectic mesomorphism by providing additional lateral intermolecular attraction[34] and by lining molecules up in a layered arrangement. We believe it is significant that **1** (Y = Z = OH) and **1** (Y = OH; Z = NH_2) are the only amino or phenolic esters that display a focal-conic texture, indicating smectic liquid crystallinity. The structures of these two esters are particularly favorable for sidewise H bonding, being capable of association at both molecular termini. (The diamine has the requisite structure, too, but NH_2 hydrogen bonds less readily than phenolic OH.) It is pertinent also that a ring-methylated version of **1** (Y = Z = OH) is not smectic (see Experimental Section), which can be explained by lateral methyl substituents preventing close enough approach of adjoining parallel molecules to allow sidewise H bonding.

When viewed with crossed polarizers, the initial melts of both **1** (Y = Z = OH) and **1** (Y = OH; Z = NH_2) display birefringent schlieren-textured or striated zones in a pseudoisotropic matrix that flashes brightly on mechanical disturbance, indicating that it is nematic. On cooling, there is a partial transition to focal-conic texture which, although reversible, occurs at varying temperatures and is not detected as a phase change by the differential scanning calorimeter. For both melts, the flashing nematic and focal-conic smectic textures coexist well below the temperature at which the focal-conic birefringence first appears. These data suggest that the melts are partly nematic and partly smectic, with the proportion of the latter gradually increasing on cooling. This is closely analogous to the cybotactic nematic mesophases proposed by de Vries,[35] for which he postulates a combination of classical nematic molecular organization and more highly ordered bundles of molecules. The presence of both end-to-end (**15**) and sidewise (**16**) H bonds would account for the dual nematic–smectic nature of the mesophases, and interchange between these modes of H bonding is consistent with a gradual transition from nematic to smectic predominance on cooling. X-ray diffraction studies of the melts are indicated to test this hypothesis.

Looking at the other known examples of mesomorphic primary amines and phenols that are incapable of intramolecular H bonding in terms of the above discussion, it is seen that they, too, have special structural features that compensate for the usually deleterious effects of intermolecular H bonding on liquid crystallinity. Compounds **2** and **4** have the same features as the amines and phenols of this paper (phenylene rings, carbonyl groups, NH_2 or OH in conjugation with C=O) with **2** having the added advantage of the increased rigidity and extra phenylene ring provided by the biphenylene linkage. Compound **3** has the highly rigid, rod-shaped tetraphenylene ring system which is probably polarized to a considerable extent by electron donation from the NH_2 groups. In summary, there is evidence that phenolic and aromatic primary amino derivatives subject to intermolecular H bonding are mesomorphic only if they satisfy to an unusually high degree the structural criteria for liquid crystallinity.

Acknowledgment. We are grateful to Dr. Joseph A. Dilts for performing the differential scanning calorimeter experiments, and for helpful discussions concerning interpretation of the results.

Registry No.—**1** (Y = Z = CH_3O), 1962-76-1; **1** (Y = Z = OH) hydroquinone, 59138-72-6; **5**, 59138-73-7; hydroquinone, 123-31-9; *p*-benzyloxybenzoyl chloride, 1486-50-6; *p*-hydroxyphenyl *p*-benzyloxybenzoate, 59138-74-8; *p*-hydroxyphenyl *p*-nitrobenzoate, 13245-55-1; benzyloxyphenol, 103-16-2; nitrobenzoyl chloride, 122-04-3; nitrophenol, 100-02-7; *p*-benzyloxybenzoic acid, 1486-51-7; *p*-benzyloxybenzoic anhydride, 1486-49-3; benzoyl chloride, 98-88-4; *p*-methylbenzoyl chloride, 874-60-2; *p*-methoxybenzoyl chloride, 100-07-2; *p*-hexyloxybenzoyl chloride, 39649-71-3; *p*-chlorobenzoyl chloride, 122-01-0.

References and Notes

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Intramolecular Diels–Alder Reactions. 10. Syntheses and Cyclizations of Some *N*-(Cinnamyl and phenylpropargyl)cinnamamides and Phenylpropiolamides[1a]

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The nine possible unsaturated amides $Ph(C_2)CH_2NHC(=O)(C_2)'Ph$, where (C_2) and $(C_2)'$ are variously *cis*-CH=CH–, *trans*-CH=CH–, and –C≡C– groups, were synthesized. Diynic amide **6** underwent intramolecular Diels–Alder reaction in refluxing Ac_2O to form a mixture of benz[*f*]isoindoles **15a** (from cyclization in mode 1) and **16a** (from cyclization in mode 2). Under these same conditions *trans,trans*-dienic amide **8** did not cyclize, while four other amides gave cyclization in only one mode (for each) to form hydro derivatives of **15a** and **16a**. Modal selectivity in the cyclizations is interpreted in terms of relative frontier molecular orbital energy levels for the various substrate molecules.

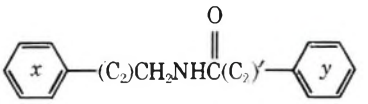
In a series of preceding papers from this laboratory[2-6] we presented the syntheses and intramolecular Diels–Alder reactions (by means of refluxing acetic anhydride) of unsaturated esters of the $Ar(C_2)CH_2OC(=O)(C_2)'Ar'$ type, where Ar and Ar′ are phenyl or substituted phenyl groups and (C_2) and $(C_2)'$ are variously –C≡C–, *cis*-CH=CH–, and *trans*-CH=CH– groups. Of the nine possible combinations for (C_2) and $(C_2)'$ only five types have thus far been synthesized, and just three of these types have been found susceptible to intramolecular Diels–Alder reaction. Successful cyclizations led to the formation of cyclolignan lactones, compounds which bear the skeletal structure of 4- (or 9-) arylnaphtho[2,3-c]-furan-1(3*H*)-one. An extension of these studies to the syntheses and cyclizations of the analogous amides $Ph(C_2)$-$CH_2NRC(=O)(C_2)'Ph$, where R = H or benzyl, is underway in our laboratory. Studies on four *N*-benzyl amides have already been reported,[7] while the present paper describes the syntheses of all nine possible parent amides (R = H) and studies on cyclizations of six of them. Cyclization of a seventh parent amide will be considered in a subsequent paper.[8]

Used in the syntheses of the unsaturated amides were the hydrochloride salts of *trans*-cinnamylamine (**1**),[9] phenylpropargylamine (**2**), and *cis*-cinnamylamine (**3**). Amine salt **2** was obtained in 79% overall yield by Gabriel synthesis from phenylpropargyl chloride.[10] Low-pressure catalytic hydrogenation of **2** in the presence of Pd–$BaSO_4$–quinoline gave nearly a quantitative yield of **3**. Schotten–Baumann condensations between these amine salts and the freshly prepared acid chlorides from phenylpropiolic acid, *trans*-cinnamic acid, and *cis*-cinnamic acid produced the nine crystalline amides **4–12**, in yields of 57–81% (Table I). *N*-(*cis*-Cinnamyl)-*trans*-cinnamamide (**7**) was also obtained (55%) by hydrogenation of *N*-(phenylpropargyl)-*trans*-cinnamamide (**9**) in the presence of Lindlar catalyst plus quinoline.

Of special interest in the syntheses of **10–12** is the handling of *cis*-cinnamic acid. Saponification of ethyl *cis*-cinnamate[11] gave *cis*-cinnamic acid, which could be stored in dry benzene at 0–10 °C in the dark for several months without isomerization. Just before use, the acid was converted into its sodium salt by means of sodium hydride, and then into *cis*-cinnamoyl chloride (in high isomeric purity) by means of thionyl chloride.

Identities of the amides were checked by ultraviolet, ^1H NMR, and infrared spectra (as well as by elemental analyses). In particular, absorption bands were found for N–H stretching at ca. 3440 cm^{-1} (weak) and for the carbonyl moiety of an N-substituted amide at 1650–1670 cm^{-1} (strong) in all compounds.[12a] Bands for the trans-disubstituted alkene linkage[12b] at ca. 970 cm^{-1} and for the triple bond in the acid moiety[12c] at 2220 cm^{-1} were also appropriately observed.

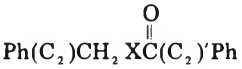
Table I



Registry no.	Compd	(C_2) unit	$(C_2)'$ unit	Yield,[a] %	Mp,[b] °C
59015-31-5	4	*cis*-CH=CH–	–C≡C–	61	101.5–102.5[c]
59015-32-6	5	*trans*-CH=CH–	–C≡C–	80	111–112[d]
59015-33-7	6	–C≡C–	–C≡C–	66	123.5–124.5[e]
59015-35-9	7	*cis*-CH=CH–	*trans*-CH=CH–	79	137–138[d]
59015-34-8	8	*trans*-CH=CH–	*trans*-CH=CH–	81	129–130[e]
59015-36-0	9	–C≡C–	*trans*-CH=CH–	59	142–143[e]
59015-37-1	10	*cis*-CH=CH–	*cis*-CH=CH–	58	62–63[c]
59015-38-2	11[f]	*trans*-CH=CH–	*cis*-CH=CH–	72	64.5–65.5[c]
59015-39-3	12	–C≡C–	*cis*-CH=CH–	57	96.5–97.5[c]

[a] Of amide product (from Schotten–Baumann reaction) after one crystallization from solvent. [b] For analytically pure product. [c] Recrystallized from benzene–petroleum ether (bp 60–90 °C). [d] Recrystallized from aqueous ethanol. [e] Recrystallized from ethanol. [f] This compound was chromatographed (silica gel–$CHCl_3$) before crystallization.

Table II. Comparison of [4 + 2] Cycloaddition Products from Unsaturated Amides and Esters in Refluxing Acetic Anhydride

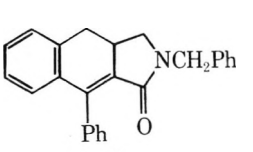


(C_2) unit	$(C_2)'$ unit	X[a]	Isolated cyclization product(s) Formula(s)	Total Yield, %	Mode(s) of cyclization
trans-CH=CH–	*trans*-CH=CH–	O,[5] NH, NCH_2Ph[7]		None[b]	None[b]
trans-CH=CH–	–C≡C–	O[5]	17	46[c]	1
		NH	13a	74	1
		NCH_2Ph[7]	13c	100	1
trans-CH=CH–	*cis*-CH=CH–	O[2]	27[d]	(20)	(1)
		NH	26	25	2
–C≡C–	*trans*-CH=CH–	O[5]		None[b]	None[b]
		NH	14a, 16a	75	2
		NCH_2Ph[7]	16c, 22c	17	2
–C≡C–	–C≡C–	O[5]	18	39	1 (and 2)[e]
		NH	15a, 16a	72[f]	1 and 2
		NCH_2Ph[7]	15c	14	1
–C≡C–	*cis*-CH=CH–	NH	14a, 16a[g]	23	2
cis-CH=CH–	–C≡C–	NH	13a	32	1

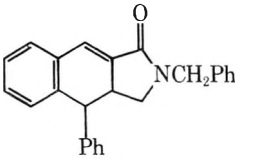
[a] Reference numbers are those given at the end of this paper. [b] Cyclization did not occur. [c] Overall yield from phenylpropiolic acid. [d] Reaction has been tried only with substituted phenyl groups. [e] Only mode 1 product was obtained with unsubstituted phenyl groups. Substituted phenyl groups gave mixtures of products from both modes 1 and 2.[4] [f] Ratio of 15a:16a 1.3:1. [g] Plus [2 + 2] cycloaddition product.

Solutions of amides **4–6, 8, 9** and **11** in acetic anhydride (usually under high-dilution conditions of 1 g of amide per 250–1250 ml of solvent) were refluxed for 4–7 h and processed further for isolation of products. *N*-(*trans*-Cinnamyl)-*trans*-cinnamamide (**8**) formed a red, viscous liquid, believed to contain only polymeric materials (as based on TLC and ^1H NMR analyses). Failure of *N*-benzyl-*N*-(*trans*-cinnamyl)-*trans*-cinnamamide[7] and of *trans*-cinnamyl-*trans*-cinnamate[5] (plus a number of its ring-substituted derivatives)[4] to undergo cyclization under these conditions has been noted previously. The nonreactivity toward intramolecular Diels–Alder cyclization of all of these trans,trans dienic compounds may be ascribed to steric hindrance to the attainment of the geometry required in the transition state.[4]

In contrast, each of the other five amides formed a crystalline intramolecular cycloaddition product of the Diels–Alder type. It should be noted, however, that two modes of intramolecular Diels–Alder reaction are possible. Mode 1 involves action of the $(C_2)'$ unit of the acid moiety as a "dienophile" and of the $Ph(C_2)$ unit of the amine moiety as a "diene". Cyclization thereby occurs into the phenyl ring of the amine moiety (ring *x*) in the manner expected for a normal Diels–Alder reaction. Alternatively, mode 2 involves action of the (C_2) unit of the amine moiety as a "dienophile" and of the $Ph(C_2)'$ unit of the acid moiety as a "diene". Cyclization in this mode occurs into the phenyl ring of the acid moiety (ring *y*) in an "abnormal" Diels–Alder manner. Both modes of cyclization were found in this study. They are distinguished by structural investigation of the product(s) formed—in particular by transformation (where necessary) into the reference compounds **15** and **16**, respectively. Scheme I summarizes these transformations. Table II gives yields of the N-acetylated products formed (from X = NH), the mode(s) of cycli-

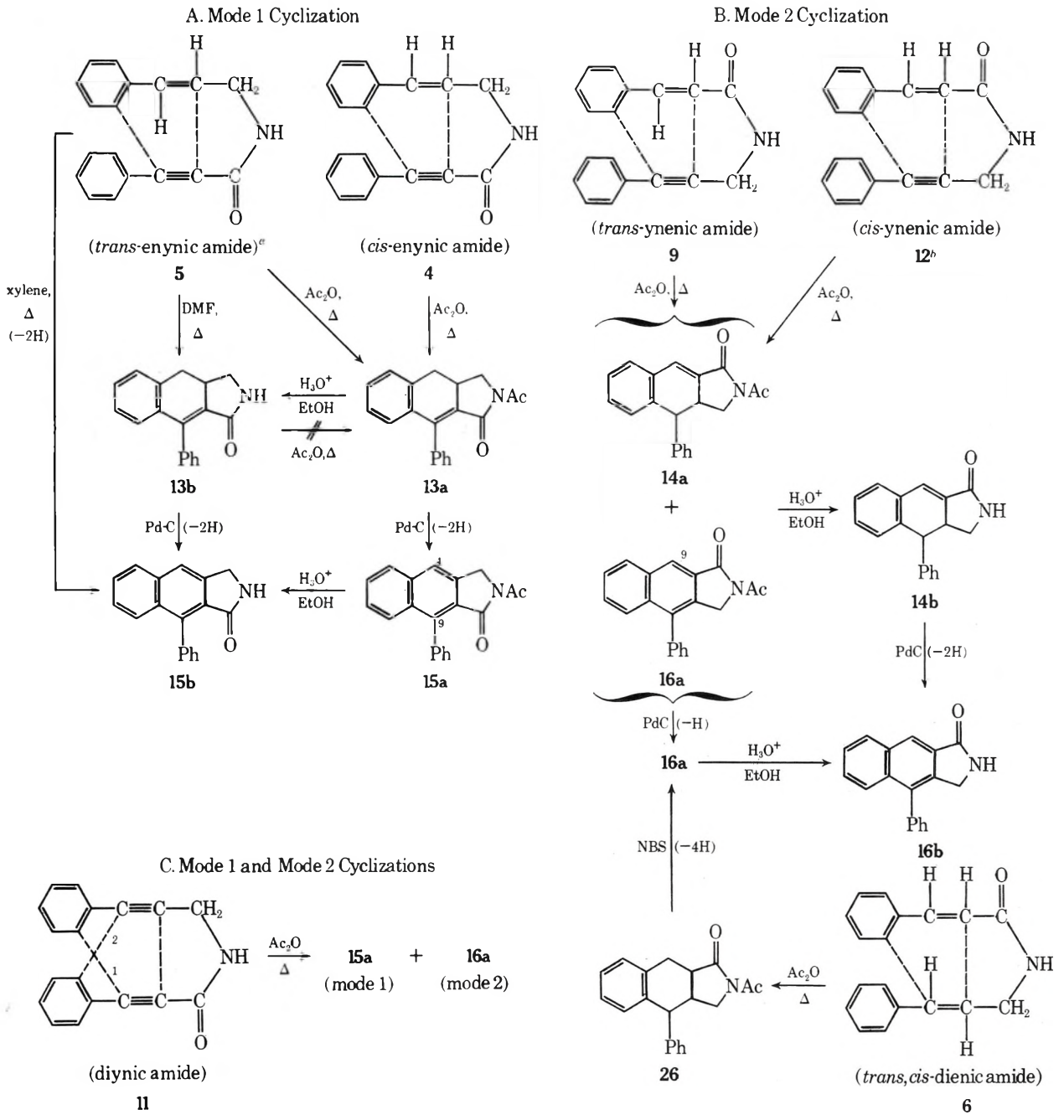


13c

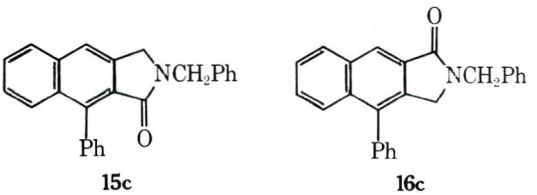


14c

Scheme I. Correlation of Structures in Cyclization Products from Amides



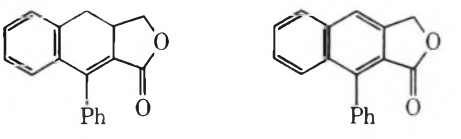
[a] The chemical natures of (C_2) and (C_3) (in the order given) are indicated beneath the formula. [b] A [2 + 2] cycloaddition product is also formed (cf. ref 8).



15c 16c

zation, and comparative data for analogous ester and *N*-benzyl amide cyclizations. A discussion of the relationships in Scheme I is presented in subsequent paragraphs.

Cyclization of *N*-(*trans*-cinnamyl)phenylpropiolamide (**5**, $C_{18}H_{15}NO$) gave acetylated compound **13a** ($C_{20}H_{17}NO_2$), hydrolyzed to lactam **13b** ($C_{18}H_{15}NO$) on treatment with ethanolic hydrochloric acid. That cyclization had, indeed, occurred was apparent from the facts that the infrared spectrum of **13a** lacked bands for the C≡C and NH functions present in **5**, but exhibited carbonyl bands at 1690 and 1720 cm^{-1} (for an N-acetylated γ-lactam)[12d] in place of the original band at 1650 cm^{-1}. Deacetylated product **13b**, on the other hand, showed a single carbonyl band at 1700 cm^{-1}, as well as NH absorption at 3450 cm^{-1}. The ultraviolet spectra of **13a** and **13b**, moreover, were closely similar to the spectrum of 9-phenyl-3a,4-dihydronaphtho[2,3-*c*]furan-1(3*H*)-one (**17**).[5]

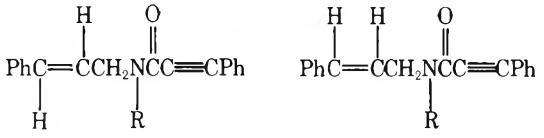


17 18

Ultraviolet and infrared spectra, however, were insufficient to clearly distinguish **13a** and **13b** from the isomeric compounds **14a** and **14b** (respectively), products expected for cyclization by mode 2 rather than by mode 1 (as found). On the other hand, the ^1H NMR spectrum of the acetylated

product was consistent only with **13a** since it showed no evidence for the presence of a vinyl proton (expected for structure **14a**), though it did exhibit a singlet for the *N*-acetyl group at ca. δ 2.5. Final proof of structures **13a** and **13b** was obtained by dehydrogenation of these compounds to **15a** (88%) and **15b** (56%), rather than to **16a** and **16b**, by means of Pd/C in refluxing *p*-cymene. Product **15a** had a ^{1}H NMR spectrum which consisted of a ten-proton complex in the aromatic region of δ 7.1–8.0, a methylene singlet at δ 4.90, and an *N*-acetyl singlet at δ 2.57. In contrast, the ^{1}H NMR spectrum of **16a** should have included a singlet at ca. δ 8.3–8.5 for the aromatic proton at C-9[4] (vide infra). As expected, the ultraviolet spectra of **15a, 15b**, and 9-phenylnaphtho[2,3-c]furan-1(3*H*)-one[5] (**18**) were closely similar.

Cyclization of **5** is consistent with observations on the *N*-benzyl derivative **19b** and a large number of *trans*-enynic esters, all of which undergo cyclization in mode 1.[3-7,10,13-16]



19 **20**

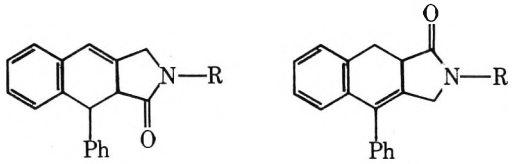
a, R = Ac; **b**, R = $PhCH_2$

For this reason, further studies on the conditions which foster cyclization of **5** were made. As expected for a thermal reaction, evaporative distillation of **5** at 240 °C gave **13b**, albeit in low yield (cf. observations made on a substituted *trans*-enynic ester).[15] Better results (55% yield of **13b**, 51% yield of **15b** formed by cyclization–dehydrogenation) were obtained in a solvent at 140–155 °C (refluxing dimethylformamide or xylene, respectively; cf. in situ ester cyclizations[13] in DMF), while cyclization did not occur in a solvent at ca. 80 °C (refluxing benzene or ethanol). When lactam **13b** was refluxed in acetic anhydride for 6 h no acetylation to form **13a** occurred. Instead, **13b** was recovered unchanged. When, however, open-chain amide **5** was treated with NaH in glyme at 0 °C and then with Ac_2O at 0–25 °C two products, **13a** (isolated yield 37%) and recovered **5**, were found. Neither TLC nor ^{1}H NMR analyses of the total reaction product mixture indicated the presence of any acetylated open-chain amide **19a** therein. It, therefore, appears that the reaction sequence in Ac_2O may be **5** → **19a** → **13a** (where the second step is much faster than the first one), but it is clearly not **5** → **13b** → **13a**. Previously, we noted that the *N*-benzyl derivative **19b** undergoes quantitative conversion into **13c** in refluxing Ac_2O and even cyclizes to a limited extent during recrystallization from ethyl acetate.[7] It is apparent, therefore, that substitution of an acetyl or a benzyl group on the nitrogen atom of **5** facilitates cyclization, perhaps by effecting a conformational change in the molecule which brings the dienic and dienophilic entities nearer to the configuration of the transition state.

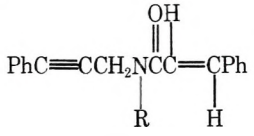
Cyclization of *N*-(*cis*-cinnamyl)phenylpropiolamide (**4**, an isomer of **5**) also gave **13a**, albeit in considerably lower yield. The possibility that formation of **13a** involves a preliminary rapid isomerization of **4** to **5** is unlikely, since interruption of the reaction after only 1 h of refluxing showed no spectral evidence for the presence of **5** in the total product mixture. From molecular models in seems probable that the reaction pathway is **4** → **20a** → **13a**. No other *cis*-enynic substrate has yet been used in our studies.

The diynic amide *N*-(phenylpropargyl)phenylpropiolamide (**6**) formed a solid reaction product which appeared to be a mixture of **15a** (cyclization mode 1) and **16a** (cyclization mode 2) in the ratio of 1.3:1, respectively, as based on ^{1}H NMR analysis (singlet for H-9 of **16a** at δ 8.48, two sets of methylene and acetyl singlets). Separation of these isomers was not accomplished, however. The combined yield (72%) of the isomers was surprising inasmuch as total product yields (one or two isolable isomers) varied from 14 to 39% in four other cases of diynic substrates.[4,5,7]

From Diels–Alder cyclization of *N*-(phenylpropargyl)-*trans*-cinnamamide (**9**) one would expect to obtain either **21a** (mode 1) or **22a** (mode 2). Although a crystalline product (**24**)



21 **22**



23

a, R = Ac; **b**, R = H; **c**, R = $PhCH_2$

of narrow melting range (271–272 °C) and appropriate elemental composition was obtained, spectral evidence was inconsistent with either of the expected structures. Dehydrogenation of **24** with Pd/C led to a single product which was assigned structure **16a**, inasmuch as its ^{1}H NMR spectrum included a singlet for one proton at δ 8.48 plus other expected resonances for one component of the aforementioned mixture of **15a** and **16a** from cyclization of **6**. A 100-MHz ^{1}H NMR spectrum of **24** indicated that it was, indeed, a mixture of **14a** and **16a** in the molar ratio of ca. 4:1. This assignment was corroborated by ultraviolet and infrared spectra. The former spectrum of **24** was a composite of those of 3,4-dihydro-2-naphthoic acid[17] and **16a**, while the latter showed a medium-intensity band at 830 cm^{-1} (ascribed to C–H deformation in a trisubstituted alkene).[12b] Deacetylation of **24** produced crystalline **14b**, free of **16b** as based on ^{1}H NMR and ultraviolet spectra.

In previous investigations it was found that **23c**, the *N*-benzyl derivative of **9**, also cyclized in mode 2 to give a mixture (17% total) of **16c** and **22c**.[7] No **14c** was detected. The conversions **22a** → **14a** and **22c** → **14c** should be acid catalyzed.[18] Hence, formation of **14a** from **9** may be ascribed to the reaction sequence

$$\mathbf{9} + Ac_2O \rightarrow \mathbf{23a} + HOAc$$

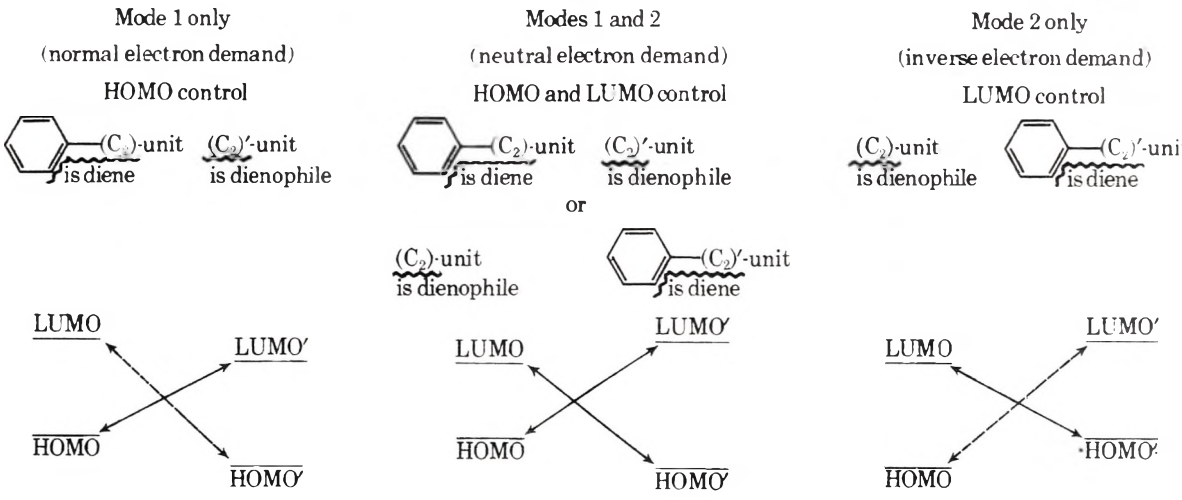
$$\mathbf{23a} \rightarrow \mathbf{22a} \xrightarrow{HOAc} \mathbf{14a}$$

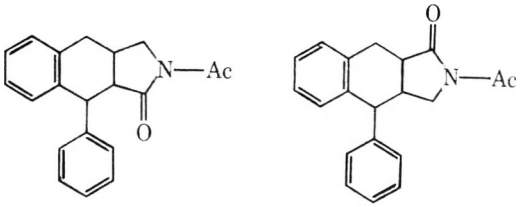
where the HOAc formed in the first step serves as a catalyst in the last step. In contrast, cyclization of **23c** to **22c** is not accompanied by the in situ formation of HOAc, and isomerization of **22c** to **14c** does not occur. It is noteworthy that phenylpropargyl *trans*-cinnamate, in contrast to **9** and **23c**, failed to undergo cyclization.[5]

Cyclization of *N*-(*trans*-cinnamyl)-*cis*-cinnamamide (**11**) produced a crystalline product with appropriate elemental and spectral properties for either structure **25** or **26** (stereochemistry not established). Oxidation of this substance with *N*-bromosuccinimide led to aromatic compound **16a** (rather than **15a**), consistent with the conversion **11** → **26** (cyclization in mode 2). In previous studies the ring-substituted compound *trans*-3,4-methylenedioxycinnamyl *cis*-3,4,5-trimethoxycinnamate was found to cyclize in mode 1 to give **27**.

Table II summarizes the modes of intramolecular [4 + 2] cycloadditions in corresponding amides (X = NH) and esters (X = O), as well as some *N*-benzyl amides (X = NCH_2Ph). Only five analogous cases[19] have thus far been investigated in each of the first two series (under comparable conditions

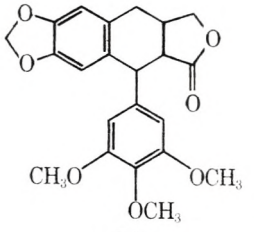
Scheme II. Proposed Frontier Orbital Relationships Involved in Modal Selectivity in Intramolecular [4 + 2] Cycloadditions of $Ph(C_2)CH_2OC(=O)(C_2)'Ph$ and $Ph(C_2)CH_2NHC(=O)(C_2)'Ph$





25

26



27

of refluxing Ac_2O). For these cases, similar modes of cyclization were found in two systems (mode 1 for the *trans*-enynic compounds; a combination of modes 1 and 2 for the diynic compounds); no cyclization occurred for the *trans,trans*-dienic compounds; opposite modes of cyclization were found in one case (*trans,cis*-dienic compounds); cyclization vs. no cyclization occurred in one case (*trans*-ynenic compounds). It is clear that the ease and mode of intramolecular Diels–Alder reaction are markedly dependent on the nature of X, as well as on (C_2) and $(C_2)'$. One generalization which can be made on the basis of the results thus far obtained (including observations made on *N*-(phenylpropargyl)-*cis*-cinnamamide (**12**)[8] is that in either an enynic or an ynenic compound the C≡C unit assumes the role of the dienophile, in those cases where cyclization does occur. In the formalism of the Mulliken charge-transfer theory[20] electronic charge is transferred from the HOMO (highest occupied molecular orbital) of the diene (electron donor) to the LUMO (lowest unoccupied molecular orbital) of the dienophile (electron acceptor)[21] during the process of reaction. It has been noted repeatedly that the C≡C is less readily attacked by electrophiles than is the C=C.[22,23]

Considerations of regioselectivity are of pertinence in the intermolecular Diels–Alder reaction. They are not, however, of direct concern in the intramolecular Diels–Alder reaction on our substrates. Once the mode (1 or 2) of cyclization has been selected by one of our substrate molecules, conformational constraints (imposed through energetically allowed bond lengths and bond angles) would seem to permit [4 + 2] cycloaddition to occur in only one regioselective way.[24]

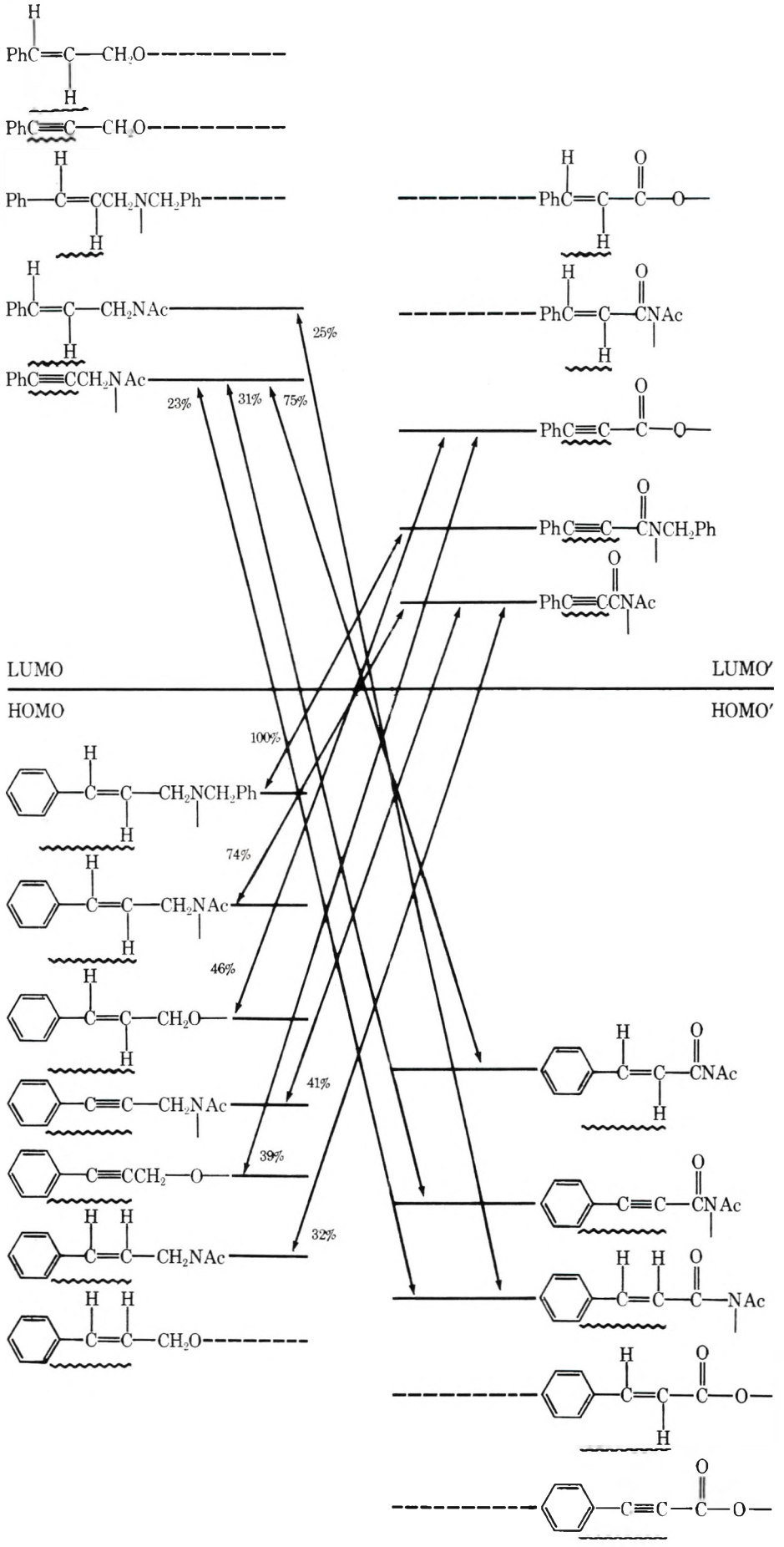
Contrariwise, modal selectivity can be interpreted qualitatively in terms of a modification of Sustmann's frontier orbital model,[25] as depicted in Scheme II. In this idealized scheme HOMO energy levels refer to the dienic unit in the $Ph(C_2)$ or $Ph(C_2)'$ moiety, while LUMO energy levels refer to the dienophilic unit (C_2) or $(C_2)'$. Frontier orbital energy levels are represented with different spacings for the (C_2) and $(C_2)'$ ends of the molecule and these orbital pairs may be shifted vertically with respect to one another. For the case of neutral electron demand cyclization in modes 1 and 2 are equally probable (as represented by two solid double-headed arrows which join orbitals that interact to significant extents). When electron demand of one end of the molecule surpasses that of the other end the orbital pairs shift so that one mode of cyclization prevails (solid arrow). The case of neutral electron demand is approximated by cyclization of diynic amide **6** and by some ring-substituted diynic esters which have been investigated.[4] Changing from an amide to an ester substrate (cf. Table II) or deleting substituents from the aromatic rings of the ester shift the ratio of mode 1/mode 2 cyclization away from a value of 1:1. As yet no systematic study of small variations in the diynic substrate molecules or of variations in the cyclizing medium on the modal ratio has been made. However, cyclization in mode 1 only or in mode 2 only can be considered to result from extreme modifications of the case of neutral electron demand.

Scheme III is an effort to depict (in a semiquantitative manner) the relative distributions of the frontier orbital energy levels for the (C_2) ends (left half of the scheme) and the $(C_2)'$ ends (right half of the scheme) of most of the substrate molecules listed in Table II. Omitted are some of the energy levels for *N*-benzyl substrates and for those (shown as broken lines) which are not pertinent to the cyclization processes. Cyclization in mode 1 is indicated by arrows which join levels in the upper right and lower left quadrants of the scheme, while cyclization in mode 2 is indicated by arrows which join levels in the upper left and lower right quadrants. In general, this scheme is constructed on the basis of the following anticipated relationships. (1) A (C_2) end is a better electron donor (upward displaced HOMO and LUMO energy levels) than is a $(C_2)'$ end (lower corresponding levels). (2) Of $(C_2)'$ units, the C≡C group is the strongest electron acceptor. (3) Of (C_2) units, the *trans*-CH=CH group is the strongest electron donor. (4) Yields of cyclization products generally increase with decreasing separation between the pertinent HOMO and LUMO energy levels, and vice versa.

Experimental Section[26]

Phenylpropargylamine Hydrochloride (2). *N*-(Phenylpropargyl)phthalimide was prepared from phenylpropargyl chloride[10] and K phthalimide in a manner similar to that previously described,[27] mp

Scheme III



152.5–153.5 °C (lit. 158–160 °C). A stirred mixture of 130 g of this imide, 17 g of hydrazine (95+%), and 1.3 l. of MeOH was refluxed for 2 h, allowed to cool, treated with 350 ml of concentrated hydrochloric acid, and refluxed 30 min longer. The mixture was cooled to 0 °C, filtered to remove precipitated phthalhydrazide (washed with cold MeOH), and evaporated to dryness. The residue was extracted with 500 ml of absolute EtOH at room temperature and the filtered extract was reevaporated. Crystallization of the residue from *i*-PrOH gave 70 g (84%) of platelets: mp 215–217 °C dec, raised to 216–217 °C dec on recrystallization from EtOH–Et_2O (1:1 v/v) (lit.[28] mp 216–217 °C); ν (KBr) 2250 (w, C≡C), 745 and 680 cm^{-1} (s, 5 vicinal aromatic H); NMR (D_2O) δ 7.9–7.4 (m, 5 aromatic H), 4.81 (s, 3.8 H, NH_3^+ plus H_2O), and 4.25 (s, 2 H, methylene).

Anal. Calcd for $C_9H_{10}ClN$: C, 64.48; H, 6.01; Cl, 21.15; N, 8.36. Found: C, 64.25; H, 6.28; Cl, 21.52; N, 8.15.

***cis*-Cinnamylamine Hydrochloride (3).** A mixture of 0.25 g of 5% Pd/$BaSO_4$ (Baker), 0.2 ml of synthetic quinoline, and 40 ml of EtOH was agitated in hydrogen gas at 1 atm until the catalyst became black (ca. 1 h). A solution of 5 g of preceding amine salt **2** in 150 ml of EtOH was added and agitation was continued until 1 molar equiv of hydrogen was absorbed (ca. 3 h). The catalyst was removed by filtration and washed throughly with EtOH. Combined solutions were evaporated to leave a residue which was washed with ether and dried in vacuo (quantitative yield). Repeated crystallization from *i*-PrOH–Et_2O gave platelets: mp 169–170 °C (lit.[27] mp 177–178 °C); ν (KBr) 765 (s) and 690 cm^{-1} (s, 5 vicinal aromatic H); NMR (D_2O) δ 7.6–7.2 (m, 5 aromatic H), 6.87 (d of t, J = 11.5 and 1.8 Hz, 1 H, CH=$CHCH_2$), 6.06 (d of t, 1 H, CH=C**H**CH_2), 5.12 (broad s, 3 H, NH_3^+), and 4.09 (d of d, J = 1.8 and 6.5 Hz, 2 H, methylene).

Anal. Calcd for $C_9H_{12}ClN$: C, 63.72; H, 7.13; Cl, 20.90; N, 8.26. Found: C, 63.46; H, 7.13; Cl, 20.95; N, 8.55.

Other Starting Materials. *trans*-Cinnamyl chloride[29] was converted successively into *N*-(*trans*-cinnamyl)phthalimide and *trans*-cinnamylamine hydrochloride[9] (**1**): ν (KBr) 960 (s, trans-disubstituted alkene), 735 and 685 cm^{-1} (s, 5 vicinal aromatic H); NMR (D_2O) δ 7.8–7.4 (m, 5 aromatic H), 6.96 (d, J = 16 Hz, 1 H, CH=$CHCH_2$), 6.49 (m, 1 H, CH=C**H**CH_2), 4.94 (s, 4.1 H, NH_3^+ plus H_2O), and 3.93 (d, J = 6.5 Hz, 2 H, CH=CH**CH_2**). *trans*-Cinnamoyl and phenylpropiolyl chlorides, obtained from the corresponding acids, were used immediately to form the amides.

cis-Cinnamic acid was obtained by hydrolysis of ethyl *cis*-cinnamate[11] with a refluxing solution of NaOH (15% excess) in 80% EtOH. The solution was concentrated in vacuo, treated with water, benzene, and 2 N H_2SO_4 (to pH 2), and shaken. The benzene layer was stored in the dark over Na_2SO_4 at 0–10 °C until needed (stable for 3 months or longer). Thereupon, the solution was evaporated in vacuo to give a viscous, red-brown liquid (89% yield, >95% cis by NMR spectrum). A solution of 4.4 g of this liquid in 50 ml of dry benzene was added dropwise to a stirred suspension of NaH (1.39 g, added as a 51.5% dispersion in mineral oil) in 50 ml of benzene in a nitrogen atmosphere at room temperature. After 2 more h of stirring the suspension was treated dropwise with a solution of 3.53 g of fresh, reagent grade $SOCl_2$ in benzene. This solution, containing *cis*-cinnamoyl chloride, was stirred 2 h longer and used directly in further reactions.

Syntheses of Unsaturated Amides. To a cold (0 °C), vigorously stirred suspension of 0.007–0.12 mol of amine hydrochloride (**1**, **2**, or **3**) in 100 ml of benzene were added (simultaneously and dropwise) solutions of (a) aqueous 2 N NaOH and (b) 0.01–0.13 mol of a crude, preceding acyl chloride in 100 ml of benzene. The molar ratio of amine hydrochloride to acyl chloride varied from 0.67 to 1.2. The total molar amount of NaOH used equaled that of the HCl formed. The mixture was stirred for 2 h at room temperature. The benzene layer was separated, washed successively with H_2O, dilute hydrochloric acid, 10% aqueous Na_2CO_3, and H_2O, dried (Na_2SO_4), and evaporated. The residue was crystallized repeatedly to constant melting range of 1 °C (Table I). Analytical and spectral data are presented in the following paragraphs.

Amide 4. ν 3450, 2230, 1650 cm^{-1}; λ_{max} 249 nm (log ϵ 4.52), 258 sh (4.45); NMR δ 7.7–7.1 (m, 10 aromatic H), 7.0–6.75 (broad m, 1 H, NH), 6.59 (d of t, J = 11.5 and 1.8 Hz, 1 H, CH=$CHCH_2$), 5.69 (d of t, 1 H, CH=C**H**CH_2), and 4.4–4.0 (2 overlapping d of d, J = 6.5, 5.5, and 1.8 Hz, 2 H, methylene).

Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.73; H, 5.88; N, 5.68.

Amide 5. ν 3440, 3020, 2220, 1650, 965 cm^{-1}; λ_{max} 255 nm (log ϵ 4.55); NMR δ 7.6–7.0 (m, 10 aromatic H), 7.0–6.5 (broad, NH), 6.48 (d, J = 16 Hz, CH=$CHCH_2$), 6.12 (d of t, CH=C**H**CH_2) (3 H total for range 7.0–5.8), and 4.05 (t, J = 5.5 Hz, 2 H, CH=CH**CH_2**).

Anal. Calcd for $C_{18}H_{15}NO$: vide supra. Found: C, 83.04; H, 5.78; N, 5.68.

Amide 6. ν 3500, 2240, 1660 cm^{-1}; λ_{max} 242 nm (log ϵ 4.51), 252 (4.51); NMR δ 7.9–6.9 (m, 11 H, aromatic H plus NH) and 4.36 (d, J = 5.5 Hz, 2 H, C**H**$_2$NH).

Anal. Calcd for $C_{18}H_{13}NO$: C, 83.37; H, 5.05; N, 5.40. Found: C, 83.14, H, 5.23; N, 5.48.

***N*-(*cis*-Cinnamyl)-*trans*-cinnamamide (7).** A suspension of 250 mg of Lindlar catalyst[30] in 0.2 ml of synthetic quinoline and 40 ml of EtOAc was shaken with hydrogen gas at 1 atm for 1 h. A solution of 0.5 g of *N*-(phenylpropargyl)-*trans*-cinnamamide (**9**) in 100 ml of EtOAc was then added and agitation was continued until 1 molar equiv of hydrogen was absorbed (ca. 1 h). The catalyst was removed by filtration and washed with ethanol. Evaporation of the filtrate gave a solid which formed needles from aqueous EtOH, mp 136–137 °C (55%), raised to 137–138 °C on recrystallization, melting point undepressed on admixture with **7** from Schotten–Baumann synthesis; ν 3440, 1670, 975 cm^{-1}; λ_{max} 271 nm (log ϵ 4.49), 222 (4.33); NMR δ 7.62 (d, J = 16 Hz, CH=CHC=O) which overlaps 7.5–7.0 (m, 11 H total), 6.55 (d of t, J = 11.5 and 1.5 Hz, C**H**=$CHCH_2$) which overlaps 6.47 (d, J = 16 Hz, CH=C**H**C=O) and 6.7–6.4 (broad m, NH) (3 H total in region 6.7–6.3), 5.70 (d of t, J = 11.5 and 6.5 Hz, 1 H, CH=C**H**CH_2), and 4.5–4.1 (m, 2 H, methylene).

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51: N, 5.32. Found: C, 81.81; H, 6.55; N, 5.47.

Amide 8. ν 3440, 1670, 970 cm^{-1}; λ_{max} 268 nm (log ϵ 4.52), 222 sh (4.26), 216 (4.25); NMR δ 7.68 (d, J = 16 Hz, 1 H, CH=CHC=O) which partially overlaps 7.7–7.0 (m, 11 H, aromatic H plus NH), 6.68 (d, CH=C**H**C=O), 6.50 (d, J = 16 Hz, C**H**=$CHCH_2$) which partially overlaps 6.5–5.8 (m, CH=C**H**CH_2) (3 H total in region 6.9–5.8), and 4.10 (t, J = 5.5 Hz, 2 H, methylene).

Anal. Calcd for $C_{18}H_{17}NO$: vide supra. Found: C, 82.31; H, 6.40; N, 5.26.

Amide 9. ν 3450, 1660, 973 cm^{-1}; λ_{max} 242 nm (log ϵ 4.35), 251 (4.39), 279 sh (4.43), 273 (4.44); NMR δ 7.72 (d, J = 16 Hz, CH=CHC=O) which partially overlaps 7.7–7.0 (m, aromatic H plus NH), 6.61 (d, CH=CHC=O) (13 H total in region 8.0–6.4), and 4.45 (d, J = 5 Hz, 2 H, methylene).

Anal. Calcd for $C_{18}H_{15}NO$: vide supra. Found: C, 82.53; H, 5.80; N, 5.45.

Amide 10. ν 3440, 1660 cm^{-1}; λ_{max} 248 nm (log ϵ 4.35); NMR δ 7.6–7.0 (m, 10 aromatic H), 6.71 (d, J = 13 Hz, CH=CHC=O) which partially overlaps 6.49 (d of t, J = 12 and 1.5 Hz, CH=$CHCH_2$), 6.2–5.8 (broad m, NH) on which is superimposed 5.93 (d, CH=CHC=O) (2 H total in region 6.2–5.8), 5.52 (d of t, J = 12 and 6.5 Hz, CH=C**H**CH_2) (1 H in region 5.8–5.2), and 4.3–3.9 (m, 2 H, methylene).

Anal. Calcd for $C_{18}H_{17}NO$: vide supra. Found: C, 82.43; H, 6.44; N, 5.39.

Amide 11. ν 3450, 1660, 965 cm^{-1}; λ_{max} 291 nm sh (log ϵ 3.77), 282 sh (3.96), 252 (4.45); NMR δ 7.6–7.0 (m, 10 aromatic H), 6.61 (d, J = 13 Hz, CH=CHC=O) and 5.89 (d, CH=CHC=O) which are superimposed on 6.8–5.6 (m, 5 H total, including CH=C**H**CH_2 and NH), and 3.89 (t, J = 5.5 Hz, 2 H, methylene).

Anal. Calcd for $C_{18}H_{17}NO$: vide supra. Found: C, 81.78; H, 6.53; N, 5.36.

Amide 12. ν 3450, 1670 cm^{-1}; λ_{max} 223 nm (log ϵ 4.20), 250 (4.42), 240 (4.44); NMR δ 7.6–6.9 (m, 10 aromatic H), 6.72 (d, J = 12.5 Hz, 1 H, CH=CHC=O), 6.5–6.1 (broad m, 1 H, NH), 5.95 (d, 1 H, CH=CHC=O), and 4.20 (d, J = 5.5 Hz, 2 H, methylene).

Anal. Calcd for $C_{18}H_{15}NO$: vide supra. Found: C, 82.99; H, 5.92; N, 5.44.

2-Acetyl-9-phenyl-2,3,3a,4-tetrahydro-1*H*-benz[*f*]isoindol-1-one (13a). A. Low-Dilution Method. A solution of 0.5 g of amide **5** in 4 ml of Ac_2O was refluxed for 6 h. Refrigeration of the cooled solution gave crystals which were washed with ice-cold Ac_2O and then with MeOH and dried: yield 0.264 g (46%); mp 182–184 °C; raised to 184–185 °C on recrystallization (prisms) from MeOH (Norit); ν 1720 and 1690 cm^{-1}; λ_{max} 308 nm (log ϵ 4.27), 240 (4.35); NMR δ 7.6–6.8 (m, 9 aromatic H), 4.5–4.0 (m, 1 H), 3.6–2.6 (m, 4 H), and 2.47 (s, 3 H, Ac); mass spectrum *m/e* 303 (100, M^+), 260 (33, M^+ − Ac), 232 (40), 231 (64), 218 (46), 203 (78, $C_{16}H_{11}^+$), 202 (74, $C_{16}H_{10}^+$), 43 (48, Ac^+).

Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.29; H, 5.56; N, 4.92.

B. High-Dilution Method. A solution of 0.5 g of amide **5** in 200 ml of Ac_2O was refluxed for 4 h and then evaporated to dryness in vacuo. The residue was crystallized from MeOH to give 0.45 g (74%) of **13a** as prisms, mp 179–180 °C.

C. **Low-Temperature Method.** A solution of 0.5 g of **5** in 25 ml of glyme was added dropwise to a stirred, cold (0 °C) mixture of 89 mg of NaH (used as a 51.5% dispersion in mineral oil) in 20 ml of glyme (nitrogen atmosphere). When hydrogen evolution ceased (15 min) a

mixture of 121 mg of Ac_2O in glyme (5 ml) was added dropwise. Stirring was continued at 0 °C for 15 min and then at room temperature for 2 h. The solvent was evaporated and the residue was extracted with $CHCl_3$. TLC (silica gel/$CHCl_3$) of the extract showed only two spots which corresponded to **5** and **13a**. Evaporation of the extract and recrystallization of the residue from EtOH gave 210 mg (37%) of needles of **13a**, mp 176.5–180 °C.

9-Phenyl-2,3,3a,4-tetrahydro-1*H*-benz[*f*]isoindol-1-one (13b). A. From Deacetylation of 13a. A solution of 6 g of **13a** in 125 ml of concentrated hydrochloric acid and 315 ml of absolute EtOH was refluxed for 3 h and then evaporated. The residue was treated with water. The resultant solid was collected and crystallized from MeOH (crude yield 78%) to give needles: mp 238.5–239.5 °C; ν 3450, 1700 cm^{-1}; λ_{max} 295 nm (log ϵ 4.08), 235 (4.45); NMR (CF_3CO_2H) δ 7.7–6.8 (m, 10 H, aromatic H plus NH) and 4.4–2.7 (m, 5 H, aliphatic H); mass spectrum *m/e* 261 (100, M^+), 232 (46), 231 (54), 218 (32), 203 (70), 202 (59).

B. Directly from Amide 5. A solution of 0.5 g of amide **5** in 250 ml of DMF was refluxed for 6 h and then poured into water (300 ml). A $CHCl_3$ extract of the solution was washed with water, dried, and evaporated. Recrystallization of the residue from MeOH gave 315 mg (55%) of **13b**, mp 235–236 °C.

Evaporative distillation of 200 mg of **5** at 240 °C (0.01 Torr) over a period of 2 h gave 120 mg of crude **13b**, mp 234–235 °C after recrystallization from MeOH.

2-Acetyl-9-phenyl-2,3-dihydro-1*H*-benz[*f*]isoindol-1-one (15a). A mixture of 1.2 g of **13a**, 0.6 g of 30% Pd/C, and 60 ml of *p*-cymene was refluxed and stirred for 30 h. The catalyst was separated and washed with more hot solvent. Concentration of the solutions gave 1.05 g (88%) of **15a**: mp 242.5–245.5 °C, raised to 250–251 °C on recrystallization (needles) from absolute EtOH; ν 3030, 1730, and 1690 cm^{-1}; λ_{max} 347 nm (log ϵ 3.63), 338 sh (3.58), 304 (4.00), 293 (4.00), 249 (4.84); NMR δ 8.0–7.1 (m, 10 aromatic H), 4.90 (slightly split s, $J \simeq$ 1 Hz, 2 H, CH_2N), and 2.57 (s, 3, Ac); mass spectrum *m/e* 301 (42, M^+), 259 (100, $M^+ - CH_2{=}C{=}O$), 223 metastable peak (301 → 259).

Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.81; H, 4.94; N, 4.33.

9-Phenyl-2,3-dihydro-1*H*-benz[*f*]isoindol-1-one (15b). A. From 15a. Deacetylation of **15a** was effected as per **13a** to give platelets from absolute EtOH (71%): mp 258–259 °C; ν 3460, 1700 cm^{-1}; ν (KBr) 870 (lone aromatic H), 760, 750, 740, and 690 cm^{-1} (4 and 5 vicinal aromatic H); λ_{max} 335.5 nm (log ϵ 3.49), 322.5 (3.39), 300 (3.88), 289 (3.88), 278 sh (3.71), 241 (4.82); NMR δ 8.1–7.2 (m, 10 aromatic H), 7.0–6.75 (m, 1 H, NH), and 4.51 (broad s, 2, methylene); mass spectrum *m/e* 259 (100, M^+), 258 (64), 202 (40, $M^+ - CH_2NHC{=}O$).

Anal. Calcd for $C_{18}H_{13}NO$: C, 83.37; H, 5.05; N, 5.40. Found: C, 83.28; H, 5.40; N, 5.32.

B. From 13b. Dehydrogenation of **13b** was effected in the manner used with **13a**. Addition of petroleum ether (bp 30–60 °C) to the concentrated *p*-cymene solution gave 0.5 g (56%) of **15b**, mp 258–259 °C after recrystallization from EtOH.

C. From Amide 5. A solution of 498 mg of **5** in 300 ml of xylene was refluxed (N_2 atmosphere) for 5 h. The residue from evaporation of the solvent was crystallized from MeOH to give 255 mg (51%) of **15b**, mp 255–256 °C.

Cyclization of *N*-(*cis*-Cinnamyl)phenylpropiolamide (4). By the high-dilution method 1 g of amide **4** (in 700 ml of Ac_2O) gave a dark red gum. TLC of this crude product (silica gel/$CHCl_3$) showed only one fluorescent spot which corresponded to **13a**. Crystallization of the product from MeOH gave 368 mg (32%) of **13a** as needles, mp 183–184 °C.

Cyclization of *N*-(Phenylpropargyl)-*trans*-cinnamamide (9). The high-dilution method produced a 75% yield of platelets (**24**), mp 271–272 °C, from absolute EtOH. Product **24** was assigned the structure of a molecular compound (or eutectic mixture) containing about 20% of 2-acetyl-4-phenyl-2,3-dihydro-1*H*-benz[*f*]isoindol-1-one (**16a**) and 80% of 2-acetyl-4-phenyl-2,3,3a,4-tetrahydro-1*H*-benz[*f*]-isoindol-1-one (**14a**): ν 1730, 1700 cm^{-1}; ν (KBr) 830 (trisubstituted alkene in **14a**), 760 and 700 cm^{-1} (4 and 5 vicinal aromatic H); λ_{max} 318 nm sh (log ϵ 4.07), 305 (4.16), 247 sh (4.15), 237 (4.27); NMR ($CDCl_3$, 100 MHz)[31] δ 7.8–6.6 (m, aromatic H plus H-9 in **14a**), 4.1–3.0 (m, aliphatic H), and 2.58 (s, Ac), plus singlets at 8.54 (H-9), 4.70 (methylene), and 2.71 (Ac) due to the presence of **16a**; mass spectrum *m/e* 303 (100, M^+ for **14a**), 261 (93, $M^+ - CH_2{=}C{=}O$), 259 (35), 204 (37), 203 (46), 202 (62), 178 (90), 43 (61, Ac^+).

Anal. Calcd for $4C_{20}H_{17}NO_2{\cdot}1C_{20}H_{15}NO_2$: C, 79.29; H, 5.52; N, 4.62. Found: C, 79.54; H, 5.74; N, 4.63.

2-Acetyl-4-phenyl-2,3-dihydro-1*H*-benz[*f*]isoindol-1-one (16a). Dehydrogenation of preceding mixture **24** by means of Pd/C in *p*-cymene was followed by washing the catalyst with $CHCl_3$. The concentrated filtrate was treated with cyclohexane and cooled to yield 82% of leaflets, mp 276–278 °C, converted to needles (mp 277–278 °C) on recrystallization from $CHCl_3$: ν 1730 and 1690 cm^{-1}; ν (KBr) 1730, 1690, 900 (lone aromatic H), 790 (4 vicinal aromatic H), 765 and 700 cm^{-1} (5 vicinal aromatic H); λ_{max} (dioxane) 347 nm (log ϵ 3.69) 332.5 (3.59), 304 (4.04), 293, (4.02), 282 sh (3.81), 250 (4.85); NMR δ 8.48 (s, 1 H at C-9), 8.3–7.2 (m, 9 aromatic H), 4.71 (s, 2, methylene), and 2.70 (s, 3 H, Ac); mass spectrum *m/e* 301 (37, M^+), 259 (100, $M^+ - CH_2{=}C{=}O$), 258 (41), 258–257 metastable peak (259 → 258).

Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.91; H, 5.09; N, 4.34.

4-Phenyl-2,3,3a,4-tetrahydro-1*H*-benz[*f*]isoindol-1-one (14b). Mixture **24** (594 mg) was deacetylated by refluxing in a solution of 7 ml of concentrated hydrochloric acid and 500 ml of absolute EtOH to give 431 mg (84%) of platelets: mp 284.5–287 °C dec from EtOH; ν 3440, 1700 cm^{-1}; ν (KBr) 1660, 830, 765, 750, 700 cm^{-1}; λ_{max} 293 nm (log ϵ 4.16), 233 (4.40), 227 (4.38); NMR (CF_3CO_2H) δ 8.3–6.7 (m, 11 H, aromatic H, NH, plus H-9) and 4.2–3.1 (m, 4 H); mass spectrum 261 (100, M^+), 259 (36), 204 (36), 203 (37), 202 (53), 178 (75). Neither the NMR nor the ultraviolet spectrum of this sample showed evidence for the presence of **16b** (vide infra).

Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73: H, 5.79; N, 5.36. Found: C, 82.77; H, 5.70; N, 5.19.

4-Phenyl-2,3-dihydro-1*H*-benz[*f*]isoindol-1-one (16b). Deacetylation of **16a** (vide supra) gave platelets (quantitative yield) from EtOH: mp 265–267 °C raised to 268.5–269.5 °C on recrystallization; ν 3460 and 1700 cm^{-1}; λ_{max} 334 nm (log ϵ 3.55), 318 (3.47), 298 (3.95), 287.5 (3.93), 238 (4.85); NMR (CF_3CO_2H) δ 8.60 (s, 1 H at C-9), 8.4–7.1 (m, 10 H, aromatic H plus NH), and 4.70 (broad s, 2 H, methylene); mass spectrum *m/e* 259 (100, M^+), 258 (53), 230 (33), 202 (32), 182 (57).

Anal. Calcd for $C_{18}H_{13}NO$: C, 83.37; H, 5.05; N, 5.40. Found: C, 83.35; H, 5.15; N, 5.75.

Dehydrogenation of **14b** (vide supra) gave platelets (78%) of **16b**, mp 255–260 °C raised to 265–266 °C on recrystallization.

Cyclization of *N*-(Phenylpropargyl)phenylpropiolamide (6). Cyclization of **6** occurred at high dilution to yield a crude product which showed two overlapping spots by TLC (silica gel/$CHCl_3$). The NMR spectrum indicated the presence of a mixture of **15a** and **16a**. Integration of peaks at δ 8.48, 4.69, and 2.68 gave a ratio of 1:2:3 for signals from **16a**; and integration of peaks at 4.92 and 2.58 gave a ratio of 2:3 for those from **15a**. Integrations of the methylene signals gave a ratio of **15a**:**16a** 1.3:1. Recrystallization of the crude product from EtOH gave needles (72%): mp 240–248 °C; ν (KBr) 1730, 1690, 900, 765, 750, and 700 cm^{-1}. Efforts to effect separation of the mixture were unsuccessful.

2-Acetyl-4-phenyl-2,3,3a,4,9,9a-hexahydro-1*H*-benz[*f*]isoindol-1-one (26). Cyclization of amide **11** at high dilution (1 g in 1250 ml of Ac_2O) gave a red gum which crystallized from MeOH to form 290 mg (25%) of needles, mp 181–183 °C, converted to prisms (mp 185–186 °C) on recrystallization from the same solvent: ν 1735 and 1700 cm^{-1}; λ_{max} 306 nm (log ϵ 2.70), 252 sh (3.05); NMR δ 7.5–6.6 (m, 9 aromatic H), 4.1–2.7 (m, 7 aliphatic H), and 2.49 (s, 3 H, Ac).

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.75; H, 6.25; N, 4.57.

Dehydrogenation of 26. A mixture of 73 mg of **26**, 85.2 mg of *N*-bromosuccinimide, 2 mg of benzoyl peroxide, and 25 ml of CCl_4 was refluxed (N_2 atmosphere) for 3 h, whereupon evolution of HBr ceased. The cooled solution was filtered (to remove succinimide) and evaporated. TLC (silica gel/$CHCl_3$:EtOAc 19:1) showed two fluorescent spots. The faster moving spot had an R_f value identical with that of **16a**. The other spot was not identified. Preparative TLC of 80 mg of reaction product gave 40 mg of needles of **16a**, mp 262–265 °C.

Miscellaneous Studies. Efforts to cyclize amide **8** at high dilution gave a red, viscous liquid which resisted efforts at crystallization. TLC showed only a smear and NMR spectrometry showed broad, unresolved multiplets.

Amine hydrochloride **3** (1 g) was treated with excess 5% aqueous Na_2CO_3 solution and the free *cis*-cinnamyl amine, which was collected by extraction into ether, was refluxed with 200 ml of Ac_2O for 6 h. Evaporation of the solvent and further processing gave a dark liquid, identified as *N*-acetyl-*N*-(*cis*-cinnamyl)acetamide by NMR analysis: (CCl_4) δ 7.4–7.0 (m, 5 aromatic H), 6.58 (d of t, J = 1.5 and 11.5 Hz, 1 H, C**H**=CHCH$_2$), 5.50 (overlapping d of t, J = 6 and 11.5 Hz, 1 H, CH=C**H**CH$_2$), 4.52 (d of d, J = 6 and 1.5 Hz, 2 H, methylene), and 2.13 (s, ~6 H, 2 Ac). This compound was not obtained analytically pure.

Registry No.—**1**, 4335-60-8; **2**, 30011-36-0; **3**, 4335-62-0; **13a**,

59015-40-6; **13b**, 59015-41-7; **14a**, 59015-42-8; **14b**, 59015-43-9; **15a**, 59015-44-0; **15b**, 59015-45-1; **16a**, 59015-46-2; **16b**, 59015-47-3; **24**, 59015-48-4; **26**, 59015-49-5; *N*-(phenylpropargyl)phthalimide, 4656-94-4; *trans*-cinnamoyl chloride, 17082-09-6; *cis*-cinnamoyl chloride, 59015-50-8; phenylpropiolyl chloride, 7299-58-3; *N*-acetyl-*N*-(*cis*-cinnamyl)acetamide, 59015-51-9; *trans*-cinnamyl chloride, 21087-29-6.

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Use of Substituted Benzyl Esters as Carboxyl-Protecting Groups in Solid-Phase Peptide Synthesis

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Benzyl esters have been widely used for the protection of side-chain carboxyl groups in peptide synthesis. This paper describes the evaluation of two substituted benzyl esters of glutamic acid in solid-phase peptide synthesis. The γ-*p*-chlorobenzyl ester of glutamic acid was found to be significantly more stable to trifluoroacetic acid cleavage than the benzyl ester, and yet it could be removed without difficulty by liquid HF at 0 °C. Hence it is recommended for side-chain protection of aspartic acid and glutamic acid residues in longer syntheses. Peptides with side-chain carboxyl groups protected by *p*-nitrobenzyl esters were prepared by solid-phase peptide synthesis followed by cleavage from the resin with HBr in acetic acid. Two protected peptides were synthesized by this approach, the tripeptide H-Gly-Glu(γ-OBzl-*p*-NO_2)-Ala-OH, and the amino-terminal hexapeptide from the acyl carrier protein of *E. coli*.

Protection of the side-chain carboxyl groups of aspartic and glutamic acids in peptide synthesis has been most commonly achieved by benzyl esters.[1] This protection is very suitable, in that it is fairly stable to the conditions of peptide synthesis, and it can be removed at the end of the synthesis by strongly acidic or reducing conditions.[2]

There are important reasons, however, for seeking alternative carboxyl-protecting groups, for it has been shown[3–5] that benzyl esters are not completely stable to the conditions commonly used to remove the *t*-Boc[6,7] group during peptide synthesis. This lability gives rise to a cumulative loss of side-chain protection, and increases the possibility of branching of the peptide chain, particularly during a long synthesis.

An important potential use of more stable carboxyl-protecting groups is in the synthesis of protected peptides, which can be used in fragment syntheses and semisynthesis of proteins.[8–12] In an attempt to develop a simple method for the preparation of protected peptides, it was decided to examine the synthesis of a fully protected peptide using standard solid-phase techniques. If the side chains and amino terminus of a peptide were blocked by groups stable to acidolysis, the synthesis could be performed on a chloromethylated resin, with the usual *t*-Boc group for α-amino protection, and using HBr in acetic acid for the cleavage of the peptide from the resin.

This paper describes the evaluation of two acid-stable carboxyl-protecting groups: the *p*-chlorobenzyl ester as a group of moderately increased stability for use in longer syntheses, and the *p*-nitrobenzyl ester as a much more stable group for the synthesis of protected peptides with HBr

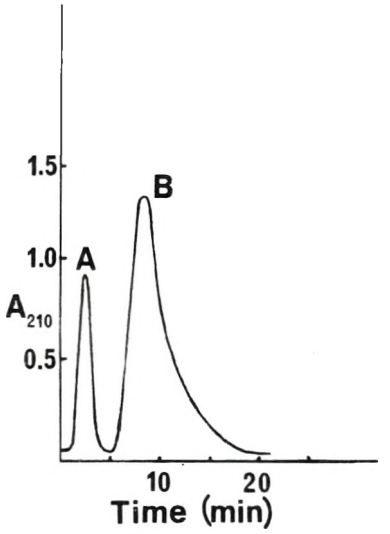

Figure 1. High-pressure liquid chromatography of a sample of Glu(γ-OBzl) partially cleaved by trifluoroacetic acid–dichloromethane (1:1). Peak A represents benzyl alcohol and impurities present in the solvent and was not quantitated. Peak B is Glu(γ-OBzl). The cleavages and analyses were carried out as described in the Experimental Section.

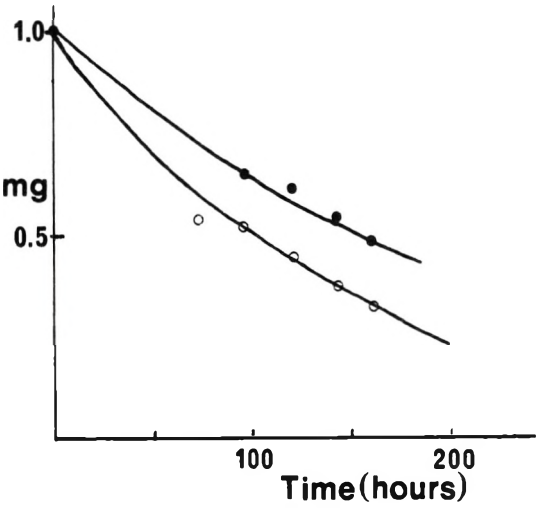

Figure 2. A study on the hydrolysis of glutamic acid monoesters by trifluoroacetic acid–dichloromethane (1:1) at 45 °C. The rate of hydrolysis was quantitated by the amount of monoester remaining using the procedures described in the Experimental Section, Glu(γ-OBzl) (○) and Glu(γ-OBzl-*p*-Cl) (●).

cleavage from the resin. In a recent communication[13] we have described a new facile method for the preparation of the substituted benzyl esters of aspartic and glutamic acids. The ready availability of these amino acid derivatives has allowed us to examine the use of more stable esters of glutamic acid in the solid-phase synthesis of several model peptides. These studies have led to the synthesis of the amino-terminal hexapeptide of the acyl carrier protein of *E. coli* in a fully protected form, suitable for use in semisynthesis.

Results and Discussion

The criteria for a more stable side-chain protecting group are that it should be readily prepared, that it should be significantly more stable to the conditions of peptide synthesis than benzyl ester protection, and that it should be readily removed at the end of the synthesis. The acid stability of the benzyl ester group can be conveniently increased by the introduction of electron-withdrawing substituents into the aromatic ring. For example, Merrifield[14] investigated the use of chlorinated benzyloxycarbonyl (Z) groups for the protection of lysine residues, and found that (4-Cl-Z)Lys was three times more stable than Z-Lys to trifluoroacetic acid in dichloromethane (1:1). Other chlorinated derivatives were found to be even more stable, some to the point of being difficult to remove by HF cleavage. Similarly Li[15] employed the 4-bromobenzyl ester for the protection of Glu residues, and claimed it to be four times as stable as the benzyl ester, but detailed evidence as to the suitability of this protecting group in peptide synthesis was not presented.

Following the above criteria, the *p*-chlorobenzyl ester was selected for investigation. It can be readily prepared by the copper-catalyzed hydrolysis method of Prestidge et al.,[13] and the starting material, *p*-chlorobenzyl alcohol, is commercially available. The stability of this ester to trifluoroacetic acid (TFA) hydrolysis was studied, and compared with the stability of the benzyl ester. In order to provide a measurable extent of hydrolysis in a reasonable time, the studies were performed at 45 °C. The samples from these hydrolyses were analyzed by high-pressure liquid chromatography (HPLC) on a Porasil silica column with potassium phosphate buffer (pH 4.0, 0.02 M) as the eluent. A typical chromatogram is shown in Figure 1. It should be noted that an aqueous buffer system was used in conjunction with a silica column. The aqueous system minimized tailing of the benzyl esters, and should prove to be a useful method for the analysis of very polar compounds on HPLC. The time course of the cleavage of para-substituted benzyl esters of glutamic acid is shown in Figure 2.

The *p*-chlorobenzyl ester was found to be twice as stable as the benzyl ester to hydrolysis by TFA–CH_2Cl_2 (1:1) at 45 °C. From the temperature dependence of Hammett ρ factors[16] it can be predicted that this stability difference will be significantly greater at room temperature. The *p*-chlorobenzyl ester was also found to be completely removed by liquid HF at 0 °C for 30 min and can therefore be recommended for the synthesis of large peptides. Although the data reported by Merrifield[3] imply that benzyl ester protection of Asp and Glu is adequate for moderate sized peptides, it should be emphasized that such protection is inadequate for small acidic proteins such as the acyl carrier protein (ACP) from *E. coli*. This protein contains 14 glutamic and 7 aspartic acid residues out of a total of 77. Using the method of Merrifield[3] it can be calculated that in a synthesis of ACP using benzyl ester protection of Asp and Glu, 5.6% of the chains would be prematurely deprotected at a glutamic residue and 2.75% at an aspartic residue. These side reactions should be reduced to an acceptable level by the use of a more stable protecting group such as *p*-chlorobenzyl.

Although many approaches to the synthesis of protected peptide fragments have been suggested, involving alternative resins and cleavage techniques,[17-31] none has found a wide application.

One disadvantage is that many of the modified resins involve lengthy syntheses.[18,19,23,24,30] More significantly, the effect of these modifications on the properties of the resin has not been evaluated, so that the routine use of such resins must await further evaluation of their behavior, particularly in longer synthesis. It has been observed that for mild, selective cleavage procedures, yields can decrease with larger peptides,[31,32] so that these methods may not be suitable for the synthesis of large protected peptides.

Most of the published approaches to solid-phase fragment synthesis involve changes in the standard procedures of synthesis. These new procedures are not only time consuming but also often contain difficulties which would make them unsuitable for routine use, or limitations which would restrict their applicability to a wide range of syntheses. For example, resins which form a labile bond to the first amino acid require the use of even more labile α-amino protection during the synthesis[23,24] which is inconvenient for routine use. Resins

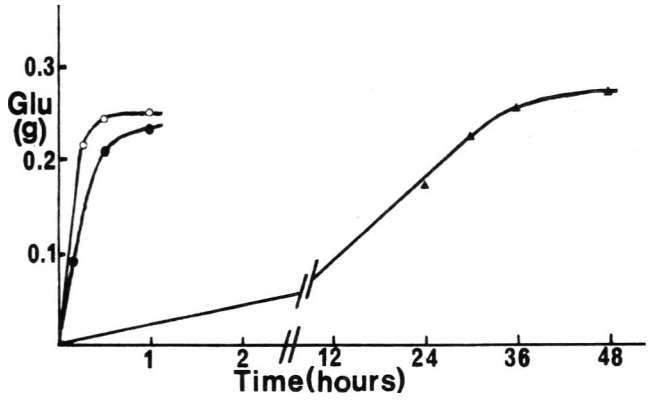

Figure 3. A study on the hydrolysis of glutamic acid monoesters by HBr and acetic acid. The rate of hydrolysis was quantitated by the amount of Glu liberated using the procedures described in the Experimental Section and gave values for Glu from Glu(γ-OBzl) (○), from Glu(γ-OBzl-*p*-Cl) (●), and from Glu(γ-OBzl-*p*-NO_2) (▲).

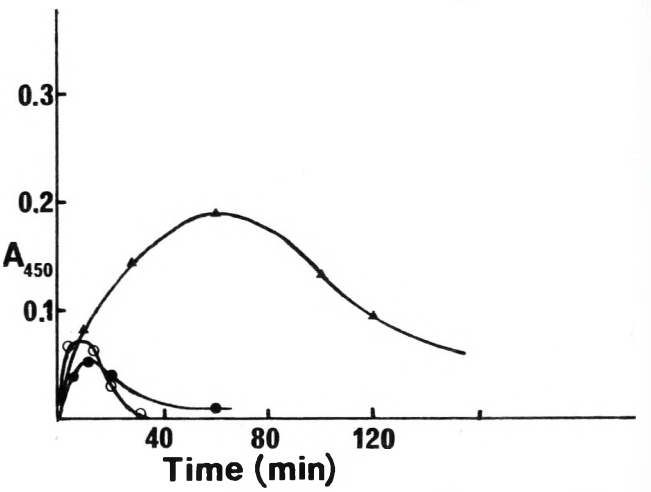

Figure 4. A study on the cleavage of protected tripeptides H-Gly-Glu(OBzl-X)-Ala-OH from the resin with HBr and acetic acid. The amount of peptide cleaved was quantitated by uv measurements, using the procedures described in the Experimental Section and gave values for X = H (○), X = *p*-Cl (●), and X = *p*-NO_2 (▲).

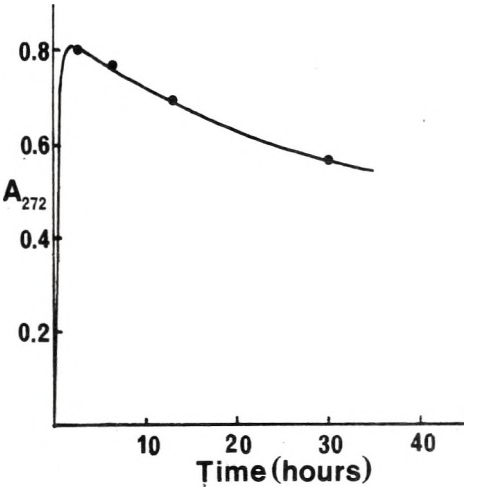

Figure 5. A study on the cleavage of the protected hexapeptide, ACP_{1-6} from the resin with HBr and acetic acid. The amount of peptide cleaved was quantitated by uv measurement, using the procedures described in the Experimental Section.

where the bond to the peptide chain is activated in the penultimate step involve treating the peptide with such reagents as peroxides or methyl iodide.[20–22] This activation step is not compatible with peptides which contain Trp, Cys, or Met, and may also cause racemization.[33]

An attractive approach to the solid-phase synthesis of protected peptides is to use standard methods of peptide synthesis with the exception that the side chains are protected by acid-stable groups. A range of protecting groups are known which are stable to HBr in acetic acid; for example, Lys(TFA), Arg(NO_2), His(DNP) Cys(Acm). If a suitable acid-stable group could be found for carboxyl protection, and the amino terminus was protected by trifluoroacetylation, HBr cleavage would release a peptide with only one free functional group, the carboxyl-terminal COOH, which could be used to form an active ester for fragment condensation.

For this reason the stability of *p*-chlorobenzyl and *p*-nitrobenzyl esters to HBr cleavage was investigated, and the results of these studies are shown in Figure 3. The *p*-chlorobenzyl ester was found to be only twice as stable to HBr as the benzyl ester, and this stability was not sufficient for the isolation of peptides protected with this group. The *p*-nitrobenzyl ester, however, was 50 times as stable as the benzyl ester, and was used for the synthesis of two protected peptides. The stability of *p*-nitrobenzyl esters to HBr cleavage is well known,[34,35] but little use appears to have been made of this property in peptide syntheses.[36,37]

The tripeptide H-Gly-Glu(OBzl-*p*-NO_2)-Ala-OH was prepared by this method, but the rate of loss of the *p*-nitrobenzyl ester was much greater than expected. This was attributed to the fact that the cleaved protected peptide was not stable to HBr/acetic acid. The data are given in Figure 4, and it can be seen by comparison with Figure 3 that benzyl, *p*-chlorobenzyl, and *p*-nitrobenzyl side-chain protection were all cleaved from this peptide at rates six times greater than that of the corresponding amino acid esters. Further analysis of the products by electrophoresis at pH 2.1 and 6.5 showed a variety of cleavage products formed on the disappearance of the protected peptide. It has been suggested[38,39] that glycine, having no side chain, facilitates intramolecular reactions in peptides containing this residue, and it may have accelerated the acidolytic decomposition of this protected tripeptide. A similar rearrangement has been observed for the aspartylglycine sequence under acidic conditions.[38] The lability of this peptide to acidolysis was confirmed by the observation that the purified peptide decomposed to the extent of approximately 50% on standing in 50% acetic acid for 24 h at 20 °C. The protected peptide, however, was isolated and purified in modest overall yield. In view of these results, and other observations,[40] it is recommended that treatment of peptides with HBr/acetic acid should be minimized. For example, two 20-min cleavages have been found to give excellent results for removal of peptides from the resin. The peptide was shown to be homogeneous on high-voltage paper electrophoresis at pH 2.1 and 6.5. The peptide was neutral at pH 6.5, which demonstrated that the *p*-nitrobenzyl ester had been retained in the cleavage reaction. The success obtained with these model peptides encouraged us to proceed to the synthesis of a larger peptide.

The 1–6-hexapeptide from the acyl carrier protein of *E. coli* was synthesized in a fully protected form using *p*-nitrobenzyl protection for the two side-chain carboxyl groups. This peptide is seen as a stringent test of synthetic technique, as it contains three carboxyl groups, two hydroxyl groups, an amino group, and a guanidino function within six residues. Serine and threonine were protected as benzyl ethers, glutamic acid as *p*-nitrobenzyl esters, the amino terminus by acetylation, and the arginine residue as the nitro derivative. The time course for cleavage of the protected peptide from the resin by HBr in acetic acid was studied by uv measurement of aliquots of the reaction mixture and the results are shown in Figure 5. It was found that two 20-min cleavages gave a good yield of peptide with minimal loss of *p*-nitrobenzyl ester protection.

Assuming $\epsilon_{275} = 1.0 \times 10^4$ for both Glu(OBzl-*p*-NO_2) and Arg(NO_2), the rate of deprotection of glutamic acid residues was calculated to be 2.1×10^{-4} min^{-1} per residue. This corresponds to a rate of deprotection of this peptide which is about half that of the free amino acid. The peptide was purified by gel filtration on Sephadex G10 and recrystallization from methanol.

It was observed in this preparation that *p*-nitrobenzyl esters confer the additional advantage of greater crystallinity, as the crude peptide could be purified by recrystallization to give a product homogeneous by electrophoresis at pH 2.1 and 6.5 and TLC in three solvents. Electrophoresis at pH 6.5 (R_f 0.35 relative to glutamic acid) showed that the glutamic, α-amino, and arginine residues were still protected. Amino acid analysis was satisfactory for the protected hexapeptide (Arg 1.0, Ile 1.0, Glu 2.2, Thr 0.8 and Ser 0.8) except for low values for serine and threonine, which can be attributed to destruction during acid hydrolysis. Moritz and Wade[41] have reported that during acid hydrolysis in the presence of Arg(NO_2), Thr and Ser can be destroyed to the extent of 40%.

In summary, we propose the use of *p*-chlorobenzyl esters for side-chain carboxyl protection in the synthesis of moderately sized peptides and proteins, in that this protecting group is easily used in solid-phase peptide synthesis, readily cleaved by HF, and gives a useful increase in stability to trifluoroacetic acid. We also propose the use of acid-stable side-chain protecting groups, including the *p*-nitrobenzyl ester protection for Asp and Glu, for the synthesis of protected peptides using conventional techniques. The *p*-nitrobenzyl ester has both the advantages of facile preparation and removal, in this case by hydrogenolysis.[35] It is hoped that this approach will greatly reduce the effort required for the synthesis of protected peptides by the solid-phase method, thus leading to a wider use of semisynthesis. For example, the protected ACP hexapeptide prepared by this method can now be used in fragment condensation, as all reactive groups are blocked with the exception of the hydroxyl group of Ser and Thr, which should not need to be blocked for a single active ester coupling.

Experimental Section

All melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Amino acid analyses were carried out on a Beckman 120C amino acid analyzer. Thin layer chromatography (TLC) was done on precoated silica gel plates (Eastman Chromagram). The *t*-Boc group was removed with HCl vapor, and TLC plates were visualized with ninhydrin. Peptide syntheses were performed on a Schwarz-Mann automated peptide synthesizer, using the procedure of Hancock et al.[42] High-pressure liquid chromatography (HPLC) was performed on a Waters Model 6000 chromatograph, and monitored by a Cecil CE212 variable wavelength uv monitor. *p*-Chlorobenzyl alcohol and *p*-nitrobenzyl alcohol were supplied by Fluka, and polystyrene–divinylbenzene resins and protected amino acids were supplied by Schwarz-Mann. All solvents were of analytical grade, or purified as in previous studies.[42]

HF cleavages were performed in an all-Daiflon HF reaction apparatus Type II (Protein Research Foundation, Japan). Mass spectrometry was performed on an AEI MS-9 instrument at a potential of 70 eV.

Synthesis of Substituted Benzyl Monoesters of Aspartic and Glutamic Acids. Amino acid diester tosylates were synthesized by the method of MacLaren, Savige, and Swan.[43] These diesters were selectively hydrolyzed by Cu(II) in the presence of base to give the side-chain esters, using the procedure recently published.[13] In a typical synthesis glutamic acid di(*p*-nitrobenzyl) ester *p*-toluenesulfonate (11 g, 20 mmol) was dissolved in ethanol (180 cm^3) and aqueous $CuSO_4 \cdot 5H_2O$ (20 g, 80 mmol in water, 350 cm^3) was added. The pH was raised to 8.0 and maintained at that value for 60 min with 1 M NaOH. The pH was then lowered to 3.0 with 3 M HCl, and the precipitate of the copper complex of Glu(γ-OBzl-*p*-NO_2) was filtered off and washed with water, ethanol, and ether. This complex was then dissolved in boiling aqueous ethylenediaminetetraacetic acid disodium salt (10 g in 100 cm^3 of water) and the product precipitated immediately. The solution was cooled and the product filtered off and washed with water and ethanol. The product (3.1 g, 54%) was obtained as a light brown powder, mp 158–159 °C (lit. 158–159 °C).[13]

Synthesis of *tert*-butyloxycarbonyl amino acid substituted benzyl esters was performed by the dimethyl sulfoxide procedure of Stewart and Young.[44] In a typical synthesis, Glu(γ-OBzl-*p*-NO_2) (9.40 g, 33 mmol) was suspended in dimethyl sulfoxide (200 cm^3) and *tert*-butyloxycarbonyl azide (6 cm^3) and triethylamine (9 cm^3) were added. The mixture was stirred at room temperature for 3 days, by which time it was homogeneous. The product was isolated by the standard procedure as a viscous yellow-brown oil (11.55 g, 94%) which was homogeneous by TLC on silica plates with 1-butanol–pyridine–water (2:2:1, R_f 0.72) and was used without further purification. The *t*-Boc *p*-chlorobenzyl ester of glutamic acid was synthesized by the same procedure, and was isolated as an oil which crystallized on standing overnight to give the product in 63% yield. The product was recrystallized from ether–petroleum ether: mp 80–81 °C; TLC (1-butanol–pyridine–water, 2:2:1) R_f 0.82, (ethanol–aqueous NH_3, 9:1) R_f 0.78. Anal. Calcd for $C_{17}H_{22}ClNO_6$ (371.41): C, 54.98; H, 5.97; N, 3.77; Cl, 9.55. Found: C, 54.91; H, 5.84; N, 4.10; Cl, 9.50.

Stability of Monoesters to Trifluoroacetic Acid Cleavage. Samples of the monoester (1 mg) were dissolved in trifluoroacetic acid–dichloromethane (1:1, 0.1 cm^3) and held at 45 °C in sealed tubes. At predetermined time intervals a tube was dried with a stream of N_2 and the residue dissolved in potassium phosphate buffer, 0.02 M, pH 4.0 (25 cm^3). These solutions were examined by HPLC on a Corasil I pellicular silica column (2 ft × 0.125 in.), eluting with the potassium phosphate buffer at 4 cm^3/min, and 2300 psi. The elution was monitored by uv absorption at 210 nm and calibrated with standard samples. The results are shown in Figure 2, and a typical chromatogram is given in Figure 1.

The rates of deprotection with TFA–CH_2Cl_2 (1:1) at 45 °C were Glu(γ-OBzl) 6.6×10^{-3} min^{-1}, Glu(γ-OBzl-*p*-Cl) 4.1×10^{-3} min^{-1}. Hence the *p*-chlorobenzyl ester is 1.6 times as stable to trifluoroacetic acid under these conditions as is the benzyl ester.

Stability of Monoesters of HBr–Acetic Acid. The monoester (500 mg) was suspended in HBr in acetic acid (33% w/w, 25 cm^3) and allowed to react at room temperature. Aliquots were taken at various times, dried by a stream of N_2, and dissolved in water (3 cm^3). A portion of this solution (10 μl) was spotted onto silica gel plates which were developed with 1-butanol–pyridine–acetic acid–water (15:10:3:12) and visualized with ninhydrin. The spots corresponding to glutamic acid and the monoester were cut out and eluted with boiling ethanol, and the absorbance of the ninhydrin color read at 565 (Glu) or 520 nm (monoester) and compared with standards. The results are given in Figure 3. The heterogeneity of the reaction mixture made rigorous kinetic analysis difficult, and therefore the time at which glutamic acid reached a stable maximum concentration was taken as the completion of the reaction: Glu(γ-OBzl) 1.5 h, Glu(γ-OBzl-*p*-Cl) 3 h, Glu(γ-OBzl-*p*-NO_2) 48 h.

Stability of Monoesters to HF Cleavage. The monoester (100 mg) was suspended in liquid HF (10 cm^3) for 30 min at 0 °C in the HF line. The HF was then evaporated off under reduced pressure, and the residue dissolved in water (100 cm^3). Aliquots of this solution (50 μl) were chromatographed on silica TLC plates with 1-butanol–pyridine–water (2:2:1). Both the benzyl and *p*-chlorobenzyl esters were completely cleaved by HF under these conditions. The *p*-nitrobenzyl ester was stable, and no free glutamic acid was detected by TLC, confirming the observation of Marglin.[39]

Synthesis of Protected Tripeptides. Peptides of the sequence H-GLY-Glu(OBzl-X)-Ala-OH, where X is H, *p*-Cl, or *p*-NO_2, were synthesized by standard solid-phase techniques.[42] *t*-Boc-alanine substituted polystyrene–1% divinylbenzene resin (1 g, 660 μmol/g) was used in each case. The *t*-Boc group was used for α-amino protection, and 50% trifluoroacetic acid in dichloromethane was used for deprotection. The coupling reagent used was dicyclohexylcarbodiimide.

Portions of the peptide resins (500 mg) were cleaved with HBr in acetic acid (30% w/w, 20 cm^3). Samples (1 cm^3) were taken at various time intervals, dried with a stream of N_2, dissolved in water (0.5 cm^3), and analyzed by high-voltage paper electrophoresis at pH 6.5 and 2.1 in pyridine–acetic acid–formic acid buffers. The electrophoretigrams were visualized with ninhydrin and the appropriate spots cut out and eluted with boiling ethanol. The absorbances of the ninhydrin colors were read at 450 nm (for protected peptides) or 400 nm (for deprotected peptides). The results are shown in Figure 4.

The tripeptide H-Gly-Glu(OBzl-*p*-NO_2)-Ala-OH was prepared by HBr cleavage of the appropriate peptide resin (509 mg) with HBr in acetic acid (33% w/w, 7 cm^3) for 1 h at room temperature. The cleavage products were evaporated under reduced pressure and the residue containing the peptide was dissolved in 50% acetic acid (3 cm^3) and

purified by gel filtration on a Sephadex G10 column (26 × 270 mm) in the same solvent. The peptide was then purified by ion exchange on a Sephadex SP-C25-120 column (16 × 95 mm) with an ammonium acetate buffer (pH 4.5, 0.01 M). The peptide was eluted from the ion exchange column as a single symmetrical peak, and gave only one spot on high-voltage paper electrophoresis at pH 6.5. The pooled peak was desalted on a Sephadex G10 column (26 × 270 mm) in 50% acetic acid and lyophilized. The peptide was recrystallized from ethanol–ether to give a white, crystalline powder (12 mg, 13% yield based on picric acid analysis of the resin peptide[45]), mp 190.5–192 °C. Amino acid analysis after acid hydrolysis (HCl–propionic acid, 1:1, for 2 h at 130 °C) gave Gly 1:1, Glu 1.0, Ala 1.1. A satisfactory elemental analysis could not be obtained, possibly because of the extremely hygroscopic nature of the peptide. Consequently the material was acetylated to increase the volatility[46] and submitted for mass spectrometry. Although the sample gave no molecular ion, a fragment was observed at *m/e* 345.0932 consistent with the loss of two water molecules from the desired tripeptide, and all further fragment peaks were consistent with the proposed structure. The peptide was homogeneous on high-voltage paper electrophoresis at pH 2.1 and 6.5 (R_f 0.75 and 0.0, respectively, relative to glutamic acid).

Synthesis of the Protected 1–6-Hexapeptide from the Acyl Carrier Protein of *E. coli*. The peptide H-Ser(Bzl)-Thr(Bzl)-Ile-Glu(OBzl-*p*-NO_2)-Glu(OBzl-*p*-NO_2)-Arg(NO_2)-resin was synthesized by standard solid-phase techniques as above. The peptide was cleaved from a portion of the resin (100 mg) using HBr in acetic acid (33% w/w, 2 cm^3). Samples (5 μl) were taken at various time intervals, diluted to 5 cm^3 with distilled water, and their uv absorption at 275 nm was measured. The results are given in Figure 5.

The hexapeptide Ac-Ser-Thr-Ile-Glu(OBzl-*p*-NO_2)-Glu(OBzl-*p*-NO_2)-Arg(NO_2)-OH was prepared by acetylation of the peptide resin (800 mg) with acetic anhydride–triethylamine (5 g of each, a 50-fold excess over the amount of peptide on the resin) for 30 min at room temperature, followed by two HBr cleavages (HBr, 33% in acetic acid, 12 cm^3) for 20 min at room temperature. The peptide was purified by gel filtration on a Sephadex G10 column (26 × 280 nm) in 50% acetic acid, and recrystallization from methanol. The peptide was obtained as an off-white powder (2.44 mg, 34.8% yield of the amount of peptide resin, mp 158–162 °C). Its purity was examined by the TLC on silica gel followed by visualization with the chlorine–starch–KI peptide spray.[47] The peptide was found to be homogeneous in the following systems: ethanol–aqueous ammonia (9:1 v/v, R_f 0.54), methanol (R_f 0.79), and 1-butanol–pyridine–acetic acid–water (15:10:3:12, R_f 0.78). On high-voltage paper electrophoresis in pyridine–acetic acid–formic acid buffers at pH 2.1 and 6.5 the product behaved as a fully protected peptide, migrating with a net charge of 0 and −1, respectively.

The peptide was hydrolyzed with HCl–propionic acid (1:1 v/v) in the presence of anisole (0.1 cm^3) at 130 °C for 30, 60, and 120 min. Amino acid analysis of the hydrolysate gave Arg 1.0, Ile 1.0 (extrapolated to infinite time), Glu 2.2, Thr 0.8, and Ser 0.8 (extrapolated to zero time).[41]

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Registry No.—*t*-Boc-*p*-chlorobenzyl glutamate, 59092-58-9; H-Gly-Glu(OBzl-*p*-NO_2)-Ala-OH, 59092-59-0; Ac-Ser-Thr-Ile-Glu(OBzl-*p*-NO_2)-Glu(OBzl-*p*-NO_2)-Arg(NO_2)-OH, 59092-60-3.

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Studies on Cyclic Peptides. 5. Conformation and Interaction with Small Molecules of Cyclic Hexapeptides Containing Glutamic Acid or Aspartic Acid Residue[1]

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Cyclic hexapeptides containing glutamic acid, aspartic acid, or their esters were synthesized, and the conformation of the cyclic peptides was investigated by NMR spectroscopy. Cyclo-(Gly-X-Gly)$_2$ [X = Glu(OBzl), Glu(OMe), Glu, Asp(OBzl), Asp] were considered to possess C_2 conformation in Me_2SO and water in which two glycyl residues preceding the X residue are intramolecularly hydrogen bonded. Substitution on the side chain carboxyl group did not influence the structure of the peptide backbone significantly, and the intramolecular interaction of the peptide backbone with the phenyl ring of benzyl ester was negligible. The effect of additives on the NMR spectra of cyclo-(Gly-X-Gly)$_2$ was examined. The resonance signal of the intramolecularly hydrogen-bonded glycyl peptide protons was shifted noticeably to lower field on addition of guanidine hydrochloride or lithium bromide in Me_2SO-d_6. The shift could be interpreted almost completely in terms of a conformational change of the peptide backbone. It was suggested that medium effects (polar effects) and increasing association with Me_2SO and with the anion of added salts accompany the conformational change. In water, on the other hand, the NH resonance signals shifted to a higher field on addition of guanidine hydrochloride or lithium bromide. This was ascribed to the salt-induced weakening of the hydration of NH.

Cyclic peptides are functionalized rigid systems and have been used to study the relationship between biological activity and conformation of biomolecules.[3] Synthetic cyclic peptides can also be used as model compounds for proteins including enzyme. Cyclic peptides are small, simple compounds in which several features of proteins can be implanted without producing an end-group effect, because they have neither an N nor a C terminus.

Conformational studies of cyclic peptides have increasing importance,[3] but investigations of cyclic peptides containing glutamic acid or aspartic acid have not yet been carried out, though acidic amino acids play an important role in enzymic reactions.[4] It is advantageous to use these cyclic peptides for the following reasons: (1) by modifying the side chain carboxyl group the effect of the side chain on the conformation of cyclic peptide can be investigated, (2) by introducing a benzyl ester group intramolecular interactions such as side chain–backbone or side chain–side chain interaction may be studied, (3) by modifying the side chain carboxyl group the cyclic peptides are made soluble in various solvents so that the effect of solvent and additives on the conformation of cyclic peptides can be investigated in detail. In the present investigation several cyclic hexapeptides containing acidic amino acid residues or their esters were synthesized, their conformation in solution was investigated by NMR spectroscopy, and their interaction with small molecules was investigated in relation to the conformational properties.

Experimental Section

NMR Spectra. NMR spectra were obtained at 100 MHz with a Varian HA-100 and at 220 MHz with a Varian HR-220 spectrometer. Assignment of resonance signals was made by spin decoupling using a Hewlett-Packard 4204A digital oscillator.

Materials. Deuterium compounds were purchased from Fabriqué par CEA-France Service des Molécules Marguées. Inorganic salts were purified by recrystallization. Anhydrous LiBr was obtained by heating at 150 °C for 2 days in vacuo.

Cyclic Peptides. Cyclic hexapeptides were synthesized from the respective tripeptide *p*-nitrophenyl esters by cyclodimerization in pyridine under a high dilution.[5,6] Melting points were uncorrected. Thin layer chromatography (TLC) was run on silica gel G plate. Solvent systems for TLC were (A) chloroform–methanol–acetic acid (95:5:3), (B) chloroform–methanol–pyridine (95:5:3), (C) 1-butanol–acetic acid–water (4:1:1), and (D) 1-butanol–acetic acid–water–pyridine (30:6:24:20). Molecular weight was obtained by a cryoscopic determination using the lactam of *cis*-hexahydro-*p*-aminobenzoic acid[7] as a solvent.

Boc-Glu(OBzl)-Gly-OH (I). To an aqueous solution of glycine (0.75 g, 0.01 mol) and sodium bicarbonate (1.68 g, 0.02 mol) was added Boc-Glu(OBzl)-ONSu[8] (4.3 g, 0.01 mol) in THF (20 ml). After 1 h the reaction mixture was evaporated to concentrate, acidified with 1 N hydrochloric acid, and then extracted with ethyl acetate. After drying over sodium sulfate the organic layer was evaporated to give an oil, which crystallized on standing after being treated with ether and *n*-hexane. Recrystallization from ethyl acetate–*n*-hexane gave 2.7 g (69%) of I: mp 116–116.5 °C; $[\alpha]^{25}D$ −8.4° (c 1.0, EtOH); R_f^A 0.63, R_f^B 0.19, R_f^C 0.82, R_f^D 0.73. Anal. Calcd for $C_{19}H_{26}O_7N_2$: C, 57.86; H, 6.64; N, 7.10. Found: C, 57.45; H, 6.58; N, 7.17.

Boc-Gly-Glu(OBzl)-Gly-OH (II). To a solution of I (3.94 g, 0.01 mol) in dioxane (10 ml) was added 4.4 N hydrogen chloride in dioxane (30 ml). The reaction mixture was allowed to stand at room temperature for 30 min. After the solvent had been evaporated to dryness under reduced pressure, the oily residue was dissolved in water (70 ml) containing sodium bicarbonate (2.5 g, 0.03 mol). The solution was extracted with ether twice, and then the THF solution of Boc-Gly-ONSu[9] (2.7 g, 0.01 mol) was added to the aqueous solution. The reaction mixture was treated as described for the preparation of I. The residual oil was treated with *n*-hexane and gave a white gel, yield 2.50 g (66%), R_f^A 0.35.

Boc-Gly-Glu(OBzl)-Gly-ONp (III). II (1.4 g, 3 mmol) and *p*-nitrophenol (0.42 g, 3 mmol) were dissolved in THF (50 ml) at 0 °C. To the solution DCC (0.62 g, 3 mmol) was added. It was kept at 0 °C for 2 h and then overnight at room temperature. The precipitated dicyclohexylurea was removed by filtration and the filtrate was concentrated. Crystallization occurred upon the addition of 2-propanol. The slightly yellow precipitate was recrystallized from 2-propanol: yield 1.29 g (75%); mp 81–84 °C; $[\alpha]^{25}D$ −10.8° (c 1.0, DMF); R_f^A 0.73, R_f^B 0.74, R_f^C 0.83, R_f^D 0.81. Anal. Calcd for $C_{27}H_{32}O_{10}N_4$: C, 56.64; H, 5.63; N, 9.79. Found: C, 56.60; H, 5.62; N, 9.58.

Cyclo-(Gly-Glu(OBzl)-Gly)$_2$ (IV). To a dioxane solution of III (614 mg, 1 mmol) was added 4 N hydrogen chloride in dioxane (3 ml). After 30 min a white precipitate was filtered and dried over P_2O_5 in vacuo, yield of HCl·Gly-Glu(OBzl)-Gly-ONp 468 mg (87%), mp 162–163 °C. It was dissolved in DMF (10 ml) containing glacial acetic acid (0.1 ml). The solution was added drop by drop into pyridine (350 ml) at 60 °C over a 3-h period. The reaction mixture was kept at room temperature overnight. After the solvent had been evaporated off; methanol (100 ml) was added to the residue to give a white solid (252 mg, 92%). Recrystallization from DMF–methanol gave 202 mg (74%) of IV: mp 298 °C; $[\alpha]^{25}D$ −29.2° (c 1.0, DMF); R_f^B 0.08, R_f^C 0.70, R_f^D 0.73; mol wt 623 ± 75 (theory 666.67). Anal. Calcd for $C_{32}H_{38}O_{10}N_6$: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.41; H, 5.70; N, 12.47. The same product is obtainable from the cyclodimerization of Boc-Glu(OBzl)-Gly-Gly-ONp [mp 112–114 °C, $[\alpha]^{25}D$ −1.5° (c 1.0, DMF)]. However, the yield of this reaction was as low as 40%.

Table I. Peptide Proton Resonances and Conformation Parameters of Cyclic Hexapeptides[a]

Cyclic hexapeptide	Solvent	Gly_I δ^b	Gly_I $d\delta^c/dT$	Gly_I $J(\Sigma)^d$	Gly_I ϕ^e	Gly_{II} δ^b	Gly_{II} $d\delta^c/dT$	Gly_{II} $J(\Sigma)^d$	Gly_{II} ϕ^e	X δ^b	X $d\delta^c/dT$	X J^f	X ϕ^e
IV	Me_2SO	7.47	0.0001	9.5	−150	8.40	0.0035	11.6	+70	8.45	0.0047	6.5	−80
VI	Me_2SO	7.51	0.0002	9.2	−150	8.29	0.0052	11.0	+60	8.35	0.0047	6.0	−75
VI	H_2O	6.65	0.0023	10.0	−140	7.33	0.0068	11.5	+70	7.28	0.0074	6.5	−80
V	Me_2SO	7.54	0.0004	10.2	−140	8.37	0.0047	10.6	+60	8.40	0.0039	6.5	−80
V	H_2O	6.64	0.0022	10.0	−140	7.34	0.0065	12.0	+70	7.28	0.0071	6.5	−80
X	Me_2SO	7.65	0.0001	9.0	−150	8.34	0.0057	11.0	+60	8.68	0.0043	6.0	−75
XI	Me_2SO	7.57	0.0006	9.2	−150	8.27	0.0056	10.6	+60	8.61	0.0068	6.0	−75

[a] Cyclic hexapeptides investigated are represented as cyclo-(Gly_I-X-Gly_{II})$_2$. [b] Tetramethylsilane in Me_2SO-d_6 and *tert*-butyl alcohol in water as internal references. [c] Temperature coefficient, ppm to a higher field per degree. [d] Sum of H–C^α–N–H coupling from NH resonance. [e] Conformational angle determined from J value and CPK model. [f] From C^αH and NH resonance in Me_2SO-d_6 and from NH resonance in water.

Cyclo-(Gly-Glu-Gly)$_2$ (V). To IV (203 mg, 0.3 mmol) was added anhydrous HF (1 ml) in the presence fo anisole (0.18 ml). After standing at 0 °C for 1 h HF was removed. The residue was solidified with ether and dried over KOH in vacuo. The product V was recrystallized from water–methanol–ether: yield 107 mg (73%); mp 246 °C; $[\alpha]^{25}D$ −17.1° (*c* 1.0, DMF); R_f^C 0.30, R_f^D 0.59. Anal. Calcd for $C_{18}H_{26}O_{10}N_6 \cdot 2H_2O$: C, 41.37; H, 5.79; N, 16.09. Found: C, 41.11; H, 5.38; N, 16.01.

Cyclo-(Gly-Glu(OMe)-Gly)$_2$ (VI). Boc-Glu(OMe)-OH[10] (11.8 g, 45 mmol), *N*-hydroxysuccinimide (5.2 g, 45 mmol), and DCC (9.3 g, 45 mmol) were reacted in ethyl acetate (150 ml) at 0 °C for 1 h and the reaction mixture was allowed to stand at room temperature overnight. After precipitated dicyclohexylurea had been filtered, the solution was evaporated. The residual oil (R_f^A 0.53) was dissolved in THF (60 ml) and was added to the aqueous solution (60 ml) of glycylglycine (5.3 g, 40 mmol) and sodium bicarbonate (6.6 g, 80 mmol). The reaction mixture was allowed to stand at room temperature for 1 h. After THF had been evaporated, the solution was extracted with ether, acidified with 1 N hydrochloric acid, and then extracted with ethyl acetate. The organic layer dried over sodium sulfate was concentrated to a colorless syrup (7.5 g, R_f^A 0.09). The residue was treated with *p*-nitrophenol (2.8 g, 20 mmol) and DCC (4.1 g, 20 mmol) in ethyl acetate (50 ml) at 0 °C. After 24 h dicyclohexylurea was removed by filtration and the filtrate was evaporated to give a slightly yellow syrup (9.8 g, R_f^A 0.22). It was washed with ether and *n*-hexane. Hydrogen chloride (4 N) in dioxane (40 ml) was added to the oil. After 20 min the solvent was evaporated to give a white solid. It was washed twice with ethyl acetate and dissolved in DMF (50 ml) containing glacial acetic acid (0.5 ml). Cyclization was accomplished in pyridine (500 ml) as described above for the preparation of IV. Recrystallization from hot water–methanol gave 245 mg of VI: mp 320 °C; $[\alpha]^{25}D$ −15.6° (c 0.5, H_2O); R_f^C 0.21, R_f^D 0.56; mol wt 537 ± 34 (theory 514.49). Anal. Calcd for $C_{20}H_{30}O_{10}N_6$: C, 46.69; H, 5.88; N, 16.34. Found: C, 46.46; H, 5.76; N, 16.27.

H-Asp(OBzl)-Gly-OH (VII). To an aqueous solution (20 ml) of glycine (0.75 g, 10 mmol) and sodium bicarbonate (1.68 g, 20 mmol) was added slowly Boc-Asp(OBzl)-ONSu[11] (4.2 g, 10 mmol) in THF (20 ml) at room temperature. After the solution was stirred for 30 min the reaction mixture was treated as described above for the preparation of I. Hydrogen chloride (4 N) in dioxane (30 ml) was added to the oily product (3.8 g). After standing at room temperature for 30 min the solvent was evaporated. The residue was taken up in ethanol (10 ml) and neutralized by triethylamine. The white mass was recrystallized from water–acetone. The yield was 2.1 g (75%): mp 170–171 °C; $[\alpha]^{25}D$ +51.5° (*c* 1.0, H_2O); R_f^C 0.46, R_f^D 0.63. Anal. Calcd for $C_{13}H_{16}O_5N_2$: C, 55.71; H, 5.75; N, 10.00. Found: C, 55.79; H, 5.77; N, 10.10.

Boc-Gly-Asp(OBzl)-Gly-OH (VIII). An ethanolic solution (40 ml) of Boc-Gly-ONSu[9] (1.36 g, 5 mmol) was added slowly to the aqueous solution of VII (1.40 g, 5 mmol) and sodium bicarbonate (0.80 g, 10 mmol). After 20 h the solution was treated as described above for the preparation of II. Recrystallization from ethyl acetate–ether gave white crystals: yield 1.45 g (66%); mp 113.5–114 °C; $[\alpha]^{25}D$ −18.3° (*c* 1.0, EtOH); R_f^A 0.50, R_f^B 0.13, R_f^C 0.75, R_f^D 0.74. Anal. Calcd for $C_{20}H_{27}O_8N_3$: C, 54.91; H, 6.22; N, 9.61. Found: C, 54.57; H, 6.23; N, 9.54.

Boc-Gly-Asp(OBzl)-Gly-ONp (IX). This compound was synthesized from VIII (1.75 g, 4 mmol), *p*-nitrophenol (0.56 g, 4 mmol), and DCC (0.82 g, 4 mmol) as described above for the preparation of III. The product was recrystallized from ethyl acetate–*n*-hexane: yield 1.90 g (85%); mp 83–85 °C; $[\alpha]^{25}D$ −21.3° (c 1.0, DMF); R_f^A 0.77, R_f^B 0.83, R_f^C 0.84, R_f^D 0.82. Anal. Calcd for $C_{26}H_{30}O_{10}N_4$: C, 55.91; H, 5.14; N, 10.03. Found: C, 55.94; H, 5.69; N, 10.08.

Cyclo-(Gly-Asp(OBzl)-Gly)$_2$ (X). Hydrogen chloride (4 N) in dioxane (3.6 ml) was added to IX (647 mg, 1.2 mmol). After 30 min the white precipitate was filtered and dried in vacuo (465 mg, mp 166–168 °C). The tripeptide ester was cyclized in pyridine (350 ml) as described above for the preparation of IV. A white solid appeared upon the addition of ethanol to the residual oil which was recovered by evaporation. It was recrystallized from DMF–water–ether. The yield was 135 mg (40%): mp 256 °C; $[\alpha]^{25}D$ −33.1° (c 1.0, DMF); mol wt 644 ± 31 (theory 638.62); R_f^B 0.05, R_f^C 0.64, R_f^D 0.65. Anal. Calcd for $C_{34}H_{34}O_{10}N_6$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.46; H, 5.69; N, 13.11.

Cyclo-(Gly-Asp-Gly)$_2$ (XI). X (220 mg, 0.35 mmol) was allowed to react with anhydrous HF and treated as described above for the preparation of V. Recrystallization from water–ethanol–ether gave 120 mg (72%) of XI, mp 270 °C. Anal. Calcd for $C_{16}H_{22}O_{10}N_6 \cdot 2H_2O$: C, 38.86; H, 5.30; N, 16.99. Found: C, 38.51; H, 5.11; N, 17.07.

Results and Discussion

Conformation of Peptide Backbone and Side Chain. Either in Me_2SO-d_6 or in water resonance signals corresponding to three amino acid residues were observed for all of the cyclic hexapeptides studied, which have six amino acid residues. It is therefore very likely that the cyclic hexapeptides possess C_2 symmetry in these solvents on the NMR time scale. It would be convenient to number the amino acid residues in the cyclic hexapeptides, when necessary, as cyclo-(Gly_I-X-Gly_{II})$_2$ [X = Glu(OBzl), Glu(OMe), Glu, Asp(OBzl), or Asp]. Parameters concerning the resonance signals for the peptide proton (NH) of the cyclic hexapeptides are described in Table I. There is very little change in chemical shift and temperature coefficient of the resonance signals for the peptide protons of the individual amino acid residues when X is varied. In Me_2SO-d_6 a resonance signal for one of the two types of glycyl peptide protons is located at higher magnetic field (δ 7.47–7.65 ppm) with a small temperature coefficient (0.0001–0.0006 ppm/deg) (represented as Gly_I in Table I; see also the text), while those for the other glycyl peptide protons (represented as Gly_{II} in Table I; see also the text) and two X peptide protons are located at lower magnetic fields (δ 8.27–8.40 and 8.35–8.68 ppm, respectively) with a large temperature coefficient (0.0035–0.0074 ppm/deg). This type of peptide proton resonance has been reported to be characteristic of the C_2-symmetric conformation consisting of two β turns with two glycyl peptide protons intramolecularly hydrogen bonded, and the other two glycyl peptide protons exposed to solvent on the NMR time scale.[12] This was the case for the five cyclic hexapeptides investigated here.

It would be valuable to definitively assign the conformational positions of the X residues in the cyclic structure and

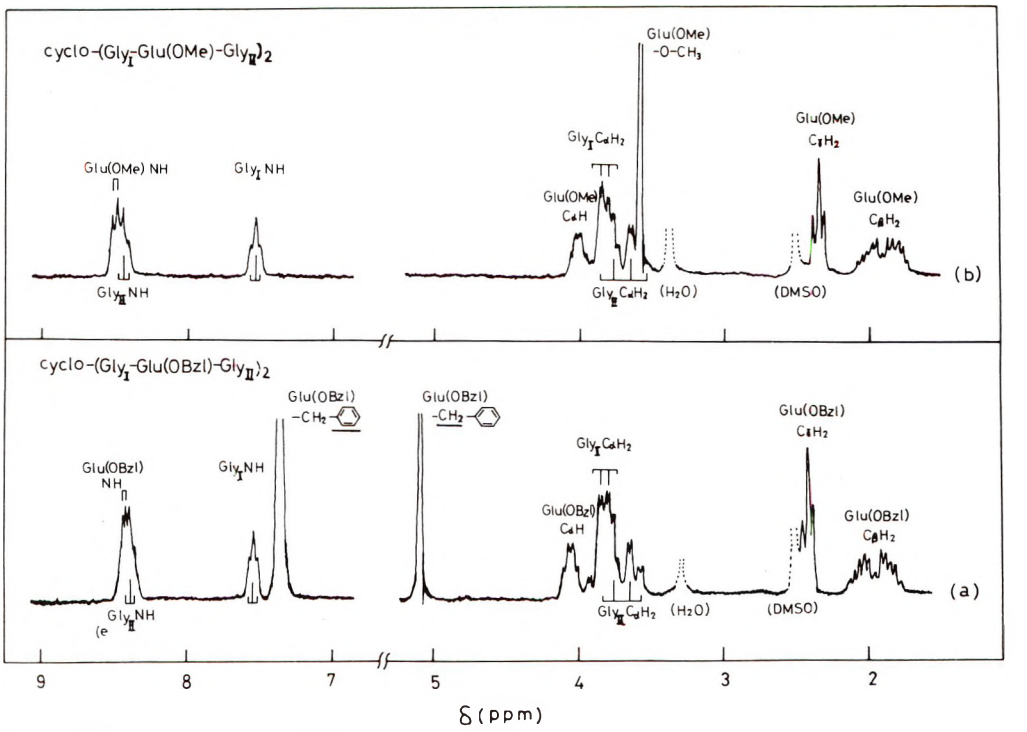

Figure 1. 220-MHz NMR spectra of IV (a) and VI (b) in Me_2SO-d_6.

to decide what glycine residues are intramolecularly hydrogen bonded. Spin-decoupling experiments revealed that the C$^\alpha$H proton of the X residue is vicinal to the NH proton in the lower field. Therefore, the X residues carrying a bulky side chain are considered to take the corner positions of the β turn, as has been reported by Kopple et al.[12-14] for mono- or 1,4-disubstituted cyclic hexapeptides. In other words, the extended parts of the cyclic structure are occupied by glycine residues. There are two types of β turn, depending on whether the residues preceding or succeeding the X residues are transannularly hydrogen bonded (type A or B according to Pease et al.[15]). Recent investigations using ^{1}H[12-14] or ^{13}C[15] NMR spectroscopy on the selectively deuterated cyclic hexapeptides showed that the type A β turn is a likely conformation for cyclo-(Gly-X-Gly)$_2$, where X = Pro, Tyr, and so on. After these investigations it was considered that two glycine residues preceding the X residues, that is Gly$_I$ in the present representation, are transannularly hydrogen bonded in the present cyclic hexapeptides.

Substitution on the side chain carboxyl group [X = Glu, Glu(OMe), or Glu(OBzl)] did not influence significantly the conformation of the cyclic hexapeptides in Me_2SO-d_6, as is clearly seen from the ϕ values shown in Table I. ϕ values were calculated using the Karplus-type equation which relates coupling constant J with dihedral angle θ of H-N-C$^\alpha$-H.[14] It is also seen that the length of the side chain did not influence the conformation of the cyclic hexapeptides in Me_2SO-d_6. This is evident from the comparison of ϕ angles of X and XI with those of IV and V, respectively.

Comparison of IV and VI will give precise information on the conformation of the side chain. Magnetic anisotropy of the benzene ring of the benzyl ester could cause an upfield shift of the NMR spectrum of the peptide backbone,[16] if the benzyl group of the side chain stacks over the peptide backbone. In Figure 1, however, there is little difference in chemical shift and H-N-C$^\alpha$-H coupling constants of the two spectra, except for the C$^\alpha$H, C$^\beta$H$_2$, and C$^\gamma$H$_2$ resonance signals of Glu(OBzl) which appear at slightly lower magnetic field than those of Glu(OMe). This difference could have been caused by the more electron-withdrawing benzyl group. The above result indicates the conformational similarity of the two cyclic hexapeptides and the absence of intramolecular interaction between the peptide backbone and the benzene ring of the side chain. This is also evident from the similarity of the chemical shifts of the phenyl protons of IV and II[17] in Me_2SO-d_6.

A large splitting of the C$^\alpha$H$_2$ resonance of the Gly$_{II}$ residue was observed: 0.19 ppm for IV and 0.21 ppm for VI. This sort of splitting has usually been interpreted in terms of a different environment of the two protons.[14] On the other hand, a small splitting of the C$^\alpha$H$_2$ resonance was observed for the Gly$_I$ residue: 0.08 ppm for IV and 0.10 ppm for VI. This small splitting indicates that the two protons are in a similar environment. It is also evident above that there is little difference in the splittings of the C$^\alpha$H$_2$ resonances of IV and VI. The splitting of the Gly$_{II}$-C$^\alpha$H$_2$ signal of IV (0.19 ppm) is only slightly larger than that of the Gly$_I$-C$^\alpha$H$_2$ signal (0.08 ppm). These experimental findings confirm that interactions of the phenyl ring with the peptide backbone are absent. If they interacted, the methylene splitting of IV would have been much larger.[13]

In aromatic cyclic dipeptides the aromatic side chain is frequently folded onto the main chain amide,[18-24] while for larger cyclic peptides such folding is rare. Kopple et al.[13] have reported that the tyrosine side chain of cyclo-(Gly-Gly-His-Gly-Gly-Tyr) and cyclo-(Gly-Gly-Gly-Gly-Gly-Tyr) might interact with the peptide backbone in Me_2SO. Walter et al.[25,26] have reported that the aromatic side chains of adjacent tyrosine and phenylalanine residues of lysine vasopressin and arginine vasopressin stack with each other so that the ring current effect caused an anomalous downfield shift of the phenylalanyl NH resonance in Me_2SO. In order for an aromatic group to associate intramolecularly with a peptide bond, a number of requirements need be fulfilled. In this respect, Kopple's observation[19] that in a homologous series of cyclo-(Gly-X) where X is phenylglycine, phenylalanine, or homophenylalanine Gly-C$^\alpha$H$_2$ is shielded by the nearby aromatic ring only in cyclo-(Gly-Phe) is very suggestive. The intramolecular aromatic–amide interaction can be achieved only when the optimum alignment of the relevant groups is attained at the expense of unfavorable side chain orientations.

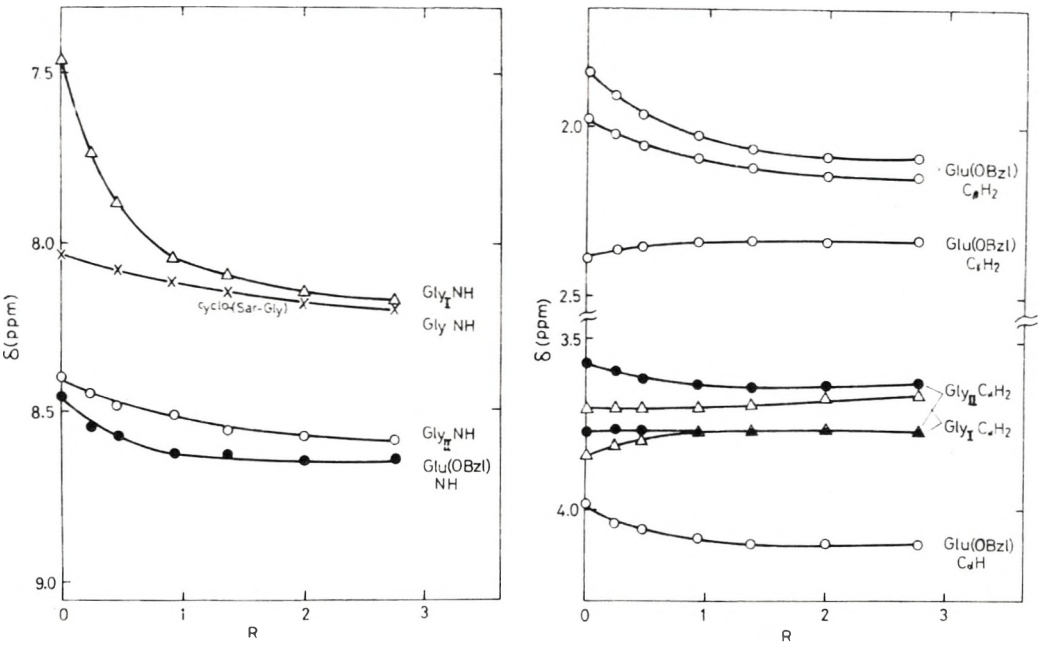

Figure 2. The shift of resonance signals of IV with the addition of guanidine hydrochloride in Me_2SO-d_6. Concentrations of IV and cyclo-(Sar-Gly) were 44 and 48 mg/ml, respectively. *R*: moles of guanidine hydrochloride per unit mole of peptide bond of IV.

The failure to maintain the folded conformation of IV and X could be due mainly to the unsatisfactory fulfillment of the above requirement.

Intermolecular aromatic–amide interactions were found to be weak, too. On addition of benzene-d_6 up to 50% to a solution of cyclo-(Gly-X-Gly)$_2$ in Me_2SO-d_6, all resonance signals shifted only slightly to lower field. The absence of interaction with benzene may be attributable to the polarity of solvent. Interactions of the cyclic peptide with strongly polar Me_2SO destroys the weak amide–aromatic compound interactions. In a previous investigation[16] the intermolecular interaction between cyclic peptides and benzene was observed only in a less polar solvent such as $CDCl_3$. Therefore, the absence of intramolecular aromatic–amide interactions in IV and X could be partly ascribed to the breakdown of the weak interactions, if any does occur, by highly dipolar Me_2SO.

The NMR pattern of peptide protons of V and VI observed in Me_2SO was also observed in water. Two solvent-shielded glycyl peptide protons (Gly$_I$-NH) and four solvent-exposed peptide protons (Gly$_I$-NH and X-NH) were present. The temperature coefficient for Gly$_I$-NH signal in water (0.002 ppm/deg) was larger than that in Me_2SO-d_6 (0.0002–0.0004 ppm/deg). So the Gly$_I$-NH proton must be more solvent exposed in water than in Me_2SO-d_6. *J* values (ϕ angles) were less sensitive to the nature of solvent (Table I). As far as the *J* values concern, V and VI assume the same conformation either in water or in Me_2SO-d_6. It can be considered that the backbone of cyclic peptides undergoes some segmental motion depending on the environment (solvent, temperature). The oscillating motion should bring the internal peptide proton in contact with solvent, a situation which is reflected in a larger temperature coefficient in water than in Me_2SO. On the other hand, this sort of oscillating segmental motion does not influence the time-averaged dihedral angle. This is the reason why the *J* values were almost insensitive to the nature of solvent, whereas the temperature coefficients were sensitive. This speculation might be supported by a T_1 study using ^{13}C NMR spectroscopy,[27] which is now underway.

In trifluoroacetic acid (TFA), only two NH resonance signals were observed with IV. The benzyl glutamyl peptide protons resonated at 8.06 ppm and the glycyl peptide protons resonated at 7.95 ppm. Their intensity ratio was 1:2. The higher field resonance signal for the glycyl peptide protons observed in Me_2SO was not observed in TFA. That only one resonance signal was present for the glycyl peptide protons could be due to fortuitous overlapping of two resonance signals, one of which is upfield in Me_2SO but shifted downfield in TFA, and the other downfield in Me_2SO but shifted upfield in TFA. These changes might have been caused by the change of the type of hydrogen bonding from Me_2SO···HN to TFA···HN, Me_2SO being a stronger proton acceptor in hydrogen bonding than TFA.[28] The same pattern of solvent effect on the chemical shifts of peptide proton signals has been observed by Kopple et al. for cyclo-[Gly(d_2)-Tyr-Gly(d_2)]$_2$ and cyclo-(Gly-Leu-Gly)$_2$.[14] These NMR changes may be interpreted as well in terms of a conformational change of the peptide backbone. In fact, the resonance signal of benzyl methylene protons was a small doublet (2 Hz at 220 MHz) in TFA. This is not caused by the decomposition of benzyl ester group, because NMR spectra were recorded soon after the solution was prepared.[29] These events are quite different from those observed in Me_2SO-d_6. To explain all the phenomena uniformly, one should consider a conformational change. Some other conformation of IV may be favored in TFA than the C_2-symmetric one in Me_2SO or water. A number of cyclic hexapeptides not containing imino acid have been synthesized and their conformation in solution has been investigated. The C_2 conformation stated above has been shown to prevail in these cyclic hexapeptides.[30] The unusual conformation of IV in TFA observed here is therefore an interesting phenomenon.

To summarize, cyclic hexapeptides containing glutamic or aspartic acid residue were synthesized and their conformation was first investigated in various solvents. They have the C_2-symmetric conformation with two internally hydrogen-bonded glycine residues in Me_2SO and water. The nature of the side chains had little effect on the conformation. A different conformation was observed for IV in TFA.

Effect of Additives. The effect of additives on the NMR spectra of cyclo-(Gly-X-Gly)$_2$ was examined in Me_2SO-d_6 and water. Figure 2 shows the shift of the NMR signals of IV caused by the addition of guanidine hydrochloride in Me_2SO-d_6. A downfield shift was observed for the NH, glutamyl C$^\alpha$H, Gly$_{II}$-C$^\alpha$H$_2$, and glutamyl C$^\beta$H$_2$ resonance signals, while an upfield shift was observed for the glutamyl C$^\gamma$H$_2$ and

Table II. Shift of NMR Signals of Cyclic Hexapeptides[a] Induced by Additives

Additives	Cyclic hexapeptide	Solvent	Concn,[b] mg/ml	R[c]	$\Delta\delta$,[d] ppm: NH Gly_I	NH Gly_{II}	NH X	β X	γ X	α X	α Gly_I	α Gly_{II}
LiBr	IV	Me_2SO	55	2	0.50	0.06	0.12	0.24	0	0.14		
								0.24				
Gu·HCl	IV	Me_2SO	55	2	0.67	0.13	0.16	0.25	−0.06	0.10	−0.04	0
								0.16			−0.07	0.06
Gu·HNO_3	IV	Me_2SO	55	2	0.13	0.01	0.01	0	0	0	0	0
LiI	IV	Me_2SO	55	2	0.06	−0.02	0.01					
LiSCN	IV	Me_2SO	55	2	0.13	0.00	0.06					
$LiClO_4$	IV	Me_2SO	55	2	0.06	−0.03	0					
$LiNO_3$	IV	Me_2SO	55	1	0	0	0	0	0	0	0	0
LiBr	VI	Me_2SO	44	2	0.62	0.11	0.14					
LiBr	VI	H_2O	22	10	−0.02	−0.21	−0.17					
Gu·HCl	VI	H_2O	22	10	0.04	−0.04	−0.04					
Gu·HCl	VI	Me_2SO	44	2	0.57	0.20	0.23					
LiBr	V	Me_2SO	33	2	0.45	0.07	0.14	0.18	−0.01	0.13		
								0.16				
Gu·HCl	V	Me_2SO	33	2	0.56	0.21	0.23	0.21	0	0.10		
								0.20				
LiBr	X	Me_2SO	33	2	0.71	0.18	−0.03	0.26		0.23		
								0.21				
Gu·HCl	X	Me_2SO	33	2	1.09	0.46	0.20	0.25		0.22	0	0
								0.17			−0.01	0.10

[a] Cyclic hexapeptides investigated are represented as cyclo-(Gly_I-X-Gly_{II})$_2$. [b] Concentration of cyclic hexapeptide. [c] Moles of additives per unit mole of peptide bond of cyclo-(Gly-X-Gly)$_2$. [d] Shift of NMR signals with the addition of the additives. Minus sign designates the shift to an upper field.

Gly_I-$C^\alpha H_2$ resonance signals. No shift was observed for benzyl resonance signals. The shift was most marked were R (moles of additive per unit mole of peptide bond) was smaller than 1, and became least marked where R exceeded 2. The effect of lithium bromide was quite similar to that of guanidine hydrochloride. It should be noted here that the downfield shift of the resonance signal of the intramolecularly hydrogen-bonded glycyl peptide protons (Gly_I-NH) appearing at upper field was far greater than that of the other two resonance signals due to the intermolecularly hydrogen-bonded peptide protons (Gly_{II}-NH, X-NH) appearing at a lower field. The effect of guanidine hydrochloride and lithium bromide on the NMR spectra of V, VI, and X in Me_2SO-d_6 was investigated as well. In all the case, the effect of additives was similar; the experimental results are summarized in Table II.

The large downfield shift of the Gly_I-NH protons induced by the salts could be explained as follows: (1) either the cation or the anion of the added salts interacts with the peptide bond of the cyclic hexapeptides, or the anion interacts with the peptide proton;[31] (2) consequently the backbone conformation of the cyclic hexapeptides is changed, so that the peptide protons emerge out of the plane of the cyclic hexapeptide and become more exposed to solvent; (3) concurrently the intramolecular hydrogen bonding is weakened; (4) the peptide protons suffer the polar effect of solvent; and (5) the exposed peptide NH associates with solvent and with the anion of the added salts.[31] The effect of added salts seemed to be complex, and any one of the reasons 1–5 alone does not seem to fully explain the experimental findings as described below.

In cyclic hexapeptides containing two L-Pro-D-Phe sequences where the internal peptide protons are almost completely shielded from solvent, the chemical shift of the internal peptide proton signal has been reported to be dependent on the strength of hydrogen bonding.[32] However, in the present cyclo-(Gly_I-X-Gly_{II})$_2$, the shielding of the Gly_I-NH by solvent is not complete and a rapid dynamic equilibrium between an intramolecular hydrogen bonding and a hydrogen bonding with solvent may have been established. For these cyclic hexapeptides it would be unsuitable to ascribe the downfield shift entirely to the weakening of the intramolecular hydrogen bonding.

Cation binding to the carbonyl oxygen and anion binding to the peptide nitrogen may take place as the result of salt addition. Since the NMR shift changes shown in Table II depend on the anion used when various lithium salts were added, the salt effect appears to be associated with the anion. However, binding of the anion to the peptide nitrogen may increase the electron density of the latter and might therefore bring about an upfield shift of the peptide proton signal. However, this was not observed. Therefore we have to postulate a significant change in the environment of the peptide protons that overcomes the effect of the anion binding and causes the peptide protons to shift downfield.

Since the anion of the added salt is not well solvated in Me_2SO, it will tend to associate with the peptide proton. This may also induce a change in conformational distribution.[31]

The conformational change of the cyclic hexapeptides induced by added salts is evident in terms of the change of ϕ angles calculated on the basis of the coupling constant $J_{H\text{-}N\text{-}C^\alpha\text{-}H}$, which are shown in Table III. As the result of the conformational change, the Gly_I-NH protons, which originally were in the plane of the cyclic hexapeptide, now protrude from the plane to some extent. It has been reported that the resonance signal of the intramolecularly hydrogen-bonded peptide protons appears at higher field due to the magnetic anisotropic effect of the peptide bond residing at the corner of the β turn.[33] On the basis of the ϕ values in the presence of the added salts and using the anisotropic magnetic susceptibility of formamide given by Tigelaar and Flygare,[34] the extent of shielding of the Gly_I-NH protons was calculated. Calculations shown in Table III revealed that the change of the magnetic anisotropy caused by the conformational change can explain about one-third the amount of the downfield shift.

The Gly_I-NH protons that become more exposed to solvent

Table III. Shielding of Peptide Protons and the Conformational Change of IV[a] in Me_2SO

	Gly_I-NH			Gly_{II}-NH			Glu(OBzl)-NH			
R[b]	δ, ppm	J[c], Hz	ϕ, deg	δ, ppm	J,[c] Hz	ϕ, deg	δ, ppm	J, Hz[d]	ϕ, deg	$\Delta\delta$,[e] ppm
0	7.47	$\Sigma = 9.5$	−150	8.40	$\Sigma = 11.6$	+70	8.45	6.5	−80	0.68
2	8.14	$\Sigma = 11.0$	−130	8.53	$\Sigma = 11.0$	+60	8.60	8.0	−90	0.46

[a] IV represents cyclo(Gly_I-Glu(OBzl)-Gly_{II})$_2$. [b] Moles of guanidine hydrochloride per unit mole of peptide bond of cyclo-(Gly-Glu(OBzl)-Gly)$_2$. [c] Sum of H-C$^\alpha$-N-H coupling constant from C$^\alpha$H and NH signals. [d] H-C$^\alpha$-N-H coupling constant from C$^\alpha$H and NH signals. [e] Calculated shielding of Gly_I-NH with respect to Gly_{II}-NH.

as a result of the conformational change should be subject to the polar effect of solvent. It has been reported that the downfield shift due to the polar effect is proportional to the square of an electric field.[35] If the value (ca. 0.15 ppm) observed for the resonance signal of the solvent-exposed peptide proton of cyclo-(Gly-Sar) (see Figure 2) is taken as a measure of the polar effect, the sum of the conformational and the polar effects can explain more than half of the downfield shift.

The rest of the shift changes (ca. 0.3 ppm) could have been caused by the increasing extent (for the formerly intramolecular hydrogen-bonded Gly_I-NH protons) of hydrogen bonding with solvent. The exposed NH will tend to associate also with the anion of the added salts which is not well solvated in Me_2SO. Insofar as the immediate interaction of NH with anion resembles hydrogen bonding, it will give rise to a downfield shift.[31] These considerations receive support from the experimental results shown in Figure 3. Firstly the temperature coefficient for the resonance signal of Gly_I-NH increased from 0.0001 ppm/deg to 0.003 ppm/deg with the addition of guanidine hydrochloride (R = 2), while those of Gly_{II}-NH and glutamyl NH decreased slightly. Secondly, the temperature coefficient for the resonance signal of Gly_I-NH in the presence of guanidine hydrochloride is small below 60 °C and then becomes larger at higher temperatures. This phenomenon can be explained as follows: Gly_I-NH becomes more associated with solvent or with anion as a result of guanidine hydrochloride induced conformational change. Since such interactions become weakened at higher temperatures, the resonance signal for the Gly_I-NH protons shows an upfield shift in the temperature rises. The temperature coefficient of the upfield shift should be larger at R = 2 where the association of NH with solvent or with anion, that is, the conformational change, is more important. However, the contribution of the association with solvent or with anion should be important only above 60 °C. At lower temperatures than 60 °C the conformation is very sensitive to the temperature change and a downfield shift of the Gly_I-NH signal due to the decrease of magnetic anisotropic effect cancels the upfield shift described above.

Deslauriers, Walter, and Smith[36] investigated the conformational change of cyclic peptide hormone oxytocin using ^{13}C NMR spectroscopy, and explained the long-range, pH-dependent effects on the ^{13}C NMR spectra in terms of the "through-space" mechanism. The argument here could be made firm by measurement of relaxation time (T_1) using pulse Fourier transform ^{13}C NMR spectroscopy.[37] If a large downfield shift is always observed for such internal peptide protons as Gly_I-NH of cyclo-(Gly_I-X-Gly_{II})$_2$ on the addition of guanidine hydrochloride to a Me_2SO solution of the cyclic peptide, the downfield shift can be used as a criterion for the peptide proton being internal.

In water different behavior was observed. The NH resonances of IV in water gradually shifted to higher field on gradual addition of guanidine hydrochloride or lithium bromide, the shift change of Gly_I-NH signal with the addition of guanidine hydrochloride being an exception (Table II). In

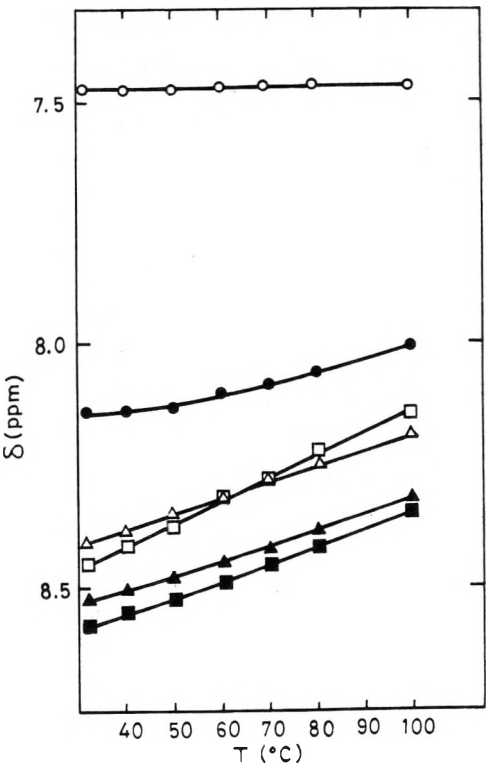

Figure 3. The temperature dependence of NH resonance signals of IV in Me_2SO-d_6: ○,● Gly_I-NH; △,▲ Gly_{II}-NH; □,■ Glu(OBzl)-NH. Full symbols represent the NH resonance signals in the presence of guanidine hydrochloride (R = 2).

Table II only the chemical shift changes induced by the salts at R = 10 are shown, which are much less marked than those observed in Me_2SO. The small changes observed in water imply that the added salts were well solvated, so that they did not bring about a serious conformational change. In fact, no change of J values was observed in water. The small changes also imply a strong solvation of the peptide protons by water. Similar shift changes have been observed for the poly(sodium glutamate)-LiBr-H_2O system[38] in the same concentration range of LiBr as employed in the present experiments. In the poly(sodium glutamate) case, the changes have been interpreted in terms of the dehydration of the polymer by an electrostriction effect. The same explanation could be applied to the present case, because the upfield shift of the resonance signal of Gly_{II}-NH protons was far greater than that of Gly_I-NH protons.

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Registry No.—I, 51782-82-2; II, 59092-61-4; III, 59092-62-5; IV, 59092-63-6; V, 59092-64-7; VI, 59092-65-8; VII, 47094-17-7; VIII, 59092-66-9; IX, 59092-67-0; X, 59092-68-1; XI, 59092-69-2; glycine,

56-40-6; Boc-Glu(OBzl)ONSu, 32886-40-1; *p*-nitrophenol, 100-02-7; HCl-Gly-Glu(OBzl)-Gly-ONp, 59092-70-5; Boc-Glu(OBzl)-Gly-Gly-ONp, 59092-71-6; Boc-Glu(OMe)-OH, 45214-91-3; glycylglycine, 556-50-3; Boc-Asp(OBzl)-ONSu, 13798-75-9; Boc-Gly-ONSu, 3392-07-2.

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Synthesis of 4-Tetracyclo[5.2.1.$0^{2,6}$.$0^{3,8}$]decene (2,4-Ethenotricyclo[3.3.0.$0^{3,7}$]octane)[1]

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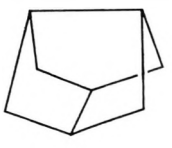
A short first synthesis of the cage olefin 2,4-ethenotricyclo[3.3.0.$0^{3,7}$]octane (**10**) is reported, from dihydrodicyclopentadiene **3** by way of a difunctionalizing and ring-inverting Wagner–Meerwein rearrangement, **4** → **5**, and a transannular carbenic insertion, **7** → **8** → **9**. The intramolecular reactions of the carbenes from *exo*-5,6-trimethylene-7-norbornanone tosylhydrazone (**14**) and the 2,3-olefinic analogue **24** have also been investigated, and are compared with the published reactions of the parent bicyclic carbenes from tosylhydrazones **17** and **26**, respectively.

The synthesis of cage-structured hydrocarbons and their derivatives has been of importance at several levels. The rigid and often symmetrical frameworks of such molecules have furthered understanding of the capabilities and limitations of diverse preparative methods, permitted the determination of new structure–reactivity relationships, and provided test compounds for force-field calculations of molecular energy and geometry. Examples of carbocyclic molecules in this class from which valuable information has been derived in recent years are adamantane,[2] bullvalene,[3] cubane,[4] iceane,[5] and twistane.[2a,c,6] Additional interest has been stimulated lately by the discovery of promising pharmacological properties of certain adamantane[7] and twistane[8] derivatives, apparently due to lipophilic character of the globular hydrocarbon moieties.

Another such spheroidal polycycloalkane, which has received relatively limited attention, is tricyclo[3.3.0.$0^{3,7}$]octane[9] (**1**). We report here a direct synthesis of 2,4-ethenotricyclo[3.3.0.$0^{3,7}$]octane (4-tetracyclo[5.2.1.$0^{2,6}$.$0^{3,8}$]decene) (**10**), the first 2,4-disubstituted derivative of this ring system and an olefin which should be useful for the construction of further new cage compounds. The molecule is the singly bridged relative of diethenotricyclooctane (**2**), recently prepared by Paquette and Wyvratt.[10]



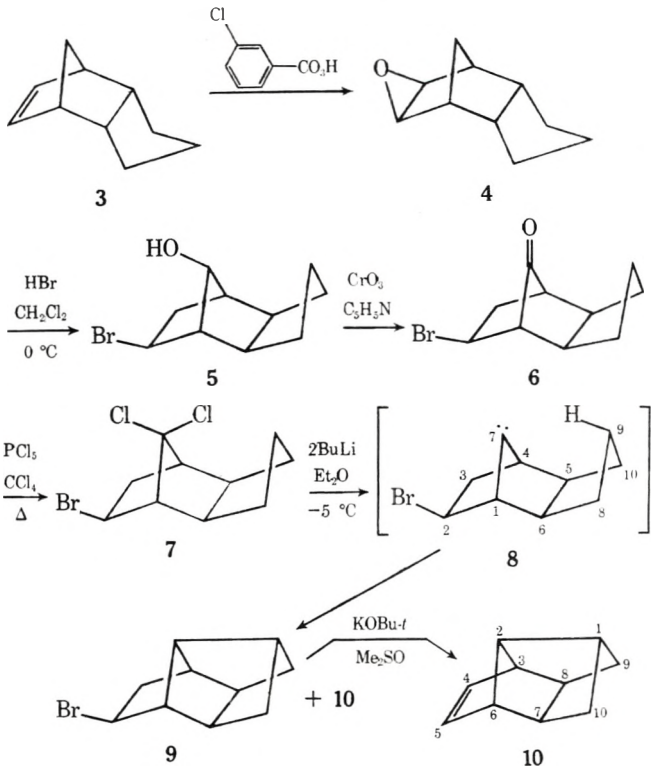
1

2

The central concepts in the synthesis of **10** were the endo → exo transformation of a 5,6-trimethylenenorborane skeleton by Wagner–Meerwein rearrangement,[11] **4** → **5**, and the transannular C–H insertion,[12] **8** → **9**, of a carbenoid constitutionally constrained against competing olefin formation by hydrogen shift.

Results and Discussion

Reaction of excess cyclopentene with cyclopentadiene according to the procedure of Cristol and co-workers[13] gave rise to a 44% yield of *endo*-5,6-trimethylene-2-norbornene (**3**), which upon reaction with *m*-chloroperbenzoic acid provided the known epoxide[14] **4** in 93.5% yield. Treatment of the epoxide with anhydrous HBr in methylene chloride solution[14c] at 0 °C produced, after recrystallization, a 65% yield of *exo*-2-bromo-*exo*-5,6-trimethylene-*syn*-7-norbornanol (**5**), mp 92.0–93.2 °C, whose ^{1}H NMR spectrum made clear that the desired Wagner–Meerwein rearrangement had occurred.

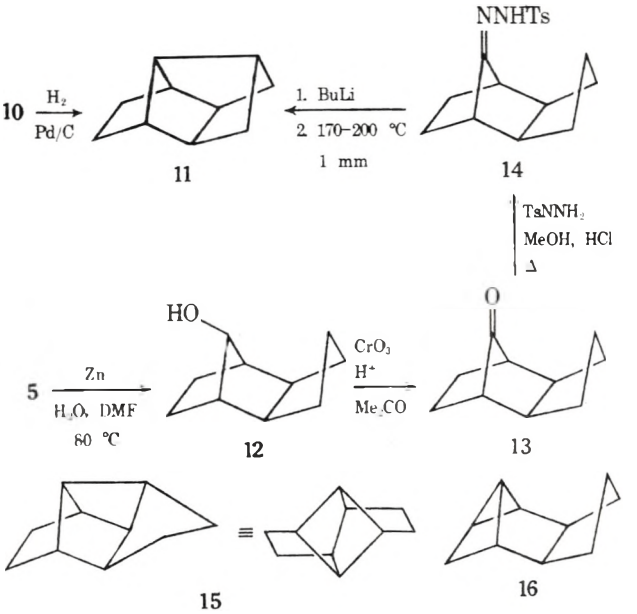


Reaction of bromohydrin **5** with Sarett's reagent[15] at room temperature gave a 79% yield, after short-path distillation, of analytically pure bromo ketone **6**, bp 103–105 °C (1 mm). Reaction of **6** with excess phosphorus pentachloride in boiling CCl_4[16] gave in ca. 75% yield the crystalline *gem*-dichloride **7**, mp 66.0–68.0 °C. From this compound by treatment with 2.0 equiv of *n*-butyllithium in ether[17] at −5 °C was generated the transient carbenoid[18] **8**, which underwent insertion into the proximal C-9 carbon–hydrogen bond to give mainly *exo*-4-bromotetracyclo[5.2.1.0^{2,6}.0^{3,8}]decane (**9**), as well as some of the subsequent elimination product, **10**, in a combined yield of ca. 60%, bp ca. 75 °C (1 mm) (short-path distillation). The conversion of bromide **9** in this mixture to the title olefin, **10**, bp 70–72 °C (13.5 mm), was accomplished in 42% two-step yield from the bromodichloride **7** by reaction with potassium *tert*-butoxide in dimethyl sulfoxide at 40–45 °C.

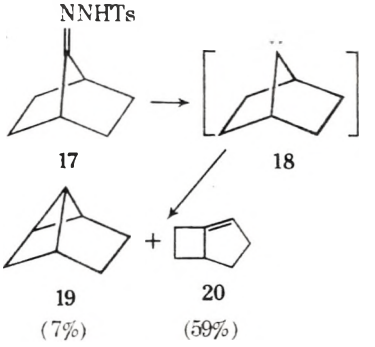
The ^{13}C NMR spectra[19] of **10** were particularly indicative of its structure. The fully proton-decoupled spectrum exhibited six lines of the expected chemical shifts and intensities, while the off-resonance spectrum showed the multiplicities appropriate to the numbers of attached protons.

Catalytic hydrogenation of a sample of olefin **10** yielded the tetracyclodecane **11**.[33] The saturated product, bp 71–72 °C (15 mm), was also prepared from bromohydrin **5** by reductive debromination with zinc dust in aqueous *N,N*-dimethylformamide, oxidation of the resultant alcohol, **12**, to ketone **13**, and vacuum pyrolysis of the lithium salt[20] of the derived *p*-toluenesulfonylhydrazone, **14**. The proton-decoupled ^{13}C NMR spectrum of **11** permitted a clear distinction between it and the two other possible insertion products, **15** and **16**. Like olefin **10**, **11** showed an appropriate six-line spectrum. Compound **15** has C_2 symmetry, dictating a five-line ^{13}C spectrum, as observed in fact for the perchloro derivative;[21] **15** is itself a known compound,[21] possessing a ^1H NMR spectrum markedly different from that of **11**. Isomer **16** lacks symmetry and should have a ten-line ^{13}C spectrum. The off-resonance ^{13}C spectrum of **11** exhibits the expected two triplets and four doublets.

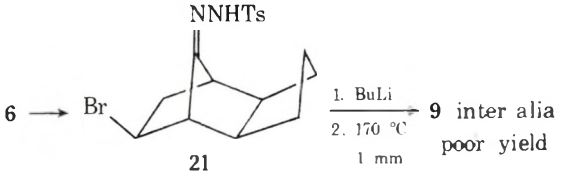
The clean conversion of tosylhydrazone **14** into hydrocarbon **11** is noteworthy in comparison with the corresponding chemistry of 7-norbornanone tosylhydrazone (**17**) studied by



Moss and co-workers.[22] 7-Norbornylidene (**18**) from this source gives rise to 7% of the strained insertion product **19** plus 59% of the rearrangement product 1-bicyclo[3.2.0]heptene (**20**). The proximity of the C-9 methylene group in **8**, then, provides an insertion pathway more favorable than both reactions characteristic of the parent carbene, **18**. It is thus apparent that the formation of **20** from the lithium salt of tosylhydrazone **17** proceeds via the carbene intermediate, **18**, rather than by an alternative concerted decomposition.



Attempted preparation of bromide **9** by analogous pyrolysis of the lithium salt of tosylhydrazone **21** was unsuccessful,



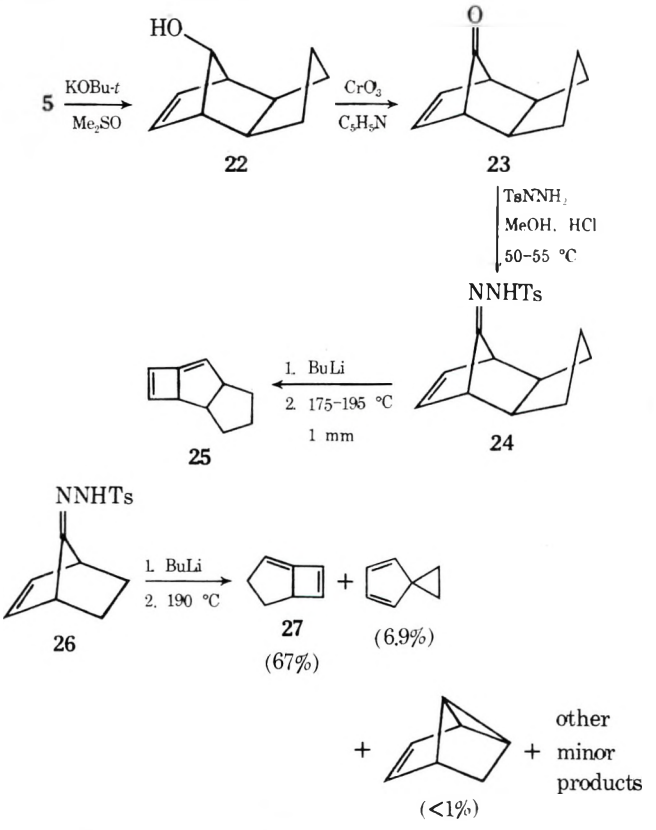
producing only a meager yield of **9** as part of a complex product mixture. The unfavorable results in this reaction are probably a consequence of the heterolytic instability of the bromide substituent at elevated temperatures.

An investigation was also conducted of the thermal decomposition of the lithium salt of the unsaturated tosylhydrazone, **24**. This reaction was of interest as a possible alternative route to the objective olefin, **10**, and also for purposes of comparison with corresponding results from the simple norbornenyl reactant **26**, as reported by Moss et al.[23] and Murahashi et al.[24]

Treatment of bromohydrin **5** with potassium *tert*-butoxide in dimethyl sulfoxide at room temperature gave exo-5,6-trimethylene-2-norbornen-*syn*-7-ol (**22**) in 66% yield after short-path distillation, mp 43.0–44.0 °C. Sarett oxidation produced the enone, **23**, in 75% yield, bp ca. 49 °C (1 mm), a

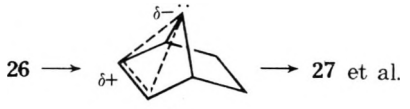
labile substance which becomes yellow over several days at room temperature and decomposed on attampted gas chromatography. Conversion of **23** to the tosylhydrazone, **24**, by reaction with *p*-toluenesulfonylhydrazine in methanol required catalysis by concentrated hydrochloric acid at a temperature of 50–55 °C; the yield was 63%.

Vacuum pyrolysis of the lithium salt of **24** gave in 60% yield a compound identified as 2,4-tricyclo[5.3.0.0^{3,6}]decadiene (**25**). This structure was suggested by that of the main product, **27**, from the parent unsaturated tosylhydrazone,[25] **26**. Diene **25**



polymerizes in a matter of minutes in air at room temperature, and over several hours under nitrogen. Its structure was effectively established, however, on the basis of its ^{1}H and ^{13}C NMR spectral features. Taking the extra cyclopentane ring of **25** into account, the chemical shifts and multiplicities of its olefinic protons are virtually identical with those of **27**.

Moss[23] and later Murahashi[24] have interpreted their results from **26** in terms of a bridged nonclassical singlet carbene intermediate **28**, stabilized by interaction of the π-bond electrons with what would otherwise be a vacant p orbital at the carbene center. This stabilization was predicted theoretically by Gleiter and Hoffman,[26] representing an early stage of carbene addition to a carbon–carbon double bond, whose consummation in this case is constitutionally precluded. The concept has been supported by several experimental studies.[27] Thus, the double bond in tosylhydrazone **26** acts in the derived



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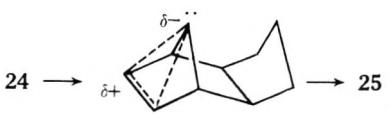

29

carbene to preempt the 7% of C–H insertion found in the saturated system, **17** → **18** → **19**.

The results with tosylhydrazone **24** constitute strengthened evidence for carbene–double bond interaction, **29**, as the olefinic function here diverts reaction entirely from the otherwise especially facile transannular C–H insertion, **14** → **11**.

Efforts to utilize the new olefin **10** in the synthesis of further novel bridged carbopolycyclic compounds are in progress.

Experimental Section

General. Melting points (uncorrected) were obtained in capillary tubes using a Thomas-Hoover melting point apparatus. Boiling points are uncorrected.

Infrared (ir) spectra were obtained on a Beckman Model IR-10 spectrophotometer using sodium chloride optics, as either ca. 2% solutions in CCl_4 (0.5-mm cells), neat thin films, or Nujol mulls.

^{1}H NMR spectra were obtained at 100 MHz using a Varian HA-100 spectrometer operating in the Fourier transform mode. Solvents used were either carbon tetrachloride or deuteriochloroform, containing tetramethylsilane as internal standard. Chemical shifts (δ values) are reported in parts per million downfield from Me_4Si.

^{13}C NMR spectra were obtained at 25.16 MHz using a Varian XL-100-15 spectrometer operated in the Fourier transform mode. All spectra were recorded using $CDCl_3$ as solvent, which also provided the heteronuclear lock. The chemical shifts (δ values) are reported in parts per million downfield from internal Me_4Si.

Mass spectra were obtained using either a Varian M-66 mass spectrometer or a Du Pont Model 21-490B GC-MS system equipped with a 21-094 MS data system.[28]

Analytical gas chromatography (GC) was performed on either a Wilkens Aerograph Hy-Fi Model 600-C or 600-D gas chromatograph equipped with a flame-ionization detector. The following columns were used throughout most of this work, using nitrogen as the carrier gas: (A) 5 ft × 0.125 in. 2% SE-30 on 60–80 mesh Chromosorb G (acid washed, DMCS treated); (B) 5 ft × 0.125 in. 10% SE-30 on 60–80 mesh Chromosorb W (AW, DMCS); (C) 10 ft × 0.125 in. 20% SE-30 on 60–80 mesh Chromosorb W (AW); (D) 10 ft × 0.125 in. 10% Apiezon M on 45–60 mesh Chromosorb W (AW, DMCS); (E) 6 ft × 0.125 in. 10% Carbowax 20M on 50–60 mesh Anakrom ABS.

Preparative-scale GC was conducted with a Barber-Colman Model 5340 thermal-conductivity gas chromatograph using column F, 5 ft × 0.25 in. 10% Apiezon M on 45–60 mesh Chromosorb W (AW, DMCS), with helium as the carrier gas.

Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

***endo*-5,6-Trimethylene-2-norbornene (3).** The procedure used was similar to that described by Cristol and co-workers.[13] In a 250-ml stainless-steel bomb (in other preparations thick-walled glass tubes were used) were placed 140 g (2.06 mol) of cyclopentene, 55 g (0.835 mol) of cyclopentadiene,[29] and several milligrams of 2,6-di-*tert*-butyl-*p*-cresol as a radical inhibitor. The sealed bomb was heated at 190–195 °C overnight, then cooled and opened, and the contents were transferred to a round-bottomed flask fitted with a 6-in. Vigreux column. The excess cyclopentene (97.5 g) was distilled off at atmospheric pressure and combined in the bomb with 50 g of cyclopentadiene and a small amount of radical inhibitor. After heating again overnight, the contents were combined with the residue from the previous run, and the excess cyclopentene was distilled off at atmospheric pressure. The product was then distilled at reduced pressure to give 94.6 g (44% based on cyclopentadiene) of a colorless liquid: bp 69–72 °C (22 mm) [lit. bp 92–94 °C (40 mm),[11a] 173–175 °C (764 mm),[11a] 29.5–33 °C (0.45–0.55 mm)[13]]; ^{1}H NMR (CCl_4) δ 0.97 (m), 1.50 (m), 2.70 (m), 6.06 (s, –CH=CH–). Analysis by GC using column C at 80 °C showed the presence of two minor impurities (relative area ca. 2% each), presumably dicyclopentadiene and the *exo*-trimethylenenorbornene isomer. The separation of dicyclopentadiene conducted by Cristol et al.[13] was not utilized here because of the low indicated impurity levels and the prospect for further purification in subsequent steps.

***endo*-5,6-Trimethylene-2-norbornene Oxide (4).** In a 1000-ml, three-necked, round-bottomed flask equipped with a mechanical stirrer, addition funnel, and thermometer were placed 32.0 g (0.157 mol) of 85% *m*-chloroperbenzoic acid (Aldrich) and 350 ml of reagent-grade methylene chloride. To this stirred solution, cooled to ca. 10 °C, was added dropwise over 25 min 20.0 g (0.149 mol) of olefin **3** in 20 ml of CH_2Cl_2. The reaction mixture was allowed to warm gradually to room temperature and stirred overnight. From the reaction mixture cooled to 0 °C was suction filtered the *m*-chlorobenzoic acid, which was washed well with CH_2Cl_2. The filtrate was then transferred to a separatory funnel and washed once with water, three

times with 10% NaOH solution, and once again with water. After drying ($MgSO_4$), rotary evaporation of the solvent gave 22.4 g of a slightly yellow semisolid. Distillation of the crude product at 1 mm through a short neck into an ice bath cooled receiver gave 22.0 g of a colorless, glassy solid (98.5%), whose purity was indicated by GC (column B at 115 °C) to be ca. 95%. Vacuum sublimation of a small sample gave a colorless, crystalline center fraction: mp 117–118 °C (lit. mp 118–119,[14a] 118 °C[14b]); ^{1}H NMR ($CDCl_3$) δ 0.76, 0.85, 1.37 (broad singlets), 1.56 (broad s, 1.49, 1.63 sh), 2.39 (broad s), 3.04 (s, oxirane).

***exo*-2-Bromo-*exo*-5,6-trimethylene-*syn*-7-norbornanol (5).** In a 500-ml, three-necked, round-bottomed flask fitted with a reflux condenser with drying tube, a gas-inlet tube, and a magnetic stirrer were placed 20.7 g of the distilled epoxide **4** and 200 ml of reagent-grade CH_2Cl_2 (stored over 4A molecular seives). The flask and its contents were tared and then cooled in an ice bath, and gaseous anhydrous HBr was introduced into the magnetically stirred solution at a moderate rate from a tared lecture bottle via the gas-inlet tube. When the weight of the lecture bottle indicated that the approximate amount of HBr had been consumed, the flask and contents were weighed. Approximately 13 g (0.16 mol, ca. 16% excess) of HBr was absorbed. After stirring in the ice bath for 1.5 h and at room temperature for 2 h, 100 ml of a saturated sodium bicarbonate solution was slowly added via the addition funnel to the vigorously stirred reaction mixture. After 15 min, the resulting two-phase mixture was transferred to a separatory funnel, and after shaking the layers were separated. The organic layer was washed with two additional portions of saturated $NaHCO_3$ solution and then with one portion of brine, and was dried over anhydrous $MgSO_4$. The dried extract was treated with charcoal and the solvents removed by rotary evaporation to give a solvent-wet white solid, which was immediately recrystallized at 0 °C from ca. 200 ml of hot hexane. After drying in vacuo, there was obtained 20.0 g (65%) of a white solid, mp 90–92 °C. An analytical sample was obtained by a second recrystallization from light petroleum: mp 92.0–93.2 °C; ir (CCl_4) 905, 1092, 1171, 1230, 1453, 2880, 2960, 3580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80–2.70 (complex m), 3.87 (d of q, CHBr), 4.10 (s, >CHO–). The absorption positions and patterns for the protons at C-2 and C-7 are markedly characteristic of exo-2- and -7-monosubstituted norbornanes[30] and establish that Wagner–Meerwein rearrangement accompanied the epoxide ring opening.

Anal. Calcd for $C_{10}H_{15}BrO$: C, 51.96; H, 6.55. Found: C, 51.77; H, 6.95.

***exo*-2-Bromo-*exo*-5,6-trimethylene-7-norbornanone (6).** In a 2-l., three-necked, round-bottomed flask equipped with a reflux condenser with attached nitrogen inlet, mechanical stirrer, and addition funnel was placed 550 ml of dry pyridine (stored over 4A molecular sieves). To the stirred solvent, cooled in a 10 °C water bath, was slowly added in small portions, under a positive nitrogen pressure, 52 g (0.52 mol) of technical chromium trioxide flakes.[15] The resulting orange suspension was stirred at 10–15 °C for 15 min, then at room temperature for an additional 20 min. To this vigorously stirred, room-temperature reagent was added dropwise from the addition funnel over 20 min 20 g (86.6 mmol) of the once recrystallized bromohydrin **5** dissolved in 125 ml of pyridine. After stirring at room temperature for 40 h, an aliquot was withdrawn, and the reaction was shown by thin layer chromatography (TLC) (Eastman silica gel, 5% ether in hexane) to be essentially complete. The reaction mixture was then poured into 1500 ml of ice–water and extracted with four portions of ether. The combined ether layer was then washed three times with water, five times with a total of 1500 ml of 10% $CuSO_4$ solution, once with water, and once with brine, and then dried over $MgSO_4$. Rotary evaporation of the ether gave 18.5 g of a crude yellow liquid, which upon short-path distillation afforded 15.6 g (79%) of a colorless, analytically pure liquid: bp 103–105 °C (1 mm); ir (neat) 668, 720, 846, 890, 942, 988, 1120, 1210, 1231, 1450, 1470, 1770, 1820, 2870, 2950 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.0–2.6 (complex m), 4.06 (d of q, CHBr). This material showed only one spot on TLC, and fully solidified upon standing in the freezer at −22 °C.

Anal. Calcd for $C_{10}H_{13}BrO$: C, 52.41; H, 5.73. Found: C, 52.28; H, 5.79.

***exo*-2-Bromo-*exo*-5,6-trimethylene-7,7-dichloronorbornane (7).** In a 500-ml, three-necked, round-bottomed flask fitted with a reflux condenser with attached nitrogen inlet, magnetic stirrer, and addition funnel were placed 120 ml of dry (stored over 4A molecular sieves) reagent-grade carbon tetrachloride and 22.8 g (0.109 mol) of phosphorus pentachloride.[16] To this stirred room-temperature suspension, under a static nitrogen atmosphere, was added in one portion from the addition funnel 10.0 g (43.6 mmol) of the pure bromo ketone **6** dissolved in 65 ml of CCl_4. After stirring at room temperature for 5 min, the reaction mixture was brought to a gentle boil under reflux and stirred for 42 h. The colorless reaction mixture was allowed to cool to room temperature and was then poured over 300 ml of crushed ice. The resulting two-phase mixture was transferred to a separatory funnel and shaken, and the layers were separated. The aqueous phase was extracted once with CCl_4, and the combined organic solution was washed once with water, three times with saturated $NaHCO_3$ solution, and once with brine, then dried over $MgSO_4$. Rotary evaporation of the solvent gave 13.0 g of a crude, colorless oil, which crystallized at −30 °C and remained solid at room temperature. The crude product was recrystallized from ca. 50 ml of hot petroleum ether (bp 30–60 °C) at −22 °C to give 9.25 g (32.6 mmol, 74.7%) of a white, crystalline powder after drying in vacuo, mp 60–63.5 °C. An analytical sample was obtained from a second recrystallization (0 °C) of a small amount of the above material: mp 66.0–68.0 °C; ir (CCl_4) 974, 1145, 1160, 1203, 1212, 1251, 1282, 1292, 1300, 1318, 1455, 2878, 2896, 2935, 2960, 2990 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.0–2.9 (complex m), 3.87 (complex d of d, CHBr). TLC showed only one component.

Anal. Calcd for $C_{10}H_{13}BrCl_2$: C, 42.28; H, 4.62. Found: C, 42.21; H, 4.60.

***exo*-4-Bromotetracyclo[5.2.1.0^{2,6}.0^{3,8}]decane (9).** In a 250-ml round-bottomed flask fitted with a serum stopper and syringe needle connected to a nitrogen by-pass line were placed 6.0 g (21.2 mmol) of the once recrystallized *gem*-dichloride **7** and 150 ml of anhydrous ether (freshly distilled from $LiAlH_4$). The resulting magnetically stirred, colorless solution was cooled to ca. −5 °C with an ice–salt bath, and 18.5 ml (44.5 mmol) of a 2.4 M solution of *n*-butyllithium in hexane was slowly injected from a syringe over ca. 10 min. (Preliminary small-scale experiments demonstrated a necessity for 2 equiv of butyllithium). The reaction was somewhat exothermic as evidenced by a rise in the bath temperature to ca. −2 °C during the addition. Also, during the addition a white precipitate (presumably LiCl) formed and the solution turned slightly yellow. After the addition was complete, the reaction was stirred at −5 to 0 °C for 1.5 h and then poured into 200 ml of ice–water with stirring. After separation of the layers, the aqueous phase was extracted with two additional small portions of ether, and the combined organic layer (light yellow) was washed once with brine and dried over $MgSO_4$. Rotary evaporation of the ether gave 5.03 g of an orange-yellow liquid, which was shown by GC (column B at 145–190 °C), TLC (silica gel G, hexane), and ^{1}H NMR to contain considerable amounts of olefin **10** as well as lesser amounts of other impurities. The crude liquid was short-path distilled to give two colorless fractions: (1) 2.36 g, bp 65–75 °C (1 mm), and (2) 250 mg, bp 75–90 °C (1 mm). GC analysis showed fraction 1 to be mainly bromide **9** and olefin **10** contaminated with several unidentified impurities, and fraction 2 to consist of ≥95% of bromide **9**. The mass spectrum (Du Pont 21-490 B), as anticipated for an *exo*-norbornyl bromide,[31] showed no molecular-ion peak (*m/e* 213) but a base peak corresponding to the M − Br ion[31] (*m/e* 133). The ^{1}H NMR spectrum (CCl_4) showed, in addition to a complex multiplet at δ 0.8–2.8 for the protons on unsubstituted carbon, a doublet of doublets at δ 4.26 indicative of the endo proton on an exo-2-substituted norbornane;[30] ir (neat) 754, 934, 1184, 1221, 1297, 1446, 2870, 2896, 2975 cm^{-1}.

The bromide **9** decomposed upon attempted preparative GC, and an analytical sample was not obtained.

The synthetic conditions described are considered less than optimal. Preliminary small-scale experiments indicated that improved yield and purity of **9** would have been achieved if the larger scale reaction temperature had been maintained at −30 to −20 °C, with slow addition of the butyllithium.

4-Tetracyclo[5.2.1.0^{2,6}.0^{3,8}]decene (10). In a 50-ml, three-necked, round-bottomed flask fitted with a reflux condenser with attached nitrogen inlet and an addition funnel were placed 1.51 g (13.5 mmol) of potassium *tert*-butoxide (Aldrich) and 15 ml of dry Me_2SO (distilled from CaH_2 and stored over 4A molecular sieves). To this magnetically stirred, room-temperature solution was added via the dropping funnel ca. 2.3 g of fraction 1 from the previous reaction (mainly bromide **9**) dissolved in 15 ml of dry Me_2SO. The reaction mixture was stirred at room temperature for 0.5 h and in a 40–45 °C oil bath for 20 h. The cooled, dark-brown solution was then poured into 150 ml of cold water and extracted with three portions of pentane. The combined pentane extract was washed twice with water and twice with brine, and then dried over $MgSO_4$. Rotary evaporation of the pentane gave 1.5 g of a crude, light-yellow liquid, which was indicated by GC (column B at 90–190 °C) to be ca. 95% of one volatile component. Short-path distillation gave 1.05 g (ca. 73%) of a colorless liquid, ≥95% pure as determined by GC and NMR: bp 70–72 °C (13.5 mm); ir (neat) 705, 726, 799, 827, 1284, 1347, 1591, 2895, 2978, 3060 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.4–2.1 (m), 2.58 (narrow m), 5.70 (t, J = 2.0 Hz, –CH=CH–); ^{13}C NMR, off-resonance decoupled, δ 35.8 (d, >CH–),

40.8 (d, >CH–), 48.3 (t, $-CH_2-$), 59.0 (d, >CH–), 130.3 (d, –CH=CH–); the mass spectrum showed a molecular-ion peak (base peak) at *m/e* 132 (Du Pont 21-490 B). Attempted purification of this material by preparative GC at 115 °C resulted in significant decomposition. The ^1H NMR spectrum of the collected material showed the major presence of **10** but indicated also complex vinylic- and allylic-proton absorptions, suggesting substantial transformation by a retro-Diels–Alder reaction. (Lowering the injector temperature did not remedy the situation.) An analytical sample of **10** was thus not obtained.

Hydrogenation of 10. In a 10-ml, two-necked, pear-shaped flask fitted with a serum stopper and a gas inlet from a hydrogen-filled buret were placed several milligrams of 5% palladium on charcoal and ca. 2 ml of Spectrograde CCl_4. A hydrogen atmosphere was established over the magnetically stirred suspension and maintained for 1 h to partially reduce the catalyst. Then 10 μl of the distilled olefin **10** was injected from a syringe. The reaction mixture was stirred under a hydrogen atmosphere for 2 h, and then suction filtered through a small pad of anhydrous $MgSO_4$ into a 10-ml pear-shaped flask. The CCl_4 solution was concentrated somewhat on the rotary evaporator, and the residue was examined by Fourier-transform ^1H NMR. With the exception of several weak absorptions due to a small amount of unreacted olefin, the spectrum was identical with that of the independently prepared saturated hydrocarbon, **11** (see below).

***exo*-5,6-Trimethylene-*anti*-7-norbornanol (12).** To a magnetically stirred suspension of 10.0 g of zinc dust in 100 ml of aqueous *N,N*-dimethylformamide (DMF) (5% water, 95% DMF, v/v) was added dropwise from an addition funnel 10.0 g (43.4 mmol) of once recrystallized bromohydrin **5** dissolved in 40 ml of the aqueous DMF solution. After stirring at room temperature for several minutes, the reaction mixture was brought to 80 °C with an oil bath and stirred for 12 h. Upon cooling to room temperature, the excess zinc and salts were filtered under suction through a bed of Celite and washed well with pentane. The filtrate was then poured into 500 ml of water and extracted with three portions of pentane. The combined organic extract was washed three times with water and once with brine, then dried over anhydrous $MgSO_4$. Rotary evaporation of the pentane gave 5 g of a crude white solid. Vacuum sublimation (60 °C at 0.5 mm) of the crude product gave 4.25 g (64.5%) of analytically pure, colorless crystals, found to be homogeneous by GC on column B at 120 °C and column E at 150 °C: mp 69.0–70.0 °C; ir (CCl_4) 1018, 1045, 1089, 1155, 1238, 1458, 2982, 2960, 3350–3500, 3635 cm^{-1}; ^1H NMR (CCl_4) δ 0.86 (s), 1.08 (m), 1.79 (m), 3.97 (broad s, >CHO–); ^{13}C NMR, fully decoupled, δ 26.0, 27.2, 32.2, 44.9, 46.5, 76.1 (>CHOH), six lines as required by the symmetry of **12**.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.88; H, 10.61. Found: C, 78.80; H, 10.54.

***exo*-5,6-Trimethylene-7-norbornanone (13).** To a mechanically stirred, cooled (0–5 °C) solution of 4.85 g (31.9 mmol) of crude alcohol **12** in 160 ml of reagent-grade acetone was slowly added from a dropping funnel 43 ml (64.5 mequiv) of Jones reagent (1.5 N)[32] over 20 min. The reaction mixture was stirred at 0–5 °C for 1 h and at room temperature for 1.75 h, then was poured into 300 ml of ice water, and the excess Cr^{VI} was destroyed by the addition of solid sodium bisulfite. The aqueous layer was then extracted four times with ether, and the combined organic layer was washed once with water, twice with saturated $NaHCO_3$ solution, and once again with water, and then dried over $MgSO_4$. Rotary evaporation of the solvent gave 4.0 g of a crude yellow liquid, which contained a trace of unreacted alcohol as evidenced by GC on column E at 135 °C. Short-path distillation afforded 2.04 g (43.5%) of a clear, colorless liquid which was homogeneous by GC (column E at 135 °C): bp 73–75 °C (0.5 mm); ir (neat) 707, 1125, 1451, 1762, 2866, 2880, 2955 cm^{-1}; ^1H NMR (CCl_4) δ 0.9–2.60 (complex m). The distilled product fully solidified in the freezer at −22 °C.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.94; H, 9.41. Found: C, 80.10; H, 9.73.

***exo*-5,6-Trimethylene-7-norbornanone Tosylhydrazone (14).** In a 25-ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser were placed 1.0 g (6.67 mmol) of pure ketone **13**, 1.37 g (7.33 mmol) of tosylhydrazine (Aldrich), and 8 ml of methanol. To this stirred solution was added 3 drops of concentrated HCl, and the reaction was brought to a gentle boil under reflux. After 46 h the reaction mixture was cooled to room temperature and placed in the refrigerator at ca. 0 °C. Suction filtration afforded 1.67 g (78%) of a white, crystalline powder, after drying in vacuo. An analytical sample was obtained by recrystallizing a small amount of the crude material from methanol at 0 °C: mp 178.0–179.0 °C; ir (Nujol) 758, 830, 900, 930, 948, 1018, 1100, 1170, 1316, 1346, 1415, 1599, 1687, 3200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–2.6 (complex m), 2.42 (s, $-CH_3$), 7.59 (d of d, aromatic).

Anal. Calcd for $C_{17}H_{22}N_2O_2S$: C, 64.11; H, 6.98. Found: C, 64.19; H, 7.06.

Tetracyclo[5.2.1.0^{2,6}.0^{3,8}]decane (11). In a 50-ml round-bottomed flask equipped with a Claisen head fitted with a serum stopper and nitrogen inlet were placed 1.50 g (4.72 mmol) of tosylhydrazone **14** and 20 ml of anhydrous ether. To this magnetically stirred suspension, cooled in an ice bath under nitrogen, was slowly injected by syringe 2.2 ml (5.19 mmol) of 2.4 M *n*-butyllithium in hexane (Ventron). After stirring in the ice bath for 0.5 h, the stirring bar was removed, and the ether was carefully stripped off on the rotary evaporator to give a white solid. As much as possible of this solid was scraped from the sides of the flask to the bottom, and the flask was put on the rotary evaporator for several more minutes. The flask was then connected to a pyrolysis apparatus consisting of a short curved adapter, fitted with a loose glass-wool plug, leading to a tared three-necked round-bottomed receiving flask which was fitted with a stopper and vacuum take-off adapter. The system was evacuated to 1 mm and allowed to stand at room temperature for 0.5 h. The receiving flask was then cooled in dry ice, and after several minutes the reaction flask was immersed in a silicone-oil bath preheated to 165 °C. The bath was allowed gradually to heat up further, and after several minutes decomposition commenced (gas evolution). The bath slowly reached a maximum of 210 °C (during which time the curved adapter was heated with a heat gun to prevent vapor condensation) and was then allowed to cool to room temperature. The receiving flask contained 540 mg of a slightly yellow liquid, which was shown by GC (column B at 90 °C, column C at 115 °C, column D at 140 °C) to be greater than 95% of one component. Short-path distillation gave 350 mg (55%) of a colorless liquid, bp 71–72 °C (15 mm). Gas chromatographic analysis showed this material to be ca. 98% pure. Two minor impurities (ca. 1% each) of similar retention times to that of the major component were observed. The mass spectrum (Varian M-66) exhibited a molecular-ion peak at *m/e* 134. An analytical sample was obtained by preparative GC at 125 °C: ir (neat) 1300, 1465, 2880, 2900, 2910, 2970 cm^{-1}; ^1H NMR (CCl_4) δ 1.2–1.7 (m, 8 H, $-CH_2-$), 1.7–2.4 (m, 6 H, >CH–); ^{13}C NMR, off-resonance decoupled, δ 25.0 (t, $-CH_2-$), 37.3 (d, >CH–), 41.0 (d, >CH–), 45.6 (t, $-CH_2-$), 47.2 (d, >CH–), 54.0 (d, >CH–).

Anal. Calcd for $C_{10}H_{14}$: C, 89.47; H, 10.53. Found: C, 89.60; H, 10.58.

***exo*-5,6-Trimethylene-*exo*-2-bromo-7-norbornanone Tosylhydrazone (21).** In a 50-ml, round-bottomed flask fitted with a reflux condenser and magnetic stirrer were placed 2.0 g (8.73 mmol) of bromo ketone **6**, 1.79 g (9.60 mmol) of tosylhydrazine, and 17 ml of methanol. To this stirred solution was added 5 drops of concentrated HCl, and the reaction mixture was brought to a gentle boil under reflux. After stirring for 21 h, the reaction mixture was cooled to room temperature, then placed in the refrigerator at 0 °C overnight. Suction filtration gave 3.02 g (88%) of a white, crystalline powder. Recrystallization from methanol at 0 °C gave small, white needles: mp 191–192 °C dec; ir (Nujol) 805, 885, 922, 927, 1014, 1088, 1161, 1232, 1345, 1403, 1598, 1705, 3218 cm^{-1}.

Preparation and Thermal Decomposition of the Lithium Salt of Tosylhydrazone 21. The procedure used was the same as that described for the saturated tosylhydrazone **14**. Thus, the lithium salt was prepared from 2.8 g (7.05 mmol) of bromotosylhydrazone **21** and 3.3 ml (7.8 mmol) of *n*-butyllithium solution in 45 ml of anhydrous ether. Pyrolysis at 170 °C (1 mm) occurred readily to give 810 mg of a yellow oil, which was shown by GC (column B at 145–190 °C) to be a complex mixture of products. ^1H NMR analysis also indicated a complex mixture containing only a small amount of the desired tetracyclic bromide, **9**.

***exo*-5,6-Trimethylene-2-norbornen-*syn*-7-ol (22).** In a 500-ml, three-necked, round-bottomed flask fitted with a reflux condenser equipped with a nitrogen inlet and an addition funnel were placed 13.5 g (0.12 mol) of potassium *tert*-butoxide (Aldrich) and 100 ml of dry dimethyl sulfoxide (distilled at reduced pressure from CaH_2 and stored under nitrogen over 4A molecular sieves). To this magnetically stirred, room-temperature solution was added dropwise over ca. 1 h 23.0 g (0.10 mol) of once recrystallized bromohydrin **5** dissolved in 100 ml of dry Me_2SO. After stirring at room temperature for 24 h, 100 ml of water was added to the reaction mixture, and the product was predominantly separated by steam distillation. The residual liquid was transferred to a separatory funnel and extracted with three portions of pentane. The combined organic materials were washed three times with water and dried over $MgSO_4$. Rotary evaporation of the pentane gave 11.9 g of a colorless oil, which was distilled at 0.7 mm through a short neck into an ice bath cooled receiving flask to yield 9.92 g (66%) of a white solid, mp 37–39 °C. A small amount of this product was sublimed (30–35 °C at 1 mm), recrystallized at −78 °C from petroleum ether (bp 30–60 °C), and resublimed (30–35 °C at 1

mm) to give an analytical sample which was homogeneous by GC on column B at 120 °C: mp 43.0–44.0 °C; ir (CCl_4) 708, 896, 1020, 1080, 1155, 1218, 1232, 1275, 1335, 1415, 2872, 2960, 3070, 3570 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.0–2.1 (m), 2.47 (narrow m, allylic CH), 4.02 (s), 6.09 (narrow t, –CH=CH–); ^{13}C NMR, fully decoupled, δ 29.8, 30.7, 44.8, 52.1, 83.6, 134.8.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.94; H, 9.41. Found: C, 79.84; H, 9.39.

***exo*-5,6-Trimethylene-2-norbornen-7-one (23).** In a 500-ml, three-necked, round-bottomed flask fitted with a reflux condenser with attached nitrogen inlet, a mechanical stirrer, and an addition funnel was placed 150 ml of pyridine (dried over KOH pellets). To the stirred solvent, cooled in an ice–water bath, was added slowly in small portions, under positive nitrogen pressure, 15.7 g (0.157 mol) of solid analytical-grade chromium trioxide.[15] After stirring at 10 °C for 15 min, the orange-yellow suspension was allowed to warm to room temperature, and after stirring an additional 15 min 5.86 g (39.1 mmol) of distilled unsaturated alcohol 22 dissolved in 20 ml of pyridine was added dropwise from the addition funnel over 15 min. The reaction mixture was stirred at room temperature for 45 h, then poured into 1000 ml of ice water and extracted with four portions of ether. The combined ether extract was washed once with water, three times with 10% sulfuric acid solution, once with water, twice with saturated $NaHCO_3$ solution, and once with brine, then dried over $MgSO_4$. Rotary evaporation of the ether gave 4.82 g of a slightly yellow liquid. Short-path distillation afforded 4.32 g (75%) of an analytically pure, colorless liquid: bp 49 °C (1 mm); ir (neat) 693, 765, 800, 1105, 1455, 1773, 2873, 2900, 3002 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.0–2.2 (complex m), 2.55 (t, J = 2.5 Hz, allylic CH), 6.51 (t, J = 2.5 Hz, –CH=CH–); ^{13}C NMR, fully decoupled, δ 28.8, 30.1, 43.3, 51.4, 134.3 (–CH=CH–), 207.2 (>C=O).

Anal. Calcd for $C_{10}H_{12}O$: C, 81.03; H, 8.18. Found: C, 81.11; H, 8.20.

Upon standing at room temperature for several days the distilled product gradually turned yellow. However, it could be stored in the solid state in the dark at −22 °C without apparent decomposition.

***exo*-5,6-Trimethylene-2-norbornen-7-one Tosylhydrazone (24).** In a 25-ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser were placed 1.00 g (6.76 mmol) of pure ketone **23**, 1.30 g (7.0 mmol) of tosylhydrazine (Aldrich), 5 ml of methanol, and 4 drops of concentrated hydrochloric acid. The resulting stirred solution was then placed in a 50–55 °C oil bath for 26 h, cooled to room temperature, and finally placed in the refrigerator at 0 °C. Suction filtration gave 1.34 g (63%) of a crystalline, white powder after drying in vacuo: mp 181.5–182.0 °C dec; ir (Nujol) 711, 721, 832, 1010, 1170, 1346, 1380, 1404, 1599, 1687, 3230 cm^{-1}. The crude material was stored at −22 °C and used as soon as possible.

Preparation and Thermal Decomposition of the Lithium Salt of Tosylhydrazone 24. The procedure used was similar to that described for the saturated tosylhydrazone **14** except that the pyrolysis system was evacuated and flushed with nitrogen or helium before the final evacuation and decomposition. Thus, the lithium salt was prepared from 1.0 g (3.16 mmol) of tosylhydrazone **24** and 1.45 ml (3.48 mmol) of 2.4 M *n*-butyllithium solution in 15 ml of anhydrous ether. After evaporation of the ether, the flask containing the dry salt was connected to the pyrolysis apparatus, dried for 45 min, then pyrolyzed at 175–195 °C. After the reaction vessel had cooled, nitrogen was admitted to the evacuated, cold (−78 °C) receiving flask and, under positive nitrogen pressure, the pyrolysis flask and short neck were removed and quickly replaced with a rubber serum stopper. Approximately 3 ml of precooled (−20 °C) $CDCl_3$ was then injected into the receiving flask, and the colorless liquid product dissolved. A small portion of this cold solution was withdrawn with a syringe and placed in a nitrogen-flushed ^{1}H NMR tube. The remainder of the solution was withdrawn and placed in a nitrogen-flushed ^{13}C NMR tube which was then chilled to ca. −30 °C. The ^{1}H NMR spectrum (single sweep) was obtained at ambient probe temperature, the ^{13}C NMR spectrum (3794 transients) at −30 °C: ^{1}H NMR ($CDCl_3$) δ 0.8–2.4 (complex m), 2.65 (m), 3.00 (m), 3.26 (broad d, J = 8 Hz, 1 H), 5.06 (d, J = 4 Hz, 1 H, five-ring butadiene H), 6.45 (t, J = 2 Hz, 1 H, four-ring terminal butadiene H), 6.87 (d, J = 2 Hz, 1 H, four-ring internal butadiene H); ^{13}C NMR, fully decoupled, δ 27.3, 30.9, 32.3, 45.3, 57.5, 61.0, 112.8, 134.8, 141.8, 150.1. Upon contact with air, the product rapidly polymerized to an amorphous, yellow-brown solid, either neat or in solution (the material seemed to be somewhat more stable in $CDCl_3$ than in CS_2). While elemental analysis could not be obtained, the product structure is strongly indicated to be **25** by the close resemblance of its ^{1}H NMR spectrum to that of **27**[25] and by the ten-line pattern of its ^{13}C NMR spectrum.

Registry No.—**3**, 2826-19-9; **4**, 59121-43-6; **5**, 59054-55-6; **6**, 59054-56-7; **7**, 59054-57-8; **9**, 59054-58-9; **10**, 59054-59-0; **11**, 59054-60-3; **12**, 59121-44-7; **13**, 59054-61-4; **14**, 59054-62-5; **21**, 59054-63-6; **22**, 59054-64-7; **23**, 59054-65-8; **24**, 59054-66-9; **25**, 59054-67-0; cyclopentene, 142-29-0; cyclopentadiene, 542-92-7; HBr, 10035-10-6; phosphorus pentachloride, 10026-13-8; tosylhydrazine, 1576-35-8.

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The Ethanonoradamantanes. An Experimental Evaluation of Empirical Force Field Predictions[1]

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2,4-Ethanonoradamantane (**6**) is the most stable of 2486 possible tetracyclic ring systems of empirical formula $C_{11}H_{16}$. While empirical force-field calculations predicted **6** and 2,8-ethanonoradamantane (**7**) to be the most stable tetracycloundecanes and to have equal stability, $AlBr_3$-catalyzed isomerization of tetracyclo[6.3.0.$0^{2,6}$.$0^{5,9}$]undecane (**13**), noriceane (**9**), and methanotwistane (**14**) gave mixtures of **6** and **7** in a 97:3 (±1) ratio. The structures of **6** and **7** were established by syntheses based on the stereochemical control imposed on the C–H carbene insertion of *exo*- and *endo*-2-noradamantyl methyldiazo ketones (**19** and **20**). While **13** and **9** rearrange directly to **6** and **7** in high yield, **14** isomerized initially to **7**, which then underwent slow isomerization to the more stable **6**, accompanied by extensive disproportionation to 1-methyladamantane. Noriceane (**9**) was detected as an intermediate in the rearrangement of **14**. The mechanisms of these isomerizations are analyzed using a graph interconnecting 15 tetracycloundecanes. The overall results demonstrate the power of force field calculations, but indicate that there are still limitations in accuracy even when an isomerization between structurally related molecules is involved.

The $AlCl_3$-catalyzed rearrangement of tetrahydrodicyclopentadiene to adamantane demonstrated the synthetic potential of thermodynamically controlled polycyclic isomerizations.[3] Diamantane,[4] triamantane,[5] and many other cage molecules have now been prepared by this method.[6] A readily available precursor, generally with the same empirical formula and number of rings, is treated with a strong Lewis acid. Although exceptions are known,[7,8] rearrangement to the most stable isomer (the "stabilomer")[9] usually occurs.[6] Although it is rather obvious that adamantane should be the $C_{10}H_{16}$ stabilomer, predictions in other instances are much more difficult. For example, qualitative inspection of the structures of iceane (**1**) and of ethanoadamantane (**2**) does not provide a clear basis for understanding why the latter is the $C_{12}H_{18}$ stabilomer.[10]

Further progress in this area requires the development of a systematic method for the prediction of the stabilomer of any given saturated hydrocarbon set. We illustrate in this paper the procedure we have devised for the tetracyclic $C_{11}H_{16}$ series.

Prediction of the $C_{11}H_{16}$ Tetracyclic Stabilomer. In general, the prediction of a stabilomer will require three steps:

1. Determination and listing of all possible isomers. The number is likely to be prohibitively large.

2. Elimination of isomers expected qualitatively to be unstable on the basis of structural considerations.

3. Quantitative estimation of the free energies of formation of the remaining isomers. The isomer with the lowest free energy is predicted to be the stabilomer.

The computer program developed by Wipke for the elucidation of the number of polycyclic isomers[11] predicts that 2486 tetracyclic $C_{11}H_{16}$ ring systems are possible. This program further indicates the ring sizes present in each isomer. Since structures with three-membered rings tend to be highly strained (and do not, in any event, survive AlX_3 isomerization) these are unlikely stabilomer candidates. Elimination of such structures reduces the number of isomers to 812. Similarly, isomers with four-membered rings can also be rejected; this leaves only 68 possibilities. In order to check this latter assumption, we included the methano-bridged adamantane (**3**) in the set to be calculated, because it should be the most stable $C_{11}H_{16}$ tetracycle with a four-membered ring.[12,13]

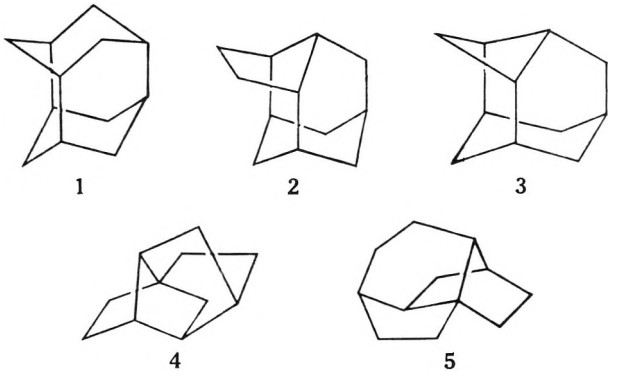
Inspection of the structures of the 68 theoretical $C_{11}H_{16}$ isomers with only five- and six-membered rings show that many have intertwined bridges or other obviously unfavorable features. While quite a manageable number of isomers remained, we chose to continue the screening process. If we had not had any access to experimental information, we would have at this point calculated the heats of formation of all viable $C_{11}H_{16}$ tetracyclic candidates by empirical force field calculations.[14,15] Estimation of the entropy and the free energies would have completed the process. Instead, we took

Table I. Structural Analysis of $C_{11}H_{16}$ Tetracyclic Ring Systems[a,b]

No. of unique C atoms	Total no. of $C_{11}H_{16}$ ring systems	No. of systems with n quaternary C atoms		
		$n = 0$	$n = 1$	$n = 2$
4	4	3	1	0
5	5	1	1	3
6	14	6	4	4
7	7	5	1	1
8	4	1	2	1
9	1	0	0	1
10	0	0	0	0
11	33	11	19	3

[a] Restricted to systems not containing three- or four-membered rings. [b] Based on the results of a computer program written by Professor T. Wipke.[11]

advantage of another feature of Wipke's program: its ability to give the number of unique carbon atoms in a given isomer, and the number of quaternary carbons in each structure (Table I). This information, in conjunction with ^{13}C NMR spectra of the $C_{11}H_{16}$ stabilomer (obtained by $AlBr_3$ isomerization, see below), further reduced the number of force field calculations required. The fully decoupled ^{13}C NMR spectum of the chief 97 ± 1% $AlBr_3$ rearrangement product exhibited six resonances, but the intensities suggested that there might be an accidental degeneracy, i.e., structures with seven unique carbons could not be excluded. Of the 14 structures with six unique carbons and seven with seven unique carbons (Table I), 13 can be eliminated from consideration because they possess highly strained intertwined bridges. The off-resonance decoupled ^{13}C NMR spectrum of the rearrangement product indicated that no quaternary carbons were present, eliminating two additional ring systems, tetracyclo[5.3.1.$0^{4,9}$.$0^{4,11}$]undecane (**4**) and tetracyclo[5.2.2.$0^{1,6}$.$0^{4,9}$]-undecane (**5**). In addition, these isomers contain elaborate norbornane structures which should be relatively high in strain.



1 **2** **3** **4** **5**

Empirical force field calculations[14,15] were carried out on the remaining six isomers, **6, 7, 9–12.** To these (Table II) were added 2,9-ethanonoradamantane (**8**) and methanoadamantane (**3**). Except for **10–12,** these choices could have been derived based on prior experience and calculations on related tricyclic and tetracyclic systems. Thus, ring contractions by elimination of a methylene group from various positions of ethanoadamantane (**2**), the $C_{12}H_{18}$ tetracyclic stabilomer,[10] gives **3** as well as **6–8.** These three ethanonoradamantanes (**6–8**) can also be arrived at by adding a $-CH_2CH_2-$ bridge to the C_9H_{14} tricyclic stabilomer, noradamantane.[16] Noriceane (**9**)[17] also seems intuitively to be a good stabilomer candidate, because it contains only five- and six-membered rings.

Both force fields [Engler,[14] designated (E); Allinger,[15] 1971, (A)] indicate 2,4-ethanonoradamantane (**6**) and 2,8-ethanonoradamantane (**7**) to have equal enthalpies of formation and both to be substantially more stable than any other isomers (Table II). Since both **6** and **7** have rigid structures, the same number of CH_2 and CH groups, and the same symmetry number (one), entropy differences are expected to be negligible.[18] Although the force field calculations pertain to the gas phase, relative energies of alkane isomers do not change much in the liquid phase.[18] Therefore, the calculations lead to the prediction that **6** and **7** should be formed in about equal amounts to the exclusion of any other $C_{11}H_{16}$ tetracyclic isomers at thermodynamic equilibrium at room temperature.[50]

Results

Three $C_{11}H_{16}$ isomers, tetracyclo[6.3.0.$0^{2,6}$.$0^{5,9}$]undecane (**13**), noriceane (**9**), and methanotwistane (**14**), were utilized as precursors for rearrangement into more stable tetracyclic undecane systems.

When (D_3)-trishomocubane (**15**) was prepared by $AlBr_3$ isomerization of a pentacyclic $C_{11}H_{14}$ precursor (**16**), two by-products (~5%, ~2%) both having *m/e* 148 ($C_{11}H_{16}$) formed.[19] Since the sample of **16** used in the rearrangement contained 6% of tetracyclic **13,** the latter seemed a logical precursor for the initial $C_{11}H_{16}$ isomerization studies.

Pure **13** was prepared by Wolff–Kishner reduction of the readily available tetracyclic diketone **17.**[20,21] Treatment of **13** with three times its weight of aluminum bromide in carbon disulfide at room temperature for 1.5 h gave in up to 84% yield a mixture of two *m/e* 148 isomers in a ratio 97:3. Small amounts of disproportionation products, adamantane (~1%) and 1-methyladamantane (~10%), were identified by characteristic GLC retention times and GC–MS. The amounts of the disproportionation products varied with the experiment, but tended to increase with longer reaction times. A small amount (~1%) of a *m/e* 146 isomer identified (GLC, GC–MS) as (D_3)-trishomocubane[19] was also observed. When the progress of the reaction was monitored by GLC no buildup of significant amounts of any additional intermediate rearrangement products was observed. The major component with *m/e* 148 was isolated by preparative GLC, mp 167–168 °C (designated as the solid isomer). Its ^{13}C NMR spectrum exhibited six resonances (one possible coincidence) and the chemical shifts were consistent with either **6** or **7.** 2,4-Ethanonoradamantane (**6**) and **7** are equally close mechanistically (Scheme I) to **13** in that both need involve only two 1,2-alkyl shifts.

Scheme I

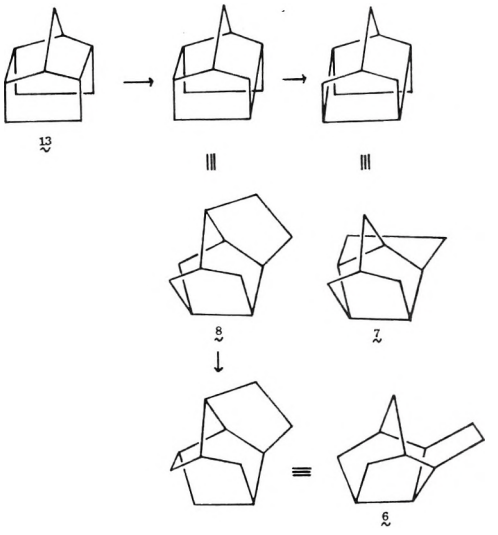
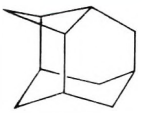
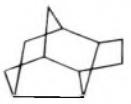
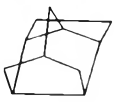
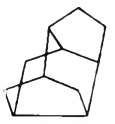
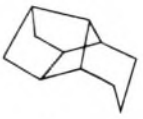
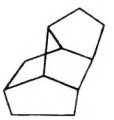
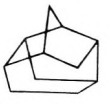
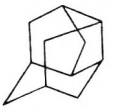
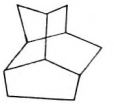
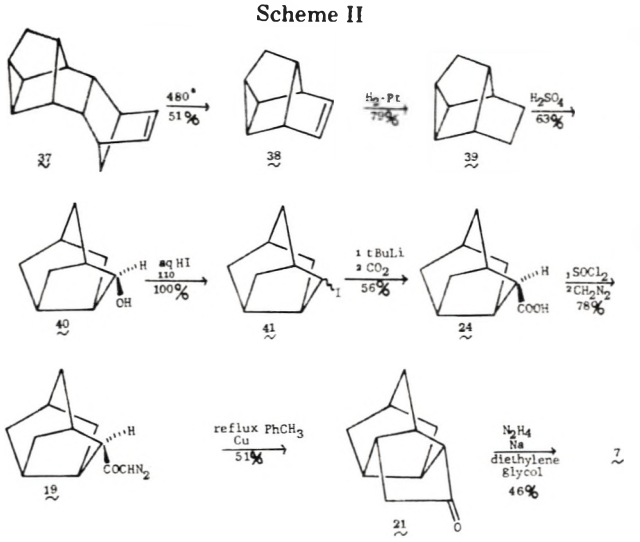


Table II. Molecular Mechanics Calculations of Selected $C_{11}H_{16}$ Hydrocarbons

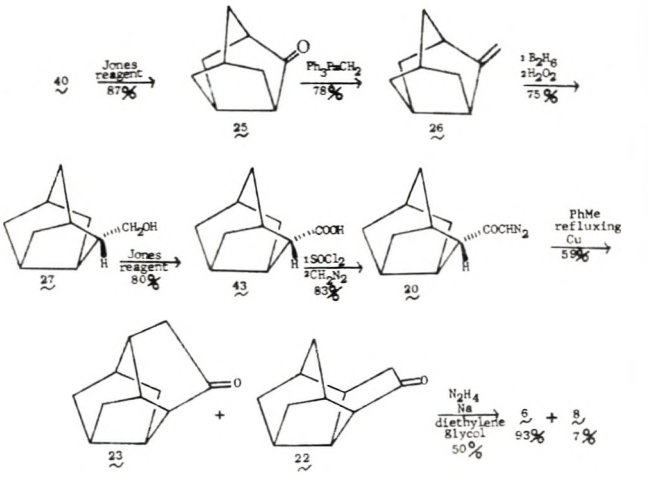
Compd			$\Delta H_f°$[a]
Tetracyclo[5.3.1.$0^{2,5}$.$0^{4,9}$]undecane		E[b]	7.61
(Methanoadamantane) (3)		A[c]	7.68
Tetracyclo[5.3.1.$0^{2,6}$.$0^{3,9}$]undecane		E	−13.21
(2,4-Ethanonoradamantane) (6)		A	−13.16
Tetracyclo[6.2.1.$0^{2,6}$.$0^{5,10}$]undecane		E	−13.19
(2,8-Ethanonoradamantane) (7)		A	−13.17
Tetracyclo[6.2.1.$0^{2,9}$.$0^{5,9}$]undecane		E	−5.38
(2,9-Ethanonoradamantane) (8)		A	−7.16
Tetracyclo[5.3.1.$0^{2,6}$.$0^{4,9}$]undecane		E	−7.42
(Noriceane) (9)		A	−10.42
Tetracyclo[5.3.1.$0^{2,6}$.$0^{4,11}$]undecane		E	7.34
(Trimethylenebisnoradamantane) (10)		A	10.58
Tetracyclo[5.4.0.$0^{3,10}$.$0^{5,9}$]undecane		E	−3.71
(11)		A	−3.91
Tetracyclo[6.2.1.$0^{2,6}$.$0^{4,9}$]undecane		E	14.23
(12)		A	8.13
Tetracyclo[6.3.0.$0^{2,6}$.$0^{5,9}$]undecane		E	−4.00
(13)		A	−2.22
Tetracyclo[6.2.1.$0^{2,7}$.$0^{4,9}$]undecane		E	0.17
(Methanotwistane) (14)		A	−4.86
Tetracyclo[5.4.0.$0^{2,9}$.$0^{4,8}$]undecane		E	−5.04
(Brexabrendane) (29)		A	−6.63
Tetracyclo[5.3.1.$0^{2,6}$.$0^{3,8}$]undecane		E	−2.54
(Brexatwistbrendane) (30)		A	−4.34
Tetracyclo[5.3.1.$0^{2,6}$.$0^{4,8}$]undecane		E	−2.15
(31)		A	−3.45
Tetracyclo[6.2.1.$0^{2,6}$.$0^{4,10}$]undecane		E	−8.27
(Methanoprotoadamantane) (32)		A	−7.62
Tetracyclo[6.3.0.$0^{2,6}$.$0^{3,10}$]undecane		E	−10.11
(33)		A	−5.80
Tetracyclo[6.2.1.$0^{2,6}$.$0^{3,9}$]undecane		E	4.04
(34)		A	2.05

[a] Kcal/mol, gas phase, 25°C. Strain energies can be calculated by adding 38.61 (E) and 38.88 (A) to respective heats of formation. Ref 1. [b] Engler force field. Ref 14. [c] Allinger 1971 force field. Ref 15.

Scheme II

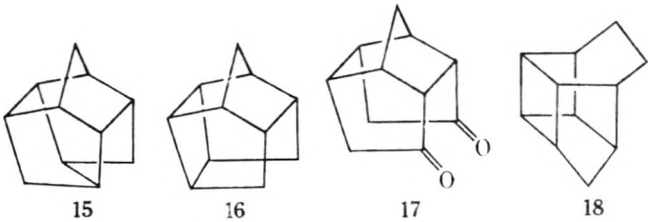


Scheme III



Noriceane[17] (**9**) reacted more smoothly (faster, less disproportionation) but gave essentially the same results as for **13**. Treatment of **9** with $AlBr_3$ under the same conditions as for **13** afforded after 1 h the same mixture of the two isomers (95 and 3%) as obtained above as well as 2% of 1-methyladamantane.

Methanotwistane (**14**), prepared by catalytic hydrogenolysis of the strained C–C bond of pentacyclo[6.2.1.$0^{2,7}$.$0^{4,9}$]undecane (**18**),[22] behaved somewhat differently from **13** and **9**. Upon contact with $AlBr_3$, **14** disappeared almost instantly and the same *m/e* 148 isomers were produced. However, the ratio of these isomers formed initially was quite different from that previously encountered, and thus afforded an opportunity to obtain the "other" (designated the liquid isomer) $C_{11}H_{16}$ rearrangement isomer. The new *m/e* 148 isomer, isolated by preparative GLC, was a liquid which showed seven resonances in the decoupled ^{13}C NMR spectrum; the structure therefore was compatible with either **6** or **7**. Prolonged treatment of the reaction mixture with $AlBr_3$ gradually reversed the ratio of the two isomeric products until the ratio of solid to liquid isomers approached 5:1. Extensive disproportionation to 1-methyladamantane (amounting to 93% of the mixture) did not allow accurate measurement of the equilibrium ratio. When the pure liquid isomer (synthetic sample, see below) was treated with $AlBr_3$, a 98:2 ratio of solid to liquid isomers was reached after 2 days at room temperature.



Two additional features of the methanotwistane (**14**) rearrangement merit special attention. During very early stages of rearrangement (up to 10 min), a small peak identified as noriceane (**9**) was detected by GLC and confirmed by GC–MS. Also, in very early stages of the rearrangement of **14**, use of a Golay capillary column revealed that substantial amounts of 2-methyladamantane had formed, but that only a small amount of 1-methyladamantane was present. 2-Methyladamantane no longer was present after 40 min of reaction at room temperature; rearrangement to 1-methyladamantane was nearly complete.[6b]

No structural assignment could be made to the two isomeric $C_{11}H_{16}$ rearrangement products, one a solid of mp 167–168 °C and the other a liquid, on the basis of ^{13}C NMR spectra. In addition, the amorphous nature of the crystals of the solid product discouraged submission for possible x-ray determination of the structure. We therefore chose to synthesize **6** and **7** independently.

Synthesis of 2,8-Ethanonoradamantane (7) and 2,4-Ethanonoradamantane (6). The stereochemical control imposed on the C–H insertions of the carbenes generated from the isomeric diazo ketones **19** and **20** under high-dilution conditions[23] forms the basis for the syntheses of **6** and **7** (Schemes II and III, respectively). The exo diazo ketone **19** gives ketone **21** while the endo diazo ketone **20** yields a mixture of ketones **22** and **23**. Wolff–Kishner reduction[24] of **21** yields **7**, while reduction of **22** and **23** gives **6** and **8**.

Diazo ketone **19** was prepared from exo-noradamantanecarboxylic acid (**24**) which was obtained stereochemically pure by carboxylation of 2-noradamantyllithium.[25] The stereochemistry was confirmed by ^{13}C NMR (see below). The stereoselectivity of carboxylation must be attributed to kinetic control, as a mixture of the methyl 2-noradamantanecarboxylates when epimerized in a methanol solution containing NaOMe gave an equilibrium containing only 75% of the exo ester. Model empirical force field calculations indicate exo-2-methylnoradamantane to be only 1.0 kcal/mol more stable than the endo isomer.

The 2,8-ethanonoradamantane (**7**) obtained by this route (Scheme II) was identical with the liquid *m/e* 148 isomer which predominated during the initial stages of the methanotwistane (**14**) rearrangement and was the minor product (3 ± 1%) from isomerization of **13** and **9**. When treated with $AlBr_3$, synthetically obtained **7** yielded a mixture of **6** and **7** in a 98:2 ratio after 48 h in CS_2 solution at room temperature. This result differs somewhat from that observed when **7** was produced as an intermediate during the rearrangement of **14**. This discrepancy may be due to variations in the activity of the $AlBr_3$ catalysts employed (the extent of disproportionation in these rearrangements is known[6b] to depend on the activity of the catalyst).

Synthesis and Rearrangement of 2,4-Ethanonoradamantane (6). The preparation of the diazo ketone precursor to **6** (Scheme III) depended on the known selectivity of attack of 2-noradamantane derivatives from the less hindered exo side.[26] The desired 2-noradamantane derivative was prepared as 2-noradamantanone (**25**) was converted by a Wittig reaction[27] to 2-methylenenoradamantane[28] (**26**).

Predominant attack of **26** from the less hindered exo face by diborane,[29] followed by hydrogen peroxide oxidation, gave ~95% of *endo*-noradamantylcarbinol (**27**) and only ~5% of *exo*-2-noradamantylcarbinol (**28**). No efficient means of

Table III. Comparison of Heats of Isomerization (Gas, kcal/mol) from Various Sources

Reaction	Exptl ΔH_{isom}		Calcd ΔH_{isom}	
	From direct isomerization data	From ΔH_f° differences	1971 Allinger force field	Engler force field
2-Methyladamantane → 1-methyladamantane	−2.77[a]	−4.91[b]	−3.85[c]	−3.88[c]
1-Methyldiamantane → 4-methyldiamantane	−2.14[a,d]	−3.68[b]	−2.78[c]	−3.26[c]
3-Methyldiamantane → 4-methyldiamantane	−2.70[a,d]	−5.93[b]	−3.86[c]	−3.91[c]
Protoadamantane → adamantane	(−11.0,[e] > 7.5[b])	−11.22[b]	−11.19[c]	−11.37[c]

[a] Reference 6b. This review summarizes the available data. [b] Reference 32a. [c] References 14, 15. [d] These values would be 0.3–0.5 kcal/mol larger if theoretical instead of experimental entropies are assumed (see ref 31e). [e] Indirectly estimated ΔG_{isom} from experimental data on derivatives in solution [D. Lenoir, D. J. Raber, and P.v.R. Schleyer, *J. Am. Chem. Soc.*, 96, 2149 (1974)]. [f] Lower limit (ΔG) from equilibration of acetates in solution [H. J. Storesund and M. C. Whiting, *J. Chem. Soc., Perkin Trans. 2*, 1452 (1975)].

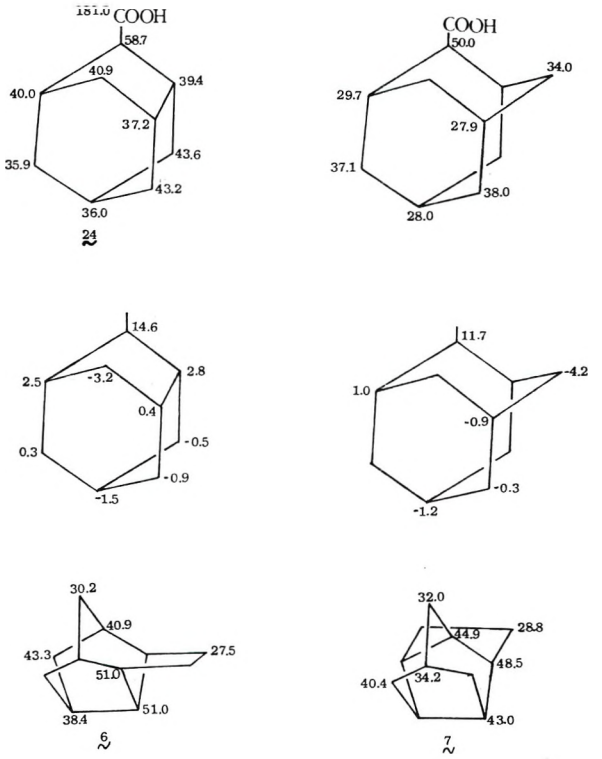


Figure 1. ^{13}C NMR of *exo*-2-noradamantanecarboxylic acid (**24**), 2-adamantanecarboxylic acid, 2,8-ethanonoradamantane (**7**), and 2,4-ethanonoradamantane (**6**). Chemical shifts for **6**, **7**, and acids indicated on molecule. Chemical shift differences for acids relative to the parent hydrocarbons are given on the noradamantane and adamantane structures.

physical separation of these isomers could be devised and **28** was carried throughout the subsequent reactions. A similar sequence as for the 2,8-ethanonoradamantane (**7**) synthesis was used (Scheme II) with comparable yields. Reduction of the mixture of ethanonoradamantanones obtained after C–H insertion (Scheme III) afforded a mixture of ~82% 2,4-ethanonoradamantane (**6**), ~11% 2,8-ethanonoradamantane (**7**), and ~7% 2,9-ethanonoradamantane (**8**).

2,4-Ethanonoradamantane, purified by preparative GLC, was identical with the solid *m/e* 148 rearrangement product, mp 167–168 °C, from **13**, **9**, and **14**. The hydrocarbon mixture of **6**, **7**, and **8** from the Wolff–Kishner reduction when treated with $AlBr_3$ in CS_2 gave an equilibrium ratio of **6**:**7** of 96:4.

^{13}C NMR. The ^{13}C NMR spectrum of *exo*-2-noradamantanecarboxylic acid (**24**) (Figure 1) provides further confirmation of its stereochemistry. In comparison with the chemical shifts for noradamantane, *one* CH_2 signal in **24** is found to be significantly shielded (syn-diaxial interaction) whereas two such shifted CH_2 signals (as in 2-adamantanecarboxylic acid) would have been expected[30] for the endo configuration.

Discussion

The rearrangement results establish 2,4-ethanonoradamantane (**6**) as the $C_{11}H_{16}$ stabilomer. The 97 (±1) to 3 (±1) equilibrium ratio of **6** to 2,8-ethanonoradamantane (**7**) observed from rearrangement of **7**, **9**, and **13** indicates a free-energy difference of approximately 2 kcal/mol. The symmetry numbers of **6** and **7** are the same and entropy differences should not be a significant factor in determining the equilibrium:[18,50] ΔH_{isom} should thus be ~2 kcal/mol. This contrasts with the prediction of both empirical force fields[14,15] that ΔH_f for **6** and **7** should be identical.[50] This discrepancy was a surprise to us. Although errors in absolute ΔH_f values calculated by empirical force field methods can be 2 kcal/mol or more, it is expected from experience (see Table III) that *energy differences* between such closely related isomers as **6** and **7** should be reproduced much more accurately.[31]

Nevertheless, empirical force field calculations have been extremely useful in directing the experiments outlined here; **6** and **7** were predicted to be the most stable isomers out of the 2486 possibilities.

In this context, it seems appropriate to point out that recent experimentally determined ΔH_f°'s of closely related isomers have relative errors on the order of 2 kcal/mol where compared with equilibration results[32] (Table III).

Isomerization Mechanisms. Several experimental observations are particularly pertinent:

1. Both **9** and **13** isomerize directly to the equilibrium mixture of **6** and **7** without the intervention of detectable intermediates.

2. Methanotwistane (**14**) rearranges to a mixture of **6** and **7** much richer in the latter than is found at equilibrium. Noriceane (**9**) is formed in the initial stages of the reaction, and may be an intermediate.

3. 2-Methyladamantane is formed rather than the more stable 1-methyl isomer from **14** by disproportionation.

4. The equilibration of **6** and **7** is slow compared to the isomerization of **9**, **13**, and **14**.

A rearrangement graph (Figure 2), similar to those for the tricyclodecanes[33] and the pentacyclotetradecanes,[31g] provides the best format for mechanistic discussions. This graph can be constructed starting from **9**, **13**, and **14** by taking all possible 1,2-alkyl shifts into account,[33] but disallowing isomers which result when they contain three- or four-membered rings or other highly strained structural features.[33] When all possibilities are examined, six additional tetracycloundecanes **29**–**34** appear as potential intermediates. These six isomers all have 11 unique carbon atoms, no quaternary carbons, and were present among the 68 structures generated by the Wipke program (Table I). The 15 ring systems **6**–**14** and **29**–**34** comprise a closed graph (Figure 2).

Calculations of ΔH_f° for the neutral possible intermediates **29**–**34** are included in Table II. From among these **32** and **33** emerge as stable ring systems which might be intermediates

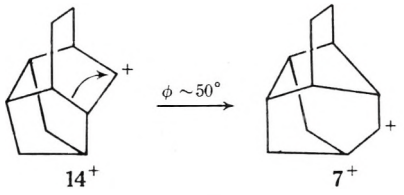
in the rearrangements. Figure 2 is constructed so that the ordinate is approximately proportional to the calculated $\Delta H_f°$'s; the most stable isomers are at the bottom. This presentation emphasizes that the tetracycloundecane energy surface has two distinct minima at **6** and **7**. Furthermore, the graph shows that any path involving **10**, **12**, or **34** is highly endothermic and can be excluded from further consideration.

The rates of 1,2-alkyl shifts in rigid polycyclic systems depend markedly on the dihedral angle between the migrating C–C bond and the "vacant" orbital of the adjacent carbenium ion.[31g,34] These dihedral angles, estimated from framework molecular models, are included in Figure 2 for each step. All possible steps involving dihedral angles >50° were omitted.

A complete treatment of the isomerization mechanism would also include calculation of the relative energies of all intermediate carbenium ions.[31f,35] In lieu of undertaking these extensive calculations, the individual rearrangement steps were examined to determine if any required energetically unfavorable bridgehead cations. This was not the case; secondary cations were found to account for all the isomerizations included in the graph.

In order to reach **6** and **7**, **13** must pass through 2,9-ethanonoradamantane (**8**) (Figure 2). The large calculated heats of reaction as well as the almost ideal dihedral angle for the paths **8** → **6** and **8** → **7** explain the rapid formation of **6** and **7** from **13**. No other intermediate other than **8** need be involved and even **8** could not be detected experimentally.

There are many possible routes from methanotwistane (**14**) to **6** and **7**. The direct pathway from **14** to **7** (eq 1) is not attractive because of the large dihedral angle required by the 1,2-alkyl shift. Therefore, the preferential formation of **7** from **14** during the early stages of the isomerization should involve at least one intermediate. Examination of the graph suggests **32** as this intermediate. The intermediacy of **32** can also account for the observation of **9** in the initial stages of the rearrangement. Since the direct route from **14** to **9** suffers from an unfavorable dihedral angle (45°), the transient appearance of **9** may best be explained as a side reaction of **32**. No good pathway from **14** to **6** is available except for mechanistically poor two-step routes involving **30** or **9**, or equally inferior three-step routes. This may explain the observed low percentage of **6** produced in the early stages of the rearrangement of **14**.



(1)

The ready rearrangement of noriceane (**9**) to the stabilomer **6** is hard to understand. The direct path from **9** to **6** involves a rather large dihedral angle (45°) for the 1,2 shift.[36] Although this possibility cannot be ruled out, the similarity of product distribution and rate of isomerization of **9** and **13** suggests the intermediacy of **11** and **8**, despite the endothermicity calculated for the step **9** → **11**. We have no experimental evidence to support this possibility.

The slow equilibration of **7** to **6** may be due to the endothermicity involved in the most likely pathways via **8**, or via **32** and **9**, or via **32** and **33**.

The preferential appearance of 2-methyladamantane rather than 1-methyladamantane in the early stages of the rearrangement of **14** is not unprecedented in the tricycloundecane family.[37] A regioselective C–C bond rupture in **14** might account for the 2-methyladamantane. However, examination of all possible C–C bond cleavages in **14** failed to reveal any

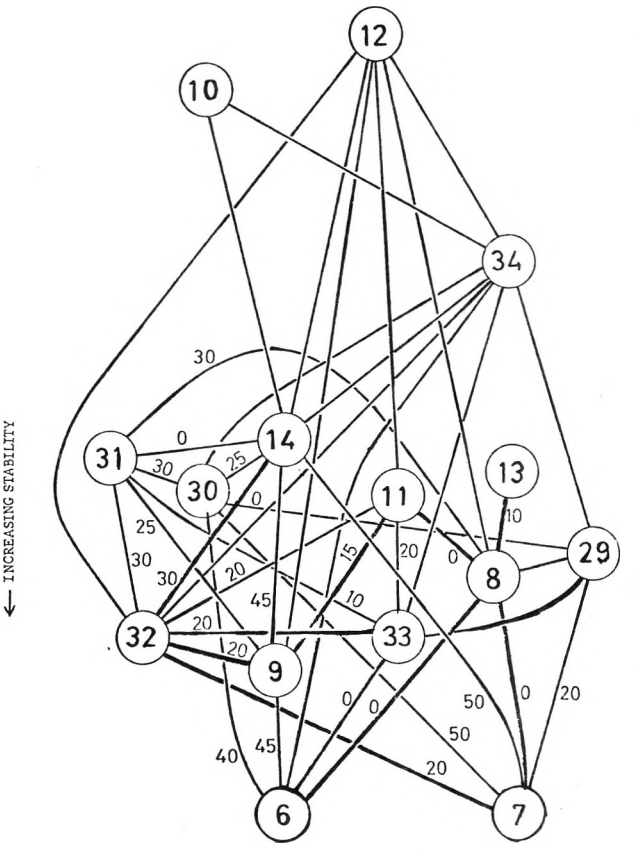
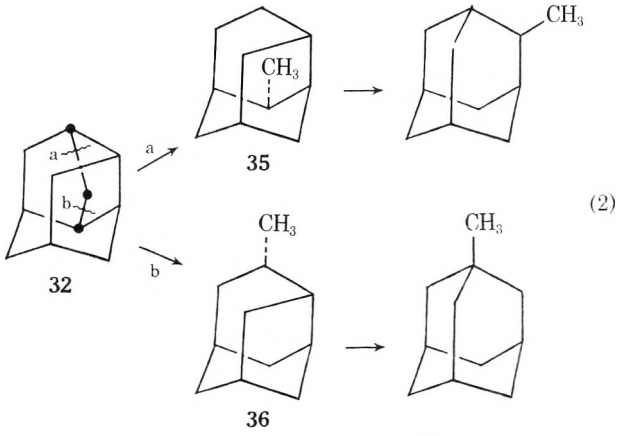


Figure 2. Tetracycloundecane graph. Numbers on each path are estimated dihedral angles between the migrating C–C bond and the empty orbital in the intermediate carbenium ion (shift proceeding to lower energy isomer). The ordinate is approximately proportional to calculated heats of formation (see text).

efficient route leading to the 2-methyl derivative. In addition, the calculated structure of **14** shows uniform strain distribution and **14** is therefore not likely to undergo C–C bond cleavage.[22,38] Examination of the structures closest to **14** in the graph indicates that of these **32** has a remarkably uneven strain distribution, e.g., in the variation of bond lengths. The calculations show that the strain is centered on the three central atoms (marked by filled circles, eq 2) of the norbornane-like moiety of **32**. Cleavage of one of these bridge bonds should result in a large amount of strain relief. Path a should predominate since it leads to 7-*exo*-methylprotoadamantane (**35**) which is 0.3 (A) and 2.0 (E) kcal/mol more stable than the product of b cleavage, 4-*exo*-methylprotoadamantane (**36**).[39] Furthermore, path a cleavage results in the placement of the positive charge at C-4 in **35**, exactly where required for subsequent rearrangement to the adamantane skeleton. The isomerization of **35** to 2-methyladamantane in the presence



(2)

of $AlBr_3$ is highly exothermic (calculated heat of reaction: 9.7 (E) and 12.4 (A) kcal/mol[39,40]) and therefore expected to be very rapid.

Experimental Section

General. Microanalyses were performed at the Combustion Analysis Center, Department of Pharmacy, Hokkaido University, and at Hoffmann-La Roche, Inc., Nutley, N.J. Infrared spectra were determined on a Perkin-Elmer 237B and a JASCO IR-G spectrophotometers. Mass spectra were taken on an AEI MS-9 spectrometer and Hitachi RMU-6D and -6E spectrometers at 70–80 eV. GC–MS analyses were performed on a Du Pont 21-490 instrument and JEOL JGC-20-KP gas chromatograph (0.01 in. × 150 ft column packed with Apiezon L or Silicone SE-30) connected to a JEOL JMS-D100 mass spectrometer. Preparative GLC was carried out on a Varian Aerograph 700 instrument. ^1H NMR spectra were recorded on a Varian A-60A and a Hitachi R-20B, while ^{13}C NMR spectra were measured on Varian XL-100 and JEOL FX-60 spectrometers.

Tetracyclo[6.3.0.$0^{2,6}$.$0^{5,9}$]undecane (13). Reduction of the known tetracyclic diketone (17)[20] by the Huang-Minlon modification of the Wolff–Kishner (using metallic sodium in place of KOH) gave camphorlike crystalline **13** in 75% yield: mp 153–4 °C; ^1H NMR (CCl_4) δ 2.05 (6 H, br s, methine), 1.56 (10 H, complex, methylene); MS *m/e* (rel intensity) 148 (M^+, 52), 119 (37), 91 (30), 81 (56), 80 (69), 79 (48), 67 (100), and 66 (99).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 88.84; H, 10.73.

Aluminum Bromide Catalyzed Rearrangement of 13. 1. Analytical Scale. In a 50-ml round-bottom flask were placed 90 mg of **13**, 300 mg of sublimed aluminum bromide, and 10 ml of carbon disulfide. With exclusion of moisture, the mixture was stirred at room temperature and the course of reaction followed by GLC analysis. Starting material disappeared completely after 1.5 h and a predominant product peak having shorter retention time appeared in addition to several minor peaks. The product distribution did not change significantly after heating the mixture for 24 h under reflux. The reaction mixture was then transferred to an aerosol tube, more aluminum bromide added, and heated at 100 °C for 1.5 h. GLC analysis revealed that about one-third of the main product disproportionated into 1-methyladamantane, but the remaining two-thirds survived. Relative GLC retention time on 3 mm × 3 m Silicone DC 550, 134 °C, N_2 21 psi: **13**, 1.79; **6**, 1.60; **7**, 1.38; 1-methyladamantane, 1.00.

2. Preparative Scale. In a 50-ml round-bottom flask, 1.22 g of **13** was dissolved in 20 ml of carbon disulfide. In the course of 1.5 h, 3.4 g of anhydrous aluminum bromide was added in three portions to the reaction flask while stirring at room temperature. The solution was decanted from the aluminum bromide sludge, which was further washed several times with carbon disulfide. The combined carbon disulfide solution was washed with water, dried over calcium chloride, and evaporated. The residue was sublimed at 100 °C (15 mmHg) to give 1.03 g (84%) of a colorless, camphorlike product. GLC analysis revealed 97% purity with 2.4, 0.2, and 0.4% minor products in decreasing order of retention time. An analytical sample of the main product, identified as **6** by comparison with an authentic sample (see below), was obtained by preparative GLC (6 mm × 9 m 5% FFAP at 119 °C, He 14 psi) followed by sublimation: mp 167–168 °C (cor, sealed tube); ^1H NMR (CCl_4) δ 2.6–2.0 (br, 6 H, methine) and 1.9–1.2 (complex with prominent peaks at 1.75 and 1.63, 10 H, methylene); ^{13}C NMR ($CDCl_3$) δ 51.1 (d, 2 C plus d, 1 C), 43.3 (t, 2 C), 41.0 (d, 2 C), 38.4 (d, 1 C), 30.1 (t, 1 C), and 27.4 (t, 2 C) (see Figure 1 for assignments); MS *m/e* (rel intensity) 148 (M^+, 84), 119 (33), 92 (37), 91 (39), 81 (43), 80 (100), 79 (91), 67 (47), and 66 (52).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.11; H, 10.88.

The main by-product (2.4%) was identified as 2,8-ethanonoradamantane (**7**) by comparison with an authentic sample (see below). The ratio of **6** to **7** obtained in a number of similar runs was 97 (±1):3 (±1). Two other side products (0.2 and 0.4%) were identified as (D_3)-trishomocubane (**15**, *m/e* 146)[19] and 1-methyladamantane (*m/e* 150), respectively, by GC–MS. In addition, GC–MS detected up to 1% of adamantane (*m/e* 136) in the reaction mixture. When the reaction was extended to 5 h at room temperature, the yield of 1-methyladamantane increased to 10%.

Aluminum Bromide Catalyzed Rearrangement of Noriceane (9). The rearrangement was performed under similar conditions as above using 90 mg of noriceane (**9**),[17] about 200 mg of sublimed aluminum bromide, and 5 ml of carbon disulfide. The reaction was followed by GLC; noriceane (rel retention time 2.09) disappeared completely after 50 min, giving a three-component mixture, **6**, **7**, and 1-methyladamantane, in the ratio 95:3:2. The usual workup gave 73 mg (81%) of this product mixture.

Table IV. Product Distribution (%) as a Function of Time in the Rearrangement of 14

Time	1-MeAd[a]	(D_3)-THC[b]	7	6	9
6 min	1	Trace	63[c]	34	2
10	5	Trace	61	33	1
20	13	1	55	32	0
40	19	1	48[d]	32	0
1 h	21	1	45	33	0
2	24	1	39	46	0
4	33	1	25	41	0
21	60	Trace	7	33	0
5 (reflux)	93	Trace	1	5	0

[a] 1-Methyladamantane. [b] (D_3)-Trishomocubane (15). [c] This peak contains about 25% of 2-methyladamantane (see text). [d] 2-Methyladamantane no longer is present.

Aluminum Bromide Catalyzed Rearrangement of Methanotwistane (14). In 15 ml of carbon disulfide, 0.1 g of methanotwistane (**14**)[22] and 0.49 g of sublimed aluminum bromide were stirred at room temperature. Methanotwistane (rel retention time 1.80) disappeared almost instantly. GC–MS analysis revealed the following change of product distribution with time (Table IV).

In a preparative run, 0.64 g of **14** was treated with 2 g of anhydrous aluminum bromide in 50 ml of carbon disulfide protected from moisture by a calcium chloride tube. After 6 min, a 10-ml aliquot was removed and quenched with water. The organic phase was worked up and subjected to GC–MS analysis. 1-Methyladamantane, (D_3)-trishomocubane (**15**), 2,8-ethanonoradamantane (**7**), 2,4-ethanonoradamantane (**6**), and noriceane (**9**) were identified by comparison of retention times and fragmentation patterns with those of authentic samples. The peak corresponding to 2,8-ethanonoradamantane (**7**) had a shoulder at a higher retention time which could be resolved only by the use of a Golay capillary column. The retention time of this shoulder was identical with that of 2-methyladamantane. Mass spectral analysis of the shoulder confirmed it to be 2-methyladamantane (M^+, *m/e* 150) mixed with 2,8-ethanonoradamantane.

The rest of the reaction mixture was quenched after 40 min of reaction at room temperature and worked up to give 0.45 g of colored oil, from which the main peak (2,8-ethanonoradamantane) was collected by preparative GLC to give about 100 mg of colorless liquid: ^1H NMR ($CDCl_3$) δ 2.2–0.8 (br m); ^{13}C NMR ($CDCl_3$) δ 48.6 (d, 2 C), 45.0 (d, 1 C), 43.1 (d, 2 C), 40.5 (t, 2 C), 34.2 (d, 1 C), 32.1 (t, 1 C), and 28.8 (t, 2 C); MS *m/e* (rel intensity) 148 (M^+, 100), 119 (71), 91 (53), 79 (75), 66 (78).

Hexacyclo[9.2.1.$0^{2,10}$.$0^{3,7}$.$0^{4,9}$.$0^{6,8}$]tetradecan-12-ene (Katz Dimer) (37). The [4 + 2] norbornadiene dimer was prepared essentially by the method of Mrowca and Katz.[41,42] Purification of the norbornadiene before introduction of the rhodium catalyst improved the yield of dimer significantly (from 15 to 50%).[43]

Typically, 1 kg of norbornadiene (Aldrich) was refluxed for 3 h with 80 g of maleic anhydride. The norbornadiene was then distilled directly into a predried, nitrogen-purged flask charged with 5 g of 5% rhodium on carbon catalyst (ROC–RIC). The suspension was then stirred and refluxed for 72–96 h. Additional 1-g portions of catalyst were added until no further change could be detected as determined by the NMR integration of the olefinic protons in norbornadiene and **37**. When the ratio of product to starting material reached 3:1, the mixture was diluted with 300 ml of pentane and filtered. The pentane and norbornadiene were distilled at atmospheric pressure and the dimers distilled at reduced pressure: bp 70–75 °C (0.4–0.5 mm) [lit.[41] bp 76–77 °C (0.8 mm)], yield about 50%.

Tetracyclo[4.3.0.$0^{2,4}$.$0^{3,7}$]non-8-ene (Deltacyclene)[44] (38). The pyrolysis of **37** was carried out in a quartz tube (65 × 2.2 cm) heated to 480 °C.[44d] A nitrogen flow of 15 ml/min was maintained as **37** was added by means of an automatic syringe pump (100 ml added over 5-h period). Distillation of the pyrolysate gave deltacyclene (**38**, 51%) as a yellow liquid, bp 52–56 °C (25 mm) [lit.[44c] bp 55–58 °C (25 mm)].

Tetracyclo[4.3.0.$0^{2,4}$.$0^{5,7}$]nonane (Deltacyclane) (39). A solution of 50 g of deltacyclene (**38**) in 100 ml of ethyl acetate was hydrogenated over platinum oxide catalyst by shaking for 4 h in a Parr hydrogenator under 45 psi hydrogen pressure. The catalyst was filtered and solvent removed at reduced pressure; 40 g (79%) of **39** was obtained as a colorless liquid, bp 48–50 °C (17 mm) [lit.[45] bp 152–153 °C (760 mm)].

***exo*-Tricyclo[3.3.1.$0^{3,7}$]nonan-2-ol (*exo*-2-Noradamantanol) (40).** A solution of 25.0 g of deltacyclane (**39**) in 250 ml of pentane was cooled in an ice bath and then added rapidly with vigorous mechanical

stirring to 650 ml of 97% sulfuric acid at −5 °C. After 4.5 min the reaction was quenched by pouring onto 2.5 kg of ice. After separation of the layers, the aqueous phase was refluxed for 5 h to ensure hydrolysis of sulfate esters, and then extracted with methylene chloride. The organic layers were washed with water, saturated aqueous bicarbonate, and water and then dried over anhydrous magnesium sulfate. Removal of solvent gave 18 g (63%) of *exo*-2-noradamantanol (**40**) as a white solid: mp 221.9–223.6 °C (lit.[26] 221–222 °C); ir (CCl_4) ν 3360, 1105, 1040, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.91 (s, 1 H), 2.70 (s, 1 H), 2.35 (m, 3 H), 2.07 (m, 3 H), 1.58 (m, 6 H).

2-Iodotricyclo[3.3.1.0^{3,7}]nonane (2-Noradamantyl Iodide) (41). A solution of 2-noradamantanol (**40**, 10.0 g in 100 ml of 47% aqueous HI) in a Fischer-Porter bottle was heated to 110 °C and kept at this temperature for 4 h. During this time the iodide formed appeared as a second liquid phase at the bottom of the bottle. The mixture was allowed to cool, then extracted with ether (100 ml, three times). The ether extracts were combined and washed with aqueous sodium bisulfite, saturated aqueous sodium carbonate, and water. The ether solution was dried over anhydrous magnesium sulfate, and the solvent was removed at reduced pressure. Column chromatography (silica gel, pentane eluent) gave 18.0 g (100%) of **41** as a clear liquid: ir (CCl_4) ν 2925, 1468, 1320, 1300, 1290, 1180, 1160, 1050, 980, 900 cm^{-1}; ^1H NMR (neat) δ 4.48 (m, 1 H), 2.88 (m, 2 H), 2.62 (m, 2 H), 1.72 (m, 7 H).

Anal. Calcd for $C_9H_{13}I$: C, 43.57; H, 5.28; I, 51.15. Found: C, 43.86; H, 5.51; I, 50.86.

***exo*-Tricyclo[3.3.1.0^{3,7}]nonane-2-carboxylic Acid (*exo*-2-Noradamantanecarboxylic Acid) (24).** Ether (50 ml) was cooled to −60 to −78 °C in a 500-ml three-neck flask fitted with a dropping funnel and kept under a nitrogen atmosphere. *tert*-Butyllithium (Ventron, 0.75 M in pentane, 50 ml) was syringed into the ether at a rate such that the temperature of the solution was maintained at −50 °C. An ether solution of the iodide **41** (8.0 g in 15 ml of ether) was added slowly over a 45-min period (temperature kept at −40 to −45 °C).[25] The 2-noradamantyllithium solution was then transferred back into the dropping funnel and added rapidly to a flask containing dry solid CO_2 cooled to liquid nitrogen temperature. (Dry solid CO_2 was obtained by subliming dry ice through a tower of calcium chloride in a nitrogen flow, then recondensing the CO_2 in a flask cooled to liquid nitrogen temperature.) The CO_2–organolithium mixture was allowed to warm slowly to room temperature, then added to water made acidic with 3 N HCl. After the ether layer was separated, the aqueous phase was extracted with ether (100 ml, three times). The ether solutions were combined and extracted with aqueous sodium carbonate in order to separate the organic acid from coupling products (e.g., 2,2′-bisnoradamantane). The aqueous solution of the acid salt was then made strongly acidic with 6 N HCl, precipitating the organic acid. This heterogeneous mixture was extracted with ether (100 ml, three times) and the ether solution was washed with a small amount of dilute aqueous sodium bicarbonate (to remove any HCl). The ether solution was then dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure, yielding 3.0 g (56%) of **24** as a white solid. Recrystallization from pentane yielded an analytically pure sample: mp 94.0–96.2 °C; ir (CCl_4) ν 3350–2800, 1710, 1425, 1325, 1265, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.9 (s, 1 H), 2.87 (m, 1 H), 2.67 (m, 1 H), 2.57 (m, 2 H), 2.17 (m, 1 H), 1.67 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 181.0 (s, 1 C), 58.7 (d, 1 C), 39.4 (d, 1 C), 40.0 (d, 1 C), 40.9 (t, 1 C), 37.2 (d, 1 C), 43.6 (t, 1 C), 43.2 (t, 1 C), 35.9 (t, 1 C), 36.0 (d, 1 C) (see Figure 1 for assignments).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.24; H, 8.51. Found: C, 72.40; H, 8.28.

***exo*-Tricyclo[3.3.1.0^{3,7}]nonane-2-carboxylic Acid Chloride (*exo*-2-Noradamantanecarboxylic Acid Chloride) (42).** *exo*-2-Noradamantylcarboxylic acid (**24**, 9.8 g) in 15 ml of anhydrous ether was added dropwise to 11.5 g of $SOCl_2$ (distilled twice from quinoline and once from triphenyl phosphite)[46] in 20 ml of ether at ambient temperature. The mixture was then heated to 50 °C for 5 h. Ether and excess $SOCl_2$ were removed at reduced pressure. **42** distilled at 52.0 °C (0.15 mm) yielding 8.4 g (78%) of a colorless liquid: ir (CCl_4) ν 2940, 1800, 1480, 1430, 1315, 1165, 1100, 1070, 1040, 1010, 900 cm^{-1}; ^1H NMR (CCl_4) δ 3.03 (m, 1 H), 2.97–2.33 (m, 3 H), 2.22 (m, 1 H), 1.68 (m, 8 H).

Anal. Calcd for $C_{10}H_{14}OCl$: C, 65.04; H, 7.09; Cl, 19.20. Found: C, 64.93; H, 7.19; Cl, 18.90.

***exo*-2-Tricyclo[3.3.1.0^{3,7}]nonyl Methyl Diazoketone (*exo*-2-Noradamantyl Methyl Diazoketone) (19). Preparation of Water- and Ethanol-Free Diazomethane.** Diazald (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, Aldrich, 25 g) dissolved in 150 ml of ether was dropped into a solution of 7.3 g of KOH, 12 ml of ether, 40 ml of $C_2H_5O(CH_2CH_2O)_2H$, and 12 ml of water heated to 65 °C. A yellow solution of ether/diazomethane codistilled from this mixture and was trapped at 0 °C. An additional 50 ml of ether was added and the distillate eventually became colorless. The diazomethane–ether solution was dried over KOH, decanted, and fresh KOH was added. The solution was decanted again and sodium added. Throughout the drying process the solution was kept at 0 °C.

The diazomethane–ether solution was added to a 1-l. flask fitted with a thermometer, a dropping funnel, and a nitrogen inlet. The solution was cooled to 0 °C under a nitrogen blanket, and the acid chloride **42** (2.0 g in 25 ml of ether) was added dropwise over a 45-min period.[47] The reaction mixture was kept at 0 °C for 2 h, then allowed to warm to room temperature overnight. The ether was removed under reduced pressure leaving 2.1 g (100%) of **19** as a yellow, gummy solid. This compound must be stored at −5 °C to avoid thermal decomposition. Ir (CCl_4) ν 2920, 2100, 1650, 1360, 1340, 1320, 1260, 1150, 1100, 1060, 1030 cm^{-1}; ^1H NMR (CCl_4) δ 5.22 (s, 1 H), 2.77 (m, 1 H), 2.47–2.00 (m, 4 H), 1.6 (m, 8 H).

Tetracyclo[6.2.1.0^{2,6}.0^{5,10}]undec-3-one (21). Anhydrous $CuSO_4$ (18.0 g)[47,48] (pale brown when dried thoroughly over P_2O_5) was suspended in 300 ml of sodium-dried toluene, in a three-neck flask fitted with a high-dilution apparatus.[23] The solution was heated to reflux and 20 ml of toluene was distilled to remove any residual water as an azeotrope. Diazoketone **19** (2.0 g) in 500 ml of toluene was added via an addition funnel fitted with a cooling jacket. Addition via the high-dilution apparatus[23] continued for an 11-h period. The reaction mixture was refluxed for 12 h after the addition was complete, and then was allowed to cool to room temperature and the $CuSO_4$ filtered. The toluene solution was washed with 100 ml of water, 75 ml of 5 N NaOH (to remove any homologous acid, typically less than 10% of such acid was formed), and twice with 50 ml of water, and then dried over anhydrous magnesium sulfate. The solution was concentrated on a rotatory evaporator, and the light brown oil obtained was charged onto a silica gel column packed in hexane. The eluent was gradually changed to toluene. The initial fractions contained a clear oil. ^1H NMR of these fractions revealed the presence of olefinic protons; no further identification was attempted. The toluene fractions contained the desired ketone **21** obtained in 51% yield as a clear oil. Preparative GLC (20% Carbowax on 80/100 Chromosorb W, 0.25 in. × 1 m) was used to prepare the analytical sample.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.15; H, 8.73.

Tetracyclo[6.2.1.0^{2,6}.0^{5,10}]undecane (2,8-Ethanonoradamantane) (7). Diethylene glycol (20 ml) was heated to 80 °C and 1.0 g of sodium metal was added in small pieces. The ketone **21** (0.8 g) was then added, followed by 1 ml of anhydrous hydrazine.[24] The mixture was heated slowly to 180 °C in a Fischer-Porter bottle to avoid loss of the very volatile hydrocarbon product. The solution was allowed to cool to ambient temperature and water (50 ml) was added. The aqueous solution was extracted with pentane, and the combined extracts were washed with saturated aqueous NaCl and dried over anhydrous magnesium sulfate. The solution was concentrated on a rotatory evaporator and yielded 0.27 g (46%) of **7** as a clear oil. Preparative GLC (0.25 in. × 5 m, 10% SE-30 on 80/100 Gaspack W) gave an analytically pure sample: ir (CCl_4) ν 2900, 1470, 1450, 1320, 1300 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17–0.83 (br m); ^{13}C NMR ($CDCl_3$) δ 48.5 (d, 2 C), 44.9 (d, 1 C), 43.0 (d, 2 C), 40.4 (t, 2 C), 34.2 (d, 1 C), 32.0 (t, 1 C), 28.8 (t, 2 C) (see Figure 1 for assignments); MS *m/e* 148 (M^+), 119, 79, 66.

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 88.81; H, 10.73.

Aluminum Bromide Catalyzed Rearrangement of 2,8-Ethanonoradamantane (7). To a solution of 2,8-ethanonoradamantane (**7**, 100 mg) in 20 ml of carbon disulfide was added about 300 mg of $AlBr_3$. After 48 h at room temperature a mixture of *m/e* 148 isomers consisting of 98% 2,4-ethanonoradamantane (**6**) and 2% 2,8-ethanonoradamantane (**7**) was obtained. In addition, disproportionation products of *m/e* 136, 146, and 150 were identified as described for the rearrangement of **13**.

Tricyclo[3.3.1.0^{3,7}]nona-2-one (2-Noradamantanone) (25). 2-Noradamantanol (**40**, 13.8 g), oxidized using the Jones reagent,[49] afforded 12.0 g of **25** (87%): mp 208.0–211.9 °C (sublimed) (lit.[26] 214.5–215 °C); ir (CCl_4) ν 2925, 1750, 1450, 1170, 1070, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.83–1.33 (br m).

2-Methylenetricyclo[3.3.1.0^{3,7}]nonane (2-Methylenenoradamantane) (26). 2-Noradamantanone (**25**, 3.2 g) was subjected to a Wittig reaction utilizing methyltriphenylphosphonium bromide, NaH, and Me_2SO.[27] Column chromatography yielded 2.5 g (78%) of **26** as a volatile solid: mp 43–44.5 °C (lit.[28] 46–47 °C); ^1H NMR ($CDCl_3$) δ 4.48 (d, 2 H), 2.77 (m, 1 H), 2.50 (m, 2 H), 2.22 (m, 1 H), 1.68 (m, 8 H).

***endo*-2-Tricyclo[3.3.1.0^{3,7}]nonanecarbinol (*endo*-2-Noradamantylcarbinol) (27).** 2-Methylenenoradamantane (**26**, 2.5 g) was converted to 2.1 g (75%) of a mixture of 95% **27** and 5% *exo*-2-norad-

amantylcarbinol (**28**) by a standard hydroboration–oxidation procedure.[29] The relative amounts of **27** and **28** were determined by ^{1}H NMR integration of the CH_2OH protons. An authentic sample of **28** was prepared by lithium aluminum hydride reduction of the corresponding acid (**24**). The mixture of alcohols was recrystallized from hexane: mp 56–59 °C; ir (CCl_4) ν 3600, 3500–3150, 1060, 1000 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.92 (d, 2 H), 2.50 (s and m, 3 H), 2.03 (m, 3 H), 1.65 (br m, 8 H).

***endo*-Tricyclo[3.3.1.0^{3,7}]nonane-2-carboxylic Acid (*endo*-2-Noradamantanecarboxylic Acid) (43).** The 95:5 mixture of the alcohols **27** and **28** (2.56 g) in 50 ml of acetone was added dropwise to Jones reagent[49] cooled at 0 °C. Rapid mechanical stirring was maintained throughout the addition. After the addition was complete, the solution was allowed to warm to room temperature. Sodium bisulfite was then added until the oxidizing agent turned deep green and a second phase appeared. The upper layer was decanted from the dense green lower layer. The lower phase was extracted with pentane. The pentane extracts were combined with the original upper phase forming a second phase. The new lower phase was added to the dense green material and extracted with pentane. The pentane extracts were combined and washed with saturated aqueous NaCl, then saturated aqueous Na_2CO_3 to remove the organic acids (**24** and **43**) as their water-soluble salts. This aqueous phase when acidified with 3 N HCl yielded a white precipitate. The slurry of the organic acids in the aqueous phase was extracted with ether, and the ether extracts were washed with a small amount of dilute aqueous $NaHCO_3$ to remove any HCl and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, yielding 2.2 g (80%) of a white solid, mp 92–98 °C. Repeated recrystallization from pentane gave a white solid, mp 101.0–104.1 °C. The mixture of acids was not separable by TLC: ir (CCl_4) ν 3400–2200, 1700, 1420, 1299, 1060, 930 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.45 (s, 1 H), 3.0–1.83 (br m, 7 H), 1.7 (m, 7 H). In addition, 0.4 g of a nonaqueous base soluble material was isolated from the pentane fraction but not identified.

***endo*-Tricyclo[3.3.1.0^{3,7}]nonane-2-carboxylic Acid Chloride (*endo*-2-Noradamantanecarboxylic Acid Chloride) (44).** The procedure described for **42** was followed giving the acid chlorides **42** and **44** (5:95) in 83% yield. No attempt was made to separate the acid chlorides: bp 72–73.5 °C (0.4 mm); ir (CCl_4) ν 3010, 1800, 1465, 1450, 1310, 1290, 1090, 1076, 1055, 1030, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.4–2.35 (m, 4 H), 2.20 (m, 1 H), 1.90 (m, 1 H), 1.70 (m, 8 H).

***endo*-2-Tricyclo[3.3.1.0^{3,7}]nonyl Methyl Diazoketone (*endo*-2-Noradamantyl Methyl Diazoketone) (20).** The procedure described for **19** was followed affording the mixture of diazoketones, **19** and **20**, in 100% yield. No attempt was made to separate the diazoketones: ir (CCl_4) ν 2915, 2100, 1650, 1350, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.35 (s, 1 H), 2.78–1.70 (br m, 6 H), 1.53 (m, 7 H).

Tetracyclo[5.3.1.0^{2,6}.0^{3,9}]undec-4-one (22) and Tetracyclo[6.2.1.0^{2,6}.0^{5,9}]undec-3-one (23). The ketones **22** and **23** were prepared from the mixture of diazoketones using the identical procedure as for **21**. Column chromatography gave a white solid in 59% yield, mp 162–165 °C. The mixture of the ketones (**21**, **22**, and **23**) could not be separated by GLC: ir (CCl_4) ν 2910, 1740, 1400, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.95–1.97 (br m, 8 H), 1.96–1.48 (br m, 6 H); MS *m/e* 162 (M^+), 121, 120, 92, 79, 78.

Anal. Calcd for $C_{11}H_{14}$: C, 81.44; H, 8.70. Found: C, 81.69; H, 8.64.

Tetracyclo[5.3.1.0^{2,6}]undecane (2,4-Ethanonoradamantane) (6) and Tetracyclo[6.2.1.0^{2,6}.0^{5,9}]undecane (2,9-Ethanonoradamantane) (8). The modified Wolff–Kishner reduction[24] (identical as for **21**) afforded a mixture of 82%, 2,4-ethanonoradamantane (**6**), 11% 2,8-ethanonoradamantane (**7**), and 7% 2,9-ethanonoradamantane (**8**) in 30% yield [0.125 in. × 16 ft Apeizon N on Chromosorb W 80/100, retention times at 150 °C: 2,8-ethanonoradamantane (**7**), 34 min; 2,4-ethanonoradamantane (**6**), 38–39 min; 2,9-ethanonoradamantane (**8**), 41 min]. The identification of **8** was made on the basis of GC–MS and mechanistic considerations: MS *m/e* 148 (M^+), 120, 119, 106, 105, 92, 91, 81, 80, 79, 78, 77. Preparative GLC (0.25 in. × 5 ft 10% SE-30, on 80/100 Gaspack W) afforded a pure sample of **6**: mp 167–168 °C; ^{13}C NMR ($CDCl_3$) δ 51.0 (d, 3 C), 43.3 (t, 2 C), 40.9 (d, 2 C), 38.4 (d, 1 C), 30.2 (t, 1 C), and 27.5 (t, 2 C).

Equilibration of 2-Methylnoradamantanecarboxylates. An ether solution of 1.7 g of a 95:5 ratio of **24** and **43** was cooled to 0 °C under a nitrogen atmosphere. A diazomethane–ether solution prepared as described for **19** was added dropwise to the acids via an addition funnel fitted with a cooling jacket. The addition was continued until the yellow color of the added diazomethane persisted for 10 min. The solution was allowed to warm to room temperature overnight, then dried over anhydrous magnesium sulfate. The ether was removed at reduced pressure, yielding 1.8 g (100%) of a clear oil, bp 60–61 °C (0.01 mm). The methyl resonances of the two isomers were distinct, the endo isomer's methyl signal being 5 Hz downfield from the exo. The esters were added to a solution of 20 mg of sodium in 10 ml of anhydrous methanol. The endo isomer slowly epimerized to the exo ester and equilibrium was reached after 96 h at 70 °C: 75% exo:25% endo; ^{1}H NMR ($CDCl_3$) δ 3.65 (endo methyl), 3.57 (exo methyl) (s, 3 H), 2.98–1.16 (m, 13 H).

Acknowledgments. We thank Professors G. J. Kent and M. Kawanisi for supplying samples of **13** and **9**, respectively. Professor E. Wenkert and Dr. E. Hagaman kindly determined some of the ^{13}C NMR spectra and provided interpretation. The research at Princeton was supported by grants from the National Institutes of Health (GM-19134) and the National Science Foundation (GP-29078X). E.O. is grateful to the Japan Society for Promotion of Science for the arrangement of International Science Cooperative Program. Computations were done at the Computer Centers of Princeton University and Hokkaido University.

Registry No.—**3**, 59014-95-8; **6**, 59014-96-9; **7**, 59014-97-0; **8**, 59014-98-1; **9**, 58008-54-1; **10**, 59014-99-2; **11**, 59015-00-8; **12**, 59015-01-9; **13**, 59015-02-0; **14**, 59015-15-5; **15**, 30114-56-8; **19**, 59015-03-1; **20**, 59042-76-1; **21**, 59015-04-2; **22**, 59015-05-3; **23**, 59015-06-4; **24**, 59015-07-5; **25**, 17931-67-8; **26**, 55795-14-7; **27**, 59015-08-6; **28**, 59042-77-2; **29**, 59015-09-7; **30**, 59015-10-0; **31**, 59015-11-1; **32**, 59015-00-8; **33**, 59015-12-2; **34**, 59015-13-3; **37**, 7781-74-0; **39**, 6567-11-9; **40**, 18117-75-4; **41**, 36280-29-2; **42**, 59015-14-4; **43**, 59042-78-3; **44**, 59042-79-4; 1-methyladamantane, 700-56-1; norbornadiene, 328-34-7; Diazald, 80-11-5; 2-adamantanecarboxylic acid, 15897-81-1.

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Formation of a Novel Norcamphor upon Treatment of 2-Hydroxy-4-isopentyl-4-methylcyclopentanone with Acid

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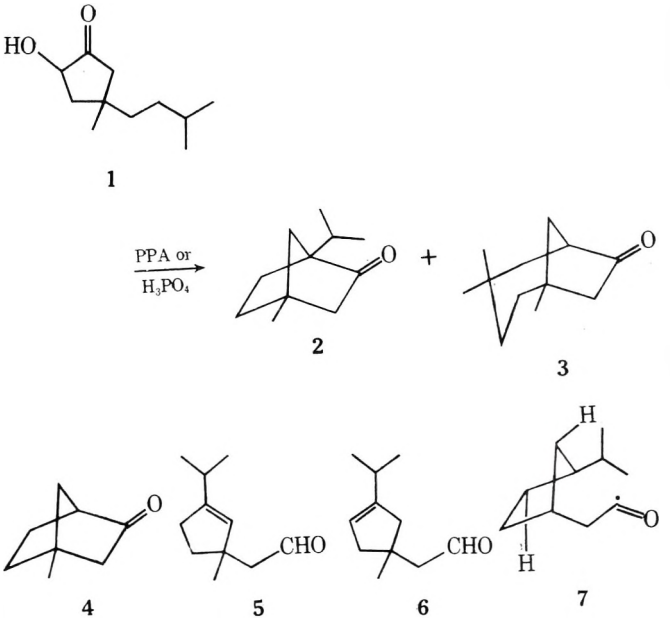
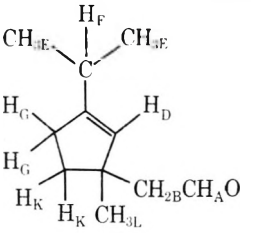
Treatment of 2-hydroxy-4-isopentyl-4-methylcyclopentanone (1) with polyphosphoric acid or 85% phosphoric acid can lead to 1-isopropyl-4-methylnorcamphor (2), as well as the previously reported 1,4,4-trimethylbicyclo[3.2.1]-octan-6-one (3). An alternative preparation of 2 from 4-methylnorcamphor (4) is described, and formation of 2 from 1 is rationalized in terms of intermediates 14–18. The series of rearrangements suggested includes a 1,5-hydride shift, an intramolecular Prins reaction, and a pinacol rearrangement.

In this report we describe the acid-catalyzed dehydration and rearrangement of acyloin 1 to 1-isopropyl-4-methylnorcamphor (2). Some years ago we observed that treatment of 1 with polyphosphoric acid first at room temperature and then overnight at 100 °C led to 58% of 3 as the only volatile product.[1] In repeating this preparation we have confirmed the earlier observation but also found that treatment of 1 with polyphosphoric acid at room temperature only or at 100 °C for a shorter time yields 2 as well as 3. Both ketones are also formed from 1 in hot 85% phosphoric acid. Separate experiments have shown that 2 is destroyed much faster than 3 by hot acid and that the ketones are not interconvertible under the reaction conditions. Below we give evidence supporting structure 2, report an independent synthesis of this ketone, and comment on the mechanism of this exceptional transformation.

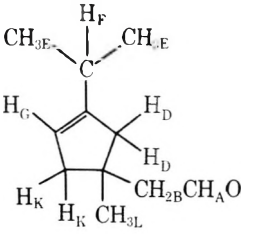


This new compound is isomeric with ketone 3, has an odor reminiscent of menthone, and has spectroscopic characteristics consistent with its formulation as an isopropyl- and methyl-substituted norcamphor. These included ir carbonyl absorption at 1744 cm^{-1}, a ^1H NMR spectrum containing a singlet methyl signal as well as absorption attributable to an isopropyl substituent with magnetically nonequivalent methyl groups, and a ^{13}C NMR spectrum compatible with the published spectra of methylnorcamphors,[2,3] particularly that of 4-methylnorcamphor (4).[3] There have been extensive investigations of the photochemistry of norcamphors,[4] and on previous occasions we have found that ultraviolet irradiation provided a convenient and informative degradation of novel bridged-ring ketones.[5] For these reasons we sought definitive structural information in photolysis of the new compound.

Table I. NMR Spectra of Aldehydes 5 and 6



5

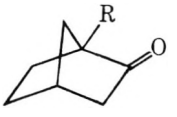


6

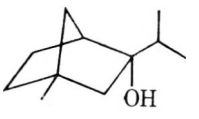
Signal, δ	
Major isomer	Minor isomer
1.02 (d, J = 7 Hz, 6 H, H_E)	0.98 (d, J = 6 Hz, 6 H, H_E)
1.15 (s, 3 H, H_L)	1.15 (s, 3 H, H_L)
1.43–1.94 (m, 2 H, H_K)	
2.00–2.57 (m, H_F, H_G) } 5 H	1.83–2.57 (m, H_D, H_F, H_K) } 7 H
2.29 (d, J = 1.5 Hz, H_B) }	2.32 (d, J = 1.5 Hz, H_B) }
5.17 (m, 1 H, H_D)	5.13 (m, 1 H, H_G)
9.67 (t, J = 1.5 Hz, 1 H, H_A)	9.68 (t, J = 1.5 Hz, 1 H, H_A)

Photochemical isomerization in benzene–methanol (λ >2800 Å) led to two products in the ratio 2:1. From spectroscopic evidence, particularly the NMR data presented in Table I, these appeared to be the unsaturated aldehydes **5** and **6**. The two aldehydes may be readily distinguished from each other since **6** has five allylic hydrogens while compound **5** has only three. One of the spectra then should have an upfield signal for the two nonallylic hydrogens. The unique signal at 1.43–1.94 ppm in the spectrum of the major photoproduct thus indicates that this is **5**. These aldehydes are accounted for most simply as products of two alternative transfers of hydrogen possible from biradical **7**, the intermediate expected on photochemical α-cleavage of ketone **2**.[6]

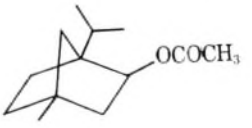
We verified these assignments of structure to **2**, **5**, and **6** by independent synthesis of **2** from 4-methylnorcamphor (**4**).[3] Treatment of **4** with isopropylmagnesium bromide gave a crude tertiary alcohol **10**, which underwent rearrangement in acetic acid containing *p*-toluenesulfonic acid to form **11**. This



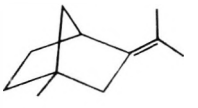
8, R = H
9, R = CH_3
13, R = $CH(CH_3)_2$



10



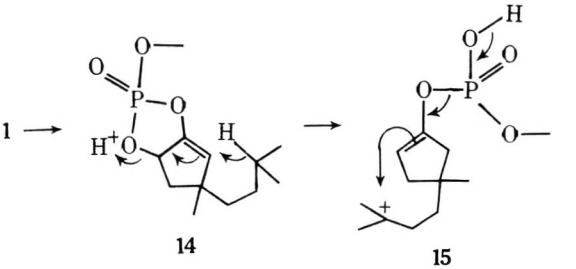
11



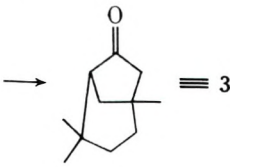
12

Wagner–Meerwein rearrangement has been used frequently for preparation of other 1-substituted 2-norbornyl alcohols and esters.[7,8] In the present case rearrangement competes with a large amount of simple dehydration, which yields **12**. Conversion of **11** to the corresponding alcohol using lithium aluminum hydride and subsequent oxidation then gave authentic **2**, identical in all respects with the ketone obtained from acyloin **1**. It was convenient to work out conditions for the conversion of **4** into **2** using norcamphor (**8**) as a model, and this led to 1-isopropylnorcamphor (**13**).

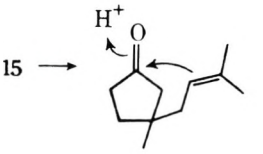
The unanticipated formation of **2** from **1** can be explained by the following series of rearrangements. Hydride transfer from side chain to ring in the protonated enol of **1** or related enol phosphate **14** leads to carbonium ion **15**. We have previously suggested this hydride shift and the subsequent cyclization of **15** as shown in accounting for formation of **3**.[1] If, instead of this cyclization, **15** undergoes ketonization and proton loss, the product is unsaturated cyclopentanone **16**. This could then undergo ring closure to **17** in an intramolecular Prins reaction. Hydride shift, or the equivalent deprotonation–reprotonation, gives the tertiary 2-norbornyl ion **18**,



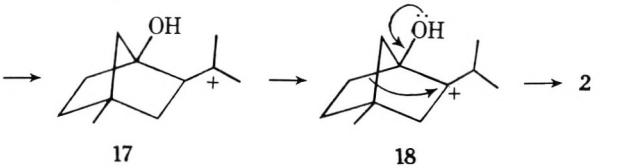
14 **15**



3



16



17 **18**

from which a simple pinacol rearrangement furnishes the required substituted norcamphor **2**.

While the combined yield of **2** and **3** at 100 °C is ~60% in both cases, the ratio of **2** to **3** is ~1:4 in polyphosphoric acid but rises to ~3:4 in 85% phosphoric acid. In terms of the mechanistic scheme outlined above this ratio depends on the fate of **15**. It is reasonable that the conversion of **15** to **16** would be favored by the availability of water in the reaction medium, and this effect would suffice to account for our observation.

The acyloin **1** thus undergoes transformations in which the originally unactivated isopentyl side chain becomes involved

in cyclizations leading both to a bicyclo[3.2.1]octan-6-one (**3**) and to a bicyclo[2.2.1]heptan-2-one (**2**) on exposure to phosphoric or polyphosphoric acid. While good precedents exist for the suggested individual steps,[9] the overall transformation of **1** into **2** and **3** remains unusual and noteworthy.

Experimental Section

Materials and Equipment. These have been previously described.[5] The VPC columns used in the present work were A, 25% QF-1, 25 ft × 0.25 in.; B, 25% DEGS, 15 ft × 0.25 in.; C, 25% QF-1, 10 ft × 0.25 in. The ^{13}C spectrum was obtained in C_6D_6 at 22.63 MHz on a Bruker HX-90 spectrometer modified for pulse operation with broad band proton decoupling and benzene as internal reference.

Formation of 1-Isopropyl-4-methylnorcamphor (2) from Acyloin 1. A mixture of polyphosphoric acid (9.0 g) and acyloin **1** (111 mg) were mixed thoroughly with a spatula and allowed to stand at room temperature for 7 h. The mixture was dissolved in water and the products were extracted into ether which was washed with aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of solvent and bulb-to-bulb distillation (140 °C, 8 mm) gave 83.4 mg of a colorless oil (83%). Analytical VPC on column A indicated the presence of three compounds in the ratio of 3:12:1. Preparative VPC on column A yielded **2**: ir 2948 (s), 2860 (m), 1744 (s), 1468 (w), 1450 (m), 1405 (w), 1382 (w), 1377 (w), 1366 (w), 1322 (w), 1178 (w) cm^{-1}; ^1H NMR (220 MHz) δ 0.907 (d, J = 7 Hz, 3 H), 0.939 (d, J = 7 Hz, 3 H), 1.24 (s, 3 H), 1.27–1.70 (m, 5 H), 1.70–2.05 (m, 4 H); ^{13}C NMR δ 215.7, 63.2, 52.7, 44.9, 40.8, 35.3, 28.3, 27.3, 21.1, 19.4, 18.8; mass spectrum m/e 166.1351 (M^+, calcd for $C_{11}H_{18}O$, 166.1357).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.34; H, 10.86.

The second and third components were identified as **3**[1] and the simple dehydration product 4-isopentyl-4-methylcyclopent-2-enone[1] by comparison of ir and NMR spectra with those of authentic samples.

Treatment of the acyloin (148 mg) with 85% phosphoric acid for 1 h at 100 °C gave a 63% yield of the same three compounds in the ratio of 6:8:1.

Photolysis of 4-Methyl-1-isopropylnorcamphor (2). A 104-mg sample of **2** in 50 ml of benzene containing 1.5 ml of methanol was degassed for 25 min with N_2 and then irradiated through Pyrex for 6 h. Usual workup[5] and preparative VPC on column B gave, in order of elution, 3-isopropyl-1-methylcyclopent-2-en-1-acetaldehyde (**5**) and 3-isopropyl-1-methylcyclopent-3-en-1-acetaldehyde (**6**) in the ratio 2:1. Characterization data are given in Table I and below. For **5**: ir 2955 (s), 2860 (m), 2720 (w), 1725 (s), 1645 (w), 1460 (m), 840 cm^{-1} (w); mass spectrum m/e 151.1126 [$(M - CH_3)^+$, calcd for $C_{10}H_{15}O$, 151.1123], 123.1155 [$(M - C_2H_3O)^+$, calcd for C_9H_{15}, 123.1174].

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.51; H, 10.83.

Characterization data for **6**: ir 2955 (s), 2925 (m), 2860 (m), 2835 (m), 2725 (w), 1725 (s), 1638 (w), 1455 cm^{-1} (w); mass spectrum m/e 151.1105 [$(M - CH_3)^+$, calcd for $C_{10}H_{15}O$, 151.1123], 123.1138 [$(M - C_2H_3O)^+$, calcd for C_9H_{15}, 123.1174].

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.58; H, 10.97.

Synthesis of 1-Isopropyl-4-methylnorcamphor (2) from 4-Methylnorcamphor (4). A 429-mg sample of **4**[3] (mp 47.5–49 °C) was treated with isopropylmagnesium bromide in refluxing ether in the usual manner and worked up by pouring into cold aqueous NH_4Cl followed by ether extraction. The crude product alcohol **10** showed ir absorption at 3610 (w), 3470 (br w), 2940 (s), 2860 (s), 1455 (m), and 1470 cm^{-1} (m), and NMR (60 MHz) absorption at δ 0.87 (d, J = 6 Hz) and 1.06 (s). This material was treated directly with 7.5 ml of acetic acid containing 10 drops of acetic anhydride and 300 mg of p-toluenesulfonic acid at 40 °C for 3 days.[8] After cooling the mixture was treated with ice and aqueous $NaHCO_3$, and the products were extracted into ether–pentane. The organic extracts were washed with water, aqueous $NaHCO_3$, and brine and then dried. Removal of solvent and bulb-to-bulb distillation yielded a volatile product mixture which from analysis on column B was largely **12** and **11** in the approximate ratio 7:1. Preparative VPC gave samples of each which were characterized as follows. For **11**: ir 2950 (s), 2860 (m), 1730 (s), 1453 (w), 1370 (w), 1265 (m), 1240 (s), 1020 cm^{-1} (m); NMR δ 0.3–1.50 with d, J = 6.5 Hz, at 0.77 and 0.88, and s at 1.10 (m, 16 H), 1.50–2.23 with s at 1.96 (m, 5 H), 4.65 (m, 1 H). For **12**: ir 2945 (s), 2920 (s), 2860 (s), 2830 (w), 1455 cm^{-1} (m); NMR δ 0.83–1.72 with s at 1.17, 1.47, and 1.58 (m, 15), 1.82 (br, 2 H), 2.77 (br, 1 H).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 88.01; H, 12.21.

A 15-mg sample of acetate **12** was reduced with $LiAlH_4$ in 25 ml of ether first at 0 °C and then at room temperature. After destruction of excess hydride with saturated aqueous Na_2SO_4 the ether solution was dried over Na_2SO_4. The solvent was removed and the remaining crude 1-isopropyl-4-methyl-2-norbornanol was oxidized in 5 ml of acetone with 5 drops of Jones reagent[10] at 10–15 °C for 45 min. Excess reagent was destroyed with 2-propanol, and the reaction mixture was worked up with water and pentane. After removal of pentane the product was purified on column B (essentially one peak) to give 8.8 mg of 1-isopropyl-4-methylnorcamphor (**2**). Retention time as well as ir and NMR spectra of this sample were virtually identical with those of **2** described above.

Synthesis of 1-Isopropylnorcamphor (13) from Norcamphor (8). The sequence of reactions described for conversion of **4** into **2** was initially developed using norcamphor (**8**). This led through the analogous intermediate alcohols and ester and yielded 1-isopropylnorcamphor (**13**). An analytical sample was obtained from column B: ir 2900 (s), 2865 (m), 1745 (s), 1470 (w), 1455 (w), 1408 (w), 1380 (w), 1365 (w), 1292 cm^{-1} (w); NMR δ 0.91 and 0.94 (2 d, $J_1 = J_2$ = 7 Hz, 6 H), 1.13–2.33 (m, 9 H), 2.50 (br, 1 H); mass spectrum m/e 152.1201 (M^+, calcd for $C_{10}H_{16}O$, 152.1200).

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Registry No.—**1**, 33315-86-5; **2**, 59247-54-0; **4**, 49664-72-4; **5**, 59247-55-1; **6**, 59247-56-2; **8**, 497-38-1; **10**, 59247-57-3; **11**, 59247-58-4; **12**, 59247-59-5; **13**, 59247-60-8; isopropyl bromide, 75-26-3; 1-isopropyl-4-methyl-2-norbornanol, 59247-61-9.

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(6) It is significant that both **5** and **6** are formed on irradiation of **2**, since photolysis of norcamphor (**8**) and 1-methylnorcamphor (**9**) yields in each case *only* the Δ^2 aldehyde corresponding to **5**, which results from hydrogen transfer from C(7). (For details and references, see ref 4.) We are currently investigating whether the transfer of hydrogen from both C(6) and C(7) in **7** is attributable to the bulky isopropyl group at C(1) or the methyl substituent at C(4).
(7) See for example, N. J. Toivonen, E. Siltanen, and K. Ojala, *Ann. Acad. Sci. Fenn., Ser. A2*, No. 64 (1955); S. Beckmann, R. Schaber, and R. Bamberger, *Chem. Ber.*, **87**, 997 (1954); J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *J. Am. Chem. Soc.*, **83**, 3986 (1961); D. C. Kleinfelter and P. v. R. Schleyer, *J. Org. Chem.*, **26**, 3740 (1961).
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A Study of the Lithium Aluminum Hydride Reduction of a Series of Nonenolizable Ketones[1]

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The lithium aluminum hydride and lithium aluminum tri(*tert*-butoxy)hydride reductions of 2,2-dimethylindandione and a series of related monoketones were examined. The range of the isomer distribution was determined to be a function of the reducing agent, temperature of the reaction, and equivalent ratio of the reactants. The possible mechanisms for the stereochemical results of such reductions are discussed.

In a recent communication[3] we reported that no intramolecular hydride transfer need be invoked for the lithium aluminum hydride ($LiAlH_4$) reduction of 2,2-dimethylindandione even though such transfers have been suggested in many $LiAlH_4$ reductions of nonenolizable β-diketones.[4,5] This type of transfer has also been invoked for related compounds, such as hydroxy ketones, in which the complexed hydroxy group is proposed to exhert a synergistic effect on the reduction of a neighboring carbonyl function.[6-11]

A specific example, by Martin et al.,[7] will illustrate this concept. The reduction of 1,5-dimethylbicyclo[3.3.1]nonane-2,9-dione with lithium aluminum tri(*tert*-butoxy)hydride [$LiA(O\text{-}t\text{-}Bu)_3H$] yielded the exo 2-hydroxy ketone. This compound was then treated with $LiAlH_4$ to yield the corresponding diols. The authors suggested that the trans diol is a result of an intramolecular hydride transfer from the aluminate to the remaining carbonyl function.

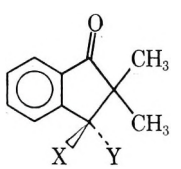
Alder and Fremery[12] had previously reported the $LiAlH_4$ reduction of a nonenolizable β-diketone, 2,2-dimethylindandione (**1a**). In this work, no mention was made of the stereochemistry of the resulting diols. This system serves as the basis for our study.

The sequence of events in $LiAlH_4$ reductions has been investigated by Eliel and Haubenstock.[13] In the $LiAlH_4$ reduction of 3,3,5-trimethylcyclohexanone, changes in the product distribution were observed when methanol, ethanol, or *tert*-butyl alcohol was added to the $LiAlH_4$ medium prior to reaction with the cyclohexanone. It was found that 2-propanol, acetone, and cyclohexanone yielded approximately the same distribution of products as did the reduction using $LiAlH_4$ alone.

A disproportionation mechanism which continuously regenerates the tetrahydrido species was proposed to explain these results. If this proposed mechanism is operative, the entire reduction is accomplished by the $LiAlH_4$ species.[13]

It has been shown that a trialkoxy lithium aluminum hydride reducing agent, like $LiAl(O\text{-}t\text{-}Bu)_3$, is a more stereospecific reducing agent, in the reduction of ketones, than is $LiAlH_4$.[13] Since it contains only one available hydride, any disproportionation or intramolecular hydride transfer mechanism can be assumed to be inoperative.

Using 2,2-dimethylindandione (**1a**) and a series of related monoketones (**1b–e**) as probes, the $LiAlH_4$ and $LiAl(O\text{-}t\text{-}Bu)_3H$ reductions were investigated. To ensure a homogeneous reaction medium, the reductions were carried out at high dilution, with the hydride solution added to a solution of the substrate in diethyl ether.



	X	Y
1a	=O	
b	H	OH
c	H	OCH_3
d	CH_3	OH
e	CH_3	OCH_3

In order to clearly delineate the relationship between the amounts of reagents used in any given experiment, the equivalent reduction ratio (ERR) must be known. The equivalent reduction ratio is defined as the number of available carbonyl functions to be reduced divided by the number of hydrides truly available for the reduction.

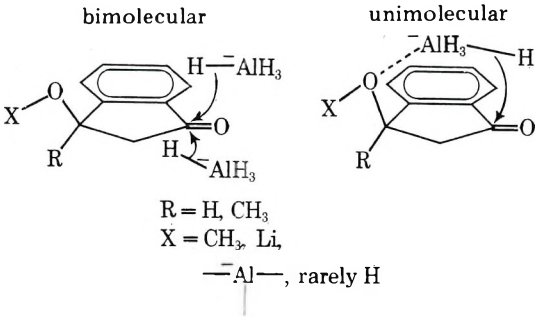
All product ratios were determined at several different times during the reaction. The unchanging ratios found in any given run assure that *all* results represent kinetic control of product formation.

Results

The results of the $LiAlH_4$ and $LiAl(O\text{-}t\text{-}Bu)_3H$ reductions for compounds 1a–e are given in Tables I and II. The results are accurate to 3%. Therefore relative percent trans of 56 may be read as 56 ± 3. Two trends are evident from the examination of these tables. Generally as the ERR value was varied from excess hydride (0.5) to a deficient amount of hydride (2.0), the amount of trans product increased; it never decreased. At identical ERR values, the more stereospecific reducing agent, $LiAl(O\text{-}t\text{-}Bu)_3H$, for the most part, yielded more of the trans compound than did $LiAlH_4$. As one might expect this pattern was more pronounced in the low-temperature runs.

Discussion and Conclusions

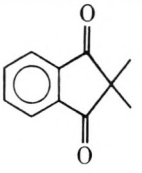
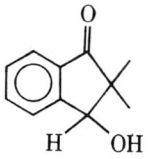
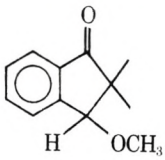
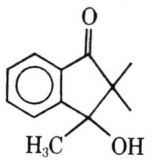
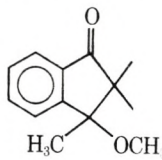
In the $LiAlH_4$ reductions, since kinetic control is operative, the changes in the product distribution with the variation in the ERR value may be viewed in terms of either a bimolecular or unimolecular interaction.



At an ERR value of 0.5 (excess hydride), the hydride species may attack the carbonyl function from either side. This bimolecular attack may be quite competitive with any unimolecular process because excess hydride is present. Such a mode of reaction can lead to a nonspecificity of products, i.e., both cis and trans product.

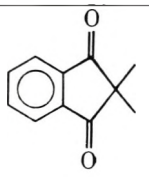
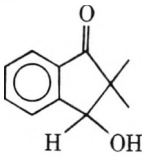
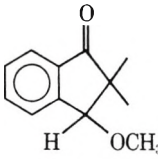
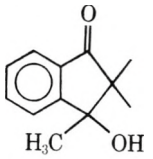
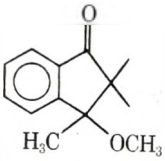
At an ERR value of 2.0 (deficient hydride), any hydride species associated with the ethereal oxygen may be transferred unimolecularly in preference to the with the ethereal oxygen may be transferred unimolecularly in preference to bimolecular pathways. This preferential attack leads to more of the trans compound.

Table I. $LiAlH_4$ Reductions

Ratio[a] of substrate to hydride	Relative percent trans									
	 1a		 1b		 1c		 1d		 1e	
	34 °C	−78 °C	34 °C	−78 °C	34 °C	−78 °C	34 °C	−78 °C	34 °C	−78 °C
0.5	46	44	29	3	100	100	61	20	27	19
1.0	64	87	48	12	100	100	65	22	32	52
2.0	71	93	53	56	100	100	62	31	32	83

[a] Equivalent reduction ratio.

Table II. $LiAl(O\text{-}t\text{-}Bu)_3H$ Reductions

Ratio[a] of substrate to hydride	Relative percent trans									
	 1a		 1b		 1c		 1d		 1e	
	34 °C	−78 °C	34 °C	−78 °C	34 °C	0 °C	34 °C	0 °C	34 °C	0 °C
0.5	88	100	26	94	100	100	48	44	54	54
1.0	100	100	77	94	100	100	46	40	63	51
2.0	100	100	86	96	100	100	47	42	90	90

[a] Equivalent reduction ratio.

The same general response is found in the $LiAl(O\text{-}t\text{-}Bu)_3H$ reductions with analogous changes in the ERR values. These changes may be similarly interpreted if the same associative mechanism is invoked, which allows the reducing species to complex with the ethereal oxygen before reduction occurs. The amount of trans product generally increases as the unimolecular process predominates.

One of the earliest attempts to unify the many different stereochemical results from $LiAlH_4$ reductions of cyclohexanones was undertaken by Dauben et al.[14] Dauben proposed that when the less stable isomer is formed preferentially in the competitive attack on a carbonyl function, from a hindered or an unhindered side, the rationale should be termed "steric approach control". Conversely, when the more stable isomer is formed preferentially an energy consideration involving the relative stability of the possible products should be invoked, and termed "product development control".[14]

The unifying rationales of Dauben have been further investigated by Eliel and Senda.[15] These workers examined the competitive rates of hydride reductions of pairs of ketones in the presence of a deficient amount of hydride. They concluded that, in general, steric approach control plays the major role and that product development control plays only a minor role in these reductions.

Our results may be interpreted to mean that a minimum of three possible pathways must be operative since the product ratios vary from >1.0 to <1.0 in a given series. The two "bimolecular" pathways must be discussed in terms of "steric approach control" vs. "product development control". At higher temperatures, where the "bimolecular" pathways should be increasingly more important, a trend to more of the cis product is apparent. This is certainly true as long as the benzylic hydrogen is not replaced by a methyl group. This trend indicates that steric approach control is the more important factor governing these "bimolecular" pathways.

The "unimolecular", associative pathway should not be discussed in the same terms. A comparison between the "unimolecular" pathway of two different substrates should be made on the basis of a preequilibrium (association), followed by rate-determining ("unimolecular") reorganization.

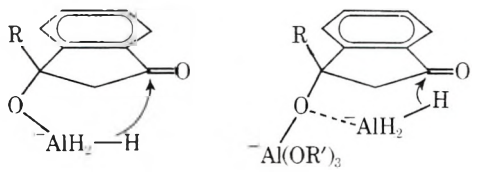
This proposed internal solvent interaction is not without precedent.[16] Most $LiAlH_4$ and/or lithium alkoxyaluminum hydride reductions are effected in ether or similar Lewis base solvents. Shirk and Shriver[17] have suggested that the AlH_4^- species exists in a solvent cage when placed in diethyl ether. This solvated species is similar to the currently accepted form of the Grignard complex solvation sphere. Benard et al.[18] have invoked a similar hypothesis to explain the results they obtained when reducing *N,N*-dimethyl-2-aminocyclohexanone with $LiAlH_4$ in benzene.

The most striking example of this effect, in our study, is surely the reduction of **1c**. At all the ERR values studied, at all the temperatures and with both reducing agents, the reduction was effectively stereospecific to yield the trans product. The "unimolecular" pathway must be greatly favored in this system. The reduction of **1e** is consistent with this explanation. Since the benzylic methyl group causes the ethereal oxygen to be a "neo" center, it seems that its reduction is not as stereospecific as that of **1c**. Association is therefore dramatically lessened and the "bimolecular" pathways compete.

The same result is not seen in comparing **1b** to **1d**. Because of the "neo" oxygen in **1d** the OH does not become OLi or $O\bar{A}l<$ as readily as does the OH in **1b**. Therefore no comparable direct comparison may be made as can be done with keto ethers **1c** and **1e**.

To further test our associative mechanism, the reduction of **1c** was repeated in dry benzene in an experiment similar to Benard's.[18] Using an equivalent amount of hydride, this reaction yielded, in 100% yield, the pure trans hydroxymethyl ether. Only starting material could be recovered from the reaction of **1a** with $LiAlH_4$ in dry benzene.

Our results are clearly consistent with Eliel's disproportionation scheme. It is possible, however, that for "unimolecular" pathway in **1a,b,d**, with $LiAlH_4$, internal hydride transfer is faster than the disproportionation pathways so that pathway a is followed and not pathway b. If this is true, the



pathway a pathway b

R = H or CH_3
R′ = alkyl

disproportionation scheme may be valid for only simple ketones and may not apply to polyfunctional carbonyl compounds.

The same kind of disclaimer may have to be applied to the competitive reduction of polyfunctional carbonyl compounds. It is legitimate for Eliel to compare the results of reductions of individual simple ketones, with equivalent or excess hydride, to the results of competitive reductions of pairs of simple ketones, with deficient hydride. Our results show that this methodology is inapplicable to polyfunctional carbonyl compounds since the isomer ratios of the products, for individual compounds, are shown to vary markedly in going from excess or equivalent hydride to deficient hydride.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 137 prism and a 337 grating spectrophotometer. Proton magnetic resonance spectra were recorded with a Varian A-60 spectrometer in $CDCl_3$ solutions (unless otherwise indicated) with tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million (δ) downfield from Me_4Si. Analytic GLC determinations were achieved using an F & M Model 720 gas chromatograph, with a thermal conductivity detector, employing a 6 ft × 0.25 in. stainless steel column packed either with 10% SE-30 or 15% SE-30 on silanized 60–80 mesh Chromosorb W. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

The $LiAlH_4$ in diethyl ether was purchased from Ventron and the normality determined according to the procedure of Felkin.[19] Known solutions of the reductants in dry diethyl ether were prepared; care was taken to exclude moisture. Both solutions were stored over a desiccant.

2,2-Dimethylindandione (1a). This compound was prepared according to the procedure of Aebi[20] and the crude product was recrystallized from heptane: mp 105–106 °C (lit.[20] 106–107 °C); NMR δ 1.30 (s, 6 H), 8.0–8.2 (m, 4 H). Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.87; H, 5.74. Found: C, 75.64; H, 5.87.

3-Hydroxy-2,2-dimethylindanone (1b). This compound was prepared according to the procedure of Aebi[20] and the crude product was recrystallized from cyclohexane: mp 89.5–91 °C (lit.[20] 89–90 °C); NMR δ 1.16 (s, 3 H), 1.30 (s, 3 H), 2.15 (d, 1 H, J = 8 Hz), 4.96 (d, 1 H, J = 8 Hz), 7.76 (m, 4 H). Anal. Calcd for $C_{11}H_{12}O_2$: C, 75.00; H, 6.81. Found: C, 74.82; H, 6.76.

3-Methoxy-2,2-dimethylindanone (1c). A procedure similar to that of Merz was followed.[21] To a solution of 0.783 g (4.44 mmol) of **1b** in 100 ml of methylene chloride was added 0.6 g of tetrabutylammonium iodide and 1.0 ml of 50% aqueous NaOH solution. After stirring vigorously for 0.5 h, 0.6 ml (6.32 mmol) of dimethyl sulfate was added with ice bath cooling and the mixture was stirred for 3 h. An additional 0.25 ml of dimethyl sulfate was added and the stirring continued for 0.5 h. A saturated NH_4Cl solution (5 ml) was added and the mixture was stirred for an additional 0.5 h. The crude product was poured into water and the organic phase separated and concentrated in vacuo. The residue was dissolved in ether and washed four times with 75 ml of H_2O. The combined ethereal layers were dried ($MgSO_4$) and concentrated in vacuo to yield a yellow oil, which was subjected to column chromatography (silica gel). Elution with $CHCl_3$ yielded the desired product: 0.707 g (84%); NMR δ 1.16 (s, 3 H), 1.35 (s, 3 H), 3.65 (s, 3 H), 4.51 (s, 1 H), 7.4–7.8 (m, 4 H). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.79; H, 7.36. Found: C, 75.47; H, 7.39.

3-Hydroxy-2,2,3-trimethylindanone (1d). To a solution of 0.8028 g (4.61 mmol) of **1a** in 75 ml of dry ether, cooled by a dry ice–acetone bath, was added 3.0 ml of 1.6 M (4.95 mmol, 10% excess) of methyllithium. After stirring for 1 h, the solution was warmed to room temperature and carefully hydrolyzed with water. The ethereal layer was washed once with 50 ml of water, and the aqueous layer was extracted thrice with 50 ml of ether. The combined ethereal layers were dried ($MgSO_4$) and concentrated in vacuo to yield a light green oil. This material was subjected to column chromatography (silica gel). Elution with $CHCl_3$ yielded unreacted starting material. Elution with 5% MeOH in $CHCl_3$ yielded 0.6013 g (68%) of product: bp 106.5–109 °C (0.3 mm); NMR (benzene-d_6) δ 1.06 (s, 3 H), 1.13 (s, 3 H), 1.27 (s, 3 H), 2.57 (s, 1 H), 7–8 (m, 4 H). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.79; H, 7.36. Found: C, 75.96; H, 7.55.

3-Methoxy-2,2,3-trimethylindanone (1e). This compound was prepared in an analogous manner to **1c**. In this case, a reaction time of 24 h was necessary. The yield was 62%: bp 92–101 °C (0.5 mm); NMR δ 1.09 (s, 3 H), 1.22 (s, 3 H), 1.52 (s, 3 H), 3.03 (s, 3 H), 7.5–7.8 (m, 4 H). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84. Found: C, 76.29; H, 7.86.

2,2-Dimethylindan-1,3-diol (2a). To a properly dried reaction vessel equipped with a reflux condenser, a mechanical stirrer, and an addition funnel was added 2.3 g (0.06 mol) of $LiAlH_4$ in 60 ml of dry diethyl ether. To this mixture was added slowly a solution of 10.0 g (0.05 mol) of **1a** in 30 ml of dry ether. After the addition was completed, the reaction mixture was refluxed for 6 h. The mixture was cooled and the excess $LiAlH_4$ destroyed by the successive addition of 3 ml of water, 3 ml of 15% NaOH, and 6 ml of water. The precipitate was placed in a Soxhlet extractor and extracted with ether for 24 h. The ethereal extract was dried ($MgSO_4$) and concentrated in vacuo to yield 8.4 g (86%) of the diol, mp 113–116 °C. Fractional recrystallization from $CHCl_3$ yielded the cis diol: mp 161–162.5 °C; NMR δ cis diol 0.95 (s, 3 H), 1.11 (s, 3 H), 2.1 (d, 1 H, J = 8 Hz), 4.53 (d, 1 H, J = 8 Hz), 7.4 (m, 4 H), trans diol 1.05 (s, 6 H), 1.83 (d, 1 H, J = 8 Hz), 4.81 (d, 1 H, J = 8 Hz), 7.4 (m, 4 H). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.16; H, 7.86. Found: C, 73.86; H, 8.15.

3-Methoxy-2,2-dimethylindanol (2c). This compound was similarly prepared from **1c**. The $LiAlH_4$ reduction yielded 97% of essentially the pure trans compound (vide supra). It was recrystallized from cyclohexane: mp 92–94 °C; NMR (benzene-d_6) δ 0.97 (s, 3 H), 1.09 (s, 3 H), 1.88 (d, 1 H, J = 10 Hz), 3.20 (s, 3 H), 3.83 (s, 1 H), 4.32 (d, 1 H, J = 10 Hz), 7.1–7.4 (m, 4 H). Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33. Found: C, 75.05; H, 8.43.

2,2,3-Trimethylindan-1,3-diol (2d). This compound was similarly prepared from **1d**. The $LiAlH_4$ reduction yielded 90% of a mixture consisting of the cis and trans diols. They were recrystallized from cyclohexane: mp 73–93 °C; NMR δ cis diol 0.90 (s, 3 H), 1.11 (s, 3 H), 1.40 (s, 3 H), 2.40 (s, 2 H), 4.53 (s, 1 H), 7.38 (m, 4 H), trans diol 0.84 (s, 3 H), 1.16 (s, 3 H), 1.51 (s, 3 H), 2.40 (s, 2 H), 4.95 (s, 1 H), 7.38 (m, 4 H). Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33. Found: C, 74.81; H, 8.39.

3-Methoxy-2,2,3-trimethylindanol (2e). This compound was similarly prepared from **1e**. The $LiAlH_4$ reduction yielded 90% of a mixture consisting of the cis and trans hydroxy ethers. After drying under a vacuum: mp 107–112 °C; NMR (acetone-d_6) δ cis ether 0.68 (s, 3 H), 1.19 (s, 3 H), 1.39 (s, 3 H), 1.80–1.92 (br s, 1 H), 2.92 (s, 3 H), 5.07 (s, 1 H), 7.22–7.39 (m, 4 H), trans ether 0.89 (s, 3 H), 1.09 (s, 3 H), 1.29 (s, 3 H), 1.80–1.97 (br s, 1 H), 3.12 (s, 3 H), 4.3 (s, 1 H), 7.22–7.39 (m, 4 H). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.73; H, 8.73. Found: C, 75.47; H, 8.91.

Analytical Reduction Procedure. To a properly dried reaction vessel was added volumetrically a known amount of the compound to be reduced in dry diethyl ether. The solution was either heated to reflux or cooled to the proper reaction temperature and the appropriate amount of hydride was added. The amount of hydride added was varied so that the equivalent reduction ratio (ERR) ranged from 0.5, excess hydride to 2.0, deficient hydride. Upon completion of the hydride addition, aliquots were periodically removed. These were hydrolyzed with 15% NaOH; the ethereal solution was filtered, then

dried ($MgSO_4$) and concentrated in vacuo. When LiAl(O-*t*-Bu)$_3$H was used as the reducing agent, the hydrolyzed solution was washed several times with water to remove the *t*-BuOH, followed by a similar workup procedure. The mixture of crude products was subjected to two methods of analysis. In the NMR method, the residue was dissolved in $CDCl_3$ and with the aid of the LSR, Eu(fod)$_3$,[22] the methyl resonances were sufficiently separated so that an integration could be obtained. In the GLC method, dissolution of the residue in dry pyridine and silylation with a mixture of hexamethyldisilazane and trimethylchlorosilane[23] was followed by gas chromatography. Both of these procedures yielded the relative amounts of each stereoisomer.

$LiAlH_4$ Reduction of 1c in Benzene. To a properly dried reaction vessel was added 0.0747 g (0.394 mmol) of **1c** in 50 ml of dry benzene. The solution was heated to reflux and 0.22 ml (0.197 mmol) of a 0.9 M $LiAlH_4$ solution was added (the ether solvent was evaporated off immediately). After a 24-h reflux period, the reaction mixture was hydrolyzed with 15% NaOH, the mixture was concentrated in vacuo, and the crude product dissolved in ether. The ether solution was washed once with 60 ml of water and the aqueous layer thrice with 25 ml of ether. The combined ethereal layers were dried with $MgSO_4$, followed by concentration in vacuo, to yield an oil. Upon NMR analysis, the oil produced the same spectrum as the reduction run in diethyl ether, i.e., the trans hydroxy ether. A similar experiment with **1a**, the dione, failed to yield any of the reduction products.

Registry No.—**1a**, 17190-77-1; **1b**, 59269-93-1; **1c**, 59269-94-2; **1d**, 59269-95-3; **1e**, 59269-96-4; *cis*-**2a**, 54884-33-2; *trans*-**2a**, 54884-34-3; *trans*-**2c**, 59269-97-5; *cis*-**2d**, 59269-98-6; *trans*-**2d**, 59269-99-7; *cis*-**2e**, 59270-00-7; *trans*-**2e**, 59270-01-8; $LiAlH_4$, 16853-85-3; LiAl(O-*t*-Bu)$_3$H, 17476-04-9.

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Electrochemical Reduction of Geranial, Farnesal, and Crotonaldehyde[1]

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The electrolytic reduction of the α,β-unsaturated aldehydes **11**, **12**, and **13** was studied and the nature of the coupling products determined. Attempts at effecting substrate orientation by carrying out the reductions in micelles were unsuccessful. The reduction of crotonaldehyde was repeated and an earlier report[4] found to be in error.

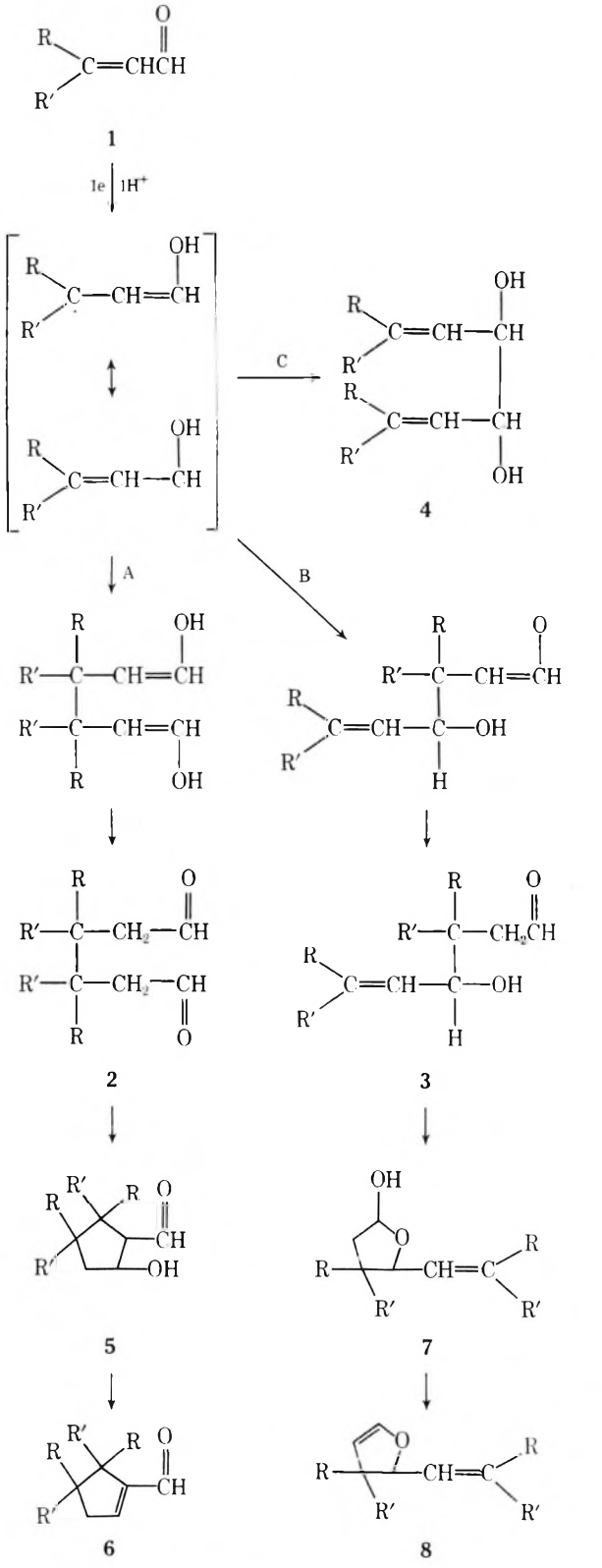
The electrochemical reduction of α,β-unsaturated aldehyde systems in acidic media results in the formation of a short-lived radical anion, which abstracts a proton from the solvent to produce an enol radical. Dimerization of this radical may take place via three different pathways:

Pathway A, the coupling of two β radicals ("tail to tail"), results in a dialdehydic compound (**2**), which may undergo an aldol condensation to produce compound **5** or **6**. Pathway B, the "head to tail" coupling of a carbonyl radical with a β radical, yields compound **3**, which may cyclize to form compound **7** or **8**. Finally, pathway C, the coupling of two carbonyl radicals ("head to head") affords a 1,2 diol (glycol), compound **4**.

One might expect steric factors to play a role in determining which pathway is favored. With acrolein (**9**) Misono[2] found compound **6** (R = R′ = H) to be the major product. This seems to indicate a preference for pathway A ("tail to tail") as the mode of coupling for the enol radical. Hindrance to the β position of acrolein should decrease products resulting from pathway A. Indeed, when the β position is subtituted with two methyl groups, as in 3-methylcrotonaldehyde (**11**) Miller[3] reported no products formed from pathway A. The methyl groups, however, are apparently not large enough to eliminate completely participation of the β radical in the coupling reaction, as evidenced by the fact that the major product from the electrochemical reduction of 3-methylcrotonaldehyde was that formed from pathway B.

We were interested to see whether increasing the size of one of the R groups at the β position would result in any decrease in the products resulting from pathway B ("head to tail" coupling) and thus make head to head coupling the prime route followed. To this end we repeated the reduction of 3-methylcrotonaldehyde,[3] and performed electrochemical reductions on geranial (**12**) and farnesal (**13**). Further, in order to determine what effect there would be in orienting the substrate during the electrochemical reduction, the electrolyses were repeated in micellar solutions. It seemed reasonable to assume that by using micelle solutions the β position would be buried in the micelle while the carbonyl position would be exposed to the reducing (aqueous) phase. This ideally would result in the formation of only the glycol (**4**).

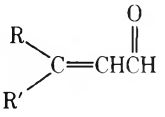
The aldehydes required for this investigation were available by short preparative schemes. 3-Methylcrotonaldehyde was prepared according to Miller.[3] Geranial was obtained by simple manganese dioxide oxidation of the corresponding commercially available alcohol. *trans,trans*-Farnesol was obtained by spinning band separation from commercially available farnesol, and was subsequently oxidized with man-



ganese dioxide to farnesal. All of the aldehydes were indicated to be of high purity by NMR and infrared analysis.

Polarographic runs were made on each of the aldehydes (**11, 12, 13**), 1×10^{-3} M in 1:1 ethanol–acetate buffer of pH 5. The half-wave potentials of all three aldehydes fell between −1.23 and −1.30 V (vs. SCE). Half-wave potentials for the aldehydes solubilized in the micelle solutions (0.05–0.50 M cetyltrimethylammonium bromide in pH 5 acetate buffer) were essentially the same, falling within the same narrow range.

Controlled potential electrolytic reductions were performed on each aldehyde (**11, 12, 13**) in both the ethanol–pH 5 acetate buffer system and the micelle solutions. In all cases the reduction was complete within 2–3 h. After workup the crude oil from the reduction of each aldehyde was found to contain two dimeric products: a hydroxytetrahydrofuran of compound type **7**, resulting from "head to tail" coupling, and a 1,2-diol (glycol) of compound type **4**, resulting from "head to head" coupling. The results are summarized in Table I.



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9 (acrolein), R = H; R′ = H
10 (crotonaldehyde), R = CH_3; R′ = H
11 (3-methylcrotonaldehyde), R = CH_3; R′ = CH_3
12 (geranial), R = CH_3; R′ = $CH_2CH_2CH{=}C(CH_3)_2$
13 (farnesal), R = CH_3; R′ = $CH_2CH_2CH{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)_2$

It is apparent that the micelle system is without effect on the course of dimerization. A possible explanation is that the reduction is occurring only on that small portion of aldehyde which is in the aqueous phase of the system. The resulting dimeric products could then be extracted into the micelles, more aldehyde could diffuse out, and the process continue. Alternatively it may be that the aldehyde is dissolved in the micelle system and is being reduced there, but the polarity of the α,β-unsaturated aldehyde results in the active site of the molecule being exposed to the aqueous phase. If the entire conjugated portion of the aldehyde were above the micellar surface, then little directing effect would be expected.

It may be seen from the results listed in Table I that while pathway B seems to be the preferred mode of coupling for a β,β-disubstituted acrolein system, increasing the size of one of the β substituents does decrease the amount of "head to tail" coupling. This could be attributed to an increased steric repulsion as the methyl group at the β position (compound **11**) is lengthened to a 6 (geranial) and 11 (farnesal) carbon chain.

A recent investigation[4] of crotonaldehyde (**10**) seems to contradict these trends. It was reported that reduction of crotonaldehyde in pH 4.7 acetate buffer yielded the glycol (compound **4**, R = CH_3; R′ = H) as the major product. Since this product was not isolated and characterized in that study, we felt that the reduction of crotonaldehyde required further investigation. We therefore repeated the reduction of crotonaldehyde and found, in accord with our other findings, that the major product (56.1% yield) was the hydroxytetrahydrofuran **7** (R = CH_3; R′ = H) resulting from pathway B. "Tail to tail" coupling (pathway A) accounted for 27.9% of the product (compound **5**, R = CH_3; R′ = H) and "head to head" coupling product (compound **4**, R = CH_3; R′ = H) was the minor constituent (16%). Thus, the previous report[4] was in error.

Experimental Section

Nuclear magnetic resonance spectra were recorded on the Varian Model EM-360 spectrometer using chloroform-*d* as solvent and tetramethylsilane as the internal standard. Infrared spectra were recorded on the Perkin-Elmer Model 257 spectrometer and were taken in solution (spectrograde chloroform) unless noted otherwise. pH was measured with a Corning Model 12 pH meter. Polarographic runs were made using a Princeton Applied Research Model 170 electrochemistry system with a dropping mercury electrode (DME) and saturated calomel electrode (SCE). The controlled potential electrolysis experiments were also carried out with this instrument, using the electrolysis cell described below.

3-Methylcrotonaldehyde (**11**). This aldehyde was prepared according to Miller:[3] NMR δ 2.0, 2.2 (s, 6 H), 5.85 (d, 1 H, J = 8 Hz), 9.85 (d, 1 H, J = 8 Hz); ir 2900 (m), 2750 (m), 1670 (s), 1450 (m), 1050 cm^{-1} (m).

Table I. Distribution of Electrolysis Products

Aldehyde	$E_{1/2}$,[a] V	Grams used	Solvent system	% yield[b]	% dimer	
					Furan	Glycol
3-Methylcrotonaldehyde	−1.27	0.50	EtOH–buffer[c]	54	85	15
3-Methylcrotonaldehyde	−1.30	0.50	0.1 M CTABr[d]	46	85	15
Geranial	−1.25	1.25	EtOH–buffer	54	66	34
Geranial	−1.25	1.25	0.0 M CTABr	70	62	38
Geranial	−1.23	1.25	0.1 M CTABr	43	62	38
Geranial	−1.25	1.25	0.5 M CTABr	67	64	36
Farnesal	−1.28	1.83	EtOH–buffer	51	64	36
Farnesal	−1.30	1.83	0.5 M CTABr	32	62	38

[a] Vs. SCE. [b] Yield of dimeric material. [c] 50:50 ethanol–0.25 M acetate buffer at pH 5, aqueous KCl as supporting electrolyte. [d] Cetyltrimethylammonium bromide in 0.25 M acetate buffer at pH 5.

Geranial (12). Under a nitrogen atmosphere, 200 ml of benzene (dried over Na) and 20 g of fresh, activated MnO_2 (Winthrop Labs) were placed in a 500-ml flask equipped with a magnetic stirrer, Dean-Stark trap, and condensor. This mixture was refluxed for approximately 2 h until no more water was being collected. The flask contents were cooled to room temperature, the Dean-Stark trap removed, and 2.00 g of commercial geraniol in 5 ml of benzene was added. The mixture was stirred overnight at room temperature. The benzene solution was then filtered through Celite, the MnO_2 residue being washed with ethyl ether. The organic filtrates were combined and dried over anhydrous Na_2SO_4. Evaporation of this solution gave 1.91 g of geranial (96%). (It was found that lowering the ratio of oxidant from 10:1 to 5:1 did not significantly alter either the yield or quality of the product, as long as fresh MnO_2 was used.) NMR δ 1.65, 1.7 (s, 6 H), 2.2 (m, 7 H total), 5.1 (broad s, 1 H), 5.8 (d, 1 H, J = 8 Hz), 9.85 (d, 1 H, J = 8 Hz); ir 2920 (m), 1640 (s), 1635 (w), 1150 cm^{-1} (m).

Farnesal (13). Farnesal was prepared from *trans,trans*-farnesol by oxidation with fresh, activated MnO_2 using the same method as described for geranial. Farnesol (8.2 g) oxidized with 30 g of MnO_2 gave 6.74 g of farnesal (82%): NMR δ 1.6, 1.66 (s, 12 H), 2.1 (m, 8 H), 5.1 (m, 2 H), 5.8 (d, 1 H, J = 9 Hz), 9.9 (d, 1 H, J = 8 Hz); ir 2900 (s), 1660 (s), 1440 (m), 1360 (m), 1120 cm^{-1} (m).

Preparation of pH 5 Buffer. The buffer used in both the polarography and the electrolysis of the aldehydes (**11, 12, 13**) was a 0.25 M acetate system. It was prepared by adding sufficient 1 M acetic acid solution to 250 ml of 1 M NaOH to bring the pH near 5. The solution was then diluted to almost 1 l., and the pH was adjusted to 5. The solution was then diluted to exactly 1 l.

Purification of Surfactant. The cetyltrimethylammonium bromide was purified[5] by shaking with anhydrous ethyl ether and filtering through a Buchner funnel. This material was then dissolved in a minimum amount of hot methanol and cooled to crystallize. The solid was collected and redissolved in methanol to which ether was then added. This mixture was heated to redissolve the salt and cooled again to crystallize. The crystalline product was collected by suction filtration and dried in a vacuum desiccator at room temperature for 3 h (0.5 mmHg).

Polarography of Aldehydes (11, 12, 13). The polarographic measurements were made with a Princeton Applied Research Model 170 electrochemistry system, using a DME and SCE in a 10-ml H-type polarographic cell. The solutions, each 1.0×10^{-3} M in aldehyde, were purged with N_2 for 10–15 min before each run. The micelle systems foamed a good deal, but this did not seem to affect their polarographic behavior. In each case, a blank run on the solvent system (50:50 EtOH–0.25 M acetate buffer at pH 5) or micelle solution (0.05–0.50 M cetyltrimethylammonium bromide in 0.25 M acetate buffer at pH 5) alone was made to ensure that waves observed were actually due to the aldehyde. The half-wave potentials were closely grouped, falling between −1.23 and −1.30 V; the individual $E_{1/2}$ values are listed in Table I.

Controlled Potential Electrolysis of Aldehydes (11, 12, 13). The Princeton Applied Research Model 170 was also used for the controlled potential electrolyses. The electrolysis cell was a conventional three-electrode system: a mercury (instrument grade) pool working electrode (cathode), a saturated calomel reference electrode, and a Ag/AgCl auxiliary electrode (anode), which was separated from the solution by a fritted glass disk. All reductions were carried out under nitrogen atmosphere. The mercury pool was stirred rapidly throughout the electrolyses with a magnetic stirrer. In each case aqueous KCl was used as a supporting electrolyte. Prior to each electrolysis the system was purged with nitrogen for approximately 20 min until a steady background current for the solvent system, 150 ml of 50:50 ethanol–pH 5 acetate buffer (0.25 M), was obtained. The aldehyde (0.008 mol), which had been dissolved in 10 ml of ethanol, was then added slowly so as not to exceed a current of 1 A.

The reactions employing micelles were carried out in much the same fashion. The solvent system, 50 ml of 0.05–0.50 M cetyltrimethylammonium bromide in pH 5 acetate buffer (0.25 M) with aqueous KCl as supporting electrolyte, was purged slowly with nitrogen (foaming) until a steady background current was obtained. The aldehyde (0.008 mol) was dissolved in about 100 ml of the micelle solution and then added slowly to the electrolysis chamber. All of the electrolyses were conducted at −1.30 V vs. SCE and were complete in 2 h as indicated by a return to background levels of current. In all cases the workup involved extracting the aqueous solutions three times with ethyl ether (50 ml each). There was some tendency of the micelle solution to form emulsions, but these would separate if allowed to stand undisturbed. The ether extracts were combined for each reaction and washed with an aqueous solution of saturated NaCl. The organic extracts from each reduction were then dried over anhydrous Na_2SO_4 and concentrated to oils (often with odor of acetic acid). The results of each electrolysis are given in Table I. Separation and identification of the products is discussed below.

Product Isolation and Identification. 3-Methylcrotonaldehyde in EtOH–pH 5 Buffer. Electrolysis of 0.5 g (0.008 mol) as described previously and workup gave a yellow oil (0.55 g) which was chromatographed on 15 g of Silicar CC-7. Hexane, benzene/hexane, benzene, benzene/ether, ether, and then ethanol and methylene chloride were used as solvent. Two peaks were eluted. The first totaled 235 mg and was identified as the hydroxyfuran derivative (**7**, R = CH_3; R′ = CH_3); the second totaled 36 mg and proved to be the glycol (**4**, R = CH_3; R′ = CH_3) (ratio of 87:13 furan/glycol). Total isolated dimer was 271 mg (54% yield). A second run with 0.5 g of 3-methylcrotonaldehyde under the same conditions gave 242 mg of furan (**7**, R = CH_3; R′ = CH_3) and 48 mg of glycol (**4**, R = CH_3; R′ = CH_3) (ratio of 83:17) for a total of 290 mg (58% yield).

Peak 1. 4,4-Dimethyl-2-hydroxy-5-(2-methyl-1-propenyl)tetrahydrofuran[3] (**7**, R = CH_3; R′ = CH_3): NMR δ 1.05 (s, 6 H), 1.65 (m, 6 H), 2.1 (m, 2 H), 4.1 (m, 2 H), 4.4 (m, 1 H), 5.3 (m, 2 H); ir 3300 (broad), 2880 (s), 1685 (w), 1050 cm^{-1} (m).

Peak 2. 2,7-Dimethyl-2,6-octadiene-4,5-diol[3] (**4**, R = CH_3; R′ = CH_3): NMR δ 1.7 (s, 12 H), 2.25 (broad s, 2 H), 4.25 (m, 2 H), 5.25 (m, 2 H); ir 3550 (s), 2900 (s), 1660 (m), 1370 (m), 980 cm^{-1} (m).

3-Methylcrotonaldehyde in Micelle. Electrolysis of 0.5 g (0.008 mol) of aldehyde in 0.1 M cetyltrimethylammonium bromide as described in the general procedure previously gave an isolated yield of 197 mg of hydroxyfuran (**7**, R = CH_3; R′ = CH_3) and 34 mg of glycol (**4**, R = CH_3; R′ = CH_3) (product ratio of 85:15). Total isolated dimer was 231 mg (46% yield). The spectra of these materials were identical with those reported above. No other product was isolated from any of the runs with 3-methylcrotonaldehyde.

Geranial in EtOH–pH 5 buffer. Electrolysis of 1.25 g (0.008 mol) of geranial (**12**) in EtOH–buffer as described previously gave 0.9 g of crude reduction product on workup. This was chromatographed on 40 g of Silicar CC-7, eluting with hexane, ether/hexane, and ether with the percentage of ether increased in 5% increments. Two products were isolated. The first, totaling 412 mg, proved to be the hydroxyfuran [**7**, R = CH_3; R′ = $CH_2CH_2CH{=}C(CH_3)_2$] and the second, 192 mg, was the glycol [**4**, R = CH_3; R′ = $CH_2CH_2CH{=}C(CH_3)_2$]. Total isolated product was 604 mg (48% yield) with a ratio of furan to glycol

of 68:32. A second run employing the same quantity of geranial gave 480 mg of hydroxyfuran and 266 mg of glycol for a ratio of 64:36. Total yield in this case was 746 mg (60%).

Peak 1. Hydroxyfuran [7, R = CH_3; R′ = $CH_2CH_2CCH{=}C(CH_3)_2$]. NMR δ 0.93 (d, 3 H, J = 7 Hz), 1.64 (s superimposed on multiplet, 18 H total), 2.07 (m, 6 H), 3.85 (broad singlet, 1 H), 4.35 (m, 1 H), 5.09 (m, 3 H), 5.51 (m, 1 H); ir 2500 (w), 2950 (s), 2920 (s), 1710 (w), 1640 (w), 1440 (m), 900 cm^{-1} (s).

Peak 2. Glycol [4, R = CH_3; R′ = $CH_2CH_2CH{=}C(CH_3)_2$]. NMR δ 1.61, 1.7 (s, 18 H), 2.2 (m, 8 H), 4.25 (doublet of doublets, 2 H total), 5.12 (m, 4 H); ir 3550 (broad), 2900 (s), 1660 (m), 1440 (m), 1370 (m), 980 cm^{-1} (m).

Geranial in Micelles. In the manner described previously, geranial (**12**) was reduced in the presence of three different micelle concentrations. A 1.25-g portion reduced in 0.05 M cetyltrimethylammonium bromide gave, after chromatography, 544 mg of hydroxyfuran [**7**, R = CH_3; R′ = $CH_2CH_2CH{=}C(CH_3)_2$] and 334 mg of glycol [**4**, R = CH_3; R′ = $CH_2CH_2CH{=}C(CH_3)_2$] for a product ratio of 62:38. Total isolated yield was 878 mg (70%). The same quantity reduced in 0.1 M micelle solution gave 334 mg of the hydroxyfuran and 207 mg of the glycol (ratio 62:38). Total yield here was 541 mg (43%). An equal amount of geranial was also reduced in presence of 0.5 M micelle. This run gave 533 mg of the hydroxyfuran and 298 mg of the glycol (ratio 64:36). Total isolated yield was 831 mg (67%). The spectral properties are essentially those described in the previous section.

Farnesal in EtOH–pH 5 Buffer. Farnesal (**13**, 1.83 g, 0.008 mol) was reduced in the manner described previously. Upon workup (1.303 g of crude product) and chromatography on 60 g of Silicar CC-7 with the solvent system described for geranial, 601 mg of hydroxyfuran [**7**, R = CH_3; R′ = $CH_2CH_2CH{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)_2$] and 332 mg of glycol [**4**, R = CH_3; R′ = $CH_2CH_2CH{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)_2$] was isolated for a product ratio of 64:36 furan:glycol. Total isolated yield was 933 mg (51%).

Peak 1. Hydroxyfuran [7, R = CH_3; R′ = $CH_2CH_2CH{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)_2$]. NMR δ 0.93 (d, 3 H, J = 7 Hz), 1.63, 1.67 (s, 21 H), 2.05 (m, 16 H), 4.09 (m, 1 H), 4.51 (m, 1 H), 5.07 (m, 5 H), 5.39 (m, 1 H); ir 3400 (broad), 2920 (s), 1720 (w), 1660 (w), 1440 (m), 1380 (m), 1100 cm^{-1} (m).

Peak 2. Glycol [4, R = CH_3; R′ = $CH_2CH_2CH{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)_2$]. NMR δ 1.63, 1.67 (s, 24 H), 2.09 (m, 16 H), 4.23 (doublet of doublet, 2 H), 5.12 (m, 6 H); ir 3400 (broad), 2960 (s), 2920 (s), 1620 (w), 1380 (s), 1080 cm^{-1} (m).

Farnesal in Micelles. Farnesal (1.83 g) was reduced in 0.5 M micelle–buffer solution in the manner described previously. Chromatography of the product on 60 g of Silicar CC-7 with the solvent system used for geranial gave 368 mg of the hydroxyfuran and 226 mg of the glycol. The product ratio was 62:38 furan:glycol. The yield of dimeric material totaled 594 mg (32%). These materials had the same spectral properties as described above for materials produced in a system without micelles.

Crotonaldehyde (10). Commercial crotonaldehyde was fractionally distilled (bp 104.5 °C) under N_2 to give a clear, colorless liquid. It was necessary to store the crotonaldehyde under N_2 in the refrigerator to prevent polymerization: NMR δ 2.05 (d of d, 3 H), 6.10 (m, 1 H), 7.00 (m, 1 H), 9.50 (d, 1 H); ir 2740 (w), 2810 (w), 1690 (s), 1645 cm^{-1} (m, sh).

Preparation of pH 4.7 Buffer. This buffer, used in both the polarography and electrolysis of crotonaldehyde, was prepared in exactly the same manner as the pH 5 buffer, except that the pH was adjusted to 4.7.

Polarography of Crotonaldehyde. This was conducted with the same apparatus that was used for the polarographic studies of the aldehydes (**11**, **12**, **13**). After the system was purged with N_2 for approximately 15 min, a blank run was made on the solvent system, 0.25 M acetate buffer at pH 4.7, 5% EtOH. No reduction of the solvent occurred in the potential range −0.10 to −1.60 V. A solution of 1.0×10^{-3} M crotonaldehyde in 0.25 M acetate buffer at pH 4.7, 5% EtOH was placed in the polarographic H cell and purged with N_2 for approximately 15 min. The polarogram was run, and the half-wave potential of crotonaldehyde was determined to be −1.25 V vs. SCE.

Controlled Potential Electrolysis of Crotonaldehyde. The same apparatus employed in the reduction of the other aldehydes (**11**, **12**, **13**) was used for the electrolysis of crotonaldehyde. pH 4.7 buffer, 5% EtOH (200 ml) was placed in the electrolysis cell with Hg and magnetic stirrer. The system was purged with N_2 for 15–20 min, and the electrodes were connected. The potential was set at −1.30 V. After a stable background current was obtained, 2.00 g (0.286 mol) of crotonaldehyde dissolved in 10 ml of EtOH was added at a rate such that a current of 1 A was not exceeded. The mercury pool was stirred vigorously during the electrolysis. Aqueous KCl was added periodically to prevent electrical overloading. The reduction was complete in 2 h, as indicated by a return to background level of current.

The pH of the aqueous solution was adjusted to 8 by the addition of saturated Na_2CO_3. The solution was extracted five times with chloroform (50 ml each). The organic extracts were combined and dried over anhydrous $MgSO_4$. The chloroform solution was concentrated to a clean, colorless, viscous liquid weighing 1.73 g (86.5%). It was necessary to store the oil under N_2 and in the cold. GC analysis showed that three products were present in the oil (none of which were starting material). This crude (0.95 g) was chromatographed on 70 g of Silicar CC-7, eluting successively with hexane, ether/hexane, and ether. Three peaks were obtained totaling 900 mg (94.7%). The first peak, 505 mg (56.1%), was eluted in 40% ether/hexane and was identified as the hydroxytetrahydrofuran (**7**, R = CH_3; R′ = H) by NMR and ir analysis. The second peak, 251 mg (27.9%), eluted in 60% ether/hexane was identified as the aldol (**5**, R = CH_3; R′ = H). The final peak, 144 mg (16.0%), eluted in 90% ether/hexane was identified as the glycol (**4**, R = CH_3; R′ = H). The evidence for these compounds is given below.

Peak 1. Hydroxytetrahydrofuran (7, R = CH_3; R′ = H) NMR δ 1.00 (d, 3 H, J = 6 Hz), 1.75 (d, 3 H, J = 5 Hz), 4.70 (m, 1 H), 5.55 (m, 2 H); ir 1670 (w), 1710 (w), 3380–3600 cm^{-1} (m).

Peak 2. Aldol (5, R = CH_3; R′ = H). NMR δ 1.00 (d, 6 H, J = 4 Hz), 3.20 [s (broad), 1 H], 4.48 (m, 1 H), 9.75 (d, 1 H, J = 4 Hz); ir 1720 (s), 2720 (w), 3400–3600 cm^{-1} (m).

Peak 3. Glycol (4, R = CH_3; R′ = H). NMR δ 1.75 (d, 6 H, J = 5 Hz), 4.05 (d, 2 H, J = 6 Hz), 5.65 (m, 4 H); ir 1670 (m), 1700 (w), 3400–3600 cm^{-1} (s).

Registry No.—**4** (R = R′ = CH_3), 28405-69-8; **4** (R = CH_3; R′ = $CH_2CH_2CH{=}C(CH_3)_2$), 18927-19-0; **4** (R = CH_3; R′ = $CH_2CH_2CH{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)_2$), 59015-27-9; **4** (R = CH_3; R′ = H), 4486-59-3; **5** (R = CH_3; R′ = H), 25801-68-7; **7** (R = R′ = CH_3), 28405-68-7; **7** (R = CH_2; R′ = $CH_2CH_2CH{=}C(CH_3)_2$), 59015-28-0; **7** (R = CH_3; R′ = $CH_2CH_2CH{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)_2$), 59015-29-1; **7** (R = CH_3; R′ = H), 59015-30-4; **10**, 4170-30-3; **11**, 107-86-8; **12**, 141-27-5; **13**, 502-67-0; *trans,trans*-farnesol, 106-28-5; geraniol, 106-24-1.

References and Notes

(1) This paper is taken from a portion of the Ph.D. Dissertations of James D. Faulkner, 1975, and Judy C. Johnston.
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Organosilicon Compounds with Functional Groups Proximate to Silicon. 13. Cleavage and Rearrangement Reactions of Epoxyethylsilanes[1]

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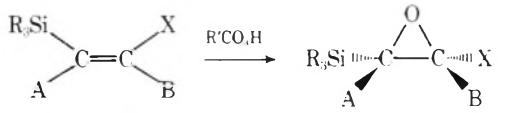
Acid- and base-promoted cleavage and rearrangement processes of the following epoxides were examined: epoxyethyl(triphenyl)silane (**2a**), *cis*-α,β-dideuterioepoxyethyl(triphenyl)silane (**2b**), α-deuterioepoxyethyl(triphenyl)silane (**2c**), and the cis and trans isomers of β-trimethylsilylstyrene oxide (**5a** and **5b**). As nucleophiles, phenyllithium, benzylamine, piperidine and morpholine and diisobutylaluminum hydride or deuteride and, as electrophiles, magnesium bromide and hydrogen chloride were evaluated. The thermal reactions of the epoxides **2a** and **2c** and the intermediate ring-opened epoxide cleavage products were studied. In general, the nucleophiles attacked preferentially the epoxide carbon α to the silicon in **2** and **5**, either directly with the subsequent loss of R_3SiOH or indirectly via a carbenoid intermediate with the subsequent loss of Li_2O. Phenyllithium reacted with **2a** to form styrene and $(C_6H_5)_4Si$; **2b** gave a 1:1 mixture of *cis*- and *trans*-α,β-dideuteriostyrene; and **2c** gave α-deuteriostyrene. Diisobutylaluminum deuteride and **2a** yielded only β-deuterio-β-triphenylsilylethanol. Electrophiles tended to give products arising from both modes of epoxide ring cleavage. **2a** with HCl yielded β-triphenylsilylacetaldehyde, β-chloro-α-triphenylsilylethanol, and chloro(triphenyl)silane. Magnesium bromide and **2a** gave the aldehyde with ca. equal distribution of the deuteron between C_1 and C_2. Finally, pyrolysis of **2c** at 275 °C gave the triphenyl(vinyloxy)silane with 60% of the deuteron β-cis to the silicon, 20% β-trans, and 20% α to silicon. The foregoing cleavage, elimination, and rearrangements are unified by polar mechanistic paths, some of whose intermediates have been subjected to trapping and stereochemical tests.

Curiosity as to how a triorganosilyl substituent would influence the reactivity and mode of cleavage of an adjacent epoxide group prompted our original studies on the synthesis[2] and the hydride reduction[3] of epoxyethylsilanes. Such an effort was rewarded by the observation of an unusual lithium aluminum hydride rupture of these epoxides, which led to the 2-silylethanols by a direct hydride attack at the epoxide carbon α to silicon.[3] Interactions of silyl epoxides with other nucleophiles, such as amines[4] or triphenylphosphonium methylide,[5] apparently involved both epoxide cleavage and silicon–oxygen migrations, for silanols and disiloxanes were found among the products. On the other hand, electrophilic attack on such silyl epoxides led either to the formation of β-silylcarbonyl derivatives[3,6] or, by protodesilylation, to silicon-free carbonyl derivatives.[7] In fact, this latter mode of cleavage is basic to the recent use of epoxyalkylsilanes as carbonyl precursors in novel organic syntheses.[8]

Therefore, we were encouraged to undertake a more extensive survey of the acid- and base-promoted cleavages of epoxyethylsilanes. To permit monitoring of the regiochemistry or stereochemistry involved in such cleavages, reaction was conducted not only on epoxyethyl(triphenyl)silane (**2a**), but also on *cis*-α,β-dideuterioepoxyethyl(triphenyl)silane (**2b**), α-deuterioepoxyethyl(triphenyl)silane (**2c**), and the cis and trans isomers of β-trimethylsilylstyrene oxide (**5a** and **5b**), all of which were prepared by the epoxidation of the corresponding vinylsilanes (eq 1).



(1)

1a, R = C_6H_5; A, B, X = H
b, R = C_6H_5; A, B = D; X = H
c, R = C_6H_5; A = D; B, X = H

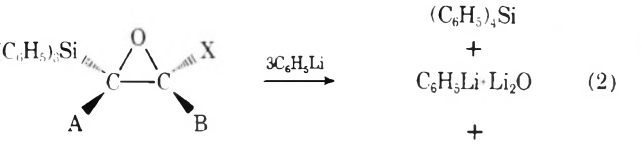
2a, R = C_6H_5; A, B, X = H
2b, R = C_6H_5; A, B = D; X = H
2c, R = C_6H_5; A = D; B, X = H
5a, R = CH_3; A, B = H; X = C_6H_5
5b, R = CH_3; A, X = H; B = C_6H_5

In the following report we shall describe reaction pathways for the cleavage of these epoxides by, in turn, phenyllithium, primary and secondary amines, dialkylaluminum hydride, and hydrogen chloride. Certain of these reactions will be compared with recently published preliminary reports on the thermal rearrangements[9] and organocuprate cleavages[10] of silyl epoxides, in order to arrive at a unified mechanistic view of epoxyalkylsilane chemistry.

Results

Cleavage by Phenyllithium. Epoxyethyl(triphenyl)silane (**2a**) with phenyllithium in ether at 0 °C formed styrene and tetraphenylsilane. One equivalent of **2a** required ca. 3 equiv of phenyllithium. Thus, when equimolar amounts of **2a** and the lithium reagent were admixed, the isolated yields of pure tetraphenylsilane realized were 23–27% with material balances of 91–94%. Lithium bromide present in the phenyllithium solution did not play a role in this reaction (possibly by inducing a rearrangement of **2a**).[3,6] The reaction of **2a** with lithium halide free phenyllithium[11] gave identical results.

To learn at which carbon of epoxide **2a** the attachment of phenyllithium occurred, the α-deuterated epoxide **2c** was subjected to cleavage. The styrene formed in 86% yield was shown by NMR analysis to be exclusively α-deuteriostyrene (**3c**), and thus the phenyllithium had ultimately attacked the carbon α to silicon in **2c** (eq 2).



(2)

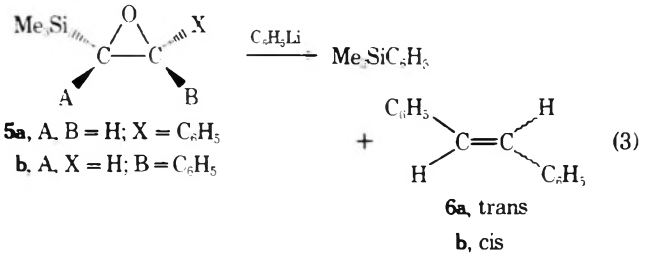
2a, A, B, X = H
b, A, B = D; X = H
c, A = D; B, X = H

3a, A, B, X = H
b, A, B = D; X = H
c, A = D; B, X = H

A corresponding reaction of **2b** with phenyllithium established that the formation of styrene was nonstereospecific; the α,β-dideuteriostyrene (**3b**) was a 1:1 mixture of the cis and trans isomers.

From the observed stoichiometry of eq 2, it would seem that the lithium oxide thus formed might be responsible for complexing with and thereby deactivating 1 equiv of the phenyllithium employed.[12]

Both *cis*- and *trans*-β-trimethylsilylstyrene oxides gave ca. 95% of *trans*-stilbene and traces of *cis*-stilbene, together with trimethyl(phenyl)silane (eq 3).

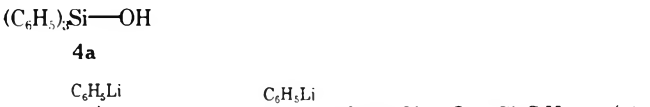


5a, A, B = H; X = C_6H_5
b, A, X = H; B = C_6H_5

6a, trans
b, cis

(3)

To learn if the olefin formation in eq 2 and 3 might result from the elimination of lithium triorganosilanolate (cf. infra), such a salt was treated with phenyllithium under the same conditions. However, treatment of triphenylsilanol (**4a**) with 4 equiv of phenyllithium in diethyl ether gave only traces of tetraphenylsilane, with the latter undoubtedly arising by way of hexaphenyldisiloxane (eq 4).

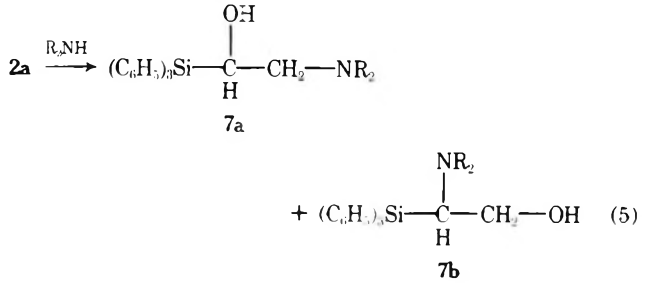


4a

(4)

No intermediates could be detected in the reaction of epoxide 2a with phenyllithium at low temperatures: at −78 °C no reaction occurred, and at −23 °C only styrene and tetraphenylsilane were formed. The absence of triphenylsilanol in this low-temperature reaction and its failure to undergo efficient conversion to tetraphenylsilane by phenyllithium (eq 4) argue against its being an intermediate in eq 2.

Cleavage by Primary and Secondary Amines. Epoxyethyl(triphenyl)silane (**2a**) with benzylamine, piperidine, or morpholine at 110–155 °C formed triphenylsilanol (**4a**) and hexaphenyldisiloxane (**12**). Isolation of intermediates by conducting the reaction under milder conditions proved to be impossible, but their detection by NMR monitoring was informative. Although no new peaks were observed, whose chemical shifts would be consonant with the simple adducts (eq 5), new doublet peaks at high field (0.8–1.6 ppm) appeared,

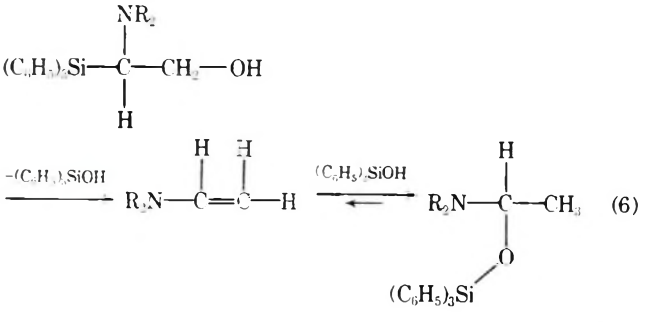


7a

7b

(5)

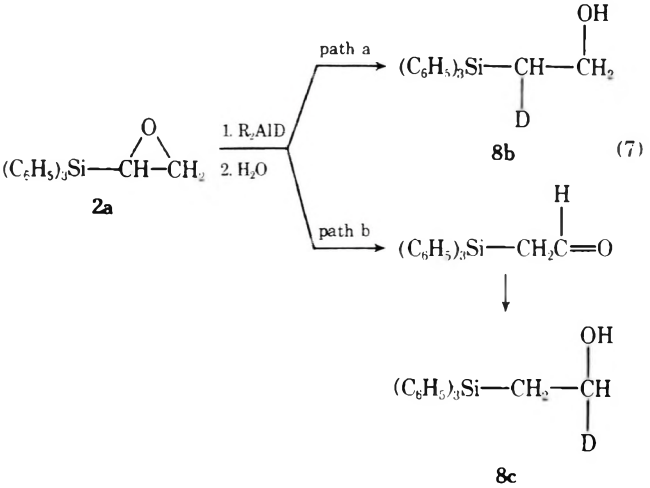
whose origin could be ascribed to the rearrangement product of the latter intermediate (**7b**), as in eq 6. The enamine intermediate could undergo polymerization under the reaction conditions, thus preventing the detection of acetaldehyde when the reaction mixture was treated with an acidified 2,4-dinitrophenylhydrazine solution. That the silanol **4a** (disiloxane **12**) was formed furnishes indirect evidence for the preferred formation of adduct **7b**, for only this adduct would be expected to have a facile pathway leading to the loss of triphenylsilanol (cf. eq 6). As to the origin of the disiloxane **12**, it is known that heating **4a** in basic solvents leads to the formation of **12**.[13]



(6)

The behavior of the less reactive *cis*-β-trimethylsilylstyrene oxide (**5a**) with benzylamine tends to support the foregoing description of such cleavages. An NMR monitoring of the early stages of reaction did reveal doublets of equal intensity whose chemical shifts (4.47 and 2.12 ppm) are consonant with presence of the intermediate, $C_6H_5CHOHCHNR_2SiMe_3$, in solution.

Cleavage by Dialkylaluminum Hydride. Although lithium aluminum hydride has already been shown to attack **2a** by direct hydride attack at the carbon α to silicon,[3] it was interesting to learn how an electrophilic hydride reagent like diisobutylaluminum hydride would behave. Treatment of **2a** with this hydride in hexane gave rapid reduction and a high yield of β-triphenylsilylethanol (**8a**). To learn whether direct reduction (path a) or reduction with preliminary rearrangement (path b) took place (eq 7), the reduction of **2a** was repeated with diisobutylaluminum deuteride.



2a

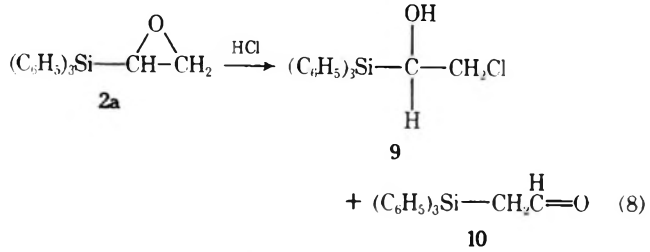
8b

8c

(7)

However, an NMR analysis of the product and comparison with an authentic sample[3] demonstrated that only **8b** was formed.

Cleavage with Hydrogen Chloride. Epoxyethyl(triphenyl)silane with anhydrous hydrogen chloride in benzene gave both epoxide cleavage and isomerization (eq 8).



2a

9

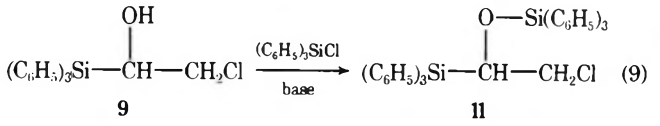
10

(8)

The structure of **9** was established by means of the lanthanide shift reagent, Eu(fod)$_3$,[14] which caused the one-proton packet of **9** to be shifted downfield to the greatest extent.

Chloro(triphenyl)silane was also formed in the course of this reaction, either by the dissociation of **9** into acetaldehyde and this chlorosilane or directly from **16** (cf. eq 13 and 14). This point was established by heating purified **9** and trapping the evolved acetaldehyde in a solution of 2,4-dinitrophenylhydrazine.

Because of the presence of chloro(triphenyl)silane in the original reaction mixture, workup with alkaline reagents led to the formation of β-triphenylsiloxy-β-triphenylsilylethyl chloride (**11**), which was shown to arise from the action of the chlorosilane on **9**.

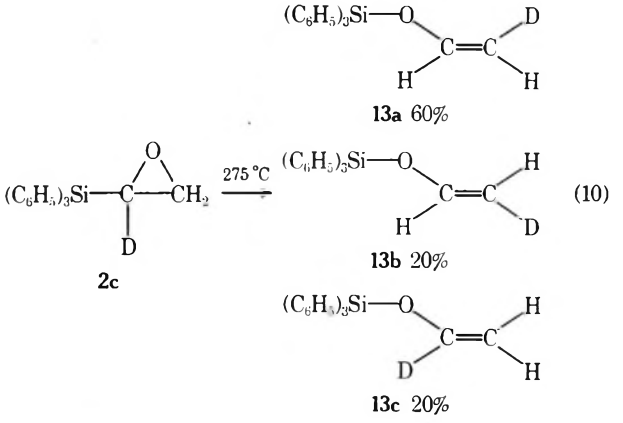


9 **11** (9)

Rearrangements of Epoxyethyl(triphenyl)silane. In the midst of our studies on the thermal rearrangements of epoxyalkylsilanes, a preliminary report of a very comprehensive study appeared.[9] Hence, we shall restrict ourselves to mentioning only our complementary findings.

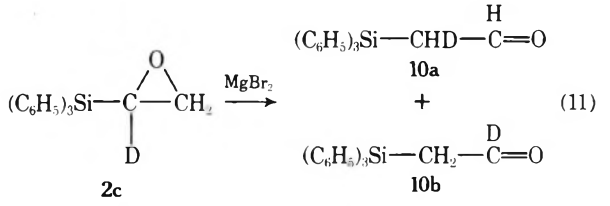
For our thermal isomerizations of **2a** in the liquid phase there was some indication that traces of acid remaining on the glassware catalyzed the isomerization of **2a** to triphenyl(vinyloxy)silane. Isomerizations conducted with carefully rinsed glassware were slower. The presence of air or hydroquinone retarded the reaction as well.

Isomerization of the α-deuterio isomer **2c** at 275 °C led to the formation of principally (ca. 80%) the β-deuteriovinyloxysilanes, **13a** and **13b**, in a 3:1 ratio and probably 20% of the α-deuterio isomer, **13c**.



(10)

The magnesium bromide catalyzed isomerization of **2c** to the aldehyde **10** was also undertaken, in order to learn what the deuterium label would reveal about the reaction course. Treatment of **2c** with magnesium bromide led to an equimolar mixture of 1- and 2-deuterated isomer of **10**.



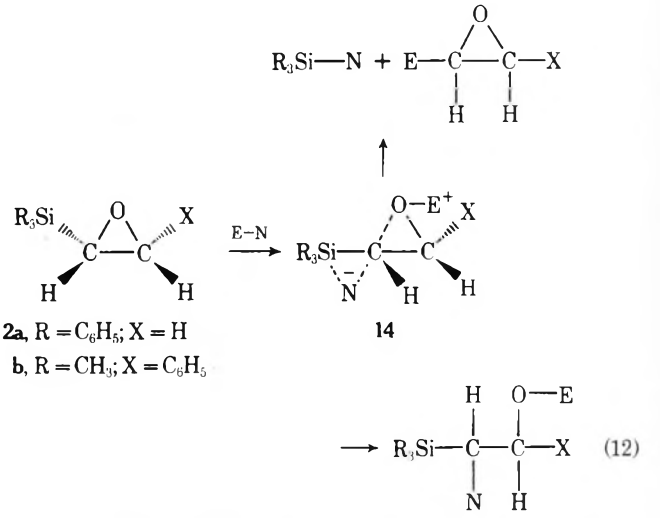
(11)

Discussion

Three aspects of epoxyalkylsilane chemistry deserve general consideration, namely the regiochemistry of epoxide ring opening, the ensuing desilylative elimination reactions of such ring-opened adducts, and the attendant rearrangement processes of both epoxides and their reaction intermediates.

Regiochemistry of Epoxide Opening. In the foregoing reactions of epoxyethylsilanes (**2a, 5a,** and **5b**) with phenyllithium or with diisobutylaluminum hydride, attack of these reagents was shown to be indisputably regiospecific for the epoxide carbon α to the silicon. The same regiospecificity most probably also obtains for the rupture of epoxides **2a** and **5a** by primary or secondary amines (eq 5 and 6). Attack of these amines preferentially at the epoxide carbon α to silicon (giving adducts of type **7b**) is indirectly proved, for only such adducts could easily permit the ready, observed elimination of the triorganosilanol (eq 6). However, the formation of $R_3SiC_6H_5$, rather than R_3SiOH, in the reactions of epoxides **2** and **5** with phenyllithium reveals an unusual feature of such interactions.

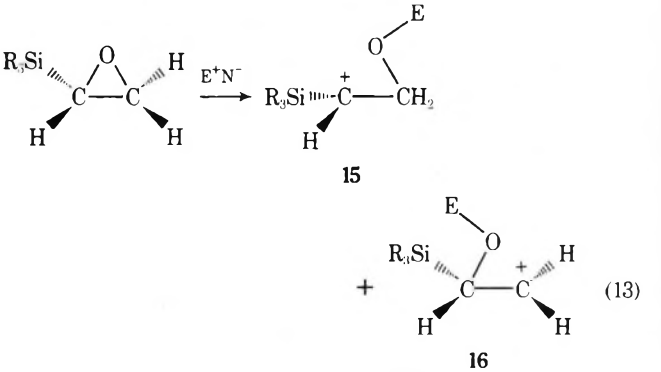
These results can be incorporated into a generalized view of nucleophilic attack on epoxyalkylsilanes, which has already been adumbrated in discussing the lithium aluminum hydride opening of such epoxides.[3] Nucleophilic attack can be viewed as proceeding through a three-centered transition state **14**, which can lead to rupture of the carbon–oxygen bond with assistance by some Lewis acid (E = Li^+, R_2AlH, H · · · NR_2) or which can give rise to direct nucleophilic attack on silicon with the displacement of the epoxide ion (eq 12).



(12)

Nucleophilic attack on the carbon α to silicon (cf. **14**) is considered to be favored by simultaneous interaction of the approaching electron pair with the antibonding orbital on the epoxide carbon and the vacant 3d orbitals of silicon.

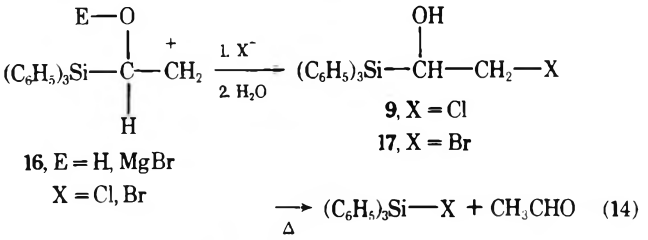
Where the nucleophilicity of the reagent is low, ring opening would be expected to be governed by the relative stability of the incipient carbonium ions generated by electrophile E^+ (eq 13).



(13)

As judged by electronegativities (X_{Si} = 1.8 vs. X_H = 2.1), the transition state leading to **15** should be of lower energy. This view seems to accommodate nicely the behavior of epoxide **2a** toward magnesium bromide or hydrogen chloride. In both reactions products are formed that can be ascribed as arising via both intermediates **15** and **16**. With hydrogen chloride, the formation of β-triphenylsilylacetaldehyde (**10**) can be viewed as stemming from **15** via a hydride shift, while the chlorohydrin **9** would result by the capture of **16** with the chlorine ion (eq 8). With magnesium bromide, it is known that **2a** gives principally the acetaldehyde **10** (75% yield); this supports the above assumption that **15** is formed via a lower

energy pathway. Although no bromohydrin **17** (analogous to chlorohydrin **9**) has been isolated from this reaction, variable amounts of triphenylsilanol have been detected.[3,4] Most likely this silanol results from the hydrolysis of bromo(triphenyl)-silane, which in turn arises from the decomposition of β-bromo-α-triphenylsilylethanol. The latter intermediate would represent the capture product of **16** by bromide ion and would be expected to be even more prone to β-elimination than **9**[15] (eq 14).



16, E = H, MgBr
X = Cl, Br

9, X = Cl
17, X = Br

$$\xrightarrow[\Delta]{} (C_6H_5)_3Si{-}X + CH_3CHO \qquad (14)$$

Although this explanation of epoxide opening by electrophiles fits most of the facts, the subsequent discussion of rearrangements will address subtle complexities in these reactions.

Desilylative Eliminations. β-Eliminations of halohydrins **9** and **17** have been intensively studied.[15] Since it is known that β-silylalkanols undergo base-promoted elimination of triorganosilanol[10,16,17] it was initially believed that the interaction of phenyllithium with both epoxides **2a** and **5a** led to a β-silylethanol, which then underwent desiloxylation (path a).

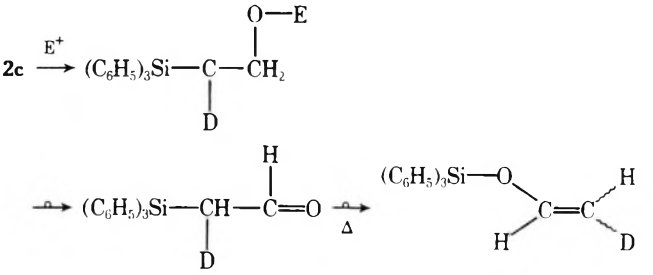
However, the nonstereospecificity in the olefins formed [1:1 mixture of *cis*- and *trans*-dideuteriostyrenes from **2b** (eq 2) and >95% *trans*-stilbene from **5a** or **5b** (eq 3)] is not in accord with path a, which elimination is stereospecific.[17] Nor can the observed formation of $R_3Si{-}C_6H_5$ be reconciled with this path: even if R_3SiOH were eliminated, it has been shown not to yield significant amounts of $R_3Si{-}C_6H_5$ with phenyllithium under the reaction conditions. Path b suffers disadvantages similar to path a. Only if **20** were to react more rapidly with phenyllithium to yield **23** than undergo direct elimination to provide **24** would this mechanism fit the facts. However, that **20** should undergo exclusively an intermolecular reaction to yield **23** and undergo no trace of intramolecular decomposition to **24** and R_3SiO^- seems highly unlikely. Hence, an alternative path must be sought.

Only a direct nucleophilic attack of phenyllithium on silicon, with the formation of the epoxide anion (**21**, path c), does offer a suitable route to $R_3Si{-}C_6H_5$ and **24**. Such an anion would be expected to yield a carbenoid **22** by α-elimination[18] and **23** would be formed by the trapping of **22** by phenyllithium. Loss of Li_2O by **23** would then yield the olefin **24** in a nonstereospecific fashion.

The elimination of R_3SiOH in the reactions of these epoxides with primary or secondary amines most likely occurs in a fashion analogous to path a in Scheme I, with intermediates such as **7b** undergoing silicon–oxygen interaction and elimination.

Rearrangements. In contrast to the retro-Wittig rearrangements[19] encountered in the foregoing epoxide reactions with nucleophiles, the electrophile-catalyzed rearrangement of α-deuterioepoxyethyl(triphenyl)silane led to isomeric aldehydes **10a** and **10b** (eq 11). The finding of ca. equal distribution of the deuteron between C_1 and C_2 forces one not only to postulate a hydride shift in **15** to account for **10**, but also to invoke a migration of R_3Si in intermediate **16** from one carbon to another. Such acid-catalyzed 1,2-silyl groups shifts have previously been reported.[20]

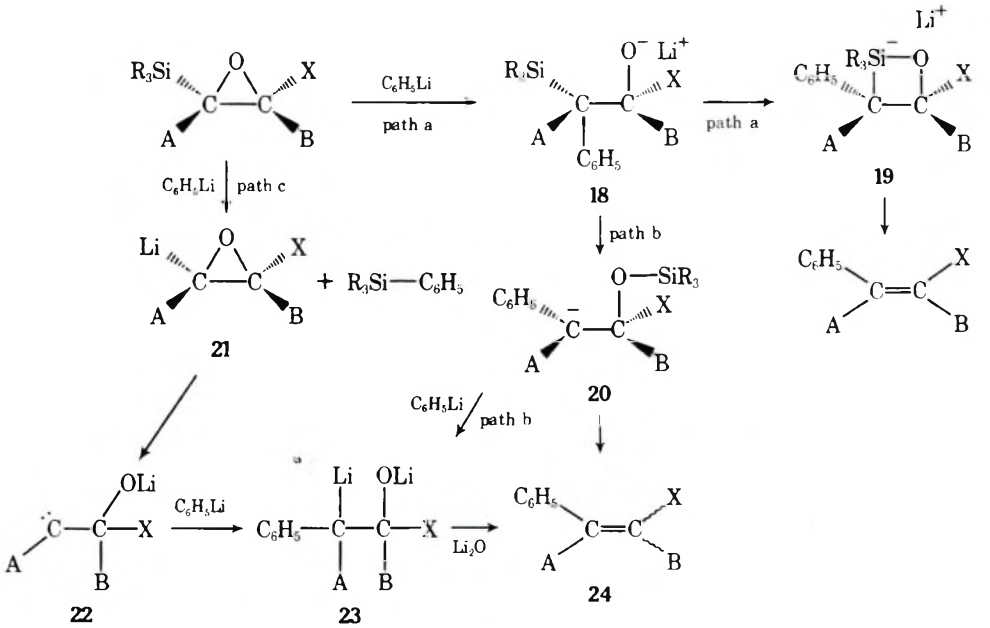
The unusual thermal rearrangement of this epoxide **2** reported in this study is similar to those recently described by Brook and co-workers.[9] From our limited data, we are inclined to believe that this reaction is acid catalyzed and may proceed via the formation of β-triphenylsilylacetaldehyde (**10**), which is known to rearrange readily to triphenyl(vinyloxy)silane.[6]



10a (15)

Although such a rationale accounts for some of the facts, the stereoselective formation of **13a** is puzzling. Extensive studies to learn about the possible role of adventitious catalysts or surface reactions remain to be carried out.

Scheme I



Experimental Section

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are corrected. Infrared spectra were recorded of samples as potassium bromide disks, mineral oil suspensions, or solutions in pure solvents by means of a Perkin-Elmer spectrophotometer, Model 457. Proton magnetic resonance spectra were recorded with Varian spectrometers, either a Model A-60 or a Model HA-100D, the latter being equipped with a proton and deuterium decoupler (Model HP-205AG). Such NMR data are presented on the δ scale in parts per million relative to tetramethylsilane, followed by the integrated intensities and the coupling constants in hertz. Mass spectra were obtained with a Du Pont spectrometer, Model 21-491BR, equipped for the gas chromatographic introduction of samples. Separate gas chromatographic analyses were performed with an F & M instrument, Model 720, equipped with dual columns of 10% silicone gum rubber on 60–80 mesh Chromosorb W. Elemental analyses were carried out by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

All reactions of the epoxides with organometallic compounds or other cleavage reagents were conducted under an atmosphere of dry nitrogen and in anhydrous solvents.

Starting Materials. Triphenyl(vinyl)silane (**1a**),[2] ethynyl(triphenyl)silane,[21] trimethyl[(*E*)-β-styryl]silane,[22] and trimethyl[(*Z*)-β-styryl]silane[22] were prepared and purified according to published procedures. Epoxyethyl(triphenyl)silane (**2a**) was prepared by the epoxidation of triphenyl(vinyl)silane either with peroxytrifluoroacetic acid[3] or with *m*-chloroperbenzoic acid (cf. infra).

cis-β-Trimethylsilylstyrene oxide (**5a**) and *trans*-β-trimethylsilylstyrene oxide (**5b**) were prepared from the corresponding trimethyl(β-styryl)silanes by adding dropwise a solution of 40 mmol of the styrylsilane in 20 ml of chloroform to 44 mmol of *m*-chloroperbenzoic acid (85% pure) in 90 ml of chloroform cooled to 0 °C. After the addition, the solution was stirred at 20–25 °C for 48 h. The resulting white suspension was taken up in benzene and the solution then extracted, in turn, with aqueous sodium bicarbonate, aqueous sodium bisulfite, and aqueous sodium bicarbonate solutions. Drying the benzene layer over anhydrous sodium sulfate, solvent removal, and distillation gave the epoxides: (1) cis isomer **5a,** bp 55–59 °C (0.5 mm), 65% yield (>95% pure by NMR and GC, but may rearrange without detection on GC; cf. infra), NMR (CCl_4) δ 0.20 (s, 9), 2.77 (d, 1, J = 5.5 Hz), 4.52 (d, 1, J = 5.5 Hz), and 7.65 (s, 5); (2) trans isomer **5b,** bp 60–62 °C (0.5 mm), 70% yield (>95% pure by NMR, but underwent rearrangement on GC with inlet at 270 °C) after purification by chromatography on a Florisil column with a hexane elution, NMR (CCl_4) δ 0.49 (s, 9), 2.53 (d, 1, J = 3.2 Hz), 3.97 (d, 1, J = 3.2 Hz), and 7.54 (s, 5).[9,23]

***cis*-α,β-Dideuteriovinyl(triphenyl)silane (1b).** A solution of ethynyl(triphenyl)silane[21] (9.88 g, 34.8 mmol) and anhydrous *N*-methylpyrrolidine (4.68 g, 55 mmol) in 100 ml of hexane was cooled to −78 °C and slowly treated with diisobutylaluminum deuteride (7.87 g, 55 mmol, ca. 95% pure). The mixture was allowed to attain room temperature slowly and then was heated at reflux for 25 h. The solution was cooled and cautiously treated with 13 ml of deuterium oxide (99.9%). The separated organic product was brought into solution with methylene chloride. The organic extract was dried over anhydrous magnesium sulfate and the solvent then removed. Column chromatography on Florisil in the published manner and recrystallization from 95% ethanol gave an adequately pure product, mp 60–61 °C, in low yield, since contaminants were difficult to remove: NMR ($CDCl_3$) δ 5.70 (t, 1, J = 3 Hz) and 7.0–7.6 (m, 15).

α-Deuteriovinyl(triphenyl)silane (1c). α-Deuteriovinyl chloride[24] was prepared from 2-bromo-1,1-dichloro-1-deuterioethane (11.5 g, 64 mmol) and dried thoroughly by vaporizing it successively through columns packed with phosphorus pentoxide and calcium hydride, respectively. The gas thus dried was passed into a flask containing a stirred mixture of magnesium turnings (1.20 g, 49 mmol) in 25 ml of dry tetrahydrofuran.[25] A cold-finger condenser charged with solid carbon dioxide and acetone was used to retain the vinyl chloride in the flask. After the Grignard reagent had formed, chloro(triphenyl)silane (10.5 g, 35 mmol) in 50 ml of tetrahydrofuran was added and the solution heated at reflux for 24 h. Usual workup gave 8.0 g (43%) of pure product: mp 69–70 °C; NMR ($CDCl_3$) δ 5.70 (ca. sextet, 1, $J \simeq 3$ Hz), 6.13 (m, 1), and 7.0–7.6 (m, 15).

α-Deuterioepoxyethyl(triphenyl)silane (2c) and *cis*-α,β-Dideuterioepoxyethyl(triphenyl)silane (2b). A solution of **1c** (5.86 g, 19 mmol) and *m*-chloroperbenzoic acid (85%, 5.3 g, 26 mmol) in 30 ml of chloroform was allowed to stand at 20–25 °C for 24 h. The solidified mixture was dissolved in benzene and the resulting solution washed several times with 5% aqueous sodium bicarbonate, 5% aqueous sodium bisulfite, and again with the bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed. Column chromatography on Florisil gave 1.27 g of recovered **1c** and 4.35 g of the epoxide **2c** (94% yield). Recrystallized from a 95% ethanol–methylene chloride pair, **2c** melted at 85–86 °C: NMR ($CDCl_3$) δ 2.43 (d, 1, J = 5 Hz), 2.81 (d, 1, J = 5 Hz), and 6.9–7.6 (m, 15).

In a similar manner, **1b** was converted to epoxide **2b:** NMR ($CDCl_3$) δ 2.41 (br, s, 1) and 6.9–7.6 (m, 15).

Reaction of Epoxyethyl(triphenyl)silanes with Phenyllithium. A. Epoxyethyl(triphenyl)silane.[4] When 1.50 g (5 mmol) of **2a** in 50 ml of anhydrous diethyl ether was treated at 0 °C with 4.3 mmol of phenyllithium in 25 ml of ether for 45 min, subsequent hydrolysis and separation of the ether layer led to the detection of styrene, tetraphenylsilane (27%, mp 225–228°C), and recovered **2a** (64%, mp 68–72 °C).

A similar run allowed to react at 20–25 °C for 20 h gave a 23% yield of tetraphenylsilane (mixture melting point and ir spectrum) and a 71% recovery of **2a.**

An 88-mg sample of **2a** (2.9 mmol) in 30 ml of dry ether was titrated at 0 °C with an ethereal solution of 12.6 mmol of phenyllithium until the Gilman Michler's ketone color test on an aliquot just turned permanently positive. Upon the basis of a simple acid–base assay of the phenyllithium, this titration indicated that ca. 4 equiv of the lithium reagent was required per mole of **2a.** That this value was high was shown by adding 0.16 mmol of **2a** to turn the Gilman test negative and by treating the solution with solid carbon dioxide. Benzene and aqueous potassium hydroxide were then added and the benzene layer reextracted with more base, dried over anhydrous magnesium sulfate, and stripped of solvent and biphenyl. The resulting residue was essentially pure tetraphenylsilane, 1.0 g (96%), mp 233–236 °C after recrystallization from cyclohexane.

The aqueous layer yielded 0.32 g of benzoic acid upon acidification. Since this accounts for 2.6 mmol of the phenyllithium employed, 10 mmol of the lithium reagent had reacted with 3.1 mmol of **2a.**

B. α-Deuterioepoxyethyl(triphenyl)silane (2c). A solution of 1.66 g of **2c** (5.4 mmol) in 15 ml of diethyl ether was rapidly treated at 20–25 °C with 16.2 ml of 1.0 M phenyllithium in ether. After a 2-min period 2 ml of water was cautiously added. The precipitated tetraphenylsilane was dissolved by the addition of methylene chloride and the resulting solution dried over anhydrous magnesium sulfate. The solvents were removed at 25 °C under 20 mm pressure and then the styrene was condensed into a dry ice cooled trap by heating at 50 °C under 0.1 mm pressure. An NMR analysis showed that only α-deuteriostyrene (500 mg, 86%) was present. The nonvolatile residue was essentially pure tetraphenylsilane, 1.52 g (83%), mp 233–237 °C, after recrystallizations from a 95% ethanol–methylene chloride pair.

C. *cis*-α,β-Dideuterioepoxyethyl(triphenyl)silane (2b). A similar reaction was carried out with **2b** and phenyllithium. The styrene isolated and purified twice by GC collection was shown by NMR spectral analysis to be a mixture of *cis*- and *trans*-dideuteriostyrene: relative integrated intensities of aromatic:cis-β:trans-β protons 5.0:0.5:0.5 (±0.1).

D. Search for Intermediates. Treatment of 1.0 mmol of **2a** in 10 ml of ethyl ether with 4.2 mmol of phenyllithium in 4 ml of ether at −78 °C (dry ice–acetone bath) gave no reaction after 2 h.

An analogous reaction at −23 °C (dry ice–CCl_4 bath) led to a precipitate of tetraphenylsilane after a few minutes. Hydrolysis after 30 min at −23 °C and usual workup revealed the presence of only styrene, tetraphenylsilane, and **2a.** Specifically, no triphenylsilanol could be detected.

E. Control Reaction of Triphenylsilanol with Phenyllithium. Treatment of 1.104 g (4 mmol) of **4a** in 20 ml of ethyl ether with 16 ml (16.8 mmol) of ethereal phenyllithium over a period of 2 h at 25 °C gave a homogeneous solution. After 15 min hydrolysis and usual workup gave only 57 mg (4%) of tetraphenylsilane; the rest was recovered **4a.**

Reaction of the β-Trimethylsilylstyrene Oxides with Phenyllithium. A. Cis Isomer (5a).[23] A solution of 1.45 g (7.5 mmol) of **5a** (96% pure) in 20 ml of anhydrous diethyl ether was treated with 24 mmol of phenyllithium in ether, whereupon a marked exotherm resulted. After 30 min the mixture was hydrolyzed cautiously. The separated organic layer was dried over anhydrous sodium sulfate and the volatile components were distilled off at normal pressure. The residue was shown by a combination of GC and NMR analysis to contain *trans*-stilbene (**6a**), only a trace of *cis*-stilbene (**6b,** <5%), trimethyl(phenyl)silane, and biphenyl. The *trans*-stilbene was isolated by recrystallization from methanol and identified; the silane was separated by volatilization from the residue at reduced pressure.

B. Trans Isomer (5b).[23] In a similar manner, 3 mmol of **5b** and 12 mmol of phenyllithium gave only the trans isomer of stilbene, together

with trimethyl(phenyl)silane and biphenyl. The trans isomer was isolated and identified by mixture melting point and ir spectral comparisons.

Reaction of Epoxyethyl(triphenyl)silane (2a) with Diisobutylaluminum Hydride. To a stirred suspension of **2a** (604 mg, 2.0 mmol) in 10 ml of hexane was added 0.40 ml (2.2 mmol) of the hydride. The mixture became warm and homogeneous. After 1 h at 20–25 °C the solution was cooled and cautiously treated with 1.0 ml of water and then with 50 ml of methylene chloride. The solution was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. β-Triphenylsilylethanol (**7a**) separated from the concentrated solution in 83% yield (516 mg, mp 87–89 °C). Recrystallization from hexane gave a product, mp 99–100 °C, which by mixture melting point and ir spectra was identical with an authentic sample.[3]

The reaction of **2a** with diisobutylaluminum deuteride[26] was conducted in a similar manner. The product was shown to be exclusively β-deuterio-β-triphenylsilylethanol (**7b**) by comparison with an authentic sample.[3]

Reaction of Epoxyethyl(triphenyl)silane (2a) with Hydrogen Chloride. To an ice-cooled solution of **2a** (9.06 g, 30 mmol) in 60 ml of benzene was added, in one portion, 57 ml (30 mmol) of a 0.562 M solution of anhydrous hydrogen chloride in benzene. The solution was allowed to come to room temperature over 15 h. Removal of the solvent under reduced pressure gave a semisolid residue that was chromatographed on a Florisil column using an ether–hexane (1:9 v/v) eluent. The combined crystalline fractions were recrystallized from an ether–hexane pair to yield 5.25 g (51%) of product, which by NMR analysis was shown to contain ca. 80% of **9** and 20% of triphenylsilylacetaldehyde (**10**) (doublet at 2.97 and triplet at 9.61 ppm). Repeated recrystallization gave the pure chlorohydrin (**9**): mp 110–111 °C; NMR ($CDCl_3$) δ 2.20 (s, 1), 3.8–4.3 (m, 3), and 6.9–7.7 (m, 15).[4]

Anal. Calcd for $C_{20}H_{19}ClOSi$: C, 70.88; H, 5.65; Cl, 10.46. Found: C, 71.17; H, 5.54; Cl, 10.42.

Incremental additions of $Eu(fod)_3$ in a $CDCl_3$ solution of **9** and NMR spectral monitoring at 100 MHz caused the three-proton multiplet to resolve eventually into a one- and a two-proton packet. Since the one-proton packet was shifted the most by higher $Eu(fod)_3$ concentrations, the hydroxyl must be α to the silicon and the structure of **9** is then β-chloro-α-triphenylsilylethanol.

When the reaction of **2a** with hydrogen chloride was conducted as above, except that the benzene solution was stirred for 30 min with an excess of powdered, anhydrous sodium carbonate, subsequent workup yielded 20% of **9**, together with 30% of the triphenylsilyl ether of **9** (cf. infra). The isolation of this ether (**11**) demonstrated the presence of chlorotriphenylsilane in the reaction mixture.

β-Triphenylsiloxy-β-triphenylsilylethyl Chloride (11). A mixture of **9** (328 mg, 1.0 mmol), chlorotriphenylsilane (300 mg, 1.01 mmol), and anhydrous pyridine (120 mg, 1.51 mmol) was heated at reflux in 10 ml of hexane for 20 h. An additional 20 ml of hexane was used to aid a hot filtration of the suspension. Concentration and cooling of the filtrate gave 186 mg (31%) of the product, mp 138–140.5 °C. An analytical sample of **11** from cyclohexane melted at 143–144 °C and was shown to be identical with the product from the reaction of **1a** with hydrogen chloride.

Anal. Calcd for $C_{38}H_{33}ClOSi_2$ (597): C, 76.41; H, 5.56; C., 5.94. Found [mol wt (Rast), 590]: C, 76.01; H, 5.31; Cl, 5.94.

Thermal Decomposition of β-Chloro-α-triphenylsilylethanol and the Identification of Acetaldehyde. Under argon gas a sample of **9** (328 mg, 1 mmol) was gradually heated up to 200 °C as a slow, purging stream of argon was passed through the reaction vessel and into an acidified solution of 2,4-dinitrophenylhydrazine in ethanol. When gas evolution had ceased, 58 mg of acetaldehyde 2,4-dinitrophenylhydrazone (25%) was isolated, mp 161–163 °C (lit. 148, 168 °C) after recrystallization. It was identified by mixture melting point and ir spectral comparison.

Reactions of the Epoxyethylsilanes with Amines. A. Epoxyethyl(triphenyl)silane (2a). A solution of 3.0 g (10 mmol) of **2a** in 30 ml of benzylamine (distilled beforehand from phosphorus pentoxide) was heated at 160–165 °C for 12 h. Removal of the amine by distillation at reduced pressure and trituration of the solid residue with benzene gave a colorless powder, mp 218–222 °C (92%), which was recrystallized from xylene, mp 228–229 °C. By mixture melting point and infrared spectral comparison this substance was shown to be hexaphenyldisiloxane (**12**).[4]

In a search for intermediates, 1:1 and 1:2 neat mixtures of **2a** and benzylamine were heated in an NMR tube at 150–155 °C for various periods and then examined by NMR spectroscopy ($CDCl_3$). After 15–30 min new peaks appeared at 0.8 (d, J = 5 Hz), 1.05 (d, J = 5 Hz), 1.60 (d, J = 5 Hz, ca. thrice as intense as the other doublets), and 4.15 ppm (br, s, ca. same intensity as peak at 1.60). These peaks persisted up to 1 h, but after 45 min hexaphenyldisiloxane (**12**) began to precipitate. Attempts to isolate acetaldehyde 2,4-dinitrophenylhydrazone by treating the final reaction mixture with acidified, ethanolic 2,4-dinitrophenylhydrazine gave only solids melting over a broad range.

Similarly, heating a 1:1 mixture of **2a** and anhydrous morpholine at 150–155 °C for 15 min caused the appearance of new doublets in the NMR spectrum: 0.95 (J = 6 Hz) and 1.12 ppm (J = 6.5 Hz) in an intensity ratio of 2:1.

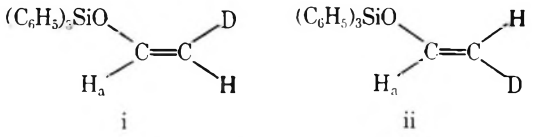
When a solution of **2a** (1.5 g, 5 mmol) and anhydrous piperidine (1 ml, 5 mmol) in 25 ml of xylene was heated at reflux for 10 h and the solvent then removed, dilution of the residue with ether gave 0.3 g of hexaphenyldisiloxane (**12**, 23%). Chromatography of the mother liquor on Florisil and elution with ether gave 0.9 g of impure triphenylsilanol (**4a**, 66%, mp 126–145 °C). This solid melted at 152–155 °C after recrystallization from cyclohexane.

B. *cis*-β-Trimethylsilylstyrene Oxide (5a). Heating 1:1 mixtures of **5a** and anhydrous benzylamine at 150–155 °C and monitoring periodically by NMR analysis revealed new peaks after 20 min: 0.4 (s), 0.45 (s), 0.48 (s), 2.12 (d, J = 5 Hz), 3.15 (br s), and 4.47 ppm (d, J = 5 Hz). The peaks at 2.12, 3.15, and 4.47 ppm were of the same intensity. After 60 min the epoxide peaks had almost disappeared and the singlet at 0.48 ppm had increased relative to that at 0.5 ppm.

A similarly conducted reaction between **5a** and anhydrous morpholine revealed after 45 min at 150–155 °C that new peaks developed at 0.40 (s), 0.45 (s), 0.64 (s), 3.33 (d, J = 5 Hz), and 4.32 ppm (d, J = 5 Hz).

Pyrolysis of Epoxyethyl(triphenyl)silanes. A. Undeuterated Silane (2a). A 200-mg sample of epoxyethyl(triphenyl)silane was heated in an NMR tube under a dry nitrogen atmosphere for 2 h at an oil bath temperature of 290 ± 10 °C. Cooling of the sample, dissolution in deuteriochloroform, and recording of the NMR spectrum showed that 40% of **2a** had isomerized to triphenyl(vinyloxy)silane (**13**).

B. α-Deuterioepoxyethyl(triphenyl)silane (2c). When this compound was heated at 275 ± 5 °C for 1.5 h, a 25% conversion to the corresponding triphenyl(vinyloxy)silane was realized. Doublets in relative intensities of 3:1 were observed at 4.05 and 4.53 ppm, which corresponded to the presence of i (J = 6 Hz) and ii (J = 14 Hz), respectively; a complicated multiplet ascribable to the H_a proton was centered at 6.35 ppm. In other runs, narrow multiplets were observable within the individual doublets centered at both 4.05 and 4.53 ppm. These multiplets indicate the probable presence of some $(C_6H_5)_3SiOCD{=}CH_2$. The ratio of such α-deuteriovinyloxy product to the total of the β-deuteriovinyloxy products was ca. 20:80.



C. α-Deuterioepoxyethyl(triphenyl)silane (2c) under Varying Conditions. There was some indication that thermal rearrangements occurred more readily when conducted in NMR tubes that had been soaked in chromic acid solution and just rinsed in distilled water. Accordingly, the following runs were conducted in NMR tubes which were cleaned in chromic acid solution, soaked in aqueous sodium bicarbonate solution, and repeatedly rinsed with distilled water.

Three comparative pyrolyses were carried out in NMR tubes on 100–200 mg of **2c** for 2 h at 270 ± 5 °C. Upon cooling an accurately known quantity of toluene was added (30–40 mg) as an internal standard, the sample diluted with a known quantity of deuteriochloroform, and the NMR spectrum recorded. The conditions of pyrolysis, percentage of **2c** remaining, percentage of vinyloxysilane, and ratio of β-cis:β-trans $(C_6H_5)_3SiO(D)C{=}CH_2$ pertinent to each run were the following: (1) under a nitrogen atmosphere, 55% of **2c**, 45% of **13** in a 66:33 ratio; (2) with 0.5% by weight of hydroquinone, 80% of **2c**, 20% of **13** in a 75:25 ratio; and (3) in air, 80% of **2c**, 20% of **13** in a 75:25 ratio (error limits of ±10%).

Rearrangement of α-Deuterioepoxyethyl(triphenyl)silane (2c) to β-Triphenylsilylacetaldehyde (10) by Means of Magnesium Bromide Etherate. Magnesium bromide etherate was prepared by adding ethylene bromide to a stirred suspension of an equivalent amount of magnesium turnings in dry diethyl ether. Then a solution of 1.20 g (4 mmol) of **2c** in 20 ml of benzene was treated with an excess of magnesium bromide etherate and the solution refluxed for 1 h. Workup according to a published procedure gave the aldehyde (**10**), whose NMR spectrum showed the characteristic doublet at 2.97 ppm

in addition to a broadened singlet within this doublet. At 9.61 ppm a clear doublet was evident (4 Hz). These signals are consistent with the presence of both $(C_6H_5)_3SiCHDCHO$ (**10a**) and $(C_6H_5)_3SiCH_2CDO$ (**10b**) in ca. equal amounts.

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Registry No.—**1a,** 18666-68-7; **1b,** 59231-24-2; **1c,** 59231-25-3; **2a,** 18666-55-2; **2b,** 59231-26-4; **2c,** 59231-27-5; **4a,** 791-31-1; **5a,** 56920-26-4; **5b,** 56920-25-3; **9,** 59231-28-6; **11,** 59231-29-7; (*E*)-trimethyl(β-styryl)silane, 19372-00-0; (*Z*)-trimethyl(β-styryl)silane, 19319-11-0; ethynyl(triphenyl)silane, 6229-00-1; diisobutylaluminum deuteride, 59231-30-0; α-deuteriovinyl chloride, 4984-12-7; phenyllithium, 591-51-5; tetraphenylsilane, 1048-08-4; diisobutylaluminum hydride, 1191-15-7; hydrogen chloride, 7647-01-0; chlorotriphenylsilane, 76-86-8; benzylamine, 100-46-9.

References and Notes

(1) Part 13 of the series "Organosilicon Compounds with Functional Groups Proximate to Silicon"; for previous parts, cf. J. J. Eisch et al., *J. Org. Chem.*, **28,** 487, 2870, 2876 (1963); **29,** 254 (1964); *J. Phys. Chem.*, **67,** 2362 (1963); *J. Organomet. Chem.*, **11,** P50 (1968); **20,** P9 (1969); **50,** C18 (1973); **50,** C23 (1973); as well as related articles on organoaluminum [*J. Org. Chem.*, **36,** 3520 (1971); *J. Am. Chem. Soc.*, **97,** 4673 (1973)] and organometallic rearrangement [*J. Am. Chem. Soc.*, **95,** 4065 (1973)] studies, which can be considered as parts in this series.
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(15) (a) A. W. P. Jarvie, *Organomet. Chem. Rev., Sect. A,* **6,** 153 (1970). (b) Present evidence does not permit any conclusion as to how important σ,π-conjugation from proximate silicon–carbon bonds might be in stabilizing the transition states leading to **15** and **16.** Such vertical stabilization may well be decisive in determining the mode of cleavage of silyl epoxides by electrophiles. Cf. N. A. Clinton, R. S. Brown, and T. G. Traylor, *J. Am. Chem. Soc.*, **92,** 5228 (1970).
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(17) (a) P. F. Hudrlik and D. Peterson, *J. Am. Chem. Soc.*, **97,** 1464 (1975). (b) The stereospecific syn elimination of trimethylsilanol, observed in the treatment of β-hydroxyalkylsilanes with potassium hydride in a tetrahydrofuran medium, may well ensue in a manner similar to that of pathway b in Scheme I, except that the carbanion resulting from the silicon–oxygen migration would have to be too short lived to undergo inversion. Alternatively, pathway a might be considered as offering a four-centered cyclic *intermediate* **19,** whose collapse would yield the olefin stereospecifically. However, orbital symmetry considerations would argue against a concerted passage from this planar intermediate to the olefin and the trialkylsilanoate anion, since this would be a thermally forbidden [$_\sigma 2_s + {}_\sigma 2_s$] process. Cf. R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1971, p 172.
(18) (a) J. K. Crandall and L.-H. C. Liu, *J. Am. Chem. Soc.*, **89,** 4527 (1967), have proposed the formation of such epoxide anions and carbenoids to explain the behavior of *tert*-butyllithium toward epoxides. (b) Ongoing studies in this laboratory have shown that the reaction of lithium alkyls with epoxyethyl(triphenyl)silane can, in certain solvents, pursue largely a different course: in ethyl ether or tetrahydrofuran the principal product is 1-hexen-2-yl(triphenyl)silane (>70% yield in THF), while in hexane the formation of *n*-butyl(triphenyl)silane is in accord with the pathway followed by phenyllithium (eq 15). Analogously, others have observed that epoxyethyl(trimethyl)silane and *tert*-butyllithium in THF yielded 3,3-dimethyl-2-butenyl(trimethyl)silane.[10] The action of Grignard reagents on these epoxides, as reported by these same workers to yield 1-trimethylsilyl-2-alkanols,[10] obviously involves magnesium bromide catalyzed isomerizations of these epoxides to the 2-silylacetaldehydes, as depicted in eq 11 for epoxyethyl(triphenyl)silane. As would be expected, magnesium halide free dialkylmagnesium reagents open such epoxides without rearrangement,[10] in the same manner as that of organocuprate reagents.[10]
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Demethylations of Quaternary Pyridinium Salts by a Soft Nucleophile, Triphenylphosphine. Electronic and Steric Accelerations[1]

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N-Methyl quaternary pyridinium salts are easily demethylated by PPh_3 in DMF. The relative rate constants are determined by NMR with a competition technique for 18 compounds. The range of reactivity is 10^3. The reaction is accelerated with electron-withdrawing substituents on the pyridine ring. The Hammett and Bronsted equation constants are $\rho = +2.34$; $\alpha = +0.387$. Ortho substituents increase the rate constants by strain release (a factor of 103 for the 2-*t*-Bu). The correlation with the opposite quaternization reactions is excellent (correlation coefficient $R = 0.994$). Linear free-energy relationships are obtained both with electronic and steric parameters, and give further insight into the structure of the transition state of these reactions.

Compared to the number of mechanistic and structural studies on the quaternization of pyridines,[3] no quantitative results have yet been reported for dequaternization of pyridinium salts.

Until recently no general method existed for N-dealkylation of quaternary salts of heteroaromatic amines. The techniques applied to ammonium salts are inadequate: they use hard nucleophiles and (or) high temperatures,[4–15] so that sensitive

Table I. Relative Rate Constants for Demethylation of Pyridinium Iodides by PPh_3 in Boiling DMF (153 °C)

Compd	Substituent on pyridine ring	k/k_H	pK_a of the pyridinium salt[22]	σ constants[23]
1	H	1	5.19	0
2	3,4-di-Me	0.255	6.48	−0.239[a]
3	3-NH_2	0.263	6.04	−0.16
4	3,5-di-Me	0.279	6.15	−0.138
5	4-Me	0.566	6.00	−0.170
6	3-Me	0.619	5.70	−0.069
7	2-Me	1.00	5.96	
8	2-Et	1.49	5.89	
9	3-$CONH_2$	2.37	3.35	0.28
10	2-*i*-Pr	2.88	5.83	
11	2-Ph	8.40	4.77	
12	3-Br	9.76	2.85	0.391
13	2-PhO	10.9		
14	3-Cl	6.68	2.81	0.373
15	2-*t*-Bu	50.2	5.76	
16	2-Cl	70.4	0.49	
17	2-CHO	74.2	3.77	
18	2-CN	163	−0.26	

[a] σ constants of di-Me are considered as additive.

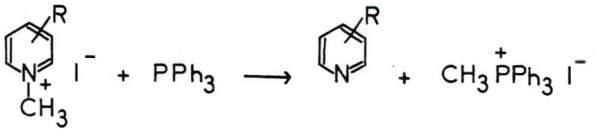
functions[4-6,8] as well as the heteroaromatic ring can be affected.[16] Recently soft nucleophiles (PPh_3, NH_2CSNH_2)[17] or DMF[18] were reported to give clean dealkylations.

We wish to report that the use of a soft nucleophile in an aprotic solvent permits the easy dealkylation of pyridinium salts. This study allowed us to determine the role of substitution on the behavior of these dealkylation reactions.

Results and Discussion

In Table I are reported the relative rate constants for the demethylation of 18 quaternary pyridinium iodides, including nine ortho-substituted compounds, by reaction with PPh_3 in DMF (Scheme I).

Scheme I



There is only evidence for a nucleophilic substitution by PPh_3 on the carbon atom of the methyl group, with displacement of the substituted pyridine.[19] Comparable yields of recovered amines are obtained with a reflux period much shorter than with DMF alone.[18]

The relative rate constants of demethylation have been measured by a competition technique[21] using the intensities of the N–Me NMR signals of each compounds and of a suitable standard. In the series studied there is a range of reactivity of 10^3. The relative values agree with preliminary reports which indicate an acceleration of the reaction with electron-withdrawing substituents.[18] However, the rate ratio of compounds **7** and **15** is good evidence that steric effects are also involved with ortho substituents.

With 3, 4, and 5 substituents there is a correct Hammett relation $\log k/k_H = \rho\sigma$ with a correlation coefficient $R = 0.971$ (Figure 1). The sign and magnitude of $\rho = +2.34$ is consistent with the direct displacement by PPh_3 of the substituted pyridine, since the positive charge of the nitrogen atom is released in part in the transition state.[24,37] Moreover, in the transition state of an SN2 process the C–N bond should be

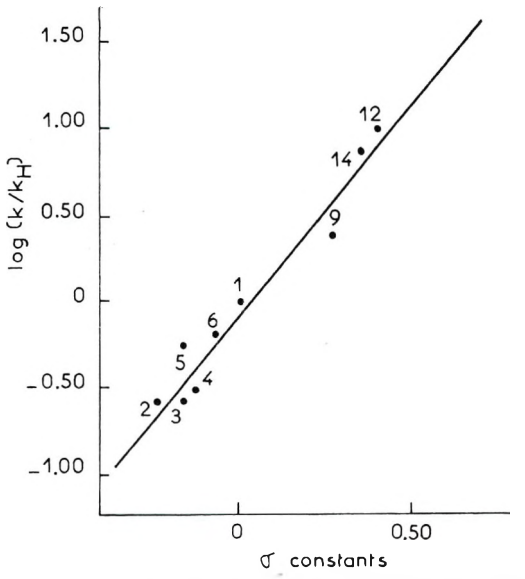


Figure 1. Plot of log (k/k_H) vs. Hammett substituent constants for the demethylation of 3- and 4-substituted pyridinium iodides by PPh_3. The numbers in the graph correspond to those in Table I.

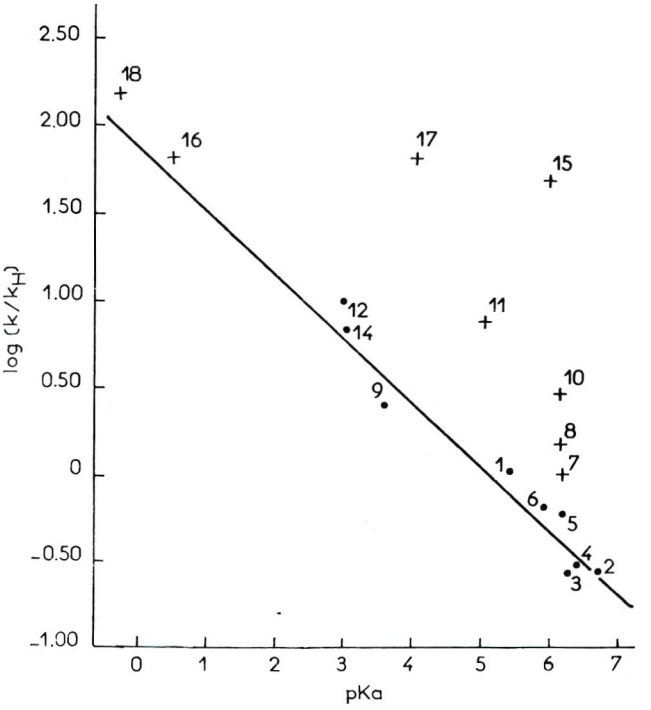
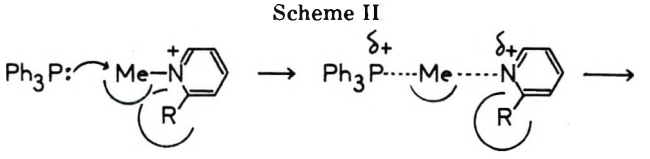


Figure 2. Plot of log (k/k_H) for demethylation of pyridinium iodides by PPh_3 vs. pK_a of the corresponding pyridinium ions. The numbers in the graph correspond to those of compounds in table I. Pyridinium salts are substituted in 2 position (+) or in 3, 4, or 5 position (●).

weakened and thus steric interactions of an ortho substituent with the methyl group be released in part (Scheme II).

Scheme II



The Bronsted relation (Figure 2) shows a good correlation ($R = 0.971$) with the 3 and 4 substituents. The slope $\alpha = 0.387$ corresponds to a lower reactivity for the more basic amines (the lower the pK_a, the better is the free base as leaving group).

Table II. Demethylation of Pyridinium Iodides vs. Methylation of Pyridines

Compd	Substituent on pyridine ring	Registry no.	Demethylation[a] k/k_H	Demethylation[a] $\log (k/k_H)$	Methylation[b,c] k/k_H	Methylation[b,c] $\log (k/k_H)$
1	H	110-86-1	1	0	1	0
2	3,4-di-Me	583-58-4	0.255	−0.593	4.23	0.626
3	3-NH_2	462-08-8	0.263	−0.580	4.01	0.603
4	3,5-di-Me	591-22-0	0.279	−0.554	3.97	0.599
5	4-Me	108-89-4	0.566	−0.247	2.22	0.346
6	3-Me	108-99-6	0.619	−0.208	2.08	0.318
9	3-$CONH_2$	98-92-0	2.37	0.376	0.375	−0.426
12	3-Br	626-55-1	9.76	0.989	0.100	−1.00
14	3-Cl	626-60-8	6.68	0.824	0.090	−1.05

[a] Of the *N*-methylpyridinium iodides by PPh_3 in boiling DMF (153 °C). [b] Of the corresponding pyridines by ICH_3 in CH_3CN at 30 °C. [c] The relative rates of methylation are very little solvent dependent in polar aprotic solvents.[31]

Table III. Demethylation vs. Methylation of Ortho-Substituted Pyridines

2 substituent	Demethylation[a] k/k_{Me}	Demethylation[a] $\log (k/k_{Me})$	Methylation[b] k/k_{Me}	Methylation[b] $\log (k/k_{Me})$
Me	1.00	0	1.00	0
Et	1.49	0.163	0.63	−0.20
i-Pr	2.88	0.459	0.13	−0.88
t-Bu	50.20	1.70	0.00068	−3.16

[a] Of the pyridinium iodide by PPh_3 in DMF at 153 °C. [b] Of the corresponding pyridine with ICH_3 in NO_2Ph at 30 °C.[27]

However, there is a reactivity higher than expected from the pure basicity for the 2 substituents. The steric accelerations by strain release of the ortho substituents can be evaluated from the deviations above the Bronsted plot and give the following values: Me = 2.4, Et = 3.4, *i*-Pr = 6.3, *t*-Bu = 103, Ph = 7.1, CHO = 26, Cl = 1.3, CN = 1.6.

The question remains of the scatter of the points for the 3 and 4 substituents in the Bronsted and Hammett relations; this scatter is of common occurrence, and appears when kinetic (k) and thermodynamic (σ, pK_a) data are compared.[25] It may be due, in part, to the fact that Hammett σ constants do not apply very well to pyridines.[26] The direct (N-methylations) and reverse (N-demethylations) reactions in the pyridine series should afford better relations since this is a comparison of two sets of kinetic data.

The results of quaternization by ICH_3 of 3- and 4-substituted pyridines are reported in Table II. There is an excellent relation (correlation coefficient R = 0.994) with the demethylation reactions by PPh_3 of the corresponding pyridinium iodides. The slope δ = −0.89 indicates a sensitivity to electronic effects of the same magnitude but of opposite sign (Figure 3).

The steric acceleration evidenced in Figure 2 may also be treated quantitatively through a linear free-energy relationship with ortho substituents of different size which bring almost no change to the basicity of the amine (e.g., the α series of Ingold: Me, Et, *i*-Pr, *t*-Bu). The results of demethylation vs. methylation of 2-alkylpyridines are reported in Table III. The excellent correlation observed (correlation coefficient R = 0.999) has a slope δ = −0.53, which means that the reactivity of ortho-substituted pyridines is decreased in quaternization reactions and increased in dequaternization reactions (Figure 4). The nonbonded interactions between the ortho-substituted pyridine and the methyl group lead to a steric compression (front strain)[28] in methylation reactions and to a steric decompression (relief of front strain)[29] in demethylations. The

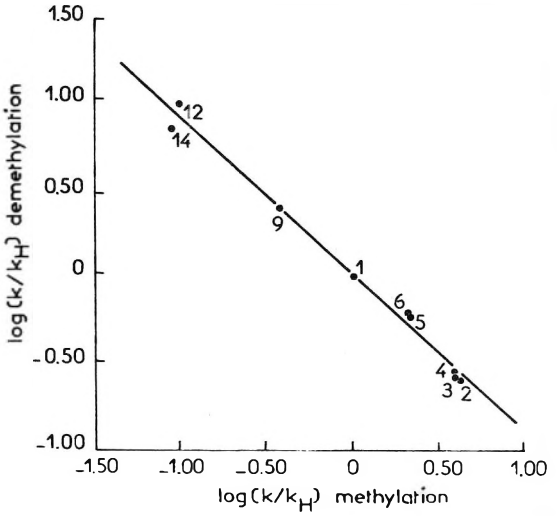


Figure 3. Plot of log (k/k_H) for demethylation of pyridinium iodides by PPh_3 vs. log (k/k_H) for methylation of the corresponding pyridines by ICH_3. The numbers in the graph correspond to those of compounds in Table III.

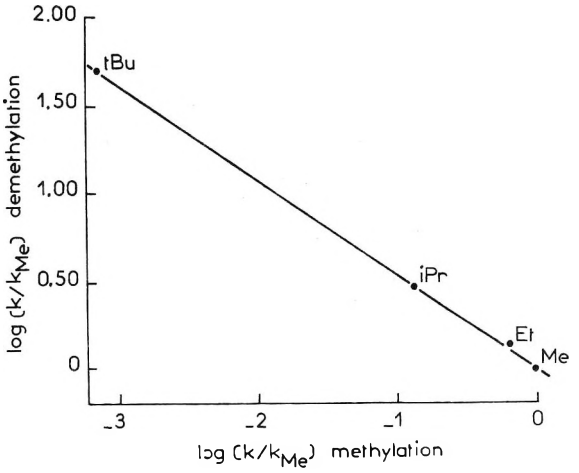


Figure 4. Plot of log (k/k_{Me}) for demethylation of 2-alkylpyridinium iodides by PPh_3 vs. log (k/k_{Me}) for methylation of the corresponding pyridines by ICH_3.

sensitivity to steric effects is twice as important in methylations as in demethylations.

Brown et al. measured the steric strains in transition states of N-methylations of ortho alkylpyridines and evaluated the steric strain in pyridinium salts by considering homomor-

phous complexes of pyridines and Lewis acids; they estimated the strain in the transition state of N-methylation reactions to be ⅔ of the strain of the final product.[30] Our present finding of a ratio of ⅓ to ⅔ in demethylation vs. methylation is in agreement with the above hypothesis.

The present study could also be applied to an evaluation of the position of the transition state, if one considers the dealkylation reaction as a reverse Menschutkin reaction. Indeed, recent results, obtained on quaternization of sterically crowded pyridines,[32] have shown that the position of the transition state could be estimated, in agreement with the Hammond postulate;[33] such an evaluation has also been possible, based on results of the Menschutkin reaction, by varying the nature of the leaving group of the alkylating agent.[34] Our present work on the dealkylation reaction could then be taken as a complement to these studies.[34,35]

In summary the use of a soft nucleophile PPh_3 allows the quantitative study of the dealkylation of pyridinium salts. With this method free-energy values can be obtained for the reversible process N-alkylation–N-dealkylation thus opening a new way for the quantitative study of the structure of the transition state in SN2 reactions.[36]

Experimental Section

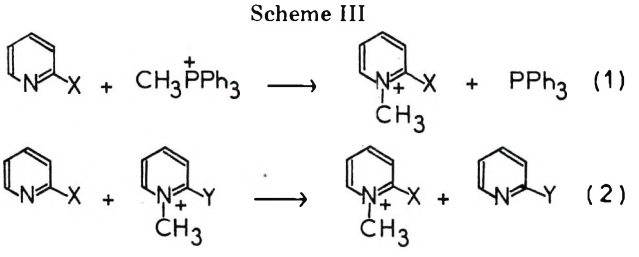
Materials. The methiodides were prepared according to literature data.[21,28] The DMF was dried over sodium carbonate, fractionally distilled and stored over molecular sieves. Fluka triphenylphosphine was used without further purification.

Relative Rate Determinations. The relative rates of demethylations were obtained by a competitive method. Pairs of salts were allowed to react with an excess of triphenylphosphine in DMF at the boiling point of the solvent (153 °C). After 25–70% reaction the consumption of the salt was determined by NMR analysis of the *N*-methyl signals. The ring protons of mesitylene were used as integration standard. The rate constant ratio (k_1/k_2) was calculated from the knowledge of the initial and final concentrations of the salts by the use of the equation

$$k_1/k_2 = \frac{\log (\text{salt}_1)_0/(\text{salt}_1)_t}{\log (\text{salt}_2)_0/(\text{salt}_2)_t}$$

The rate constant ratio determined at various stages of the reaction (25–70%) agreed to ±10%. NMR spectra and GC indicated that the reactions were clean, in accordance with previous studies.[17,18] Two possible side reactions were considered (Scheme III).

Scheme III



Path 1 is the reverse of the demethylation studied. Control experiments with the most reactive nucleophiles, pyridine and 2-methylpyridine, showed that no reaction of this type took place under the reaction conditions.

Path 2 was checked by treating the more nucleophilic pyridine with the easier demethylated salt of the pairs used in the demethylation experiments. Pairs on different level of the reactivity scale were studied. In all cases, except one, no cross methylation product was formed. When 1 mmol of 2-methylpyridine was allowed to react with 1 mmol of 1-methyl-2-isopropylpyridinium iodide in refluxing DMF and in the presence of triphenylphosphine, 90% of the salt was demethylated and ca. 4% of 1,2-dimethylpyridinium salt was indeed formed. This side reaction introduces an error of the same size as the error of the rate measurements (ca. 10%) and was neglected in the calculations.

A typical procedure for a demethylation reaction is as follows: 1–1.5 mmol of each salt, ca. 0.7 mmol of mesitylene, and ca. 5 mmol of triphenylphosphine were weighed into a 5-ml flask; 2 ml of DMF was added and the solution refluxed for 2 min to 5 h depending upon the reactivity of the salts. The reaction mixture was directly analyzed by NMR. The rate data are mean values of two to four, usually three, experiments. The spectra were recorded using a Perkin-Elmer R-32, JEOL HM-100, or a Varian EM-360 spectrometer.

Registry No.—**1**, 930-73-4; **2**, 6283-41-6; **3**, 7630-05-9; **4**, 22739-24-8; **5**, 2301-80-6; **6**, 10129-51-8; **7**, 872-73-1; **8**, 52806-01-6; **9**, 6456-44-6; **10**, 54125-84-7; **11**, 52806-02-7; **12**, 32222-42-7; **13**, 58801-92-6; **14**, 32188-17-3; **15**, 58801-93-7; **16**, 14338-32-0; **17**, 3784-97-2; **18**, 3785-03-3; PPh_3, 603-35-0; ICH_3, 74-88-4.

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Synthesis and Stereochemistry of (*E,E*)-1,4-Diacetoxy-2-methyl-1,3-butadiene and Related Compounds

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Enol acetylation of aldehyde **2**, prepared from **1** by SeO_2 oxidation, has led to crystalline (*E,E*)-1,4-diacetoxy-2-methyl-1,3-butadiene (**6**) together with lesser amounts of the *Z,E* isomer **7** and the *E,Z* isomer **8**. The overall yield of **6** + **7** + **8** from isoprene was about 20%. Stereochemical assignments followed from the uv and NMR spectra of the dienes and constituted a revision of an earlier assignment.[2] Unlike dienes **7** and **8**, diene **6** was at least as reactive in a Diels–Alder reaction toward benzoquinone as the known *E,E* diene **10**. The *E,E* stereochemistry of **6** was confirmed by conversion of **6** into diacetate **14** and diol **20**. These latter two substances were prepared from diene **16** via photooxygenation followed by reduction and acetylation.

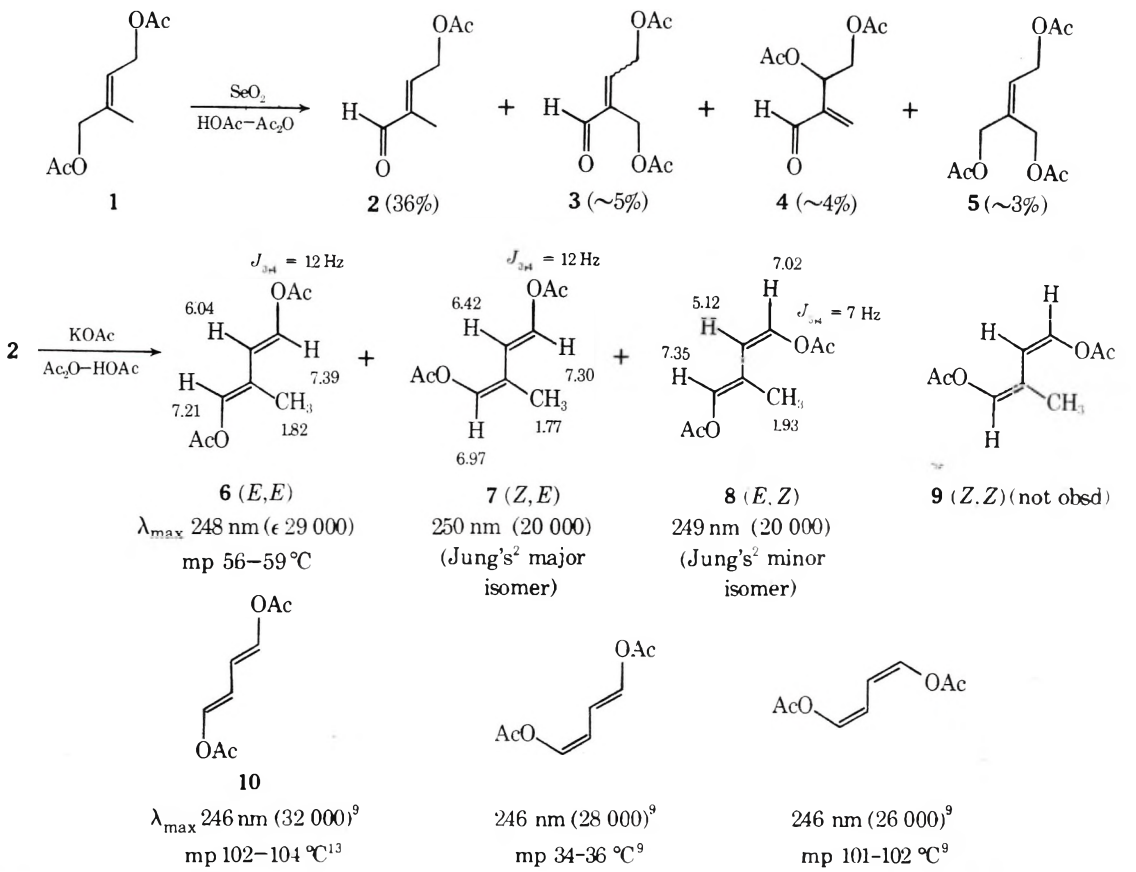
Recently, Jung[2] described a stereoselective synthesis of two oily isomers of 1,4-diacetoxy-2-methyl-1,3-butadiene. The *E,E* stereochemistry **6** and the *Z,Z* stereochemistry **7** were assigned to these substances based primarily on the NMR spectra of the substances and their tricyclic precursors. In connection with our synthetic program related to tetrodotoxin,[3] we have prepared (*E,E*)-1,4-diacetoxy-2-methyl-1,3-butadiene (**6**), mp 56–59 °C, by a different route and find the substance to be neither of those isomers previously described.[2] Herein, we describe our synthesis of **6** together with chemical and spectroscopic evidence which permits stereochemical assignment of all three presently known isomers of 1,4-diacetoxy-2-methyl-1,3-butadiene.

In our approach diacetate **1**[4] (predominantly the *E*[5] isomer) (Chart I), readily prepared by bromination[6] (84% yield) of isoprene followed by reaction (95% yield) of the dibromide mixture with KOAc–HOAc,[4] was oxidized with SeO_2 in HOAc–Ac_2O, producing the known[7] aldehyde **2** as the predominant product together with small quantities of aldehydes **3** and **4** and triacetate **5**. The structures of the latter three compounds followed from the analytical and spectral data given in the Experimental Section. Conversion of aldehyde **2** into a mixture of diacetoxydienes **6**, **7**, and **8** (67:16:17) was accomplished in 81% yield (after distillation) (20% overall from isoprene) by reaction of **2** with KOAc–Ac_2O–HOAc.[8] Upon cooling the isomeric mixture to −4 °C, the *E,E* isomer separated out as white crystals, obtained in 10% yield, mp 56–59 °C, after sublimation.

The stereochemical assignments shown in Chart I were deduced from the uv and NMR spectra as follows. Of the three isomers, crystalline **6** has the largest molar extinction coefficient in its uv spectrum. In the normethyl isomer series, crystalline (*E,E*)-1,4-diacetoxy-1,3-butadiene (**10**) also shows the largest ϵ value.[9]

With NMR spectra of three of the four possible *E,Z* isomers of 1,4-diacetoxy-2-methyl-1,3-butadiene in hand, one can

Chart I

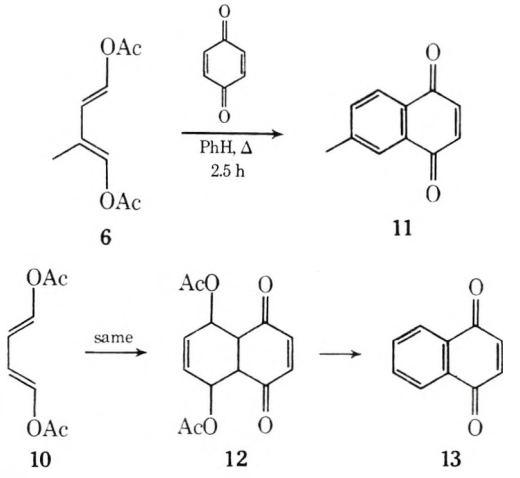


complete the stereochemical assignments by noting that in a conjugated diene, a vinyl proton cis to the other carbon–carbon double bond should be more deshielded than a proton in the trans position.[10] Secondly, a vinyl proton cis to an acetoxy group attached to the same double bond should be more deshielded than a corresponding trans proton.[11]

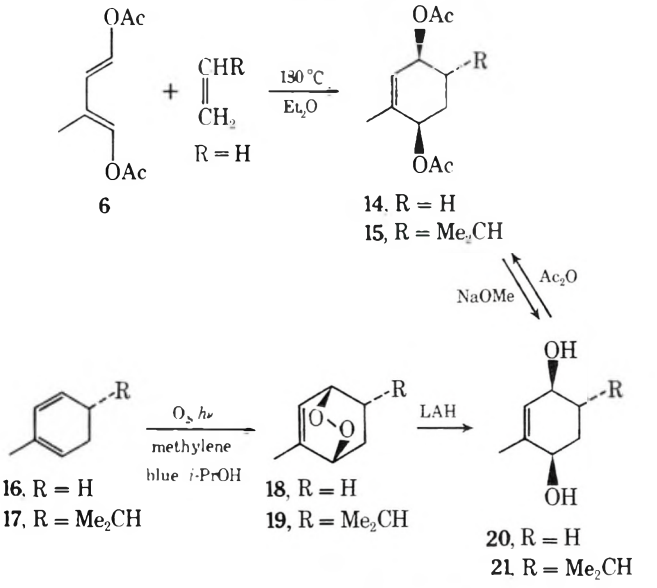
An inspection of the NMR data included with structures **6**, **7**, and **8** in Chart I shows the stereochemical assignments to be completely consistent with these earlier observations. It is clear from the magnitudes of $J_{3,4}$ that the *E* configuration about the $\Delta^{3,4}$ double bond obtains in isomers **6** and **7**. One would therefore predict that since H-3 is cis to the C-4 acetoxy group in **6** and **7**, the resonance (6.04 and 6.42 ppm, respectively) for this proton should appear at lower field than that of H-3 (5.12 ppm) in isomer **8**. Also, since H-4 is cis to the other carbon–carbon double bond in **6** and **7**, the resonance (7.39 and 7.30 ppm, respectively) for this proton should appear at lower field than that of H-4 (7.02 ppm) in isomer **8**. Both predictions are correct.

In order to assign the configuration about the $\Delta^{1,2}$ double bond in these isomers, one observes that H-1 appears at 7.21 and 7.35 ppm in compounds **6** and **8**, consistent with H-1 being cis to the other carbon–carbon double bond in these isomers. However, a value of 6.97 ppm for H-1 in isomer **7** requires that this isomer have the *Z* configuration about the $\Delta^{1,2}$ double bond. Based on these assignments, the major isomer of Jung[2] is the *Z,E* isomer **7**. Jung's minor isomer is the *E,Z* isomer **8** and our crystalline isomer is the *E,E* isomer **6**.

The following chemical evidence also corroborates the stereochemical assignments above. While Jung's major isomer **7** was unreactive toward benzoquinone in boiling benzene (no reaction after 18 h),[2] our *E,E* isomer **6** was at least as reactive as (*E,E*)-1,4-diacetoxy-1,3-butadiene (**10**).[13] Reaction was complete after 2.5 h, **6** affording naphthoquinone **11** in good yield and **10** affording the rather unstable, crystalline adduct **12** which slowly aromatized in solution to **13**. Hill and Carlson[12] have also described this latter reaction, obtaining directly naphthoquinone **13** together with small amounts of anthroquinone.



An independent confirmation of the *E,E* stereochemistry of **6** was obtained as follows. Reaction of **6** with ethylene at 180 °C afforded Diels–Alder adduct **14** in good yield. Methanolysis (NaOMe, MeOH) of **14** produced diol **20**. These latter two substances were synthesized by a stereospecific route which paralleled the known photooxygenation and subsequent transformations of α-phellandrene (**17** → **19** → **21** → **15**).[14] Thus, photooxygenation of 2-methyl-1,3-cyclohexadiene (**16**)[15] followed by reduction of the resulting epidioxide **18** with $LiAlH_4$ led to diol **20**. Both diol **20** and its diacetate **14** obtained in this way were identical with those substances obtained by the Diels–Alder reaction.



Crystalline **6** shows evidence of decomposition after exposure to air for 1 h. Samples stored in sealed vials at −20 °C show discoloration after several days. Crude samples are best sublimed and then stored at −20 °C under frozen cyclohexane. However, in view of the superior reactivity of *E,E* isomer **6** in the Diels–Alder reaction, the distilled mixture of isomers (see above) is probably suitable for many synthetic purposes.

Experimental Section[16]

Oxidation of Diacetate 1 with SeO_2. A. (*E*)-4-Acetoxy-2-methyl-2-butenal (2). A mixture of 64.4 g (0.345 mol) of freshly distilled 1,4-diacetoxy-2-methyl-2-butene[4] (**1**) (~4:1 *E:Z* by NMR), 32.7 g (0.294 mol) of SeO_2, 16 ml of Ac_2O, and 160 ml of HOAc was heated with stirring under N_2 at 115 °C for 3 h. The precipitated black Se (14.96 g, 65% based on SeO_2) was removed by filtration. Distillation of the filtrate through a heated column afforded crude **2** in two fractions, 16.57 g [bp 90–95 °C (12 mm)] and 2.80 g [bp to 70 °C (0.05 mm)]. A high-boiling fraction [bp 70–120 °C (0.05 mm)] was collected (20.63 g) and retained for further separation (see below). Redistillation of crude **2** afforded 17.8 g (36%) of **2**, bp 88–96 °C (12 mm) [lit.[7] bp 66–72 °C (2 mm)]; 2,4-DNP mp 164–166 °C (lit.[7] mp 166 °C).

The high-boiling fractions from two similar preparations of **2** were combined, amounting to 41.3 g. This mixture came from a total of 119 g of **1** and by NMR was about 1:1:1 **3:4:5**. Repeated distillation (see below) afforded fractions enriched in one or the other of the components.

B. 2-(Acetoxymethyl)-4-acetoxy-2-butenal (3). A 6.03-g fraction (5%), bp 82–90 °C (0.025 mm), was obtained by spinning band distillation and was shown to be essentially pure **3** by VPC on column B at 185 °C (t_R 4.0 min). Preparative VPC produced an analytical specimen as a colorless oil: NMR δ 2.06 (s, 3, Ac), 2.13 (s, 3, Ac), 4.86 (s, 2, CH_2), 5.05 (d, J = 6 Hz, 2, CH_2), 6.72 (t, J = 6 Hz, 1, vinyl), 9.50 (s, 1, CHO); ir 2815, 1745, 1695 cm^{-1}; uv max 218 nm (ε 11 500).

Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.04. Found: C, 53.82; H, 6.05.

A 2,4-DNP derivative was prepared by the method of Pattenden,[7] mp 151–153 °C (orange plates from MeOH).

Anal. Calcd for $C_{15}H_{16}N_4O_8$: C, 47.37; H, 4.24. Found: C, 47.42; H, 3.93.

C. 3,4-Diacetoxy-2-methylenebutanal (4). A 5.30-g fraction (4%), bp 62–73 °C (0.025 mm), was obtained by spinning band distillation and was shown to be essentially pure **4** by VPC on column B at 185 °C (t_R 2.0 min). A pure sample of **4** was obtained as a colorless oil by preparative VPC: NMR δ 2.05 (s, 3, Ac), 2.12 (s, 3, Ac), 4.29 (d, J = 5 Hz, 2, CH_2), 5.87 (t, J = 5 Hz, 1, H-3), 6.24 (bs, 1, vinyl), 6.52 (bs, 1, vinyl), 9.58 (s, 1, CHO); ir (film) 2830, 1750, 1690 cm^{-1}; uv max 212 nm (ε 8100).

A 2,4-DNP derivative was prepared by the method of Pattenden,[7] mp 170.5–171.5 °C (yellow needles from MeOH).

Anal. Calcd for $C_{15}H_{16}N_4O_8$: C, 47.37; H, 4.24. Found: C, 47.29; H, 4.20.

D. 1,4-Diacetoxy-2-(acetoxymethyl)-2-butene (5). A 3.9-g fraction (3%), bp 100–110 °C (0.025 mm), was obtained by spinning band distillation and was shown to be essentially pure **5** by VPC analysis on column B at 185 °C (t_R 5.8 min). Preparative VPC pro-

duced the analytical specimen of **5** as a colorless oil: NMR δ 2.06–2.08 (s, 9, Ac), 4.63 (s, 2, CH_2), 4.71 (s, 2, CH_2), 4.75 (d, J = 6 Hz, 2, CH_2), 5.87 (bt, J = 6 Hz, 1, vinyl); ir 1740, 1230 cm^{-1}; no uv max; MS *m/e* 244.092 (calcd for $C_{11}H_{16}O_6$, 244.095), 184, 171, 129.

(*Z*)-1,4-Diacetoxy-2-methyl-2-butene. A 1.51-g sample of (*Z*)-2-methyl-2-butene-1,4-diol[6] was treated with 1.50 g of KOAc (fused) in 3.0 ml of Ac_2O at 100 °C for 1 h. The mixture was diluted with Et_2O and $CHCl_3$ and the salt was removed by filtration. Distillation afforded 1.66 g (60%) of the title compound, bp 60–63 °C (0.10 mm). Preparative VPC afforded the analytical sample as a colorless oil: NMR δ 1.82 (s, 3, Me), 2.04 (s, 3, Ac), 2.07 (s, 3, Ac), 4.65 (s, 2, CH_2), 4.67 (d, J = 7 Hz, 2, CH_2), 5.59 (t, J = 7 Hz, 1, vinyl).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.72; H, 7.75.

(*E,E*)-1,4-Diacetoxy-2-methyl-1,3-butadiene (6). A solution of 3.91 g (27.6 mmol) of freshly distilled aldehyde **2** and 4.5 g (46 mmol) of KOAc (fused) in 5 ml of HOAc and 40 ml of Ac_2O was heated at 100–115 °C under N_2 for 19 h. Dilution with $CHCl_3$, removal of the salts by filtration, and distillation of the filtrate through a heated column produced 4.11 g (81%) of a mixture of **6, 7,** and **8,** bp 63–65 °C (0.03 mm). An average of five integrations of the C-3 protons in the NMR spectrum indicated the isomeric composition of the mixture to be 67% (*E,E*)-**6,** 16% (*Z,E*)-**7** and 17% (*E,Z*)-**8.** Upon standing overnight at −4 °C the mixture crystallized. The mass was warmed to 25 °C, slurried, and then filtered, washing with cyclohexane. The crystals were immediately sublimed (bath 50 °C, 0.005 mm), producing 532 mg (10%) of pure **6:** mp 53–58 °C; NMR δ 1.82 (s, 3, Me), 2.15 (s, 3, Ac), 2.18 (s, 3, Ac), 6.04 (d, J = 12 Hz, 1, H-3), 7.21 (s, 1, H-1), 7.39 (d, J = 12 Hz, 1, H-4); ir ($CHBr_3$) 1745, 1633, 1370, 1220, 930 cm^{-1}; uv max 248 nm (29 000); MS *m/e* 184.075 (calcd for $C_9H_{12}O_4$, 184.074), 142, 100. Our best sample of **6** showed mp 56–59 °C.

Relative Reactivities of Diene 6 and Diene 10 toward Benzoquinone. The reactions were run in NMR tubes following the procedure of Jung.[2] Tube I contained 17 mg (0.10 mmol) of diene **10** and 11 mg (0.10 mmol) of benzoquinone in 0.30 ml of CCl_4 (containing 3 drops of $CHCl_3$ per milliliter); tube II contained 17 mg (0.10 mmol) of diene **10** and 11 mg (0.10 mmol) of benzoquinone in 0.30 ml of benzene; tube III contained 23 mg (0.13 mmol) of diene **6,** mp 56–59 °C, and 14 mg (0.13 mmol) of benzoquinone in 0.38 ml of benzene; tube IV contained 22 mg (0.12 mmol) of diene **6** and 13 mg (0.12 mmol) of benzoquinone in 0.36 ml of CCl_4 (containing 3 drops of $CHCl_3$ per milliliter). All tubes were placed in an oil bath maintained at 86 ± 1 °C. The crystalline dienes dissolved on heating. After 2.5 h the tubes were cooled to 25 °C.

A. 5ξ,8ξ-Diacetoxy-5,8,9β,10β-tetrahydro-1,4-naphthoquinone (12). The solvent was removed from the crystalline mass obtained upon cooling tube I. THe 28-mg residue was essentially pure **12** by NMR. Crystallization from EtOAc–hexane afforded 13 mg, mp 90–94 °C. Recrystallization from $CHCl_3$–hexane afforded the analytical sample of **12:** mp 99–101 °C; NMR δ 2.02 (s, 6, OAc), 3.72 (dd, J = 2 and 4 Hz, 2, H-9, 10), 5.42 (dd, J = 2 and 4 Hz, 2, H-5, 8), 6.02 (bs, 2, H-6, 7), and 6.76 (s, 2, H-2, 3); uv max 233 nm (ϵ 8350) and 330 (570); MS *m/e* 278.078 (calcd for $C_{14}H_{14}O_6$, 278.079), 236, 219, 176, 136.

The NMR spectrum observed directly on tube II indicated that only quinone **12** was present. The solution darkened upon standing and the formation of quinone **13** was shown by the NMR spectrum. Chromatography over silica gel afforded 9 mg (50%) of yellow, crystalline quinone **13.** Sublimation afforded a sample of mp 116–120 °C (lit.[17] mp 125–126 °C).

B. 6-Methyl-1,4-naphthoquinone (11). The solvent was removed from tube III. An NMR spectrum of the residue showed that quinone **11** was the major product. The sample was combined with tube IV and chromatographed, affording 25 mg (73%) of quinone **11.** Sublimation afforded yellow crystals, mp 88–90 °C (lit.[18] mp 90–91 °C).

***cis*-3,6-Diacetoxy-1-methylcyclohexene (14).** A 1-l. high-pressure hydrogenation reactor was charged with 90 ml of ether and 1.426 g (7.75 mmol) of diene **6,** mp 50–57 °C. The reactor was sealed and pressurized with ethylene (cylinder pressure, 80 atm) (ca. 3 mol of ethylene added). The reactor was heated at 180–190 °C for 53 h (occasional agitation). After cooling, the reactor was vented and the contents were filtered. The filtrate was concentrated and distilled, affording 1.168 g (71%) of adduct **14** as a colorless oil, bp 65–69 °C (0.03 mm). A portion was chromatographed over silica gel and then purified by preparative VPC on column B at 180 °C (t_R 2.5 min): NMR δ 1.72 (s, 3, Me), 1.88 (m, 4, CH_2), 2.06 (s, 3, Ac), 2.10 (s, 3, Ac), 5.22 (m, 2, H-3, 6), 5.79 (m, 1, vinyl).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.55. Found: C, 62.34; H, 7.50.

***cis*-1-Methylcyclohexene-3,6-diol (20).** A solution of 982 mg (4.56 mmol) of diacetate **14** in 10 ml (9.2 mmol) of 0.92 M NaOMe in MeOH was stirred at 0 °C for 1 h and then neutralized with HOAc and evaporated. The oily residue was chromatographed over silica gel. Elution with EtOAc afforded 495 mg (97%) of pure diol **20** as a colorless oil: NMR δ 1.82 (m, 7), 3.9–4.2 (m, 2, H-3, 6), 5.60 (m, 1, vinyl); MS *m/e* 128.085 (calcd for $C_7H_{12}O_2$, 128.084), 118, 95.

Diol 20 and Diacetate 14 from Photooxygenation of Diene 16. The procedure of Stolow[14] was followed. An ice-cooled solution of 100 mg of diene **16,** obtained[15] by preparative VPC, and 1 mg of methylene blue in 50 ml of isopropyl alcohol was irradiated with a 275-W GE sun lamp in the presence of excess O_2. When the chromophore at 259 nm reached a minimum (75 min), the solution was evaporated, giving 64 mg of a blue oil. Preparative TLC produced 28 mg (21%) of pure epidioxide **18** as a colorless, sharp-odored oil: NMR δ 1.45 (d, J = 8 Hz, 2, H-7, 8), 1.95 (d, J = 2 Hz, 3, Me), 2.25 (d, J = 8 Hz, 2, H-7, 8), 4.44 (bs, 1, H-1), 4.59 (bd, J = 6 Hz, 1, H-4), 6.30 (bd of q, J = 2 and 6 Hz, 1, H-3).

The entire sample was dissolved in 5 ml of ether and treated with 10 mg of $LiAlH_4$. After 1 h at 25 °C the usual workup afforded 25 mg (88%) of diol **20,** identical with the hydrolyzed Diels-Alder product (see above) by NMR, ir, and TLC behavior. Acetylation of diol **20** (prepared from epidioxide **18**) afforded 38 mg (90%) of diacetate **14,** identical with the Diels-Alder product by NMR, ir, TLC, and VPC behavior.

Acknowledgment. We thank the National Science Foundation (09413) for generous financial support.

Registry No.—*E*-**1,** 59054-99-8; *Z*-**1,** 59055-00-4; **2,** 26586-02-7; **3,** 59055-01-5; **3** 2,4-DNP, 59055-02-6; **4,** 59055-03-7; **4** 2,4-DNP, 59055-04-8; **5,** 59055-05-9; **6,** 52884-86-3; **10,** 15910-11-9; **12,** 59055-06-0; **14,** 59055-07-1; **16,** 1489-57-2; **18,** 59055-08-2; **20,** 59055-09-3; (*Z*)-2-methyl-2-butene-1,4-diol, 40560-13-2.

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Spiro Piperidines. 1. Synthesis of Spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ones, Spiro[isobenzofuran-1(3*H*),4′-piperidines], and Spiro[isobenzotetrahydrothiophene-1(3*H*),4′-piperidines][1]

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Improved synthetic procedures for spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ones (**3**) and spiro[isobenzofuran-1(3*H*),4′-piperidines] (**5**) are described. Elaboration of o-bromobenzyl mercaptan by conversion to o-lithiobenzyl mercaptide can be effected at very low temperature (−100 °C) without appreciable alkylation of mercaptide by *n*-butyl bromide, formed by exchange with *n*-butyllithium. Preparations of new systems including spiro[isobenzotetrahydrothiophene-1(3*H*),4′-piperidines] (**27**) and imines of spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (**13**) are described.

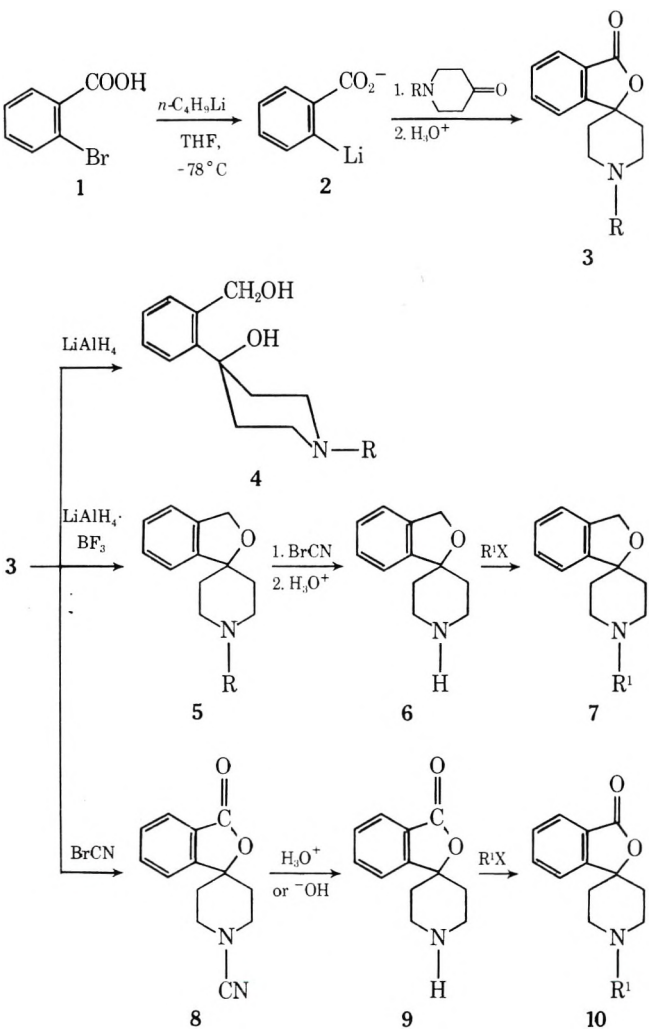
The preparation of the spiro[isobenzofuran-1(3*H*),4′-piperidine] ring system was recently described for the first time.[3] Intermediate spirophthalides of type **3** were prepared by initial reaction of the magnesium derivative of 2-(2-bromophenyl)-4,4′-dimethyloxazoline (Meyers method[4]) with *N*-alkylpiperidones, a process which gave low yields (~35%) because of competing enolization of the ketone, or, more conveniently, by initial reaction of the lithium salt of 2-lithio-*N*-phenylbenzamide[5] with the corresponding piperidones (~50% yield). We have had a continuing interest[2,3b] in this heterocyclic system and wish to report improved procedures for its preparation, as well as the syntheses of related materials including new sulfur analogues.

The sequence shown in Scheme I was developed as part of our elaboration of isomeric bromobenzoic acids by halogen–metal exchange at low temperature,[6] and has the advantages that (a) no blocking of the carboxylic acid group other than conversion to carboxylate is required, (b) enolization of the ketone is not a serious side reaction with lithium reagents since good yields of phthalides **3** result, and (c) the method can theoretically be extended to a variety of substituted *o*-bromobenzoic acids since it is now known that at very low temperature many reactive groups (COO^-,[6] NO_2,[7] CN,[8] CH_2Cl[9]) do not react with *n*-butyllithium. The ketones employed in this work were cyclohexanone, *N*-methyl-4-piperidone, and tropinone; lactones prepared in this way are described in entries 1–3 of Table I.

Reduction of **3** (R = CH_3) with $LiAlH_4$ gave diol **4** in 86% yield while reduction with $LiAlH_4$ in the presence of boron trifluoride etherate[11] gave **5** (R = CH_3) in 76% yield. Phthalan **5** (R = CH_3) had previously been prepared[3] as its hydrochloride and was obtained in good yield by reduction of **3** (R = CH_3) with diborane. Similarily, reduction of lactone **11** (Table I) gave the corresponding spirotropane **12** (entry 7, Table I) in 81% yield. Both lactone **3** (R = CH_3) and phthalan **5** are efficiently demethylated in high yield (see Table I) to **9** and **6**, respectively, by reaction with cyanogen bromide[12] with subsequent removal of the *N*-cyano function by acid or base hydrolysis.

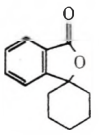
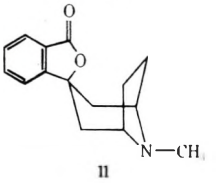
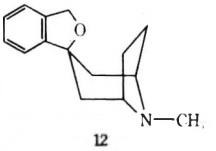
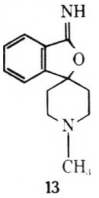
The sequence shown in Scheme I would appear to be the method of choice for the preparation of compounds of type **3**–**10** for those cases where starting bromo acids (**1**) are readily available. A modification of this sequence based on our reported utilization of 2-lithiobenzonitrile[8a] also provides ready access to the hitherto unknown imine derivatives of spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ones. This concept was demonstrated by preparation of **13** (entry 9, Table I) in 72% yield from 2-lithiobenzonitrile and *N*-methyl-4-piperidone.

Scheme I



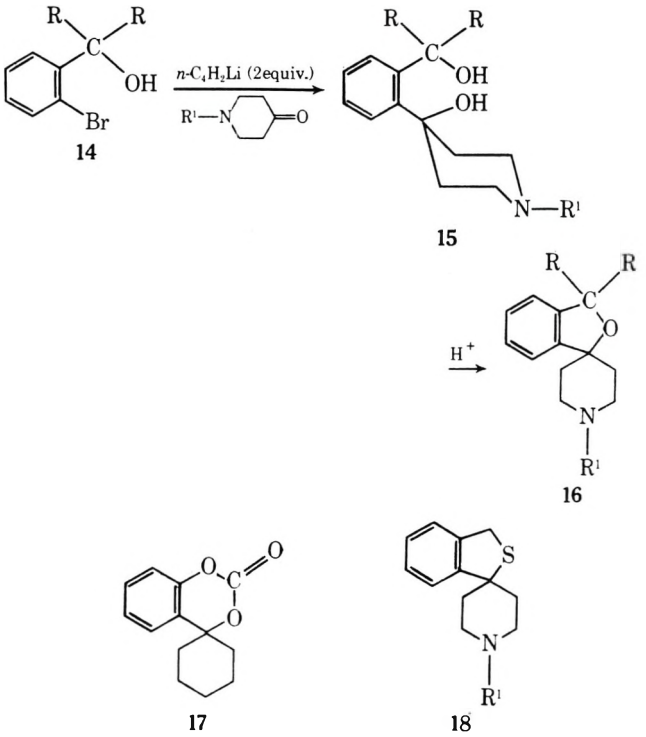
Prior to our development of low-temperature halogen–metal exchange for isomeric bromobenzoic acids,[6] we explored an alternate route to spiro[isobenzofuran-1(3*H*),4′-piperidines] (**16**), spirocarbonates (**17**), and the hitherto unknown spiro[isobenzotetrahydrothiophene-1(3*H*),4′-piperidines] (**18**) as illustrated in Scheme II. The route shown in Scheme II is an extension of that described[13] for the preparation of carbocyclic diols and phthalans. Diols **15**, together with related compounds prepared in this way, are shown in Table II.

Table I. Lactones and Phthalans from Scheme I[10]

Entry	Reactants	Product	Yield, %	Mp, °C
1	Cyclohexanone + **2**		69	81–82[a,b]
2	*N*-Methylpiperidone + **2**	**3** (R = CH_3)	61	151–152[c,d]
3	Tropinone + **2**	 **11**	58	134–135[e]
4	**3** (R = CH_3) + BrCN	**8**	77	182–183[c]
5	**8** + H_3O^+	**9**	83	132–133[c]
6	**3** + $LiAlH_4 \cdot BF_3$	**5**	82	78–80[f]
7	**11** + $LiAlH_4 \cdot BF_3$	 **12**	81	60–62[g]
8	**5** (R = CH_3) + BrCN then H_3O^+	**6**	76	84–86[f]
9	*o*-Bromobenzonitrile + *n*-C_4H_9Li (1 equiv) at −100 °C, then *N*-methylpiperidone	 **13**	72	96–99[a] [137–142 °C (0.03 Torr)]

[a] From ligroin (bp 60–90 °C). [b] $\nu_{C=O}$ 1740 cm^{-1}. [c] From $CHCl_3$–ligroin (bp 30–60 °C). [d] $\nu_{C=O}$ 1750 cm^{-1}; lit.[3a] mp 147–148 °C. [e] From H_2O. [f] By sublimation at 60–65 °C (0.02 Torr). [g] By sublimation of crude solid (mp 53–55 °C) at 50 °C (0.02 Torr).

Scheme II



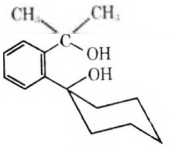
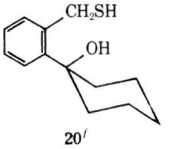
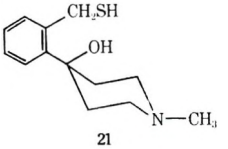
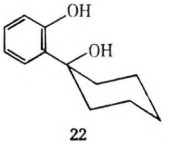
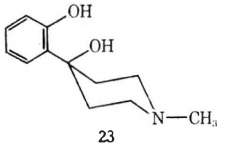
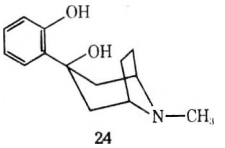
Attention should be called to the temperature sensitivity of the reaction involving halogen–metal exchange of 2-bromobenzyl mercaptan leading to **20** and **21** (entries 5 and 6, Table II). These reactions were carried out at −100 °C; at higher temperatures (−78 °C) the products were contaminated by products derived by butylation of mercaptide ion with *n*-butyl bromide formed during exchange with *n*-butyllithium. Such alkylation did not occur at −100 °C. The yields of phenols (entries 7–9), prepared by initial lithium–bromine exchange using *o*-bromophenol at −20 °C, were generally low; some dehydration of the tertiary alcohol occurred during processing. The alkenes formed in this way were prepared in high yield (see Experimental Section) by dehydration of **22–24** with 2 N sulfuric acid.

The cyclic carbonate **17** (Scheme II) was prepared in 43% yield by reaction of **22** (entry 7, Scheme II) with phosgene (THF at 0 °C); however, dehydration occurred in similar reactions with the amino diols **23** and **24** leading to alkenes and the corresponding carbonates were not obtained.

The hitherto unknown spiro[isobenzotetrahydrothiophene-1(3*H*),4′-piperidine] (**18**) (Scheme II) as well as a number of related phthalides and phthalans were prepared by reaction of the corresponding mercapto alcohols or diols shown in Table II with mild acid; yields and conditions are summarized in Table III. While the sequence **14** → **15** → **16** gives excellent yields in some cases, and provides considerable latitude as to substitution (i.e., dialkylphthalans of type **28** and **29**, and sulfur analogues such as **25** and **27**), the sequence is not as convenient as that shown in Scheme I for the preparation of diols of type **4** or phthalans of type **5**.

A variety of alkyl or acyl derivatives of the demethylated spiro piperidine **6** and spiro piperidone **9** were also prepared

Table II. Diols and Related Materials from Scheme II[10]

Entry	Product	Yield, %	Mp (or bp), °C
1	**15** (R = H; R′ = CH_3)	51	138.5–140[a]
2	**15** (R = H; R′ = $CH_2C_6H_5$)	60	132–135.5[c]
3	15 (R = R′ = CH_3)	71	130[d]
4	 **19**	70	152.5[e]
5	 **20**[f]	60	(110–113, 0.09 Torr)
6	 **21**	43	151–152[e]
7	 **22**	57–80	111–112[e]
8	 **23**	29	175–176[g] 169–170[h]
9	 **24**	20	168–169[h]

[a] From EtOH–C_6H_6. [b] The same product obtained in 86% yield from **3** was recrystallized from $CHCl_3$–ligroin (bp 30–60 °C). [c] Hexane–acetone. [d] Ligroin (bp 30–60 °C). [e] $CHCl_3$–ligroin (bp 30–60 °C). [f] From *o*-bromobenzyl mercaptan, *n*-butyllithium (2 equiv) at −100 °C and ketone. [g] From acetone. [h] Analytical sample sublimed at 130 °C (0.02 Torr). [h] From acetone.

by alkylation or acylation; products, together with conditions employed, are shown in Table IV.

Experimental Section

Synthesis of Spiro Lactones. General Procedure. 1′-Methylspiro[isobenzofuran-1(3*H*)-4′-piperidin]-3-one (3, R = CH_3). *o*-Bromobenzoic acid (10.05 g, 0.05 mol) was added to a dry 300-ml three-necked flask equipped with an addition funnel, low temperature thermometer, nitrogen inlet, and mechanical stirrer. Dry THF (200 ml, distilled from $LiAlH_4$) was added and the solution was cooled to −78 °C in a dry ice–ether bath under positive N_2 pressure. *n*-Butyllithium (50.0 ml of 2.0 M solution in hexane, 0.10 mol) was slowly added (3 h) while maintaining the mixture below −70 °C and the resulting solution was stirred for an additional 2 h at −78 °C. Freshly distilled *N*-methyl-4-piperidone (7.9 g, 0.07 mol) in dry hexane (25 ml) was added over 30 min while maintaining the mixture below −70 °C. The mixture was allowed to warm to room temperature and was added to 300 ml of H_2O and 200 ml of ether. The basic layer was extracted with ether (five 100-ml portions) and was acidified with concentrated HCl (to pH 2–3) and extracted with ether. The acidic solution was boiled for 1 h and was then cooled (0–5 °C) and made alkaline (to pH 9–10) with cold aqueous NaOH. The cold solution was rapidly extracted with five 200-ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with H_2O (100 ml), dried ($MgSO_4$), and concentrated to give 7.9 g of light yellow solid (mp 129–146 °C). Recrystallization of this product from $CHCl_3$–ligroin (bp 30–60 °C) gave 6.65 g (61% yield) of pure **3**[10] (R = CH_3), mp 151–152 °C, ir $\nu_{C=O}$ 1750 cm^{-1} (lit.[3a] mp 147–148 °C).

Lactones shown in entries 1–3 of Table I were prepared in a similar manner using the corresponding ketone and the appropriate workup.

Synthesis of Diols and Related Materials (Table II). General Procedure. 4-(2-Hydroxymethylphenyl)-1-methyl-4-piperidinol (4, R = CH_3). Method A. A mixture prepared from dry THF (50 ml) and $LiAlH_4$ (0.91 g, 0.024 mol) was stirred under N_2 for 30 min and lactone **3** (R = CH_3, 1.3 g, 0.006 mol) in dry THF (25 ml) was added over a 30-min period. The mixture was refluxed for 3 h under N_2 and then hydrolyzed by addition of H_2O (1 ml) and 15% NaOH (1 ml) and finally with more H_2O (3 ml). The solution was filtered (sintered glass) and the precipitate was washed with THF (10 ml). The combined THF solution was dried ($MgSO_4$) and concentrated to give 1.3 g of **4** (mp 120–127 °C). Recrystallization of this product from $CHCl_3$–ligroin (bp 30–60 °C) gave pure **4**, mp 136–137 °C (86% yield).

Method B. The dilithio derivative prepared[13] from o-bromobenzyl alcohol (5.00 g, 0.0268 mol) was maintained at −20 °C while a solution of *N*-methyl-4-piperidone (4.20 g, 0.0369 mol) in dry hexane (15 ml) was added. The resulting slurry was maintained at −20 °C for 2 h and allowed to warm to room temperature (16 h). The resulting mixture was cooled (0 °C) and adjusted to pH 2 with 20% hydrochloric acid and was then extracted with ether. The acid solution was cooled (0 °C) and adjusted to pH 12 with aqueous NaOH. Extraction of the alkaline solution with ether gave 3.00 g of **4** (50.7% yield, mp 137–140 °C; mp 138.5–140 °C[10] from EtOH–benzene).

Other materials prepared by procedure B are described in Table II. Special comments follow.

Mercapto Alcohols 20 and 21. o-Bromobenzyl mercaptan[10,14] was prepared from *o*-bromobenzyl bromide, thiourea, and 95% EtOH [76% yield,[10] bp 42 °C (0.05 Torr)]. Lithium–halogen exchange was effected with *n*-butyllithium in the usual way[6] (1 h) but at −100 °C (liquid nitrogen–diethyl ether bath); ketone in hexane was added at −95 °C and after 1 h at this temperature the mixture was added to hydrochloric acid and processed as above.

Phenols 22–24. Reaction of *o*-bromophenol and *n*-butyllithium in THF was effected at −20 to −30 °C (3 h). The solutions were then cooled to −78 °C, ketone was added at −78 °C (3 h), and the resulting solution was allowed to warm to room temperature prior to addition to acid.

For 22 the acid solution was extracted with $CHCl_3$. The product was further characterized by its (0.005 mol) conversion into the cyclic carbonate by reaction with *n*-butyllithium (0.01 mol in hexane) in THF (20 ml) at 0 °C followed by addition of phosgene [0.0055 mol in benzene (3.5 ml)]. The resulting mixture was filtered and concentrated and the oil was chromatographed [silica gel using ether–ligroin (bp 30–60 °C) as eluent] to give an olefin (NMR) and solid (lower R_f, mp 77–80 °C). The solid was recrystallized from ligroin (bp 60–90 °C) to give the pure cyclic carbonate **17** (43% yield, mp 80–81 °C).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.32; H, 6.28.

For 23 the reaction was carried out as described for **22.** The acidic solution was adjusted to pH 8–9 with aqueous bicarbonate and extracted with $CHCl_3$ in a continuous extractor for 3 days.

Diol 23 was converted into **4-(2′-hydroxyphenyl)-1-methyl-4-piperidinol dipropionate** by reaction with propionic anhydride (6 h, 32 °C). The crude dipropionate obtained in the usual way was distilled [short path, 140–145 °C (0.5 Torr); 79% yield] and the product solidified[10] (mp 67–77 °C dec).

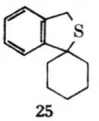
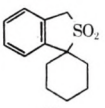
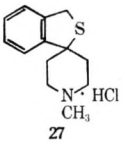
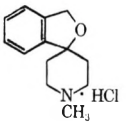
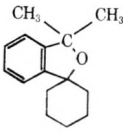
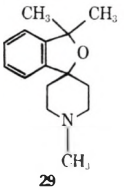
Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.83; H, 7.98; N, 4.17.

For 24 the procedure used was that described for **22.** The crude product (mp 105–107 °C) was mostly **24** but contained some 3-(2′-hydroxyphenyl)-2-tropene. The mixture was resolved by preparative TLC [600 g of basic alumina with ligroin (bp 30–60 °C)–EtOH as eluent]. The material with highest R_f was 3-(2′-hydroxyphenyl)-2-tropene (1.8% yield, mp 143–144 °C). Pure **24** was isolated in 20% yield.

For 15 (R = R[1] = CH_3) and 19. α,α-Dimethyl-2-bromobenzyl alcohol was prepared in 94% yield by reaction of methyl 2-bromobenzoate with CH_3MgI, bp 74–81 °C (0.09–0.07 Torr).

Synthesis of Spiro Piperidines (Tables I and III). 1′-Methylspiro[isobenzofuran-1(3*H*),4′-piperidine] (5, R = CH_3). Method A. From Lactones. General Procedure. A mixture of lactone **3** (R = CH_3) (1.3 g, 0.006 mol) and freshly distilled boron trifluoride eth-

Table III. Conversion of Mercapto Alcohols or Diols to Spirobenzofurans 16 or Analogues[10]

Product	Conditions	Yield, %	Mp (or bp), °C
 25	**20** + 2 N H_2SO_4, 5 h, 100 °C	56	(90, 0.03 Torr)
 26	**25** + H_2O_2 in CH_3COOH	99	107–108[a]
 27	**21** + 4 N H_2SO_4, 18 h, 100 °C	*b*	>218 sublimes and dec
	**15** (R = H; R′ = CH_3) + formic acid, isolated as the hydrochloride	>60[c]	278–281[d]
5 (R = H; R′ = CH_3)	**15** (R = H; R′ = CH_3) + 1 N H_2SO_4, 4 h, 100 °C	58[e]	78–80
5 (R = $CH_2C_6H_5$)	**15** (R = H; R′ = $CH_2C_6H_5$) + 1 N H_2SO_4, 4 h, 100 °C	67	62–63[f]
 28	**22** + boron trifluoride etherate, 36 h, 32 °C in benzene	88	(56–58, 0.08 Torr)
 29	**23** + boron trifluoride etherate, 24 h, 32 °C in benzene	92	108[g]

[a] From $CHCl_3$–ligroin (bp 30–60 °C). [b] The crude free amine was obtained as an oil in nearly quantitative yield; however, it was difficult to purify. The hydrochloride was prepared from a $CHCl_3$ solution with ethereal HCl and was fractionally recrystallized from $CHCl_3$ with considerable loss of product. [c] Free base obtained as an oil. [d] From $CHCl_3$, lit. 281–282 °C. [e] Purified by preparative TLC (silica gel PF-254), ether eluent. [f] From solvent, previously reported as the hydrochloride. [g] From ligroin (bp 30–60 °C).

erate solution (25.5 g, 0.18 mol BF_3) was added slowly to a cold (5–10 °C) suspension of $LiAlH_4$ (0.91 g, 0.024 mol) in dry THF (100 ml). After addition was complete the stirred mixture was allowed to warm to room temperature (1 h) and was then heated at the reflux temperature under N_2 for 3 h. The mixture was cooled and hydrolyzed by addition of 25 ml of 5% hydrochloric acid and 25 ml of H_2O. The solution was concentrated (rotary evaporation) to ~50 ml and 25 ml of concentrated hydrochloric acid was added. The solution was refluxed for 6 h, then cooled and adjusted to pH 4 with concentrated aqueous NaOH. The mixture was extracted with ether. The acidic layer was cooled and adjusted to pH 9–10 with alkali; the resulting basic solution was extracted with five 100-ml portions of $CHCl_3$. The solid (1.5 g, mp 55–70 °C) obtained from the dried $CHCl_3$ extract was sublimed (60–65 °C, 0.02 Torr) to give 1.0 g (82% yield) of **5**[10] (R = CH_3, mp 78–80 °C)

1′-Methylspiro[isobenzofuran-1(3*H*),4′-tropane] (12) was prepared in a similar way from **11** (Table I) and was isolated pure from the crude product (mp 53–59 °C) by sublimation (50 °C, 0.02 Torr) in 18% yield[10] (mp 60–62 °C) as white crystals.

Method B. From Diols (Table II). General Procedure (Table III). A solution of 4-(2-hydroxymethylphenyl)-1-methyl-4-piperidinol (**4**, R = CH_3) (0.75 g, 3.39 mol) in 2 N sulfuric acid (20 ml) was stirred at the reflux temperature for 4 h. The mixture was then cooled, adjusted to pH 9 with alkali, and extracted with $CHCl_3$ (5 × 25 ml). The dried ($MgSO_4$) organic extract was concentrated to a yellow oil (0.69 g) which was purified by preparative TLC (silica gel PF-254 using anhydrous ether as eluent). The principal band was separated with MeOH to give 0.50 g of **5** (mp 69–70 °C). This product was sublimed (at 0.02 Torr) to give pure **5** (R = CH_3) (58% yield, mp 78–79 °C).

Other spirobenzofuran derivatives prepared[10] by similar procedures are presented in Table III; special comments follow.

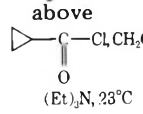
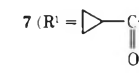
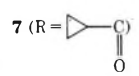
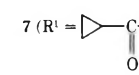
For 25. The product was extracted directly from the acid solution ($CHCl_3$) and was distilled. The product was also obtained in nearly quantitative yield from **20** (0.0023 mol) by using P_2S_5 (2 equiv) in CS_2 (100 ml) (48 h at 32 °C). The product was isolated from the filtered (6-cm bed of Celite) crude reaction mixture. Compound **25** was also characterized by its conversion to the sulfone **26**[10] (see Table III).

For 27. The crude oily product obtained from **21** (R = H; R^1 = CH_3) was dissolved in $CHCl_3$–ether and converted to the hydrochloride by addition of ethereal HCl. The crude hydrochloride was obtained in high yield; however, considerable loss occurred during fractional recrystallization from $CHCl_3$. The pure[10] hydrochloride (0.12 g from 2 g of crude base) (R = H; R^1 = CH_3) melted >218 °C with decomposition.

For 28. A solution of 1-*O*-(α,α-dimethyl-α-hydroxybenzyl)cyclohexanol (**19**, 2.0 g, 0.0085 mol) in benzene (100 ml) and boron trifluoride etherate (9.4 g, 0.128 mol) was stirred at room temperature for 36 h. The solution was washed with H_2O (100 ml) and aqueous bicarbonate (150 ml). Nearly pure **28** (1.80 g, 99% yield) obtained from the dried benzene was distilled to give pure **28** (1.7 g, 88% yield, see Table III). This product was also obtained in essentially quantitative yield by dehydration of **19** with P_2O_5 (1.5 equiv) in THF (24 h at 32 °C).

For 29. The procedure using **15** (R = R^1 = CH_3) and boron trifluoride etherate was quite similar to that used for **28**. Water (100 ml) and aqueous NaOH (to pH 14) was added and the mixture was ex-

Table IV. Akylation or Acylation of 6 and 9[10]

Substrate	Conditions	Product	Yield, %	Mp or (bp), °C
9	Styrene oxide, 100 °C, 2 h, no solvent	10 (R^1 = $CH_2CH(OH)C_6H_5$)	76	170–172[a]
9	$C_6H_5CH_2CH_2Br$ (2 equiv), K_2CO_3 (2.5 equiv) in 95% ethanol, 48-h reflux	10 (R^1 = $CH_2CH_2C_6H_5$)	72	103–105[b]
6	Styrene oxide, 105 °C, 2 h, no solvent	7 (R^1 = $CH_2CH(OH)C_6H_5$)	65	154.5–155.5[a]
6	$C_6H_5CH_2CH_2Br$, as above	7 (R^1 = $CH_2CH_2C_6H_5$)	45	96–98.5[c]
6	CH_2=$CHCH_2Br$, K_2CO_3 as above	7 (R^1 = CH_2CH=CH_2)	57	(100–105, 0.6 Torr)
6	 $(Et)_3N$, 23°C	7 (R^1 = 	55	109–111[c,d]
7 (R = )	$LiAlH_4$ in THF	7 (R^1 = )	80	(112–115, 0.8 Torr)
6	CH_2=$CHCH_2CH_2Br$ + K_2CO_3, alcoholic	7 (R^1 = CH_2CH_2CH=CH_2)	71	(105–108, 0.1 Torr)

[a] From $CHCl_3$–ligroin (bp 30–60 °C). [b] Crude product sublimed (75–80 °C, 0.02 Torr). [c] By sublimation 60 °C (0.02 Torr). [d] Cyclopropanecarboxylic acid was removed at 55 °C (0.05 Torr) prior to sublimation.

tracted with $CHCl_3$. The crude product (mp 104 °C) obtained from the organic extracts was dissolved in petroleum ether, treated with Norite, and, subsequent to filtration, crystallized to give pure **29**[10] (92% yield, Table III).

Demethylation Using Cyanogen Bromide. 1′-Cyanospiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (8). A solution of lactone **3** (R = CH_3) (10.86 g, 0.05 mol) in $CHCl_3$ (100 ml) was added slowly to a stirring boiling solution of NCBr (10.59 g, 0.1 mol) in $CHCl_3$ (100 ml) under N_2 and the resulting solution was refluxed for 3 h. The resulting solution was extracted with 50 ml of 5% hydrochloric acid and then with 25 ml of H_2O. The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated to give 10.1 g of solid, mp 179–181 °C. This product was recrystallized from $CHCl_3$–ligroin (bp 30–60 °C) to give 8.8 g (77% yield) of pure[10] **8** (mp 182–183 °C).

1′-Cyanospiro[isobenzofuran-1(3*H*),4′-piperidine] was obtained as a solid in quantitative yield; however, this material was used without purification for conversion into **6**.

Spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (9). A mixture of **8** (11.4 g, 0.05 mol) and 20% hydrochloric acid (200 ml) was stirred under N_2 at the reflux temperature for 6 h. The mixture was cooled (5 °C), the pH was adjusted to 9–10, and the mixture was extracted rapidly with five 200-ml portions of $CHCl_3$. The product obtained from the dried $CHCl_3$ was recrystallized from $CHCl_3$–ligroin (bp 30–60 °C) to give 8.4 g (83% yield) of pure **9** (mp 132–133 °C). This product was also obtained pure[10] in 76% yield by hydrolysis of **8** with alkali.

Spiro[isobenzofuran-1(3*H*),4′-piperidine] (6) was obtained (mp 84–86 °C from $CHCl_3$) from crude 1-cyanoisobenzofuran-1(3*H*),4′-piperidine pure[10] in 76% yield by acid hydrolysis and in 68% yield by basic hydrolysis, by procedures identical with that described above for **9**.

Alkylation and Acylation Reactions (Products in Table IV). General Prodcedures and Comments. 1′-(β-Hydroxy-β-phenylethyl)spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one [10, R = $CH_2CH(OH)C_6H_5$]. A mixture of styrene oxide (1.2 g, 0.01 mol) and lactone **9** (2.0 g, 0.01 mol) was heated at 95–10 °C under a small air condenser for 3 h. The solid obtained when the mixture was cooled was washed with 10 ml of cold ligroin (bp 30–60 °C) and recrystallized from $CHCl_3$–ligroin (bp 30–60 °C) to give pure[10] **10** (R = $C_6H_5CHOHCH_2$, mp 170–172 °C, 76% yield).

1′-(2-Phenylethyl)spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (10, R = $C_6H_5CH_2CH_2$). A solution of β-phenylethyl bromide (1.4 g, 0.0075 mol) in 95% EtOH (30 ml) was added slowly (12 h) to a boiling solution prepared from lactone **9** (1.0 g, 0.005 mol) in 95% EtOH (10 ml) under N_2. The resulting mixture was refluxed for an additional 36 h under N_2. The solution was concentrated (25 ml, rotary evaporator) and acidified (pH 2–3) with 10% hydrochloric acid and the solution was boiled for 30 min. The cooled solution (0 °C) was solution of NaOH (10%) was added to pH 9–10. This cold solution was rapidly extracted with five 100-ml portions of $CHCl_3$ and the combined $CHCl_3$ extracts were washed with H_2O (50 ml). The crude product was obtained from the dried $CHCl_3$ extracts and was purified by two sublimations (75–80 °C, 0.02 Torr) to give pure[10] **10** (R = $C_6H_5CH_2CH_2$, mp 103–105 °C, 1.11 g, 72% yield). This product crystallized well from EtOH–H_2O.

Other alkylated products were prepared as described for **10** or by conventional procedures; yields and pertinent data are shown in Table IV.

Dehydration of Diols 15 (R = H, R^1 = CH_3), and 22 and 24. General Procedure. A stirred solution of **15** (R = H; R^1 = CH_3) (2.07 g, 0.01 mol) in 2 N sulfuric acid (50 ml) was refluxed for 4 h. The solution was cooled, saturated bicarbonate was added to pH 9, and the mixture was extracted with $CHCl_3$. The solid obtained from the dried $CHCl_3$ extract was recrystallized twice from $CHCl_3$–ligroin (bp 30–60 °C) to give pure[10] **4-(2′-hydroxyphenyl)-1-methyl-3-piperidine** (mp 152–153 °C, 50% yield).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.00; H, 8.10; N, 7.26.

4-(2′-Hydroxyphenyl)-2-tropene [mp 143–144 °C from $CHCl_3$–ligroin (bp 30–60 °C); 89% yield] and **2-(1′-cyclohexenyl)-phenol** (100% yield, analytical sample collected by GLC) were prepared in a similar manner from **24** and **22** respectively.

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.39; H, 7.96; N, 6.25.

Preparation of 1′-Methylspiro[isobenzofuran-1(3*H*)-4′-piperidin]-3-imine (13). *o*-Bromobenzonitrile (5.00 g, 0.027 mol) in THF was converted into 2-lithiobenzonitrile at −78 °C (dry ice–acetone) as previously described[8]; *N*-methyl-4-piperidone (3.4 g, 0.03 mol) was added at such a rate that the temperature did not exceed −72 °C. Water (~100 ml) was added and the mixture was extracted rapidly with $CHCl_3$. The oil obtained from the dried ($MgSO_4$) $CHCl_3$ extract was distilled to give 4.2 g (72% yield of **13**[10] [Table I, bp 137–142 °C (0.03 torr); mp 96–99 °C] from ligroin (bp 60–90 °C).

Registry No.—**2**, 59043-34-4; **3** (R = Me), 54595-70-9; **4** (R = Me), 59043-35-5; **5** (R = Me), 56657-95-5; **5** (R = CH_2Ph), 37663-43-7; **6**, 38309-60-3; **7** (R^1 = c-C_3H_5C=O), 59043-36-6; **7** (R^1 = $CH_2CH(OH)$-Ph), 59043-37-7; **7** (R^1 = CH_2CH_2Ph), 59043-38-8; **7** (R^1 = CH_2CH=CH_2), 59043-39-9; **7** (R^1 = c-$C_3H_5CH_2$), 56657-96-6; **7** (R^1 = CH_2CH_2CH=CH_2), 59043-40-2; **8**, 59043-41-3; **9**, 37663-46-0; **10** (R^1 = $CH_2CH(OH)Ph$), 59043-42-4; **10** (R^1 = CH_2CH_2Ph), 56657-84-2; **11**, 59043-43-5; **12**, 59043-44-6; **13**, 59043-45-7; **15** (R = H; R^1 = Me), 59043-35-5; **15** (R = H; R^1 = CH_2Ph), 56658-29-8; **15** (R = R^1 = CH_3), 59043-46-8; **17**, 59043-47-9; **19**, 59043-48-0; **20**, 59043-49-1; **21**, 59043-50-4; **22**, 59043-51-5; **23**, 59204-52-3; **24**, 59043-52-6; **25**, 28893-45-0; **26**, 59043-53-7; **27**, 59043-54-8; **28**, 59043-55-9; **29**, 59043-56-0; cyclohexanone, 108-94-1; spiro[isobenzofuran-1(3*H*),-1′-cyclohexan]-3-one, 5651-49-0; *N*-methylpiperidone, 1445-73-4; 59043-57-1; spiro[isobenzofuran-1,4′-piperidine]-1′-methyl HCl, 54596-08-6; styrene oxide, 96-09-3; $C_6H_5CH_2CH_2Br$, 103-63-9; CH_2=$CHCH_2Br$, 106-95-6; c-C_3H_5C(=O)Cl, 4023-34-1;

CH_2=$CHCH_2CH_2Br$, 5162-44-7; 4-(2′-hydroxyphenyl)-1-methyl-4-piperidinol dipropionate, 59043-58-2; 3-(2′-hydroxyphenyl)-2-tropene, 59043-59-3.

References and Notes

(1) The authors gratefully acknowledge assistance from the Eli Lilly Research Foundation for support of part of this work.
(2) Taken in part from the undergraduate independent study theses of (a) R. W. Thraikill, Duke University, 1974; (b) G. E. Keyser, Duke University, 1975.
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Metathesis of 1-Alkene

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In the WCl_6/Bu_4Sn catalyzed metathesis of 1-alkene, the addition of esters, acetonitrile, phenylacetylene, dicyclopentadiene, and ethers raised the selectivity to the metathesis by depressing side reactions including double bond migration, and the products of the metathesis reaction were obtained in high yield. This is a very easy and effective process for the direct synthesis of the symmetric internal alkenes. In the metathesis of 1-octene catalyzed by the WCl_6·CH_3COO-*n*-Pr/Bu_4Sn system at 80 °C, the optimum range of the Bu_4Sn/WCl_6 ratio was 2–8 and that of the 1-octene/WCl_6 ratio 20–400. The cis:trans isomer ratio of the product olefin approached its equilibrium value at the end of the reaction.

The metathesis of 1-alkene gives an ethylene and a symmetric internal alkene as follows:

$$\begin{matrix} CH_2{=}CH{-}R \\ + \\ CH_2{=}CH{-}R \end{matrix} \rightleftarrows \begin{matrix} CH_2 \\ \| \\ CH_2 \end{matrix} + \begin{matrix} HCR \\ \| \\ HCR \end{matrix}$$

It has been reported that this reaction is often accompanied by side reactions such as double bond migration and polymerization of alkenes[1-3] and that the yield of the metathesis products is low, except in a few cases.[4,5]

In this paper, we report that the WCl_6·CH_3COOR (R = Et, *n*-Pr, *n*-Bu, and *sec*-Bu)/Bu_4Sn and the WCl_6·CH_3CN/Bu_4Sn systems catalyzed the metathesis of 1-alkenes with high activity and high selectivity. This result appears to increase the merit of the metathesis reaction in synthetic chemistry.

Results and Discussion

Effects of Additives in the Metathesis of 1-Octene. In this study, tetrabutyltin[6] was employed as a cocatalyst because of the stability and the easiness to treat of the compound. Trichloroethylene[7] was used as a solvent, for it gave a good yield of the metathesis products without the formation of the undesirable Friedel–Crafts products in the metathesis of 2-heptene.

The WCl_6/Bu_4Sn catalyst system in combination with 1-octene afforded a mixture of alkenes ranging from C_2 to C_{14} in trichloroethylene at room temperature. At 80 °C, the amount of consumed 1-octene greatly increased, and the increase in the yield of alkenes ranging from C_9 to C_{14} was recognized. A polymerization reaction probably took place at the same time, since the amount of product alkenes was much less than that of the consumed 1-octene. The addition of *n*-propyl acetate to the reaction system suppressed the formation of alkenes ranging from C_9 to C_{13} and from C_3 to C_7, and the polymerization, but 7-tetradecene and ethylene were formed in high yield and in high selectivity. The addition of ethyl acetate, *n*-butyl acetate, and *sec*-butyl acetate also provided high yield of 7-tetradecene and high selectivity, respectively. The distribution of the alkenes ranging from C_8 to C_{14} was not influenced by the presence of air. In the WCl_6/Bu_4Sn catalyzed 1-octene metathesis, *cis*- and *trans*-2-octene, which are produced by the double bond migration of 1-octene, were detected by a capillary squalane column. Presumably alkenes ranging from C_2 to C_{14} were formed not only by the self-metathesis of 1- and 2-octene and by the cross-metathesis of 2-octene with 1-octene but also by the successive reactions of product alkenes such as the isomerization of 1-heptene into 2-heptene and the self- and the cross-metathesis of 2-heptene. The WCl_6·CH_3COO-*n*-Pr/Bu_4Sn system reduced the amounts of *cis*- and *trans*-2-octene and the product alkenes ranging from C_9 to C_{13}. This fact indicates that the addition of *n*-propyl acetate suppresses the isomerization of 1-octene to 2-octene. These results are shown in Table I. Acetonitrile showed an excellent effect at the CH_3CN/WCl_6 ratio of 2, though the yield of 7-tetradecene decreased at the CH_3CN/WCl_6 ratio of 4. Phenylacetylene, dicyclopentadiene, ethyl ether, *n*-propyl ether, and tetrahydrofuran were also found to be comparatively effective additives. Water, hydrochloric acid, benzoic acid, tri-*n*-butylamine, tri-*n*-butylphosphine, and tetrahydrothiophene were not effective ones. In the presence of such compounds, the catalytic activity was hardly recognized at the additive/WCl_6 ratio of 1 and 4. Water, hydrochloric acid, and benzoic acid might destroy the catalyst. However, the addition of 1-propanol gave 11% 7-tetradecene at the equimolar amount to tungsten. Tri-*n*-butylamine, tri-*n*-butylphosphine, and tetrahydrothiophene induced yellow precipitations with a solution of tungsten hexachloride. Probably the stable acid–base tungsten complexes were formed.

Effects of Temperature and of the Amount of *n*-Propyl Acetate. The effects of temperature and of the CH_3COO-*n*-Pr/WCl_6 ratio on the yield and the selectivity were inves-

Table I. Effects of Additives in the Metathesis of 1-Octene[a]

Additive	Additive/WCl_6	Distribution of alkenes, mol %[b]						Selectivity,[c] %
		C_8	C_9	C_{10}	C_{12}	C_{13}	C_{14}	
None[d,e]	0	87.8	1.4	0	0.2	0.5	1.4	23.0
None[e]	0	6.7	5.1	1.8	2.3	2.6	2.8	6.0
None[f]	0	14.7	7.2	2.0	4.0	4.7	5.1	12.1
n-Propyl acetate	4[e]	64.3	1.0	0.8	0.4	0.6	14.8	82.9
	4[g]	57.5	1.1	0.9	0.2	0.9	16.9	79.5
Ethyl acetate	4	68.2	0.4	0.8	0.2	0.3	14.1	88.7
n-Butyl acetate	4	69.2	0.5	0.7	0.2	0.3	13.7	89.0
sec-Butyl acetate	4	74.5	0.6	0.4	0.2	0.3	11.3	88.6
Acetonitrile	2	60.2	0.1	0	0.2	0.1	19.4	97.5
	4	73.5	0	0	0	0	13.2	100
Phenylacetylene	4	44.1	3.2	1.4	0.9	2.6	17.0	60.8
	8	44.8	2.3	1.5	0.7	1.7	16.1	58.5
Dicyclopentadiene	4	37.5	4.0	1.1	1.6	3.1	15.4	49.3
	8	51.7	1.6	0.5	1.6	1.2	15.4	64.0
Ethyl ether	4	30.8	6.3	1.6	1.6	3.9	12.1	34.8
	8	38.5	5.1	1.7	1.5	3.6	15.3	49.9
n-Propyl ether	4	22.1	7.5	1.5	2.0	4.7	9.9	25.4
	8	36.9	5.6	1.5	1.5	3.3	13.7	43.4
Tetrahydrofuran	4	73.4	0.8	0.5	0	2.7	9.4	70.4
	8	84.9	0	0	0	0	4.5	59.6
1-Propanol	1	43.7	8.2	2.1	1.2	3.8	10.6	37.7
	4	100	0	0	0	0	0	

[a] The mixture of 1-octene (1.2 M), WCl_6 (0.024 M), Bu_4Sn (0.048 M), and an additive was heated in trichloroethylene in the absence of air at 80 °C for 3 h. [b] Mole % of each alkene based on the amount of 1-octene used. The product alkenes lower than C_8 were not determined. [c] % selectivity = (moles of 7-tetradecene × 2) × 100/moles of 1-octene consumed. [d] The reaction was carried out at room temperature. [e] The reaction was carried out in the presence of air. [f] Detected octenes were composed of 1-octene (0.11 M), *trans*-2-octene (0.04 M), and *cis*-2-octene (0.02 M). Detected C_{14} components contained *cis*- and *trans*-7-tetradecene mainly, with several other components. 7-Tetradecene contained 21% cis isomer. [g] Detected octenes were composed of 1-octene (0.67 M), *trans*-2-octene (0.02 M), and trace of *cis*-2-octene. No other C_{14} component except 20% *cis*- and 80% *trans*-7-tetradecene was detected.

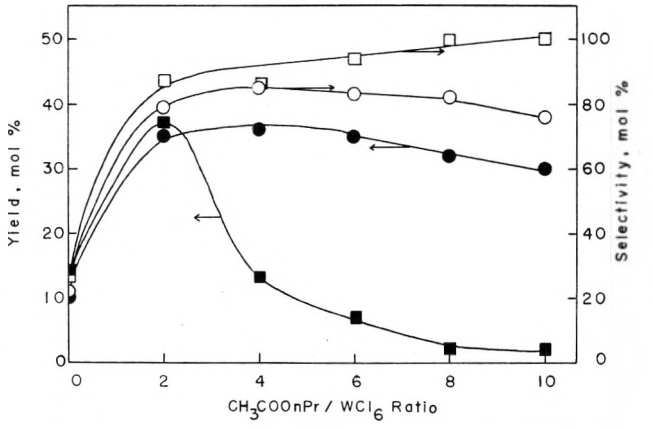

Figure 1. Effects of temperature and of the amount of *n*-propyl acetate: 60 °C, ■ yield, □ selectivity; 80 °C, ● yield, ○ selectivity. % yield = (moles of 7-tetradecene × 2) × 100/moles of 1-octene used. % selectivity = (moles of 7-tetradecene × 2) × 100/moles of 1-octene consumed. The mixture of 1-octene (1.2 M), WCl_6 (0.024 M), Bu_4Sn (0.048 M), and *n*-propyl acetate was heated in trichloroethylene in the absence of air for 3 h.

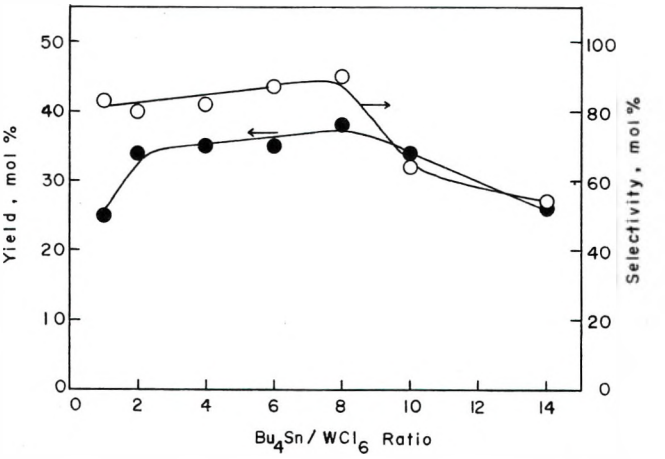

Figure 2. Effect of Bu_4Sn/WCl_6 ratio: ● yield; ○ selectivity. The mixture of 1-octene (1.2 M), WCl_6 (0.024 M), Bu_4Sn, and *n*-propyl acetate (0.096 M) was heated in trichloroethylene in the absence of air at 80 °C for 3 h.

tigated in the metathesis of 1-octene catalyzed by the WCl_6-CH_3COO-*n*-Pr/Bu_4Sn system (Figure 1). At room temperature, *n*-propyl acetate hindered the reaction at the CH_3COO-*n*-Pr/WCl_6 ratio of 2. At 60 °C, 37% yield and 87% selectivity were obtained at the same CH_3COO-*n*-Pr/WCl_6 ratio, though the yield decreased sharply with the increase in the CH_3COO-*n*-Pr/WCl_6 ratio. At 80 °C, the yield of 36–32% and the selectivity of 85–79% were obtained at the CH_3COO-*n*-Pr/WCl_6 ratio of 2–8. The yield gradually decreased with increasing the amount of *n*-propyl acetate when the CH_3COO-*n*-Pr/WCl_6 ratio was higher than 4. However, 27% yield and 74% selectivity were obtained even at the CH_3COO-*n*-Pr/WCl_6 ratio of 20. This result means that an excess amount of *n*-propyl acetate inhibits the metathesis and that heating promotes the metathesis and extremely widens the optimum range of the CH_3COO-*n*-Pr/WCl_6 ratio.

Effect of the Bu_4Sn/WCl_6 Ratio. In the metathesis of 1-octene catalyzed by the WCl_6-CH_3COO-*n*-Pr/Bu_4Sn system at 80 °C, the yield of 38–34% and the selectivity of 90–80% were obtained at the Bu_4Sn/WCl_6 ratio of 2–8 (Figure 2). The optimum range was extremely wider than those of the cocatalyst/WCl_6 ratio in the metathesis of 2-heptene in benzene at room temperature.[6,8] This result shows that the catalyst effective for the metathesis of 1-alkene is easily prepared from WCl_6, Bu_4Sn, and *n*-propyl acetate in trichloroethylene.

Table II. Metathesis of Various 1-Alkenes [a]

Registry no.	Reactant	Product	Additive	Yield, mol %	Cis isomer content, %
109-67-1	1-Pentene	4-Octene	(A)	38	22
			(B)	28	34
592-41-6	1-Hexene	5-Decene	(A)	41	20
			(B)	40	21
592-76-7	1-Heptene	6-Dodecene	(A)	32	33
			(B)	24	32
111-66-0	1-Octene	7-Tetradecene	(A)	43	19
			(B)	43	20
872-05-9	1-Decene	9-Octadecene	(A)	45	
			(B)	44	

[a] The mixture of 1-alkene (1.5 M), WCl_6 (0.024 M), Bu_4Sn (0.048 M), and *n*-propyl acetate (0.096 M) (A) or acetonitrile (0.048 M) (B) was heated in trichloroethylene in the absence of air at 80 °C for 3 h.

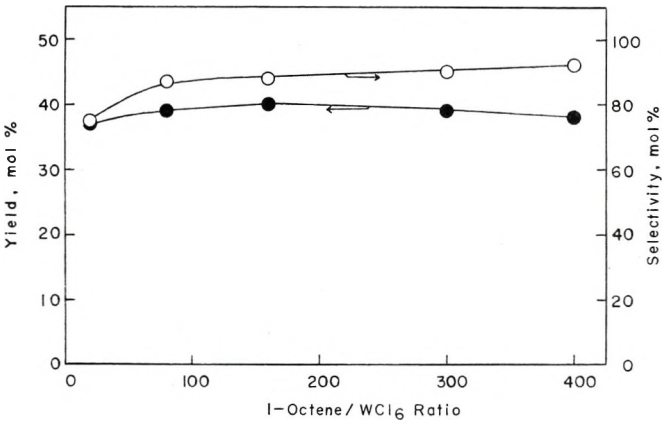

Figure 3. Effect of 1-octene/WCl_6 ratio: ● yield; ○ selectivity. The mixture of 1-octene, WCl_6 (0.024 M), Bu_4Sn (0.048 M), and *n*-propyl acetate (0.096 M) was heated in trichloroethylene in the absence of air at 80 °C for 3 h.

Effect of the 1-Octene/WCl_6 Ratio. In the metathesis of 1-octene catalyzed by the WCl_6-CH_3COO-*n*-Pr/Bu_4Sn system at 80 °C, the yield of 40–37% and the selectivity of 92–75% were obtained at the 1-octene/WCl_6 ratio of 20–400 (Figure 3). The selectivity increased with an increase in the 1-octene/WCl_6 ratio. The maximum yield was obtained at the 1-octene/WCl_6 ratio of 160. When the 1-octene/WCl_6 ratio was higher than 160, the increase in the amount of 1-octene led to the slight decrease in the yield. Also, the yield decreased from 38 to 14% when the concentration of WCl_6 was changed from 0.024 M to 0.008 M at the 1-octene/WCl_6 ratio of 400. At 0.008 M of the WCl_6 concentration, the yield of 14–9% and the selectivity of 99–93% were obtained at the 1-octene/WCl_6 ratio of 400–800. In the reaction of 2-heptene catalyzed by the WCl_6/Bu_4Sn system in benzene at room temperature, the yield of 5-decene considerably changed with the variation of the 2-heptene/WCl_6 ratio, where the optimum range was ~50–200. However, heating and the addition of *n*-propyl acetate gave the markedly wide optimum range in the reaction in trichloroethylene. This result also means that this reaction does not require certain strict reaction conditions.

Metathesis of Various 1-Alkenes. The yield and the cis-isomer content of the reaction product from the metathesis of 1-alkene using the WCl_6-CH_3COO-*n*-Pr/Bu_4Sn or the WCl_6-CH_3CN/Bu_4Sn catalyst system are shown in Table II. Symmetric internal alkenes were obtained in good yield. The additives prevented the double bond migration but permitted the geometric isomerization, for the ratio of cis isomer in the product alkene approached its equilibrium value[9] at the end of the reaction.

When the ethylene formed was removed from the reaction system by liquefaction with liquid nitrogen in the metathesis of 1-octene catalyzed by the WCl_6-CH_3COO-*n*-Pr/Bu_4Sn system in trichloroethylene at 80 °C for 5 h, 59% yield and 94% selectivity were obtained. The reaction also proceeded without solvent.

Experimental Section

Materials. 1-Alkenes were purified by distillation under nitrogen. Trichloroethylene was dried over anhydrous $CaSO_4$ (Drierite) and distilled under nitrogen. Tungsten hexachloride was purified by preferential sublimation of the more volatile contaminants, WO_2Cl_2 and $WOCl_4$, under nitrogen at ca. 200 °C, leaving a residue of pure WCl_6. Tetrabutyltin was purchased and used without further purification.

An Example of Metathesis Reaction. To a dried glass tube sealed with a neoprene rubber cap, 1-octene (0.18 ml, 1.2 mmol), a trichloroethylene solution of WCl_6 (0.024 mmol), *n*-propyl acetate (11 μl, 0.096 mmol), and a trichloroethylene solution of Bu_4Sn (0.048 mmol) were injected, in this order, by means of hypodermic syringes. The total volume of the reaction mixture was 1 ml. After air was evacuated, the glass tube was sealed. The reaction mixture was heated at 80 °C for 3 h, and then analyzed by gas–liquid chromatography.

Analytical Procedures. Quantitative GLC analyses were routinely performed on a JEOL GC-1100 chromatograph, or a Shimadzu GC-4APF chromatograph, using a 1 m × 3 mm column or a 1.5 m × 3 mm column packed with 10% SE-30 on 80–100 mesh Chromosorb W and a 2 m × 3 mm column packed with 20% FFAP on 60–70 mesh Anakrom ABS. *n*-Undecane was used as an internal standard. Isomer content of olefin was obtained with a 90 m × 0.25 mm capillary column coated with squalane. Products were identified by gas–liquid chromatography using authentic samples.

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Kinetic Study of Elimination Reactions Promoted by Crown Ether Complexed Potassium *tert*-Butoxide in *tert*-Butyl Alcohol

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Kinetics of eliminations from 1-bromo-2-arylethanes and 1-chloro-2-phenylethane promoted by 18-crown-6 ether complexed alkali *tert*-butoxides in *tert*-butyl alcohol have been carried out. The reaction rate (ca. 250-fold larger than that of elimination induced by uncomplexed alkali *tert*-butoxides) appears to be influenced by the nature of the cation, complexed *t*-BuOK being 4.5 times more reactive than complexed *t*-BuONa. Moreover, the second-order rate constants appear to increase as the base concentration increases. From kinetic data obtained at the same concentration of complexed *t*-BuOK values of 8, 19, and 2.8 have been calculated for the deuterium kinetic isotope effect, Br/Cl leaving group effect, and the reaction constant ρ, respectively. Since the corresponding data for the same reactions promoted by *t*-BuOK in *t*-BuOH, in the absence of crown ether, are 8.16, 23, and 2.5, it appears that complexation of the base (which should lead to dissociated *tert*-butoxide ions) has little effect on the transition state structure of anti eliminations from 2-phenylethyl derivatives.

Macrocyclic polyethers are known to convert contact ion pairs and ionic aggregates into loose ion pairs or separated ions.[1] Thus, a large number of elimination reactions promoted by crown ether complexed *t*-BuOK in *t*-BuOH (dissociated *t*-BuOK) have been carried out in order to ascertain the role of base association upon stereochemistry and both geometrical and positional orientation of E2 reactions.[2] However, no kinetic information on the eliminations carried out in this base–solvent system is available and even the magnitude of the rate enhancement which occurs when the base is changed from associated to dissociated *t*-BuOK is unknown. Moreover, the sole result concerning the effect of the base association on the transition state structure of elimination reactions refers to a syn elimination and is not derived from a kinetic study.[3]

In order to acquire information on the effect of ion pairing on the kinetic aspects and transition state structure of anti eliminations promoted by *t*-BuOK in *t*-BuOH we have investigated the reactions of 1-bromo-2-arylethanes, 1-bromo-2,2-dideuterio-2-phenylethane, and 1-chloro-2-phenylethane with crown ether complexed *t*-BuOK in *t*-BuOH.

The aim of this work was also that of determining to what extent the effects of base association on the geometrical and positional orientation of elimination reactions can be discussed in terms of effects on the transition state structure.

Results and Discussion

Kinetic experiments were brought about by following spectrophotometrically the formation of styrene or substituted styrene. In each case the optical densities at the infinity time indicated a quantitative yield of olefin. The substrate concentration was ca. 8×10^{-5} M whereas the base concentration was in the range 10^{-3}–10^{-2} M. Measurements at concentrations larger than 10^{-2} M were not possible since complexed *t*-BuOK was found, in these cases, to absorb significantly at the wavelengths used for the kinetic study (see Experimental Section). The reaction of 1-bromo-2-*p*-nitrophenylethane was extremely fast and was kinetically studied by using a stopped-flow spectrophotometer. The macrocyclic polyether was 18-crown-6 ether (henceforth indicated as 18C6) and in one run *t*-BuOK was replaced by *t*-BuONa.

In all experiments the base was always in large excess with respect to the substrate and first-order plots exhibited an excellent linearity, up to 75–80% of reaction. A 1:1 18C6/base molar ratio was not sufficient to assure a complete complexation of the cation in the range of base concentration 1×10^{-3}–5×10^{-3} M. Accordingly, at constant base concentration the derived second-order rate constants (k_2) leveled off only when the 18C6/base molar ratio was at least 2:1 with *t*-BuOK, and 5:1 with *t*-BuONa, in agreement with the fact that potassium is more strongly complexed than sodium by macrocyclic polyethers.[1a] Some representative data for the reaction with *t*-BuOK are reported in Table I.

Table I. Kinetic Data for the Elimination Reactions of 1-Bromo-2-phenylethane in *t*-BuOK–*t*-BuOH in the Presence of Varying Amounts of 18-Crown-6 Ether at 30 °C

[*t*-BuOK], M	[18C6], M	18C6/*t*-BuOK	k_1, s^{-1}	k_2, M^{-1} s^{-1}
2.05×10^{-3}	2.33×10^{-3}	1.14	2.69×10^{-3}	1.31
1.99×10^{-3}	4.48×10^{-3}	2.25	3.24×10^{-3}	1.63
2.09×10^{-3}	6.70×10^{-3}	3.20	3.30×10^{-3}	1.58
2.09×10^{-3}	10.50×10^{-3}	5.02	3.09×10^{-3}	1.48

Interestingly enough, complexed *t*-BuOK is more reactive (4.5-fold) than complexed *t*-BuONa (Table II, note *d*), the difference in reactivity being larger than that exhibited by the uncomplexed bases. This result is surprising since the reactivity of loose or separated ion pairs should be less sensitive to the nature of the cation than that of tight ion pairs and ionic aggregates. Probably even in the presence of a crown ether, ion pairing of alkali *tert*-butoxides in *t*-BuOH plays a significant role with respect to reactivity.

When the concentration of *t*-BuOK was changed significant changes in the k_2 values were observed (Table II), an increase in the base concentration determining a substantial enhancement of the rate. For all of the substrates the k_2 increase is ca. 2.5-fold for a tenfold increase in the base concentration, which corresponds to an apparent order of ca. 1.4 in complexed *t*-BuOK. In contrast, k_2 values for the elimination from 1-bromo-2-phenylethane induced by *t*-BuOK in *t*-BuOH in the absence of crown ether are independent of base concentration,[4,5] as also confirmed by our own results in Table II.

The dependence of the k_2 values on the base concentration for the reactions with complexed *t*-BuOK is difficult to rationalize and, at present, we can only tentatively indicate some possible explanations. Although the addition of KNO_3 does not seem to influence the reaction rate (Table II, note c), salt effects could be at the origin of the phenomenon since in a medium of low polarity such as *t*-BuOH, specific ionic effects can be important and solvated *tert*-butoxide anion might exert a positive effect on the rate while other anions are ineffective. Another suggestion could be that the active nucleophile is some multiple negative ion in equilibrium with the ion

Table II. Kinetic Data for the Elimination Reactions of 1-Bromo-2-arylethanes and 1-Chloro-2-phenylethane Promoted by Crown Ether Complexed *t*-BuOK in *t*-BuOH

Registry no.	Substrate[a]	Temp, °C	[*t*-BuOK], M	[18C6], M	k_2, M^{-1} s^{-1}[b]
103-63-9	H	30	0.022		7.26×10^{-3}
	H	30	0.415		7.13×10^{-3}
	H	30	1.03×10^{-3}	2.09×10^{-3}	1.03
23088-37-1	2,2-d_2	30	1.03×10^{-3}	2.09×10^{-3}	0.13
	H	30	3.25×10^{-3}	6.88×10^{-3}	1.74
	2,2-d_2	30	3.25×10^{-3}	6.88×10^{-3}	0.20
14425-64-0	*p*-OCH_3	30	3.25×10^{-3}	6.88×10^{-3}	0.46
6529-51-7	*p*-CH_3	30	3.25×10^{-3}	6.88×10^{-3}	0.76
1746-28-7	*p*-Br	30	3.25×10^{-3}	6.88×10^{-3}	11.72
	H	30	3.45×10^{-3}	6.90×10^{-3}	1.84
	2,2-d_2	30	3.45×10^{-3}	6.90×10^{-3}	0.23
	H	30	3.86×10^{-3}	1.15×10^{-2}	1.92[c]
	H	30	5.15×10^{-3}	1.13×10^{-2}	2.20[d]
	p-OCH_3	30	5.15×10^{-3}	1.13×10^{-2}	0.91
	p-CH_3	30	5.15×10^{-3}	1.13×10^{-2}	0.99
	p-Br	30	5.15×10^{-3}	1.13×10^{-2}	20.68
5339-26-4	*p*-NO_2	30	5.15×10^{-3}	1.13×10^{-2}	11 650
	H	30	5.40×10^{-3}	1.15×10^{-2}	2.04
	2,2-d_2	30	5.40×10^{-3}	1.15×10^{-2}	0.29
	H	30	1.09×10^{-2}	2.31×10^{-2}	2.56
	2,2-d_2	3		1.09×10^{-2}	2.31×10^{-2}
0.31					
	H	30	1.15×10^{-2}	2.30×10^{-2}	2.66
	2,2-d_2	30	1.15×10^{-2}	2.30×10^{-2}	0.33
	H	39.7	3.25×10^{-3}	6.88×10^{-3}	3.28
	2,2-d_2	39.7	3.25×10^{-3}	6.88×10^{-3}	0.44
	H	39.7	3.45×10^{-3}	6.90×10^{-3}	3.61
	2,2-d_2	39.7	3.45×10^{-3}	6.90×10^{-3}	0.48
	H	48.2	3.45×10^{-3}	6.90×10^{-3}	5.53
	2,2-d_2	48.2	3.45×10^{-3}	6.90×10^{-3}	0.78
622-24-2	$C_6H_5CH_2CH_2Cl$	30	0.492		3.14×10^{-4}
	$C_6H_5CH_2CH_2Cl$	30	1.02×10^{-2}	2.10×10^{-2}	0.14

[a] H refers to 1-bromo-2-phenylethane. [b] Average of at least two determinations. The average error is ±5% using the same batch of solvent. With different batches of *t*-BuOH the error can rise to ±9%. [c] In the presence of 7.92×10^{-3} M KNO_3. This value is compared with that (1.84 M^{-1} s^{-1}) obtained at a concentration of complexed base of 3.45×10^{-3} M. The small difference in k_2 is probably due to the fact that the kinetic experiment in the presence of KNO_3 has been carried out at a slightly larger *t*-BuOK concentration than that in the absence of the salt. [d] This value can be compared with that (0.49 M^{-1} s^{-1}) obtained when the base was complexed *t*-BuONa at a very similar concentration (4.91×10^{-3} M) with a 18C6/*t*-BuONa molar ratio of 5.

pair, thus leading to an order in *t*-BuOK greater than one.[6] Besides, two further possibilities should be considered: an increase in the basicity of the medium that is more rapid than the increase in the base concentration (even at the low concentrations used) and an increase in the elimination rate faster than that in the medium basicity. With respect to the latter possibility it is interesting to note that also in the reaction of 1-bromo-2-phenylethane with *t*-BuOK in Me_2SO–*t*-BuOH the rate was found to rise faster than H_- of the medium as Me_2SO concentration was increased.[4] However, in such a case k_2 was practically insensitive to changes in base concentration at a fixed composition of the mixed solvent.

Complexed *t*-BuOK is also, as expected, much more reactive than the uncomplexed base. At a concentration of 3.45×10^{-3} M, a 250-fold increase in the elimination rate is observed. This increase is due to enthalpic and entropic factors since both the value of $\Delta H^{\ddagger}$ (11.1 ± 1.5 kcal mol^{-1}) and $\Delta S^{\ddagger}$ (−20.7 ± 5 cal mol^{-1} K^{-1}) for the reaction of 1-bromo-2-phenylethane with complexed *t*-BuOK, calculated from data at the same base concentration, are significantly different from those ($\Delta H^{\ddagger}$ = 12.8 kcal mol^{-1} and $\Delta S^{\ddagger}$ = −26 cal mol^{-1} K^{-1}) obtained in the same reaction promoted by *t*-BuOK in the absence of crown ether.[4,7]

From the data of Table II the Hammett ρ value, the deuterium kinetic isotope effect (k_H/k_D), and the leaving group effect (k_{Br}/k_{Cl}) for the reaction promoted by complexed *t*-BuOK have been calculated using, in each case, kinetic data obtained at the same base concentration. The results are reported in Table III together with the corresponding ones for the reaction induced by uncomplexed *t*-BuOK. It appears immediately clear that in spite of the large effect on the reaction rate, the complexation of *t*-BuOK has not a significant

Table III. Hammett Parameters, Deuterium Isotope Effects, and Leaving Group Effects for the Reactions of 1-Bromo-2-arylethanes with *t*-BuOK–*t*-BuOH in the Absence and Presence of 18C6 at 30 °C

Base–solvent	ρ	k_H/k_D	k_{Br}/k_{Cl}
t-BuOK–*t*-BuOH	2.53[a]	8.16[b]	23[c]
t-BuOK–18C6-*t*-BuOH	2.77[d]	8.05 ± 0.39[e]	19[c]

[a] From ref 4; this value has been confirmed by the recent work of Blackwell et al.[8] Reference 9 reports a value of 2.08. [b] From ref 4; ref 10 reports 7.89. [c] See Table II. [d] Calculated by a least-squares analysis (r = 0.996, S = 0.18) at a base concentration of 5.15×10^{-3} M (substituents: *p*-OCH_3, *p*-CH_3, H, *p*-Br, *p*-NO_2). The σ^- value was used for the *p*-NO_2 group.[10] At a base concentration of 3.25×10^{-3} M (substituents: *p*-OCH_3, *p*-CH_3, H, *p*-Br) the ρ value was 2.80 (r = 0.992, S = 0.10). [e] Average of values calculated at different base concentrations (see Table II). From the values of k_H/k_D at 30, 39.7, and 48.2 °C (Table II) an A_H/A_D ratio of 0.84 can be calculated, which would indicate the absence of a tunneling contribution.

effect on the transition state structure of the elimination reactions of 1-bromo-2-phenylethanes. At most, a very small increase in the carbanion character of the transition state could be suggested.

A like situation has been observed in a study of the effect of added Me_2SO on the elimination reactions of 1-bromo-2-phenylethane in *t*-BuOH.[4] Also in that case, in contrast to the effect on rate, the transition state structure did not appear to change appreciably by increasing the basicity of the medium. The finding was explained by considering that in the transition state the base is substantially the same species (partially neutralized *tert*-butoxide anion), differences in rates being due to differences in the solvation of the base and in the tightness of its pairing with cation.

Clearly, also our own results can be rationalized in the same way. However, we feel that data with substrates different from 1-bromo-2-arylethanes are necessary before the above conclusion is definitely assessed. In this respect it is worth noting that in the syn elimination from *trans*-2-arylcyclopentyl tosylate[3] complexed *t*-BuOK was found to bring about a significant increase in the carbanion character of the transition state with respect to associated *t*-BuOK, the ρ value rising from 2.2 (in the absence of crown ether) to 3.1. However, in this case, rather than to a basicity effect, the increase in the carbanion character of the transition state of the reaction in going from associated to dissociated *t*-BuOK could probably be due to the fact that the associated base produces a more synchronous transition state by allowing the simultaneous coordination of the counterion with the base and leaving group,[12] which does not occur with dissociated *t*-BuOK. Of course, it is also possible that the transition state structure for a syn elimination displays a sensitivity to the basicity of the medium different from that of the transition state of an anti elimination.

Finally, the present results allow the conclusion that the significant effects exerted by base association on geometrical and positional orientation of anti eliminations cannot be traced back to effects on the transition state structure. Probably substantial changes in the product composition of an E2 reaction are determined by differences in the energy of the transition states which are too small to produce appreciable variations in the sensitivity of the reaction rate to substituent effects, leaving group effect, and kinetic isotope effect.

Experimental Section

Materials. **1-Bromo-** and **1-chlorophenylethane** were commercial products (Fluka) purified by distillation. The other 1-bromo-2-arylethanes were prepared according to a procedure described in the literature.[13] Their properties were as follows.

1-Bromo-2-*p*-methylphenylethane, bp 100–101 °C (9 mm), $n^{24}D$ 1.5508 [lit.[4] bp 97–99 °C (6 mm), $n^{26}D$ 1.5472].

1-Bromo-2-*p*-methoxyphenylethane, bp 92–94 °C (1 mm), $n^{24}D$ 1.5590 [lit.[4] bp 126–128 °C (6 mm), $n^{28}D$ 1.5571].

1-Bromo-2-*p*-bromophenylethane, bp 97–98.5 °C (1 mm) [lit.[4] bp 127 °C (6 mm)].

1-Bromo-2-*p*-nitrophenylethane, mp 68–70 °C (lit.[4] mp 69 °C).

1-Bromo-2,2-dideuterio-2-phenylethane was prepared as described by Saunders and Edison.[10] The mass spectrum showed that the sample contained 1.92 atoms of D/molecule.

18-Crown-6 ether (18C6), a commercial material (Fluka), was purified by crystallization from *n*-hexane, mp 38.5–39.5 °C (lit.[14] mp 39.5–40.5 °C).

Base–Solvent Solution. *tert*-Butyl alcohol was distilled after treatment with potassium metal. Solutions of alkoxide were obtained by reactions, under nitrogen, of freshly cut potassium and sodium with *tert*-butyl alcohol.

Kinetic Studies. For all compounds, with the exception of 1-bromo-2-*p*-nitrophenylethane, kinetics were carried out in a stoppered two-limb silica cell. In one limb was placed the substrate solution (1 ml) and in the other the base solution (1 ml) obtained mixing identical volumes of alkali *tert*-butoxide in *tert*-butyl alcohol and 18C6 in *tert*-butyl alcohol. The cell was placed in the thermostated compartment of a Beckman DB-GT spectrophotometer. After 20 min, the solutions of the kinetic run were mixed throughly and the cell rapidly placed again in the cell compartment of the spectrophotometer. Absorbances were measured at the following wavelengths (nm): 250 for styrene; 252 for *p*-methylstyrene; 258 for *p*-methoxystyrene; 254 for *p*-bromostyrene. The reference cell contained a solution of alkali *tert*-butoxide and 18C6 in *tert*-butyl alcohol, both at the same concentration used in the kinetic run, to compensate for the significant absorption exhibited by complexed *t*-BuOK at 250–260 nm. The compensation, however, turned out to be not effective when the base concentration was larger than 0.01 M. The eliminations from 1-bromo-2-*p*-nitrophenylethane were followed on a Durrum-Gibson D-110 stopped-flow spectrophotometer. The wavelength used in this case was 300 nm. In some kinetic runs for 1-bromo-2-phenylethane and 1-bromo-2,2-dideuterio-2-phenylethane the mixed kinetic method described by Jones was also used.[15] The values of k_2 obtained with this method were in good agreement with those obtained with the procedure previously described.

The k_2 values at temperatures different from 30 °C were not corrected for the solvent expansion.

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Registry No.—Crown ether, 17455-13-9; *t*-BuOK, 865-47-4; *t*-BuOH, 75-65-0.

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(5) The fact that the k_2 values in *t*-BuOK–*t*-BuOH are independent of the base concentration allows one to conclude that only ion pairs and (or) ionic aggregates (having similar reactivity) are the active nucleophiles in this base–solvent system. On the basis of this conclusion the observed effect of *t*-BuOK concentration on both the geometrical and positional orientation of some elimination reactions[2a] is probably to be attributed to an equilibrium between ion pairs and ionic aggregates (in these cases of different reactivity) rather than to an equilibrium between dissociated and associated *tert*-butoxide ions. Accordingly, whereas the difference in reactivity between associated and dissociated *t*-BuOK must be very large, as shown by the effect of the addition of crown ether, and therefore significant with any substrate, that between ion pairs and ionic aggregates could be much smaller. Thus, it is not unreasonable to suggest that the latter difference may be of importance with some substrates[2a] and insignificant with others (1-bromo-2-phenylethane and 1-phenyl-2-chloropropane[2b]).
(6) An equilibrium of this kind has been suggested to explain the three-halves order dependence of reaction rates on *t*-BuOK concentration found in the reaction of 1-halo-2,2-diphenylethylenes in *t*-BuOK–*t*-BuOH: J. G. Pritchard and A. A. Bothner-By, *J. Phys. Chem.*, **64**, 1271 (1960).
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Reactivity of Carbon Disulfide with Aryl Radicals

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Carbon disulfide reacts with carbenes and thioketocarbenes to afford cycloaddition products on double bond C=S, and thus reacts with diaryldiazomethane[1] to yield 3,6-dimethylene-1,2,4,5-tetrathiocyclohexanes and with 1,2,3-benzothiadiazole[2] affording benzo-1,3-dithiol-2-thione, though the latter reaction may be seen as 1,3-dipolar addition. We wish to report some experimental results on the reactivity of carbon disulfide toward aryl radicals generated by reduction of aryldiazonium fluoroborates by iodide ions.[3] The reaction, carried out at room temperature by adding sodium iodide to a solution of the appropriate aryldiazonium fluoroborate (**1**) in a 1:1 acetone/carbon disulfide mixture, gives diaryl disulfide (**2**), diaryl trithiocarbonate (**3**), and small quantities of iodoarene (Scheme I).

Scheme I

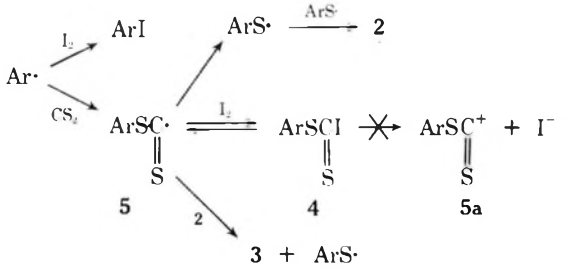
$$\underset{\mathbf{1}}{ArN_2^+BF_4^-} + CS_2 \xrightarrow{NaI} ArI + \underset{\mathbf{2}}{ArSSAr} + \underset{\mathbf{3}}{(ArS)_2CS}$$

As it can be seen in Table I, yields of disulfides are good, and this reaction may represent an alternative to the traditional Leukart reaction → oxidation pathway[4] to symmetrical disulfides, except for some derivatives such as OCH_3 and SCH_3.[5]

The first step of this reaction is very likely the attack of aryl radical on the sulfur atom of carbon disulfide leading to the radical **5**. Three kinds of reactions are possible from this intermediate: (1) loss of carbon monosulfide generating arylthio radicals which afford **2** by dimerization; (2) homolytic substitution SH2 on a sulfur atom of S–S bond of **2** to give **3**, and (3) reversible reaction with iodine to afford **4** (Scheme II).

Scheme II

$$\underset{\mathbf{1}}{ArN_2^+BF_4^-} + NaI \longrightarrow [ArN_2I] \longrightarrow Ar\cdot + N_2 + I\cdot$$



The reaction carried out at 0 °C (under nitrogen) leads actually to the separation of the highly instable aryl iododithioformate (**4**) which is easily converted by light or heating at 30–40 °C into **2**, **3**, and iodine (Scheme III).

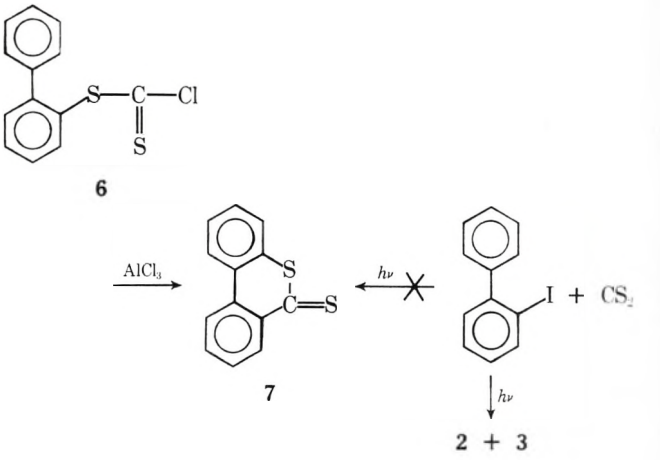
A cationic mechanism with **5a** as intermediate can be ruled out by examining products of the heterolytic Friedel–Crafts type reaction[17] between 2-biphenylyl chlorodithioformate (**6**) and $AlCl_3$ in carbon disulfide. **2**, Ar = *o*-PhPh, and **3**, Ar = *o*-PhPh, are not present in the reaction mixture and dibenzo[c,*e*]thiin-2-thione (**7**) was obtained in quantitative yield. On the other hand, when 2-iodobiphenyl was photolyzed in an ether/carbon disulfide mixture the products isolated were **2**, Ar = *o*-PhPh, and **3**, Ar = *o*-PhPh, but no traces of **7** were found in agreement with results obtained from the decomposition of **1**, Ar = *o*-PhPh, with NaI (Scheme IV).

Scheme III

$$\mathbf{1} + CS_2 \xrightarrow{NaI} \underset{\mathbf{4}}{Ar{-}SC(=S){-}I} \xrightarrow[30\text{–}40\ ^\circ C]{light} \mathbf{2} + \mathbf{3} + I_2$$

Ar = *o*-PhPh

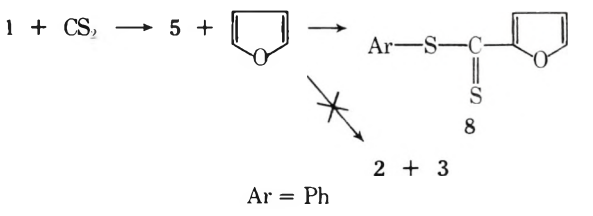
Scheme IV



The intervention of **5** as intermediate was further on demonstrated by decomposing **1**, Ar = Ph, in a 1:1 furan/carbon disulfide mixture. In this case aryl 2-dithiofuroate (**8**) was obtained in 75% yield together with trace amounts of **2**. No substitution products deriving from attack of aryl radicals on the furan ring were detected by GLC though the furan is known to be highly reactive in homolytic aromatic substitution.[18]

This fact indicates that carbon disulfide is an effective scavenger of aryl radicals (Scheme V).

Scheme V



Ar = Ph

Experimental Section

GLC analyses were carried out with a Varian 1440/1 instrument (5% SE-30 on a Varaport column). The reaction products were all identified by comparison (mixture melting point, NMR, and mass spectra) with authentic samples prepared independently. NMR spectra were recorded with a JEOL 60-MHz instrument and mass spectra with a JEOL D-100 instrument. All the aryldiazonium fluoroborates,[19] diphenyl trithiocarbonate (**3**),[20] and 2-mercaptobiphenyl[4] were prepared according to the procedures described in the literature. Only

Table I. Yields[a] of Ar–S–S–Ar (2) from Reaction of $ArN_2^+BF_4^-$ (1) with NaI in a 1:1 Acetone/Carbon Disulfide Mixture

Ar	Registry no.	Yield, %	Ar	Registry no.	Yield,[a] %
Phenyl[6]	882-33-7	47	*m*-Anisyl[11]	59014-89-0	46
o-Tolyl[7]	4032-80-8	60	*p*-Tolyl[12]	103-19-5	45
o-Anisyl[8]	13920-94-0	10	*p*-Anisyl[13]	5335-87-5	45
2-Biphenylyl[4]	19813-97-9	33	*p*-Nitrophenyl[14]	100-32-3	34
o-Phenylthiophenyl[9]	58074-47-8	45	*p*-Chlorophenyl[15]	1142-19-4	40
o-Methylthiophenyl[10]	59014-88-9	0	2,6-Xylyl[16]	2905-17-1	30

[a] Based on the starting aryldiazonium fluoroborate (1).

well-dried samples of diaryldiazonium fluoroborates were used. Carbon disulfide was dried with calcium chloride and then distilled twice. Acetone was refluxed over $KMnO_4$ and distilled over P_2O_5 twice.

Decomposition of Aryldiazonium Fluoroborate (1). General Procedure. The salt (0.01 mol) was dissolved in acetone (30 ml). To the solution was first added CS_2 (30 ml) and then NaI (1.5 g) in small quantities under stirring. After nitrogen evolution the mixture was refluxed for 30 min and the solvent evaporated. The crude was dissolved in chloroform, washed with water and dried and the solvent removed under vacuum. The mixture was analyzed on GLC or chromatographed on a silica gel column.

A. From 1 (R = Ph) diphenyl disulfide (**2**, 47%) and diphenyl trithiocarbonate (**3**, 35%) were separated by column chromatography on silica gel, using light petroleum as an eluent.

B. From 1 (R = *o*-PhPh) were obtained 2-iodobiphenyl, 2-biphenylyl disulfide (**2**, 33%), and a yellow product identified as di-2-biphenylyl trithiocarbonate (**3**, 30%): mp 119 °C; mass spectrum *m/e* 414 ($M^{\cdot+}$, 11), 370 (6), 338 (35), 229 (100), 197 (40), 185 (39), 184 (43), 152 (40). Anal. Calcd for $C_{25}H_{18}S_3$: C, 72.42; H, 4.38; S, 23.22. Found: C, 72.1; H, 4.4; S, 23.4.

C. From 1 (R = o-PhPh) at 0 °C. The salt (0.01 mol) was dissolved in acetone (30 ml) under nitrogen in the dark and CS_2 (30 ml) was added. The solution was cooled to −5 to 0 °C and NaI (1.5 g) was added slowly under stirring. After 10 min, the nitrogen flow was increased and the solvent evaporated at 0 °C. The crude was rapidly extracted with light petroleum, and the organic layer filtered on silica gel (h = 15 cm) under nitrogen. A dilute solution of 2-biphenylyl iododithioformate (**4**) was obtained, and was kept at −20 °C. This solution, gently heated at 30–40 °C, or exposed to uv light, rapidly affords iodine, 2-biphenylyl disulfide (**2**), and di-2-biphenylyl trithiocarbonate (**3**) identified by TLC. An alcoholic solution of **4** gives a positive test with alcoholic $AgNO_3$: mass spectrum *m/e* 356 ($M^{\cdot+}$) (0.5), 280 (100), 184 (35), 185 (45), 153 (100).

D. From 1 (R = Ph) in Furan. The salt (0.01 mol) was suspended in a furan (30 ml) and CS_2 (30 ml) mixture, and NaI (1.5 g) was added in small quantities under stirring at room temperature. The solution was stirred for 5 h, washed with water, and dried, and the solvent was evaporated. By column chromatography of the crude on silica gel were separated diphenyl disulfide (**2**, traces) and phenyl 2-dithiofuroate (**8**, 75% yield) as a red oil: bp 85 °C (1 mm); mass spectrum *m/e* 220 ($M^{\cdot+}$, 21), 111 ($M^{\cdot+}$ − PhS·, 100). Anal. Calcd for $C_{11}H_8OS_2$: C, 59.97; H, 3.66; S, 29.11. Found: C, 60.0; H, 3.65; S, 29.4.

Photolysis of 2-Iodobiphenyl. A solution of 2-iodobiphenyl (0.9 g, 0.005 mol) in Et_2O (8 ml) and CS_2 (2 ml) mixture was photolyzed using a low-pressure mercury lamp Hanau Type P.L. 368 for 12 h. By column chromatography of the reaction mixture on silica gel, unreacted starting product (0.7 g), 2-biphenylyl disulfide (**2**, 30%), and di-2-biphenylyl trithiocarbonate (**3**, 30%) were separated.

Reaction of 2-Biphenylyl Chlorodithioformate (6) with $AlCl_3$. A solution of **6** (2.4 g, 0.0092 mol) in CS_2 (35 ml) was added at room temperature to a suspension of $AlCl_3$ (1.37 g, 0.0103 mol) in CS_2 (23 ml) under stirring. The mixture was refluxed for 1 h, and then poured into a cold solution of $NaHCO_3$, then extracted with Et_2O. The organic layer was dried and the solvent removed under vacuum. Dibenzo[*c*,*e*]thiin-2-thione (**7**) was obtained in quantitative yield as a red solid, mp 106–107 °C, which crystallizes from light petroleum (bp 75–120 °C): mass spectrum *m/e* 228 ($M^{\cdot+}$, 100), 184 (65). Anal. Calcd for $C_{13}H_8S_2$: C, 68.38; H, 3.53; S, 28.08. Found: C, 68.4; H, 3.53; S, 28.2.

2-Biphenylyl chlorodithioformate (6) was prepared according to the general procedure described by Rivier:[21] bp 164–165 °C; mass spectrum *m/e* 264 ($M^{\cdot+}$, 15), 229 (14), 185 (100), 152 (29).

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Registry No.—1 (R = Ph), 369-57-3; 1 (R = *o*-MePh), 2093-46-1; 1 (R = *o*-MeOPh), 17685-76-6; 1 (R = *o*-PhPh), 318-13-8; 1 (R = *o*-PhSPh), 59014-91-4; 1 (R = *o*-MeSPh), 52959-17-8; 1 (R = *m*-MeOPh), 17569-84-5; 1 (R = *p*-MePh), 459-44-9; 1 (R = *p*-MeOPh), 459-64-3; 1 (R = *p*-NO_2Ph), 456-27-9; 1 (R = *p*-ClPh), 673-41-6; 1 (R = 2,6-diMePh), 2192-33-8; 3 (R = Ph), 2314-54-7; 3 (R = *o*-PhPh), 59014-92-5; 4 (R = *o*-PhPh), 59014-93-6; 6, 54199-77-8; 7, 54199-60-9; 8 (R = Ph), 59014-94-7; NaI, 7681-82-5; carbon disulfide, 75-15-0; 2-iodobiphenyl, 2113-51-1.

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A New Route to Acetylenes

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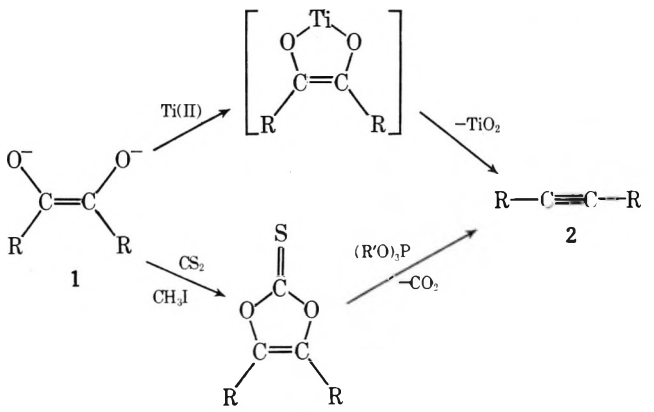
Most synthetic approaches to the formation of carbon–carbon triple bonds[1] involve eliminations which, unless the reactant is suitably constituted, can also lead to isomeric allenes, dienes, etc. A particularly useful acetylene synthesis, especially for strained cyclic acetylenes, is the conversion of an α-diketone to its bishydrazone, followed by oxidation (net *reduction* of carbon) with, e.g., mercuric oxide[2] or lead tetraacetate.[3]

In our quest for synthetic routes to a novel cyclic acetylene,

we attempted under many conditions but without success to make the bishydrazone of a tetra-α-substituted cyclic diketone. We attributed these failures to steric hindrance of attack at the carbonyl groups, as previously seen in attempts to make the 2,4-DNP derivative of hindered α-diketones such as dipivaloyl.[4] During this period there appeared in the literature two novel olefin syntheses which we hoped could be extended to acetylenes. McMurry[5] found that treatment of certain carbonyl compounds with titanium trichloride–lithium aluminum hydride complex led to olefins via reductive coupling. Similarly, Paquette[6] reported that vicinal diols react with carbon disulfide to form thiocarbonates, which give olefins upon treatment with phosphite esters.

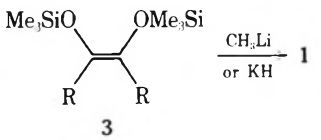
Scheme I



1a, R = C_6H_5
b, R = n-C_3H_7
c, 2R = $-(CH_2)_{10}-$

Scheme I shows how both of these might be used in acetylene syntheses. The key to this route is anion **1**, which is the intermediate in the acyloin condensation, and can also be prepared by reducing the corresponding α-diketones with ethylmagnesium bromide.[7] Note, however, that the success of Scheme I depends on **1** having cis stereochemistry, which is almost certainly less favorable than the trans isomer on both steric and electrostatic grounds. In fact **1** should resemble an α-diketone, but its barrier to rotation should be higher. Except when the R groups comprise a small ring, α-diketones prefer the s-trans geometry.[8] Thus we were not discouraged when initial attempts to make acetylenes via this route were unsuccessful. We also attempted without success to prepare **1** from α-diketones with "activated" magnesium,[9] in hopes that the incipient magnesium ions would coordinate best to cis oxygens.

The need for a covalent precursor to *cis*-**1** was, however, filled by the known[10] bis(trimethylsilyl) ethers (**3**), the stereoisomers of which are usually separable. Treatment of the cis diether with methyllithium[11] or potassium hydride[6] would then give only *cis*-**1**.[10d]



3

Starting with the known[10] ethers **3a–c**, attempts were first made to treat the corresponding anions **1a–c** with McMurry's reagent.[5] The reaction mixtures were complex, comprising only ca. 5% of the desired acetylenes, together with major amounts of the related olefins, diketones, ketones, and acyloins. A control experiment suggested that the acetylene products were themselves reduced to olefins by McMurry's reagent, although the reaction was not clean.[10e]

However, treatment of **1a–c** with carbon disulfide, followed by reaction with triethyl phosphite, afforded the corresponding acetylenes in moderate yield. These results are summarized in Table I.

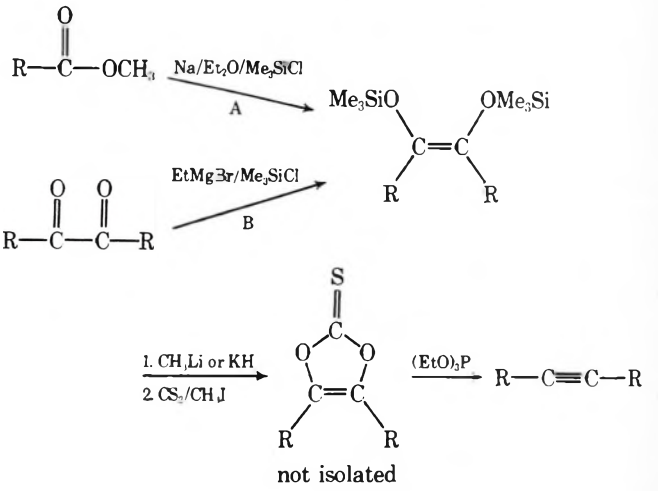


Table I. Yields of Acetylenes and Their Precursors

R	Yield of bis-Me_3Si ether, % A	Yield of bis-Me_3Si ether, % B	Yield of acetylene based on ether, %
C_6H_5	35 (100% cis)	33 (57% cis)	35
n-C_3H_7	90 (100% cis)		28
$2R = -(CH_2)_{10}-$	50 (100% cis)	35 (100% cis)	25

Significantly, when the bis-Me_3Si ether (**4**) of dipivaloyl [R = $C(CH_3)_3$], which is known to be trans,[12] is treated under these conditions, no di-*tert*-butylacetylene[13] is observed, further evidence for the cis requirement of the intermediate.

While this method constitutes a new route to acetylenes from diketones, combined yields are somewhat lower than via the bishydrazone. However, if one must first make the diketone from a diester, this method represents a considerable improvement.

Initial attempts to employ this procedure with the highly hindered diketone alluded to above have failed at the bis ether stage. Further work is being carried out to see if other low valent soluble transition metal ions might effect reduction of **1** to **2**.

Experimental Section

Materials and Methods. Methyl benzoate, methyl pivalate, ethyl butyrate, dodecanedioic acid, benzil, triethyl phosphite, and carbon disulfide were purchased from Aldrich Chemical Co. Cyclododecane-1,2-dione was prepared from known procedures.[16] Methyllithium was purchased from Alfa-Ventron Corp.

The following instruments were employed: Perkin-Elmer 337 infrared spectrophotometer (calibrated with polystyrene); Varian A-60 and T-60 [δ, parts per million downfield from internal $(CH_3)_4Si$]; Bruker HFX-90 (^{13}C data are given in parts per million upfield from CS_2); Hitachi RMU-7 (70 eV).

Melting and boiling points are not corrected.

Preparation of bis-Me_3Si ethers 3a–c and 4 was carried out by method A, as described previously.[10] Physical data for these compounds are summarized below.

3a: bp 83–85 °C (0.03 mm) [lit.[10a] 145–146 °C (2.2 mm)]; ir (neat) 3045, 3010, 2945, 1635, 1275, 839 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.16 (s, 18 H), 6.9–7.3 (m, 10 H); MS *m/e* 356 (45), 147 (100).

3b: bp 106–108 °C (12 mm) [lit.[10b] 105–108 °C (12–13 mm)]; ir (neat) 1675, 1245, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.16 (s, 18 H), 0.90 (t, J = 6.5 Hz, 6 H), 1.50 (m, 4 H), 2.05 (m, 4 H).

3c:[10c] bp 96–98 °C (0.20 mm); ir (neat) 1676, 1238, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.16 (s, 18 H), 1.38 (s, $\Delta\nu_{1/2}$ = 8 Hz, 16 H), 1.85–2.25 (m, 4 H); MS *m/e* 342 (3), 148 (100).

4: bp 70–72 °C (0.1 mm); mp 48–49 °C (Et_2O) [lit.[12] bp 88–95 °C (1 mm); mp 47–49 °C]; ir ($CHCl_3$) 1255, 1245, 1145, 840 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0.24 (s, 18 H), 1.16 (s, 18 H).

Preparation of 3c by Method B.[7] A THF solution of ethylmagnesium bromide was prepared from magnesium (4.86 g, 0.20 mol), ethyl bromide (25.06 g, 0.23 mol), and 125 ml of dry THF. The solution was cooled to 10–15 °C and 9.8 g (0.05 mol) of cyclododecane-1,2-dione in 30 ml of THF was added dropwise over a 30-min period. After the mixture was stirred at room temperature for 2 h, the reaction vessel was cooled in an ice bath and 21.6 g (0.20 mol) of chlorotrimethylsilane was added dropwise in approximately 30 min. After the mixture was stirred overnight at ambient temperature, pentane (500 ml) was added to the reaction solution to precipitate most of the inorganic salts. The mixture was filtered through alumina, concentrated in vacuo, and distilled to yield 5.98 g (35%) of clear colorless **3c.**

When benzil was subjected to the above conditions, a mixture of *cis*-**3a** (57%) and *trans*-**3a** (δ 0.05 ppm, 43%) was obtained in 33% yield.

Preparation of Acetylenes from Bis-Me_3Si Ethers. General Procedure A (Better of Two). Into a 65-ml round-bottom flask equipped with a magnetic stirring bar, a pressure-equalized dropping funnel, a nitrogen atmosphere, and cooled in a dry ice–acetone bath were placed the bis-Me_3Si ether (2 mmol) and 7.0 ml of dry THF. Methyllithium (4 mmol) in Et_2O was introduced dropwise to the reaction vessel over 10 min. The flask was allowed to warm slowly to room temperature then stirring was continued overnight at 30 °C. A solution of carbon disulfide (156 μl, 2.6 mmol) in 5.0 ml of THF was added at 0 °C, and the mixture was stirred at room temperature for 30 min, then at 70 °C for 30 min. The flask was cooled in an ice bath, and methyl iodide (156 μl) in THF (2 ml) was added, followed by stirring at room temperature for 30 min and then at 60 °C for 30 min. After cooling to room temperature, the mixture was diluted with 50 ml of ether. The ethereal solution was washed with water and brine, filtered through alumina, and concentrated in vacuo to yield an orange oily residue. Triethyl phosphite (2 ml) was added to the orange residue; the solution was gently refluxed under nitrogen for 3 days. The cooled reaction mixture was extracted with hexane (4 × 15 ml), and the combined organic layers were washed with water, dried, and evaporated under reduced pressure. The residue was chromatographed on silica gel (pentane elution) to yield the acetylenes, which were identical with authentic materials.

General Procedure B. To a 65-ml round-bottom flask containing pentane-washed potassium hydride (~700 mg) and dry THF (5 ml) was added a solution of bis-Me_3Si ether (2 mmol) in THF (10 ml) and this was stirred at 35 °C overnight under a nitrogen atmosphere. A solution of carbon disulfide (156 μl, 2.6 mmol) in 5 ml of THF was added to the reaction vessel, and the mixture was stirred at room temperature for 30 min, then at 70 °C for 30 min. The flask was cooled in an ice bath, and a solution of methyl iodide (156 μl) in THF (2 ml) was added, followed by stirring at room temperature for 30 min, then heating at 60 °C for 30 min. After cooling to room temperature the mixture was diluted with 50 ml of ether; then the entire solution was centrifuged. The organic solution was decanted from the residue which was subsequently washed with more ether (10 ml). The combined organic layers were treated with *tert*-butyl alcohol (5 ml) to destroy residue potassium hydride, filtered through a short column of alumina, and evaporated to leave an orange residue. After triethyl phosphite (2 ml) was added to the orange residue, the solution was gently refluxed under nitrogen for 3 days. The cooled reaction mixture was extracted with hexane (4 × 15 ml), and the combined organic layers were washed with water, dried, and evaporated. The residue was chromatographed on silica gel (pentane elution) to yield the acetylene.

Analytical Data for Acetylenes. 2a: mp 57–59 °C (lit.[14] 58–60 °C); ir ($CHCl_3$) 3070, 3050, 3000, 2210, 1600, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.75 (m).

2b: bp 130–131 °C (lit.[15] 131.8 °C); ir (neat) 2970, 1460, 1380, 1340, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, *J* = 6.5 Hz, 6 H), 1.51 (m, 4 H), 2.12 (t, *J* = 5.5 Hz, 4 H).

2c:[16] ir (neat) 2220, 1099, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (m, $\Delta\nu_{1/2}$ = 10 Hz, 16 H), 2.21 (m, 4 H); ^{13}C NMR (CS_2) 111.2, 166.4, 167.3, 173.8 ppm; MS *m/e* 164 (3), 66 (100).

Acknowledgment. This work was generously supported by a grant from USPHS-NIH, 5 R01 AI 11690.

Registry No.—**1a,** 59034-61-6; **1b,** 59034-62-7; **1c,** 59034-63-8; **2a,** 501-65-5; **2b,** 1942-45-6; **2c,** 1129-90-4; **3a,** 37980-77-1; **3a** trans isomer, 26312-21-0; **3b,** 59034-64-9; **3c,** 59034-65-0; **4,** 59034-66-1; cyclododecane-1,2-dione, 3008-41-1; chlorotrimethylsilane, 75-77-4.

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New Reactions and Reagents. 5. Ketalization of 1,3-Dihydroxy-2-propanone with Alkanols. Formation of Acyclic and Cyclic Ethers Derived from Pyruvic Aldehyde[1]

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The transformations of 1,3-dihydroxy-2-propanone (dihydroxyacetone, DHA) and its derivatives have been of interest for over 20 years. DHA itself has been shown to undergo a variety of isomerization and dehydration reactions.[2,3] Among the more important homologues of DHA, the transformations of cortisone and related steroids containing a C-17 dihydroxypropanone moiety have been the subject of several reports. In this context it has been known for many years that the ketalization of these steroids resulted in low yields of the expected products. The generation of β-keto acetals as the by-products of these reactions was subsequently discovered in several laboratories. Their formation was eloquently postulated in terms of a Mattox rearrangement[4] involving a dehydration–ketalization sequence (Scheme I).[5–9] The rear-

Scheme I

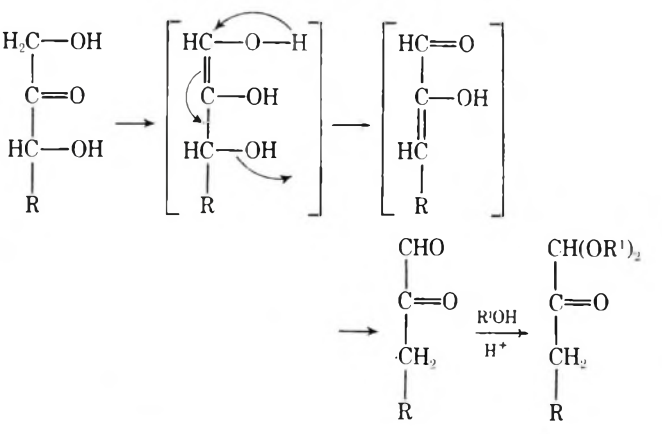


Table I. Preparation of 1,1-Dialkoxy-2-propanones (1) from DHA and Alkanols

Compd	R substituent in 1	% yield GLC	% yield Isolated	Bp, °C (mm)	NMR, δ ($CDCl_3$, Me_4Si)
1a	CH_3	96	82	82 (70)	2.2 (s, 3 H), 2.4 (s, 6 H), and 4.3 (s, 1 H)
1b	C_2H_5	99	92	82 (50)	1.23 (t, 6 H), 2.2 (s, 3 H), 3.7 (m, 4 H), and 4.53 (s, 1 H)
1c	$CH_3(CH_2)_2$	98.5	90	82 (14)	0.91 (t, 6 H), 1.57 (m, 4 H), 2.15 (s, 3 H), 3.55 (m, 4 H), and 4.5 (s, 1 H)
1d	$(CH_3)_2CH$	98	85	59 (14)	1.1 (pair of doublets, 12 H), 2.11 (s, 3 H), 3.86 (m, 2 H), and 4.55 (s, 1 H)
1e	$CH_3(CH_2)_3$	95	90	92 (29)	0.93 (m), and 1.5 (m, total 14 H), 2.15 (s, 3 H), 3.61 (m, 4 H), and 4.5 (s, 1 H)

rangement–acetalization sequence postulated in Scheme I, however, has so far not been investigated with DHA.[10] The present work reports the acid-catalyzed transformations of DHA in the presence of mono-, di-, and trihydric alkanols and the structures of the resulting ether products.

Results and Discussion

A. Reaction of DHA with Monohydric Alkanols. The protonated cation-exchange resin catalyzed reaction of DHA with monohydric alkanols resulted in the exclusive formation of the corresponding 1,1-dialkoxy-2-propanones (**1**, eq 1). GLC

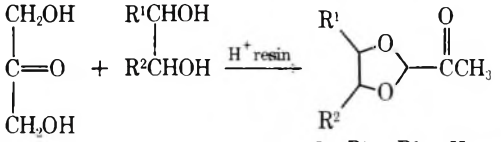
$$CO(CH_2OH)_2 \xrightarrow[H^+ \text{ resin}]{\text{ROH (excess)}} \underset{\displaystyle CH_3}{\overset{\displaystyle CH(OR)_2}{\overset{|}{\underset{|}{CO}}}} \qquad (1)$$

1

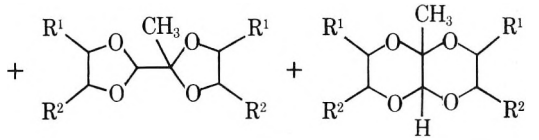
analysis of the reaction mixtures indicated that formation of potential by-products, such as 1,1,2,2-tetraalkoxypropanes or alkyl α,α-dialkoxypropionates, did not occur. Yields and characterization data of representative 1,1-dialkoxy-2-propanones prepared by this procedure are given in Table I.

B. Reaction of DHA with Dihydric Alkanols. The 1,2-diols offered the possibility of providing bicyclic products in addition to expected keto acetals **2**. Indeed, compounds of type **3** and **4** were also isolated from the reaction of DHA with ethylene glycol, 1,2-propanediol, and 2,3-butanediol (Scheme II). In contrast to the 1,2-diols, reaction of DHA with a 1,3-

Scheme II



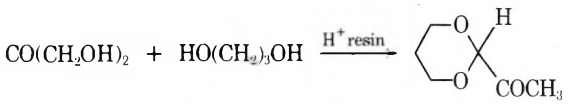
2a, $R^1 = R^2 = H$
b, $R^1 = H; R^2 = CH_3$
c, $R^1 = R^2 = CH_3$



3a, $R^1 = R^2 = H$
b, $R^1 = H; R^2 = CH_3$
c, $R^1 = R^2 = CH_3$

4a, $R^1 = R^2 = H$
b, $R^1 = H; R^2 = CH_3$
c, $R^1 = R^2 = CH_3$

diol, for example, 1,3-propanediol, gave 2-acetyl-1,3-dioxane (**5**) exclusively. The structures of **2a–c** and **5** were established by ir, NMR, mass spectral, and C, H microanalytical data. The relative structural identity of the compounds analogous to **3**



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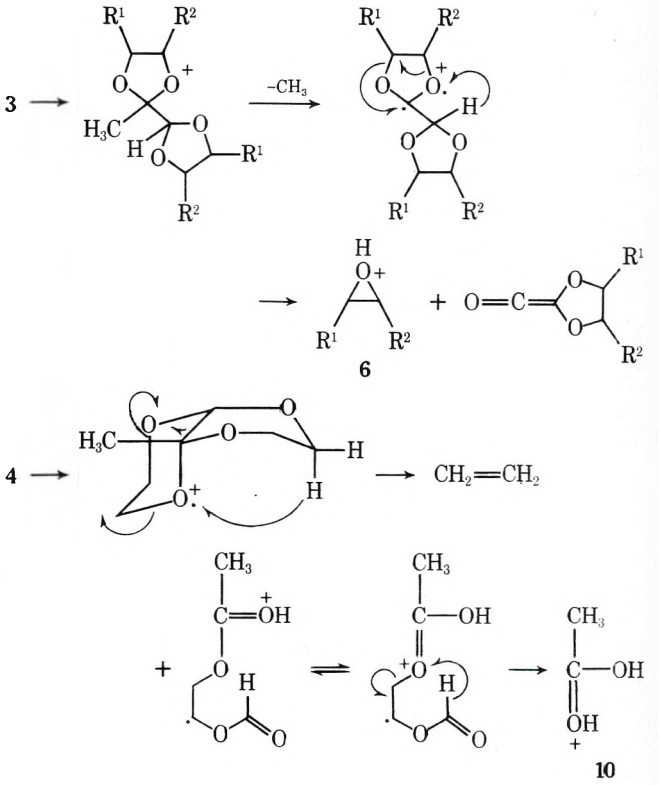
and **4** has been a subject of controversy.[11] NMR and mass spectral data have been used for this purpose in recent years.[12] It was determined during the present investigation that electron-impact induced fragmentation of **3** leads characteristically to the formation of a protonated oxirane ion (**6**),[13] whereas the protonated acetic acid ion (**10**) is produced from the fragmentation of **4** (Scheme III). The principal cations

Scheme III



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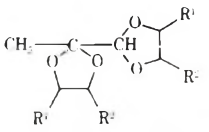
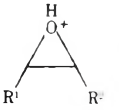
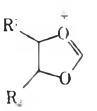
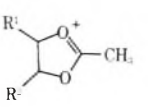
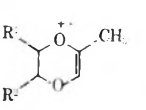
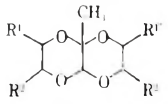
produced from **3** and **4** by electron impact are summarized in Table II.

The determination of the isomerism and stereochemistry of cyclic ethers **3** and **4** produced via DHA–glycol reactions offers a challenging problem. Compounds of type **3** derived from *dl*-1,2-propanediol, for example, may occur in eight possible *RS* stereomers resulting from the respective placement of methyl substituents on the two dioxolanyl moieties. Compound **3** derived from *meso*-2,3-butanediol should sim-

Table II. Principal Mass Spectral Fragments of 2-Methyl-2-(1,3-dioxolanyl)-1,3-dioxolanes (3) and 2-Methylhexahydro-*p*-dioxino[2,3-*b*]-*p*-dioxins (4)

 3	[M]$^+$	$CH_3C{\equiv}O^+$	 6	 7	 8	 9
a, $R_1 = R_2 = H$	160 (1)	43 (95)	45 (84)	73 (74)	87 (100)	100 (18)
b, $R_1 = H; R_2 = CH_3$	188 (0.4)	43 (82)	59 (35)	87 (27)	101 (100)	114 (18)
c, $R_1 = R_2 = CH_3$	216 (–)	43 (87)	73 (73)	101 (25)	115 (100)	128 (30)

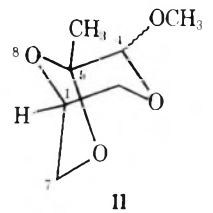
 4	[M]$^+$	$CH_3C{\equiv}O^+$	$HO{-}C(CH_3){=}OH^+$ 10	7	8	9
a, $R_1 = R_2 = H$	160 (49)	43 (100)	61 (50)	73 (95)	87 (98)	100 (26)
b, $R_1 = H; R_2 = CH_3$	188 (40)	43 (100)	61 (68)	87 (96)	101 (98)	114 (31)
c, $R_1 = R_2 = CH_3$	216 (1.1)	43 (100)	61 (8)	101 (23)	115 (98)	128 (28)

ilarly have the possibility of providing four meso isomers.[14,15] *p*-Dioxino-*p*-dioxins **4** pose a stereochemical situation where in addition to the possibility of cis or trans ring junction,[12,16] several regiopositioned methyl substituents resulting in *RS* and meso forms are conceivable. This facet of the structural chemistry of **3** and **4** is beyond the scope of present work.

C. Reaction of DHA with Trihydric Alkanols. The acid-catalyzed reaction of DHA with glycerol resulted in the formation of a polymeric material. However, upon fortuitous addition of methanol as a solvent in this reaction, the formation of three products was detected by GLC. Component A was subsequently separated by spinning band distillation of the reaction mixture. Based on ir, NMR (60 MHz), mass

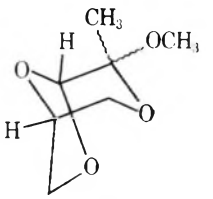
$$CO(CH_2OH)_2 + HOCH(CH_2OH)_2 + CH_3OH \xrightarrow{H^+} \underset{50\%}{\mathbf{1a}} + \underset{30\%}{A} + \underset{5\%}{B}$$

spectral, GLC (single peak, three different columns), and CH microanalytical data, three possible structures (**11**, **12**, **13**) were postulated for this product. The 100-MHz ^{1}H NMR spectrum revealed the methyl resonance as two singlets (1:1 ratio, $\Delta = 1.8$ Hz), the methoxyl protons as two singlets (1:1 ratio, $\Delta = 5$ Hz), and C-4 proton as two singlets (1:1 ratio; $\Delta = 18$ Hz). These data indicated a 1:1 mixture of C-4 axial–equatorial methoxy substituted **11** to be the most likely composition of A.[17] This fact was further supported by a ^{13}C NMR spectrum of A which showed seven pairs of peaks.



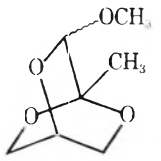
11

4-methoxy-5-methyl-3,6,8-trioxabicyclo[3.2.1]octane



12

4-methoxy-4-methyl-3,6,8-trioxabicyclo[3.2.1]octane



13

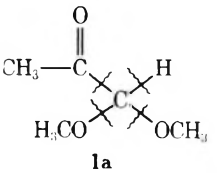
1-methyl-6-methoxy-2,5,7-trioxabicyclo[2.2.2]-octane

Product **11** was also synthesized according to eq 2.[18] The preparation of **11** containing a C-4 ethoxy or isopropoxy substituent instead of methoxy was carried out via the reaction of DHA with glycerol in the presence of corresponding alkanol.

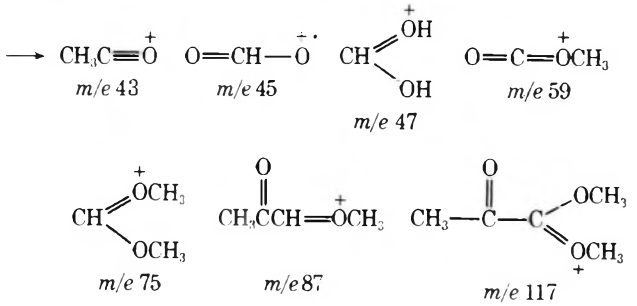
$$\mathbf{1a} + HOCH(CH_2OH)_2 \xrightarrow[\Delta]{H^+} \mathbf{11} + CH_3OH \qquad (2)$$

Experimental Section[19]

Reaction of DHA with Monohydric Alkanols (Table I). The following preparation of 1,1-dimethoxy-2-propanone (**1a**) is representative. A mixture of DHA[20] (90 g), methanol (270 ml), and Amberlyst-15[21] (9 g) was stirred at 100–110 °C for 4 h in a pressure vessel. After removal of catalyst by filtration, the filtrate was diluted with water and then extracted with methylene chloride. The distillation of the organic extract gave the title compound in 82% yield (GLC purity 98%). Mass spectrum (70 eV): principal cations follow.



1a



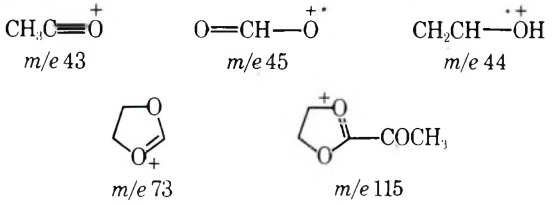
m/e 43 *m/e* 45 *m/e* 47 *m/e* 59

m/e 75 *m/e* 87 *m/e* 117

Reaction of DHA with Ethylene Glycol. A mixture of DHA[20] (36 g, 400 mmol), ethylene glycol (100 ml), and Amberlyst-15[22] (3.6 g) was stirred at 100–110 °C for 4 h. After cooling, the reaction mixture was diluted with water (400 ml), filtered, and extracted with methylene chloride (2 × 100 ml). GLC analysis of the extract showed the

presence of **2a**, **3a**, and **4a** in 9:69:22 ratio, respectively. After drying ($MgSO_4$) the solvent was evaporated to give 40.7 g of a clear liquid. Distillation gave 34.7 g of a product, bp 52–59 °C (1.5 mm). Fractionation on a spinning band column provided the following three compounds.

2-Acetyl-1,3-dioxolane (**2a**): yield 1 g; bp 46 °C (7 mm); n^{24}D 1.4270; ir (neat) 2900, 1730, 1355 cm^{-1}; NMR 2.20 (s, 3 H), 4.05 (s, 4 H), and 5.0 ppm (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 116 (0.8), 115 (2), 73 (100), 45 (84), 44 (57), 43 (87); principal cations follow.



Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.90. Found: C, 51.20; H, 6.80.

2-Methyl-2-(1,3-dioxolanyl)-1,3-dioxolane (**3a**): yield 5.2 g; bp 68–69 °C (5 mm); n^{24}D 1.4459; ir (neat) 2975, 2880, 1475, 1450, 1375, 1250, 1190, 1120, 1050, 950, 880, 810, 690 cm^{-1}; NMR 1.31 (s, 3 H), 3.73–4.13 (m, peaks at 3.96, 4.0, 4.03, 8 H), and 4.85 ppm (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 160 (1), 101 (3.5), 100 (17.5), 99 (6), 87 (100), 73 (74), 59, 58, 57, 56, 55, 43 (95).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.50; H, 7.50. Found: C, 52.88; H, 7.62.

2-Methylhexahydro-*p*-dioxino[2,3-*b*]-*p*-dioxin (**4a**): yield 2.6 g; bp 74 °C (5 mm); n^{24}D 1.4611; ir (neat) 2950, 2875, 1455, 1375, 1290, 1190, 1140, 1100, 1005, 950, 930, 895, 870, 860, 790, 635 cm^{-1}; NMR 1.43 (s, 3 H), 3.41–4.26 (m, 22 peaks, 4 H), and 4.5 ppm (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 160 (49), 133 (2.4), 100 (26), 87 (98), 73 (95), 61 (50), 55 (16), 43 (100).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.50; H, 7.50. Found: C, 52.17; H, 7.36.

Reaction of DHA with 1,2-Propanediol. DHA (36, g, 400 mmol) was treated with 1,2-propanediol (100 ml) in the presence of Amberlyst-15 (3.6 g) at 100–110 °C for 4 h. Usual workup gave, after distillation, 51.1 g of product, bp 59–61 °C (1.5 mm). Fractionation on a spinning band column gave a low-boiling product, presumably **2a**, a pure fraction of **3b**, and a fraction containing **3b** and isomeric **4b**. Isomeric mixture of **4b** was then separated by GLC from the latter mixture for mass spectral characterization.

2,4-Dimethyl-2-(4-methyl-1,3-dioxolanyl)-1,3-dioxolane (**3b**): yield 30.8 g; bp 69–70 °C (5 mm); n^{24}D 1.4352; ir (neat) 2975, 2925, 2875, 1450, 1375, 1250 cm^{-1}; NMR 1.2–1.43 (m, 9 H), 3.3–3.71 (m, 2 H), 3.88–4.61 (m, 4 H), 4.8, 4.81, 4.93 ppm (s, total 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 188 (0.4), 140 (80), 114 (18), 109 (87), 101 (100), 87, (27), 85 (21), 81 (22), 73 (2.5), 71 (4), 59 (35), 56, 55, 54, 53, 52, 43 (82).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.50; H, 8.50. Found: C, 57.30; H, 8.61.

2,5(or 6),8(or 9)-Trimethylhexahydro-*p*-dioxino[2,3-*b*]-*p*-dioxin (**4b**): mass spectrum (70 eV) *m/e* (rel intensity) 189 (2.6), 188 (40), 115 (5), 114 (31), 101 (98), 87 (96), 73 (8), 61 (68), 59 (89), 43 (100).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.50; H, 8.50. Found: C, 57.20; H, 8.62.

Reaction of DHA with *meso*-2,3-Butanediol. DHA (36 g, 400 mmol) was treated with *meso*-2,3-butanediol (100 ml) in the presence of Amberlyst-15 (3.6 g) in the usual manner. GLC examination of the reaction mixture showed three products in 10:50:40 ratio. The distillation gave 26.2 g of product, bp 50–54 °C (0.5 mm). Fractionation gave two pure and one rather contaminated fractions. The latter was believed (GLC retention time) to be 2-acetyl-4,5-dimethyl-1,3-dioxolane (**2c**), and was not characterized further.

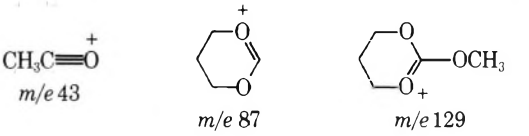
2,4,5-Trimethyl-2-(4,5-dimethyl-1,3-dioxolanyl)-1,3-dioxolane (**3c**): yield 5 g; bp 68–70 °C (4 mm); n^{24}D 1.4283; ir (neat) 3000, 2970, 2880, 1455, 1285, 1190, 1135, 1095, 1000, 950, 895, 870, 860, 790, 635 cm^{-1}; NMR 1.2–1.46 (m, 15 H), 3.51–4.0 (m, 4 H), and 4.91 ppm (m, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 143 (9.3), 129 (15), 128 (30), 115 (100), 101 (25), 99 (15), 85 (13), 73 (73), 56 (67), 55 (68), 43 (87).

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.11; H, 9.20. Found: C, 60.77; H, 9.04.

2,5,6,8,9-Pentamethylhexahydro-*p*-dioxino-[2,3-*b*]-*p*-dioxin (**4c**): yield 2.0 g; bp 74 °C (4 mm); n^{24}D 1.4345; ir (neat) 2975, 2925, 2860, 1460, 1450, 1380, 1260, 1205, 1120, 1100, 1060 cm^{-1}; NMR 1.01–1.53 (m, 9 peaks, 15 H), 3.43–4.01 (m, 2 H), 4.05–4.65 (m, 2 H), and 4.73 ppm (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 216 (1.1), 170 (3), 143 (5), 129 (10), 128 (28), 116 (20), 115 (98), 101 (23), 99 (16), 85 (17), 73 (98), 61 (8), 56 (94), 55 (87), 43 (100).

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.11; H, 9.20. Found: C, 61.01; H, 8.80.

Reaction of DHA with 1,3-Propanediol. A mixture of DHA (36 g), 1,3-propanediol (100 ml), and Amberlyst-15 (3.6 g) was stirred at 100–110 °C for 4 h. GLC examination revealed the formation of one product. Usual workup gave 26.1 g of a crude product which after distillation gave 18.1 g of 2-acetyl-1,3-dioxane (**5**): bp 66 °C (5 mm); n^{24}D 1.4369; ir (neat) 2941, 2857, 1739, 1429, 1282, 1242, 1149, 1111, 1042, 909, 854 cm^{-1}; NMR 1.25–1.63 (m, 2 H), 2.18 (s, 3 H), 3.6–4.38 (m, 4 H), 4.75 ppm (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 130 (0.5), 129 (4.6), 101 (11), 87 (100), 73 (21), 59 (74), 43 (84), 41 (68); principal cations follow.



Anal. Calcd for $C_6H_{10}O_3$: C, 55.67; H, 7.82. Found: C, 55.30; H, 7.70.

Reaction of DHA with Glycerol. A mixture of DHA (36 g, 0.4 mol), glycerol (100 ml), and Amberlyst-15 (3.6 g) was stirred at 100–110 °C for 4 h. The ir spectrum of the reaction mixture indicated the absence of any carbonyl absorptions. After the usual workup the organic extract gave no product upon distillation of solvent. This reaction was, consequently, not pursued further.

Reaction of DHA with Glycerol in the Presence of Methanol. A mixture of DHA (36 g, 0.4 mol), glycerol (36 g, 0.4 mol), methanol (100 ml), and Amberlyst-15 (3.6 g) was shaken in a Parr apparatus at 100–110 °C for 4 h. The cooled reaction mixture upon GLC examination showed the presence of 1,1-dimethoxy-2-propanone (50%), products A (30%), and B (5%). After filtration the excess solvent was distilled off and the liquid residue diluted with water (200 ml) and extracted with methylene chloride. The distillation gave 30 g of liquid product, bp 40–44 °C (0.3 mm). Fractionation on spinning band column gave 15 g of A: bp 51 °C (1.5 mm); n^{24}D 1.4450; ir (neat) 2941, 1449, 1399, 1379, 1250, 1235, 1212, 1198, 1117, 1081, 1047, 1027, 952, 909, 870 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) 1.39 and 1.41 (two s, total 3 H), 3.44 and 3.49 (two s, total 3 H), 3.7–4.06 (m, 3 H), 4.12 (s, 0.5 H), 4.18 (m, 1 H), 4.30 (s, 0.5 H), and 4.44 (br t, 1 H); ^{13}C NMR ($CDCl_3$) (14 peaks in 7 pairs, each pair is approximately of equal intensity) 104.56 and 104.02; 101.46 and 98.74; 74.47 and 73.41; 68.47 and 67.69; 66.34 and 62.75; 56.02 and 54.86; 18.79 and 17.85; mass spectrum (70 eV) *m/e* (rel intensity) 160 (0.34), 144 (3.4), 128 (18), 99 (66), 87 (3), 73 (17), 72 (5), 61 (13), 59 (13), 58 (29), 58 (38), 55 (6), 45 (5), 44 (11), 43 (100), 52 (10).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.50, H, 7.5. Found: C, 52.58; H, 7.42.

Preparation of 11 from 1a and Glycerol. A mixture of **1a** (30 g), glycerol (30 g), and Amberlyst-15 (3.0 g) was stirred at 100–105 °C for 4 h. The usual workup provided 20.0 g of a liquid which was further purified by spinning band distillation to give 10.5 g of **11**. This was found identical (GLC, ir, NMR, mass spectrum) with product **11** obtained in the preceding experiment.

Reaction of DHA with Glycerol in the Presence of Ethanol. A mixture of DHA (30 g), glycerol (30 g), ethanol (90 ml), and Amberlyst-15 (3.6 g) was shaken in a Parr apparatus at 100–110 °C for 4 hr. The usual workup followed by distillation gave 19.4 g of a product, bp 85–93 °C (16 mm). Fractionation on a spinning band column gave 9.0 g of 4-ethoxy-5-methyl-3,6,8-trioxabicyclo[3.2.1]octane: bp 67 °C (4 mm); n^{20}D 1.4418; ir (neat) 2975, 2895, 1450, 1395, 1380, 1250, 1115, 1025, 960, 928, 835, 710 cm^{-1}; NMR ($CDCl_3$) 1.25 (t, 3 H, J = 7 Hz), 1.43 (s, 3 H), 3.26–4.36 (m, about 26 peaks, 7 H), and 4.48 (br d, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 149 (1.3), 145 (12), 129 (23), 115 (2), 101 (39), 100 (81), 85 (3), 73 (37), 61 (12), 58 (42), 57 (55), 43 (100).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.17; H, 8.04. Found: C, 54.93; H, 8.04.

Reaction of DHA with Glycerol in the Presence of 2-Propanol. A mixture of DHA (60 g), glycerol (60 g), 2-propanol (150 ml), and Amberlyst-15 (6.0 g) was allowed to react and worked up in the above manner. After spinning band distillation, 12.1 g of 4-isopropoxy-5-methyl-3,6,8-trioxabicyclo[3.2.1]octane was obtained: bp 100–105 °C (19 mm); n^{20}D 1.4480; ir (neat) 2970, 2895, 1450, 1250, 1105, 1030, 870 cm^{-1}; NMR ($CDCl_3$) 1.2 (t, 6 H, J = 7 Hz), 1.36 (s, 3 H), and 3.26–4.56 ppm (m, 8 H); mass spectrum (70 eV) *m/e* (rel intensity) 186 (0.8), 145 (56), 129 (45), 116 (6), 100 (89), 85 (14), 86 (7), 73 (33), 61 (7), 58 (54), 57 (69), 43 (100).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.42; H, 8.56. Found: C, 57.64; H, 8.34.

Acknowledgments. The author wishes to thank Dr. G. Chmurny for NMR spectral data, Messrs. T. G. Sinay, Jr., and

H. J. Slater for expert technical assistance, and Drs. R. K. Blackwood and E. B. Whipple for stimulating discussions.

Registry No.—**1a,** 6342-56-9; **1b,** 5774-26-5; **1c,** 19358-00-0; **1d,** 59044-05-2; **1e,** 19255-82-4; **2a,** 19358-03-3; **2c,** 59044-06-3; **3a,** 10374-97-7; **3b,** 38167-23-6; **3c,** 59044-07-4; **4a,** 59044-08-5; **4b,** 59043-78-6; **4c,** 59044-09-6; **5,** 59044-10-9; **11,** 59044-11-0; **14,** 59044-12-1; DHA, 96-26-4; methanol, 67-56-1; ethanol, 64-17-5; 1-propanol, 71-23-8; isopropyl alcohol, 67-63-0; 1-butanol, 71-36-3; ethylene glycol, 107-21-1; 1,2-propanediol, 57-55-6; *meso*-2,3-butanediol, 5341-95-7; 1,3-propanediol, 504-63-2; glycerol, 56-81-5; 4-ethoxy-5-methyl-3,6,8-trioxabicyclo[3.2.1]octane, 59044-13-2; 4-isopropoxy-5-methyl-3,6,8-trioxabicyclo[3.2.1]octane, 59044-14-3.

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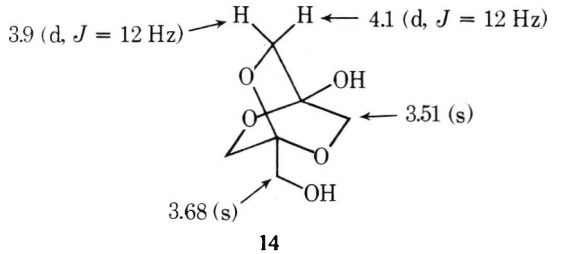
(20) Commercially available DHA (Wallerstein, Aldrich) was used in this study. DHA imparts tanning effect on skin. In addition to known monomeric and several dimeric forms,[22] we have NMR (D_2C solution) evidence for yet another possible dimer structure **14** for this compound. DHA (monomer) shows a singlet at δ 4.36 (D_2O).



14

(21) Amberlyst-15 is a sulfonated cation-exchange resin (H^+ form) marketed by Rohm and Haas, inc. In our work we have used several brands of strongly acidic, sulfonated ion-exchange resins (H^+ form) with equally effective results.
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Novel One-Pot Synthesis of 4-Aminoquinazolines

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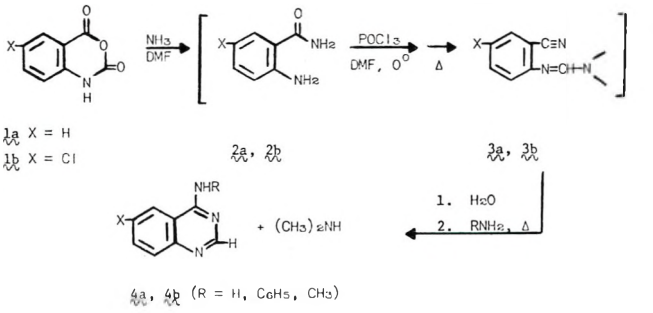
The biological activity of 4-aminoquinazolines has prompted development of many syntheses,[1] most of which are based on conversion of a quinazolone to a 4-chloroquinazoline that affords the desired product on treatment with an amine. However, several workers have reported syntheses based on conversion of *o*-aminonitriles or amides to amidines that cyclize to give the 4-aminoquinazoline directly.[2-5] We wish to report a general synthesis of this type (Scheme I) that can be carried out in one vessel starting with the readily available isatoic anhydrides (**1**, Scheme I). The intermediates in Scheme I need not be isolated.

Scheme I



The reaction of isatoic anhydride with ammonia has been reported to give good yields of anthranilamide only in dilute aqueous solution,[6] and 5-chloroisatoic anhydride (**1b**) gives only about 50% yields of **2b**.[7,8] We have found that treatment of **1a** or **1b** with NH_3 in DMF gives very high yields of **2a** or **2b**. Conversion of **2** to **3** is a modification of the work of Jones and Cragoe.[9] It was found that excellent yields of **3** can be obtained if the $POCl_3$ addition is carried out at 0–15 °C, followed by heating briefly at 40–60 °C. The intermediate, **3**, may be isolated, if desired, in ~80% yield, based on **1**, by dilution of the mixture with H_2O and neutralization with NaOH to cause **3** to precipitate.

In the final step a primary aliphatic or aromatic amine undergoes amidine interchange with **3** followed by cyclization and rearrangement to give the desired 4-aminoquinazoline **4** (Scheme II). Although **4** is produced by heating the final acidic DMF solution, much better yields were obtained when the mixture was made basic before heating. (See Experimental Section.)

Scheme II

This method appears to be a general, one-pot method for synthesis of 4-aminoquinazolines in high yields and is much less time consuming than previous methods.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Model 137 instrument; NMR spectra were obtained with Varian EM-360 and Jeolco MH-100 spectrometers. Mass spectra were taken with a Consolidated Electrodynamics Corp. Model 21-110B spectrometer system.

Preparation of 4-Aminoquinazolines. General Procedure. Ammonia was bubbled into a mixture of an isatoic anhydride (0.05 mol) in DMF (50 ml) at room temperature. The reaction was monitored by ir spectra of aliquots, and when complete conversion was indicated (~15–30 min) the mixture was degassed with N_2 to remove $(NH_4)_2CO_3$. $POCl_3$ (8.5 ml) was then added dropwise at 0–15 °C. The resulting mixture was heated for 30 min at 40–60 °C, then cooled to room temperature, and H_2O (15–20 ml) was added. A primary amine or ammonia was then added until the mixture was basic,[10] and the resulting solution was heated at 100 °C until TLC indicated conversion to the desired product. On cooling, the product crystallized and was isolated by filtration. In some cases addition of H_2O was necessary to cause crystallization.

The following compounds were prepared as described:[11] **4a**, R = H (47%, mp 268–269 °C[1]); **4a**, R = CH_3 (63%, mp 196–197 °C); **4a**, R = C_6H_5 (44%, mp 218–220 °C[2]); **4b**, R = H (79%, mp >310 °C[12]); **4b**, R = CH_3 (66%, mp 256–257 °C[13]); **4b**, R = C_6H_5 (51%, mp 229–230 °C).

Acknowledgments. We wish to thank Professor E. C. Taylor for helpful discussions.

Registry No.—**1a**, 118-48-9; **1b**, 4743-17-3; **4a** (R = H), 15018-66-3; **4a** (R = CH_3), 7154-47-4; **4a** (R = C_6H_5), 34923-95-0; **4b** (R = H), 19808-35-6; **4b** (R = CH_3), 32084-63-2; **4b** (R = C_6H_5), 59169-66-3; ammonia, 7664-41-7; methylamine, 74-89-5; phenylamine, 62-53-3.

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(10) Alternatively, only 2–3 equiv of amine may be added with enough 50% NaOH to make the mixture basic.
(11) No attempt was made to optimize yields, but we feel that yields >60% would be easily attainable in all cases. Yields are isolated yields based on **1a**, **1b**. Satisfactory ir, NMR, mass spectral, and elemental analyses were obtained for all compounds.
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An Unusual Addition–Fragmentation Reaction between Bisulfite and a Methallyl Ether

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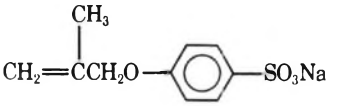
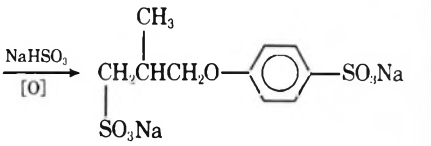
Received February 10, 1976

The formation of organic sulfonates by the addition of bisulfite to nonconjugated olefins appears to be a radical process accelerated by oxygen or other oxidizing agents.[1,2] Thus, isobutylene and sodium bisulfite give a good yield of sodium 2-methylpropanesulfonate.[1] While investigating radical reactions of polymerizable olefins, we have discovered a novel variant of the bisulfite–olefin reaction.

The reaction of sodium *p*-sulfophenyl methallyl ether (**1**) with a slight excess of sodium bisulfite gave the expected addition product, disodium *p*-sulfophenyl 2-methyl-3-sulfopropyl ether (**3**), in good yield when the aqueous reaction



1



3

medium was about 1 M in bisulfite. The structure of **3** was confirmed by elemental analysis and NMR spectrum. Analysis of mixtures of **1** and **3** was possible using high-pressure liquid chromatography (HPLC, see Experimental Section).

When **1** was combined with a dilute solution of bisulfite (ca. 10^{-3} M) only trace amounts of **3** were formed; after separation from unreacted **1** by column chromatography, the new products were identified as sodium phenolsulfonate (**6**) and sodium methallylsulfonate (**5**) by comparison of NMR spectra with spectra of the known compounds. The presence of **6** was fur-

Chart I

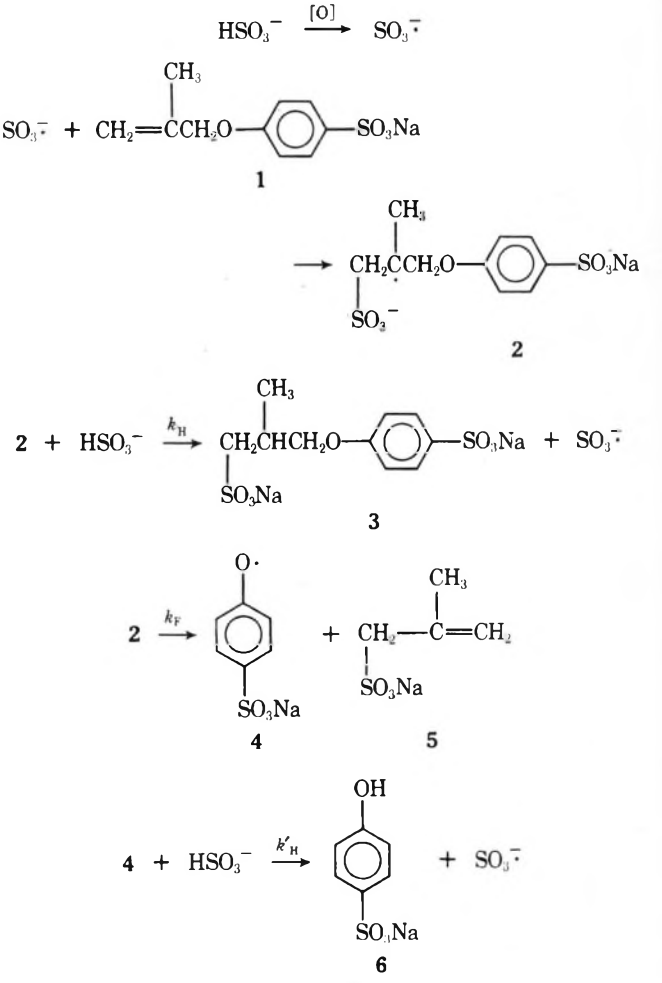


Table I. Reaction of Sodium *p*-Sulfophenyl Methallyl Ether (1) with Bisulfite [a]

$[1]_0$	$[HSO_3^-]_0$	[3]/[6]
0.008	0.024	0.15
0.008	0.040	0.44
0.008	0.080	1.6
0.008	0.100	2.6
0.004	0.100	2.4
0.004	0.090	2.1
0.004	0.080	1.8
0.004	0.060	1.3
0.002	0.070	1.5
0.002	0.060	1.4
0.002	0.050	1.0
0.002	0.030	0.30
0.008	0.004	<0.05
0.008	1.00	>25

[a] Reaction conditions 100 °C, 10 min; 0.01 equiv of potassium persulfate (based on sodium bisulfite) was also present in each run. Where excess bisulfite was employed conversion of 1 to products was quantitative.

ther indicated by a shift in ultraviolet absorption to longer wavelength in basic solution.

The course of the reaction of 1 with bisulfite was largely unaffected by temperature (25–100 °C) or pH (2–7). Addition of a small amount of persulfate greatly improved product yield but did not alter product identity. At bisulfite concentrations intermediate between 1 and 10^{-3} M a mixture of products **3**, **5**, and **6** was obtained. These observations suggest the mechanism shown in Chart I wherein a radical derived from bisulfite adds to 1 to give an intermediate (**2**) which may either form 3 by transfer of hydrogen from bisulfite (k_H) or fragment (k_F) to form, after hydrogen transfer, **5** and **6**. The overall reaction to give 5 and 6 is thus viewed as a rather unusual radical addition–fragmentation reaction. A direct determination of the rate of the fragmentation reaction is made difficult by the fact that the process is too rapid to follow using HPLC analysis for **3** and **6**. An estimate of the relative rates (k_H/k_F) can, however, be obtained from the product data given in Table I. With reference to Chart I, the formation rates of **3** and **6** are given by

$$\frac{d[3]}{dt} = k_H[2][HSO_3^-]$$

$$\frac{d[6]}{dt} = k'_H[4][HSO_3^-]$$

Applying the steady-state approximation[3] to the radical **4**,

$$k_F[2] = k'_H[4][HSO_3^-]$$

Hence,

$$\frac{d[6]}{dt} = k_F[2]$$

and

$$\frac{d[3]}{d[6]} = \frac{k_H}{k_F}[HSO_3^-]$$

Thus, the relationship

$$\frac{[3]}{[6]} = \frac{k_H}{k_F}[HSO_3^-]_t$$

predicts that a plot of bisulfite concentration vs. the molar ratio of **3** to **6** as a function of time will be linear with slope k_H/k_F. $(HSO_3^-)_t$ can be approximated by the initial bisulfite concentration provided that it is in sufficient excess over **1** as to undergo little concentration change during the reaction.[4]

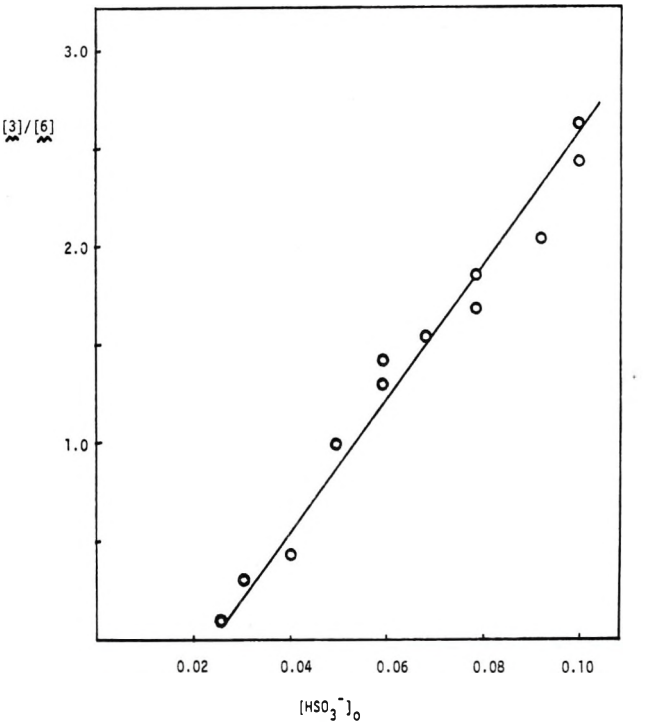


Figure 1. Initial bisulfite concentration vs. product ratio for the reaction of bisulfite with **1**.

Figure 1 shows this plot, from which a value of $k_H/k_F = 35$ is derived. The plot, which presumably should pass through the origin, is unreliable at low $(HSO_3^-)_0$ because of the difficulty in maintaining the excess of bisulfite required for the approximation of $(HSO_3^-)_t$ with $(HSO_3^-)_0$. Note, however (Table I), a value of [3]/[6] < 0.05 for $(HSO_3^-)_0 = 0.004$.

Radical transfer of hydrogen from bisulfite is, in general, a rapid process.[5] Hence the addition–fragmentation reaction is seen to be quite facile, probably because of the stability of the phenolic radical **4**.

The possibility that products **5** and **6** were formed from **3**

$$3 + SO_3^{\cdot-} \rightarrow 2 + HSO_3^-$$

$$2 \rightarrow \rightarrow 5 + 6$$

was ruled out by combining bisulfite with **3** under reaction conditions for formation of **5** and **6** from **1**. **3** was recovered unchanged.

Experimental Section

Reaction of Sodium *p*-Sulfophenyl Methallyl Ether (1) with Sodium Bisulfite in Concentrated Solution. A solution of 0.10 mol of 1 (prepared by the method of Masson[6] and recrystallized from aqueous ethanol), 0.12 mol of sodium bisulfite, and 0.001 mol of potassium persulfate in 200 ml of water adjusted to pH 3 with sulfuric acid was stirred at the boil for 30 min. Titration of an aliquot of the solution with iodine to a starch end point indicated that 80% of the bisulfite had reacted. The solution was evaporated to about one-tenth its original volume and the solid which separated was isolated by filtration, dried, and weighed (32.5 g). This represents a 92% yield of disodium *p*-sulfophenyl 2-methyl-3-sulfopropyl ether (**3**): NMR (D_2O) δ 1.58 (J = 7 Hz, methyl), 4.33 (J = 6 Hz, CH_2O), 3.26, 3.58 (J = 14 Hz, $CH_2SO_3^-$), 2.82 (CH), 7.41, 8.17 (aromatics, AA′BB′ pattern).

Anal. Calcd for $C_{10}H_{12}O_7S_2Na_2$: C, 33.90; H, 3.41; S, 18.10; Na, 12.98. Found: C, 33.49; H, 3.70; S, 18.95; Na (by atomic absorption spectroscopy), 13.0.

Reaction of 1 with Sodium Bisulfite in Dilute Solution. A solution of 4 mmol of 1, 2 mmol of sodium bisulfite, and 0.1 mmol of potassium persulfate in 500 ml of water adjusted to pH 3 with sulfuric acid was stirred at the boil for 30 min. Separation of the reaction products from unreacted 1 was accomplished by adsorption of the components on Amberlite XAD-2 resin (a nonionic, cross-linked polystyrene with a macroreticular structure, from Rohm & Haas Co.)

followed by elution with 2% LiCl/20% MeOH/78% H_2O. Under these conditions, **1** is retained on the column. Products (contaminated with LiCl) were isolated by evaporation of the column eluent to dryness. An NMR spectrum of these products was essentially identical with a spectrum of an equimolar mixture of sodium phenolsulfonate (**6**) and sodium methallylsulfonate (**5**) (δ 2.33, 4.07, 5.47, and 5.53 for **5**). An aqueous solution of the products showed the ultraviolet shift expected for **6** when the solution pH was raised (λ_{max} 231 nm at pH 6, 254 nm at pH 10).

Analysis of Reaction Products by High-Pressure Liquid Chromatography (HPLC). A Waters Associates ALC 202 liquid chromatograph equipped with a Model U6K injector and a Bondapak AX anion exchange column was used. With 0.05 M $NaClO_4$ in 90% H_2O/10% MeOH as the mobile phase components were eluted in the order **6**, **1**, **3**, and were detected using a Perkin-Elmer Model LC-55 variable wavelength detector set at 231 nm.

Acknowledgments. The author is grateful to E. W. Wilburn, W. W. Lanier, and H. A. Taylor for product separations and analyses using liquid chromatography, and to Claudette Deatherage for NMR analyses.

Registry No.—**1**, 1208-67-9; **3**, 59219-47-5; **5**, 1561-92-8; **6**, 825-90-1; sodium bisulfite, 7631-90-5.

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A Simple Synthesis of 2-Alkylcyclohexenones[1]

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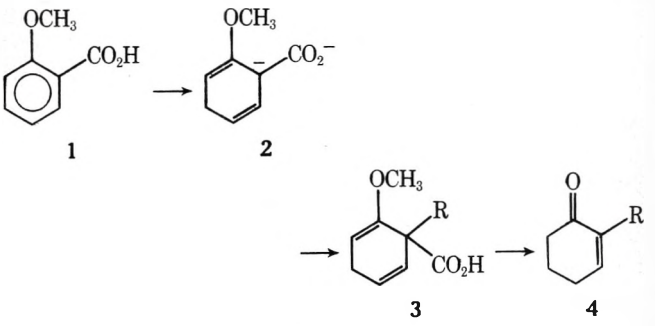
Cyclohexenones are versatile intermediates in organic synthesis. Among other applications, they are useful precursors to substituted cyclohexanones by conjugate addition,[2] enolate trapping,[3] and Diels–Alder addition,[4] as well as to alkynyl aldehydes.[5] While several procedures[6] have been employed for the preparation of 2-alkylcyclohexenones, by and large these procedures are lengthy or lead to isomeric mixtures of products.

The report[7] of the reductive alkylation of an *o*-methoxy substituted benzoic acid derivative led us to investigate this approach as a possible simple approach to 2-alkylcyclohexenones. Thus, addition of alkali metal to a suspension of the ammonium salt of **1** in liquid ammonia should give the dianion **2**, which could be alkylated. Evaporation of the ammonia followed by the hydrolysis of **3** with aqueous acid should then give the cyclohexenone **4**.

Scheme I



1 **2** **3** **4**

In fact, this one-pot procedure (see Experimental Section) works well, and is amenable to large-scale application. Thus, the enones listed (Table I) were prepared pure in gram quantity from the inexpensive acid **1**. Even given the modest yields achieved, this is currently the method of choice for preparing most 2-alkylcyclohexenones.

Experimental Section

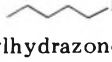
General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalysis was performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. All chemicals were used as received, except for allyl chloride, which was distilled immediately prior to use. Tetrahydrofuran was stored over Linde 4A molecular sieve after opening. NMR spectra were recorded on a JEOLCO MH-100 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer.

The general procedure for reductive alkylation followed by hydrolysis is illustrated by the synthesis of 2-allylcyclohexenone.

2-Allylcyclohexenone. A 1-l. three-neck round-bottom flask was charged with 15.2 g (100 mmol) of *o*-methoxybenzoic acid and 100 ml of THF. The solution was stirred magnetically, and ammonia (400 ml) was distilled in to give a thick white suspension. The reaction mixture was then maintained at reflux under a nitrogen atmosphere. Lithium wire (washed sequentially with hexane, methanol and hexane) was added in 7-cm pieces until a blue solution was maintained.[9] The reaction vessel was cooled in a dry ice–acetone bath and 1,2-dibromoethane (2 ml) was added, followed by allyl chloride (12.0 ml, 120 mmol).

The reaction mixture was allowed to warm to room temperature under a stream of nitrogen. The resultant brown slurry was diluted with 100 ml of ethylene chloride, then acidified with 100 ml of concentrated aqueous HCl (*foams!*). Water (100 ml) and hydroquinone (200 mg) were added, and the two-phase mixture was refluxed for 30 min. The mixture was diluted with water (300 ml), the organic phase was separated, and the aqueous phase was extracted with one 50-ml portion of ethylene chloride. The combined organic phase was washed with 100 ml of aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was distilled through a 10-cm Vigreux column to yield 3.65 g (27%) of colorless oil: bp 67–68 °C (3.2 mm); NMR ($CDCl_3$) δ 1.98, m, 2 H; 2.36, m, 4 H; 2.88, bd, J = 6 Hz, 2 H; 4.92, bd, J = 12 Hz, 2 H; 5.5–6.0,

Table I. Preparation of 2-Substituted Cyclohexenones

Registry no.	Alkylating agent	Bp, °C (mm)	Yield, %	Lit. bp, °C (mm)	Mp of derivative, °C	Lit. mp, °C	Ref.
107-05-1		67–68 (3.2)	27	98–103 (15)	174[a]	171[a]	6a
107-08-4		65–66 (2.4)	30	95 (14)	172[a,b]	163–164[a]	8
75-30-9		56–58 (2.3)	26	150	168[c]	163–164[c]	6g
110-53-2		74 (0.5)	27	72–78 (0.5)	113[a]	112[a]	6b

[a] 2,4-Dinitrophenylhydrazone. [b] Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.58; H, 5.70; N, 17.61. Found: C, 56.88; H, 5.78; N, 17.53. [c] Semicarbazone.

m, 1 H; 6.61, t, J = 4 Hz, 1 H. Ir (CCl_4) 3070, 2920, 1670, 1630, 910 cm^{-1}.

Registry No.—I, 579-75-9; II (R = $CH_2CH{=}CH_2$, 38019-50-0; II (R = Pr), 59034-18-3; II (R = Pr) 2,4-DNPH, 59034-20-7; II (R = Pr-*i*), 59034-19-4; II (R = $(CH_2)_4CH_3$), 25435-63-6.

References and Notes

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(4) T. Harayama, H. Cho, and Y. Inubishi, *Tetrahedron Lett.*, 2693 (1975).
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(9) The thick white suspension is the ammonium salt of the *o*-methoxybenzoic acid. As lithium metal is added this suspension dissolves to give a pale yellow solution. As more lithium is added this color deepens to a dark orange, which deepens further to a brown before going to the blue color typical of the presence of excess lithium. On addition of 1,2-dibromethane to consume the lithium the blue color is discharged, leaving a reddish-orange solution which fades to a yellow-white suspension almost immediately on the addition of the alkylating agent.

N,N,N′,N′-Tetramethylmethanediamine. A Simple, Effective Mannich Reagent

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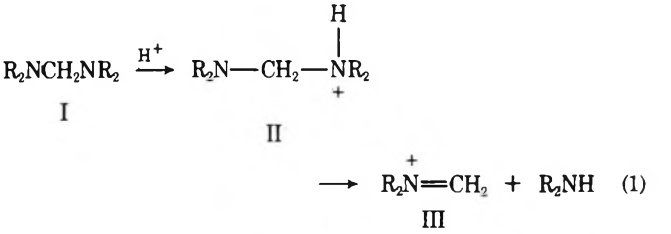
The Mannich reaction followed by β-elimination has long been used to convert a ketone into an α,β-unsaturated analogue. Under the usual reaction conditions, a methylenebisamine (I) is formed which, under acid conditions, forms the resonance-stabilized aminocarbonium ion (III) (eq 1).[1]

Ahond et al.[2,3] found that a similarly reactive intermediate formed by the treatment of trimethylamine oxide with a methylene chloride solution of trifluoroacetic anhydride proved to be an excellent Mannich reagent. Using this principle, Taylor[4] used *N,N,N′,N′*-tetramethylmethanediamine and acetic anhydride to generate an α,β-unsaturated ketone without utilizing the Mannich base.



(1)

In the preparation of the recently discovered uricosuric saluretics, (1-oxo-2,2-disubstituted-5-indanyloxy)acetic acids,[5] it was desired to introduce a methylene group under Mannich conditions α to an alkyl aryl ketone. Treatment of $ArC(=O)CH_2$-aryl with paraformaldehyde, dimethylamine hydrochloride, and acetic acid[6] did not afford high yields of α,β-unsaturated ketone in our hands.[7]

The desired transformation was successfully carried out by using *N,N,N′,N′*-tetramethylmethanediamine and acetic anhydride constituting an extension of the reaction described by Taylor. We found that the mild conditions employed allowed for the isolation of the α,β-unsaturated ketones in excellent yields with no by-products. For reaction to take place at <40°C, enhanced activation of the adjacent methylene by both the ketone and aryl moieties, $ArC(=O)CH_2$-aryl, was necessary since ketones of the type $ArC(=O)CH_2$-alkyl did not react under similar conditions. However, treatment of $ArC(=O)CH_2$-alkyl compounds with *N,N,N′,N′*-tetramethylmethanediamine and acetic anhydride at higher temperatures (90°C) did give the desired α,β-unsaturated ketones in good yields.

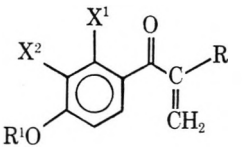
Experimental Section

General Procedure. Acetic anhydride (50 ml) was added dropwise to a suspension of the alkyl aryl ketone (0.1 mol) in *N,N,N′,N′*-tetramethylmethanediamine (50 ml). The reaction temperature was maintained at <40°C by ice-bath cooling. After 1 h of stirring at 25 °C, the solution was added slowly to crushed ice–water (1 l.) with stirring to precipitate analytically pure product in 80–100% yield (Table I).

Acknowledgments. The author wishes to thank Dr. E. J. Cragoe, Jr., and Mr. O. W. Woltersdorf, Jr., for their guidance and assistance throughout this work.

Registry No.—2,3-Dichloro-4-phenylacetylanisole, 59043-83-3; 2-chloro-3-methyl-4-phenylacetylanisole, 59043-84-4; 2,3-dichloro-4-phenylacetyl-α-carboxyanisole ethyl ester, 59043-85-5; 2,3-dichloro-4-[(*p*-bromophenyl)acetyl]anisole, 59043-86-6; 2,3-dichloro-

Table I



Registry no.	R	R¹	X¹	X²	Mp, °C	% yield	Empirical[a] formula
57296-59-0	C_6H_5	CH_3	Cl	Cl	87–89	98	$C_{15}H_{12}Cl_2O_2$
59043-79-7	C_6H_5	CH_3	Cl	CH_3	81–85	85	$C_{17}H_{15}ClO_2$
59043-80-0	C_6H_5	$CH_2CO_2C_2H_5$	Cl	Cl	60–64	78	$C_{19}H_{16}Cl_2O_4$
57296-97-6	4-BrC_6H_4	CH_3	Cl	Cl	110–116	97	$C_{16}H_{11}BrCl_2O_2$
59043-81-1	4-FC_6H_4	CH_3	Cl	Cl	102–104	80	$C_{16}H_{11}Cl_2FO_2$
59043-82-2	C_2H_5	CH_3	Cl	Cl	46–48	86[b]	$C_{12}H_{12}Cl_2O_2$

[a] Satisfactory analytical data (±0.4% for C and H) for all compounds were submitted for review. [b] At <40 °C, no reaction; at 90 °C, 86% yield.

4-[(-*p*-fluorophenyl)acetyl]anisole, 59043-87-7; 2,3-dichloro-4-propionylanisole, 41715-70-2; *N,N,N′,N′*-tetramethylmethanediamine, 51-80-9.

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Communications

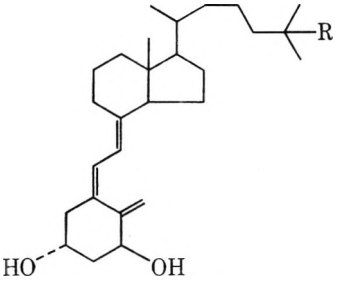
Hydroxylation with Ozone on Silica Gel. The Synthesis of 1α,25-Dihydroxyvitamin D_3

Summary: A convenient synthesis of 1α,25-dihydroxyvitamin D_3, the natural calcium regulating hormone, based on a regioselective C_{25}-hydroxylation of 1α,3β-diacetoxy-6β,7α-dibromocholestane by means of ozone absorbed on silica gel, is reported.

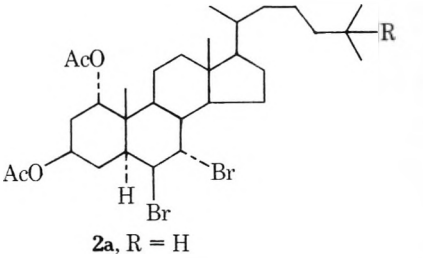
Sir: As a further development of our studies on the functionalization of unactivated carbon atoms,[1] we report on the utilization of the recently published method of dry ozonation[2] for a relatively simple synthesis of the calcium regulating hormone, viz., the 1α,25-dihydroxyvitamin D_3 (**1b**).[3]

The key step in this synthesis is the highly regioselective C_{25}-hydroxylation of a tetrasubstituted cholestane derivative, the dibromide **2a**, which is an intermediate in the preparation of a physiological useful substitute of **1b**, viz., the 1α-hydroxyvitamin D_3[4] (**1a**). We obtained this dibromide intermediate, **2a**, in a five-step synthesis from cholesterol, by the following sequence: cholesterol → **3a** → **4a** → **5a** → **5c** → **2a**.[4]

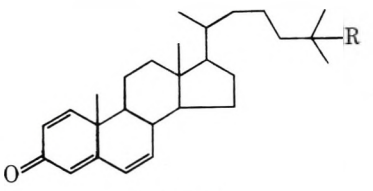
Silica gel for chromatography (Merck-Kieselgel 60, 70–220 mesh) containing 1% by weight of adsorbed **2a** was saturated with ozone (generated from Welsbach ozonizer) at −78 °C and allowed to warm to room temperature. This procedure was repeated altogether five times. Elution and chromatographic separation yielded, in addition to recovered starting material **2a**, the C_{25}-hydroxy derivative, **2b**, mp 174–175 °C, $[\alpha]_D$ −24°, as the only isolated product (11% conversion and 51% yield). The presence of OH at C_{25} in **2b** was indicated by its NMR spectrum which was similar to that of the starting compound **2a**[4] except for the signals due to the methyl protons at C_{25} appearing as a singlet at δ 1.20 ppm instead of a doublet at 0.85 and by its mass spectrum [M^+ at *m/e* 660 (^{79}Br) and 59 of $(CH_3)_2C^+OH$]. The structure of **2b** was proved by comparison of its C_{25} acetate, **2d** [NMR δ 1.41, 1.96 ppm (CH_3 and OAc at C_{25}); mass spectra M^+ at *m/e* 702 (^{79}Br) and 101 of $(CH_3)_2C^+OAc$] with a compound synthesized by us from the previously described C_{25}-hydroxy epoxide **4b**.[5,6] Reduction of the epoxide with Li/NH_3 in the presence of NH_4Cl resulted in 20% Δ^6-triol, **5b**[7] [mp 193–196 °C; $[\alpha]_D$ −62°; NMR ($CDCl_3$) δ 0.70 (s, 3, C_{18} H), 0.80 (s, 3, C_{19} H), 0.91 (d, 3, J = 7 Hz, C_{21}



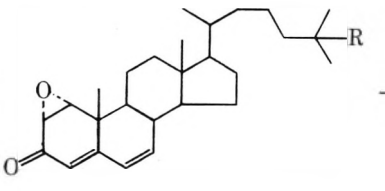
1a, R = H
b, R = OH



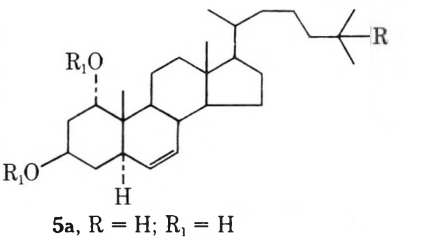
2a, R = H
b, R = OH
c, R = $OCOCF_3$
d, R = OAc



3a, R = H
b, R = OH



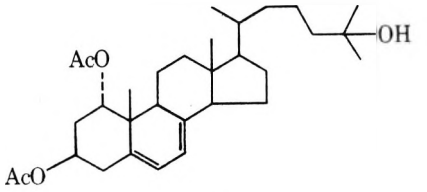
4a, R = H
b, R = OH



5a, R = H; R_1 = H
b, R = OH; R_1 = H
c, R = H; R_1 = Ac
d, R = OAc; R_1 = Ac

H), 1.19 (s, 6, C_{26},C_{27} H), 3.80, 3.93 (m, 2, C_4,C_5 H) 5.33, 5.21 ppm (ABq, J = 11.4 Hz, C_6,C_7 H)] which was acetylated with Ac_2O and pyridine at 80 °C to yield the triacetate **5d** (mp 89–91 °C). Bromination in $CHCl_3$ with $C_6H_5IBr_2$ gave the dibromide **2d** which was found to be identical with the product obtained from **2a**.

The C_{25}-hydroxy dibromide **2b** was treated with $(CF_3CO)_2O$ at room temperature for 4 h, and the C_{25}-trifluoroacetate, **2c**, obtained after evaporation to dryness, was dehydrobrominated by heating at 135 °C for 2 h in hexamethylphosphoramide containing 10% triethylmethylammonium dimethylphosphate[4,8] to give 20% 1α,3β-diacetoxy-25-hydroxycholesta-$\Delta^{5,7}$-diene (**6**)[5,9,10] [uv λ_{max} 262, 271, 282, and 294 nm; NMR ($CDCl_3$) δ 0.61 (s, 3, C_{18} H), 1.14 (s, 3, C_{19} H), 1.18 (s, 6, $C_{26}C_{27}$, H), 1.94, 1.97 (s, 6 OAc), 4.87 (m, 2, C_1,C_3



6

H), 5.29, 5.39 (AB q, J = 10.3 Hz, C_6,C_7 H)], accompanied by the $\Delta^{4,6}$-diene (uv λ_{max} 230, 240, 249 nm). The $\Delta^{5,7}$-diene, **6**, was transformed by irradiation, heating, and hydrolysis, as described elsewhere,[5,10] to the desired 1α,25-dihydroxyvitamin D_3 (**1b**) [uv λ 264 nm (ϵ 18 000); mass spectra M^+ at m/e 416; rapidly stimulating the formation of calcium binding protein and increasing the calcium content in the intestine of rachitic chicks].[3,5,10]

The direct introduction of OH into the side chain of a cholestane derivative at C_{25} significantly simplifies the synthesis of 1α,25-dihydroxyvitamin D_3; its photoprecursor, the $\Delta^{5,7}$-diene, can now be obtained from cholesterol by a seven-step reaction sequence.

Acknowledgment. The mass spectra were done by Dr. Zeev V. Zaretskii and the biological assay by Dr. Arieh Bar of the Volcani Institute, Rehovot, to whom we are greatly indebted.

Supplementary Material Available. The experimental details for preparation of new compounds (3 pages). Ordering information is given on any current masthead page.

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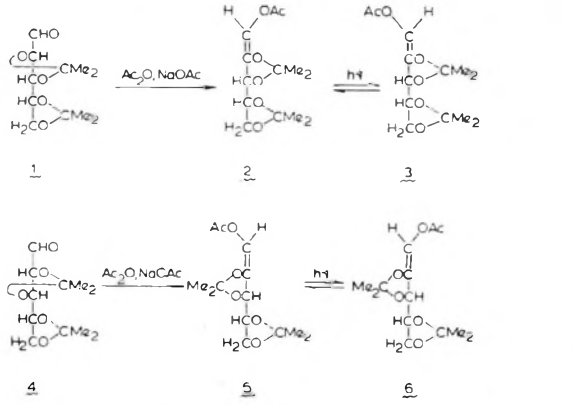
Enol Acetates of Aldehydo Sugar Derivatives. Synthesis and Crystallographic Determination of Double-Bond Geometry[1,2]

Summary: Enol acetates produced by action of acetic anhydride–sodium acetate on 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose and -D-xylose are shown by X-ray crystallography to be the *Z* isomers, and they undergo photoisomerization to the *E* isomers.

Sir: Although aldehydo and keto derivatives of sugars are frequently used in synthesis and their derived enediols often postulated as reaction intermediates,[3] there have been few reports of stable derivatives of such enediols. Enol acetates of keto sugars have been studied in one of our laboratories,[4] and this communication reports the synthesis and characterization of enol acetates derived from some aldehydo sugar derivatives.

Heating 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose[5] (**1**) or the D-ribose analogue in an excess of acetic anhydride containing sodium acetate for 30 min at 140 °C gave in 60% yield the *Z* isomer (**2**) of 1-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-D-*erythro*-pent-1-enitol, mp 100–100.5 °C, $[\alpha]^{23}D$ +1.85° (chloroform), whose general structure, except for the geometry about the double bond, was evident from its NMR and mass spectra. Photoisomerization of **2** in benzene–acetone with uv light gave the *E* isomer **3** as an oil, $[\alpha]^{24}D$ +122° (chloroform). Similarly, acetic anhydride–sodium acetate converted 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-xylose[6] (**4**) into (*Z*)-1-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-D-



threo-pent-1-enitol (**5**), mp 61–62 °C, $[\alpha]^{22}D$ +8.4° (chloroform), which gave a first-order NMR spectrum (100 MHz) in acetone-d_6 and which could be photoisomerized to the *E* isomer (**6**), mp 68–70 °C, $[\alpha]^{24}D$ −198° (chloroform).

Assignment of double-bond geometry was achieved by crystallographic analysis of single crystals of **2** grown from ether–pentane and of **5** obtained from absolute ethanol. Intensities were collected on a Philips diffractometer with Cu Kα radiation and structures were solved by use of the Riche phase function.[7] The erythro compound (**2**, $C_{13}H_{20}O_6$) was monoclinic, space group $P2_1$, cell dimensions a = 5.435, b = 14.703, c = 9.332 Å, β = 104.15°, Z = 2, and volume 723 Å^3. The threo compound (**5**) was orthorhombic, space group $P2_12_12_1$, cell dimensions a = 5.543, b = 8.240, c = 32.336 Å, Z = 4, and volume 1477 Å^3. All hydrogen atoms were located on difference Fourier syntheses and their coordinates refined. The final R indices were 0.04 for **2** and 0.05 for **5**. Figure 1 presents a three-dimensional view of each molecule, listing bond distances, and short interatomic contacts, and Figure 2 depicts Newman projections along each carbon–carbon bond to show dihedral bond angles.

The crystallographic structures establish that the stereochemistry about the double bond is *Z* in **2** and **5**. The C-2–C-5 carbon–carbon chain of the erythro isomer (**2**) is approxi-

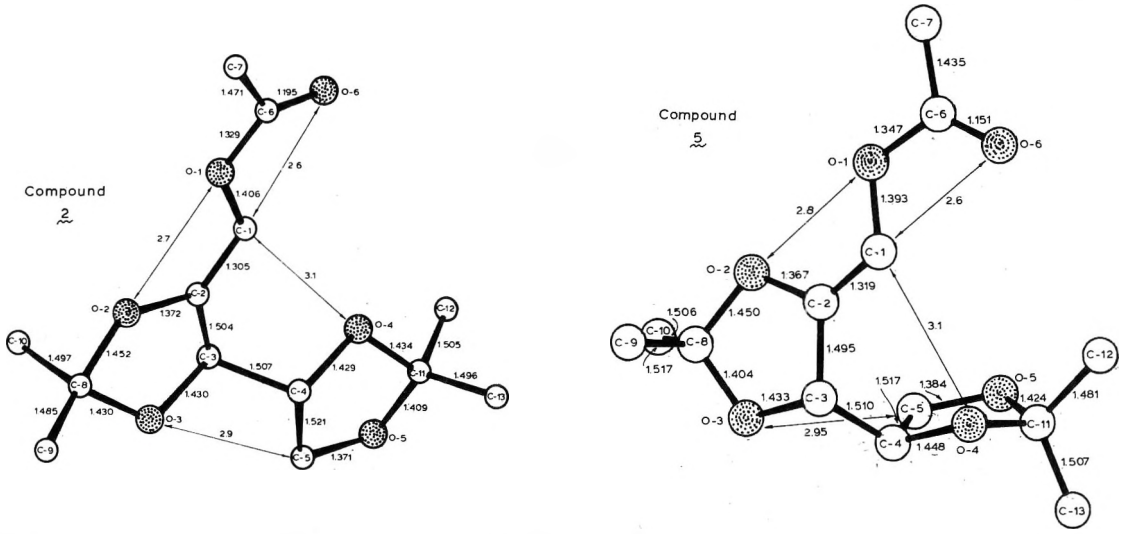


Figure 1. Crystal-structure diagrams for (*Z*)-1-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-D-*erythro*-pent-1-enitol (**2**) and its *Z* D-threo analogue (**5**), showing bond lengths and short interatomic contacts (in Å).

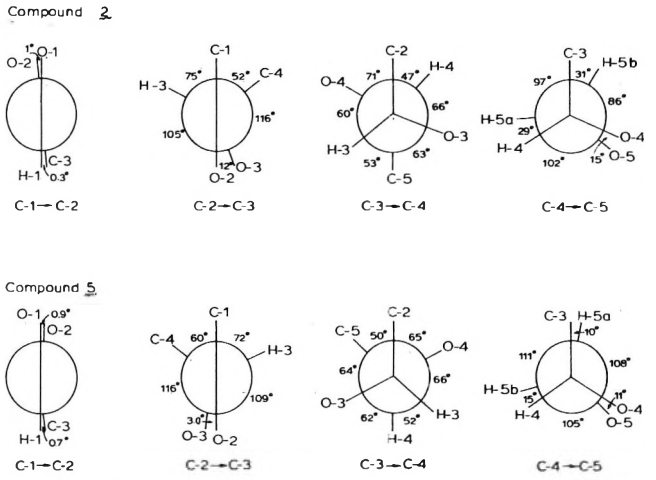


Figure 2. Newman projections along each carbon–carbon bond for compounds **2** and **5**, showing dihedral angles between substituents.

mately planar zigzag, in accord with the general conformational predictions that may be made for open-chain sugar derivatives.[8,9] In contrast, that of the threo isomer (**5**) has a sickle conformation, again as predicted by consideration of avoidance of a parallel disposition of O-2 and O-4 on the same side of the chain; the observed small (3.5 Hz) $J_{3,4}$ coupling indicates that the H-3–H-4 antiparallel rotamer is also not favored in solution. In both **2** and **5** there is an antiparallel disposition between O-3 and O-4. Envelope conformations are observed for the 4,5-dioxolane ring in **2** and the 2,3 ring in **5**, whereas the 2,3 ring in **2** and the 4,5 ring in **5** adopt twist conformations.

The observed proton–proton dihedral angles in crystalline **5** are compared in Table I with the proton–proton spin–spin couplings observed in acetone solution. It may be seen that the qualitative generalization that small couplings denote dihedral angles near 60° and large couplings indicate eclipsed or antiparallel protons is valid, but quantitative extensions to attribute precise angles from spin couplings are unjustified, as has been pointed out previously.[10] Use of the Karplus equation,[11] either with[12] or without[11] correction for electronegativity effects, to calculate predicted couplings from observed dihedral angles in the crystal, show (Table I) qualitative but not quantitative correspondence with observed couplings. Some variation between these sets of values is, of course, to be expected for compounds in solution because of absence of intermolecular packing interactions and the possibility of time averaging between conformations not differing greatly in relative free energy.

Table I. Comparison of Crystallographic Dihedral Angles and NMR Coupling Data for Compound 5

Vicinal protons	Crystallographic dihedral angle, deg	NMR proton–proton coupling constants, Hz		
		Obsvd[a]	Calcd[b]	Calcd[c]
3,4	52	3.5	2.8	4.1
4,5	137	6.4	4.9	6.4
4,5′	15	7.2	7.6	8.4

[a] At 100 MHz in acetone-d_6. [b] From the crystallographic angles by the Karplus[11] equation: $^3J_{H,H} = 4.22 - 0.5 \cos\phi + 4.50 \cos 2\phi$. [c] From the crystallographic angles by a modified[12] equation: $^3J_{H,H} = (7.8 - \cos\phi + 5.6 \cos 2\phi)(1 - 0.1X)$, where $X = \Sigma_1^4 (X_n - X_H)$ and X_n is the electronegativity of substituent n, X_H that of hydrogen.

References and Notes

(1) Part of this work was supported by Grant No. GM-11976 (OSURF Project 1820) from the National Institutes of Health.
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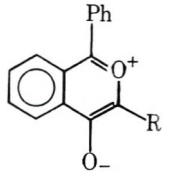
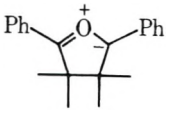
Photogeneration and Reactions of Acyclic Carbonyl Ylides[1]

Summary: The photoinduced formation of carbonyl ylides and their addition to dipolarophiles is illustrated with several typical precursors, including 3,3-dicyanostilbene oxide and related compounds, and the mechanism discussed.

Sir: Thermal as well as photochemical generation of azomethine ylides from aziridines has been studied extensively and the stereochemical predictions based on orbital symmetry considerations have been verified.[2] While the thermal formation of carbonyl ylides from oxiranes also has been investigated thoroughly,[3,4] studies of the photochemical counterpart of this process are complicated by the propensity of many oxiranes to undergo competitive [3 → 2 + 1] photocycloelimination to carbenes purportedly by way of carbonyl ylide intermediates. [5]Indirect evidence that such ylides are photolabile and do give carbenes upon irradiation has been presented;[6-8] however, to date the interception of photogenerated ylides has been limited to cyclic cases including **1a**,[9a] **1b**,[9b] and **2**,[9c] which are not disposed to form carbenes. This may be



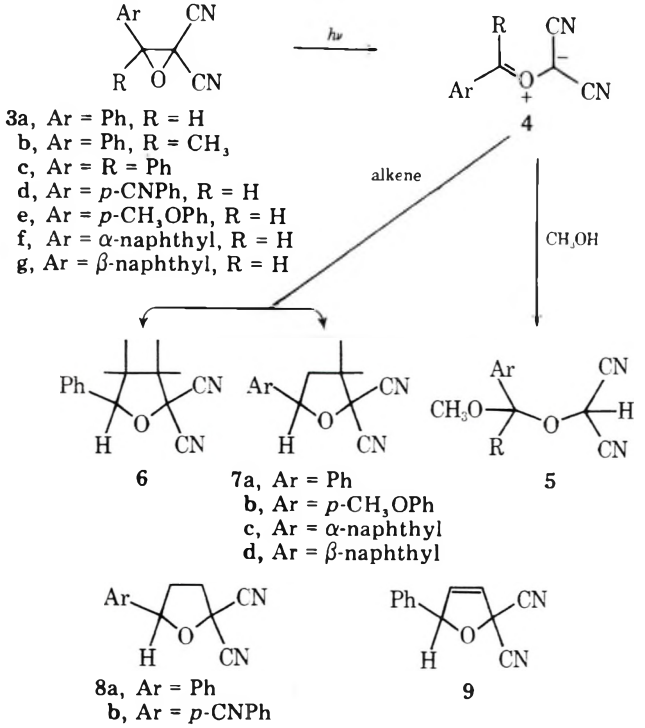
1a, R = Ph
b, R = CH_3



2

attributed to stabilizing features inherent in cyclic ylides, and/or efficient reversible ketocarbene formation. Intervention of reversible C–O bond cleavage could also occur. It should be noted that spectroscopic evidence for carbene formation could not be obtained with higher homologues of **2**.[7]

We have demonstrated that the photofragmentation of oxiranes is suppressed in the absence of vicinal diaryl substitution and this led to investigate the photochemistry of a series of dicyanooxiranes **3**.[6,7] The thermochemical properties of **3a, 3b, 3c,** and **3e,** as well as the related ethyl α-cyanophenylglycidates had been studied;[4] however, our recent investigations conducted at ambient and subambient temperatures have revealed some novel aspects of carbonyl ylide chemistry which are of mechanistic as well as synthetic significance.[1]



3a, Ar = Ph, R = H
b, Ar = Ph, R = CH_3
c, Ar = R = Ph
d, Ar = *p*-CNPh, R = H
e, Ar = *p*-CH_3OPh, R = H
f, Ar = α-naphthyl, R = H
g, Ar = β-naphthyl, R = H

4

6

7a, Ar = Ph
b, Ar = *p*-CH_3OPh
c, Ar = α-naphthyl
d, Ar = β-naphthyl

5

8a, Ar = Ph
b, Ar = *p*-CNPh

9

Table I. Photocycloaddition of Oxiranes to Dipolarophiles

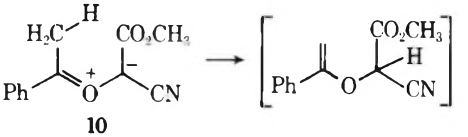
Oxirane[a]	Dipolarophile[b]	Irradiation time, hr	Product	% yield
3a	2,3-dimethyl-2-butene	6	**6**	51[c]
	Isobutylene	4	**7a**	90
	Ethylene	6	**8a**	84
	Acetylene	6	**9**	54
3d	Ethylene	6	**8b**	60
3e	Isobutylene	6	**7b**	34[c]
3f	Isobutylene	18	**7c**	78
3g	Isobutylene	6	**7d**	90

[a] Oxirane samples of 0.5–0.67 mmol were employed. [b] Degassed benzene solutions were saturated with the gaseous alkenes. [c] Aldehydes or oxetanes (~15–20%) were detectable by NMR.

The ylides **4a–e** may be generated by photolysis at 254 nm, while **4f** and **4g** form at 350 nm.[10] With the exception of **4d** all may be intercepted with protic solvents such as methanol with formation of the ketals or acetals **5**.[11] Precedent exists for cyclopropane photosolvolysis with C–C bond cleavage although further study is required to clarify the mechanism.[12] The adducts **5**, acetals or ketals of cyanohydrins, are unstable, but were characterized by NMR and hydrolyzed to the expected aldehydes or ketones.

The cycloaddition of ylides **4** (excluding **4b** and **4c**) generated photochemically from the oxiranes **3** to dipolarophiles also may be accomplished in solution at ambient or subambient temperatures. Efficient trapping may be achieved even with highly volatile dipolarophiles such as ethylene and acetylene to give **8** and **9**, respectively, and this provides a distinct synthetic advantage over thermal methods. Benzene was found to be one solvent of choice in such reactions. The [3 → 2 + 1] cycloelimination reactions are suppressed in benzene and the implications of this observation are discussed later. The oxiranes **3a** and **3d–g** give the corresponding cycloadducts in moderate to high yields. The conversion level is a function of the oxirane and dipolarophile structures (see Table I). Methyl α-cyano- and α-carbomethoxyphenylglycidates behave similarly in photocycloaddition reactions and will be the subject of a future communication.

In the case of **4b** photocycloadditions are circumvented and several dark intractable products are formed in low yield. From our experience with the carbomethoxy analogue **10**, where the photoreaction is cleaner, proton transfer occurs to



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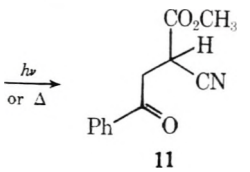

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give the enol ether which subsequently undergoes a [1,3]-sigmatropic shift to form methyl 2-cyano-3-benzoylpropionate (**11**). The structure of this product was confirmed by independent synthesis through base-catalyzed alkylation of phenacyl bromide with cyanoacetic ester. Furthermore, those factors which promote ylide stability and/or suppress cycloaddition allow for an increase in ylide steady-state concentration and concomitant absorption. For example, **4c** does

not undergo cycloaddition reactions which could be attributed to an increase in adverse steric interactions with methyl substituted alkenes and thus the probability of photocleavage is enhanced.[13]

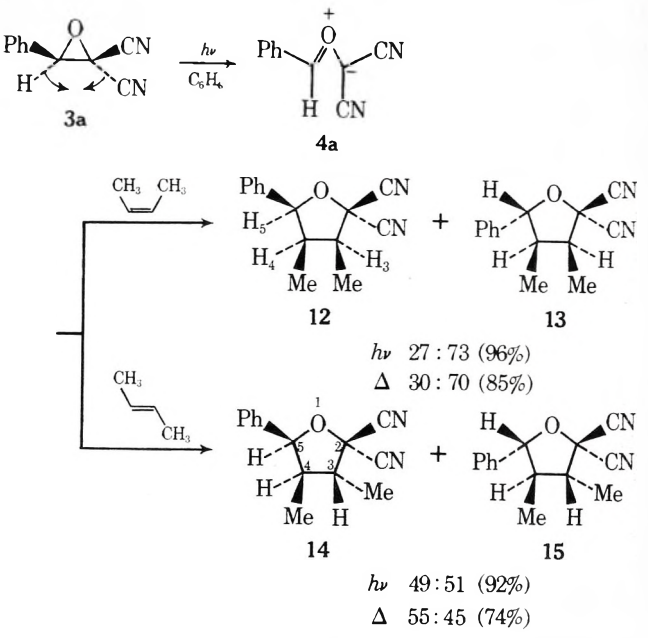
The unusual activity displayed by benzene as a solvent suggested that the nature of the excited states implicated in the photoconversion of the oxiranes **3** to the ylides **4** should be investigated. While acetone (E_T = 79 kcal mol^{-1}) was found to be ineffective as a solvent sensitizer for **3a**, the formation of the ylide **4g** derived from the corresponding β-naphthyl analogue **3g** which gives the adduct **7d** is effectively sensitized (>90%) by benzophenone (E_T = 69 kcal mol^{-1}). More surprising is the fact that anthraquinone (E_T = 62 kcal mol^{-1}) is capable of sensitizing the formation of **4g** from **3g**, as evidenced by interception of the former with methanol or isobutylene. In the case of **3g** even a visible source is sufficient to achieve oxirane C–C single-bond cleavage to **4g** in the presence of anthraquinone. That triplet states of the sensitizers were effectively populated in these instances was demonstrated by utilization of uranyl glass and naphthalene filters to preclude direct oxirane excitation. We conclude from the data that ylide formation is at least in part a triplet process and that benzene behaves as a high energy (E_T = 84 kcal mol^{-1}) solvent sensitizer in the reactions described for **3a** and related oxiranes. *trans*-1,3-Pentadiene (E_T = 59 kcal mol^{-1}) was found to quench ylide formation with **3a** which is not unexpected in view of the magnitude of the triplet energy of this oxirane (i.e., 79–84 kcal mol^{-1}).

While the nascent ylides may be formed in their triplet states, the subsequent [3 + 2 → 5] cycloaddition reactions to dipolarophiles are regioselective and stereospecific. These are features which characterize the corresponding ground-state reactions and indicate that intersystem crossing to the singlet manifold occurs prior to cycloaddition.[3] In view of these results it is tempting to propose that the competitive [3 → 2 + 1] cycloelimination reactions of the oxiranes **3** to carbenes may occur from the singlet manifold. Thus the data accumulated do not preclude intervention of cheletropic and/or sequential components in which the excited singlet oxirane undergoes concerted and/or stepwise fragmentation to dicyanocarbene and the carbonyl component, perhaps with initial C–O bond cleavage.

Regioselective addition reactions of the photogenerated carbonyl ylides **4** to alkenes may be demonstrated by irradiation (254 nm)[10] of **3a** (0.5 mmol) in benzene saturated with isobutylene. The sole adduct is **7a** whose structure is evident from NMR data. The typical spin-coupling between methylene and benzyl protons as well as the absence of detectable shielding of either methyl group precludes the alternate regioisomer. Similar results were found with **4e** (254 nm)[10] as well as **4f** and **4g** (350 nm)[10] where the adducts formed with isobutylene are **7b, 7c,** and **7d,** respectively.

The stereospecific character of these reactions is evident from the results obtained upon addition of **4a** to either *cis*- or *trans*-2-butene in benzene. *cis*-2-Butene reacts with **4a** to give a pair of epimeric tetrahydrofurans (**12** and **13**) which differ from those (**14** and **15**) obtained when *trans*-2-butene is the dipolarophile. The isomeric structures of the photoproducts **12–15** were established from combustion analytical, ir, mass spectral, and NMR data. The presence of an NOE observed between H_3 and H_4 and their vicinal *cis*-methyl groups at C_4 and C_3, respectively, in **14** (10%) and **15** (10%), but not **12** and **13,** serves to differentiate the *trans*-dimethyl epimeric set **14** and **15** from their cis counterparts **12** and **13.**

In systems studied by Huisgen[3c] the magnitude of such vicinal ring coupling constants proved unreliable for stereochemical assignments in tetrahydrofurans bearing aryl groups at the 2 and 5 positions. We have observed that the trans



coupling constants for **14** and **15** ($J_{3,4}$ = 11.0 and 11.5 Hz, respectively) are significantly higher than those for the cis isomers **12** and **13** ($J_{3,4}$ = 5.5 and 7.5 Hz, respectively) in a broad spectrum of adducts. Similar trends have been noted by Robert[4b] and Vandewalle[14] in related dicyanotetrahydrofurans and dimethylcyclopentanes, respectively. Thus it appears that coupling constant values can furnish reliable stereochemical information in such systems provided caution is exercized in cases where bulky substituents are present which might disrupt orientational factors responsible for the effect in conformationally mobile systems.

It should be noted that the adduct **13** is formed in higher yield from **4a** and *cis*-2-butene than the alternate epimer **12.** The magnitude of the difference is in accord with expectations based upon minimum steric interactions in the "two planes" orientation complex for the transition state leading to cycloaddition in the ground state.[3e,f] The results of the addition of **4a** to *trans*-2-butene are more difficult to assess since little significance may be attached to the apparent minor preference for the more stable adduct **15.** The relative amounts of the epimeric adducts (i.e., 12:13 and 14:15) are within experimental error of that obtained thermally at 120 °C which provides additional support for the contention that the cycloaddition reactions are ground-state processes.

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(11) A metastable ketal–enol ether formed by addition of ethanol to **1a** has been proposed as a rational intermediate in a mechanistic scheme leading to the ultimate isolable photoproducts obtained from this ylide in ethanol; however, this adduct was characterized solely by chemical transformations conducted without isolation in which ultraviolet spectroscopy served as the only analytical tool. See E. F. Ullman and W. A. Henderson, *J. Am. Chem. Soc.*, **88**, 4943 (1966).
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(15) Department of Chemistry, Louisiana State University, Baton Rouge, La. 70803.

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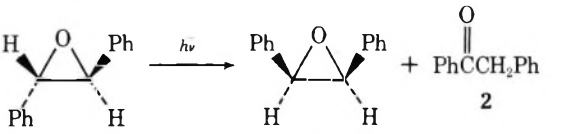
Photochemistry of *cis*- and *trans*-Stilbene Oxides

Summary: Stilbene oxides undergo photochemical ring opening from both singlet and triplet excited states to form carbonyl ylides which have been trapped with electron-deficient olefins; the resulting tetrahydrofuran adducts are formed stereoselectively in moderate yields from the singlet excited oxiranes, but are quantitatively obtained in a novel, synthetically useful fashion from triplet sensitized reaction mixtures.

Sir: The photochemistry of aryloxiranes has attracted considerable synthetic interest and mechanistic scrutiny within recent years.[1] *vic*-Diaryloxiranes have been observed to undergo photochemical [3 → 2 + 1] cycloelimination to produce synthetically useful yields of carbenes and carbonyl compounds.[1a,2] One of the interesting mechanistic features of these reactions is the apparently competitive fission of the oxirane C–C and C–O bond producing reactive intermediates which lead to the observed products.[3-5] Photochemical cleavage of the oxirane C–C bond produces carbonyl ylides which previously had been postulated[6] and more recently detected and characterized by spectroscopic means.[7] While the thermal ring opening of aryl oxiranes is well known to produce carbonyl ylides which were studied and trapped in subsequent 1,3-dipolar cycloaddition reactions,[8,9] the photochemically formed ylides have been less well characterized.[10,11] In the present paper, we wish to describe briefly data pertaining to the mechanistic aspects and synthetic utility of the photochemistry of the parent aryloxiranes, the *cis*- and *trans*-stilbene oxides.

Simultaneous irradiation[12] of the *trans*- and *cis*-stilbene oxide isomers in acetonitrile and in hexane with 2537-Å light at ambient temperature effects photoisomerization as outlined in Scheme I.[13]

Scheme I



1a 1b 2

90%[a]	CH_3CN[b]	1.0%	2.7%
89%[a]	C_6H_{14}[b]	1.3%	1.3%

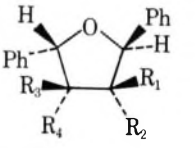
1b $\xrightarrow{h\nu}$ **1a** + **2**

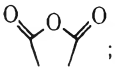
83%[a]	CH_3CN[b]	3.9%	0.7%
82%[a]	C_6H_{14}[b]	4.5%	0.7%

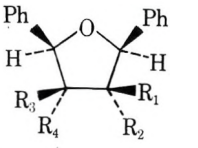
[a] Indicates amount of unconsumed starting material. [b] Solvent.

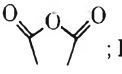
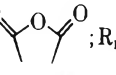
It is evident that *cis*-stilbene oxide photoisomerizes to its trans isomer, **1a**, much more readily than is observed for the reverse process, while the formation of deoxybenzoin (**2**) occurs ~6–7 times more readily from **1a** than from **1b**.

Examination of molecular models suggests that orientation of the phenyl π electrons relative to the C–C or C–O oxirane bond may control which products are preferentially formed. In **1a**, the absence of steric constraints permits aryl π overlap with the cleaving C–O σ bond leading to formation of deoxybenzoin. In **1b** this overlap is sterically hindered and instead aryl π overlap with the oxirane C–C bond appears favored, permitting facile cis–trans isomerization.[14] Similar arguments have been advanced previously to explain photochemical transformations of small-ring carbonyl compounds[15] and arylcyclopropanes.[16] Models also suggest a precedence for orbital participation in oxirane ring opening in the photolysis of 9,10-phenanthrene oxide reported by Griffin[17] and Chapman.[18]



3a, $R_1 = CO_2CH_3$; $R_2 = R_3 = R_4 = H$
b, $R_2 = CO_2CH_3$; $R_1 = R_3 = R_4 = H$
c, $R_1 = R_3 =$  ; $R_2 = R_4 = H$



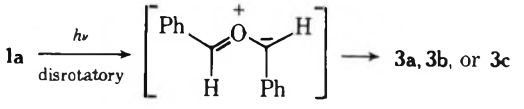
4a, $R_1 = CO_2CH_3$; $R_2 = R_3 = R_4 = H$
b, $R_2 = CO_2CH_3$; $R_1 = R_3 = R_4 = H$
c, $R_1 = R_3 =$  ; $R_2 = R_4 = H$
d, $R_2 = R_4 =$  ; $R_1 = R_3 = H$

When *trans*- or *cis*-stilbene oxide is irradiated directly with 2537-Å light in the presence of methyl acrylate or maleic anhydride, a product mixture containing previously observed photoproducts (vide supra),[1-4] as well as new tetrahydrofuran (THF) adducts **3** and **4**, was obtained. The yields of these adducts are given in Table I.[19] The photocycloaddition of stilbene oxides with electron-deficient olefins can be rationalized by the assumption that the electronically excited oxi-

Table I. Adduct Yields from Photolysis of Stilbene Oxides in the Presence of Dipolarophiles[19]

Stilbene oxide	Dipolarophile	Solvent	Total adduct yield, %	Relative adduct ratios, %	
				3a/3b	4a/4b
1a	Methyl acrylate	CH_3CN	23	62/27	8/3
1b	Methyl acrylate	CH_3CN	30	9/2	66/24
1a	Methyl acrylate	C_6H_{12}	18	61/26	6/7
1b	Methyl acrylate	C_6H_{12}	20	17/5	36/42
				3c	4c/4d
1a	Maleic anhydride	CH_3CN	26	91	4/5
1b	Maleic anhydride	CH_3CN	31	14	47/39

rane undergoes C–C fission to give carbonyl ylide intermediates, **5** and **6**. In each case it is apparent that the predominant mode of ylide formation is the result of an allowed[21] photo-



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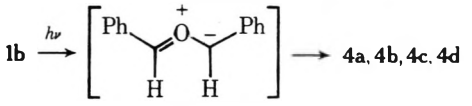

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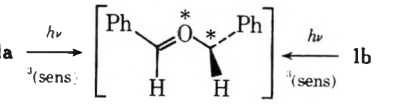
chemical disrotatory opening of the stilbene oxide. The stereochemistry of the isolated adducts from **1a** and **1b** confirms the identity of ylides proposed earlier by Trozzolo and Griffin[7] from low temperature spectroscopic studies of oxirane photolyses. With both oxirane isomers, a slightly higher yield of THF adducts was obtainable using the polar acetonitrile than with cyclohexane. Furthermore, photolysis of **1b** in cyclohexane containing methyl acrylate resulted in significantly depressed adduct stereoselectivity, as well as a reversal in the relative amounts of **4a** and **4b**. Additional studies are required to interpret these solvent effects.[22]

Irradiation of **1a** and **1b**[23] with methyl acrylate in solvents containing sufficient acetone to absorb >99% of the light ($h\nu$ >300 nm) resulted in much cleaner reaction mixtures and afforded high yields of the THF adducts **3** and **4**. Identical adduct isomer ratios were obtained regardless of the stereochemistry of the starting oxirane. In addition, the ratio and yields of adduct isomers varied depending on whether acetonitrile or benzene was employed as the solvent. These results

Table II. Adduct Yields from Acetone Sensitized Photolysis of Stilbene Oxides with Methyl Acrylate[23]

Stilbene oxide	Solvent	Total adduct yield, %	Relative adduct ratios, %	
			3a/3b	4a/4b
1a	CH_3CN	56	19/8	51/22
1b	CH_3CN	50	19/8	51/22
1a	C_6H_6	99	23/10	40/27
1b	C_6H_6	99	23/10	40/27

are given in Table II. It is evident from these data that the use of benzene/acetone as a reaction media provides a very simple and useful new synthetic procedure for making tetra- and dihydrofurans. The identity of photoadduct ratios from either **1a** or **1b** clearly implicates a common intermediate in the reactions. One possible candidate for this intermediate would



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be the orthogonal biradical, **7**, derived from the triplet excited state of the stilbene oxide.[24] Addition of the olefin to this intermediate would produce another biradical capable of free rotation prior to ring closure. Alternatively, in analogy with Salem's surface for nitrile ylide opening,[26] the triplet excited state of the oxirane may give an open minimum, which deactivates to the same mixture of cis and trans ylides, regardless of the precursor. The sharp contrast between the photosensitized reaction mixtures and those produced by direct irradiation suggests that, in the latter case, singlet excited oxiranes may ring open to planar carbonyl ylides (such as **5** and **6**) which have resonance delocalization to preserve their stereochemical integrity.[27]

Finally, we wish to comment on the role which frontier molecular orbital theory appears to play in the trapping of carbonyl ylides. Based on estimated frontier orbital energies for carbonyl ylides substituted with alkyl or conjugating substituents, Houk[28] has suggested that these ylides will react readily with electron-deficient dipolarophiles, and less readily or not at all with conjugated or electron-rich dipolarophiles. The formation of THF adducts from stilbene oxide and electron-deficient olefins, as well as our inability to detect adducts from **1a** or **1b** and norbornene,[29] supports Houk's conclusions. Additional effort is currently underway to further elucidate the scope and mechanistic implications of the above observations.

Acknowledgment. I wish to express appreciation to Professor A. Padwa for support and encouragement during the early stages of this work, and to Professors G. Griffin and K. Houk for helpful comments. I am indebted to Phil Briggs for mass spectral interpretations.

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(24) Attempted sensitization of **1a** in the presence of methyl acrylate with acetophenone gave no reaction (capable of producing acrylate triplets only).[25]
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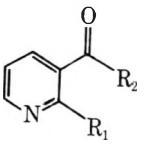
Synthesis of 2,3-Disubstituted Pyridines. Ortho-Formylation and Ortho-Acylation of 2-Alkylpyridines

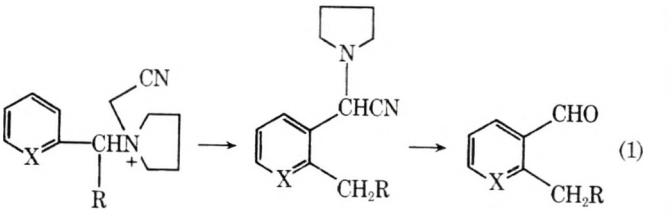
Summary: A general synthesis of 2-alkyl-3-acylpyridines and 2-alkyl-3-formylpyridines via [2,3]-sigmatropic rearrangements of α-pyrrolidinyl-2-alkylpyridines is described; the initially obtained α-cyanoamine can be hydrolyzed to an aldehyde, reductively cleaved to an amine, or alkylated and hydrolyzed to a ketone.

Sir: As part of our studies involving the structure[1] and reactivity[2] of nicotine and various nicotine analogues, we required a series of 2-alkyl-3-acylpyridines (**1**). Because of the substituent pattern involved and the well-known resistance of pyridine toward Friedel-Crafts alkylation and acylation, compounds generalized by structure **1** are difficult to prepare. We now report a sequence of reactions involving α-cyano-



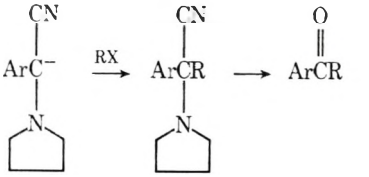
1

amines in which the α-cyanoamines (**1**) are the migrating moiety in a Sommelet–Hauser rearrangement; and (**2**) are utilized as acyl carbanion equivalents to effect alkylations.



2 **4** **3** (1)

a, X = CH, R = H
b, X = N

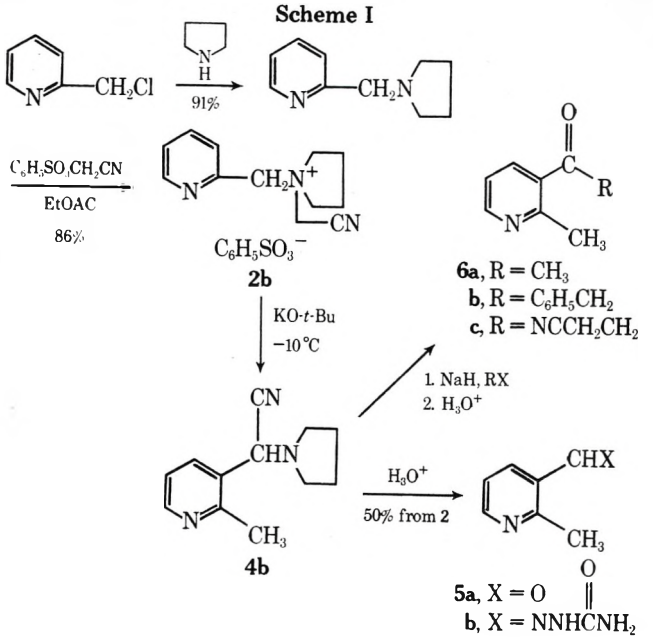


(2)

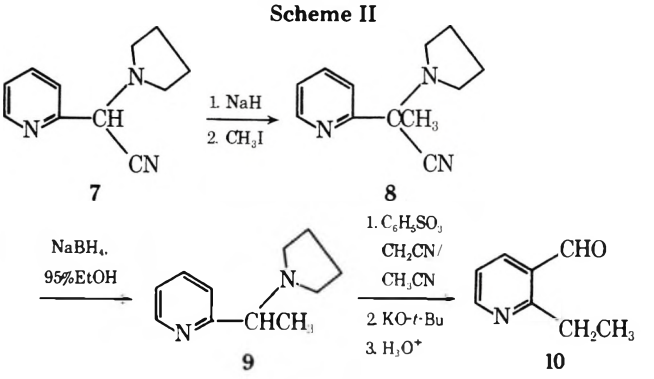
While the synthetic utility of [2,3]-sigmatropic rearrangements is well known in aliphatic and homocyclic chemistry,[3] only one application of this type of reaction in alkylpyridine chemistry has been reported.[4] Recently, Mander and Turner[6] reported the transformation of **2a** with KO-*t*-Bu to *o*-methylbenzaldehyde (**3a**) via the α-cyanoamine **4a**. This rearrangement seemed particularly attractive to us because the α-cyanoamine generated in the reaction was considered capable of undergoing alkylation.[7] In addition, as shown in Schemes I and II, the combination of the alkylation–rearrangement reactions adds remarkable versatility toward the general synthesis of **1**.

Treatment of the crystalline quaternary salt **2b** (R = H),[8] prepared via alkylation with cyanomethyl benzenesulfonate[9] (Scheme I), with KO-*t*-Bu in THF–Me_2SO at −10 °C, followed by acid hydrolysis of the crude product, gave (50%) 2-methyl-3-pyridinecarboxaldehyde (**5a**). Treatment of the crude product with semicarbazide hydrochloride gave a 34% yield of semicarbazone **5b**.[10] This procedure represents a considerable improvement over the published synthesis of **5a** which was obtained in 15% yield via a five-step synthesis from ethyl 3-aminocrotonate and 3-ethoxyacrolein diethyl acetal.[10]

Scheme I



Scheme II



Having successfully ortho-formylated 2-picoline,[9] we turned our attention to alkylation of intermediate **4b** to achieve ortho-acylation of 2-picoline. Rearrangement of **2b** (R = H) was carried out as above. After the reaction was complete, as judged by TLC and NMR, 1 equiv of sodium hydride was added followed by 1 equiv of methyl iodide. Acid hydrolysis of the crude product gave 3-acetyl-2-picoline[11] (**6a**, 78%). The corresponding benzyl ketone **6b**[11] was obtained in a similar fashion by alkylation with benzyl bromide (87%). Further investigation showed that this procedure could be simplified by using sodium hydride to effect both rearrangement and alkylation. Thus, the salt **2b** (R = H) was treated with 2 equiv of sodium hydride; after the rearrangement and second anion formation were complete, 3-bromopropionitrile was added followed by acid hydrolysis to give **6c** (48%).

The demonstration that these α-cyanoamines are alkylated with relative ease allows further generalization of this procedure for the preparation of 2-alkyl-3-acylpyridines. Since α-halo-2-alkylpyridines are not readily obtained by direct halogenation of the respective 2-alkylpyridines, the alkylation reaction described above was utilized. The α-cyanoamine **7**, prepared from 2-pyridinecarboxaldehyde, pyrrolidine, and KCN (58%), was treated with sodium hydride and methyl iodide giving **8** which, upon treatment with sodium borohydride in 95% ethanol, underwent reductive cleavage[12,13] to **9** (70% from **7**). Alkylation (Scheme II), rearrangement, and hydrolysis to **10**, isolated as its semicarbazone (10%), were achieved as described above.[14]

The preparation of 2-alkyl-3-acylpyridines using these procedures appears limited only by the nature of those alkyl halides capable of being alkylated by the α-cyanoamine anions.[14] We are currently investigating the scope of these alkylations as well as exploring other transformations of α-cyanoamines which could extend the use of these procedures for the synthesis of more complex heterocyclic systems.

Acknowledgment. We thank Dr. Jerry F. Whidby and Mr. Ron Bassfield for technical assistance.

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(13) In the sequence **7** → **9**, cyanoamine **7** can be regarded as an α-amino carbanion equivalent.
(14) Thorough investigation of the product mixture from the alkylation–rearrangement and hydrolysis of **9** indicates that a significant portion of the quaternary salt rearranges via a 1,2 shift; i.e., Stevens rearrangement. We are presently studying the effect of reaction conditions on product composition.

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Protonated Cyclobutadieneiron Tricarbonyl, a σ–π Bonded Cyclobutadiene Hydridoiron Tricarbonyl Cation[1]

Summary: ^1H and ^{13}C NMR spectroscopic study of cyclobutadieneiron tricarbonyl in fluorosulfuric acid solution at low temperature shows iron protonation with formation of a static σ–π complex resulting from an unusual π to σ change in the metal–ligand bonding; the observation of the geminal $^1H_4$–Fe–^1H_x (29 Hz) and ^{13}C–Fe–H_x (81.2 Hz) coupling substantiates the proposed structure; evidence of σ–π complex formation was further provided by studies in deuterated fluorosulfuric acid solution.

Sir: The enhanced stability of organometallic carbonyl cations has been well recognized and the nature of metal–ligand bonding in these ions has also been extensively investigated using both spectroscopic methods and quantum mechanical calculations.[2] Brookhart and Harris[3] first reported the π to σ change in metal–ligand bonding yielding stable σ–π complex when bicyclo[6.1.0]nonatrienemolybdenum tricarbonyl was protonated by excess fluorosulfuric acid in SO_2F_2 solution. Evidence for it was also found by Whitesides and Arhart[4] in the case of butadieneiron tricarbonyl complexes. Using ^{13}C

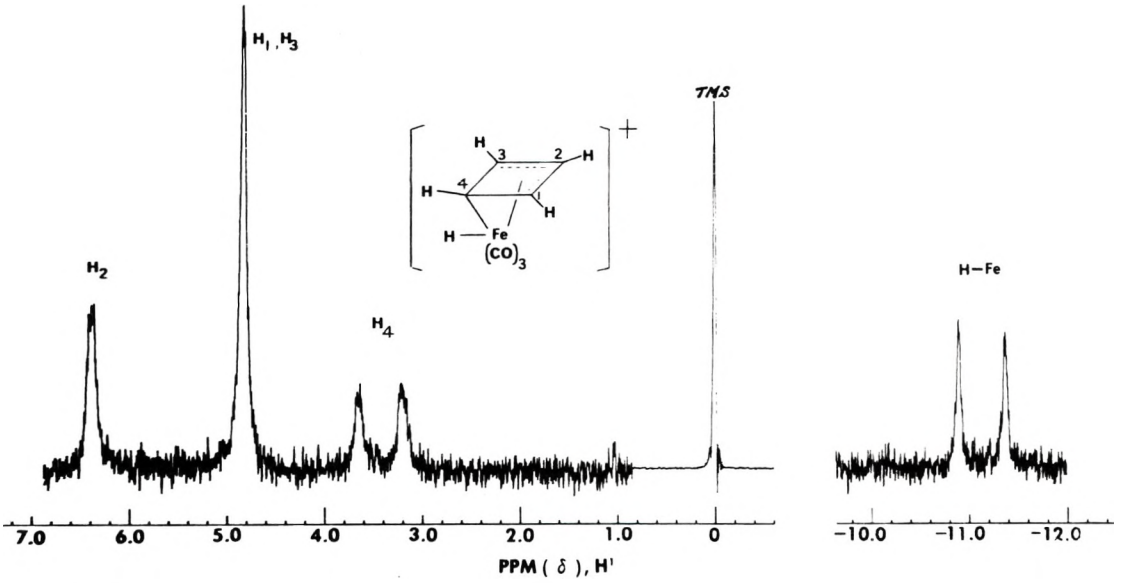
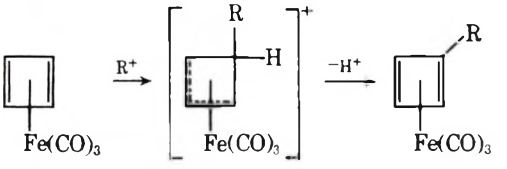


Figure 1. 60-MHz ^1H NMR spectrum of the protonated cyclobutadieneiron tricarbonyl in FSO_3H–SO_2 at −85 °C.

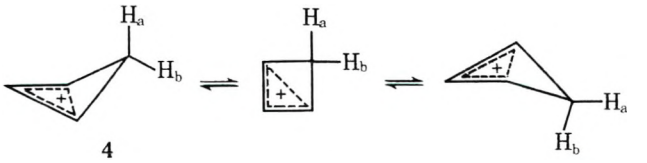
NMR spectroscopy, we have recently investigated the protonation of butadieneiron tricarbonyl[5] and its nonconjugated analog, norbornadieneiron tricarbonyl,[5] in fluorosulfuric acid–sulfur dioxide solution at low temperatures. The direct observation of geminal ^{13}C–Fe–^1H coupling in the protonated butadieneiron tricarbonyl (73.7 Hz) and norbornadieneiron tricarbonyl (38.2 Hz) complexes can indeed be explained only in term of σ–π-type complex formation.

Cyclobutadieneiron tricarbonyl (**1**), which was originally prepared and studied by Pettit and coworkers[6] has been regarded as aromatic in the sense that it underwent electrophilic substitution reactions via the assumed π-cyclobutenyliron tricarbonyl cation (**2**) to give substituted cyclobutadieneiron



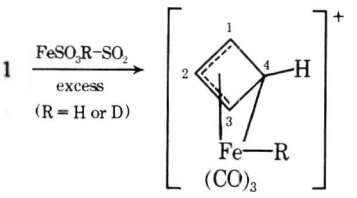
1 **2** **3**

tricarbonyl complexes **3**. Cation **2** should be closely related to the cyclobutenyl (homocyclopropenyl) cation **4** which we re-



4

cently reported, a homoaromatic 2-π system adoping nonplanar geometry undergoing rapid ring flipping process.[7] We wish to report now that **1** upon protonation undergoes π to σ isomerization and gives the σ–π complex **5** which was directly observed and studied by both ^1H and ^{13}C NMR spectroscopy.[8]



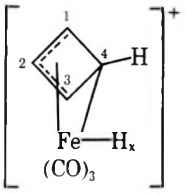
5, R = H
6, R = D

Careful addition (with good stirring) of a solution of **1** in sulfur dioxide to excess FSO_3H–SO_2 at −78 °C gave a dark reddish brown solution. The 60-MHz ^1H NMR spectrum (Figure 1) of this solution taken at −85 °C exhibited three-proton absorptions centered at δ 6.44 (broad singlet, H_2), 4.86 (broad singlet, H_1 and H_3), 3.45 (broad doublet, J = 29.0 Hz, H_4), and −11.16 (doublet, J = 29.0 Hz, H–Fe). The species did not show temperature dependent NMR spectra and slowly decomposed above −50 °C. When deuterated fluorosulfuric acid–sulfur dioxide was used, the 60-MHz ^1H NMR spectrum of the species also showed three-proton absorptions centered at δ 6.44 (broad singlet, H_2), 4.86 (broad singlet, H_1 and H_3), and 3.42 (broad singlet, H_4). The upfield broad doublet at δ 3.42 originally found in the species derived from **1** in excess FSO_3H–SO_2 solution collapsed into a broad singlet, when FSO_3D–SO_2 was used, while the doublet at δ −11.16 was absent, indicating the disappearance of the internal proton–proton coupling.

The Fourier transform ^{13}C (proton coupled) NMR spectrum of the species obtained in FSO_3H–SO_2 at −90 °C showed three-carbon resonances centered at $\delta_{^{13}C}$ 117.3 (doublet, $J_{^{13}C-H}$ = 191.2 Hz, 1 C), 65.8 (doublet, $J_{^{13}C-H}$ = 202.9 Hz, 2 C), and 9.0 (doublet of doublets, $J_{^{13}C-H}$ = 191.4 and 81.2 Hz) which were assigned to C_2, C_1 and C_3, and C_4, respectively. In addition, there were two-carbon absorptions at $\delta_{^{13}C}$ 202.7 (singlet, 1 C) and 200.0 (singlet, 2 C) in the carbonyl region. In FSO_3D–SO_2 solution, the species showed the same two low field doublets at $\delta_{^{13}C}$ 117.7 ($J_{^{13}C-H}$ = 191.2 Hz) and 65.8 ($J_{^{13}C-H}$ = 202.7 Hz), while the upfield signal at $\delta_{^{13}C}$ 9.0 became a broadened doublet ($J_{^{13}C-H} \simeq$ 190 Hz).

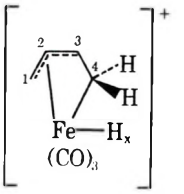
The ^1H and ^{13}C NMR spectra of the observed species from cyclobutadieneiron tricarbonyl (**1**) in excess acid are in good agreement with the formation of σ–π complexes **5** and **6**. Since C_4 is σ bonded to the iron atom, the large coupling constants $J_{H_4-Fe-H_x}$ (29.0 Hz) and $J_{^{13}C_4-Fe-H_x}$ (81.2 Hz) are as expected. In addition, both H_4 and C_4 are highly *shielded* indicating the formation of C_4–Fe σ bond. Chemical shifts and coupling constants for the C_1–C_3 moiety are consistent with that for a π-allyl system. We have previously reported that large geminate coupling constants are found in both protonated butadieneiron tricarbonyl (**7**)[5] (static) and norbornadieneiron tricarbonyl (**8**)[5] (rapidly equilibrating). The protonated cyclobutadieneiron tricarbonyl complex should also be described as static σ–π complex **5**. Cyclobutadieneiron tricarbonyl (**1**) thus undergoes protonation (or deuteration) on iron and the

present NMR spectroscopic data are inconsistent with the originally suggested C-protonated cyclobutenyliron tricarbonyl cation (**2**, R = H),[6] although this ion still could be formed under kinetically controlled conditions, but is not the thermodynamically favored species.



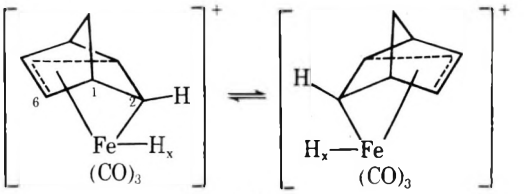
5

$J_{H_4\text{-}Fe\text{-}H_x}$ = 29.0 Hz
$J_{^{13}C_4\text{-}Fe\text{-}H_x}$ = 81.2 Hz



7

$J_{H_4\text{-}Fe\text{-}H_x}$ = 22 Hz
$J_{^{13}C_4\text{-}Fe\text{-}H_x}$ = 73.7 Hz



8

$J_{H_{2(6)}\text{-}Fe\text{-}H_x}$ = 13 Hz (av)
$J_{^{13}C_{2(6)}\text{-}Fe\text{-}H_x}$ = 37.8 Hz (av)

Both experimental data and theoretical calculations have shown the homoaromatic nature of the parent cyclobutenyl cation **4** and its puckered structure.[7] Nonplanar structures are also indicated in a number of cyclobutenylmetal complexes,[9] such as the σ complex of tetramethylcyclobutadiene with aluminum trichloride.[10] Although the present NMR spectra obtained for the protonated (deuterated) cyclobutadieneiron tricarbonyl **5** (**6**) indicate that **5** should possess a plane of symmetry, they do not allow clear differentiation as to whether the ion is planar or puckered. They indicate, however, clearly, the formation of a new carbon–iron σ bond, and the transformation of the original nonconjugated cyclobutadiene system into an allylic cyclobutenyl system.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

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Organomercury Compounds as Synthetic Intermediates. Coupling of Arylmercuric Salts

Summary: Arylmercuric salts are converted to biaryls in high yield upon treatment with copper and a catalytic amount of palladium chloride in pyridine.

Sir: The preparation of biaryls is ordinarily accomplished by the metal promoted decomposition of aryl halides, which includes the Ullmann reaction[1] and the use of zerovalent nickel complexes.[2] In addition, the reaction of an arylmagnesium halide[3] or aryllithium reagent[3e-g,4] with a salt such as a thallium, uranium, or first group transition metal salt has also been found to be preparatively useful for the generation of biaryls. The Ullmann reaction, however, is often unsatisfactory since (1) temperatures in excess of 200 °C are frequently required; (2) the reaction fails when the aromatic nucleus carries functional groups such as $-NH_2$, $-NHCOCH_3$, and $-NHCH_3$; and (3) a satisfactory result may require the use of relatively inaccessible aryl iodides when an activating substituent is not present. The alternative coupling of aryl halides with a zerovalent nickel complex suffers from one or more operational disadvantages which include air[2] and thermal sensitivity[2a] of the complex and the generation of difficulty separable by-products.[2b,c] Finally, the generation of biaryls from arylmagnesium halides or aryllithium reagents is suitable only in the absence of reactive functional groups.

We wish to report that arylmercuric salts are converted to biaryls in high yield (Table I) and under mild reaction conditions by treatment with copper metal and a catalytic amount of palladium chloride in the presence of pyridine according to eq 1. The reaction is compatible with most functional groups, and the arylmercuric salts required as starting materials are readily available[5] and are easily purified by crystallization. Ordinarily, the reaction is complete within 1 or 2 h at reflux temperature, but longer reaction times are not ordinarily harmful and serve to ensure completion of the reaction.

$$2ArHgX + Cu \xrightarrow[PdCl_2,\ 115\ °C]{\text{pyridine}} Ar\text{–}Ar + Hg + CuX_2 \qquad (1)$$

The experimental procedure is illustrated by the conversion of 4-chlorophenylmercuric acetate to 4,4′-dichlorobiphenyl.

A mixture of 4-chlorophenylmercuric acetate (2.001 g, 5.48 mmol), copper powder (1.501 g, 23.62 g-atoms), and palladium chloride (0.101 g, 0.57 mmol) in 20 ml of pyridine was heated under reflux in a nitrogen atmosphere with stirring for 5 h. The resulting mixture was filtered while hot through Celite, and the inorganic residues were washed with 75 ml of benzene. The combined filtrates were washed three times with 50-ml portions of 15% ammonium hydroxide, three times with 50-ml portions of 3 M HCl, and once with 50 ml of saturated brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give 0.515 g of tan needles. Recrystallization from ethanol afforded pure 4,4′-dichlorobiphenyl (0.377 g, 62%), mp 145–148 °C (lit.[6] mp 147–148 °C).

It is known that exposure of diarylmercury compounds to temperatures of 200–400 °C either in the absence[7] or presence[8]

Table I. Coupling of Arylmercuric Salts with Palladium Chloride and Copper in Pyridine [a]

Arylmercuric salt	Coupling product	Yield, %[b]
Phenylmercuric acetate	Biphenyl	86
2-Methoxyphenylmercuric acetate	2,2′-Dimethoxybiphenyl	84
4-Methoxyphenylmercuric acetate	4,4′-Dimethoxybiphenyl	90
4-Aminophenylmercuric acetate	Benzidine	76
4-Acetamidophenylmercuric acetate	4,4′-Diacetamidobiphenyl	69
4-Chlorophenylmercuric acetate	4,4′-Dichlorobiphenyl	62[c]
2-Chloromercurifuran	2,2′-Bifuran	86
2-Chloromercurithiophene	2,2′-Bithophene	95
1-Chloromercurinaphthalene	1,1′-Binaphthalene	47
4-Chloromercuribenzoic acid	None	0
4-Chloromercuriphenol	None	0
Mesitylmercuric acetate	None	0

[a] The reactions were carried out at reflux under a nitrogen atmosphere for a period of 22 h unless otherwise specified. [b] Isolated yield. [c] A reaction period of 5 h was used.

of metals such as Pd, Pt, Ag, Au, Co, Cu, Fe, and Ni results in the extrusion of elemental mercury and the formation of biaryls in modest to very low yields. In addition, several literature reports describe the conversion of diarylmercury compounds[9] and arylmercuric salts[9,10] to biaryls in low yield by treatment with palladium salts. As a result of one or more deficiencies which include low yields, by-product formation, and vigorous reaction conditions, these previous reports do not, however, describe a synthetically useful route to biaryls.

The use of pyridine as the solvent is an important factor in the success of the reaction. The use of nonbasic solvents such as dibutyl ether and toluene results in low yields of coupling product and the formation of by-products. In addition, both copper metal and catalytic amounts of palladium chloride are necessary. The omission of either copper[11] or palladium chloride results in a failure of the coupling reaction. The precise physical form of the copper is unimportant, however, and both wire and powder are equally suitable.

The reaction set forth in eq 1 has two modest limitations which are illustrated by the entries in Table I. The presence of acidic functional groups such as hydroxyl and carboxyl serve to inhibit the coupling reaction. The Ullmann reaction, however, also fails in the presence of these groups as well as in the presence of $-NH_2$ and $-NHCOCH_3$ groups.[1] In contrast, the present reaction affords high yields of biaryls in the presence of $-NH_2$ and $-NHCOCH_3$ groups (Table I).

The presence of bulky ortho substituents has an undesirable effect on the reaction. The preparation of 1,1′-binaphthalene proceeds in a somewhat modest yield of 47%. The presence of two ortho substituents, in the case of mesitylmercuric acetate, results in a complete failure of the coupling reaction.

Preparation of the unsymmetrical compound, 4-methoxybiphenyl, by crossed coupling of equimolar amounts of phenylmercuric acetate and 4-methoxyphenylmercuric acetate resulted in the formation of 33% biphenyl, 48% 4-methoxybiphenyl, and 19% 4,4′-dimethoxybiphenyl.[12] Consequently, very little selectivity is observed as the product distribution is close to a statistical 1:2:1 ratio.

The mechanism of the coupling reaction is unclear. It may be noted, however, that a highly satisfactory method for symmetrization of organomercuric salts consists of their reaction with copper in the presence of pyridine (eq 2).[13] If this symmetrization reaction occurs as an initial step, the resulting diarylmercury compound would be expected to undergo rapid reaction with catalytic amounts of either palladium metal or a palladium salt to form an unstable arylpalladium derivative which would decompose to yield the observed biaryl.[9,14]

$$ArHgX + Cu \rightarrow Ar_2Hg + 2CuX + Hg \qquad (2)$$

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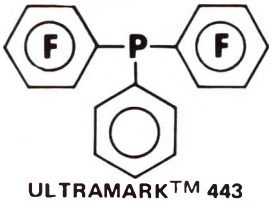

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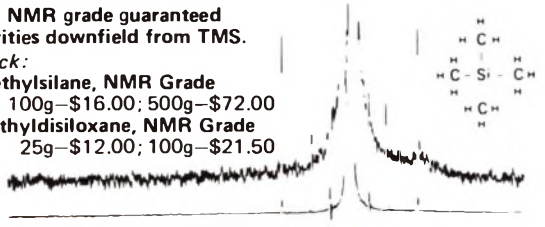

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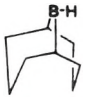
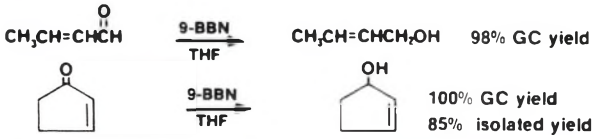
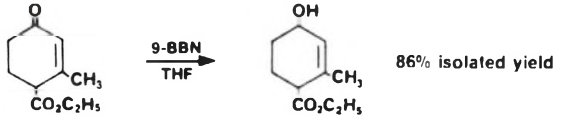


9-BBN (9-borabicyclo[3.3.1]nonane) is a very useful hydroboration reagent[1] which has been available from Aldrich for some time. Recently, a new application for **9-BBN** was reported.[2]

The conversion of α,β-unsaturated aldehydes and ketones to **allylic alcohols** has plagued chemists for years.[3] Now, the use of **9-BBN** in tetrahydrofuran (THF) solves most of the problems. Thus, 2-enones are cleanly reduced to the corresponding **allylic alcohols.**[2]



A detailed investigation of the reactivity of various representative functional groups toward **9-BBN** in THF indicates that this reduction of 2-enones can tolerate the presence of a large variety of sensitive functional groups.[4] Specific examples include carboxylic acid, ester, amide, epoxide, oxime, nitrile, nitro, azo, azoxy, halogen, sulfide, disulfide, sulfoxide, sulfone, and tosylate groups.[4] The following selective reduction of a 2-enone in the presence of an ester provides an interesting example.[2]



In general, **9-BBN** in THF appears to be the reducing agent of choice for the conversion of conjugated aldehydes and ketones to allylic alcohols.

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1) For a discussion of 9-BBN as a hydroboration reagent, please send for our detailed technical information bulletin.
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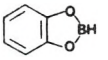
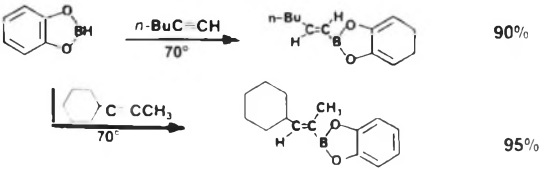
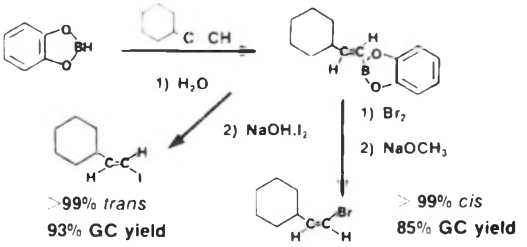


Catecholborane (1,3,2-benzodioxaborole) is a useful, stable new hydroboration reagent for the conversion of alkynes to alkeneboronic esters.[1] The reaction is both regioselective and stereospecific.



Such alkeneboronic esters can be converted into **alkenyl iodides** with complete *retention of stereochemistry*.[2] Amazingly, reaction with bromine provides a versatile synthesis of **alkenyl bromides** with complete *inversion of stereochemistry*.[3]



An important application of alkenyl halides is their conversion to alkenyllithium reagents and the corresponding cuprates with *retention of stereochemistry*. The lithium compounds and the cuprates likewise react with retention. This provides one of the key steps in the synthesis of prostaglandins.[4]

Catecholborane also shows particular promise as a mild reducing agent.[5]

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4) C.J. Sih *et al.*, *ibid.*, **97**, 857, 865 (1975), and references cited therein.
5) G.W. Kabalka and J.D. Baker, *J. Org. Chem.*, **40**, 1834 (1975).

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