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THE JOURNAL OF Organic Chemistry®

VOLUME 39, NUMBER 17

AUGUST 23, 1974

Isolation and Structural Elucidation of Allamandin, an Antileukemic Iridoid Lactone from *Allamanda cathartica*[1]

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Received March 12, 1974

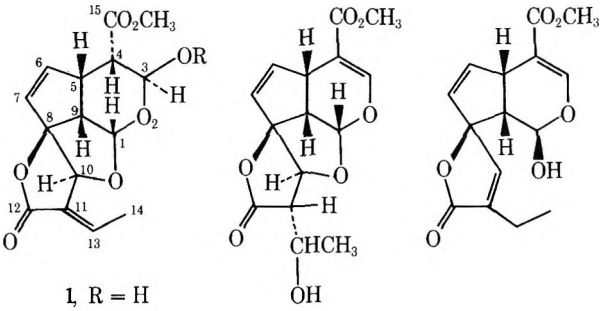
The isolation and structural elucidation of a new antileukemic iridoid lactone, allamandin (1), and the new companion iridoids, allamandicin (3) and allamdin (4), are reported. Elemental analysis and mass spectrometry established a $C_{15}H_{16}O_7$ molecular formula for allamandin (1), and the structure was established by spectral studies and dehydration to the previously known and cooccurring plumericin (5). Assignment of configuration was effected by spin-decoupling studies of acetylallamandin (2). The isomeric iridoid, allamandicin (3), was characterized by dehydration to plumericin (5) and additional chemical and spectral studies. The structure of allamdin (4) was deduced by spectral studies, and proven by direct X-ray crystallographic analysis.

In the course of a continuing search for tumor inhibitors of plant origin, an ethanolic extract of *Allamanda cathartica* Linn. (Apocynaceae)[2] was found to show significant activity *in vivo* against the P-388 leukemia in the mouse and *in vitro* against cells derived from human carcinoma of the nasopharynx (KB)[3] (Table I). Reported herein are the fractionation of an active extract of *A. cathartica* and the isolation and structural elucidation of a new antileukemic iridoid lactone, allamandin (1), and the new companion iridoids,[4] allamandicin (3) and allamdin (4).

Table I
Activity of Fractions from *A. cathartica* against KB Tissue Culture

Fraction	ED_{50}, μg/ml	Fraction	ED_{50}, μg/ml
A	4.6	H	3.1
B	>100	**1**	2.1
C	>100	**3**	>10
D	0.48	**4**	>10
E	0.8	**5**	2.7
F	0.25	**6**	2.6
G	1.6		

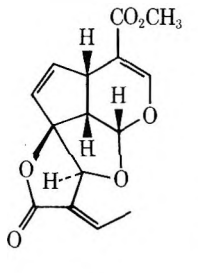
Fractionation of the ethanol extract (A) (Chart I) revealed that the *in vivo* activity was concentrated, successively, in the chloroform layer (D) of a chloroform–water partition, the aqueous methanol layer of a 10% aqueous methanol–petroleum ether partition, the aqueous methanol layer of a 20% aqueous methanol–carbon tetrachloride partition, and the chloroform layer (G) of a chloroform–40% aqueous methanol partition. Rapid column chromatography of the final chloroform-soluble material gave a fraction which was further separated into two major bands by preparative thin layer chromatography. Rechromatography of the higher R_f band gave the known iridoids plumericin (5) and isoplumericin (6), identified by comparison of their physical and spectral characteristics with those recorded previously.[5,6] Rechromatography of the second band yielded allamandin (1), allamandicin (3), and allamdin (4).



1, R = H
2, R = Ac

3

4



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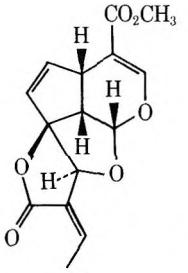

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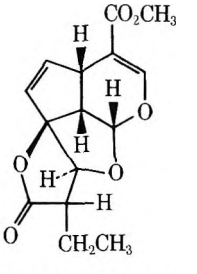
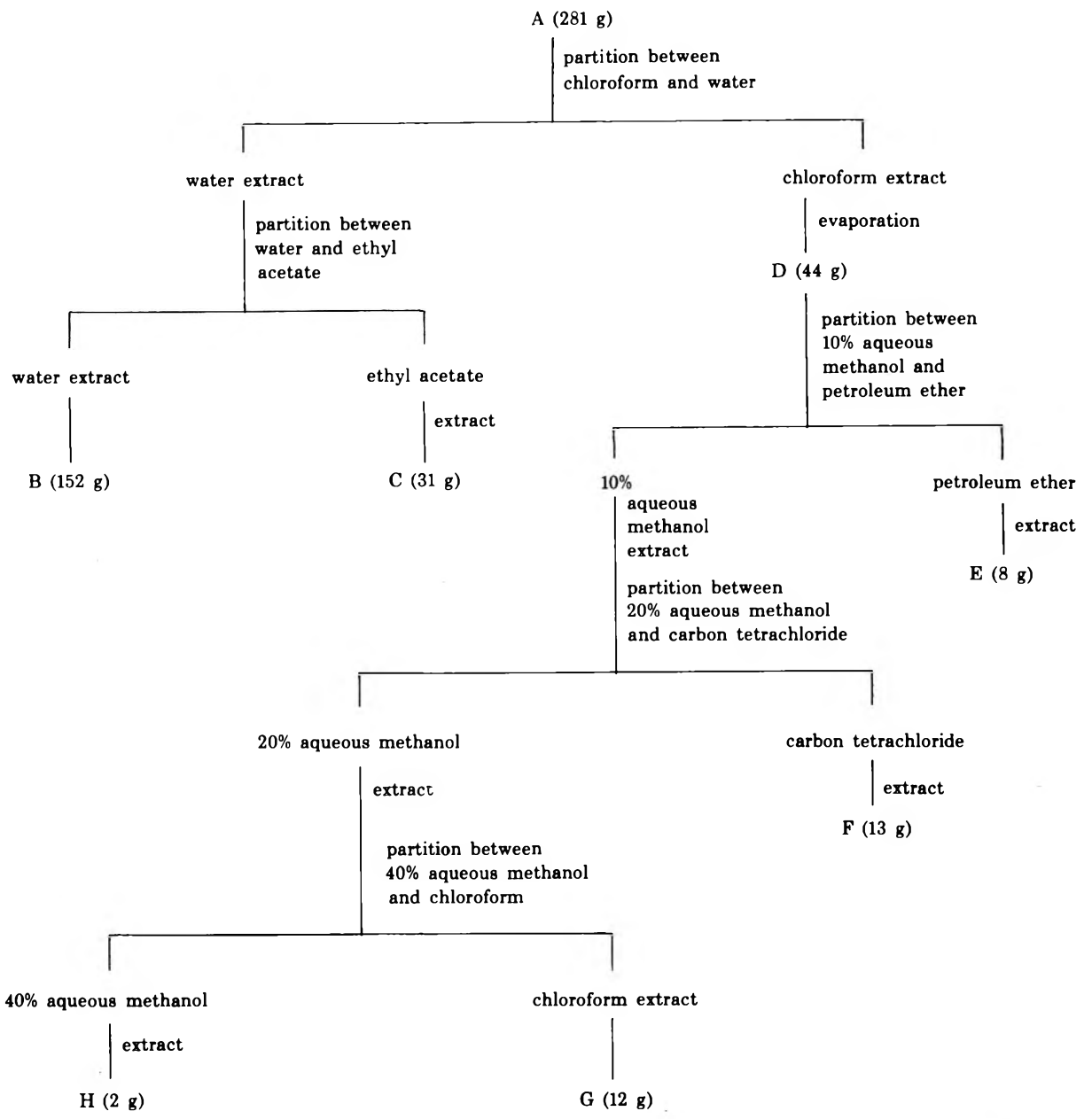


7, α-H; β-CH_2CH_3
8, β-H; α-CH_2CH_3

Elemental analysis and mass spectrometry established a molecular formula of $C_{15}H_{16}O_7$ for allamandin (1). This corresponded to the addition of the elements of water to either plumericin (5) or isoplumericin (6), and, indeed, the infrared spectrum of 1 showed hydroxyl absorption (2.98 μ). Attempted acetylation of 1 in pyridine resulted in dehydration to plumericin (5). The ir and uv spectra of 1 revealed the presence of the α,β-unsaturated lactone and the absence of an α,β-unsaturated methyl ester system. Acetylation to acetylallamandin (2) was ultimately effected (in the absence of base), and the nmr spectrum (Table II) of 2 proved to be most significant. The spectrum showed no signal at τ 2.64 [assigned to the olefinic C-3 proton in plumericin (5)[6]], but did show a one-proton doublet at τ 3.72 (J = 8 Hz), corresponding to the C-3 proton of 2. Double-reso-

Chart I
Fractionation of Cytotoxic Extract from *A. Cathartica*



nance studies demonstrated that irradiation of the C-3 proton doublet caused collapse of a doublet of doublets centered at τ 7.11 [leaving a doublet (J = 4.5 Hz)], assignable to the C-4 proton. Irradiation of the multiplet at τ 6.43 caused the collapse of the C-4 proton doublet of doublets to a doublet (J = 8 Hz) and the two doublets of doublets due to the C-6 and C-7 olefinic protons to doublets (J = 6 Hz). Assignment of the τ 6.43 multiplet to the C-5 proton was confirmed as follows. Irradiation of the C-1 proton doublet at τ 4.49 (J = 4.5 Hz) led to the assignment of the doublet of doublets at τ 6.93 (J = 8, 4.5 Hz) to the C-9 proton. Then, irradiation of these peaks caused not only the collapse of the doublet at τ 4.49 (C-1 proton), but sharpening of the multiplet at τ 6.43, indicating the coupling of the protons at the ring junction. Careful examination of Dreiding models indicated that the six-membered ring may assume a half-chair conformation with C-1, C-9, C-5, and C-4 held in the same plane and with the protons attached to these carbons on the same side of the ring. This conformation accords with the observation of the same coupling constant between the protons at C-1 and C-9 ($J_{1,9}$ = 4.5 Hz) and the protons at C-4 and C-5 ($J_{4,5}$ = 4.5 Hz). The latter coupling, along with that seen for the C-3 and C-4 protons ($J_{3,4}$ = 8 Hz), accords only with the configuration bearing the carbomethoxy group in the α orientation and the proton at C-3 also α and in an axial conformation.

Allamandicin (3) was characterized as an isomer of 1 on the basis of elemental analysis and mass spectral data. The ir spectrum indicated the presence of a hydroxyl group and the ir and uv spectra the presence of an α,β-unsaturated methyl ester and a saturated lactone. The nmr spectrum of allamandicin showed a one-proton singlet at τ 2.65, assignable to the C-3 olefinic proton. The spectrum also contained a three-proton doublet at τ 8.65 (J = 6 Hz), indicative that the C-14 methyl was not vinylic in nature. The splitting for this signal demonstrated the presence of but one proton on the adjacent carbon (C-13), corresponding to a broad multiplet at τ 5.61. Irradiation of the multiplet caused the methyl doublet to collapse to a singlet and the doublet for the C-11 proton at τ 7.32 (J = 1.5 Hz) to be-

Table II
Nuclear Magnetic Resonance Data[a]

Compd	C-1	C-3	C-4	C-5	C-6[b]	C-7[b]	C-9	C-10	C-11	C-13	C-14	OCOMe, other
2	4.49 d (4.5)	3.72 d (8)	7.11 dd (8, 4.5)	6.43 m	4.03 dd (6, 2)	4.14 dd (6, 2)	6.93 dd (8, 4.5)	4.88 d (1.5)		2.78 dq (1.5, 7)	8.00 d (7)	6.30 s Ac 7.99 s
3	4.56 d (6)	2.65 s		6.12 td (2, 8)	4.14 dd (5, 2)	4.32 dd (5, 2)	6.69 dd (8, 6)	5.34 s	7.32 d (1.5)	5.61 m	8.65 d (6)	6.30 s OH 7.5 m
4	5.00 dd (5, 3)	2.62 d (3)		6.20 m	3.63 dd (6, 5)	4.66 dd (6, 2)	7.03 dd (8, 3)	3.29 t (1.5)		7.74 dq (1.5, 8)	8.88 t (8)	6.30 s OH 5.8 br d (5)
5[c]	4.52 d (6)	2.63 s		6.08 td (2, 9)	4.03 dd (6, 2)	4.45 dd (6, 2)	6.66 dd (9, 6)	4.98 br s		2.9 dq (1.5, 7)	7.98 d (7)	6.30 s

[a] Spectra were determined on a Varian HA-100 spectrometer in deuteriochloroform solutions. Values are given in τ units relative to tetramethylsilane as an internal standard. Multiplicity of signals is designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Numbers in parentheses denote coupling constants in hertz. [b] Assignments for these protons are made on the basis of analogy to those for **4** and published values for similar cases (ref 10). The assignment differs, however, from that made in the case of **5** (ref 4). [c] The spectrum for isoplumericin (**6**) differs only at C-13 [τ 3.27 q (7)] and C-14 [τ 7.75 d (7)].

come a sharp singlet. In addition, the signal for the hydroxyl proton at *ca.* τ 7.50 became sharper. The α orientation of the hydroxyethyl group could be inferred from the nature of the signal assigned the proton at C-10.[6] The singlet observed (τ 5.34) for this proton is consistent with the β orientation of the proton at C-11, by analogy with spectra of α-dihydroplumericin (**7**) and β-dihydroplumericin (**8**). Molecular models indicate that maximum orbital overlap with the C-10 hydrogen occurs when the C-11 proton is in the α configuration, and, accordingly, a doublet for the C-10 proton appears in the spectrum of **7**.[6] A β orientation for the C-11 proton provides little orbital overlap, and, indeed, a singlet for the C-10 proton is observed in the spectrum of **8**.

Allamandicin (**3**) was readily dehydrated to give plumericin (**5**) upon attempts at acetylation and upon treatment with phosphorus oxychloride in pyridine.[7] The latter reaction is known to involve trans elimination,[8] and favors the *S* configuration for the C-13 carbon.

The molecular formula of allamdin (**4**), $C_{15}H_{16}O_6$, was established on the basis of elemental analysis and mass spectrometry. The ir spectrum of **4** indicated the presence of a hydroxyl group and both α,β-unsaturated lactone and α,β-unsaturated methyl ester systems. The uv spectrum (τ 3.30) was not strongly coupled to the C-13 protons (J = 2 Hz). Double-resonance studies demonstrated that the proton at C-1 (τ 5.00) appeared as a broad doublet of doublets (J = 5, 3 Hz) coupled to both the hydroxyl proton and the C-9 proton. The positions of the remaining protons on the six-membered ring were confirmed using this technique. The protons attached to the olefinic 6 and 7 carbons appeared as two doublets of doublets, at τ 3.63 and 4.66. The set of peaks farther downfield was assigned to the C-6 proton, owing to its greater secondary coupling constant (J = 5 Hz). The apparent increased mobility of the six-membered ring in **4**, when compared to the other compounds, presents the opportunity for increased orbital overlap between the C-5 and C-6 protons. Presumably, this effect increases the value of the coupling constant between these protons ($J_{5,6}$) more than the coupling constant between the protons on C-5 and C-7 ($J_{5,7}$). The negative molecular rotation of allamdin ([M]D −102°) favored the β configuration for the C-1 hydroxyl group.[9]

The configuration at C-1 and the detailed structure and stereochemistry of allamdin (**4**) were proven by direct X-ray crystallographic analysis.[11] A view of the allamdin molecule as found in the crystal is shown in Figure 1. The molecular structure found clearly corresponds to **4**, and the β orientation of the C-1 hydroxyl group is firmly established. Although brief reports have been given of X-ray structure

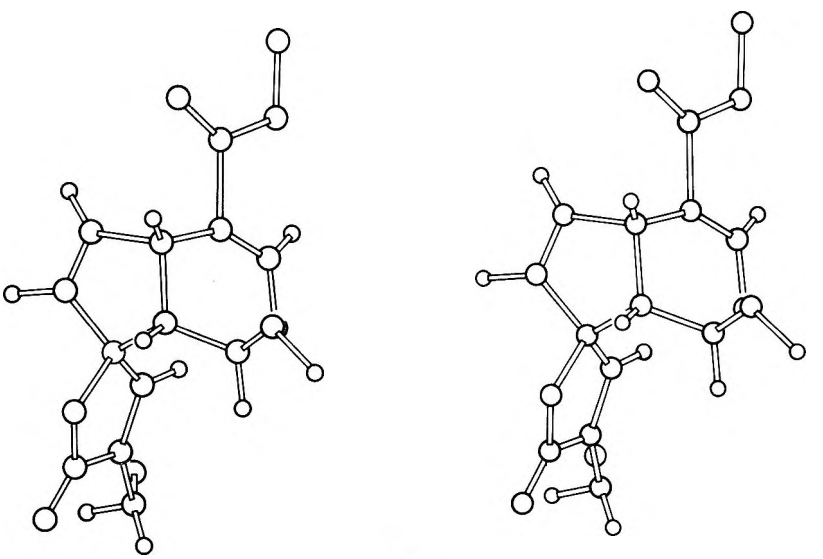


Figure 1. Stereoscopic view of the allamdin molecule as found in the crystal. The hydrogen atoms attached to the two methyl carbon atoms were not located in the analysis and are not shown.

confirmed the presence of the unsaturated chromophores. The nmr spectrum of **4** revealed that carbons 13 and 14 constituted an ethyl side chain. The olefinic proton at C-10

determinations of both a Rb salt of monotropein[12] and a derivative of loganin,[13] in neither case were atomic coordinates provided, so that this report gives the first detailed description of the molecular geometry of an iridoid.

Internal agreement between individual measurements of bond distances for equivalent bond types is good. Thus, the average of the four C_{sp^3}–C_{sp^3} bond distances is 1.54 ± 0.03 Å, of the four C_{sp^3}–C_{sp^2} distances 1.51 ± 0.02 Å, and of the three C_{sp^2}=C_{sp^2} distances 1.32 ± 0.02 Å. All of these average values are close to the standard values for the various bond types.[14] By contrast, of the two C_{sp^2}–C_{sp^2} distances, C-11–C-12 is longer than normal, probably owing to strain in the unsaturated lactone ring and indicating a minimum of conjugation between C-10–C-11 and the carbonyl group of the ring, while C-4–C-15 is of a more normal length. The two C=O bonds are of normal length, 1.18 and 1.19 Å, while the three C_{sp^3}–OR bonds average 1.49 ± 0.02 Å and the three C_{sp^2}–OR bonds 1.35 ± 0.02 Å. The hydroxyl bond at C-1 is somewhat shorter than the standard value of 1.426 (5) Å.

The intraring valence angles in the dihydropyran ring have fairly normal values as compared to cyclohexene, but the substitution of the oxygen atom 2 with its corresponding open valence angle of 116° produces significant changes in angles in the rest of the ring which would otherwise be expected to be equivalent, *e.g.*, 122° at C-4 *vs.* 126° at C-3, and 110° at C-5 *vs.* 115° at C-9. The intraring valence angle at C-1 is close to the regular tetrahedral value and the extraring valence angles involving the hydroxyl group are both less than the regular tetrahedral value. It has commonly been assumed[15] in the calculation of minimum energy conformations of six-membered rings that substitution at tetrahedral carbon atoms will lead to increased values for the corresponding intraring valence angles. While there is ample evidence that this is so for methyl substituents, the arrangement here suggests that attention should also be paid to the nature of the substituent atoms involved.

A similar pattern of valence angles occurs at each of the three sp^2-carbon atoms C-4, C-12, and C-15. In each case the double bond is flanked by two angles >120° while the third angle is significantly <120°. At both C-12 and C-15 the smaller of the two largest valence angles is found adjacent to an ether oxygen atom, the larger adjacent to an sp^2 carbon. The limiting steric interaction in each case seems to be the maintenance of a 1,3 O···O separation of around 2.22 Å.

Within the cyclopentene ring the valence angles at both sp^2 and sp^3 carbons are reduced by about the same amount, *ca.* 7°, from the regular trigonal and tetrahedral values. More severe closures of the intraring C_{sp^2} angles are found in the unsaturated lactone ring at C-11 and C-12 than at C-10, reflecting the enhanced length of C-11–C-12 already mentioned. A pronounced asymmetry of the extraring angles at C-11, 132° *vs.* 122°, occurs and is to be associated with the near coplanarity of the lactone ring with the ethyl group at C-11. This brings H-10 into close proximity with the C-14 methyl group (C-14···H-10, 2.60 Å) and suggests a locking of the methyl group by interposition of H-10 between two of the methyl hydrogens. However, the methyl group hydrogen atoms have not been located in the final electron-density maps.

The valence angles at the spiro atom C-8 show equal intraring values of 103° in both the cyclopentene and lactone rings, but a fair asymmetry in the remaining angles. The angle between the two planes defined by C-7, C-8, C-9, and C-10, C-8, O-20 is 87.5°.

The pattern of torsion angles in the dihydropyran ring shows it to have a 1,2-biplanar (sofa) conformation.[15] Torsion angles about bonds not involving O-2 have values very close to those calculated for the minimum energy conformation of this type in cyclohexene.[15] The 1,2-biplanar arrangement is calculated to be about 1.5 kcal/mol greater in energy than the monoplanar (half-chair) conformation for cyclohexene. The observed reduction in the torsion angles about C-1–O-2 and O-2–C-3 is about 10° in each case from the value expected for the corresponding bonds in this form of cyclohexene. This type of reduction is to be expected on substitution of an oxygen atom for a methylene group, as this involves an opening of the valence angle at this position in the ring from about 112° to 116° and is accompanied by a reduction in the length of the bonds to this position. The overall result is a flattening of the ring in the vicinity of O-2 as compared to the corresponding cyclohexene.

The torsion angles of the cyclopentene ring show it to have C_s symmetry in a plane from C-9 perpendicular to and passing through the midpoint of the double bond C-6=C-7. The mean deviation of the four atoms C-5, C-6, C-7, and C-8 from the mean plane through them is 0.007 Å (maximum 0.009 Å) and C-9 is displaced from this plane by −0.37 Å.

In the α,β-unsaturated lactone ring the low values of the torsion angles indicate a near-planar arrangement of the atoms and this impression is initially confirmed upon calculation of a least-squares mean plane through the five atoms of the ring and O-19. The mean deviation from this plane is 0.14 Å, and the maximum −0.23 Å. However, a closer inspection reveals that the four carbon atoms of the ring are coplanar to within 0.001 Å whereas O-20 is displaced from that plane by fully 0.07 Å. The exact conformation of the ring is thus shown to deviate significantly from coplanarity. The displacements from the four-atom plane in the ring for O-19, C-13, and C-14 are 0.03, 0.04, and −0.07 Å, respectively.

The stereochemistry at the dihydropyran–cyclopentene ring junction is cis. The combination of this cis stereochemistry and the unusual spiro linkage of the cyclopentene and lactone rings is clearly linked to the β orientation of the C-1 hydroxyl group and the conformation of the dihydropyran ring. In the dihydropyran C-1 is displaced out of the rough plane through the other atoms of the ring by about 0.5 Å in a direction nearly perpendicular to the plane of the lactone ring. C-1 approaches C-10 in a 1,4 interaction within 2.98 Å, while H-1 is only 2.92 Å from C-10 and 3.36 Å from C-11. A hydroxyl group α at C-1 in this particular conformation of the dihydropyran ring would be involved in sterically unfavorable interactions with C-10 and C-11 while not being able to compensate for these stresses by intramolecular hydrogen bonding with either O-19 or O-20, since the hydroxyl hydrogen atom would be behind both oxygens in a position sterically unfitted for hydrogen bond formation. Other close intramolecular approaches involve O-2 with O-2···H-10 2.67 Å and O-2···C-10 only 2.96 Å in a 1,5 orientation.

The C-1 hydroxyl group takes part in intermolecular hydrogen bond formation with O-19, the carbonyl oxygen of the lactone ring, in a neighbor. This leads to linearly connected strings of molecules in the crystal.

Experimental Section[16]

Extraction and Preliminary Fractionation of *Allamanda cathartica*. The dried ground roots of *A. cathartica* (1.61 kg) were continuously extracted with hot 95% ethanol for 45 hr and the ethanol extract was concentrated under reduced pressure to a dark brown residue (A, 281 g). Fraction A was partitioned between water (1.5 l.) and chloroform (2.0 l.), and the aqueous layer was further extracted with ethyl acetate (2 l.). The water and ethyl acetate portions were evaporated to give fractions B (152 g) and C (31

g), respectively. The chloroform extract was evaporated to give D (44 g), which was then partitioned between 10% aqueous methanol (1 l.) and petroleum ether (1 l.). Evaporation of the petroleum ether gave E (8 g). The aqueous methanol fraction was diluted with water, and the resulting 20% aqueous methanol solution (1.225 l.) was extracted with carbon tetrachloride (1.5 l.). The carbon tetrachloride was evaporated to give F (13 g). The 20% aqueous methanol portion was diluted with water to give 40% aqueous methanol (1.5 l.), which was extracted with chloroform (2 l.). The chloroform and aqueous methanol solutions were evaporated to give fractions G (12 g) and H (2 g), respectively.

Isolation Procedure. A larger fraction (83 g) corresponding to G was obtained from another extract of plant material (5.7 kg). This fraction was subjected to column chromatography (silica gel 60) and eluted with chloroform followed by 2% methanol in chloroform. The column fractions were combined according to analytical tlc results and yielded 40 g of a fraction containing the desired materials. Preparative tlc of a 4-g portion (Silplates, 20 × 20 × 2 mm) with 5% methanol in chloroform resulted in two major fractions (I and J). The higher R_f fraction (I, 1.16 g) deposited crude crystals on standing.

This crude crystalline material was subjected to preparative tlc (Silplates, 20 × 20 × 0.25 mm) with chloroform as a solvent. The material from the higher R_f band was recrystallized from methylene chloride–hexane to give isoplumericin (**6**) as colorless plates (350 mg, mp 195–198°), identified by melting point, nmr, ir, and mass spectral comparison with published data.[5,6] The material from the lower R_f band from the preparative tlc was treated in the same way to give plumericin (**5**), as colorless plates (460 mg, mp 209–212°), identified as for **6** above.

The second major band from the preparative tlc with the 2-mm thick plates (J, 2.00 g) was subjected to dry column chromatography.[17] The column was charged with 130 g of SilicAR CC-7 packed in 5-cm flat diameter nylon tubing, and eluted with 3% methanol in ether. The bulk of the material from the column was eluted from a uv-fluorescent band (R_f *ca.* 0.5). On standing, this fraction deposited a crystalline material. Trituration with chloroform gave allamandin (**1**, 37 mg). Recrystallization from methanol–ethyl acetate gave thin plates: mp 212–215°; $[\alpha]^{21}D$ +15° (c 0.06, methanol); uv λ_{max} (MeOH) high end absorption; ir λ_{max} (KBr) 2.98, 3.38, 5.79, 5.99, 6.94, 8.35, 8.52, 9.90 μ; mass spectrum *m/e* 308 (M^+), 290, 277, 262, 258, 230, 211, 179, 161, and 151.

Anal. Calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.17; H, 5.11.

The dry column fraction (546 mg) from the zone between the band which gave **1**, and a dark blue fluorescent band (uv) at the solvent front, was subjected to preparative tlc on ChromAR to yield two major fractions (K, 248 mg, low R_f; L, 138 mg, high R_f).

Fraction K was rechromatographed twice (Silplates, 20 × 20 × 0.5 mm, 1% methanol in chloroform followed by ChromAR plates, ether–hexane, 1:1) to yield a residue which was crystallized (ether–hexane) as colorless plates. Recrystallization gave allamandicin (**3**, 27 mg): mp 117–118°; $[\alpha]^{21}D$ +293° (c 0.42, chloroform); uv λ_{max} (EtOH) 238 nm (ϵ 11,500); ir λ_{max} (KBr) 2.87, 3.24, 3.38, 5.64, 5.91, 6.08, 6.96, 8.45, 9.22 μ; mass spectrum *m/e* 308 (M^+) 290, 279, 261, 246, 233, 230, 218, 214, 198, 197, 188, 186, 170, and 150.

Anal. Calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.76; H, 5.38.

Fraction L was subjected to the same sequence and gave a residue which was crystallized (ether–hexane) to give prisms of allamdin (**4**, 35 mg): mp 131–132° dec; $[\alpha]^{21}D$ −35° (c 0.46, chloroform); uv λ_{max} (EtOH) 238 nm (ϵ 14,000, sh) and high end absorption; ir λ_{max} (KBr) 2.92, 3.22, 3.24, 3.36, 5.77, 5.90, 6.11, 6.98, 7.77, 9.00, 9.37 μ; mass spectrum *m/e* 292 (M^+), 274, 263, 232, 231, 214, 203, 186, 175, and 162.

Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.89; H, 5.56.

Dehydration of Allamandin (1). A solution of allamandin (**1**, 16.2 mg) in dry pyridine (2 ml) was treated with acetic anhydride (1 ml). The mixture was stirred at room temperature for 19 hr. The solvent and excess reagent were removed under vacuum and the residue was applied to three Silplates (20 × 20 × 0.25 mm), which were developed in 1% methanol in chloroform. The major band yielded a solid (10 mg) which was recrystallized (methylene chloride–hexane) to give colorless plates of **5**, mp 207–211°, characterized by melting point, mixture melting point, and comparison of nmr and mass spectra with those of authentic material.

Acetylallamandin (2). A suspension of allamandin (**1**, 17 mg) in acetic anhydride (7.5 ml) was stirred at 70° for 18.5 hr. The solvent was removed under vacuum and the residue was applied to three ChromAR plates (20 × 20 × 0.25 mm). Development with ether–hexane (2:1) was effected twice, and the material from the major band was eluted and crystallized from ether to yield acetylallamandin (**2**, 11 mg). Recrystallization from methylene chloride–hexane gave needles: mp 173–177°; $[\alpha]^{21}D$ +61° (c 0.36, chloroform); uv λ_{max} (EtOH) high end absorption; ir λ_{max} (KBr) 3.38, 5.62, 5.74, 5.78, 5.95, 6.98, 8.18, 9.30, 9.97, 10.6 μ; mass spectrum *m/e* 350 (M^+), 308, 291, 277, 253, 211, 193, 179, 161, 140, and 98.

Dehydration of Allamandicin (3). A solution of allamandicin (**3**, 13 mg) in dry pyridine was cooled to 2° and treated with phosphorus oxychloride (5 drops). After 4 min, the mixture was allowed to warm to room temperature and the solvent was removed under vacuum. A chloroform solution of the residue was filtered and applied to two Silplates (20 × 20 × 0.25 mm). The plates were developed three times with chloroform and the material eluted from the two high R_f bands was obtained as crude crystals. Recrystallization (methylene chloride–hexane) gave, as the major product, plumericin (**5**, 6.5 mg), mp 208–211°, characterized by melting point, mixture melting point, tlc, and comparison of ir ($CHCl_3$) and mass spectra with those of authentic material. The minor product (<1 mg) was identified as isoplumericin (**6**) by comparison of its mass spectrum and tlc behavior with those of an authentic sample.

X-Ray Crystallographic Structural Data for Allamdin ($C_{15}H_{16}O_6$): orthorhombic, space group $P2_12_12_1$, a = 13.211 (2), b = 13.736 (2), c = 7.858 (1) Å, ρ_{obsd} = 1.34, Z = 4, ρ_{calcd} = 1.36, μ (Cu Kα) = 9 cm^{-1}.

The space group was determined from precession photographs from the systematic absences in the axial reflections with h, k, or l odd. Unit cell dimensions were obtained by a least-squares fit to the values of $\pm 2\theta$ for 18 general reflections measured at room temperature on the diffractometer (λ = 1.5418 Å). For the measurements of intensity a crystal block (1.0 × 0.5 × 0.2 mm^3) was mounted with the c* axis parallel to the ϕ axis of a Picker four-circle diffractometer operated under the control of an XDS Sigma 2 computer. Cu Kα radiation was used, made monochromatic by Bragg reflection from the (002) planes of a highly oriented graphite crystal. The reciprocal lattice was surveyed at some 1150 points out to sin θ/λ = 0.545 and diffracted intensity significantly above background [$I > 3.0\sigma(I)$] was measured at 1097 of them. The $\theta/2\theta$ scan method was used with a scan range of 3.5° and a scan rate of 2°/min. Background intensity was calculated for each reflection from a predetermined survey of the variation of background as a function of 2θ over the operating range of the diffractometer with the crystal in place.

Structure Determination and Refinement. The structure was solved by use of the program MULTAN of Germain, Main, and Woolfson.[18]

The structural parameters were refined by block-diagonal least-squares methods to R = 0.14 with individual isotropic thermal parameters assumed, and to R = 0.10 on the assumption of anisotropic thermal parameters. Of the 16 hydrogen atoms in the molecule all except those associated with the two methyl groups were clearly identifiable from a difference electron-density function calculated at this stage. They were included in the refinement with isotropic thermal parameters and the refinement continued to give R = 0.081 at convergence.

No convincing distinction between the two possible enantiomeric structures emerged when contributions for the anomalous dispersion corrections for the oxygen atoms were included in separate structure factor calculations, nor could conclusive differences in Bijvoet pairs of reflections be detected, so that the absolute configuration of allamdin was not determined by this analysis.

With the exception of MULTAN all programs used in the analysis were written in this laboratory for the Sigma 2 computer. Scattering functions for the atoms were taken from the compilation of Hanson, *et al.*[19] No account was taken of effects due to absorption. The comparatively high residual is most probably attributable to this neglect, but is likely to have little effect on the final positional parameters. A final difference electron-density map showed only random distribution of residual peaks of height not exceeding ±0.2 $e/Å^3$. Weighting functions for the least-squares refinement were based on the treatment suggested by Killean, *et al.*[20]

Registry No.—**1**, 51820-82-7; **2**, 51820-83-8; **3**, 51838-83-6; **4**, 51820-84-9.

Supplementary Material Available. Positional parameters defining the crystal structure, the thermal parameters of the atoms, and diagrams showing the bond lengths, bond angles, torsion angles, and other features of the molecular geometry of allam-

din will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2477.

References and Notes

(1) (a) Tumor Inhibitors. 95. Part 94: S. M. Kupchan and R. M. Schubert, *Science*, in press. (b) This investigation was supported by grants from the National Cancer Institute (CA-11718 and CA-11760) and the American Cancer Society (CI-102J), and a contract with the Division of Cancer Treatment, National Cancer Institute (N01-CM-12099). A. L. D. was a National Institutes of Health Postdoctoral Fellow, 1972–1974.

(2) Roots were collected in Oahu, Hawaii, in March 1972. The authors acknowledge with thanks receipt of the dried material from Dr. R. T. Hirano, Harold L. Lyon Arboretum, University of Hawaii, under a program supported by the National Cancer Institute.

(3) Cytotoxicity (Table I) and *in vivo* activity were assayed under the auspices of the National Cancer Institute. The procedures were those described in *Cancer Chemother. Rep.*, **25**, 1 (1962).

(4) *Cf.* J. M. Bobbitt and K.-P. Segebarth in "Cyclopentanoid Terpene Derivatives," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N. Y., 1969, p 1.

(5) (a) B. R. Pai, P. S. Subramanian, and U. R. Rao, *Indian J. Chem.*, **8**, 851 (1970); (b) K. Jewers, A. H. Manchanda, and A. V. Castillo, *Asian J. Pharm.*, **2**, 5 (1971).

(6) G. Albers-Schonberg and H. Schmid, *Helv. Chim. Acta*, **44**, 1447 (1961).

(7) In view of the ease of dehydration of allamandin (**1**) and of allamandicin (**3**), it is conceivable that plumericin (**5**) and isoplumericin (**6**) could be artifacts formed during the extraction process.

(8) D. V. Banthorpe, "Reaction Mechanisms in Organic Chemistry," Vol. 2, American Elsevier, New York, N. Y., 1963, p 154.

(9) O. Halpern and H. Schmid, *Helv. Chim. Acta*, **41**, 1109 (1958).

(10) H. Inouye, T. Arni, and Y. Miyoshi, *Chem. Pharm. Bull.*, **12**, 888 (1964).

(11) See paragraph at end of paper regarding supplementary material.

(12) N. Masaki, M. Hirabayashi, K. Fuji, K. Osaki, and H. Inouye, *Tetrahedron Lett.*, 2367 (1967).

(13) P. J. Lentz, Jr., and M. G. Rossman, *Chem. Commun.*, 1269 (1969).

(14) References to standard values of bond lengths in the text are to L. E. Sutton, Ed., *Chem. Soc., Spec. Publ.*, **No. 18**, S14s (1965).

(15) R. Bucourt and D. Hainaut, *Bull. Soc. Chim. Fr.*, 1366 (1965).

(16) Melting points were determined on a Fisher-Johns melting point apparatus or a Mettler Model FP2 hot stage. Uv absorption spectra were determined on a Beckman Model DK-2A recording spectrophotometer. Ir spectra were determined on a Perkin-Elmer Model 257 recording spectrophotometer. Nmr spectra were determined on a Varian HA-100 spectrometer with tetramethylsilane as an internal standard. Nmr data are listed in Table II. Mass spectra were obtained from Hitachi Perkin-Elmer RMU-6E and AEI Model MS-902 spectrometers. Values of $[\alpha]_D$ were determined on a Perkin-Elmer Model 141 automatic polarimeter. Thin layer chromatography (tlc) was carried out on Brinkmann Silplates or Mallinckrodt 7GF ChromAR plates. Material was eluted from preparative tlc plates by removing the desired band and eluting with solvent, usually acetone–absolute ethanol. Analytical tlc plates were visualized with ultraviolet light and/or concentrated sulfuric acid–vanillin–ethanol (20:1:3) spray followed by heating. Silica gel 60, from EM Laboratories, Inc., was employed for column chromatography, and SilicAR CC-7, from Mallinckrodt Chemical Works, was used in dry column work. Petroleum ether refers to the fraction with bp 60–68°. Evaporations were carried out at reduced pressure below 40°. Analyses were carried out by Spang Microanalytical Laboratories, Ann Arbor, Mich.

(17) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).

(18) G. Germain, P. Main, and M. M. Wolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).

(19) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr.*, **17**, 1040 (1964).

(20) D. F. Grant, R. C. G. Killean, and J. L. Lawrence, *acta Crystallogr.*, **17**, 781 (1964).

Nucleosides. LXXXVII. Total Synthesis of Pentopyranine A, an α-L Cytosine Nucleoside Elaborated by *Streptomyces griseochromogenes*[1]

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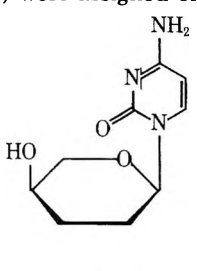
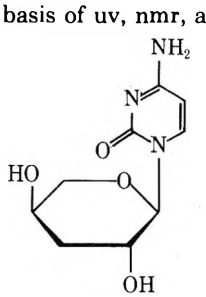
The nucleoside 1-(2,3-dideoxy-α-L-*glycero*-pentopyranosyl)cytosine (**1**) was synthesized by a series of reactions from tri-*O*-acetyl-L-arabinopyranosyl bromide. The identity of **1** with the naturally occurring pentopyranine A was established by ir, uv, and mass spectral comparisons. The synthetic sequence and physicochemical data for **1** reported herein provide confirming evidence for the structure previously assigned to pentopyranine A.

Two cytosine nucleosides, pentopyranine A and C, have been isolated by Seto, *et al.*,[2] from the fermentation broth of *Streptomyces griseochromogenes*, a blasticidin S producing microorganism.[3] The structures of these nucleosides (**1** and **2**) were assigned on the basis of uv, nmr, and mass



1
pentopyranine A

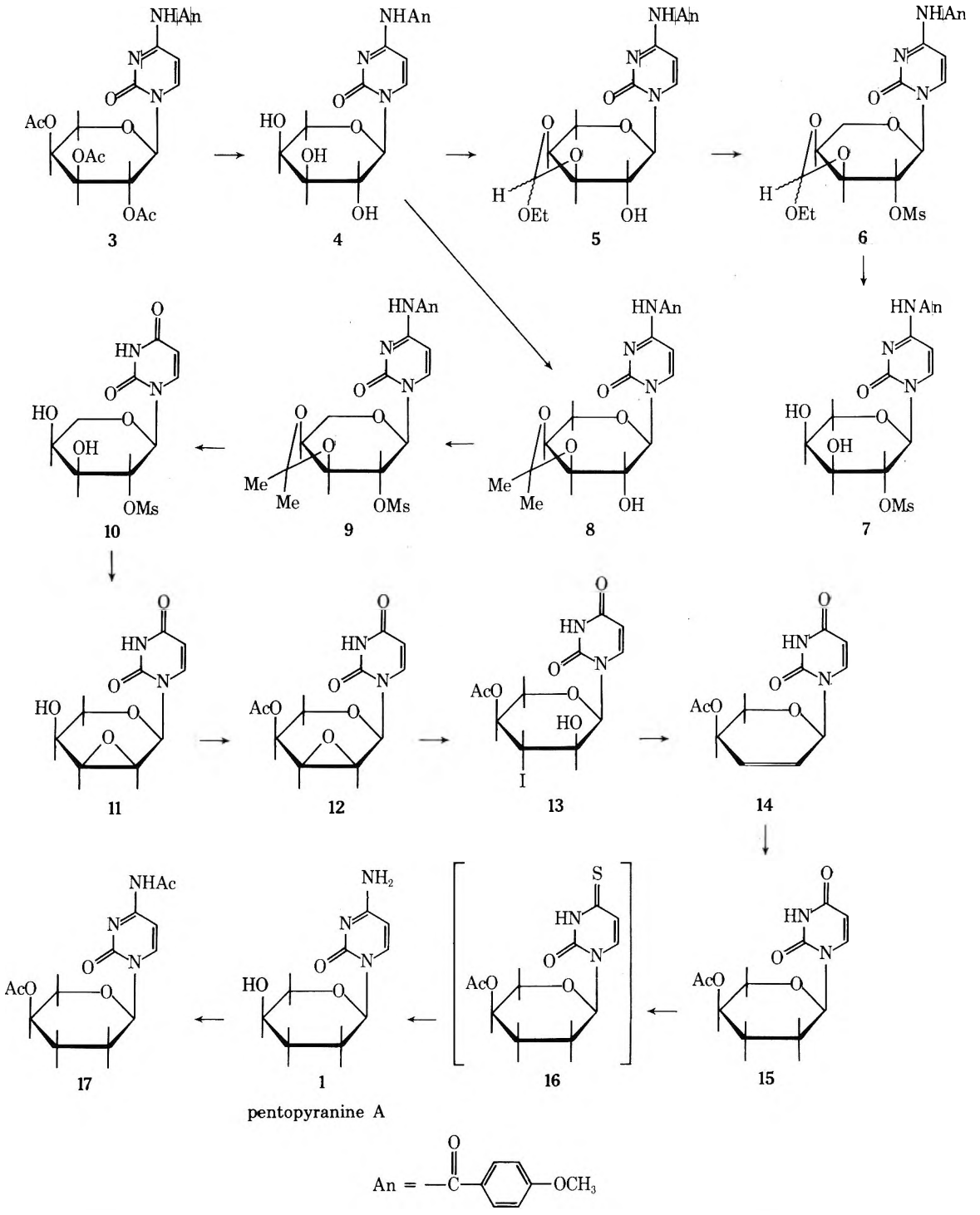


2
pentopyranine C

spectral evidence of these and their acetyl derivatives.[2] Pentopyranine A and C are the first naturally occurring nucleosides possessing the α-L configuration. Recently,[4] we reported the total synthesis of pentopyranine C, 1-(3-deoxy-α-L-*threo*-pentopy ranosyl)cytosine (**2**), from 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*xylo*-hexofuranose. In this paper we describe the total synthesis of 1-(2,3-dideoxy-α-L-*glycero*- pentopyranosyl)cytosine (**1**) from L-arabinose and its identity with pentopyranine A.

Condensation of tri-*O*-acetyl-L-arabinosyl bromide with N^4-anisoylcytosine in nitromethane in the presence of mercuric cyanide[5] gave the protected nucleoside **3** in crystalline form. Treatment of **3** with sodium methoxide in methanol selectively removed the acetyl groups to afford nucleoside **4** in ~70% yield. Isopropylidenation of **4** gave pure **8** which precipitated from the reaction mixture in high yield. After mesylation of **8**, the product **9** was isolated and treated with aqueous acetic acid at room temperature to remove the isopropylidene group.[6] It was found, however, that under these conditions hydrolytic deamidation of **9** occurred to a considerable extent. Therefore, the reaction mixture was refluxed in 80% acetic acid to complete the deamidation reaction[7] from which uracil nucleoside derivative **10** was obtained in good yield.

Treatment of **10** with sodium methoxide in methanol gave the epoxide **11**. After acetylation of **11**, the product **12** was treated with sodium iodide in a mixture of acetic acid



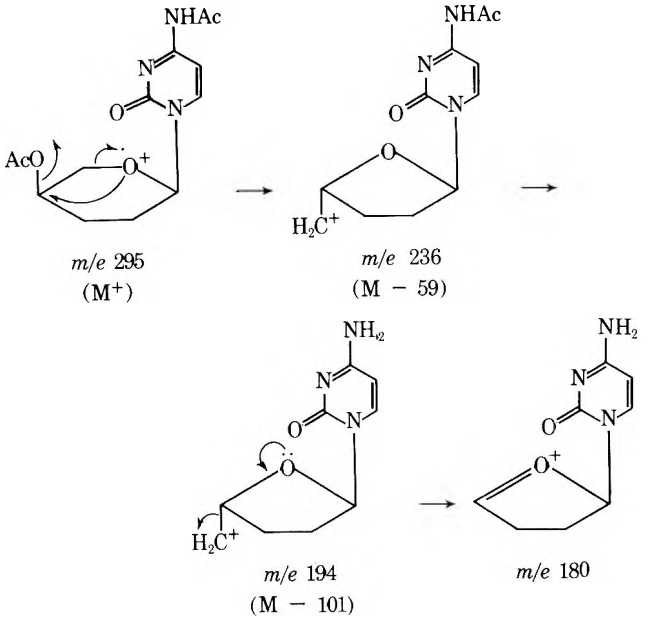
and acetone.[8,9] The crystalline iodohydrin **13** thus obtained was converted into the olefinic sugar derivative **14** by treatment with mesyl chloride in pyridine.[8,9] Hydrogenation of **14** gave the crystalline 2′,3′-dideoxy nucleoside derivative **15** in good yield. Thiation of **15** with phosphorus pentasulfide in dioxane[10] gave a syrupy product which resisted crystallization even after chromatographic purification. The chromatographically homogeneous thiouracil derivative **16** was treated with methanolic ammonia and the cytosine nucleoside **1** was obtained in good yield. Although the melting point of this compound (browning at ~235° and effervescence at 253–256°) is different from that reported[2] for pentopyranine A (mp 258° dec), a direct comparison of this compound with an authentic sample of pentopyranine A showed them to be identical. The melting point (mixture melting point showed no depression), uv, and ir characteristics were the same for both the synthetic and natural products. Acetylation of **1** afforded a cyrstalline diacetate (**17**) which was identical in all respects (melting point, uv, ir, and nmr spectra) with the diacetate prepared from pentopyranine A. These data not only provide proof of the identity of **1** with the natural product but also, by virtue of the route employed for its total synthesis, strongly support the assignment of the structure given by Seto, *et al.*,[2] for pentopyranine A.

It is noted that in the total synthesis shown, a cytosine nucleoside (**3–9**) was converted to uracil derivatives (**10–15**) and finally converted to a cytosine nucleoside (**1**) by thiation to **16**. This rather lengthy route was necessitated by the susceptibility of the 4-acylamino group of **9** to acid hydrolysis conditions required for deketalization. The introduction of the more readily removable group at the 3′,4′ positions was attempted. Thus treatment of **4** with ethyl orthoformate in DMF in the presence of hydrogen chloride[11]

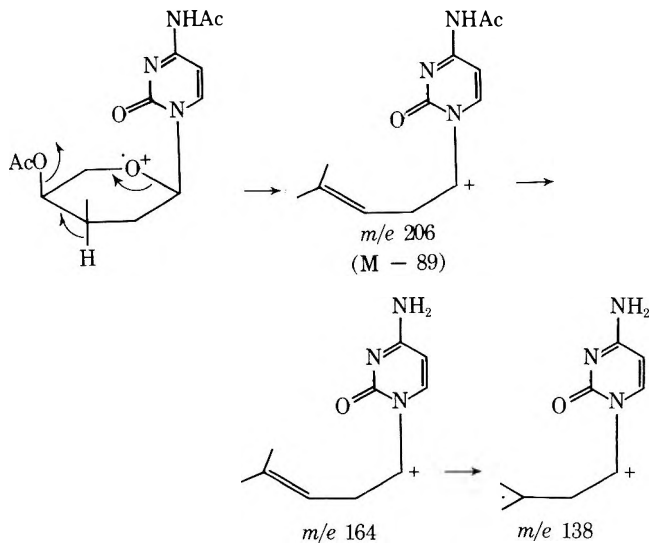
afforded a syrupy mixture of the 3′,4′-ethoxymethylidene diastereoisomers (**5**), from which one of them was obtained in crystalline form. Mesylation of crystalline **5** yielded the 2′-mesylate **6** in good yield. Removal of the ethoxymethylidene grouping was readily achieved by brief acid treatment to afford **7**. Attempts to convert **7** to the 2′,3′-epoxide by treatment with sodium methoxide gave a mixture of several products, none of which was formed in predominant amounts. This approach was therefore abandoned.

Data obtained from a mass spectral investigation of synthetic pentopyranine A and its diacetate **17** are fully consistent with the structure assigned. In the high-mass region, synthetic **1** shows peaks at *m/e* 211 (M^+), 112 (B + 2), 111 (B + 1), and 100 (S).[12] Ion peaks corresponding to (M − 30) and (B + 30) are absent, indicating that the compound contains neither a terminal hydroxymethyl function nor a hydroxyl group at C-2′.[13] More definitive information was obtained from the mass spectrum of the diacetate **17**, which exhibits fragmentation peaks which are best rationalized by the following sequences.

Sequence A



Sequence B



Sequence A requires a pyranoid → furanoid rearrangement. Such a rearrangement has been observed in the mass spectra of 2,3-diacetoxypyran[14] and of several hexopyranose pentaacetates.[15] The ion peaks at *m/e* 295 (M^+), 154 (BA + 2), 153 (BA + 1), and 143 (S) as well as those listed in sequences A and B are consistent only with the presence of an acetoxy function at C-4′ of a 2,3-dideoxypentopyranosyl sugar moiety.

Experimental Section

General Procedure. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are corrected. The nmr spectra were recorded on a Varian A-60 or XL-100 using TMS as internal standard. Chemical shifts are reported in parts per million (δ) and signals are described as s (singlet), d (doublet), t (triplet), and q (quartet). Values given for coupling constants are first order. Thin layer chromatography (tlc) was performed on silica gel GF_{254} (Merck), developed in a chloroform–methanol (9:1) system, and spots were detected by uv absorbance or by spraying with 20% v/v sulfuric acid–ethanol and heating. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

N^4-Anisoyl-1-(tri-*O*-acetyl-α-L-arabinosyl)cytosine (3). A suspension of N^4-anisoylcytosine (37.5 g, 0.15 mol) and mercuric cyanide (75 g, 0.3 mol) in nitromethane (1700 ml) was dried by azeotropic distillation of approximately 200 ml of the solvent. To the stirred suspension was added a dichloromethane solution (~500 ml) of tri-*O*-acetyl-L-arabinopyranosyl bromide which was prepared by the following procedure.

Tetra-*O*-acetyl-β-L-arabinopyranose (95 g, 0.3 mol) was shaken in ~30% hydrogen bromide in acetic acid (800 ml) until a clear solution was obtained. The solution was left standing for 15 min, then partitioned between dichloromethane (1000 ml) and ice–water (1000 ml). The organic layer was separated and washed with cold water (2 × 1000 ml), saturated sodium bicarbonate solution (500 ml), and water (1000 ml), then dried over sodium sulfate. The solvent was concentrated to ~500 ml.

The condensation reaction mixture was refluxed for 2 hr, during which time the dichloromethane was removed by distillation. After cooling, the precipitate (N^4-anisoylcytosine, 19 g, 50%) was removed by filtration, and the filtrate was evaporated to near dryness. The residue was shaken with a mixture of dichloromethane (500 ml) and 30% potassium iodide solution (500 ml). The organic layer was separated and extracted with 30% potassium iodide solution (500 ml) and water (2 × 500 ml) and dried over sodium sulfate. The solution was concentrated to ~200 ml *in vacuo* and cooled to 0° overnight. Compound **3** (32 g, 43%) was obtained as colorless, fine needles: mp 227–228°; $[\alpha]^{27}D$ +53° (c 0.9, dioxane); nmr (DMSO-d_6), OAc, δ 1.93 (s, 3 H), 1.98 (s, 3 H), 2.18 (s, 3 H); OCH_3, δ 3.86 (s, 3 H); H-1′, δ 6.10 (d, 1 H, $J_{1',2'}$ = 8.0 Hz); uv λ_{max} (MeOH) 289 nm, λ_{min} (MeOH) 242 nm.

Anal. Calcd for $C_{23}H_{25}N_3O_{10}$: C, 54.87; H, 5.01; N, 8.35. Found: C, 54.93; H, 5.31; N, 8.12.

N^4-Anisoyl-1-(α-L-arabinopyranosyl)cytosine (4). Compound **3** (15 g, 0.03 mol) was dissolved in dioxane (150 ml) and the solution was diluted with methanol (150 ml). To the solution was added dropwise 1 *M* sodium methoxide in methanol (5 ml). After 15 min the mixture was neutralized with Dowex 50 (H^+, 20 ml). The resin was removed by filtration and the filtrate was concentrated to ~50 ml. Water (150 ml) was added to the mixture, which was then concentrated to ~100 ml and cooled at 0°. Compound **4** (7.2 g, 65%) was obtained as colorless needles: mp 231–233°; $[\alpha]^{27}D$ +59° (c 1.3, DMF). The product analyzed best for a hydrate.

Anal. Calcd for $C_{17}H_{19}N_3O_7 \cdot H_2O$: C, 51.64; H, 5.35; N, 10.62. Found: C, 52.19; H, 5.31; N, 10.20.

This product was not further purified but used directly in the syntheses of **5** and **8**, both of which afforded correct analyses (see below).

N^4-Anisoyl-1-(3,4-*O*-ethoxymethylidene-α-L-arabinopyranosyl)cytosine (5). Compound **4** (2.0 g, 5.3 mmol) was dissolved in DMF (20 ml). To the solution was added triethyl orthoformate (2 ml) followed by 10 *M* hydrogen chloride in DMF (1 ml). After 2 hr, another charge of triethyl orthoformate (3 ml) and 10 *M* hydrogen chloride in DMF was added and the mixture was left overnight at room temperature. Solid sodium bicarbonate (4 g) was added and the mixture was stirred for 4 hr; then the insoluble inorganic material was removed by filtration. The filtrate was evaporated to a syrup from which crystals slowly separated. After 20 hr at room temperature, the mixture of syrup and crystals was triturated with ethanol (15 ml). The crystals were filtered and washed with ethanol (0.9 g, 39%): mp 211–212°; $[\alpha]^{27}D$ +69° (c 1.3, dioxane); nmr (DMSO-d_6) δ 1.15 (t, 3 H, CH_2CH_3), 3.58 (q, 2 H, CH_2CH_3), 3.85

(s, 3 H, OCH_3), 5.53 (d, 1 H, H-1′, $J_{1',2'}$ = 9.5 Hz), 6.02 (s, 1 H, ethoxymethylidene).

Anal. Calcd for $C_{20}H_{23}N_3O_8$: C, 55.42; H, 5.34; N, 9.70. Found: C, 55.42; H, 5.33; N, 9.63.

N^4-Anisoyl-1-(3,4-*O*-ethoxymethylidene-2-*O*-mesyl-α-L-arabinopyranosyl)cytosine (6). To a solution of compound **5** (433 mg, 1 mmol) in pyridine (5 ml) was added msyl chloride (0.6 ml) at 0°, and the mixture was kept at 0° for 16 hr, then partitioned between ice-cold water (30 ml) and dichloromethane (30 ml). The organic layer was separated, washed with 30 ml each of water, sodium bicarbonate, and water, and then dried over sodium sulfate. The solution was evaporated to dryness and the residue was dissolved in dichloromethane (~1 ml); then the solution was diluted with ethanol (~4 ml). Compound **6** crystallized as pale yellow needles (452 mg, 88%): mp 173° (sintered), 174–177° (effervesced); $[\alpha]^{27}D$ +100° (c 1.3, $CHCl_3$); nmr (DMSO-d_6) δ 1.23 (t, 3 H, CH_2CH_3), 3.21 (s, 3 H, OMs), 3.63 (q, 2 H, CH_2CH_3), 3.87 (s, 3 H, OCH_3), 5.97 (s, 1 H, ethoxy*methylidene*), 5.97 (d, 1 H, H-1′, $J_{1',2'}$ = 7.5 Hz).

Anal. Calcd for $C_{21}H_{25}N_3O_{10}S$: C, 49.31; H, 4.93; N, 8.22; S, 6.27. Found: C, 49.45; H, 4.92; N, 7.99; S, 5.88.

N^4-Anisoyl-(2-*O*-mesyl-α-L-arabinopyranosyl)cytosine (7). To a solution of **6** (382 mg, 0.75 mmol) in dioxane (15 ml) was added 1 *N* HCl (4 ml) with stirring. After 25 min, the mixture was diluted with ethanol (46 ml) and the solvent was removed *in vacuo* below 40°. The residue was coevaporated several times with ethanol until pale yellow microcrystals were obtained. After one recrystallization from ethanol, **7** was obtained as colorless, fine needles: mp 205° (sintered), 208–209° (effervesced); $[\alpha]^{27}D$ +47° (c 1.3, pyridine); nmr (DMSO-d_6) δ 3.20 (s, 3 H, mesyl CH_3), 4.79 (t, 1 H, H-2′, $J_{1',2'} \simeq J_{2',3'} \simeq$ 9.0 Hz), 5.91 (d, 1 H, H-1′, $J_{1',2'} \simeq$ 9.0 Hz).

Anal. Calcd for $C_{18}H_{21}N_3O_9S$: C, 51.07; H, 5.00; N, 9.93. Found: C, 50.77; H, 5.21; N, 10.12.

N^4-Anisoyl-(3,4-*O*-isopropylidene-α-L-arabinopyranosyl)cytosine (8). A mixture of **4** (12 g, 0.032 mol), *p*-toluenesulfonic acid (2 g), and 2,2-dimethoxypropane (20 ml) in acetone (480 ml) was vigorously stirred for 24 hr. Compound **8** (7.5 g) separated as colorless needles which were filtered and washed with acetone: mp 230–231°; $[\alpha]^{27}D$ +78° (c 1.3, DMF); nmr (DMSO-d_6) δ 1.24 (s, 3 H, isopropylidene CH_3), 1.54 (s, 3 H, isopropylidene CH_3), 3.87 (s, 3 H, OCH_3), 5.54 (d, 1 H, H-1′, $J_{1',2'}$ = 9.5 Hz).

Anal. Calcd for $C_{20}H_{23}N_3O_7 \cdot H_2O$: C, 55.17; H, 5.79; N, 9.65. Found: C, 55.21; H, 5.95; N, 9.67. The presence of 1 mol of water of crystallization was shown by the nmr spectrum.

To the combined filtrate and washings was added solid sodium bicarbonate (3 g) and the mixture was stirred for 5 hr. Insoluble solid was filtered and washed with a small amount of acetone. the solid was suspended in water (40 ml), stirred for 1 hr, and then filtered and dried to give additional product **8** (3.8 g, mp 229–231°).

N^4-Anisoyl-(3,4-*O*-isopropylidene-2-*O*-mesyl-α-L-arabinopyranosyl)cytosine (9). A mixture of **8** (7.5 g, 0.018 mol) in pyridine (100 ml) was cooled in an ice bath. Mesyl chloride (3 ml) was added to the mixture with stirring. After 4 hr, the reaction mixture was poured into a mixture of ice and water (500 ml), and then the mixture was extracted with chloroform (2 × 250 ml). The combined chloroform extracts were washed with water (250 ml), sodium bicarbonate solution (2 × 250 ml), and water (250 ml), and then dried over sodium sulfate. The solution was concentrated to dryness and the residue was coevaporated several times with ethanol until a crystalline residue was obtained. The residue was recrystallized from ethanol to give colorless needles: 7.2 g (81%); mp 199–200° dec; $[\alpha]^{27}D$ +102° (c 1.1, DMF); nmr (DMSO-d_6) δ 1.37 (s, 3 H, isopropylidene CH_3), 1.58 (s, 3 H, isopropylidene CH_3), 3.21 (s, 3 H, SCH_3), 3.85 (s, 3 H, OCH_3), 5.93 (d, 1 H, H-1′, $J_{1',2'}$ = 8.5 Hz).

Anal. Calcd for $C_{21}H_{25}N_3O_9S$: C, 50.90; H, 5.09; N, 8.48; S, 6.47. Found: C, 50.86; H, 4.78; N, 8.50; S, 6.51.

1-(2-*O*-Mesyl-α-L-arabinopyranosyl)uracil (10). Compound **9** (7.0 g, 0.014 mol) was dissolved in warm acetic acid (320 ml) and the solution was cooled to room temperature. Water (80 ml) was added to the solution and the mixture was stirred overnight and then refluxed for 3 hr. Evaporation of the solvent and subsequent addition and evaporation of toluene (3 × 100 ml) gave a semisolid residue which was triturated with chloroform (2 × 30 ml). The residue was crystallized from ethanol to give **10** as colorless, hard needles: 2.2 g (73%); mp 202–205° dec (effervesced); $[\alpha]^{27}D$ +79° (c 1.3, DMF).

1-(2,3-Anhydro-α-L-ribopyranosyl)uracil (11). A mixture of **10** (1.8 g, 5.6 mmol), 1 *M* sodium methoxide in methanol (7 ml), and ethanol (20 ml) was refluxed for 45 min and then cooled to room temperature. The precipitates were removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in a 4:1 chloroform–methanol mixture (~5 ml) and chromatographed over a silica gel G column (50 g, 7 × 4 cm diameter) using 4:1 chloroform–methanol system as the eluent. The uv-absorbing fractions were collected and concentrated to dryness. The crystalline residue was recrystallized from ethanol: 970 mg (77%); mp 164–165°; $[\alpha]^{27}D$ +15° (c 0.8, pyridine).

Anal. Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.39. Found: C, 47.81; H, 4.51; N, 12.23.

1-(4-*O*-Acetyl-2,3-anhydro-α-L-ribopyranosyl)uracil (12). Acetic anhydride (1 ml) was added to a solution of **11** (800 mg, 3.5 mmol) in pyridine (16 ml). The mixture was stirred overnight, after which it was treated with ethanol (10 ml). After evaporation of the mixture, the residue was triturated with ether (20 ml) and then crystallized from ethanol to give colorless needles: 721 mg (75%); mp 238–244° dec; $[\alpha]^{27}D$ −27° (c 1.4, pyridine).

Anal. Calcd for $C_{11}H_{12}N_2O_6$: C, 49.26; H, 4.51; N, 10.44. Found: C, 49.39; H, 4.47; N, 10.20.

1-(4-*O*-Acetyl-3-deoxy-3-iodo-α-L-xylopyranosyl)uracil (13). A mixture of **12** (540 mg, 2 mmol), sodium iodide (1.7 g), sodium acetate (90 mg), and acetic acid (2.8 ml) in acetone (10 ml) was refluxed gently for 30 min. Evaporation of the solvent and subsequent addition and evaporation of toluene (2 × 10 ml) gave a solid residue which was then shaken with a mixture of water (20 ml) and chloroform. Slightly yellowish needles crystallized out. They were filtered and washed with a small amount of chloroform (624.5 mg, 80%): mp 193–195°, 198–199° (effervesced); $[\alpha]^{27}D$ +24° (c 1.2, pyridine).

Anal. Calcd for $C_{11}H_{13}N_2O_6I$: C, 33.33; H, 3.28; N, 7.07; I, 32.07. Found: C, 32.94; H, 3.67; N, 6.95; I, 32.03.

1-(4-*O*-Acetyl-2,3-dideoxy-α-L-*glycero*-pent-2-enopyranosyl)uracil (14). To a solution of **13** (590 mg, 1.5 mmol) in pyridine (5.5 ml) was added mesyl chloride (0.4 ml, 5.2 mmol) and the mixture was kept at room temperature for 16 hr. The very dark colored reaction mixture was partitioned between chloroform (20 ml) and water (20 ml). The aqueous layer was washed with chloroform (20 ml). The combined chloroform solutions were washed successively with 20 ml each of water, 0.1 *M* sodium thiosulfate (4 ×), and water, dried over sodium sulfate, and evaporated. The residue was coevaporated several times with ethanol until crystallization occurred. The product was recrystallized from ethanol to give fine needles: 173 mg (52%); mp 153–154°; $[\alpha]^{27}D$ −84° (c 1.1, dioxane).

Anal. Calcd for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.14; H, 4.68; N, 10.98.

An additional amount (72 mg, mp 151–153°) was obtained from the mother liquor.

1-(4-*O*-Acetyl-2,3-dideoxy-α-L-*glycero*-pentopyranosyl)uracil (15). Compound **14** (222 mg, 1 mmol) was dissolved in dioxane (10 ml) and hydrogenated over 10% palladium on carbon (~25 mg) at room temperature and atmospheric pressure. After 1 mol of hydrogen was taken up, the catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue was crystallized from ethanol to give colorless needles: 156 mg (71%); mp 146–147°; $[\alpha]^{27}D$ +39° (c 0.9, dioxane).

Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 51.89; H, 5.57; N, 11.18.

1-(4-*O*-Acetyl-2,3-dideoxy-α-L-*glycero*-pentopyranosyl)-4-thiouracil (16). To a stirred solution of **15** (115 mg, 0.5 mmol) in dioxane (8 ml) was added phosphorus pentasulfide (112 mg, 0.5 mmol) and the mixture was refluxed for 45 min. A second charge of phosphorus pentasulfide (82 mg) was then added and heating was resumed for another 45 min. Only one spot (less polar than **15**) was detected on tlc by this time. The mixture was cooled and the supernatant was decanted from a small amount of insoluble material and evaporated to dryness. The residue was triturated with a small amount (~5 ml) of warm water (~60°) for a few minutes, and the mixture was extracted with chloroform (2 × 5 ml). The combined chloroform extracts were washed with sodium bicarbonate and water (5 ml each) and dried over sodium sulfate. After removal of the solvent by evaporation, the residue (98 mg, 82%) was dissolved in ~2 ml of chloroform and spotted on a glass plate (20 × 20 cm) coated with silica gel PF_{254} and developed in a chloroform–methanol (9:1) system. The uv-absorbing band was removed and extracted with chloroform–methanol (9:1). After evaporation of the solvent, 72 mg of yellow syrup was obtained. The syrup was used directly in the next step.

1-(2,3-Dideoxy-α-L-*glycero*-pentopyranosyl)cytosine (1). Compound **16** (52 mg, 0.2 mmol) was dissolved in ~2 ml of methanolic ammonia (saturated at 0°) in a test tube which was sealed

and heated at 100° for 48 hr in a steel container. The dark yellow reaction mixture was concentrated to dryness and the residue was mixed with water (2 ml) and decolorized with charcoal Darco 60. The colorless aqueous solution was evaporated to dryness and coevaporated several times with ethanol. The residue was triturated twice with chloroform (2 ml each) and the residue was finally crystallized from water–ethanol to give colorless needles: 27.4 mg (60%); mp ~235° (browning), 253–256° (effervesced).

N^4-Acetyl-1-(4-*O*-acetyl-2,3-dideoxy-α-L-*glycero*-pentopyranosyl)cytosine (17). A mixture of 1 (17 mg), acetic anhydride (0.5 ml), and pyridine (2 ml) was kept at room temperature for 16 hr. The reaction was stopped by addition of water (5 ml) followed by extraction with chloroform (2 × 5 ml). The organic extracts were washed with 5 ml each of water, saturated sodium bicarbonate solution, and water and dried over sodium sulfate. After removal of the solvent, traces of pyridine were removed by coevaporation of ethanol. The crystalline residue was recrystallized from ethanol, 7 mg, mp 200–202°, unchanged on admixture with an authentic sample.[2]

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Registry No.—**1**, 39057-02-8; **3**, 51838-76-7; **4**, 51820-58-7; **5**, 51820-59-8; **6**, 51820-60-1; **7**, 51820-61-2; **8**, 51820-62-3; **9**, 51820-63-4; **10**, 51820-64-5; **11**, 51838-77-8; **12**, 51820-65-6; **13**, 51838-78-9; **14**, 51820-66-7; **15**, 51820-67-8; **16**, 51820-68-9; **17**, 51820-69-0; N^4-anisoylcytosine, 51820-70-3; tri-*O*-acetyl-L-arabinopyranosyl bromide, 51830-02-5.

References and Notes

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant CA 08748).
(2) H. Seto, *Agr. Biol. Chem.*, **37**, 2415 (1973); H. Seto, N. Otake, and H. Yonehara, *Tetrahedron Lett.*, 399 (1972); *Agr. Biol. Chem.*, **37**, 2421 (1973).
(3) S. Takeuchi, K. Hirayama, K. Ueda, H. Sakai, and H. Yonehara, *J. Antibiot., Ser. A*, **11**, 1 (1958). For recent reviews, see J. J. Fox, K. A. Watanabe, and A. Bloch, *Progr. Nucleic Acid Res. Mol. Biol.*, **5**, 251 (1966); R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley, New York, N. Y., 1970.
(4) T. M. K. Chiu, H. Ohrui, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, **38**, 3622 (1973).
(5) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965); K. A. Watanabe and J. J. Fox, *J. Heterocycl. Chem.*, **6**, 109 (1969).
(6) T. M. K. Chiu, D. H. Warnock, K. A. Watanabe, and J. J. Fox, *J. Heterocycl. Chem.*, **10**, 607 (1973).
(7) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2384 (1956); D. H. Warnock, K. A. Watanabe, and J. J. Fox, *Carbohyd. Res.*, **18**, 127 (1971).
(8) K. A. Watanabe, I. Wempen, and J. J. Fox, *Chem. Pharm. Bull.*, **18**, 2368 (1970).
(9) R. U. Lemieux, E. Fraga, and K. A. Watanabe, *Can. J. Chem.*, **46**, 61 (1968); K. A. Watanabe, R. S. Goody, and J. J. Fox, *Tetrahedron*, **26**, 3883 (1970).
(10) R. S. Klein, I. Wempen, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, **35**, 2330 (1970).
(11) J. Zemlicka, *Chem. Ind. (London)*, 581 (1964).
(12) M^+ = molecular ion, B = cytosine residue, BA = acetylcytosine residue, S = glycosyl residue.
(13) K. Biemann and J. A. McCloskey, *J. Amer. Chem. Soc.*, **84**, 2005 (1962).
(14) M. Venugopalan and C. B. Anderson, *Chem. Ind. (London)*, 370 (1964).
(15) K. Biemann, D. C. DeJongh, and H. K. Schnoes, *J. Amer. Chem. Soc.*, **85**, 1763 (1963).

Electrolytic Decarboxylation Reactions. I. Electrosyntheses of γ-Substituted Butyrolactones and γ-Substituted α,β-Butenolides from γ-Substituted Paraconic Acids

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The product-selective electrolytic decarboxylation of γ-substituted paraconic acids has been studied (1) in dry methanol using sodium methoxide by addition of iron powder or ferric nitrate on platinum electrodes, (2) in dry methanol using sodium methoxide on carbon rod electrodes, and (3) in a mixed solvent of triethylamine–pyridine–water on carbon rod electrodes. Conditions 1 and 2 resulted in exclusive formation of γ-substituted butyrolactones in 80–99% yields, whereas condition 3 provided α,β-unsaturated butenolides in 70–90% yields. By means of the butenolide synthesis *dl*-3-carboxy-8-hydroxy-Δ^3-menthene γ-lactone, a key intermediate for the preparation of *dl*-menthone, could be prepared.

The value of non-Kolbe type electrolytic reactions for the preparation of synthetic intermediates has been discussed recently.[1] Choices of electrodes, solvents, supporting electrolytes, additives, etc., in relation to product selectivity have been the subject of several investigations.[2] We report herein the product-selective electrolytic decarboxylation reaction of γ-substituted paraconic acids (1), which led to the discovery of a chemically controlled electrolysis.

Preliminary electrolysis[3] of 1 [R_1, R_2 = $-(CH_2)_5-$][4] in dry methanol using sodium methoxide as a supporting electrolyte on platinum electrodes (Table I, run 1) afforded lactone derivatives of **2** (32%), **3** (49%), and **4** (10%). However, addition of iron powder or ferric nitrate in the electrolytic

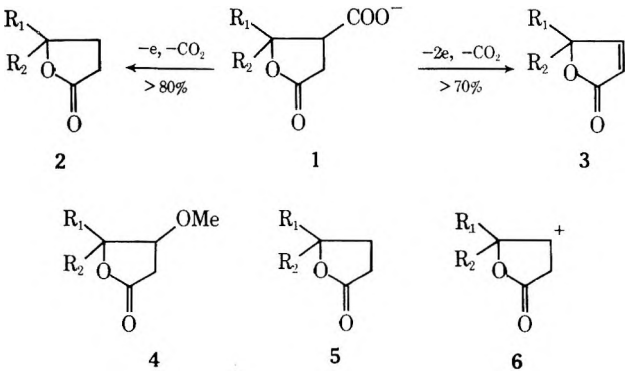


Table I
Electrolytic Conditions for the Anodic Oxidation of γ,γ-Pentamethyleneparaconic Acid (300 mg)

Run	Electrode	Supporting electrolyte (mg)	Solvent (ml)	Current, A	Applied voltage, V	Temp, °C	Time, hr	Product, %[a] 2	3	4
1	Pt	MeONa (940)	MeOH (40)	1.25	10–17	20	12	32	49	10
2	Pt	MeONa–Fe (940:100)	MeOH (40)	1.25	10–17	20	12	80		
3	C	MeONa (940)	MeOH (40)	1.5	7–15	25–35	20	99		
4	C	Et_3N (30)	Py-H_2O (30:4)	0.25–0.1	60–80	20	12		78	

[a] Yields are calculated on isolated product.

Table II
Electrosynthesis of γ-Butyrolactones (2)

Product, butyrolactones (2) R_1	R_2	Registry no.	Results, % yield[a] MeOH–MeONa–Fe–(Pt) (run 2)	MeOH–MeONa–(C) (run 3)	Ref
Me	Me	3123-97-5	97	92	*b*
Me	n-C_3H_7	3284-93-3	99	94	*b*
Me	n-C_6H_{13}	7011-83-8	99	95	*c*
$-(CH_2)_4-$		33448-80-5	81	98	*d*
$-(CH_2)_5-$		699-61-6	80	99	*e*

[a] Yields are calculated on isolated product. [b] S. Dev and C. Rai, *J. Indian Chem. Soc.*, **34**, 266 (1957). [c] R. L. Frank, P. G. Arvan, J. W. Richter, and C. R. Vanneman, *J. Amer. Chem. Soc.*, **66**, 4 (1944). [d] This work; see Experimental Section. [e] Reference 12.

the unique formation of **3** can possibly be explained by assuming exclusive reduction of cation **6**, even if it arises, to **5** by iron ion as follows: $Fe^{2+} - e \rightarrow Fe^{3+}$. On the other hand, it is possible that the significant difference between carbon and platinum electrodes may be due to the presence of paramagnetic centers on the carbon anode which entirely adsorb any radicals formed.[2a] The results shown in Tables I (run 3) and II are insufficient to give definitive explanations for the formation of **2**; however, it may be tentatively concluded that coupling of **5** with hydrogen atoms occurs on the carbon electrode before desorption.

During the electrolysis of **1** in triethylamine–pyridine–water using platinum electrodes, evolution of carbon dioxide was observed on the anode surface when the applied voltage reached 60 V (cell voltage 1.58–1.59 *vs.* sce, Table IV). In this reaction, exclusive formation of α,β-unsaturated lactone **3** from **6** should be assisted by abstraction of hydrogen atom at the α position by amines.

Table III
Electrosynthesis of Δ²-Butenolides (3) from Paraconic Acids (1)

Paraconic acids (1) R_1	R_2	Registry no.	Butenolides (3) Bp (mp), °C (mm)	Yield,[a] %	Registry no.	Formula	Elemental analysis, % Calcd C	Calcd H	Found C	Found H
Me	Me[b]	79-91-4	89–91 (1)	68[h]	20019-64-1	$C_6H_8O_2$				
Me	n-C_3H_7[c]	51820-72-5	105–107 (1)	73	51820-73-6	$C_8H_{12}O_2$	68.55	8.63	68.53	8.46
Me	n-C_6H_{13}[c]	38840-98-1	130–131 (1)	85	51820-74-7	$C_{11}H_{18}O_2$	72.49	9.95	72.64	9.80
H	n-C_6H_{13}[d]	20597-52-8	105–104 (2)	70[i]	2518-53-8	$C_{10}H_{16}O_2$				
$-(CH_2)_4-$[e]		18363-10-5	112–113 (1)	77	5732-90-1	$C_9H_{10}O_2$	69.55	7.30	69.32	7.45
$-(CH_2)_5-$[f]		2819-56-9	117–119 (2)	78[j]	4435-19-2	$C_9H_{12}O_2$				
$-(CH_2)_{11}-$[g]		15210-24-9	(85.0–86.3)	90	51820-75-8	$C_{15}H_{24}O_2$	76.23	10.24	76.14	10.31

[a] Yields are calculated on isolated product. [b] R. Fittig and B. Frost, *Justus Liebigs Ann. Chem.*, **226**, 370 (1884). [c] See ref 11. [d] R. Fittig and A. Schneegans, *Justus Liebigs Ann. Chem.*, **227**, 79 (1885). [e] See ref 10. The paraconic acid used in this experiment was obtained in the manner described in the Experimental Section. [f] S. F. Birch, W. Henry, and G. Armand. *J. Chem. Soc.*, **119**, 1315 (1921). [g] H. Nozaki, T. Mori, R. Noyori, and M. Kawanishi, *Can. J. Chem.*, **45**, 1804 (1967). [h] R. Fittig and C. Geisler, *Justus Liebigs Ann. Chem.*, **208**, 37 (1881). [i] K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Amer. Chem. Soc.*, **95**, 6137 (1973). [j] See ref 13.

solution and/or replacement of electrodes from platinum plates to carbon rods were found to be the most critical factors in obtaining butyrolactones (runs 2 and 3). The results are shown in Table II.

A further remarkable change in the electrolytic reaction was observed when a mixed solvent of triethylamine–pyridine–water (run 4)[5] was employed instead of the methanol–sodium methoxide solution. The results of the latter experiment, giving butenolides (**3**), are listed in Table III.

In the course of the electrolytic oxidation of **1**, either a radical or a cation intermediate such as **5** and **6** must be produced. A notable feature in the electrolysis of **1** in a mixed solvent of triethylamine–pyridine–water(run 4) is the exclusive formation of **3** *via* the cation intermediate **6**, whereas formation of **2** from **1** (runs **2** and **3**) can be considered to arise from the radical intermediate **5** followed by abstraction of hydrogen from the medium.

Although no evidence has been found for a catalytic effect of iron ion or iron metal in the electrolytic solution,[6]

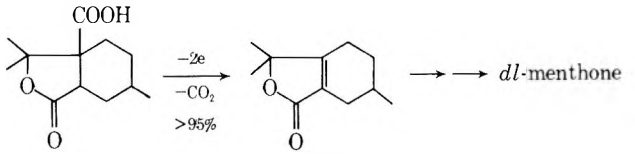
Table IV
Electrolytic Voltages in Triethylamine–Pyridine–Water Solution

Applied voltage, V	Cell voltage,[a] V
30	1.38
40	1.43–1.44
50	1.50–1.51
60	1.58–1.59
70	1.63–1.66
80	1.69–1.71
90	1.76–1.78

[a] Platinum electrodes (*vs.* sce).

Electrolytic decarboxylation of acid **7** to butenolide **8** was carried out successfully; subsequent hydrogenation gave in good yield the corresponding saturated lactone[7]

which can serve as a precursor for the preparation of *dl*-menthone.



7 8

Experimental Section[8]

Electrolysis Apparatus. Type I consisted of two smooth platinum electrodes (3 cm^2) which were placed parallel to each other 2 mm apart. The electrolysis cell was a water-jacketed beaker, 3.2 cm in diameter and 10 cm high, fitted with a gas lead pipe, a thermometer, and a magnetic stirrer.[9] Current was controlled by manually adjusting the applied voltage as required. The direction of current was changed every 30 sec by means of a commutator. Type II consisted of two carbon rods cut perpendicularly into two parts (10 mm in diameter and 10 cm long), being immersed into a electrolytic solution in a depth of 5–6 cm and placed parallel to each other 3 mm apart.

γ,γ-Tetramethyleneparaconic Acid [1, R_1, R_2 = $-(CH_2)_4-$]. A solution of cyclopentanone (3.54 ml, 0.04 mol) and zinc powder (8.16 g, 0.125 mol) in dry tetrahydrofuran (10 ml) was refluxed for 30 min. To this solution iodine (5 mg) was added and the mixture was stirred for several minutes. To the mixture methyl α-bromosuccinate in benzene (10 ml) was added dropwise over a period of 20 min. When the addition was completed, the mixture was heated to maintain gentle reflux for 2 hr. After cooling, the excess zinc powder was decomposed by dropwise addition of 20 ml of 10% aqueous acetic acid. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic phases were washed with water, 10% aqueous ammonium hydroxide, dilute aqueous hydrogen chloride, and water, and dried (Na_2SO_4). Removal of the solvent gave an oil (7.7 g), bp 130–150° (3 mm). Without further purification, the oil was subjected to hydrolysis with excess methanolic potassium hydroxide at room temperature, after work-up as an usual manner, to give 3 g of 1 [R_1, R_2 = $-(CH_2)_4-$]: mp 133.0–134.5° (lit.[10] mp 134°); ir (Nujol) 3300–3000 (COOH), 1750 cm^{-1} (C=O).[11]

Methyl γ,γ-tetramethyleneparaconate, mp 35.5–36.0°, was obtained by esterification of 1 [R_1, R_2 = $-(CH_2)_4-$] with diazomethane: ir (neat) 1768 (lactone C=O), 1740 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 1.60–2.10 (m, 8 H, CH_2), 2.50–2.90 (m, 2 H, CH_2C=O), 3.10–3.50 (m, 1 H, CHC=O), 3.70 (s, 3 H, CH_3O).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.50; H, 7.15.

Preparation of γ-Substituted γ-Butyrolactones (2). Electrolytic Procedure I (Table I, Run 2). A solution of 1 [R_1, R_2 = $-(CH_2)_5-$] (300 mg, 1.5 mmol), sodium methoxide freshly prepared from sodium metal (400 mg, 17.4 mg-atoms), and iron powder (100 mg), after being dried up in an oven at 100° for 1 hr in dry methanol (40 ml), was electrolyzed (apparatus type I) without separation of electrolytic cells at a current of 1.25 A at 20° for 12 hr. The reaction mixture was diluted with water (50 ml) and most of the methanol was removed in a rotary evaporator. The aqueous solution was extracted with ether. The extracts were washed with diluted mineral acid and water, dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel with *n*-hexane–ether (4:1) to afford 190 mg (80%) of 2 [R_1, R_2 = $-(CH_2)_5-$], bp 110–112° (1 mm) [lit.[12] bp 50° (0.05 mm)], whose spectral data are identical with those of an authentic sample.

Electrolytic Procedure II (Table I, Run 3). The same mixed solution described in Table I (run 2), without addition of iron powder, was electrolyzed using carbon electrodes (apparatus type II) at a current of 1.4–1.5 A at 25–35° for 20 hr. The crude product was chromatographed over silica gel with *n*-hexane–ether (4:1) to give 230 mg of 2 [R_1, R_2 = $-(CH_2)_5-$] in a quantitative yield.

In the similar manner, electrolysis of 1 [R_1, R_2 = $-(CH_2)_4-$] gave 2 [R_1, R_2 = $-(CH_2)_4-$] in 98% yield: bp 104–106° (1 mm); ir (neat) 1770 (C=O), 1163 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 140 (23, M^+), 111 (100), 98 (78), 85 (20), 83 (22).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.55; H, 8.56.

Preparation of Δ^2-Butenolide [3, R_1, R_2 = $-(CH_2)_5-$] (Table I, Run 4). A stirred solution of 1 [R_1, R_2 = $-(CH_2)_5-$] (300 mg, 1.5 mmol), triethylamine (30 mg), and water (4 ml) in pyridine (30 ml) was electrolyzed using carbon rods as electrodes (apparatus type II) at a current of 0.25–0.10 A at 20° for 12 hr. The reaction mixture was concentrated in a rotary evaporator. The residue was taken up in benzene (40 ml). The benzene solution was washed with aqueous 10% hydrogen chloride, followed with aqueous sodium hydrogen carbonate and water, and dried (Na_2SO_4). Removal of the solvent gave a crude oil (190 mg), which was purified by a capillary distillation to give 180 mg (78%) of 3 [R_1, R_2 = $-(CH_2)_5-$]: bp 117–119° (2 mm) [lit.[13] bp 84° (0.1 mm)]; ir (neat) 3070 (HC=C), 1770, 1756 (C=O), 1607 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.68 (broad, 10 H, CH_2), 6.00 (d, 1 H, *J* = 6 Hz, HC=C), 7.47 (d, 1 H, *J* = 6 Hz, HC=C); mass spectrum (70 eV) *m/e* 152 (M^+).

***dl*-3-Carboxy-8-hydroxy-Δ^3-menthene γ-Lactone (8).** A stirred solution of *dl*-3,4-dicarboxy-8-hydroxymenthane γ-lactone (7, 500 mg, 2.21 mmol), triethylamine (30 mg, 0.3 mmol), and water (4 ml) in pyridine (30 ml) was electrolyzed (apparatus type II) at a current of 0.20 A (terminal voltage 50 V) at 25–30° for 5 hr. The reaction mixture was concentrated under diminished pressure. After work-up in the usual manner, the residue was distilled to give 380 mg (95%) of 8: bp 128–129° (3 mm); mp 52–53°; ir (neat) 1755 (lactone C=O), 1675 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.09 (d, 3 H, *J* = 6 Hz, CH_3), 1.42 (s, 6 H, CH_3); mass spectrum (70 eV) *m/e* 180 (M^+).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.32; H, 8.82.

Registry No.—7, 51820-76-9; 8, 51820-77-0; methyl γ,γ-tetramethyleneparaconate, 18363-04-7; cyclopentanone, 120-92-3; methyl α-bromosuccinate, 760-90-7.

References and Notes

(1) (a) N. L. Weinberg and H. R. Weinberg, *Chem. Rev.*, **68**, 499 (1968); (b) L. Eberson, "Chemistry of the Carboxyl Group," S. Patai, Ed., Interscience, New York, N. Y., 1969, p 53; (c) R. Brettle, "Modern Reactions in Organic Synthesis," Van Nostrand-Reinhold, Princeton, N. J., 1970, p 155; (d) L. Eberson, "Organic Electrochemistry," M. M. Baizer, Ed., Marcel Dekker, New York, N. Y., 1973, p 470.

(2) (a) W. J. Koehl, *J. Amer. Chem. Soc.*, **86**, 4686 (1964); (b) S. D. Ross and M. Finkelstein, *J. Org. Chem.*, **34**, 2923 (1969); (c) L. Eberson and N. L. Weinberg, *Chem. Eng. News*, **49**, 41 (January 25, 1971); (d) S. D. Ross, J. E. Barry, M. Finkelstein, and E. J. Rudd, *J. Amer. Chem. Soc.*, **95**, 2193 (1973).

(3) A commonly used electrolytic condition was employed: (a) E. J. Corey, N. L. Bauld, R. T. La Londe, J. Casanova, and E. T. Kaiser, *J. Amer. Chem. Soc.*, **82**, 2645 (1960); (b) J. A. Waters, E. D. Becker, and E. Mosettig, *J. Org. Chem.*, **27**, 4689 (1962); (c) P. G. Gassman and B. L. Fox, *J. Org. Chem.*, **32**, 480 (1967).

(4) S. F. Birch, W. H. Gough, and G. A. R. Kon, *J. Chem. Soc.*, 1315 (1921).

(5) (a) P. Radlick, R. Klem, S. Spurlock, J. J. Sims, E. E. von Tamelen, and T. Whitesides, *Tetrahedron Lett.*, 5117 (1968); (b) H. H. Westberg and H. J. Dauben, *Tetrahedron Lett.*, 5123 (1968).

(6) The use of Fe^{2+} and other metal ions has been shown to suppress the Kolbe reaction completely; see ref 1b, p 62.

(7) S. Torii, T. Oie, H. Tanaka, J. D. White, and T. Furuta, *Tetrahedron Lett.*, 2471 (1973).

(8) Melting points and boiling points are uncorrected. Nmr spectra were recorded on Hitachi R-24 and/or R-20 instruments. Ir spectra were determined with a Hitachi EPI-S2, with only major absorptions being cited. Mass spectral analyses were carried out with a Hitachi RMS-4 mass spectrometer. Microanalysis was performed by Mr. Tsutomu Okamoto of our Laboratory.

(9) S. Torii, H. Tanaka, and T. Okamoto, *Bull. Chem. Soc. Jap.*, **45**, 2783 (1972).

(10) S. F. Birch and J. F. Thorpe, *J. Chem. Soc.*, 1821 (1922).

(11) K. Sisido, S. Torii, and M. Kawanisi, *J. Org. Chem.*, 29, 904 (1964).

(12) P. E. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, *J. Org. Chem.*, **37**, 1947 (1972); M. J. Bogdanowicz, T. Ambelang, and B. M. Trost, *Tetrahedron Lett.*, 923 (1973).

(13) L. J. Haynes and E. R. H. Jones, *J. Chem. Soc.*, 954 (1946).

Photoisomerization of 9-Substituted Verbenones

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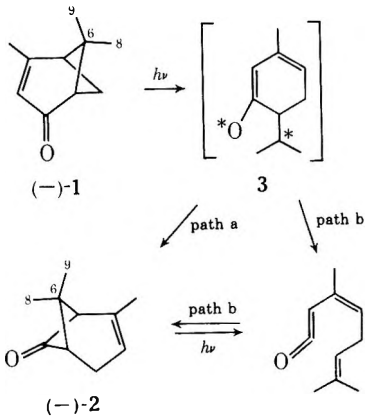
Irradiation of 9-trideuterioverbenone (4) in cyclohexane or acetic acid gave a 1:1 mixture of 8- and 9-trideuteriochrysanthenon e (6 and 7). Irradiation of 9-acetoxyverbenone (5) gave 9- and 8-acetoxychrysanthenone (9 and 10). The ratio 9:10 was solvent dependent. The results are best explained by a nonconcerted diradical or dipolar mechanism.

The photoisomerization of verbenone (1) to chrysanthenone (2)[1] was shown by Erman[2] to proceed by two pathways, one (path a) with optical retention and the other (path b) with racemization (Chart I).

Chart I



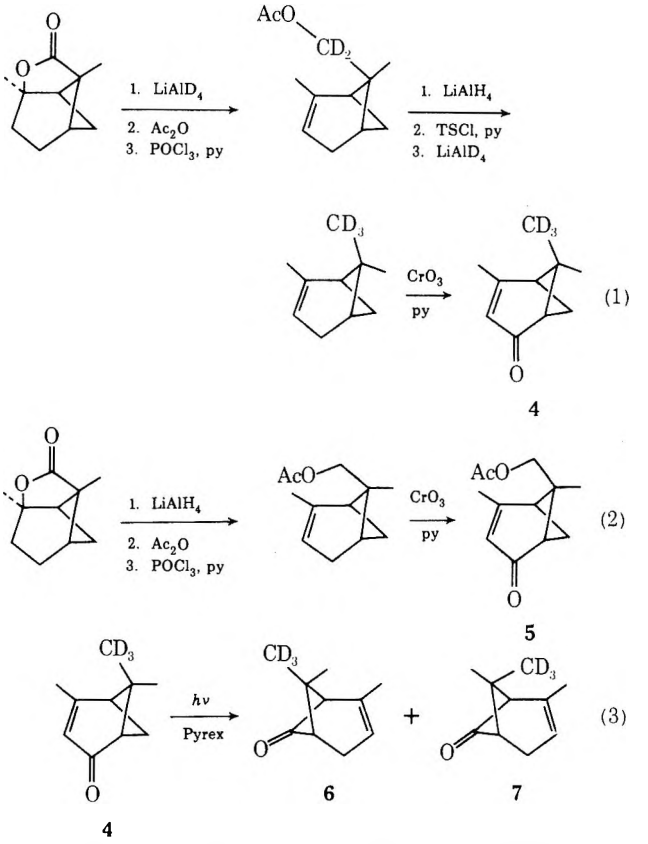
(−)-1 3 (−)-2

Until now, the nature of species 3 and the stereochemical fate of the migrating carbon atom (C-6) have not been determined. The present research has been directed toward elucidation of these mechanistic aspects of the rearrangement.

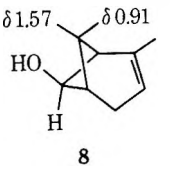
The irradiation of two 9-substituted verbenones, 9-trideuterioverbenone (4) and 9-acetoxyverbenone (5), has been studied. These substituted verbenones were prepared by allylic oxidation with chromium trioxide–pyridine[3] of the corresponding α-pinene derivatives, which in turn were prepared according to the procedures of Gibson and Erman[4] (eq 1 and 2). Phosphorus oxychloride dehydration of the tertiary alcohols to the α-pinenes occurred with formation of minor amounts of the β-pinene derivatives.[4] In both cases, the pinene mixture was oxidized and purification of the substituted verbenones was accomplished by silica gel chromatography. The nmr spectrum of 4 was identical with that of verbenone[2] except for the absence of the C-9 methyl singlet at δ 1.01.

Irradiation of 4 in either cyclohexane or acetic acid gave 8- and 9-trideuteriochrysanthenone (6 and 7) in a ratio of approximately 1:1 (eq 3). The nmr spectrum of chrysanthenone has absorption for the *gem*-dimethyl group as two singlets (6 hydrogens) at δ 1.19 and 1.22. The nmr spectrum of the trideuteriochrysanthenone mixture obtained from irradiation of 4 has these same two singlets (3 hydrogens) in equal intensity, thus showing the presence of both C-8 and C-9 methyl groups.

Further evidence of a 1:1 mixture was obtained by reduction of the photoproduct to trideuteriochrysanthenol, whose nmr spectrum has two methyl singlets of nearly equal intensity at δ 0.91 and 1.57 coincident with the methyl absorptions of chrysanthenol (8).[1] The chrysanthenol nmr singlet at δ 1.57 was assigned to the methyl group in close proximity to the hydroxyl group.



4 5 6 7



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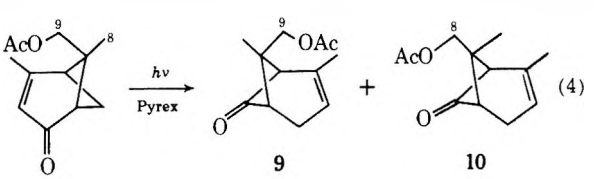
Trideuterioverbenone, recovered after irradiation, gave an nmr spectrum identical with that obtained before irradiation. Therefore, species 3 does not reclose to verbenone with scrambling of the methyl groups.

Irradiation of 5 gave two major photoproducts (eq 4) which were isolated in 50–60% yield by chromatography on silica gel followed by rechromatography on silica gel impregnated with silver nitrate. On the basis of spectral data



5 9 10

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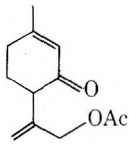
(see Experimental Section), the structures were assigned as 9- and 8-acetoxychrysanthenone (**9** and **10**). The stereochemistry at C-6 was established by reduction of **9** and **10** with lithium aluminum hydride. One of the diols obtained had an nmr methyl singlet at δ 0.95 and the other had a singlet at δ 1.64. The δ 0.95 methyl singlet can be assigned to the C-9 methyl group in analogy with α-pinene (δ 0.84), α-*trans*-bergamotene (δ 0.85),[5] and chrysanthenol (δ 0.91). Consequently, the chrysanthenone precursor of this diol was assigned structure **10.**

The ratio **9:10** was quite dependent on the solvent system and either isomer could be preferentially obtained with the proper choice of conditions (see Table I).

The acetoxychrysanthenones **9** and **10** did not photochemically interconvert under the conditions of irradiation and there was no evidence for the formation of 8-acetoxyverbenone during the irradiation of **5.** The major volatile by-product (7% yield) from irradiation of **5** in cyclohexane was identified on the basis of spectral data as 9-acetoxyisopiperitenone (**11**).



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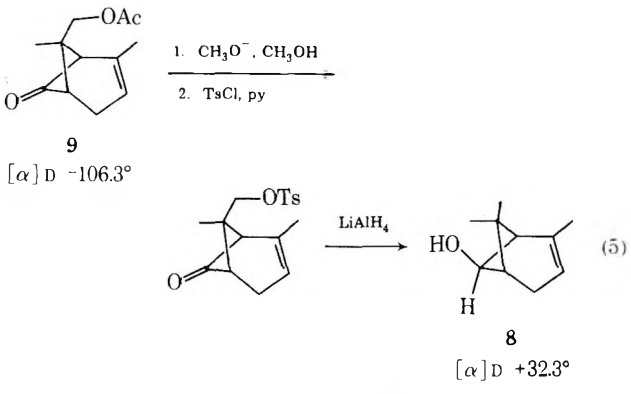
The optical activity of **9** and **10** was essentially independent of solvent (Table II). At first, this result appeared in conflict with that of chrysanthenone (**2**), where the optical purity was dramatically lowered when the irradiation solvent was changed from acetic acid to cyclohexane (−76 and −36°, respectively).[2] However, when the irradiation of verbenone (**1**) was repeated in both acetic acid and cyclohexane, **2** of comparable optical rotation could be isolated from either solvent (Table II) provided that irradiation was terminated prior to complete disappearance of **1.** The rearrangement of **1** to **2** is more rapid in cyclohexane than in acetic acid; so, if the irradiation time is extended in cyclohexane, **2** is readily racemized (Table II) through photoisomerization to the ketene followed by reclosure (Chart I).

Acetoxychrysanthenone **9** also rapidly racemizes under the conditions of irradiation. After 1 hr of irradiation in cyclohexane, a sample of **9** with a rotation of −107° was recovered with a rotation of −26.3°. The racemization of **10** was not tested.

An estimate of the amount of 9-acetoxyverbenone (**5**) that photoisomerizes *via* each pathway is possible if **9** and/or **10** of known rotation are correlated with **2**, since the absolute rotation of **2** is known[2] (−108°).

9-Acetoxychrysanthenone (**9**) was converted to chrysanthenol (**8**) (eq 5), which was identical with an authentic



9
$[\alpha]_D$ −106.3°

8
$[\alpha]_D$ +32.3°

(5)

sample. The nmr spectrum of **8** derived from **9** was devoid of any singlet at δ 1.19 corresponding to 7-epichrysanthenol.[6] A corresponding conversion of **10** to **8** was unsuccessful.[7]

Table I
Ratio of 9:10 Obtained from Irradiation of 5

Solvent	Ratio 9:10	Solvent	Ratio 9:10
Cyclohexane	1.9	Cyclohexane–silica gel	0.9
Neat (30°)	1.2	Methanol	0.9
Acetic acid	1.0	Neat (−65°)	0.3

Table II
Optical Rotations of Chrysanthenones Obtained from Pyrex-Filtered Irradiation of Verbenones

Photoproduct	Irradiation solvent	$[\alpha]^{25}D$, deg
9	Acetic acid	−106.3
9	Methanol	−107.0
9	Cyclohexane	−102.8
10	Acetic acid	−82.8
10	Cyclohexane	−78.5
2	Acetic acid (0.11 *M*, 1.5 hr)	−91.5
2	Cyclohexane (0.11 *M*, 0.4 hr)	−81.2
2	Cyclohexane (0.11 *M*, 1.5 hr)	−62.2

Lithium aluminum hydride reduction of **2** with a rotation of −91.5° (85% optically pure) gave **8** with a rotation of +38.7°. Since this reduction of **2** is known[6] to give **8** stereospecifically, the absolute rotation of **8** can be estimated to be +45.5°. Therefore, the optical purity of **9** is approximately 71%.

The 9-acetoxypinene used for the synthesis of **5** was optically pure as determined by conversion[4] to optically pure α-pinene (−55.4°). Since allylic oxidation of 9-acetoxypinene should not affect the optical purity, the racemization of **9** must have occurred during the irradiation of **5.** Therefore, at least 71% of the **9** from **5** is formed *via* path a. However, since the chrysanthenones rapidly racemize under the conditions of irradiation, there is a possibility that verbenones photoisomerize >90% *via* path a. The highest amount of path a isomerization that we were able to demonstrate was 85% in the case of **2.**

Regarding the nature of species **3,** scrambling of the methyl groups during formation of trideuteriochrysanthenone (**6** and **7**) from irradiation of **4** indicates that **3** is best represented as a discrete intermediate of diradical or dipolar nature. A photochemical concerted 1,3-sigmatropic rearrangement, controlled by local symmetry, should have occurred with retention of stereochemistry at C-6, and 8-trideuteriochrysanthenon e (**6**) should have been the only product.

In polar solvents, near room temperature, rearrangement of **5** also occurs with nearly complete scrambling of the acetoxy group. In cyclohexane, the electronic repulsion of the acetoxy and keto groups in the absence of polar solvation probably disfavors the formation of **10.** The rearrangement of **5** to **10** involves the least movement of atoms and this could explain the preferential formation of **10** in the low-temperature rigid matrix.

Experimental Section

Preparative irradiations were carried out with a 450-W medium-pressure Hanovia mercury lamp in a quartz, water-cooled, immersion probe. The filter was a glass cylinder of Pyrex (>290 nm) insertable between the lamp and the probe. Solutions were outgassed with argon before and during the irradiations.

Infrared spectra were taken as neat samples and absorptions are reported as inverse centimeters, nmr spectra were taken on a Varian A-60A as chloroform-d_1 solutions and are reported as δ units relative to TMS, and optical rotations were taken as chloroform solutions. Gas–liquid chromatography (glc) was done on a 3% OV-1 column (8 ft × 0.125 in.).

9-Acetoxyverbenone (5). To a slightly cooled solution of 143 g (1.81 mol) of anhydrous pyridine in 2400 ml of methylene chloride was added 90.0 g (0.90 mol) of chromium trioxide, and the mixture was allowed to stir at room temperature for 45 min. A solution of 13.9 g (0.072 mol) of 9-acetoxy-α-pinene[4] (90% pure, major impurity 9-acetoxy-β-pinene) in a small amount of methylene chloride was added and the mixture was allowed to stir for 24 hr at room temperature. The solution was decanted, the residue was rinsed with ether, and the combined organic phase was washed in succession with saturated sodium bicarbonate solution, 2 *N* hydrochloric acid, saturated sodium bicarbonate solution, and saturated salt solution. The organic phase was dried, filtered, and concentrated under reduced pressure, and the residual oil (16.9 g) was chromatographed on 500 g of silica gel (6 cm i.d.). Hexane–ether (3:1) eluted 1.72 g of recovered starting material. Hexane–ether (1:1) first eluted 1.94 g of several minor by-products and then 98% pure **5**: 7.86 g (59% yield); ir 1740 (s), 1680 (s), 1620 (w), 1240 (s), 1035 cm^{-1} (s); λ_{max} (EtOH) 251 nm (ϵ 5800), 315 (67); nmr δ 5.75 (1 H, q, J = 1.5 Hz, vinylic H), 3.87 and 4.16 (2 H, AB q, J = 11 Hz, H α to acetoxy), 2.39–3.12 (4 H, m, cyclobutyl H), 2.05 (3 H, d, J = 1.5 Hz, vinylic methyl H), 2.03 (3 H, s, acetoxy methyl H), 1.55 (3 H, s, methyl H); $[\alpha]^{25}D$ −119.3° (*c* 19.9).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.36; H, 7.96.

The 9-acetoxy-α-pinene that was oxidized to **5** was converted[4] to optically pure α-pinene, $[\alpha]^{25}D$ −55.4° (c 4.05) (reported rotation[8] of optically pure α-pinene in solution 54°).

9-Trideuterioverbenone (4). A mixture of 9-trideuterio-α- and -β-pinene was prepared, following the procedure of Gibson and Erman,[4] from 6,9-dimethyl-8-oxo-7-oxatricyclo[4.3.0.0^{3,9}]nonane using lithium aluminum deuteride for the appropriate reduction steps. The nmr spectrum was identical with that of a mixture of α- and β-pinene except for the absence of methyl singlets at δ 0.84 (α) and 0.72 (β). The molecular weight of each isomer was 139 (mass spectrum).

The trideuteriopinenes (1.46 g, 0.01 mol, 75% α, 25% β) were oxidized as described above with chromium trioxide–pyridine. The reaction product (1.04 g) was chromatographed on 150 g of silica gel (2.5 cm i.d., 3:1 hexane–ether) to give 9-trideuterioverbenone (**4**): 0.328 g (27% yield); ir 2100–2300 (w), 1680 (s), 1620 cm^{-1} (m); nmr identical with that of verbenone[2] except for the absence of the C-9 methyl singlet at δ 1.01; mol wt 153 (mass spectrum); identical with verbenone on glc.

Irradiation of 9-Trideuterioverbenone (4). Dilute solutions (0.03–0.06 *M*) of 9-trideuterioverbenone (**4**) in either cyclohexane or glacial acetic acid were irradiated (0.5–1.0 hr) as described above. After irradiation, when the solvent was acetic acid, the solution was partitioned between ether and water, and the ethereal solution was neutralized with sodium carbonate, dried, filtered, and concentrated. When the solvent was cyclohexane, the solution was concentrated under reduced pressure without any prior work-up. The crude reaction mixtures were chromatographed on silica gel (9:1 hexane–ether) to give trideuteriochrysanthenone (**6** and **7**): 20–25% yield; ir 2100–2300 (w), 1785 cm^{-1} (s); nmr identical with that of chrysanthenone[2] except that the *gem*-dimethyl singlets at δ 1.19 and 1.22 integrated for three rather than six hydrogens; mol wt 153 (mass spectrum); identical with chrysanthenone on glc. The nmr *gem*-dimethyl singlets at δ 1.22 and 1.19 for trideuteriochrysanthenone (**6** and **7**) from irradiation in cyclohexane were in the ratio of 54:46, respectively. For trideuteriochrysanthenone (**6** and **7**) from irradiation in acetic acid, these methyl singlets were in the ratio of 50:50.

Lithium aluminum hydride reduction of trideuteriochrysanthenone from irradiation in cyclohexane gave trideuteriochrysanthenol with *gem*-dimethyl nmr singlets at δ 0.91 (56%) and 1.57 (44%). Chrysanthenol has equal intensity nmr singlets at δ 0.91 (C-9 methyl) and 1.57 (C-8 methyl).

9-Trideuterioverbenone (**4**) recovered after irradiation in acetic acid gave an nmr spectrum identical with that obtained before irradiation.

Irradiation of 9-Acetoxyverbenone (5). Dilute solutions (0.03–0.06 *M*) of 9-acetoxyverbenone (**5**) in cyclohexane, methanol, or glacial acetic acid were irradiated (0.5–1.0 hr) as described above. Glc showed two major photoproducts, 9-acetoxychrysanthenone (**9**, 0.7 retention time relative to **5**) and 8-acetoxychrysanthenone (**10**, 0.8 retention time relative to **5**). The chrysanthenones were isolated from the irradiation mixture (58% yield in cyclohexane, 46% yield in acetic acid) by chromatography on silica gel (3:1 hexane–ether) and separated by rechromatography on silica gel impregnated with silver nitrate (20% silver nitrate, 4:1 hexane–ether). 9-Acetoxychrysanthenone (**9**) had ir 1780 (s), 1740 cm^{-1} (s); nmr δ 5.42 (1 H, m, vinylic H), 4.47 and 4.25 (2 H, AB q, J = 11 Hz, H α to acetoxy), 2.58–2.87 (4 H, m, allylic and cyclobutyl H), 2.08 (3 H, s, acetoxy methyl H), 1.75 (3 H, q, J = 1.5 Hz, vinylic methyl H), 1.27 (3 H, s, methyl H); $[\alpha]^{25}D$ −102.8° (c 1.25) (from irradiation in cyclohexane), −106.3° (c 1.20) (from irradiation in acetic acid), −107.0° (c 0.71) (from irradiation in methanol). 8-Acetoxychrysanthenone (**10**) had ir 1780 (s), 1740 cm^{-1} (s); nmr δ 5.42 (1 H, vinylic H), 4.10 (2 H, s, H α to acetoxy), 2.60–2.89 (4 H, m, allylic and cyclobutyl H), 2.07 (3 H, s, acetoxy methyl H), 1.75 (3 H, q, J = 1.5 Hz, vinylic methyl H), 1.22 (3 H, s, methyl H); $[\alpha]^{25}D$ −78.5° (c 1.30) (from irradiation in cyclohexane), −82.8° (*c* 1.16) (from irradiation in acetic acid). The high-resolution mass spectrum showed *m/e* 208.1087; the elemental composition was $C_{12}H_{16}O_3$.

The ratio of **9**:**10** changed with solvent: cyclohexane, 1.9; neat (30°), 1.2; acetic acid, 1.0; cyclohexane–silica gel, 0.9; methanol, 0.9; neat (−65°), 0.3.

A mixture of the two acetoxychrysanthenones (62% of the isomer first eluted from glc) was reduced in the normal manner with lithium aluminum hydride to a mixture of diols. The nmr spectrum of the diols had two methyl singlets at δ 0.95 (35%) and 1.64 (65%). 9-Acetoxychrysanthenone (**9**) was assigned as the isomer whose corresponding diol gave a methyl group nmr signal at δ 1.64. The nmr spectrum of the diol obtained by lithium aluminum hydride reduction of pure **9** (first eluted isomer on glc) had a methyl singlet at δ 1.64 and no absorption at δ 0.95.

Irradiation (cyclohexane, 0.06 *M*, Pyrex filter, 1 hr) of either **9** or **10** (each >90% pure) did not interconvert the isomers.

9-Acetoxychrysanthenone (**9**) rapidly racemized when irradiated. The optical rotation of **9** decreased from −107 to −26.3° (*c* 0.17) after 1 hr of irradiation as a very dilute solution (0.001 *M*) in cyclohexane.

The major volatile by-product from irradiation of **5** in cyclohexane was isolated in 7% yield by chromatography on silica gel (1:1 hexane–ether) and identified by spectral data as 9-acetoxyisopiperitenone (**11**): ir 1740 (s), 1670 (s), 1230 cm^{-1} (s); nmr δ 5.91 (1 H, q, J = 1.5 Hz, vinylic H), 5.29 and 5.02 (2 H, 2 broad s, terminal vinylic H), 4.67 (2 H, s, H α to acetoxy), 3.08 (1 H, t, J = 8 Hz, H α to ketone), 2.07 (3 H, s, acetoxy methyl H), 1.98 (3 H, broad s, vinylic methyl H).

9-Acetoxyverbenone (**5**), recovered after irradiation in acetic acid, gave an nmr spectrum identical with that obtained before irradiation.

Conversion of 9-Acetoxychrysanthenone (9) to Chrysanthenol (8). A solution of 0.102 g of **9** ($[\alpha]^{25}D$ −106.3°), 0.02 g of sodium methoxide, and 20 ml of methanol was heated under reflux in a nitrogen atmosphere for 1.5 hr. After work-up, an ir spectrum of the crude oil (0.072 g) showed OH absorption (3480 cm^{-1}), cyclobutyl carbonyl absorption (1775 cm^{-1}), and no acetate absorption (1740 cm^{-1}).

The crude hydroxy ketone was dissolved in 3 ml of anhydrous pyridine, the solution was cooled in an ice bath, and 0.3 g of recrystallized tosyl chloride was added. After stirring in the ice bath for 1 hr, the mixture was placed in a refrigerator (6°) for 2 days. The mixture was poured into cold water and extracted with ether, and the ethereal extract was washed successively with 2 *N* hydrochloric acid, half-saturated sodium bicarbonate solution, and saturated sodium chloride solution, dried, filtered, and concentrated under reduced pressure. The crude tosylate (0.115 g) was chromatographed on silica gel (1:1 hexane–ether) to give crystalline 9-tosyloxychrysanthenone: 0.080 g, 80–90% pure; ir 1777 cm^{-1} (s), no OH absorption; nmr δ 7.40 and 7.84 (4 H, AB q, J = 8.5 Hz, aromatic H), 5.36 (1 H, broad, vinylic H), 4.21 and 4.41 (2 H, AB q, J = 10 Hz, H α to tosyloxy), 2.2–2.8 (7 H, m, tosylate methyl s at 2.45), 1.66 (3 H, d, J = 1.5 Hz, vinylic methyl), 1.19 (3 H, s, methyl).

A solution of the tosylate in ether was added dropwise to a mixture of 0.3 g of lithium aluminum hydride in ether. After addition, the mixture was heated under reflux for 3 hr and cooled, and saturated ammonium chloride solution was added dropwise until a clear ether layer was obtained. The ethereal solution was decanted and the precipitate was rinsed several times with ether. The combined etherial solution was washed with water, dried, filtered, concentrated under reduced pressure, and vacuum distilled on a Kugelrohr apparatus to give chrysanthenol (**8**): 0.032 g, 90–95% pure; $[\alpha]^{25}D$ +32.3° (*c* 0.5); nmr spectrum was identical with that of **8** derived from lithium aluminum hydride reduction of **2**, and there was no detectable singlet at δ 1.19 corresponding to 7-epichrysanthenol.[5]

Attempted conversion of 8-acetoxychrysanthenone (**10**) to **8** was

unsuccessful. During reaction with sodium methoxide in methanol, rearrangement occurred to a compound tentatively identified as 2,4-dimethyl-2-hydroxymethylcyclohex-3- and -4-enecarboxylic acid lactone: ir 1775 (s), 1136 (s), 1018 cm^{-1} (s); nmr δ 5.43 (broad) and 5.20 (broad s, 1 H, vinylic H), 3.95 and 3.98 (2 H, two absorptions of AB q, H α to oxygen), 1.66 (3 H, broad s, vinylic methyl), 1.15 and 1.17 (3 H, two s, methyl); mol wt 166 (mass spectrum).

Chrysanthenone (2) from Irradiation of Verbenone (1) and Reduction to Chrysanthenol (8). Dilute solutions of **1** (2.5 g of **1** in 150 ml of solvent, 0.11 *M*) in either cyclohexane or glacial acetic acid were irradiated as described above. Chrysanthenone (**2**) was isolated from the irradiation mixture by chromatography on silica gel (**2** was eluted with 3:1 hexane–ether and then the purest fractions of **2** were rechromatographed with 9:1 hexane–ether) and distilled under vacuum on a Kugelrohr apparatus.

After 1.5 hr of irradiation in acetic acid, glc showed 26% remaining **1**; **2** isolated from this irradiation had optical rotation $[\alpha]^{25}D$ −91.5° (*c* 1.0). After 25 min of irradiation in cyclohexane, glc showed 26% remaining **1**; **2** isolated from this irradiation had optical rotation $[\alpha]^{25}D$ −81.2° (c 0.42). After 1.5 hr of irradiation in cyclohexane, glc showed essentially no remaining **1**; **2** isolated from this irradiation had optical rotation $[\alpha]^{25}D$ −62.2° (*c* 0.43).

Chrysanthenone (**2**) with rotation −91.5° was reduced with lithium aluminum hydride to chrysanthenol (**8**) with $[\alpha]^{25}D$ +38.7° (*c* 0.91).

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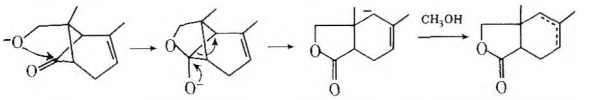
Registry No.—**4**, 51897-93-9; **5**, 51849-16-2; **6**, 51897-95-1; **7**, 51897-96-2; **9**, 51849-17-3; **10**, 51897-97-3; **11**, 51849-18-4; 9-trideuterio-α-pinene, 51897-94-0; 9-acetoxy-α-pinene, 23971-93-9; 9-trideuterio-β-pinene, 51849-19-5.

References and Notes

(1) J. J. Hurst and G. H. Whitham, *J. Chem. Soc.*, 2864 (1960).
(2) W. F. Erman, *J. Amer. Chem. Soc.*, **89**, 3828 (1967).
(3) W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969); R. Ratcliffe and R. Rodehorst, *ibid.*, **35**, 4000 (1970).
(4) T. W. Gibson and W. F. Erman, *J. Amer. Chem. Soc.*, **91**, 4771 (1969).
(5) G. F. Russell, W. J. Murray, C. J. Muller, and W. G. Jennings, *J. Agr. Food Chem.*, **16**, 1047 (1968).
(6) D. Joulain and F. Rouessac, *J. Chem. Soc. Chem. Commun.*, 315 (1972).
(7) During reaction of **10** with sodium methoxide in methanol, rearrangement occurred to a compound tentatively identified as 2,4-dimethyl-2-hydroxymethylcyclohex-3- and -4-enecarboxylic acid lactone.



(8) F. H. Thurber and R. C. Thielke, *J. Amer. Chem. Soc.*, **53**, 1030 (1931).

Configuration of 9-Imino Derivatives of Erythromycin

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Both isomers of erythromycin B oxime have been isolated and configurationally identified. The major stable isomer has been shown to be (*E*)-erythromycin B oxime by ^1H nmr and ir. The *E* isomer has been suggested to predominate in the oxime, hydrazone, and isopropylidene hydrazone of both erythromycin A and B.

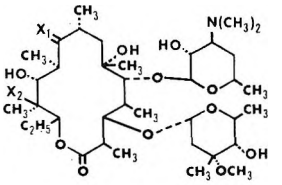
Several imino derivatives of the ketone of erythromycin A (**1**) have been prepared, including the oxime (**2**),[1,2] hydrazone (**3**),[1,3] isopropylidene hydrazone (**4**),[1] and the imine (**5**).[4,5] Interest in these derivatives centers on their utility as antibiotics and as substrates for further modification such as reduction to erythromycylamine.[1,2,4,5]We wish now to report our results in this area which concerns the preparation, isolation, and configurational assignments of the two erythromycin B oxime isomers (**7a** and **7b**) and the configurational analysis of **2, 3, 4, 8,** and **9.**

Discussion

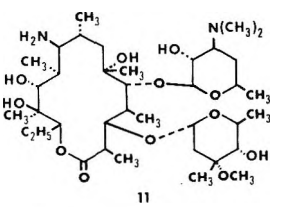
Preparation, Isolation, and Characterization of Oxime Isomers. Two new compounds analyzing for the oxime structure were obtained on reaction of erythromycin B with hydroxylamine. The major product was readily identified as an oxime in the infrared.[6] However, the minor product, which could be obtained only 80% pure, failed to show a significant band in the 1600-cm^{-1} region in both the infrared and the Raman.[7]

Positive evidence for an oxime was considered necessary, as an alternate hemiacetal type structure **12** was possible for the minor isomer. The latter structure was suggested by a band in the hydroxyl region at 3240 cm^{-1} ($\Delta\nu_{1/2}$ 100 cm^{-1}) in CCl_4 which could be interpreted as a hydrogen-bonded NH absorption of a hydroxylamine.[8] Such a structure is also consistent with the known chemistry of the erythromycins.[9]

Conclusive evidence for the oxime structure of the minor product was derived from both ^1H nmr spectra in dimethyl sulfoxide-d_6 solution and ^{13}C nmr spectra. In DMSO-d_6,



X_1	X_2 = OH	X_2 = H
O	1	6
N–OH	2	7
$N–NH_2$	3	8
$N–N=C(CH_3)_2$	4	9
NH	5	10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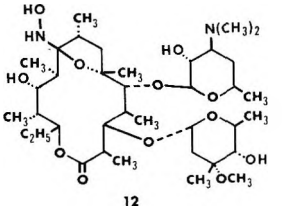
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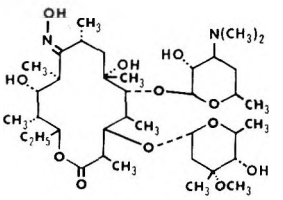
7a (E) - oxime

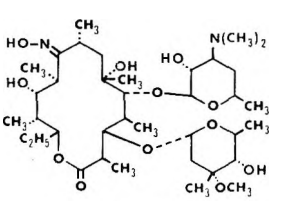
7b (Z) - oxime

Table I
Chemical Shifts of Aglycone Ring Protons in $CDCl_3$ Solution

	Major 7a	Minor 7b
H-2	2.88	~2.9
H-3	4.05	4.09
H-4	~2.2	~2.1
H-5	3.60	3.60
H-10	2.59	2.68
H-11	3.65	3.83
H-13	5.42	5.19

the major isomer showed a one-proton absorption at 10.62 ppm, which was exchangeable with D_2O. The minor isomer showed corresponding signals at 10.43 and 10.62 ppm (*ca.* 20% impurity of major isomer) also exchangeable with D_2O. These chemical shifts are clearly consistent with an oxime hydroxyl.[10] The ^{13}C nmr spectrum of the major isomer showed peaks at 177.7 and 171.1 ppm downfield from TMS for the lactone[11] and the oxime carbons[12] while the minor isomer showed peaks at 178.0 and 169.4 ppm. With the compounds firmly established as isomeric oximes, configurational assignments were made on the basis of infrared and nmr data.

Configurational Analysis of Oxime Isomers. Nuclear Magnetic Resonance. The most significant differences between the spectra of the two oxime isomers which could be observed at 100 MHz are the changes in the chemical shifts of H-11 and H-13 (Table I). Although H-11 is not α to C-9, it is significantly deshielded in the minor isomer compared to the major product. The deshielding of H-11 can be attributed to a cis hydroxyl of the oxime group and establishes that the minor isomer is **7b**, the *Z* isomer.[13] The magnitude of the deshielding is greater than that observed for β-CH protons in simple oximes and hydrazones,[14-18] which may be a reflection of the rigid conformation of the aglycone ring (Figure 1).[19-21]

The chemical shift changes of H-10 are considerably smaller and less diagnostic, which is consistent with its unfavorable orientation with respect to the OH group. Nevertheless, the minor isomer shows the expected deshielding of H-10 consistent with its syn orientation.

The shielding of H-13 in the spectrum of the minor component is unusual in view of the distance between C-9 and H-13, suggesting that the difference is not due entirely to the C-9 substituent but rather may be accentuated by a secondary effect. For example, the change in the chemical shifts may result in part from a decrease in the deshielding arising from the 11-hydroxyl group. This decrease may be caused by hydrogen bonding of the 11-hydroxyl proton to the oxygen of the lactone carbonyl. This interaction causes changes in the electronic character and therefore anisotropy of the carbonyl which is reflected in a decrease in the deshielding of H-13. The required hydrogen bonding is supported by infrared evidence which follows.

Attempts to determine the configuration of the erythromycin A oxime in a similar manner were hindered by the insolubility of the major isomer in $CDCl_3$ and the unavailability of the as yet unisolated minor isomer. Comparison of the nmr spectra of both major isomers in pyridine-d_5 shows no differences not attributable to introduction of the 12-OH in the erythromycin A isomer and which are not exactly mirrored in the comparison of the patent antibiotics (*cf.* Table II). Therefore both major isomers are assigned the same stereochemistry in pyridine-d_5 solution which is presumed to be *E*.

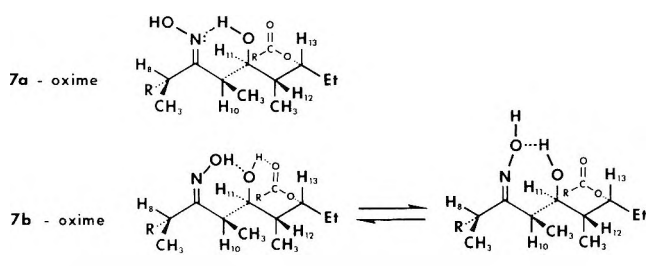

Figure 1. Schematic representation of (*E*)- and (*Z*)-oxime isomers (R = remainder of ring).

Table II
Chemical Shifts of Aglycone Ring Protons in C_5D_5N Solution

	1	6	2	7a
H-2	3.02	3.04	3.08	3.08
H-3	4.43	4.43	4.42	4.39
H-5	3.95	3.96	3.99	3.97
H-10	3.26	3.05	2.95	2.80
H-11	4.29	4.27	4.14	4.06
H-13	5.41	5.65	5.51	5.78

Table III
Chemical Shifts of Aglycone Ring Protons in $CDCl_3$ Solution

	3	4	8	9
H-2	2.80		2.80	2.90
H-3	4.00	4.04	4.01	4.02
H-4	~2.0		2.06	2.16
H-5	3.56	3.66	3.58	3.62
H-10	2.66		2.62	2.65
H-11	3.51	3.72	3.49	3.66
H-13	5.06	5.14	5.41	5.48

Infrared. At 2×10^{-3} *M* the major isomer showed peaks at 3592, 3560, and 3475 cm^{-1} and a broad complex peak at about 3330 cm^{-1}. The lactone was observed as a single strong band at 1730 cm^{-1}. When diluted to 6×10^{-5} *M* the free oxime hydroxyl at 3592 cm^{-1} increased at the expense of peaks at 3560 and 3330 cm^{-1}. The observed spectral changes indicate the oxime hydroxyl is not intramolecularly hydrogen bonded[22] and is directed away from the 11-hydroxyl group as shown for the *E* isomer **7a** in Figure 1.

The minor isomer at 2×10^{-3} *M* showed bands at 3593, 3560, 3465, and 3240 cm^{-1} in the hydroxyl region. The latter band is unusually sharp ($\Delta\nu_{1/2}$ 100 cm^{-1}) and is assigned to an intramolecularly hydrogen bonded oxime hydroxyl.[23] The carbonyl region showed two bands at 1730 and 1712 cm^{-1}, each about half as intense as that of the major isomer. The appearance of the band at 1712 cm^{-1} along with weakening of the 1730-cm^{-1} band is evidence of a mixture of hydrogen-bonded forms in which one form exists with a hydrogen bond to the lactone carbonyl.[24] On further dilution to 6×10^{-5} M the hydroxyl region showed no change, confirming the assignment of the 3240-cm^{-1} band to an intramolecular hydrogen bond. This compound is assigned as the *Z* isomer with the hydrogen-bonding arrangement as shown in **7b** (Figure 1).

Configurational Analysis of Other 9-Imino Derivatives. The same trends observed in the nmr spectra of the oxime isomers are seen in the spectra of **3**, **4**, **8**, and **9** (Table III), although the magnitudes of the changes vary depending on the nature of the 9-imino substituent. Identical correlations can be made although they suffer from lack of data for the unisolated *Z* isomers.

The largest chemical shift differences should be associated with H-8. Unfortunately, this resonance cannot be directly observed in the 100-MHz spectra of these compounds; however, the 220-MHz spectra of **8** and **9** reveal complex multiplets at ca. 3.5 ppm which can be attributed

to H-8. The comparable chemical shift in the erythromycins is 2.7 ppm. The large deshielding of H-8 indicates that the *E* isomer is present in both cases, even without the spectra of the second isomers for comparison.

In summary, the data clearly reveal that the major stable isomers of the oxime and hydrazone of the erythromycins are configurationally homogeneous *E* isomers. The isolation of the minor unstable oxime isomer represents the first and only example of a *Z* isomer.

Experimental Section

General. ^{1}H nmr spectra were obtained on Varian Associates HA-100 and HR-220 spectrometers. Chemical shifts were measured from internal TMS in $CDCl_3$ solution at 55°. ^{13}C nmr spectra were obtained on a Bucher HFX-90 spectrometer. Chemical shifts were determined in methanol and methanol-d_4 solutions and measured from an external capillary containing CS_2. Chemical shifts were converted to the TMS scale by the formula $\delta_{TMS} = 193.7 - \delta_{CS_2}$ external.[25]

Infrared data were obtained in both 3.0-mm NaCl cells and 100-mm quartz cells using a Perkin-Elmer Model 521 infrared grating spectrophotometer. Raman data were obtained on solid samples using a Cary Model 83 Raman spectrophotometer which employs an Argon-Ion laser. Melting points are uncorrected.

Preparation of Erythromycin B Oxime (7). To a solution of 15 g (20.9 mmol) of erythromycin B in 225 ml of methanol was added 9.60 ml of triethylamine and 6.30 g (90.6 mmol) of $H_2NOH\cdot HCl$. The mixture was refluxed for 65 hr and then cooled and diluted with 2.6 l. of water containing 260 ml of concentrated NH_4OH. The product was extracted with $CHCl_3$ and the combined extracts were washed with dilute NH_4OH. The $CHCl_3$ was dried over anhydrous Na_2SO_4 and the solvent was evaporated to give 17.9 g of crude product. The sample was crystallized from $CHCl_3$–hexane to give 12.3 g of oxime, mp 176–195°, obtained as a chloroform solvate. The tlc of this product (silica gel G, benzene–methanol, 80:20, atmosphere saturated with ammonia, arsenomolybdate reagent) showed two compounds, a major product with R_f value 0.4 (*ca.* 90%) and a minor product with R_f value 0.3 (*ca.* 10%). The isomers were separated by chromatography of *ca.* 2.0-g samples on a 200 g silica gel column (4 × 30 cm^2) using 98:1:1 EtOAc–H_2O–Et_3N as the solvent system.

(*E*)-Erythromycin B Oxime (7a). Fractions obtained by chromatography of 2.2 g of the isomeric mixture were combined and the solvent was evaporated to give 1.9 g of the pure *E* isomer. Crystallization from methanol–water and drying at 75° in a vacuum oven gave 1.0 g of **7a:** mp 171–174°; $[\alpha]^{24}D$ −81.4° (*c* 1.00, MeOH). *Anal.* Calcd for $C_{37}H_{68}N_2O_{12}$ (732.96): C, 60.63; H, 9.35; N, 3.82; O, 26.19. Found: C, 60.95; H, 9.40; N, 3.84; O, 26.49. Nmr (see Table I for aglycone ring proton chemical shifts): $J_{2,3}$ = 9.0; $J_{3,4} \simeq 1$; $J_{4,5}$ = 7.0; $J_{10,11}$ = 1.0; $J_{11,12}$ = 10.5; $J_{12,13} \simeq 1$; $J_{13,14}$ = 9.0, 5.0 Hz; H-1′, δ 4.43, $J_{1',2'}$ = 7.0 Hz; H-2′, δ 3.22, $J_{2',3'}$ = 10.0 Hz; H-1″, δ 4.92, $J_{1'',2''}$ = 4.5, ~ 1 Hz; H-4″, δ 2.97; H-5″, δ 4.05, $J_{4'',5''}$ = 9.0 Hz; CH_3-6, δ 1.49; OCH_3, δ 3.30; $N(CH_3)_2$, δ 2.28.

(*Z*)-Erythromycin B Oxime (7b). The minor isomer could not be obtained in pure form because of isomerization during chromatography and work-up. The purest sample contained 20–25% of the *E* isomer and was obtained by concentrating the eluent at 25° to a small volume, diluting with benzene, washing with water, drying over Na_2SO_4, and finally evaporating the benzene solution to dryness at 25° to give 0.2 g. Analytical and spectral data were collected on the glass obtained in this way: $[\alpha]^{24}D$ −84.9° (*c* 1.00, MeOH). *Anal.* Calcd for $C_{37}H_{68}N_2O_{12}$ (732.96). Found: C, 60.89; H, 9.58; N, 3.80; O, 25.90. Nmr (see Table I for aglycone ring proton chemical shifts): $J_{2,3}$ = 9.0; $J_{3,4} \simeq 1$; $J_{4,5}$ = 7.5; $J_{10,11}$ = 1.0; $J_{11,12}$ = 10.5; $J_{12,13} \simeq 1$; $J_{13,14}$ = 9.0, 5.0 Hz; H-1′, δ 4.42, $J_{1',2'}$ = 7.5 Hz; H-2′, 3.21, $J_{2',3'}$ = 10.0 Hz; H-1″, δ 4.91, $J_{1'',2''}$ = 4.5, ~ 1 Hz; H-4″, δ 2.99; H-5″, δ 4.04, $J_{4'',5''}$ = 9.5 Hz; CH_3-6, δ 1.45; OCH_3, δ 3.30; $N(CH_3)_2$, δ 2.28.

Thermal Isomerization of the *Z* Isomer. The *Z* isomer was heated at 136° for 16 hr under vacuum. The sample was identified as the *E* isomer by tlc and infrared spectrum (CCl_4, 4000–1650 cm^{-1}). The crystalline *E* isomer was unchanged by the same treatment.

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Registry No.—**7a,** 51820-81-6; **7b,** 51830-04-7; erythromycin B, 527-75-3; $H_2NOH\cdot HCl$, 5470-11-1.

References and Notes

(1) E. H. Massey, B. Kitchell, L. D. Martin, K. Gerzon, and H. W. Murphy, *Tetrahedron Lett.*, 157 (1970).
(2) S. Djokic and Z. Tamburasev, *Tetrahedron Lett.*, 1645 (1967).
(3) M. V. Sigal, Jr., P. F. Wiley, K. Gerzon, E. H. Flynn, U. C. Quarck, and O. Weaver, *J. Amer. Chem. Soc.*, **78,** 388 (1956).
(4) G. H. Timms and E. Wildsmith, *Tetrahedron Lett.*, 195 (1971).
(5) E. Wildsmith, *Tetrahedron Lett.*, 29 (1972).
(6) L. J. Bellamy, "Advances in Infrared Group Frequencies," Richard Clay (The Chaucer Press) Ltd., Bungay, Suffolk, 1968, p 50.
(7) D. Horton, E. K. Just, and B. Cross, *Carbohyd. Res.*, **16,** 239 (1971).
(8) M. Davies and N. A. Spiers, *J. Chem. Soc.*, 3971 (1959).
(9) P. H. Jones, T. J. Perun, E. K. Rowley, and E. J. Baker, *J. Med. Chem.*, **15,** 631 (1972).
(10) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p 216.
(11) J. G. Nourse and J. D. Roberts, personal communication.
(12) G. C. Levy and G. L. Nelson, *J. Amer. Chem. Soc.*, **94,** 4897 (1972).
(13) For a brief discussion of the *E–Z* nomenclature system, see E. L. Eliel, *J. Chem. Educ.*, **48,** 163 (1971).
(14) G. J. Karabatsos and N. Hsi, *Tetrahedron*, **23,** 1079 (1967).
(15) G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24,** 3347 (1968).
(16) G. J. Karabatsos and C. E. Osborne, *Tetrahedron*, **24,** 3361 (1968).
(17) G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24,** 3557 (1968).
(18) G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24,** 3923 (1968).
(19) T. J. Perun, R. S. Egan, P. H. Jones, J. R. Martin, L. A. Mitscher, and B. J. Slater, *Antimicrob. Ag. Chemother.*, 116 (1970).
(20) R. S. Egan, Ph.D. Thesis, The University of Illinois at the Medical Center, Chicago, Ill., 1971.
(21) R. S. Egan, T. J. Perun, J. R. Martin, and L. A. Mitscher, *Tetrahedron*, **29,** 7525 (1973).
(22) M. Kimura, Y. Kuroda, O. Yamamoto, and M. Kubo, *Bull. Chem. Soc. Jap.*, **34,** 1081 (1961).
(23) P. C. Cherry, W. R. T. Cottrell, G. D. Meakins, and E. E. Richard, *J. Chem. Soc. C*, 459 (1968).
(24) R. E. Kagarise and K. B. Whetsel, *Spectrochim. Acta*, **18,** 314 (1962).
(25) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N. Y., 1972, p 23.

Some Chemical and Stereochemical Modifications of the Erythromycin Lactone Rings[1]

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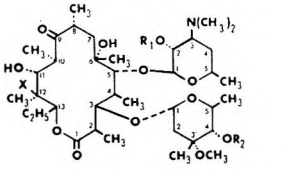
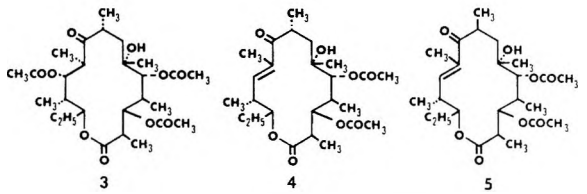
The preparation of 10,11-anhydroerythromycin B (**10**) from 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin B (**7a**) is described. C-8 epimerization of both erythromycin B and **10** was effected in aqueous acetic acid. Base-catalyzed elimination of the elements of methanesulfonic acid from 11-*O*-methanesulfonylerythromycin A (**6a**) may be controlled to lead selectively to either 10,11-anhydroerythromycin A (**13**) or 11,12-epoxyerythromycin A (**14**). Methods for effecting C-8 epimerization of **13** and **14** are described. The C-8 epimeric 11,12-epoxyerythromycins A (**14** and **16**) were readily rearranged to the corresponding C-8 epimeric 10,11-anhydroerythromycins A (**13** and **15**). 8,9-Anhydro-11,12-epoxyerythromycin A 6,9-hemiacetal (**18**) was prepared and shown not to be an intermediate in the C-8 epimerization of 11,12-epoxyerythromycin A (**14**) effected by glacial acetic acid. Compound **18** was converted to a mixture of **14** and **16** in aqueous acetic acid.

The lactone rings of the macrolide antibiotics provide important and interesting substrates for fundamental studies of the chemistry of large-ring alicyclic compounds. Knowledge of their chemistry is of practical significance with respect to the goal of preparing chemically modified macrolides with improved therapeutic properties, and should prove useful for contemplated total synthesis of these complex molecules.

The extreme sensitivity of erythromycins to both acidic and basic conditions presents a challenge with regard to effecting both chemical and stereochemical modifications. Previous studies[2] established that the erythromycins A (**1a**) and B (**2a**) are readily and irreversibly degraded by



	X	R_1	R_2
1a	OH	H	H
1b	OH	$COCH_3$	CHO
2a	H	H	H
2b	H	$COCH_3$	CHO



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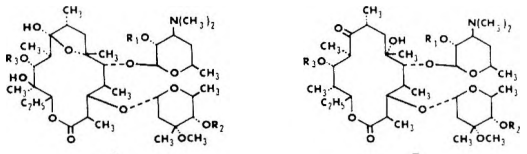
both dilute aqueous alkali and dilute mineral acid. The object of our current work is the development of methodology for chemical and stereochemical modification of the erythromycin lactone rings. Our general approach is based on the selective introduction into the erythromycin lactone rings of functionalizable sites of unsaturation. Our interest in 8-*epi*-erythromycins was stimulated by the postulate of Celmer[3] concerning the importance of the stereochemistry at C-8 to antibacterial activity.

The β-hydroxy ketone functionality present in the erythromycin lactone rings suggested the introduction of a 10,11 double bond. Although the C-8 epimeric 3,5-di-*O*-acetyl-10,11-anhydroerythronolides B (**4** and **5**) were prepared by Perun by acid-catalyzed degradation of 3,5,11-tri-*O*-acetylerythronolide B (**3**),[4] the sensitivity to acid and base of the intact erythromycins precluded direct acid- or base-catalyzed dehydration of the parent antibiotics. It was thus hoped that conversion of the 11-hydroxyl groups of the erythromycins to good leaving groups, followed by treatment of the resulting derivatives with a strong, nonnucleophilic base, would lead to the desired 10,11-anhydroerythromycins. A likely route involved preparation of the 11-*O*-methanesulfonylerythromycins.

11-*O*-Methanesulfonylerythromycins. Selective methanesulfonation of the 11-hydroxyl groups of the erythromycins required protection of the two secondary hydroxyl groups present in the desosamine and cladinose moieties. The technique for protecting the sugar hydroxyl groups was developed by Jones, *et al.*,[5] who prepared the 2′-*O*-acetyl-4″-*O*-formylerythromycins A and B, (**1b** and **2b**) and found that the parent erythromycins were readily regenerated from these diesters by mild basic hydrolysis. Treatment of the 2′-*O*-acetyl-4″-*O*-formylerythromycins A and B with methanesulfonic anhydride[6] in pyridine gave rise to the corresponding 11-*O*-methanesulfonylerythromycins A and B (**6a** and **7a**). These labile products were characterized by their nmr spectra and used in preparative reactions without purification. Methanolysis of the 2′-*O*-acetyl and 4″-*O*-formyl groups of **6a** and **7a** gave the 11-*O*-meth-



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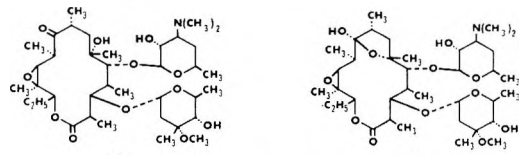
	R_1	R_2	R_3
a	$COCH_3$	CHO	SO_2CH_3
b	H	H	SO_2CH_3
c	H	H	$COCH_3$



14a 14b

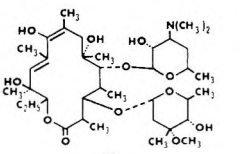


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Table I
Antibacterial Activity of Selected Erythromycins

Structure	Minimum inhibitory concentrations, g/ml[a]						
	Staphylococcus aureus 9144	*Staphylococcus aureus* Smith ER[b]	*Streptococcus faecalis* 10541	*Klebsiella pneumoniae* 10031	*Shigella sonnei* 9290	*Mycobacterium gallisepticum* S6	*Haemophilus influenzae* Patterson
1a	0.2	>100	0.05	3.1	12	0.2	1.56
2a	0.39	>100	0.05	6.2	25	0.05	
10	6.2	>100	1.6	25	>100	100	100
13	6.2	>100	1.6	12	>100	0.5	50
7b	3.1	>100	0.2	25	100	0.5	12.5
6b	50	>100	6.2	50	>100	50	>100
14	>100	>100	25	25	>100	1	>100
11	25	100	3.1	100	>100	5	>100
20c	0.39	>100	0.05	6.2	12.5	0.05	1.56
9	12.5	>100	1.56	25	>100	0.1	>100
15	12.5	>100	0.78	12.5	100	1.0	50

[a] Determined by an agar dilution method. [b] Erythromycin resistant.

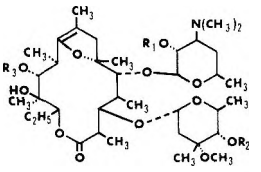
anesulfonylerythromycins A and B (**6b** and **7b**), which were isolated in about 90% purity by column chromatography and characterized spectroscopically.

It has been established[5] that while 11-*O*-acetylerythromycin B (**7c**) exists as the hydroxy ketone tautomer, 11-*O*-acetylerythromycin A exists as the hemiacetal, **6c**. Similarly nmr and ir spectra provide evidence that 11-*O*-methanesulfonylerythromycin B exists as the hydroxy ketone **7b**, while 11-*O*-methanesulfonylerythromycin A exists as the hemiacetal **6b**. The infrared spectrum of the hydroxy ketone **7b** shows carbonyl absorptions of both lactone (1727 cm^{-1}) and ketone (1704 cm^{-1}) carbonyls, while the infrared spectrum of the hemiacetal **6b** shows only a sharp symmetrical lactone carbonyl (1727 cm^{-1}). In addition, the C-10 proton resonances ($CDCl_3$) of the 11-*O*-acetyl- and 11-*O*-methanesulfonylerythromycins A (**6c** and **6b**) occur at higher field (δ 2.21 and 2.59, respectively) than those of the corresponding B derivatives, **7c** and **7b** (δ 2.99 and 3.16, respectively). This upfield shift of the C-10 proton resonances of the A derivatives relative to the B is presumably the consequence of the absence of the C-9 keto carbonyls in the hemiacetals.

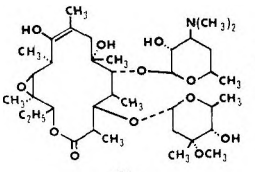
It is of interest that the 11-esters of erythromycin A, which exist as hemiacetals, have little or no antibacterial activity, while the antibacterial activities of the 11-esters of erythromycin B, which exist as hydroxy ketones, is appreciable (Table I).

The C-8 Epimeric Erythromycins B and the C-8 Epimeric 10,11-Anhydroerythromycins B. Kurath, *et al.*,[7] recently established that the erythromycins A (**1a**) and B (**2a**) are dehydrated to the corresponding 8,9-anhydroerythromycin 6,9-hemiacetals **8a** and **8b** in glacial acetic acid. It was also found[7] that the enol ether **8b** is readily hydrated in dilute aqueous mineral acid to regenerate erythromycin B (**2a**) (Scheme I). Since the C-8 carbon of **8b** is no longer an asymmetric center, the interconversion of **2a** and **8b** suggested that under suitable conditions an acid-catalyzed equilibration might be established *via* the enol ether **8b** leading to formation of 8-*epi*-erythromycin B (**9**). Treatment of erythromycin B (**2a**) with 1:1 (v/v) acetic acid–water at room temperature for 96 hr gave a mixture from which were isolated 35% of 8-*epi*-erythromycin B (**9**) and 30% of erythromycin B (**2a**). To provide chemical evidence that **9** differed from **2a** only in its configuration at C-8, it was converted to the enol ether, **8b**, in glacial acetic acid.

Comparison of the 220-MHz nmr spectra of erythromycin B and 8-*epi*-erythromycin B showed that both have essentially the same lactone ring conformations. The aglycone ring vicinal coupling constants and chemical shifts of both compounds involving H-2, -3, -11, -12, and -13 are very nearly identical. This indicates a close conformational



	R_1	R_2	R_3
8a	H	H	H
20a	$COCH_3$	CHO	H
20b	$COCH_3$	CHO	SO_2CH_3
20c	H	H	SO_2CH_3



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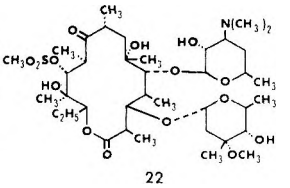

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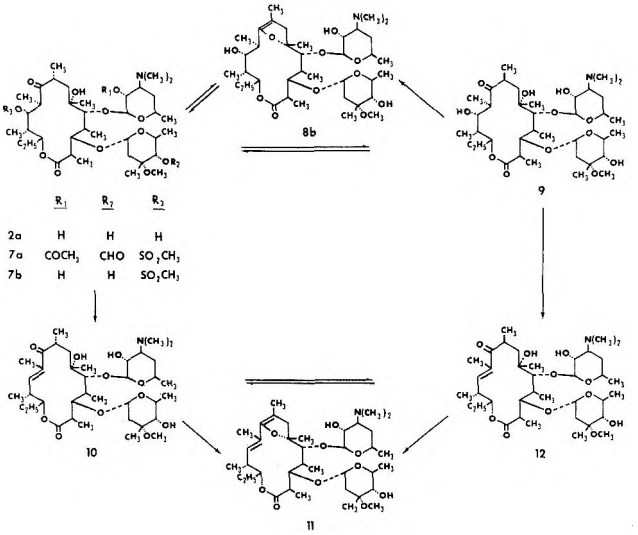
Scheme I



	R_1	R_2	R_3
2a	H	H	H
7a	$COCH_3$	CHO	SO_2CH_3
7b	H	H	SO_2CH_3

similarity of the ring segments containing these protons. Somewhat more substantial differences are observed in the chemical shifts of H-4, -7a, -7e, -8, and -10 and the $J_{4,5}$ and C-7 methylene proton coupling constants. These differences closely parallel those found when the spectra of 8-*epi*-erythronolide B and erythronolide B were compared[8] and are attributable to the same conformational reorganization involving the C-6 to C-9 ring segment as discussed in detail elsewhere.[9] The near identity of the coupling con-

stants, $J_{10,11}$, of erythromycin B (~1 Hz) and 8-*epi*-erythromycin B (~1 Hz) (Table II) established that both had the same configuration at C-10.

Since the C-10 protons and the C-11 hydroxyl groups of the erythromycins A and B (**1a** and **2a**) are antiperiplanar, it was hoped that the corresponding 11-methanesulfonates would undergo facile, base-catalyzed trans elimination to form the 10,11-anhydroerythromycins (**13** and **10**). Treatment of 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin B (**7a**) with 1,5-diazabicyclo[4.3.0]undecene-5 (DBU)[10] either under reflux for 0.5 hr or at 5° for 18 hr smoothly effected elimination of the elements of methanesulfonic acid. Methanolysis of the 2′-*O*-acetyl and 4″-*O*-formyl groups gave 10,11-anhydroerythromycin B (**10**), which was characterized by its infrared and ultraviolet spectra and by its conversion in glacial acetic acid to 8,9:10,11-dianhydroerythromycin B 6,9-hemiacetal (**11**).

Equilibration of **10** in 1:1 glacial acetic acid–water for 48 hr at room temperature gave a mixture containing 8-*epi*-10,11-anhydroerythromycin B (**12**) and 10,11-anhydroerythromycin B (**10**) in a ratio of about 10:1 as estimated from the relative areas of the corresponding C-10 methyl peaks in the nmr spectrum. Pure **12** was isolated by column chromatography.

To prove that **12** differed from **10** only in its configuration at C-8, it was converted to the enol ether **11** in glacial acetic acid. In addition, 8-*epi*-erythromycin B was converted to **12** by the same sequence of reactions used to convert erythromycin B (**2a**) to 10,11-anhydroerythromycin B (**10**).

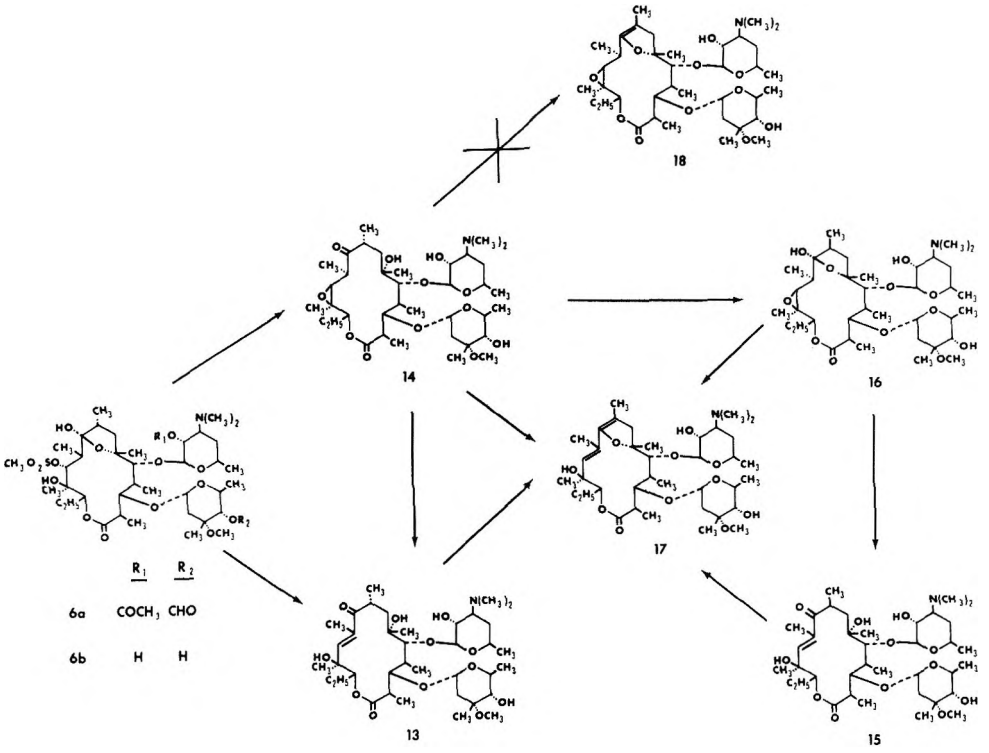
Table II
A Nuclear Magnetic Resonance Comparison of Erythromycin B (2a) and 8-*epi*-Erythromycin B (9)[a]

	Chemical shifts, ppm			Coupling constants, Hz	
	2a	**9**		**2a**	**9**
H-2	2.87	2.89	$J_{2,3}$	8.3	9.1
H-3	4.07	4.05	$J_{3,4}$	1	1
H-4	2.10	2.25	$J_{4,5}$	7.0	9.1
H-5	3.60	3.59	$J_{7a,7e}$	15.0	14.2
H-7a	2.00	2.06	$J_{7a,8}$	10.0	7.2
H-7e	1.6	1.93	$J_{7e,8}$	3.0	2.8
H-8	2.76	2.9	$J_{10,11}$	1	1
H-10	2.98	2.83	$J_{11,12}$	9.8	10.0
H-11	3.83	3.84	$J_{12,13}$	1	1.2
H-12	1.75	1.7	$J_{13,14a}$	9.0	9.1
H-13	5.35	5.31	$J_{13,14e}$	5.5	4.8
H-14a			$J_{14a,14e}$		
H-14e					
H-1′	4.43	4.32	$J_{1',2'}$	7.0	7.1
H-2′	3.21	3.24	$J_{2',3'}$	10.2	10.0
H-3′	2.47	2.53	$J_{3',4a'}$	12.0	12.1
H-4a′			$J_{3',4e'}$	3.5	3.8
H-4e′			$J_{4a',4e'}$		
H-5′	3.52	3.52	$J_{4a',5'}$	10.5	10.6
H-1″	4.89	4.87	$J_{4e',5'}$	1.8	1.6
H-2a″	1.58	1.58	$J_{1'',2a''}$	4.5	4.2
H-2e″	2.37	2.40	$J_{1'',2e''}$	1.5	<1
H-4″	3.00	3.01	$J_{2a'',2e''}$	15.5	15.1
H-5″	4.05	4.02	$J_{4'',5''}$	9.0	9.5

[a] All parameters were measured from 220-MHz spectra obtained at 55° in $CDCl_3$ solution.

The C-8 Epimeric 10,11-Anhydroerythromycins A and the C-8 Epimeric 11,12-Epoxyerythromycins A. DBU-catalyzed elimination of the elements of methanesulfonic acid from 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin A (**6a**) (Scheme II) may be controlled to lead selectively to 10,11-anhydroerythromycin A (**13**) or 11,12-epoxyerythromycin A (**14**). Treatment of **6a** with DBU in refluxing benzene for 0.5 hr followed by methanolysis of the 2′-*O*-acetyl and 4″-*O*-formyl groups of the products led to isolation of 35% of 10,11-anhydroerythromycin A (**13**) and 15% of 11,12-epoxyerythromycin A (**14**). In contrast, when the DBU-catalyzed elimination was carried out at 5° for 18 hr complete elimination of the elements of methanesulfonic acid was effected, as indicated by the nmr spectrum of the crude product, but the ir spectrum showed the absence of any α,β-unsaturated ketone. After methanolysis of the 2′-*O*-acetyl and 4″-*O*-formyl groups 11,12-epoxyerythromycin A (**14**) was isolated in 45% yield by column chromatography. A purified sample of 11-*O*-methanesulfonylerythromycin A (**6b**) was smoothly converted to **14** by DBU in benzene at 5° for 18 hr.

Scheme II



Prolonged reflux of 10,11-anhydroerythromycin A (**13**) with DBU in benzene in the presence of methanesulfonic acid effected considerable C-8 epimerization. A reaction time of 96 hr gave a mixture containing 8-*epi*-10,11-anhydroerythromycin A (**15**) and 10,11-anhydroerythromycin A in a ratio of about 3:1 as estimated from the characteristic C-10 methyl peaks in the nmr spectrum. Pure **15** was isolated by column chromatography, and both C-8 epimers, **13** and **15**, were converted to 8,9:10,11-dianhydroerythromycin A 6,9-hemiacetal (**17**) in glacial acetic acid.

Although the erythromycin enol ethers **8b** and **11** are probable intermediates in the C-8 epimerizations of erythromycin B and 10,11-anhydroerythromycin B which are effected by aqueous acetic acid, a control experiment established that the enol ether **17** is not an intermediate in the C-8 epimerization of **13** to **15** effected by DBU and methanesulfonic acid in benzene. Treatment of **17** with DBU and methanesulfonic acid in benzene under reflux for 96 hr in the presence of 1 equiv of water gave only recovered starting material. This suggests that the intermediate involved in the epimerization of **13** to **15** under these conditions is the 8,10-dien-9-ol **19**, or the corresponding dienolate anion.

An attempt to characterize 11,12-epoxyerythromycin A (**14**) by its conversion in glacial acetic acid to 8,9-anhydro-11,12-epoxyerythromycin A 6,9-hemiacetal (**18**) was unsuccessful. Instead, treatment of **14** with glacial acetic acid at room temperature for 1 hr gave 8-*epi*-11,12-epoxyerythromycin A (58%) which was found to exist as the hemiacetal **16**. The same product **16** was isolated (48%) after treatment of **14** with 1:1 acetic acid–water at room temperature for 24 hr. Both **14** and **16** were converted to 8,9:10,11-dianhydroerythromycin A 6,9-hemiacetal (**17**) in glacial acetic acid at room temperature for 46 hr. Conversion of **14** and **16** to the corresponding C-8 epimeric 10,11-anhydroerythromycins A (**13** and **15**) was effected with DBU in refluxing benzene in the presence of methanesulfonic acid for 3 hr.

The C-8 epimerization of 11,12-epoxyerythromycin A (**14**), which occurs in glacial acetic acid, is in marked contrast to the behavior of other erythromycin derivatives which are converted to 8,9-anhydroerythromycin 6,9-hemiacetals under similar conditions. To provide some insight into the mechanism of C-8 epimerization of **14** to **16**, and to add to the evidence for their structures, the preparation of 8,9-anhydro-11,12-epoxyerythromycin A 6,9-hemiacetal (**18**) was desired, and was accomplished by epoxide formation from 8,9-anhydro-11-*O*-methanesulfonylerythromycin A 6,9-hemiacetal (**20c**). The behavior of **18** in both glacial acetic acid and 1:1 acetic acid–water was investigated.

2′-*O*-Acetyl-4″-*O*-formylerythromycin A (**1b**) was converted to the enol ether **20a** in glacial acetic acid. **20a** was

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Experimental Section

Products were isolated by either benzene or chloroform extraction. The reaction mixtures were shaken with mixtures of excess 5% aqueous sodium bicarbonate and the organic solvent. The aqueous phase was separated and washed several times with the orgamic solvent. The organic solutions were washed with water and combined. Solvents were evaporated under reduced pressure. Any residual pyridine was removed by co-distillation with benzene under reduced pressure.

Optical rotations were determined with 1% solutions in methanol with a Hilger and Watts polarimeter. Ir spectra were determined with deuteriochloroform solutions using a Perkin-Elmer Model 521 grating spectrometer. The cd determinations were made with samples dissolved in spectral grade methanol using a Durrum-Jasco Model ORD/UV-5 instrument equipped with a cd attachment and operating at ambient temperatures. Nmr spectra were determined at 100 MHz, unless otherwise specified, with a Varian HA-100 spectrometer with deuteriochloroform solutions. Chemical shifts are reported in ppm from internal tetramethylsilane (0δ) and coupling constants are reported in Hz. Partition column chromatographies were carried out by the method of Oleinick and Corcoran[11] using silica gel (Merck, Darmstadt).

11-*O*-Methanesulfonylerythromycin A (6b). --- A suspension prepared from 14.4 g of 2′-*O*-acetyl-4″-*O*-formylerythromycin A[5] (1b), 7.3 g of methanesulfonic anhydride, and 108 ml of pyridine was stirred at room temperature for 19 hr. The product, 11-*O*-

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methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin A (6a, 15.1 g) was isolated as a brown foam by chloroform extraction: nmr δ 8.23 (OCOH), 3.33 (OMe), 3.02 (OSO_2Me), 2.28 (NMe_2), 2.06 (OCOMe).

A solution of 2.1 g of 6a in 50 ml of methanol was allowed to stand at room temperature for four days. The major portion of the methanol was evaporated under reduced pressure. Chloroform extraction gave 1.54 g of an orange glass. Pure (~90%) 11-*O*-methanesulfonylerythromycin A (6b, 686 mg) was isolated by partition column chromatography as a white glass: ir 3587, 3400-3550, 1727 cm^{-1}; nmr δ 3.29 (OMe), 3.09 (OSO_2Me), 2.32 (NMe_2), 1.54 (C-6 Me).

11-*O*-Methanesulfonylerythromycin B (7b). --- A suspension prepared from 7.5 g of 2′-*O*-acetyl-4″-*O*-formylerythromycin B[5] (2b), 3.6 g of methanesulfonic anhydride and 53 ml of pyridine was stirred at room temperature for 17 hr. The product, 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin B (7a, 7.8 g) was isolated as a brown foam by chloroform extraction: nmr δ 8.23 (OCOH), 3.36 (OMe), 3.12 (OSO_2Me), 2.29 (NMe_2), 2.06 (OCOMe). A solution of 13 g of 7a, prepared as described above, in 350 ml of methanol was allowed to stand at room temperature for four days. The methanol solution was treated with Darco G-60 and filtered through a celite mat. The major portion of the methanol was evaporated under reduced pressure. Chloroform extraction gave 10.9 g of a light-orange glass. Partition column chromatography of 3.0 g gave 320 mg of pure (~90%) 11-*O*-methanesulfonylerythromycin B (7b) as a white glass: ir 3595, 3540

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3470-3400, 1727 and 1704 cm^{-1}; nmr δ 3.31 (OMe), 3.09 (OSO_2Me), 2.29 (NMe_2).

8,9-Anhydro-11-*O*-methanesulfonylerythromycin A 6,9-hemiacetal (20c). --- A solution of 15.5 g of 2′-*O*-acetyl-4″-*O*-formylerythromycin A[5] and 170 ml of glacial acetic acid was allowed to stand at room temperature for 4 hr. The major portion of the acetic acid was evaporated under reduced pressure and the product, 2′-*O*-acetyl-4″-*O*-formyl-8,9-anhydroerythromycin A 6,9-hemiacetal (20a, 14 g) was isolated by chloroform extraction: nmr δ 8.20 (OCOH), 3.37 (OMe), 2.28 (NMe_2), 2.04 (OCOMe), 1.55 (C-8 Me).

A suspension of 2.0 g of 20a, 1.0 g of methanesulfonic anhydride and 20 ml of pyridine was stirred at room temperature for 4 hr. The product, 8,9-anhydro-11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin A 6,9-hemiacetal (20b, 2.0 g) was isolated by chloroform extraction.

A suspension of 2.0 g of 20b, 50 ml of methanol and 5 ml of 5% aqueous $NaHCO_3$ was stirred at room temperature for 64 hr during which time a clear solution resulted. Chloroform extraction gave 1.8 g of orange glass. The product, 11-*O*-methanesulfonyl-8,9-anhydroerythromycin A 6,9-hemiacetal (20c) was isolated as a white crystalline solid by partition column chromatography: mp 122-131°, $[\alpha]_D^{23}$ -38°; ir 3562, 3500-3400, 1735 cm^{-1}, nmr δ 3.34 (OMe); 3.17 (OSO_2Me), 2.28 (NMe_2), 1.58 (C-8 Me); 1.38 (C-6 Me).

Anal. Calcd for $C_{38}H_{67}O_{14}NS$: C, 57.48; H, 8.51; N, 1.76; S 4.04. Found: C, 58.48; H, 8.95; N, 1.69; S, 4.34.

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10,11-Anhydroerythromycin B (10). --- A solution of 7.5 g of 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin B (7a), 3.4 g of 1,5-diazabicyclo[5.4.0]undecene-5, and 50 ml of benzene was heated under reflux for 0.5 hr. The reaction mixture was cooled to room temperature and diluted with 50 ml of benzene. Water (50 ml) was added, and the resulting mixture was stirred at room temperature for one hour. Benzene extraction gave 5.48 g of an orange foam.

A solution of 10.7 g of product, prepared as described above, in 260 ml of methanol was allowed to stand at room temperature for three days. The resulting solution was treated with Darco G-60 and filtered through a celite mat. The major portion of the methanol was evaporated under reduced pressure and the product (9.1 g of white foam) was isolated by chloroform extraction. Chromatography of the latter (5.1 g) on Sephadex LH-20, followed by crystallization from ether, gave 2.42 g of 10,11-anhydroerythromycin B: mp 118-130°; $[\alpha]_D^{24}$ -51°; λ max 232nm (ε 10,640); ir 3610, 3575-3400, 1725, 1667 cm^{-1}; nmr δ 6.42 (C-11 H), 3.32 (OMe), 2.30 (NMe_2), 1.77 (C-10 Me).

Anal. Calcd for $C_{37}H_{65}O_{11}N$: C, 63.49; H, 9.36; N, 2.00. Found: C, 63.40; H, 9.63; N, 1.92.

Similar results were obtained when the reaction of 6a with DBU in benzene was carried out at 5° for 18 hr.

10,11-Anhydroerythromycin A (13) and 11,12-Epoxyerythromycin A (14). --- a.) A solution of 15.0 g of 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin A (6a), 7.0 g of DBU and 102 ml of

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benzene was heated under reflux for 0.5 hr. The resulting mixture was cooled to room temperature and diluted with 100 ml of benzene. Water (100 ml) was added, and the resulting mixture was stirred at room temperature for 40 min. Benzene extraction gave 12.0 g of an orange glass. Treatment of this product with 300 ml of methanol for 50 hr followed by chloroform extraction gave 10.7 g of yellow glass. Partition column chromatography of 2.54 g of this product yielded, in the earlier fractions, 276 mg of 11,12-epoxyerythromycin A (14 + 14a + 14b) as a white glass from chloroform solution: ir 3600-3350, 1729, 1708 cm^{-1}.

Anal. Calcd for $C_{37}H_{65}NO_{12}$: C,62.08; H, 9.15; N, 1.96. Found: C, 62.14; H, 9.34; N, 1.77.

Crystallization of 1.97 of 14[12] from ether gave 1.23 g of the pure hemiacetal tautomer 14b: mp 158-162°; $[\alpha]_D^{24}$ -90°; ir 3578, 3500-3400, 1727 cm^{-1}.

Further elution of the column gave 923 mg of 10,11-anhydroerythromycin A (13) as a white glass; $[\alpha]_D^{24}$ - 58°; λmax 233nm (ε 9479); ir 3610-3350, 1727, 1665 cm^{-1}; nmr δ 6.48 (C-11 H), 3.32 (OMe), 2.28 (NMe_2), 2.02 (C-10 Me).

Anal. Calcd for $C_{37}H_{65}NO_{12}$: C,62.08; H, 9.15; N, 1.96. Found: C, 61.88; H, 9.43; N, 1.94.

b.) A solution of 15.8 g of 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin A (6a), 6.8 g of DBU, and 98 ml of benzene was stirred at 5° for 18 hr. Benzene (98 ml) and water (98 ml) were added and the resulting mixture was stirred at room temperature for 1 hr. The product (12.9 g), isolated by benzene extraction, showed the absence of α,β-unsaturated ketone absorption

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in the infrared. A solution of 4.0 g of the product, 88 ml of methanol and 9 ml of 5% aqueous $NaHCO_3$ was stirred at room temperature for 48 hr. Chloroform extraction gave 3.58 g of product which was chromatographed on a partition column to yield 1.5 g of 11,12-epoxyerythromycin A (14) identical in all respects to that described above.

c.) A pre-cooled solution of 2.49 g of DBU in 30 ml of benzene was added to 1.84 g of 11-*O*-methanesulfonylerythromycin A (6b) and the resulting solution was stirred at 5° for 18 hr. Benzene (50 ml) and water (50 ml) were added and the resulting mixture was stirred at room temperature for 1 hr. Benzene extraction yielded 1.72 g of 11,12-epoxyerythromycin A (14) identical with that described above.

d.) A mixture of 912 mg of 11,12-epoxyerythromycin A (14), 333 mg of DBU, 0.076 ml of methanesulfonic acid and 7.6 ml of benzene was heated under reflux for 3 hour. The usual workup and benzene extraction gave 687 mg of orange glass. Partition column chromatography of 632 mg gave 357 mg of pure 10,11-anhydroerythromycin A (13).

8-*epi*-Erythromycin B (9). --- A solution of 1.0 g of erythromycin B (2a) in 17 ml of acetic acid and 17 ml of water was allowed to stand at room temperature for 96 hr. The resulting solution was added dropwise to a stirred suspension of excess $NaHCO_3$ in water. The product (719 mg) was isolated by chloroform extraction. Partition column chromatography yielded, in the

converted to 8,9-anhydro-11-*O*-methanesulfonylerythromycin A 6,9-hemiacetal (**20c**) on treatment with methanesulfonic anhydride in pyridine followed by methanolysis of the 2′-*O*-acetyl and 4″-*O*-formyl groups. Treatment of **20c** with DBU in benzene under reflux for 18 hr gave 8,9-anhydro-11,12-epoxyerythromycin A 6,9-hemiacetal (**18**) in good yield.

Treatment of **18** with 1:1 acetic acid–water for 0.5 hr at room temperature gave a mixture from which were isolated 11,12-epoxyerythromycin A (**14**, 49%) and 8-*epi*-11,12-epoxyerythromycin A (**16**, 18%). Treatment of **18** with glacial acetic acid at room temperature for 1 hr yielded 20% of starting material, 20% of the enol ether **17**, and only 9% of 8-*epi*-11,12-epoxyerythromycin A (**16**). Since the latter conditions effect essentially complete C-8 epimerization of **14** we believe that this result excludes the enol ether **18** as the intermediate in the C-8 epimerization of **14** effected by glacial acetic acid, and suggests that the epimerization occurs *via* the 8-en-9-ol **21**.

The contrast to the ease of formation of 11,12-epoxyerythromycin A (**14**) from 11-*O*-methanesulfonylerythromycin A (**6b**), effected by DBU in benzene (5°, 18 hr), identical treatment of 8,9-anhydro-11-*O*-methanesulfonylerythromycin A 6,9-hemiacetal (**20c**) led to quantitative recovery of starting material.

Hydroxy Ketone–Hemiacetal Tautomerism of the C-8 Epimeric 11,12-Epoxyerythromycins A (14 and 16). Although 11,12-epoxyerythromycin A (**14**), isolated as a glass by evaporation of chloroform from a chloroform solution, showed a single spot in several tlc systems, the nmr spectrum of a freshly prepared solution in deuteriochloroform at 35° showed **14** to be a mixture of two components in a ratio of 1.2:1, estimated from the heights of the two NMe_2 and two OMe peaks. The major component showed peaks at δ 3.35 (OMe) and 2.31 (NMe_2), while the minor component showed peaks at δ 3.36 (OMe) and 2.29 (NMe_2). A characteristic singlet appeared at δ 1.66 which was associated with the minor component and is tentatively assigned to its C-6 methyl protons. When the deuteriochloroform solution of **14** was heated at 56° for 0.5 hr, the ratio of components changed to 2.4:1 with the original major component predominating. When the solution was cooled to 35° the ratio of components remained at 2.4:1 and little change in the ratio was noted even after several days at room temperature.

Comparison of the infrared spectrum of the freshly prepared deuteriochloroform solution of **14** with that of an aliquot which had been heated at 56° for 0.5 hr showed significant increase, in the heated sample, of the ratio of intensities (log I/I_0) of the ketone carbonyl absorption (1708

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earlier fractions, 8-epi-erythromycin B (145 mg) as a white glass. Crystallisation of 485 mg[12] from methanol water gave 322 mg of prisme: mp 169-171° $[\alpha]_D^{24}$ - 95°; ir 3602, 3560-3440, 1710 cm^{-1} ($CDCl_3$); 1733, 1720 cm^{-1} (Et_3N); nmr δ 3.28 (OMe), 2.30 (NMe_2), 1.44 (C-6 Me).

Anal. Calcd for $C_{37}H_{67}O_{12}N$: C, 61.90; H, 9.40; N, 1.95. Found: C, 61.80; H, 9.65; N, 1.94.

Further elution gave 123 mg of erythromycin B.

8-epi-10,11-Anhydroerythromycin B (12). — a.) A solution prepared from 5.3 g of 10,11-anhydroerythromycin B (10), 10 ml of acetic acid, and 10 ml of water was allowed to stand at room temperature for 49 hr. The resulting solution was added dropwise to a stirred suspension of 150 g of solid $NaHCO_3$ in 800 ml of water. Chloroform extraction gave 5.2 g of white glass containing 8-epi-10,11-anhydroerythromycin B (12) and 10,11-anhydroerythromycin B (10) in a ratio of about 10 to 1 estimated from the characteristic C-10 methyl peaks in the nmr spectrum. Partition column chromatography of 1.82 g of the product gave 883 mg of pure 8-epi-10,11-anhydroerythromycin B (12) as a white glass: $[\alpha]_D^{26}$ - 54°; λ_{max} 230nm (ϵ 10,526); ir 3610 (shoulder), 3520-3400, 1723, 1664 cm^{-1}; nmr δ 6.35 (C-11 H), 3.29 (OMe), 2.29 (NMe_2), 1.83 (C-10 Me).

Anal. Calcd for $C_{37}H_{65}O_{11}N$: C, 63.49; H, 9.36; N, 2.00. Found: C, 63.43; H, 9.56; N, 1.89.

b.) A sample of 8-epi-erythromycin B (9, 382 mg) was converted to 2′-O-acetyl-4″-O-formyl-8-epi-erythromycin B (340 mg), by the method of Jones, et al.[5]. Treatment of the diester (340 mg) with

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178 mg of methanesulfonic anhydride in pyridine at room temperature for 4 hr followed by chloroform extraction gave 380 mg of crude 11-O-methanesulfonyl-2′-O-acetyl-4″-O-formyl-8-epi-erythromycin B. The latter was treated with 580 mg of DBU in 8.1 ml of benzene at room temperature for 15 hr and then under reflux for 1 hr. Treatment of the product with methanol (10 ml) at room temperature for 90 hr followed by chloroform extraction gave 256 mg of product. Partition column chromatography yielded 68 mg of pure 12, identical with that prepared as described above.

Conversion of 8-epi Erythromycin B (9) to 8,9-Anhydroerythromycin B 6,9-Hemiacetal (8b). — A solution of 320 mg of 8-epi-erythromycin B (9) in 4 ml of glacial acetic acid was allowed to stand at room temperature for 19 hr. The acetic acid was evaporated under reduced pressure, and a slurry of 5 g of $NaHCO_3$ in 50 ml of water was added to the residue. The product (293 mg) was isolated by chloroform extraction and was identical with a sample of 8,9-anhydroerythromycin B 6,9-hemiacetal (8b) prepared as described by Kurath, et al.[7], by criteria of nmr, ir and tlc.

8,9-10,11-Diamhydroerythromycin B 6,9-Hemiacetal (11). — a.) A solution of 2.1 g of 10,11-anhydroerythromycin B (10) in 25 ml of glacial acetic acid was allowed to stand at room temperature for 4 hr. The product (2.0 g) was isolated as a white glass by the method employed for the isolation of 8b, above. Partition column chromatography of 800 mg of product gave 725 mg of pure 11 as a white glass after treatment with Darco G-60: $[\alpha]_D^{24}$ - 94°; λ_{max} 262nm (ϵ 2864); ir 3595, 3545, 3500-3400, 1723 cm^{-1}, nmr δ 5.12 (C-11 H), 2.29

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(NMe_2), 1.66 (C-10 Me), 1.59 (C-8 Me), 1.47 (C-6 Me).

Anal. Calcd for $C_{37}H_{63}O_{10}N$: C, 65.17; H, 9.32; N, 2.06. Found: C, 64.92; H, 9.41; N, 1.99.

b.) A solution prepared from 211 mg of 8-epi-10,11-anhydroerythromycin B (12) in 2.5 ml of glacial acetic acid was allowed to stand at room temperature for 4 hr. The product (169 mg) was isolated as described above, and proved identical with the sample of 8,9-10,11-diamhydroerythromycin B 6,9-hemiacetal (11) prepared from 10 as described above.

8-epi-11,12-Epoxyerythromycin A (16). — a.) A solution of 11,12-epoxyerythromycin A (14) in 26 ml of glacial acetic acid was allowed to stand at room temperature for 1 hr, and then added dropwise to a stirred suspension of 50 g of $NaHCO_3$ and 300 ml of water. Chloroform extraction of the resulting mixture gave 1.92 g of white glass. Partition column chromatography of 1.77 g gave 1.17 g of pure 8-epi-11,12-epoxyerythromycin A (16):$[\alpha]_D^{26}$ - 68°; ir 3600-3550, 3510-3430, 1727 cm^{-1}, nmr δ 3.35 (OMe), 2.72 (C-11 H, $J_{10,11}$ 10.0 Hz), 2.29 (NMe_2), 1.58 (C-6 Me).

Anal. Calcd for $C_{37}H_{65}O_{12}N$: C, 62.08; H, 9.15; N, 1.96 Found:C, 61.95; H, 9.27; N, 1.90.

Later fractions gave 37 mg of 8,9-10,11-diamhydroerythromycin A 6,9-hemiacetal (11) (See below).

b.) A solution of 1.20 g of 11,12-epoxyerythromycin A (14), 20 ml of acetic acid, and 20 ml of water was allowed to stand at room temperature for 24 hr. The product was isolated by chloroform extraction as described above to yield 1.1 g of 8-epi-11,12-

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epoxyerythromycin A (16). Partition column chromatography gave 536 mg of pure 16.

8,9-10,11-Diamhydroerythromycin A (17). — a.) A solution of 1.57 g of 10,11-anhydroerythromycin A (13) in 20 ml of glacial acetic acid was allowed to stand at room temperature for 4 hr. The usual workup and chloroform extraction gave 1.23 g of 17. Repeated partition column chromatography gave 527 mg of analytically pure 17: $[\alpha]_D^{26}$ - 88°; λ_{max} 267nm (ϵ 2628); ir 3605; 3554, 3500-3400, 1727 cm^{-1}, nmr δ 5.26 (C-11 H); 3.32 (OMe), 2.28 (NMe_2), 1.88 (C-10 Me), 1.60 (C-8 Me), 1.46 (C-6 Me).

Anal. Calcd for $C_{37}H_{63}O_{11}N$: C, 63.68; H, 9.10; N, 2.01. Found: C, 63.56; H, 9.29; N, 1.94.

b.) A solution of 1.98 g of 8-epi-10,11-anhydroerythromycin A (15) in 25 ml of glacial acetic acid was allowed to stand at room temperature for 24 hr. The usual workup followed by chloroform extraction gave 1.66 g of 8,9-10,11-diamhydroerythromycin A 6,9-hemiacetal (17).

c.) A solution of 205 mg of 11,12-epoxyerythromycin A (14) in 2.5 ml of glacial acetic acid was allowed to stand at room temperature for 46 hr. The usual workup gave 162 mg of white glass. Partition column chromatography of 120 mg gave 47 mg of pure 17.

d.) A solution of 300 mg of 8-epi-11,12-epoxyerythromycin A (16) in 3.8 ml of glacial acetic acid was allowed to stand at room temperature for 46 hr. The usual workup gave 248 mg of white glass.

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Partition column chromatography gave 133 mg of pure 17.

8-epi-10,11-Anhydroerythromycin A (15). — a.) A mixture prepared from 6.0 g of 10,11-anhydroerythromycin A (13), 3.9 g of DBU, 0.51 ml of methanesulfonic acid, and 51 ml of benzene was heated under reflux for 96 hr. The usual workup gave 4.82 g of glass, the nmr spectrum of which indicated a 3 to 1 mixture of 8-epi-10,11-anhydroerythromycin A (15) and 10,11-anhydroerythromycin A (13) based on the heights of the corresponding C-10 methyl protons. Pure 15 was isolated by partition column chromatography: $[\alpha]_D^{26}$ -59°; λ_{max} 231nm (ϵ 8801); ir 3604, 3550-3400, 1728, 1664 cm^{-1}, nmr δ 6.45 (C-11 H), 3.28 (OMe), 2.28 (NMe_2), 2.08 (C-10 Me).

Anal. Calcd for $C_{37}H_{65}O_{12}N$: C, 62.08; H, 9.15; N, 1.96. Found: C, 62.15; H, 9.34; N, 1.89.

b.) A mixture of 387 ml of 8-epi-11,12-epoxyerythromycin A (16), 243 mg of DBU, 0.032 ml of methanesulfonic acid and 3.22 ml of benzene was heated under reflux for 3 hr. The usual workup and benzene extraction gave 308 mg of 8-epi-10,11-anhydroerythromycin A (15).

8,9-Anhydro-11,12-epoxyerythromycin A 6,9-Hemiacetal (18). — A solution of 2.22 g of 11-O-methanesulfonyl-8,9-anhydroerythromycin A, 6,9-hemiacetal (20c), 3.0 g of DBU and 36 ml of benzene was heated under reflux for 18 hr. The usual workup followed by benzene extraction gave 1.74 g of white glass. Partition column chromatography of 1.10 g gave 834 mg of pure 8,9-anhydro-11,12-epoxyerythromycin A 6,9-hemiacetal: $[\alpha]_D^{26}$ -42°, ir 3590 (shoulder), 3550, 3500-3400,

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1727; nmr δ 3.28 (OMe), 2.66 (C-11 H, $J_{10,11}$ = 6.2 Hz), 2.28 (NMe_2), 1.62 (C-8 Me), 1.39 (C-6 Me).

Anal. Calcd for $C_{37}H_{63}O_{11}N$: C, 63.68; H, 9.10; N, 2.01. Found: C, 63.81; H, 9.14; N, 1.90.

Treatment of 8,9-Anhydro-11,12-epoxyerythromycin A 6,9-hemiacetal (18) with Glacial Acetic Acid. — A solution of 184 mg of 18 in 2.2 ml of glacial acetic acid was allowed to stand at room temperature for 1 hr and then added dropwise to a stirred suspension of 8.7 g of $NaHCO_3$ in 87 ml of water. Benzene extraction gave 161 mg of white glass. Partition column chromatography gave 38.4 mg of recovered 18, 39 mg of 8,9-10,11-dianhydroerythromycin A (17) and 17 mg of 8-epi-11,12-epoxyerythromycin A (16).

Treatment of 8,9-Anhydro-11,12-epoxyerythromycin A 6,9-hemiacetal (18), with 1:1 Acetic Acid–Water. — A solution of 612 mg of 18, 9.6 ml of acetic acid and 9.6 ml of water was allowed to stand at room temperature for 0.5 hr and then added dropwise to a stirred suspension of 30 g of $NaHCO_3$ in 300 ml of water. Chloroform extraction gave 641 mg of white glass. Partition column chromatography gave 297 mg of 11,12-epoxyerythromycin A (14) and 109 mg of 8-epi-11,12-epoxyerythromycin A (16).

Treatment of 8,9-10,11-Diamhydroerythromycin A 6,9-hemiacetal (17) with DBU in Benzene in the Presence of Methanesulfonic Acid and Water. — A solution of 704 mg of 17, 476 mg of DBU, 0.018 ml of water, 0.065 ml of methanesulfonic acid, and 6 ml of benzene was heated under reflux for 94 hr. The usual workup, and benzene extraction gave 585 mg of recovered 17.

cm^{-1}) to the lactone carbonyl absorption (1729 cm^{-1}) from 0.5 to 0.8. This established that the minor component was the hemiacetal tautomer **14b** which was largely converted to the hydroxy ketone tautomer **14a** on heating in deuteriochloroform.

A preparative attempt to convert the 1.2:1 mixture of **14a** and **14b** to a 2.4:1 mixture by heating a chloroform solution of **14** under reflux for 0.5 hr was unsuccessful. After evaporation of chloroform under reduced pressure and drying of the residue under high vacuum at 56° for 20 hr, the hydroxy ketone to hemiacetal ratio (**14a**:**14b**) was identical with that of the starting material (1.2:1) by criteria of both nmr and ir. This result is interpreted to indicate that the 2.4:1 ratio of **14a** to **14b** in the heated chloroform solution reverted to the original 1.2:1 ratio on evaporation of solvent.

An nmr spectrum of a freshly prepared sample of **14** in methanol-d_4 showed a ratio of hydroxy ketone to hemiacetal of 1.2. On heating at 56° for 0.5 hr, the ratio changed to 0.9 favoring the hemiacetal. The identities of the two components in methanol-d_4 is based on the intensity of the singlet at δ 1.63 attributed to the C-6 methyl of the hemiacetal **14b**, relative to the intensities of the two NMe_2 peaks observed.

A pure sample of the hemiacetal tautomer **14b** was isolated (70% recovery) by crystallization from ether. The tautomeric purity of **14b** was established from the nmr spectrum of a freshly prepared solution in deuteriochloroform. When the nmr spectrum was determined after the solution had remained at room temperature overnight it was found that the sample had reverted to a 2.3:1 mixture of **14a** to **14b**. When the solution was heated at 56° for 0.5 hr the ratio of **14a** to **14b** was found to be 2.4:1.

These data indicate that the tautomers **14a** and **14b** are interconvertible, but have a sufficiently high energy barrier to interconversion to preclude rapid equilibration at room temperature in chloroform solution.

In contrast to 11,12-epoxyerythromycin A, which exists as an interconvertible mixture of tautomers **14a** and **14b**, the following evidence indicates that 8-*epi*-11,12-epoxyerythromycin A exists exclusively as the hemiacetal (**16**).

(1) The nmr spectrum of a freshly prepared solution of **16** in $CDCl_3$ showed only one sharp NMe_2 peak and one sharp OMe peak, and otherwise indicated the presence of a single component. The appearance of the spectrum did not change on prolonged heating of the solution at 56°.

(2) The ir spectra of the pure C-8 epimeric hemiacetals **14b** and **16** (in deuteriochloroform) were virtually identical. Both showed only lactone carbonyl absoprtions at 1727 cm^{-1}. In contrast the 1.2:1 mixture of **14a** and **14b** showed both lactone (1729 cm^{-1}) and ketone (1708 cm^{-1}) absorptions.

(3) The nmr spectra of the hemiacetals **14b** and **16** showed singlet *C*-methyl absorptions at δ 1.66 and 1.57, respectively, tentatively assigned to the C-6 methyl protons. In contrast the hydroxy ketone **14a** shows no such absorption in the region between δ 1.40 and 2.30.

(4) The C-10 proton resonances of the hemiacetals **14b** and **16** appear at δ 2.4 ($J_{10,11}$ = 10.0 Hz) and 2.21 ($J_{10,11}$ = 10.0 Hz), respectively, while the C-10 proton resonance of the hydroxy ketone **14a** appears at δ 3.09 ($J_{10,11}$ = 10.0 Hz). This downfield shift of the C-10 proton resonance of **14a** relative to the hemiacetals is presumably the consequence of the presence in **14a** of the C-9 keto carbonyl.

Examination of Dreiding models of the hydroxy ketone and hemiacetal tautomers of 8-*epi*-11,12-epoxyerythromycin A suggests that relief of steric interaction between the C-6 and C-8 methyl groups, resulting from cyclization to the hemiacetal **16**, may be a major factor responsible for the existence of **16** as the sole observable tautomer. In contrast, no steric interaction between the C-6 and C-8 methyl groups of either the hydroxy ketone **14a** or the hemiacetal **14b** of 11,12-epoxyerythromycin A is apparent.

Circular Dichroism of the 10,11-Anhydroerythromycins. Circular dichroism determinations have shown that the C-8 epimeric 10,11-anhydroerythromycins have quite distinctive n $\rightarrow \pi^*$ transitions of the C-9 keto carbonyls. The 10,11-anhydro ketones with the natural configuration at C-8 show circular dichroism minima (**13**, $[\theta]_{340}$ −870; **10**, $[\theta]_{327}$ −2185) while the 8-*epi*-10,11-anhydro ketones show circular dichroism maxima (**15**, $[\theta]_{310}$ +1100; **12**, $[\theta]_{320}$ +1940). The signs of the n $\rightarrow \pi^*$ bands of the C-8 epimeric 3,5-di-*O*-acetylerythronolides B (**4**, $[\theta]_{335}$ −2130; **5**, $[\theta]_{304}$ +1620) confirm the assignments of Perun.[4] The relationship of the CD curves of **4** and **5** to that of 10,11-anhydrooleandromycin diacetate has been discussed by Celmer.[3a]

Antibacterial Activities. Antimicrobial activities of many of the modified erythromycins described above, against a cross section of bacteria, are shown in Table I. None of the compounds possess *in vitro* antibacterial activity approaching that of the parent erythromycins and most are devoid of activity against many strains except at extreme levels. Earlier reference was made to the predictions of Celmer,[3b] later abandoned,[3a] concerning the possible antibacterial benefit of C-8 epimerization. It should be noted that C-8 epimerization of erythromycin B drastically lowers *in vitro* activity against wild and resistant strains, thus conforming to the current view of Celmer.[3a]

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References and Notes

(1) Preliminary communications of this work appeared: *J. Amer. Chem. Soc.*, **95**, 592, 593 (1973).
(2) For a recent review, see W. Keller-Schierlein, *Progr. Chem. Org. Natur. Prod.*, **30** 314 (1973).
(3) (a) W. D. Celmer in "Symposium on Antibiotics," March 1–3, 1971, St.

Marguerite, Quebec, Canada, Butterworths, London, 1971, pp 413–453; *Pure Appl. Chem.*, No. 4, 28 (1971). (b) W. D. Celmer in "Biogenesis of Antibiotic Substances," Z. Vaněk and Z. Hostálek, Ed., Academic Press. New York, N. Y., 1965, Chapter 10.
(4) T. J. Perun, *J. Org. Chem.*, **32**, 2324 (1967).
(5) P. H. Jones, T. J. Perun, E. K. Rowley, and E. J. Baker, *J. Med. Chem.*, **15**, 631 (1972).
(6) The authors are grateful to Dr. T. J. Perun for suggesting the use of this reagent.
(7) P. Kurath, P. H. Jones, R. S. Egan, and T. J. Perun, *Experientia*, **27**, 362 (1971).
(8) J. R. Martin, R. S. Egan, T. J. Perun, and A. W. Goldstein, *Tetrahedron*, **29**, 935 (1973).
(9) R. S. Egan, Ph.D. Thesis, University of Illinois Medical Center, 1971.
(10) DBU is extremely caustic and should be used with care. Tests with rabbits have shown it to be instantly destructive of eye tissue.
(11) N. L. Oleinick and J. W. Corcoran, *J. Biol. Chem.*, **244**, 727 (1969).
(12) Obtained from several runs.

Studies on Resin Acids. IX. Synthesis and Stereochemistry of 6-Ketoabietatrienes[1]

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In an effort to explore the stereochemistry of 6-ketoabieta-8,11,13-trienes, 18-nor-5β-abieta-8,11,13-trien-6-one (**8**), 19-nor-5β-abieta-8,11,13-trien-6-one (**14**), 19-norabieta-8,11,13-trien-6-one (**3**), and abieta-8,11,13-trien-6-one (**1**) have been prepared. 19-Norabieta-8,11,13-triene (**7**) was converted to ketone **8** by the sequence oxidation to 18-norabieta-8,11,13-trien-7-one (**5**), reduction to the 7β-ol (**6**), dehydration to 18-norabieta-6,8,11,13-tetraene (**4**), oxidation to a mixture of glycols, and dehydration to **8**. 19-Norabieta-8,11,13-trien-6-one (**3**) was prepared by a similar route using 19-norabieta-8,11,13-trien-7-one (**19**) as starting material and also by isomerization of 19-nor-5β-abieta-8,11,13-trien-6-one (**14**). Ketone **14** was obtained by oxidation of 19-nor-5β-abieta-8,11,13-trien-6β-ol (**15**), which was the principal alcoholic product from the hydroboration–oxidation of 18-norabieta-4,8,11,13-tetraene (**9**). Prolonged treatment of **9** with diborane, followed by oxidation, gave a mixture of 19-nor-5β-abieta-8,11,13-trien-7α- and -7β-ol (**17** and **18**). Abieta-8,11,13-trien-6-one (**1**) was prepared from abieta-8,11,13-triene (**23**) by the method used for the synthesis of ketones **3** and **8**. The mechanism of the anomalous hydroboration of **9** and the conformations of the various 6-ketones are discussed.

Several naturally occurring compounds, among them taxodione[2] and maytenoquinone,[3] have been isolated which contain a keto group in the 6 position of an abietane ring system. In addition to these compounds, and their derivatives, the parent compound abieta-8,11,13-trien-6-one (**1**) has been prepared,[4] as have a few other structurally related ketones.[5] In the compounds of this type in which the stereochemistry about the A–B ring fusion has been discussed, it has been either shown or assumed that the stable ring juncture is trans. However, ketones similar to **1** are essentially 9-methyl-1-decalone systems, in which it is known that there is very little energy difference between the cis and trans isomers,[6] and in the trans isomer of **1** there is also a severe axial–axial interaction between the β-methyl group (C-19) at C-4 and the angular methyl. It would thus appear that for ketones such as **1** the cis isomer should be more stable. In order to explore this apparent stereochemical inconsistency, the synthesis of **1** has been reinvestigated, and the preparation of the 18- and 19-nor ketones (**2** and **3**) and their stereochemical preferences at C-5 studied.

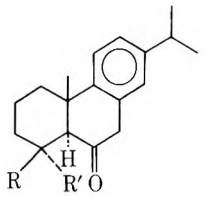
The obvious precursor of the 18-nor ketone (**2**), 18-norabieta-6,8,11,13-tetraene (**4**), was prepared from 18-norabieta-8,11,13-trien-7-one (**5**)[7] by hydride reduction to the 7β-ol (**6**) which gave olefin **4** on dehydration with toluenesulfonic acid in benzene. In order to ensure that no isomerization at C-5 had occurred under the conditions of the dehydration, olefin **4** was reduced to18-norabieta-8,11,13-triene (**7**).[8] The attempted direct conversion of ketone **5** to the olefin by reaction with toluenesulfonylhydrazine, followed by methyllithium,[9] gave a complex mixture containing no hydrocarbon.

Although olefins similar to **4** have been converted to the 6-ketones by various procedures,[4,5a] in our hands these did not prove efficient and an alternative route was chosen, which entailed oxidation of **4** to a stereoisomeric mixture of cis glycols using sodium chlorate–osmium tetroxide,[10] followed by treatment with hot formic acid to give the 6-ketone.

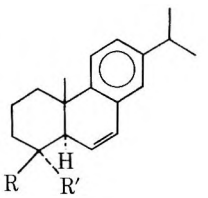
The nmr spectrum of the product ketone shows a secondary methyl signal at δ 0.84 with a coupling constant of 5 Hz, indicating that this group is equatorial,[11] consistent only with a cis A–B ring fusion and a steroidal conformation of these rings.[12] It is thus aparent that the product of this sequence is 18-nor-5β-abieta-8,11,13-trien-6-one (**8**), and that during the reaction with formic acid, isomerization to the more stable cis isomer has occurred.

19-Norabietatrien-6-one (**3**) was initially obtained *via* a fortuitous series of reactions resulting from the investigation of the hydroboration–oxidation of 18-norabieta-4,8,11,13-tetraene (**9**). It has been reported that hydroboration–oxidation of the mixture of olefins obtained by lead tetraacetate decarboxylation of abieta-8,11,13-trien-18-oic acid (dehydroabietic acid) affords, in addition to other products, 19-nor-5β-abieta-8,11,13-trien-7-one (**10**).[7] It was suggested that this ketone was probably derived from olefin **9** *via* 19-nor-5β-abieta-8,11,13-triene (**11**); however, this could not be confirmed. In subsequent work, attempts were made to obtain a homogeneous sample of hydrocarbon **9**; however, a practical method for preparation of this compound by acid-catalyzed isomerization of the mixture of olefins obtained from dehydroabietic acid could not be accomplished.[12b]

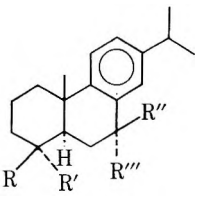
Attempted separation of a mixture of **9** and 18-nor-5β-abieta-3,8,11,13-tetraene (**12**)[12] by reaction with bis(3-methyl-2-butyl)borane, which has been utilized to separate trisubstituted from tetrasubstituted olefins, gave residual hydrocarbons with essentially the same composition as the starting mixture.[13] Both olefins apparently react with the reagent at nearly the same rate, and 18-nor-5β-abieta-8,11,13-trien-3α-ol (**13**),[12b] arising from olefin **12**, was isolated from the reaction. When the mixture of olefins from the decarboxylation of dehydroabietic acid[7] was treated



1, R = R′ = CH_3
2, R′ = CH_3; R′ = H
3, R = H; R′ = CH_3

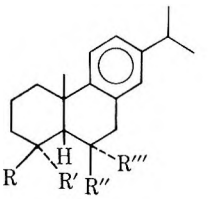


4, R = CH_3; R′ = H
21, R = H; R′ = CH_3
22, R = R′ = CH_3

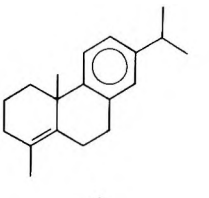


5, R = CH_3; R′ = H; R″ = R‴ = O
6, R = CH_3; R′ = R‴ = H; R″ = OH
7, R = CH_3; R′ = R″ = R‴ = H
19, R = H; R′ = CH_3; R″ = R‴ = O
20, R = R‴ = H; R′ = CH_3; R″ = OH

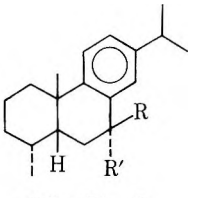
23, R = R′ = CH_3; R″ = R‴ = H
24, R = R′ = CH_3; R″ = H; R‴ = $OCOCH_3$
25, R = R′ = CH_3; R″ = H; R‴ = OH
26, R = R′ = CH_3; R″ = R‴ = O



8, R = CH_3; R′ = H; R″ = R‴ = O
14, R = H; R′ = CH_3; R″ = R‴ = O
15, R = R‴ = H; R′ = CH_3; R″ = OH
27, R = R′ = CH_3; R″ = R‴ = O



9



10, R = R′ = O
11, R = R′ = H
17, R = H; R′ = OH
18, R = OH; R′ = H

with bis(3-methyl-2-butyl)borane, there was obtained a mixture of **9** (41%) and 18-norabieta-3,8,11,13-tetraene (**12**, 5α H, 58%), from which **9** could be obtained by selective periodate–permanganate oxidation of the 3-olefin.[14]

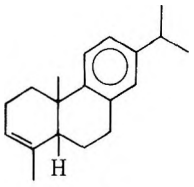
With a method available for the preparation of modest quantities of olefin **9**, uncontaminated by its isomers, the hydroboration–oxidation was carried out under the conditions reported previously.[7,12b] From this reaction there was obtained by careful chromatography an oily secondary alcohol in 43% yield. Controlled oxidation of this alcohol with Jones reagent afforded an unstable nonconjugated ketone,[15] the nmr spectrum of which permitted an unequivocal assignment of structure and stereochemistry. The C-10 methyl appears at δ 1.20, indicating that this compound almost certainly has a cis A–B ring fusion, with a steroidal conformation.[12] The secondary methyl group at C-4 appeared as a doublet (J = 7 Hz) at extremely high field (δ 0.52), which can only be accounted for by a cis ring fusion with the methyl group lying below the plane of the aromatic ring. The C-7 benzyl protons appear as an AB quartet (J = 20 Hz) at quite low field (δ 3.22 and 3.65), indicating that the carbonyl group is at C-6. The C-5 proton is a clear doublet at δ 2.38, with a coupling constant of 5 Hz consistent with a dihedral angle of approximately 60° between H-4 and H-5.[16] The only structure consistent with these data is 19-nor-5β-abieta-8,11,13-trien-6-one (**14**), which must exist in conformation **14a.**

Acid-catalyzed isomerization of **14** afforded 19-norabieta-8,11,13-trien-6-one (**3**), which has an equatorial secondary methyl group, as indicated by a coupling constant of 5 Hz for these protons.[11] The other spectral properties of this compound are in agreement with the assigned structure (see Experimental Section).

Since oxidation of the alcohol isolated from the hydroboration–oxidation sequence gave ketone **14**, this alcohol must be 19-nor-5β-abieta-8,11,13-trien-6β-ol (**15**), derived from olefin **9** by hydroboration, elimination to 19-norabieta-5,8,11,13-tetraene (**16**), and readdition of diborane. Although the thermal isomerization of alkylboranes is well known,[17a] there exist only a few examples of this type of reaction under mild conditions (*i.e.*, room temperature).[17b-e] The stereochemistry of **15** is based on the established stereochemistry of the derived ketone (**14**) and the fact that hydroboration is a stereospecific cis process.[18,19] The nmr spectrum of **15** shows a very low field (δ 1.38) angular methyl signal indicating a nonsteroidal conformation about the A–B ring fusion,[12] which is confirmed by the observation that the secondary methyl signals show a normal chemical shift (δ 1.09) with a coupling constant of 5 Hz, characteristic of an equatorial methyl group.[11]

When the hydroboration of **9** was carried out for a prolonged period, alcohol **15** could not be detected, but an inseparable mixture of two compounds was obtained as the only isolable, alcoholic product. That these were the epimeric 19-nor-5β-abieta-8,11,13-trien-7α- and -β-ols (**17** and **18**) was shown by the nmr spectrum of the mixture, which shows two C-10 methyl signals at δ 1.35 and 1.38, an equatorial secondary methyl signal at δ 0.96 (J = 6 Hz), and two low-field carbinol protons, a quasi-equatorial 7α proton (7β-ol) as a triplet (J_{app} = 3 Hz) at δ 4.48 and a quasi-axial 7β proton as a multiplet ($W_{1/2}$ = 19 Hz) at δ 4.00. Integration of the relative intensities of these protons indicated that the ratio of **18** to **17** was 3:2. Jones oxidation of the mixture afforded 19-nor-5β-abieta-8,11,13-trien-7-one (**10**).[7]

Although addition–elimination readdition sequences under mild hydroboration conditions have been reported previously,[17b-e] two successive such sequences is unusual. The stereochemical outcome of the first step of these reactions appears anomalous in that it involves attack of diborane from the more hindered β face of the molecule in contrast to the usually accepted mode of addition of this reagent. The most plausible mechanism for the general reaction of diborane with olefins is that suggested recently by Jones[20] which proposes the rapid, reversible formation of a π complex, followed by a rate-determining concerted conversion of this intermediate to the reaction products. Although the initial π complex derived from **9** should be formed more readily from the relatively unhindered α face of the molecule, the energy of activation leading to a 5α product, with an axial (4β) methyl group, would be considerably greater than that leading to a 5β-substituted product, in which there is no incipient axial–axial interaction between the secondary and angular methyl groups in the transition state. Also, the orientation of diborane in the initial π complex, assuming β attack, would almost certainly favor addition of boron at C-5, owing to the axial–axial interaction with the angular methyl group if boron were to



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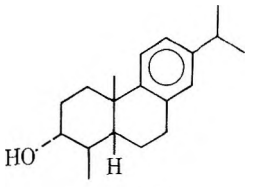

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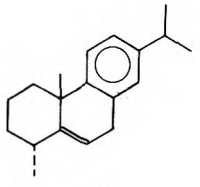

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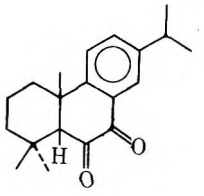

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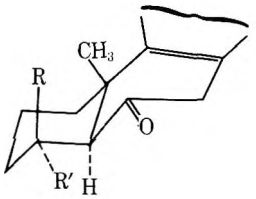
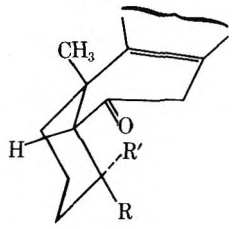
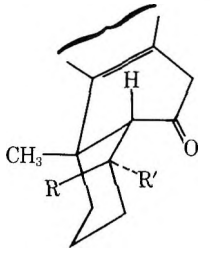


1a, R = R′ = CH_3
2a, R = CH_3; R′ = H
3a, R = H; R′ = CH_3



8a, R = CH_3; R′ = H
14a, R = H; R′ = CH_3
27a, R = R′ = CH_3



14b, R = H; R′ = CH_3
27b, R = R′ = CH_3

add from the β face of the molecule at C-4. The explanation for the β stereospecificity in the addition of diborane to **16** is not as apparent, however; examination of models of this olefin indicates that the α face of this molecule is concave and that attack from the β side may be preferred for that reason.

The structure of ketone **3**, obtained from the hydroboration–oxidation sequence, was confirmed by its synthesis *via* essentially the same route used for the preparation of 18-norabieta-8,11,13-trien-6-one (**2**). Borohydride reduction of 19-norabieta-8,11,13-trien-7-one (**19**) gave 19-norabieta-8,11,13-trien-7β-ol (**20**), which on dehydration afforded 19-norabieta-6,8,11,13-tetraene (**21**). Osmium tetroxide oxidation of **21**, followed by treatment of the mixed glycols with hot formic acid, gave ketone **3**, identical with that obtained from olefin **9** by the method described above.

Although the preparation of abieta-8,11,13-trien-6-one (**1**) from abieta-6,8,11,13-tetraene (**22**) by treatment with perbenzoic acid has been described,[4] and although a similar route has been used in the preparation of a related 6-ketone,[5a] experience in the preparation of ketone **2** indicated that not only was this not a particularly effective route for the preparation of **1**, but that the reported synthesis of olefin **22**[4] was probably not suitable for the preparation of quantities of this material.

Abieta-6,8,11,13-tetraene (**22**) was prepared most readily by a modification of the route used for the synthesis of olefins **4** and **21**. Lead tetraacetate oxidation of abieta-8,11,13-triene (**23**)[21] gave 7α-acetoxyabieta-8,11,13-triene (**24**), which on hydrolysis or metal hydride reduction afforded abieta-8,11,13-trien-7α-ol.[4] Pyrolysis of acetate **24** gave olefin **22**, although in poor yield, as did dehydration of the corresponding alcohol (**25**) with either phosphoryl chloride–pyridine or dimethyl sulfoxide.[22] As in the case of the preparation of olefins **4** and **21**, dehydration with toluenesulfonic acid–benzene gave the desired product (**22**) in acceptable yield. In contrast to the failure of the tosylhydrazone of ketone **5** to give an olefinic product, this reaction proceeded smoothly, although in mediocre yield when carried out on abieta-8,11,13-trien-7-one (**26**). The conversion of olefin **22** to abieta-8,11,13-trien-6-one (**1**) was carried out in the manner described above for the preparation of the 18-nor 5β-ketone (**2**). The initial preparation of this compound afforded a single ketone as expected from the reports of the earlier workers.[2-5] The nmr spectrum of this compound shows three methyl signals at δ 1.11, 1.17, and 1.32 which is consistent only with a trans-fused ketone of structure **1**.[12] The absence of a high-field methyl signal clearly contraindicates a cis steroidal ring fusion, which was expected if isomerization had occurred during dehydration. Attempted repetition of the dehydration of the glycols derived from olefin **22**, however, gave a mixture of three products, two of which were an inseparable mixture of **1** and, based on spectral data, the C-5 epimer of **1**, 5β-abieta-8,11,13-trien-6-one (**27**). The nmr spectrum of this mixture shows no high-field methyl signal, indicating that ketone **27** must exist preferentially in a nonsteroidal conformation, which is confirmed by the presence of a methyl signal at δ 1.56.[12] The third component of the mixture was an unstable yellow solid which showed the characteristic infrared absorptions of an α-diketone. The mass spectrum gave a parent ion at *m/e* 298, and the nmr spectrum has a methyl signal at δ 0.44. These data are consistent only with structure **28**, 5β-abieta-8,11,13-triene-6,7-dione, which must exist in a steroidal conformation and which is probably derived from ketone **27** by air oxidation. Acid-catalyzed isomerization of trans ketone **1** afforded the same mixture of cis and trans ketones obtained from the formic acid dehydration.

Although the conformational preferences of the various 6-substituted abietatriene derivatives described above seem secure based on their nmr spectra, several of these conformations are unexpected based on first-order conformational principles. As expected for the 6-ketone derived from 18-norabieta-8,11,13-triene, the cis isomer (**8**) is more stable than the trans (**2**). In the trans isomer (**2a**), there exists a severe axial–axial interaction between C-19 and the angular methyl group, which is relieved in the steroidal conformer of the cis isomer (**8a**).

It would be expected that19-nor-5β-abieta-8,11,13-trien-6-one (**14**) would exist as the nonsteroidal conformer (**14b**), in which the secondary methyl group is equatorial. However, the nmr spectrum of this compound clearly indicates that it is in the steroidal conformation, with an axial methyl group (**14a**). Examination of models shows that in the nonsteroidal conformation (**14b**), there exists a rather considerable steric interaction between C-18 and the carbonyl group. In contrast to the other 6-ketones in this series, the two benzylic protons at C-7 in ketone **14** are magnetically nonequivalent (δ 3.22 and 3.65). This difference in chemical shift can only be explained if the carbonyl group is not equidistant from each proton. These data are only consistent with a half-boat conformation for ring B, which relieves the rather severe interaction between C-19 and C-7 which exists in the half-chair conformer.

In the case of 19-nor-5β-abieta-8,11,13-trien-6β-ol (**15**), the precursor of ketone **14**, the nmr spectrum indicates that the compound is in the nonsteroidal conformation, and examination of models discloses that with an sp^3 hybrid car-

Experimental Section[24]

18-Norabieta-8,11,13-trien-7-one (5). - This material was prepared as previously described, however, the ketone, originally reported as an oil, gave crystals, mp 46-48° on standing. The other properties of this compound were identical to those reported earlier.[7]

18-Norabieta-8,11,13-trien-7α-ol (6). - To a stirred solution of 3 ml of a 70% solution of sodium bis 2-(methoxyethoxy) aluminum hydride (Red-Al) in benzene, dissolved in 20 ml of dry ether, was added slowly a solution of 1.059 g of 18-norabieta-8,11,13-trien-7-one (5) in 10 ml of dry ether. The solution was stirred at 25° under nitrogen for 4 hr. Excess hydride was decomposed with crushed ice and the inorganic salts dissolved in water. The reaction mixture was extracted with ether and the extracts dried, filtered, and evaporated to give 0.813 g (76%) of pale yellow gum which crystallized on standing. Recrystallization from hexane gave the analytical sample, mp 109-110°; nmr:[25] 1.01 (d, J=7Hz, C-4 methyl), 1.23 (s, C-10 methyl), 4.82 (m, H-7), 7.39 (br s, H-14).

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.93; H, 10.40.

18-Norabieta-6,8,11,13-tetraene (4). - A solution of 0.532 g of 18-norabieta-8,11,13-trien-7α-ol (6) in 15 ml of benzene was treated with 0.55 g of p-toluenesulfonic acid and heated at reflux, using a Dean-Stark trap, for 1 hr. After cooling, the solution was washed with successive portions of saturated sodium bicarbonate and saturated sodium chloride. The benzene layer was dried over magnesium sulfate, filtered, and evaporated to give 0.387 g of yellow oil. The crude product was dissolved in pentane and filtered through Merck alumina. Elution with pentane gave 0.337 g (67%) of colorless oil; ir 3.42μ; nmr 1.01 (d, J=7Hz, C-5 methyl), 1.04 (s, C-10 methyl), 5.78 (q, $J_{6,7}$=9.5Hz, $J_{5,7}$=3Hz, H-6), 6.40 (q, $J_{6,7}$ = 3Hz, H-7); mass spectrum m/e (rel intensity) 254 (100), 239 (40), 225 (8), 211 (15), 197 (58), 183 (15).[26]

A 0.048 g sample of the above material was hydrogenated (platinum oxide-ethanol, 50 psi, 25° for 10 min). The nmr spectrum of the hydrogenated product and comparative gas chromatography on an OV-17 column showed the hydrogenated material was 18-norabieta-8,11,13-triene (7).

18-Nor-5β-abieta-8,11,13-trien-6-one (8). - To a stirred solution of 0.256 g of sodium chlorate and a few crystals of osmium tetroxide in 15 ml of water was added 0.446 g of 18-norabieta-6,8,11,13-tetraene (4) in 5 ml of tetrahydrofuran. The reaction mixture was stirred at 25° for 6 hr and an additional 0.750 g of sodium chlorate was added. Stirring was continued at 25° for 14 hr when 25 ml of 10% sodium bisulfite solution was added and stirring continued an additional 1.5 hr. The reaction mixture was taken up in chloroform and the organic layer was washed with water, dried, filtered and evaporated to give 0.427 g of black gum which was dissolved in 40 ml of water and 2 ml of 30% sodium hydroxide solution. The mixture was heated at reflux for 16 hr after which the solvent was removed under vacuum and the product taken up in ether. The ether layer was washed with water, dried and the solvent removed to give 0.342 g of yellow gum, ir 2.87μ; the nmr shows no olefinic protons. This material is a mixture of the 6α, 7α and 6β, 7β-diols and was used in the subsequent step without purification.

A solution of 0.295 g of the mixed glycols in 10 ml of 98% formic acid was heated at reflux for 45 min. After cooling, the reaction mixture was poured over crushed ice and extracted with ether. The ether extracts were washed with water then with saturated sodium bicarbonate, dried and the solvent removed to give 0.265 g of brown oil which was dissolved in benzene and chromatographed on Woelm silica gel, Activity I. Elution with benzene-10% ethyl acetate gave 0.126 g of brown oil which was dissolved in benzene and filtered through Merck acid washed alumina. Elution with benzene gave 0.120 g (25%) of ketone 8 as an unstable pale yellow oil which was homogeneous to tlc (Silica Gel-G-benzene); ir 3.36 and 5.84μ; nmr ($CDCl_3$) 0.84 (d, J=5Hz, C-4 methyl), 1.06 (s, C-10 methyl), 3.61 (br, s, H-7); ORD: ϕ_{388} +902, ϕ_{339} +1210, ϕ_{334} +1434; mass spectrum m/e (rel intensity) 270 (59), 255 (100), 237 (56), 227 (10), 213 (10), 201 (20), 195 (17), 185 (17).[26]

Abieta-4,8,11,13-tetraene (9). - A solution of 10.11 g of the mixture of olefins obtained from dehydroabietic acid via lead tetraacetate decarboxylation[7,27] in 15 ml of tetrahydrofuran was added slowly to a solution of bis(3-methyl-2-butyl) borane prepared from 7.26 g of boron trifluoride etherate, 7.10 g of 2-methyl-2-butene and 1.43 g of sodium borohydride in 35 ml of tetrahydrofuran.[28] The reaction mixture was stirred at room temperature 2 hr, 20 ml of water were added dropwise, followed by 15 ml of 10% aqueous sodium hydroxide. To this mixture was then added slowly 15 ml of 30% hydrogen peroxide and the reaction mixture stirred at room temperature overnight. The aqueous layer was drawn off, extracted with ether, the ethereal extract was combined with the original organic phase and the combined extracts washed with brine, dried, and the solvents removed at reduced pressure to give a yellow oil. This oil was taken up in hexane and filtered through 200 g of Merck alumina. Elution with hexane gave 4.71 g of a mixture, which contained by glc 41% abieta-4,8,11,13-tetraene (9) and 59% 18-norabieta-3,8,11,13-tetraene (12, 5α-H). This hydrocarbon mixture was dissolved in 300 ml of t-butanol and added to a solution of 0.40 g of potassium permanganate, 25 g of sodium metaperiodate and 21 g of potassium carbonate in 850 ml of water. The reaction mixture was stirred at room temperature 84 hr, sodium metabisulfite was added until the reaction was colorless and the mixture was concentrated in vacuo to a small volume. After cooling, the residue was extracted with three portions of ether, which was combined, washed with brine, dried and the solvent removed at reduced pressure to give a pale yellow oil. This oil was taken up in hexane and filtered through Merck alumina to give 2.45 g of 18-norabieta-4,8,11,13-tetraene (9) contaminated with 13% of another hydrocarbon which, based on glc data, was one of the 18 or 19-norabietatrienes. The spectral properties of the reaction product were identical to those of a sample prepared previously.[7]

When 6.67 g of a mixture of 43% 18-norabieta-4,8,11,13-tetraene (9) and 57% 18-nor-5β-abieta-3,8,11,13-tetraene[12b] (12) was treated with bis(3-methyl-2-butyl) borane there was obtained 4.24 g of a mixture containing 42% olefin 9, 58% olefin 12 and 0.760 g of a mixture of alcohols from which 0.099 g of 18-nor-5β-abieta-8,11,13-trien-3α-ol (13),[12b] mp and mmp, 135-136° could be isolated.

Hydroboration of 18-norabieta-4,8,11,13-tetraene (9). A. - To a solution of 0.500 g of olefin 9 (87% purity, see above) in 10 ml of dry tetrahydrofuran containing 0.25 g of lithium aluminum hydride and maintained at 0° was added dropwise 1.0 ml of boron trifluoride etherate in 15 ml of tetrahydrofuran. The reaction mixture was stirred at 0° for one hr and at ambient temperature for an additional 2 hr. The excess diborane was decomposed by the dropwise addition of ice water, 15 ml of 10% aqueous sodium hydroxide were added, the reaction mixture was cooled to 0° and 13 ml of 30% hydrogen peroxide were added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 18 hr. The aqueous layer was drawn off and extracted with two portions of ether which were combined with the original tetrahydrofuran solution, washed with brine, dried, and the solvent removed to give 0.548 g of almost colorless oil. This oil was dissolved in hexane and chromatographed on 30 g of Woelm activity II neutral alumina. Elution with hexane gave 0.047 g (9%) of a mixture of approximately equal portions of two norabieta-8,11,13-trienes. On the basis of nmr and glc data these are 18 and 19-nor-5β-abieta-8,11,13-triene.[12b] Elution with benzene-methylene chloride gave 0.191 (43%) of 19-nor-5β-abieta-8,11,13-trien-6β-ol (15) as a colorless oil: ir 2.98μ; nmr 1.09 (d, J=5Hz, C-4 methyl), 2.78 (q, J_{app} 7Hz, 12Hz, H-7), 4.05 (q, J_{app} 7Hz, 12Hz, H-6); mass spectrum m/e (rel intensity) 272 (43), 270 (53), 257(58), 255 (100), 254 (37), 239 (65), 237 (40), 201 (83), 199 (51), 197 (65), 187 (91). For analysis a small sample of this material was rechromatographed under the conditions described above.

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.66; H, 10.36.

The later fractions eluted with the same solvent system gave an additional 0.050 g of impure 15, which on the basis of nmr data (see below) was contaminated with the 7-ols (17 and 18).

B. - The hydroboration of 0.463 g of olefin 9 was carried out as described above, however, the reaction with diborane was allowed to proceed for 18 hr. Isolation of the reaction products in the usual manner gave 0.427 g of a viscous oil. This oil was taken up in hexane and chromatographed on 30 g of Woelm neutral alumina, Activity II. Elution with hexane gave 0.154 g of starting olefin, while benzene-methylene chloride (4 to 1) gave 0.125 g (38%, based on starting material consumed) of a mixture of 19-nor-5β-abieta-8,11,13-trien-7α and 7β-ols (17 and 18) as a colorless oil. Although this material was homogeneous to tlc (silica gel-G, benzene-ethyl acetate, 8 to 1), the nmr spectrum clearly showed the presence of two alcohols: ir; 2.98, 6.23μ; nmr 0.92 (d, J=6Hz, C-4 methyl), 1.35, 1.38 (s, C-10 methyls), 4.00 (m $W_{1/2}$ 19Hz, 7βH, 0.4 protons), 4.48 (t, J_{app} 3Hz, 7αH, 0.6 protons); mass spectrum m/e (rel intensity) 272 (60), 258 (14), 257 (51), 254 (17), 240 (20), 239 (100), 229 (36), 211 (18), 201 (43), 197 (80), 186 (38), 182 (28), 162 (42), 159 (36), 141 (46).

19-Nor-5β-abieta-8,11,13-trien-6-one (14). - To a solution of 0.125 g of 19-nor-5β-abieta-8,11,13-trien-6β-ol (15) in 7 ml of acetone at 0° was added dropwise 0.47 ml (1.05 equiv.) of Jones reagent. The reaction mixture was stirred at 0° for 5 min, methanol was added to destroy the excess oxidizing agent and the reaction mixture was poured into water. The resulting suspension was extracted with two portions of ether, the ethereal extracts were combined, washed with water and brine, dried and the solvent removed at reduced pressure to give 0.100 g (80%) of ketone 14 as an unstable pale yellow oil, which was homogeneous to tlc (silica gel G, benzene); ir 5.87, 6.22μ; nmr 0.52 (d, J=7Hz, C-4 methyl), 1.20 (s, C-10 methyl), 2.38 (d, J=5Hz, H-5), 3.22 (d, J=20Hz, H-7), 3.65 (d, J=20Hz, H-7); ORD (c = 0.00053) ϕ_{400} + 700; ϕ_{338} + 920; ϕ_{326} + 1540; ϕ_{317} + 2200; ϕ_{300} 0 ϕ_{276} - 11200; mass spectrum m/e (rel intensity) 270 (75), 256 (21), 255 (100), 238 (12), 237 (58), 227 (21), 201 (88), 200 (21), 199 (25), 195 (21), 187 (33), 185 (38).[26]

19-Norabieta-8,11,13-trien-7β-ol (20). - To a solution of 0.370 g of 19-norabieta-8,11,13-trien-7-one (19)[7] in 20 ml of 95% ethanol was added 1.0 g of sodium borohydride. The mixture was heated at reflux 2.5 hr, cooled, poured into water and extracted with three portions of ether. The ether extracts were washed first with water, then with brine, dried and the solvent removed to give 0.307 g (83%) of alcohol 20 as a pale yellow glass which was essentially homogeneous to tlc (silica-gel-G, benzene-ethyl acetate 8 to 1), ir 2.85μ; nmr 0.92 (d, J=5Hz, C-4 methyl), 1.13 (s, C-10 methyl), 4.70 (m, H-7). For analysis, a small sample of the compound was dissolved in benzene and chromatographed on Woelm activity II neutral alumina. Elution with benzene-methylene chloride gave the analytical sample as a colorless glass.

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.64; H, 10.44.

19-Norabieta-6,8,11,13-tetraene (21). - To a solution of 0.307 g of alcohol 20 in 25 ml benzene was added 0.040 g of toluenesulfonic acid. The reaction was carried out and the product isolated as described above for the preparation of 18-norabieta-6,8,11,13-tetraene (4). Chromatography on Merck alumina gave 0.194 g (67%) of colorless oil which was homogeneous to tlc (silica gel-G, hexane); nmr 0.98 (d, J=5Hz, C-4 methyl), 1.00 (s, C-10 methyl), 5.88 (q, $J_{6,7}$=8Hz, $J_{5,6}$=2Hz, H-6), 6.42 (q, $J_{6,7}$=8Hz, $J_{5,7}$=3Hz).

Anal. Calcd for $C_{19}H_{26}$: C, 89.70; H, 10.30. Found: C, 89.55; H, 10.43

19-Norabieta-8,11,13-trien-6-one (3). A. - To a solution of 0.084 g of ketone (14) in 5 ml of diglyme was added 0.5 ml of 2 N hydrochloric acid and the mixture was heated on the steam bath 1 hr. The reaction mixture was poured into water and extracted with two portions of ether, the ethereal extracts were combined, washed with water, 10% aqueous sodium bicarbonate and brine, dried and the solvent removed to give 0.054 g (64%) of ketone 3 as a yellow oil. This material was combined with 0.041 g from a previous run, dissolved in benzene and filtered through 5 g of Merck acid washed alumina to give 0.069 g of pure (tlc) ketone as an unstable, pale yellow oil; ir 5.81, 6.23μ; nmr 0.92 (d, J=5Hz, C-4 methyl), 0.95 (s, C-10 methyl), 2.21 (br s, H-5), 3.34 (br s, H-7); ORD (c = 0.00038) ϕ_{400} + 1,300; ϕ_{360} + 2,000; ϕ_{326} + 3,000; ϕ_{296} - 4,900; mass spectrum m/e (rel intensity) 270 (50), 255 (100), 254 (43), 239 (43), 237 (64), 197 (21), 195 (19), 184 (29).[26]

B. - To a solution of 1.112 g of 19-norabieta-6,8,11,13-tetraene (21) in 25 ml of pyridine was added 1.00 g of osmium tetroxide. The reaction mixture was stirred at room temperature for 52 hr; 30 ml of 10% aqueous sodium bisulfite and 15 ml of pyridine were added. After stirring 2 hr, the reaction mixture was poured into water and extracted with two portions of methylene chloride. The extracts were combined, washed with water, three portions of 10% hydrochloric acid and again with water. After drying and removing the solvent there was obtained 1.133 g of a mixture of diols as a pale yellow glass, which was used in the subsequent step without purification.

A solution of 1.004 g of the mixed diols in 50 ml of 98% formic acid was heated at reflux and the product isolated as described above in the preparation of 18-nor-5β-abieta-8,11,13-trien-6-one. After chromatography there was obtained 0.563 g of ketone (3) as a pale yellow oil. This material was identical to that described in part A.

19-Nor-5β-abieta-8,11,13-trien-7-one (10). - To a solution of 0.077 g of the mixture of 7α and 7β-ols (17 and 18) described above in 5 ml of acetone was added, with stirring at 0°, 0.150 ml (1.05 equiv.) of Jones' reagent. The reaction mixture was stirred at 0° for 10 min, methanol was added and the mixture diluted with water and extracted with two portions of ether. The ethereal extracts were combined, washed with brine, dried and the solvent removed to give 0.044 g (57%) of ketone 10 as a colorless oil which crystallized on standing. Recrystallization from hexane gave white crystals mp 97-100°, mmp 99-101°, UV, 254 nm (4.04), 303 (3.31). The infrared spectrum was identical to that of material reported previously.[7]

7β-Acetoxyabieta-8,11,13-triene (24). - To a solution of 4.16 g of abieta-8,11,13-triene (23) in 32 ml of glacial acetic acid was added 8.0 g of lead tetraacetate and the mixture heated on a steam bath. After 2 hr an additional 4.0 g of lead tetraacetate was added and heating was continued 2 hr. The reaction mixture was diluted with water and extracted with ether. The ether layer was washed with successive portions of water and 5% sodium bicarbonate solution until the washings were basic to litmus, dried and the solvent removed to give 4.27 g of dark yellow oil. The crude product was dissolved in hexane and chromatographed on Merck acid washed alumina. Elution with hexane gave 1.738 g (35%) of acetate 24 as a colorless oil which crystallized on standing. Recrystallization from methanol-water gave white needles, m.p. 127-128° (dec.); ir 3.46 and 5.86μ; nmr 0.88 (s, C-4 methyls), 1.11 (s, C-10 methyl), 5.64 (t, J=5Hz, H-7).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.22; H, 9.86.

In subsequent experiments the crude product was hydrolyzed directly to the 7-ol.

Abieta-8,11,13-trien-7α-ol (25). A. - To a solution of 0.904 g of acetate 24 in 25 ml of 5% methanolic potassium hydroxide was heated at reflux for 4 hr. The reaction mixture was poured into water and extracted with ether. The ether extracts were washed with water, dried, and the solvent removed to give 0.645 g (82%) of alcohol 25 as a colorless oil; ir 2.98μ, nmr 0.91 (s, C-4β methyl), 1.10 (s, C-10 methyl), 1.20 (s, C-4α methyl), 4.68 (H-7). Although this compound was previously reported as a solid, mp 78-80°,[4] in our hands it failed to crystallize.

B. - To a solution of 0.665 g of acetate 25 in 15 ml of dry ether was added 1.5 ml of Red-Al in benzene. The reaction mixture was stirred under nitrogen for 4 hr, the excess Red-Al was destroyed with ice and the reaction mixture poured into water. The aqueous layer was drawn off, extracted with ether, and the ethereal extracts combined and washed with water. After drying, the solvents were removed to give 0.527 g (91%) of alcohol 25, identical to that prepared in part A above.

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Abieta-6,8,11,13-tetraene (22). A. - To a solution of 1.58 g of alcohol 25 in 10 ml of dry pyridine was added dropwise 2.0 ml of phosphoryl chloride. The reaction mixture was heated on a steam bath for 1 hr, diluted with water, and extracted with three 10 ml portions of ether. The extracts were combined, washed with 6N hydrochloric acid, dried over magnesium sulfate, filtered, and evaporated to give 0.250 g (17%) of colorless oil; ir 3.44, 6.05μ; nmr 0.93 (s, C-10 methyl), 1.01 (s, C-4 methyls), 5.62 (q, $J_{5,6}$=3Hz, $J_{6,7}$=9.5 Hz, H-7), 6.13 (q, $J_{5,7}$=3Hz, $J_{6,7}$ =9Hz, H-7). This material has been reported as a solid, mp 20°,[4] however, in our hands it did not crystallize at 0°.

B. - A solution of 0.250 g of alcohol 25 in 2 ml of dimethylsulfoxide was heated at 155° for 14 hr. After cooling the reaction mixture was poured into water and extracted with hexane. The extracts were dried, filtered and the solvent removed to give 0.042 g (18%) of colorless oil, identical to the material prepared above.

C. - A 0.289 g sample of acetate 24 was pyrolyzed under nitrogen at 155° for 10 min. After cooling, the reaction products were dissolved in hexane and the solution washed with successive portions of water and 5% aqueous sodium hydroxide. The hexane extracts were dried and the solvent removed to give 0.083 g (35%) of colorless oil the infrared and nmr spectra of which are identical to those reported in A above.

D. - To a stirred solution of 1.56 g of p-toluenesulfonylhydrazine in 15 ml of dry tetrahydrofuran was added 2.00 g of abieta-8,11,13-trien-7-one (26) and 5 drops of concentrated hydrochloric acid. The mixture was stirred and heated at reflux for 13 hr then cooled to 5°. To the cold stirred mixture was added 10 ml of methyllithium over a 30 min period. After 15 min an additional 8 ml of methyllithium was added and stirring continued for 30 min at 5°. Excess methyllithium was decomposed with crushed ice and the reaction mixture was extracted with hexane. The extracts were dried and evaporated to give 1.66 g of yellow oil. Chromatography on Merck neutral alumina and elution with hexane gave 0.750 g (40%) of colorless oil identical to the material described in part A.

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E. - A solution of 2.10 g of alcohol 25 in 40 ml of benzene was added to a solution of 0.237 g of p-toluenesulfonic acid in 10 ml of benzene. The reaction was carried out and the product isolated as described above for the preparation of 18-norabieta-6,8,11,13-tetraene (4). Chromatography on Merck alumina gave 1.03 g (52%) of a very pale yellow oil identical to the material described in part A.

Abieta-8,11,13-trien-6-one (1). - The preparation of ketone 1 was carried out in the same manner as described for the preparation of 18-nor-5β-abieta-8,11,13-trien-6-one (8). From 0.501 g of olefin 22, there was obtained as a crude product 0.183 g of a greenish yellow gum. This material was dissolved in hexane and chromatographed on Merck acid washed alumina. Elution with hexane gave 0.100 g of pale yellow oil which was not homogeneous to tlc. Rechromatography of 0.086 g of this material on Woelm acidic alumina, Activity II, and elution with hexane-benzene (2:1) gave 0.033 g of ketone 1 as an unstable pale yellow oil which was homogeneous to tlc (silica gel-benzene); ir 5.84μ(reported, 5.83μ[4]); nmr 1.11 (s, C-4 methyl), 1.17 (s, C-10 methyl), 1.32 (s, C-4 methyl), 2.42 (br, s, H-5), 3.61 (br s, H-7), ORD: C=0.00225. ϕ_{328} + 8463; mass spectrum, m/e (rel intensity) 284 (56), 269 (100), 251 (11), 241 (17), 227 (33), 213 (22), 199 (39), 197 (22). Although this material has been reported as a solid, mp 40°,[4] in our hands it failed to crystallize.

When an attempt was made to repeat this experiment using 0.364 g of diol mixture in 15 ml of 98% formic acid there was obtained 0.345 g of greenish yellow gum. This material was dissolved in hexane and chromatographed on Merck acid washed alumina. Elution with hexane gave 0.130 g of yellow oil, while elution with benzene gave 0.087 g of dark yellow oil. Neither fraction was homogeneous to tlc. The fractions were combined, dissolved in hexane and rechromatographed on Woelm silica gel, Activity I.

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Elution with hexane-benzene (1:1) gave 0.054 g of a mixture of ketones 1 and 27 as a pale yellow oil which showed two spots of almost identical R_f on tlc (silica gel-benzene); ir 3.40 and 5.84μ; nmr 1.11 (s, C-4 methyl, 5α), 1.14 (s, C-10 methyl, 5α), 1.32 (s, C-4 methyl, 5α), 1.48 (s, C-4 methyl, 5β), 1.56 (s, C-10 methyl, 5β). 2.43 (br, s, H-5), 3.61 (br, s, H-7); mass spectrum, m/e (rel intensity) 284 (87), 269 (100, 241 (27), 227 (70), 199 (73).

Elution with benzene gave 0.062 g of yellow oil which crystallized on standing. Recrystallization from hexane gave bright yellow crystals of 5β-abieta-8,11,13-trien-6,7-dione (28) m.p. 89-91°; ir (CCl_4) 3.39, 5.81, 5.94μ; nmr 40.44 (s, C-4α-methyl), 1.01 (s, C-4β-methyl), 1.26 (s, C-10 methyl), 2.71 (br, s, H-5), 8.01 (d, J = 2H, H-14). Mass spectrum m/e (rel intensity) 298 (46), 283 (7), 270 (27), 255 (69), 239 (100), 214 (69). This material decomposed on attempted purification for analysis.

Isomerization of abieta-8,11,13-trien-6-one (1). - To a solution of 0.030 g of ketone 1 in 3 ml of diglyme was added 3.0 ml of 2N hydrochloric acid, the mixture was heated on a steam bath for 18 hr, poured into water and extracted with two portions of ether. The extracts were combined, washed with water, dried and evaporated to give 0.028 g of brown gum. The crude product was dissolved in benzene and chromatographed on Merck acid washed alumina. Elution with benzene gave 0.017 g of brown oil which shows two spots of nearly identical R_f value of tlc (silica gel-G-benzene). The spectral properties of this material were identical to those of the mixture of ketones 1 and 27 described above.

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bon at C-6, the equatorial methyl group at C-4 is gauche to both C-6 substituents, in contrast to the situation which prevails when C-6 is trigonal. As expected, ketone **14** proved unstable relative to the trans isomer (**3**) in which the secondary methyl group is equatorial (**3a**).

It was expected that if 5β-abieta-8,11,13-trien-6-one (**27**) could be obtained from the trans ketone, it would exist in the steroidal conformation (**27a**). However, the nmr data for the mixture of ketones obtained by isomerization clearly indicates that this is not the case, and that this compound exists in the nonsteroidal conformation (**27b**) in spite of the axial–axial methyl interaction. Although the reasons for this are not immediately obvious, a study of the models indicates that in **27b** with a half-boat conformation for ring B there exists a moderate interaction between the carbonyl group and C-19, while in the half-chair conformation there is a severe interaction between C-7 and C-18. Some confirmation for the latter conclusion is found in the fact that dione **28**, in which C-7 is trigonal, exists in the steroidal conformation.

Although the earlier workers[2-5] found no evidence for an equilibrium between cis and trans 6-ketones similar to **27** and **1**, it is quite apparent that such an equilibrium can be established under vigorous conditions. It was noted by Wenkert that xanthoperol, a 6,7-diketone similar to **28**, was resistant to enolization, owing to very unfavorable nonbonded interactions between C-18 and the oxygen at C-6 in the enol.[23] Similar interactions would exist in the enol derived from **1** or **27** in which the double bond is directed toward C-5, and we suggest that this steric inhibition of enolization which would cause isomerization is responsible for the reported observations regarding the stereochemistry at C-5 in ketones similar to **1**.[2-5]

Registry No.—**1**, 15372-59-5; **3**, 51820-96-3; **4**, 51838-79-0; **5**, 22566-08-1; **6**, 51820-97-4; **8**, 51820-98-5; **9**, 23963-77-1; **10**, 22566-11-6; **14**, 51820-99-6; **15**, 51829-69-7; **17**, 51821-00-2; **18**, 51821-01-3; **19**, 22566-09-2; **20**, 51821-02-4; **21**, 51821-03-5; **22**, 26906-88-7; **23**, 19407-28-4; **24**, 51821-04-6; **25**, 26920-02-5; **26**, 26920-03-6; **27**, 51821-05-7; **28**, 51821-06-8.

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References and Notes

(1) Part VIII: J. W. Huffman and J. J. Gibbs, *J. Org. Chem.*, **38,** 2732 (1973).
(2) S. M. Kupchan, A. Karim, and C. Marcks, *J. Amer. Chem. Soc.*, **90,** 5923 (1968).
(3) L. D. Martin, *Tetrahedron*, **29,** 2553 (1973).
(4) G. Defaye-Duchateau, *Bull. Soc. Chim. Fr.*, 1469 (1964).
(5) (a) K. Mori and Matsui, *Tetrahedron*, **26,** 3467 (1970); (b) R. C. Cambie and R. A. Franich, *Aust. J. Chem.*, **24,** 571 (1971).
(6) A. Ross, P. A. Smith, and A. S. Dreiding, *J. Org. Chem.*, **20,** 905 (1955).
(7) J. W. Huffman, *J. Org. Chem.*, **35,** 478 (1970).
(8) A. W. Burgstahler and J. N. Marx, *J. Org. Chem.*, **34,** 1562 (1969).
(9) (a) R. H. Shapiro and M. J. Heath, *J. Amer. Chem. Soc.*, **89,** 5734 (1967); (b) R. H. Shapiro and J. H. Duncan, *Org. Syn.*, **51,** 66 (1971).
(10) L. Blaha, J. Weichet, J. Zvachek, S. Smolik, and B. Kahac, *Collect. Czech. Chem. Commun.*, **25,** 237 (1960).
(11) F. Johnson, N. A. Starkousky, and W. D. Curowitz, *J. Amer. Chem. Soc.*, **87,** 3492 (1965).
(12) (a) E. Wenkert, A. Alonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30,** 713 (1965); (b) J. W. Huffman, *ibid.*, **37,** 17 (1972). The effect of steroidal *vs.* nonsteroidal conformations on the chemical shift of the angular methyl group in 5β-abieta-8,11,13-triene derivatives is also discussed in some detail in ref 7.
(13) R. S. Monson, "Advanced Organic Synthesis," Academic Press, New York, N. Y., 1971, p 37.
(14) C. R. Bennett, R. C. Cambie, R. A. Franich, and T. J. Fullerton, *Aust. J. Chem.*, **22,** 1711 (1969), have reported a similar selective oxidation, which could not be reproduced under their conditions (see Experimental Section). Although *a priori* one would expect that **9** and **12** could be separated in a similar manner, this mixture was inert to periodate–permanganate.
(15) The use of excess Jones reagent or dimethyl sulfoxide–acetic anhydride [D. J. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **87,** 4214 (1965)] gave complex mixtures from which no ketone could be isolated.
(16) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 51.
(17) (a) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962; (b) P. Pernelle and G. Ourisson, *J. Org. Chem.*, **30,** 1744 (1965); (c) W. Herz and J. Schmid, *ibid.*, **34,** 3464 (1969); (d) A. M. Krubiner, N. Gottfried, and E. P. Oliveto, *ibid.*, **33,** 1715 (1968); (e) B. E. Cross and P. L. Myers, *J. Chem. Soc. C*, 471 (1968).
(18) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 109–110, and many references therein.
(19) It might be argued that the 6-ol could be derived from a 6,8,11,13-abietatetraene. However, it has been reported (ref 4) that hydroboration of abieta-6,8,11,13-tetraene gives a mixture of 6- and 7-ols. Hydroboration of 18-norabieta-6,8,11,13-tetraene (**4**) gives the 7α-ol as the major product: J. W. Huffman and J. J. Gibbs, unpublished work.
(20) P. R. Jones, *J. Org. Chem.*, **37,** 1886 (1972). This author has pointed out that the generally accepted four-centered transition state mechanism for the hydroboration reaction suggested by Brown [ref 17a, p 145; see also H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **82,** 4708 (1960); **83,** 2544 (1961)] has a significant symmetry barrier.

(21) M. Kitadani, A. Yoshikoski, Y. Kitahara, J. Campello, J. D. McChesney, D. J. Watts, and E. Wenkert, *Chem. Pharm. Bull.*, **18**, 407 (1970), have reported the preparation of this compound by the lithium aluminum hydride reduction of 18-tosyloxyabieta-8,11,13-triene; however, in our hands this reduction failed. Hydrocarbon **23** was prepared by Wolff–Kishner reduction of the aldehyde derived from dehydroabietic acid by a modification of the procedure described in ref 8.
(22) V. J. Traynelis and W. L. Hergenrother, *J. Org. Chem.*, **27**, 2377 (1962).
(23) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **80**, 211 (1958).
(24) Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were taken as films or potassium bromide pellets on a Perkin-Elmer Model 137 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60 spectrometer using deuteriochloroform as a solvent and tetramethylsilane as an internal standard. Signals are reported in parts per million relative to this standard (δ). Optical rotatory dispersion and circular dichroism measurements were made in methanol using a Jasco ORD/UV-5 spectropolarimeter. Glc data were obtained using an F and M Model 810 chromatograph with a 10 ft × 0.125 in. OV-17 on Chromosorb W column at a temperature of 260°. Mass spectra were determined using a Du Pont 21-4'0 mass spectrometer at 70 eV ionization potential. Unless otherwise noted, all compounds were homogeneous by tlc and/or glc.
(25) For this and all compounds in this series the isopropyl group appears as a doublet, J = 6–7 Hz, at δ 1.20 ± 0.05. H-15 is a multiplet centered in the region of δ 2.80.
(26) This compound was unstable, and satisfactory analyical data could not be obtained.
(27) J. W. Huffman and P. G. Arapakos, *J. Org. Chem.*, **30**, 1604 (1965).
(28) R. A. Benkeser and E. M. Kaiser, *J. Org. Chem.*, **29**, 955 (1964).

Synthesis of Prostaglandins by Conjugate Addition and Alkylation of a Directed Enolate Ion. 11-Deoxyprostaglandins[1]

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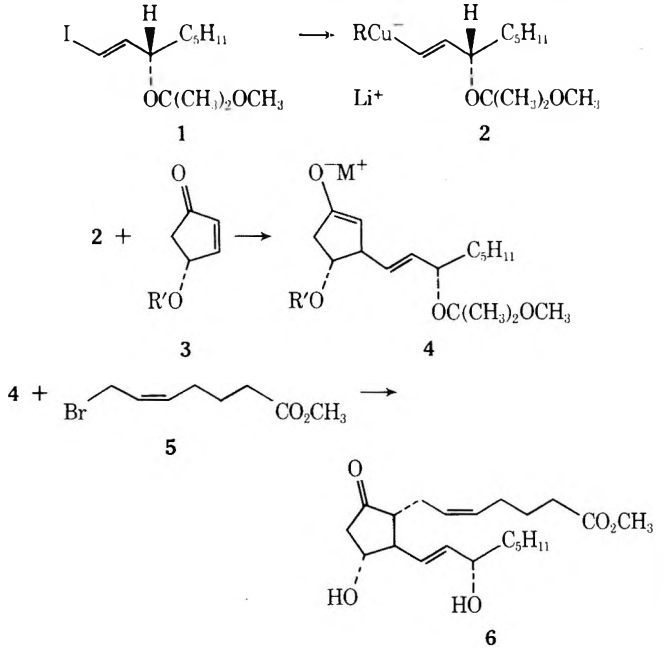
Bis[*trans*-3-(2'-methoxy-2'-prop-2'-oxy)-1-octenyl]copper lithium (**2**) has been added to cyclopent-2-enone and the resultant enolate ion converted to the silyl enol ether **8**. This silyl enol ether was then alkylated with methyl *cis*-7-bromooct-5-enoate to yield 11-deoxyprostaglandin E_2 methyl ester (**10**). By similar reactions (±)-5,6-dehydro-11-deoxyprostaglandin E_2 and (±)-11,15-deoxyprostaglandin E_2 methyl esters (**15** and **20**) were prepared.

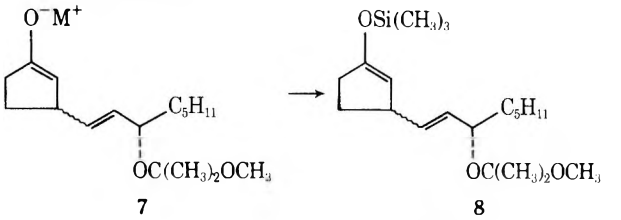
Conjugate addition of an organocopper reagent followed by alkylation of the resulting nonequilibrated enolate ion is a convenient method for converting α,β-unsaturated ketones to vicinally dialkylated ketones.[2,3] The use of the cuprate derived from 3-(*S*)-*trans*-1-iodo-1-octen-3-ol in prostaglandin synthesis *via* conjugate addition to 2-alkylated cyclopentenones has been actively investigated in these laboratories[4] and elsewhere.[5] With the goal of developing a short and converging synthesis of prostaglandins, we were interested in employing this conjugate addition in conjunction with an alkylation of the resultant enolate ion (**4**) to a protected 4-hydroxycyclopent-2-enone, *e.g.*, **3**, in



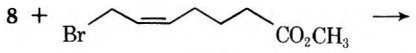
order to introduce both functionalized side chains characteristic of these natural products. Based on steric considerations, we expected that such an approach would give prostaglandins, incorporating mainly the trans,trans stereochemical relationship at carbons 8, 11, and 12, while the use of the cuprate **2** obtained from 3-(*S*)-*trans*-1-iodo-1-octen-3-ol methoxy isopropyl ether (**1**)[4] would establish the natural α configuration at C-15. Thus the prostaglandins resulting from such a sequence of reactions would be predominantly a mixture of PGE_2 (**6**) and 8,11,12-*epi*-PGE_2.[6]

We wish to describe here the application of this method to the synthesis of several 11-deoxyprostaglandins.

11-Deoxyprostaglandin E_2 (10).[7] Our initial attempts to alkylate enolate ion **7** obtained from the addition of achiral cuprate **2** (R = *trans*-CH=CHCH[OC$(CH_3)_2OCH_3$]C_5H_{11}[4]), to cyclopent-2-enone were unsuccessful under a variety of conditions. Consequently, we turned to the expedient of trapping the enolate ion as the trimethylsilyl ether (**8**). This intermediate was not sufficiently stable for characterization or extensive purification. However, extraction of the trimethyl phosphite–copper iodide complex from a hexane solution of **8** with DMSO gave silyl ether **8** of adequate purity for the alkylation step.



In the alkylation procedure employed here, the achiral lithium enolate **7** (M = Li) was generated in liquid ammonia by reaction of silyl ether **8** with lithium amide. An excess of the alkylating agent, methyl *cis*-7-bromo-5-heptenoate (**9**), was added and, after a suitable period at −35°, the reaction was quenched with ammonium chloride. Aqueous acetic acid removed the methoxy isopropyl ether group, resulting in a mixture of (±)-11-deoxy-PGE_2 and (±)-11-deoxy-15-*epi*-PGE_2 methyl esters (**10** and **11**). By use of a fourfold ratio of allylic bromide to enolate ion



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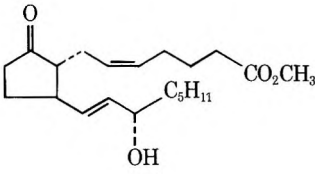

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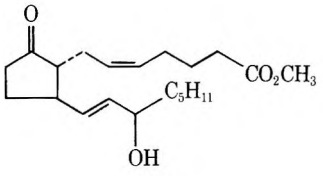

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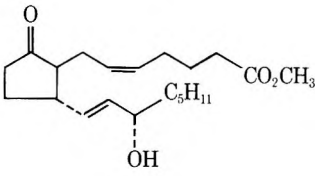
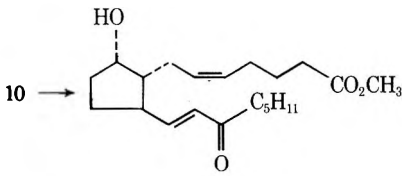


11a

and a 3-min reaction period, we have been able to isolate the racemic monoalkylation products **10** and **11**, essentially free of polyalkylated materials.[8] An overall yield of 47% for this sequence of reactions consisting of cuprate addition, enolate trapping and regeneration, and alkylation has been obtained.

In a similar process, utilizing chiral cuprate **2** (R = 1-pentynyl),[9] we have also prepared optically active PGE_2 methyl ester. Thus the chiral enolate ion obtained from cyclopenten-2-one and the mixed cuprate reagent **2** (R = 1-pentynyl) was trapped with trimethylsilyl chloride to yield the chiral enol ethers **8**. The copper pentyne was removed from the crude product by precipitation from cold hexane and the silyl enol ether was then alkylated as described above to yield a mixture of 11-deoxy-PGE_2 and 11-deoxy-8,12-*epi*-PGE_2 methyl esters (**10** and **11a**) in 40% yield.

The proof of structure for compound **10** is based on spectral and chromatographic identity with 11-deoxy-PGE_2 which was prepared independently from PGA_2 isolated from *Plexaura homomalla via* reduction of the 10,11 double bond with zinc in acetic acid–methanol.[10] The fact that product **11a** differs from 11-deoxy-PGE_2 methyl ester only with respect to the absolute stereochemistry of carbons 8 and 12 was established by reduction of **10** and **11a** with potassium tri-*sec*-butylborohydride to the 9α alcohols followed by oxidation of the 15-hydroxyl groups with DDQ to yield hydroxy enones **12** and **13**. Compounds **12** and **13** were identical except for possessing mirror-image ORD spectra.



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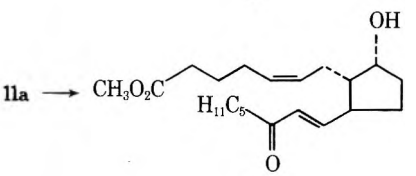
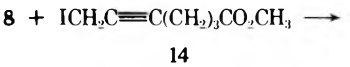


13

(±)-5,6-Dehydro-11-deoxyprostaglandin E_2 (15, R = H). In addition to 11-deoxy-PGE_2, we have also prepared (±)-5,6-dehydro-11-deoxy-PGE_2 (**15**, R = H) by use of methyl 7-iodo-5-heptynoate (**14**) as the alkylating agent. Unfortunately, in this case we were unable to find conditions which gave clean monoalkylation. However, the monoalkylated products (**15** and **16**, R = CH_3) were sufficiently stable to be removed from the product mixture by evaporative distillation at 150° (0.005 mm). The volatile fraction of the product mixture was contaminated with the nonalkylated cyclopentanone, 3-(*trans*-3-hydroxy-1-octenyl)cyclopentan-1-one. This impurity was readily removed by hydrolysis of the methyl esters in compounds **15** and **16**, R = CH_3, followed by extraction of the neutral products. The free acids **15** and **16**, R = H, were then separated by chromatography on silica gel in 19.5% yield.



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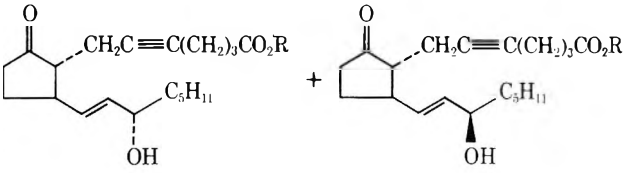
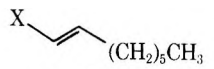
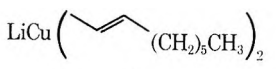


15 16

(±)-11,15-Deoxyprostaglandin E_2 (20, R = H).[11] An analogous sequence of reactions produced (±)-11,15-deoxy-PGE_2 (**20**, R = H). Hydroalumination[12] and bromination of the intermediate vinyl alane transformed 1-octyne into *trans*-1-bromo-1-octene (**17**, X = Br). Reaction



17, X = Br
X = Li



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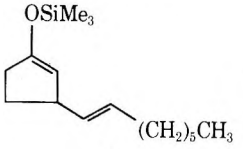

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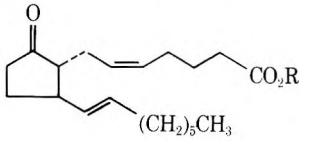

20

with lithium gave the corresponding lithium reagent (**17**, X = Li), which was converted to the cuprate **18** by treatment with cuprous iodide. This dialkylcopper lithium reagent was then treated with cyclopent-2-enone and the enolate ion trapped with trimethylsilyl chloride to yield the enol ether **19** in 97% yield. This silyl ether was then alkylated with methyl 7-bromo-*cis*-5-heptenoate (**9**) to yield (±)-11,15-deoxy-PGE_2 methyl ester (**20**, R = CH_3) in 60% yield. Saponification gave the free acid, (±)-11,15-deoxy-PGE_2 (**20**, R = H).

Acknowledgments. The authors wish to thank Dr. A. Van Horn and Mr. D. Wren for the preparation of additional samples of 3-(*S*)-*trans*-iodo-1-octen-3-ol and methyl *cis*-7-bromohept-5-enoate, and Dr. L. Tökés, Dr. M. Maddox, Mrs. J. Nelson, Mr. B. Amos, and Mr. V. Hayashida for physical data.

Registry No.—**8**, 51751-82-7; **9**, 51751-83-8; (±)-**10**, 35120-22-0; (−)-**10**, 37794-69-7; **11**, 38698-63-4; **11a**, 51819-56-8; **12**, 51751-84-9; **13**, 51794-45-7; **14**, 31776-12-2; **15** (R = H), 51751-85-0; **16** (R = H), 51751-86-1; **17**, 51751-87-2; **19**, 51751-88-3; **20** (R = CH_3), 51751-89-4; **20** (R = H), 40098-57-5; (*S*)-*trans*-1-iodo-1-octen-3-ol, 39647-93-3; 11-deoxy $PGF_{2\alpha}$ methyl ester, 33854-16-9; *ent*-11-deoxy-15-*epi*-$PGF_{2\alpha}$ methyl ester, 51751-90-7; (±)-*trans*-1-iodo-1-octen-3-ol, 39647-88-6.

Miniprint Material Available. Full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the miniprinted and supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036.

Experimental Section[13]

(13) Infrared spectra were recorded with a perkin-Elmer 237B grating spectrometer. Nmr spectra were obtained with a Varion HA-100 instrument in deuteriochloroform with TMS as internal standard unless otherwise indicated. Mass spectra were recorded on Atlas werke CH-4 or CH-7 spectrometers. Combustion analyses were performed by the Syntex Analytical Laboratory.

(±)11-Desoxy Prostaglandin E_2 and (±)11-desoxy-15-epi Prostaglandin E_2 methyl esters (10 and 11). A solution of 5.0 mmol. of the achiral cuprate 2 was prepared as previously described.[4] This solution was cooled to -78° and treated with 0.396 g of cyclopent-2-enone in 3 ml of ether. The reaction was stirred at -78° for 15 min. and then diluted with 25 ml of THF. Trimethylchlorosilane (3 ml) and triethyl amine (4 ml) were added and the reaction mixture allowed to warm to 0°, and then poured into 300 ml of hexane and 200 ml of ice water. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was dissolved in 20 ml of DMSO and the silyl ether recovered by extraction with hexane (4 x 50 ml). The combined hexane extracts were washed twice with 100 ml of saturated sodium bicarbonate, dried over sodium sulfate and concentrated in vacuo to yield the silyl enol ether (8).

The crude silyl ether (8) was dissolved in 10 ml of THF and added to a mixture of lithium amide prepared from 82 mg of lithium, 80 ml of ammonia, 30 ml of THF and a trace of ferric nitrate. After 20 min at reflux, 4.0 g of methyl cis-7-bromo-5-heptenoate in 5 ml of THF was added over 30 sec. The reaction mixture was allowed to reflux for 3 min. and then quenched with ammonium chloride. A stream of nitrogen was used to remove the ammonia, and when the reaction mixture reached -15°, it was poured into a slurry of 200 g of ice, 150 ml of ether and 50 ml of acetic acid. The organic layer was separated and the aqueous layer extracted with 150 ml of ether. The combined ethereal solutions were treated with 20 ml of acetic acid, 20 ml of water and 50 ml of methanol, and then stirred at room temperature for 1 hr. The ether solution was then washed twice with 300 ml of brine, dried over sodium sulfate and concentrated in vacuo. Toluene (150 ml) was added and removed in vacuo to azeotrope the acetic acid. The resulting residue was chromatographed on 200 g of silica gel eluting with 20 to 30% ethyl acetate/hexane (v/v) · 0.370 g (21%) of (±)11-desoxy-15-epi-PGE_2 methyl ester (11) was eluted first: ir (film) 3500 (OH) and 1740 cm^{-1} (C=O and CO_2CH_3); nmr δ 5.6 (m, 2, trans CH=CH), 5.4 (m, 2, cis CH=CH), 4.1 (m, 1, C_{15}-H) 3.67 (s, 3, CO_2CH_3) and 0.90 ppm (t, 3, J=6Hz, CH_3); mass spectrum (70 eV) m/e (rel intensity) 350 (5), 332 (65), 300 (14), 279 (2), 191 (23), 109 (47) and 83 (100).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.16; H, 9.69.

0.429 g (26%) of (±)11-Desoxy PGE_2 methyl ester (10) was eluted next: ir (film) 3500 (OH) and 1740 cm^{-1} (C=O and CO_2CH_3); nmr δ 5.6 (m, 2, trans CH=CH), 5.4 (m, 2, cis CH=CH), 4.1 (m, 1, C_{15}-H), 3.67 (s, 3, CO_2CH_3) and 0.90 ppm (t, 3, J=6Hz, CH_3); mass spectrum (70 eV) m/e (rel intensity) 350 (1), 332 (10), 300 (5), 279 (5), 191 (2), 109 (87) and 83 (100).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.20; H, 9.86.

(-)11-Desoxy Prostaglandin E_2 and (+)11-desoxy-8,12-epi Prostaglandin E_2 methyl esters (10 and 11a). A solution of 2.64 g of (+)trans-1-iodo-1-octen-3-ol in 10 ml of isopropenyl methyl ether was cooled to 0° and treated with 5 drops of dichloroacetic acid. After 15 min, the ice bath was removed and the reaction allowed to continue at room temperature for 1 hr. Ten drops of triethyl amine were added and the excess isopropenyl methyl ether removed in vacuo.

The residue was dissolved in 20 ml of ether, cooled to -78° and treated with 14 ml of 1.6 N t-butyl lithium over a 10 min period under argon. After stirring at -78° for 20 min, this solution of vinyl lithium reagent was transferred via a double-tipped needle to a second flask containing a solution of 1.30 g of copper pentyne and 4 ml of HMP in 50 ml of ether. The second reaction vessel was also cooled in a dry ice/acetone bath and equipped with a mechanical stirrer. Following the transfer of the vinyl lithium reagent, the reaction was stirred at -78° for 20 min and then treated with 0.80 g of cyclopent-2-enone in 4 ml of ether. After another 15 min at -78°, 40 ml of THF, 4 ml of chlorotrimethyl silane and 3 ml of HMPA were added to the reaction mixture. The cooling bath was removed and the solution allowed to warm to 10° over 30 min. This mixture was then poured into 300 ml of hexane, 5 ml of triethyl amine and 300 ml of ice water. The organic phase was separated, dried over sodium sulfate and concentrated in vacuo. The oily residue thus obtained was dissolved in 10 ml of hexane, cooled to 0° and filtered to remove the precipitated copper pentyne. The filtrate was concentrated in vacuo to yield silyl enol ether 8 of sufficient purity for the alkylation reaction.

A solution of 82 mg of lithium in 110 ml of ammonia and 30 ml of THF was converted to lithium amide by addition of a crystal of ferric nitrate. Upon disappearance of the blue color, the silyl enol ether (8) from above in 10 ml of THF was added. This reaction mixture was stirred at -30° for 10 min and then treated with 4.0 g of methyl cis-7-bromohept-5-enoate in 5 ml of THF. This addition required 15 sec and the reaction was allowed to stir at -30° for an additional 2 min. The reaction was quenched by addition of ammonium chloride and the ammonia evaporated under a stream of nitrogen. The residue was poured into 300 ml of ether, 200 ml of ice and 80 ml of acetic acid. The organic layer was separated and the aqueous layer extracted twice with 100 ml ether. The combined ether extracts were treated with 50 ml of acetic acid and 30 ml of water and stirred at room temperature for one hour. The ethereal solution was washed with brine, dried over sodium sulfate and concentrated in vacuo. Toluene (200 ml) was then evaporated in vacuo from the residue to azeotrope any acetic acid present. The resulting residue was chromatographed on 300 g of silica gel, employing a continuous gradient of 15 to 25% ethyl acetate-hexane to yield 11-desoxy prostaglandin E_2 and 11-desoxy-8,12-epi-prostaglandin E_2 methyl esters (10 and 11). 0.446 g (13%) of (+)11-desoxy-8,12-epi-prostaglandin E_2 methyl ester (11a) was eluted first: $[\alpha]^{25}D$ +48.6° (C 0.65, CH_3OH); ir (film) 3500 (OH) and 1740 cm^{-1} (C=O and CO_2CH_3); nmr δ 5.6 (m, 2, trans CH=CH), 5.4 (m, 2, cis CH=CH), 4.1 (m, 1, C_{15}-H) 3.67 (s, 3, CO_2CH_3) and 0.90 ppm (t, 3, J = 6Hz, CH_3); mass spectrum (70 eV) m/e (rel intensity) 350 (1), 332 (5), 300 (3), 279 (2), 191 (16), 109 (50) and 83 (100).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.68; H, 9.78.

0.598 g (17%) of (-)11-Desoxy prostaglandin E_2 methyl ester (10) was eluted next: $[\alpha]^{25}D$ -41.0° (C 0.43, CH_3OH); ir (film) 3500 (OH) and 1740 cm^{-1} (C=O and CO_2CH_3); nmr δ 5.6 (m, 2, trans CH=CH), 5.4 (m, 2, cis CH=CH), 4.1 (m, 1, C_{15}-H), 3.67 (s, 3, CO_2CH_3) and 0.90 ppm (t, 3, J = 6Hz, CH_3); mass spectrum (70 eV) m/e (rel intensity) 350 (1), 332 (5), 300 (3), 278 (2), 191 (16), 109 (50) and 83 (100).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.19; H, 9.98.

Methyl-(+)9α-hydroxy-15-ketoprosta-5(c),13(t)-dienoate (12). A solution of 0.160 g of 11-desoxy PGE_2 methyl ester (10) in 6 ml of THF was cooled to -35° and treated with 2.0 ml of 0.5 N potassium tri-sec-butyl borohydride in THF with magnetic stirring. After 40 min at -30°, the reaction was quenched by addition of 2 ml of acetone. The reaction mixture was diluted with 100 ml of ice water and extracted three times with 75 ml ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated at reduced pressure. The residue was dried at 50°/0.01 mm to remove tri-sec-butyl borane and then chromatographed on 70 g of silica gel. Elution with 10 to 20% (v/v) ethyl acetate/hexane gave 0.094 g (59%) of 11-desoxy $PGF_{2\alpha}$ methyl ester: $[\alpha]^{25}D$ +59.6° (C 0.287, CH_3OH); ir (film) 3450 (OH) and 1735 cm^{-1} (CO_2CH_3); nmr δ 5.45 (m, 4, vinyl), 4.20 (m, 1, C_{15}-H), 4.05 (m, 1, C_9-H), 3.65 (s, 3, CO_2CH_3) and 0.87 ppm (t, 3, J = 6Hz, CH_2CH_3); mass spectrum (70 eV) m/e (rel intensity) 352 (1), 334 (4), 316 (20), 281 (5), 175 (40) and 67 (100).

Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.22; H, 10.37.

A solution of 0.070 g of 11-desoxy $PGF_{2\alpha}$ methyl ester and 0.160 g of DDQ in 5 ml of dioxane was heated at 55° under nitrogen for 4 hrs. The reaction mixture was cooled to room temperature, diluted with 100 ml of 5% aqueous sodium bisulfite and extracted twice with 100 ml of ether. The ether extracts were dried over sodium sulfate and concentrated in vacuo. The resulting residue was chromatographed on 70 g of silica gel and elution with 10 to 25% ethyl acetate/hexane gave 0.060 g (86%) of methyl 9α-hydroxy-15-ketoprosta-5(c),13(t)-dienoate (12): $[\alpha]^{25}D$ +89.1° (C 0.547, CH_3OH); uv (CH_3OH) 230 mμ (ε 12,600); ir (film) 3470 (OH), 1740 (CO_2CH_3), 1679 and 1625 cm^{-1} (CH=CH-C=O); nmr δ 6.68 (dd, 1, J = 16 and 8Hz, CH=CHCO); 6.07 (d, 1, J = 16Hz, CH=CHC=O), 5.38 (m, 2, cis CH=CH), 4.23 (m, 1, C_9-H), 3.65 (s, 3, CO_2CH_3) and 0.88 ppm (t, 3, J = 6Hz, CH_2CH_3); mass spectrum (70 eV) m/e (rel intensity) 350 (4), 332 (5), 226 (35), 191 (40) and 99 (100).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.72; H, 9.82.

Methyl(-)ent-9α-hydroxy-15-ketoprosta-5(c),13(t)-dienoate (13). In a similar reaction to that described above, 0.170 g of 11-desoxy-8,12-epi PGE_2 methyl ester (11) was reduced with potassium tri-sec-butyl borohydride to 0.133 g (78%) of ent-11-desoxy-15-epi $PGF_{2\alpha}$ methyl ester: $[\alpha]^{25}D$ -51.4° (C 0.335, CH_3OH); ir (film) 3450 (OH) and 1735 cm^{-1} (CO_2CH_3); nmr δ 5.45 (m, 4, vinyl), 4.20 (m, 1, C_{15}-H), 4.05 (m, 1, C_9-H), 3.64 (s, 3, CO_2CH_3) and 0.87 ppm (t, 3, J = 6Hz, CH_2CH_3); mass spectrum (70 eV) 334 (4), 316 (22), 28 (5), 119 (79) and 67 (100).

Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.25; H, 10.18.

In the manner described above for the preparation of methyl 9α-hydroxy-15-ketoprosta-5(c),13(t)-dienoate (12), 0.104 g of ent-11-desoxy-15-epi-$PGF_{2\alpha}$ methyl ester was oxidized with DDQ in dioxane to yield after silica gel chromatography 0.065 g (60%) of methyl ent-9α-hydroxy-15-ketoprosta-5(c),13(t)-dienoate (13): $[\alpha]^{25}D$ -94.0° (C 0.59, CH_3OH); uv (CH_3OH) 231 mμ (ε 14,100); ir (film) 3470 (OH), 1740 (CO_2CH_3), 1670 and 1625 cm^{-1} (CH=CH-C=O); nmr δ 6.68 (dd, 1, J = 16 and 8Hz, CH=CHC=O); 6.07 (d, 1, J = 16Hz, CH=CHC=O), 5.38 (m, 2, cis CH=CH), 4.23 (m, 1, C_9-H), 3.65 (s, 3, CO_2CH_3) and 0.88 ppm (t, 3, J = 6Hz, CH_2CH_3); mass spectrum (70 eV) m/e (re intensity) 350 (4), 332 (5), 226 (35), 191 (40) and 99 (100).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.64; H, 9.70.

(±)5,6-Dehydro-11-desoxyprostaglandin E_2 (15, R = H). As described above, 2.64 g of (±)-trans-1-iodo-1-octen-3-ol was converted via the lithio derivative to the mixed cuprate reagent 2 and then to the (±) silyl enol ether 8. This intermediate (8) was subjected immediately to the following alkylation procedure.

A suspension of lithium amide prepared from 0.10 g of lithium, 125 ml of liquid ammonia, 30 ml of tetrahydrofuran and a trace of ferric nitrate was cooled to -40° and treated with crude silyl ether 8 in 10 ml of tetrahydrofuran. After 10 min at -40°, a solution of 9.0 g of methyl 7-iodo-5-heptynoate (14) in 10 ml of tetrahydrofuran was added to the reaction mixture. The reaction was allowed to proceed at -40° for 5 min, at -30° for 5 min and then quenched with ammonium chloride. The ammonia was evaporated under a stream of nitrogen until the pot temperature reached -15°. The residue was poured into 300 ml of ice water and 80 ml of acetic acid. This mixture was stirred for 1 hr and then extracted with ether (3 x 100 ml). The combined ether layers were washed with brine, dried over sodium sulfate and concetrated in vacuo. 100 ml of toluene was added and then removed in vacuo to azeotrope any acetic acid present. The resulting residue (3.1 g) was subjected to evaporative distillation (150°/0.005 mm) to yield 0.942 g of volatile products. This mixture of monoalkylated products (15 and 16, R = CH_3) could not be chromatographically separated, hence was hydrolysed to the carboxylic acid.

A solution of 0.942 g of distilled esters 15 and 16, R = CH_3, 10 ml of water, 10 ml of methanol and 0.70 g of potassium hdyroxide was stirred at room temperature for 3 hrs. The organic solvents were removed in vacuo and the reaction mixture diluted with 50 ml of water. The aqueous solution was extracted with ether (2 x 100 ml), acidified to pH4 and extracted with ethyl acetate (3 x 100 ml). The combined ethyl acetate extracts were washed with brine, dried over sodium sulfate and concentrated in vacuo. The resulting oil was chromatographed on 200 g of silica gel, eluting with a gradient of 5/2/93 to 25/4/71% ethyl acetate/acetic acid/hexane (V/V) mixtures, and gave acids 15 and 16. 0.312 g (9.3%) of (±)5,6-Dehydro-11-desoxy-15-epiprostaglandin E_2 (16, R = H) was eluted first: ir (film) 1740 (C=O) and 1710 cm^{-1} (CO_2H); nmr δ 5.65 (m, 2, CH=CH), 4.1 (m, 1, C_{15}-H) and 0.88 ppm (5, 3, J = 6Hz, CH_3); mass spectrum (70 eV) m/e (rel intensity) 334 (2), 316 (10), 263 (37), 244 (49), 181 (50), 163 (83) and 43 (100).

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Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.48; H, 8.96.

0.342 g (10.2%) of (±)5,6-Dehydro-11-desoxyprostaglandin E_2 (15, R = H) was eluted next: ir (film) 1740 (C=O) and 1710 cm^{-1} (CO_2H); nmr δ 5.65 (m, 2, CH=CH), 4.1 (m, 1, C_{15}-H) and 0.88 ppm (s, 3, J = 6Hz, CH_3); mass spectrum (70 eV) m/e (rel intensity) 334 (2), 316 (10), 263 (42), 244 (51), 181 (67), 163 (100), 43 (90).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.63; H, 8.88.

(±)3-(trans-1-octenyl)-1-trimethyl siloxy cyclopentene (19). 7.64 g of trans-1-bromo-1-octene (40 mmol) in 12 ml of ether was added over 30 min to 0.79 g of lithium wire containing 1% sodium in 40 ml of ether under argon with magnetic stirring. The reaction temperature was held at -5 to -10° for 2 hr. This solution was then added to a slurry of 3.80 g (20 mmol) of cuprous iodide in 20 ml of THF at -35°. After stirring at -35° for 15 min, a solution of 1.64 g (20 mmol) of cyclopent-2-enone in 4 ml of THF was added to the reaction mixture. Following a 10 min period at -40°, 5 ml of chlorotrimethyl silane was added to the reaction mixture and the cooling bath removed. On warming to room temperature, the reaction mixture was poured into 200 ml of hexane, 3 ml of triethyl amine and ice water. The hexane solution was separated, washed with saturated bicarbonate, dried over sodium sulfate and concentrated in vacuo. Short path distillation gave 5.211 g (97%) of enol ether (19): bp 93-98° (0.1 mm); ir (film) 1640 cm^{-1} (OC=CH); nmr (CCl_4) 5.30 (m, 2, CH=CH), 4.42 (m, 2, OC=CH), 3.2 (m, 1, C=CH-CH-CH=CH), 0.91 (t, 3, CH_2CH_3), and 0.20 ppm (s, 9, $Si(CH_3)$); mass spectrum (70 eV) m/e (rel intensity) 266 (8), 195 (25), 181 (100), 75 (18), 73 (90).

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Anal. Calcd for $C_{16}H_{30}OSi$: C, 72.10; H, 11.35. Found: C, 71.97; H, 11.45.

(±)11,15-Desoxyprostaglandin E_2 methyl ester (20, R = CH_3). A solution of 1.33 g of silyl enol ether 19 (5 mmol) in 10 ml of tetrahydrofuran was added to a suspension of lithium amide prepared from 73 mg of lithium, 80 ml of ammonia, 30 ml of tetrahydrofuran and a trace of ferric nitrate. The reaction mixture was stirred magnetically and protected from atmospheric moisture by means of a nitrogen atmosphere. After stirring for 10 min at -35°, a solution of 4.45 g (20 mmol) of methyl cis-7-bromo-5-heptenoate in 5 ml of tetrahydrofuran was added over a 30 sec interval. Following an additional reaction period of 3 min at -35°, the reaction was quenched with ammonium chloride. The ammonia was evaporated under a stream of nitrogen and the resulting residue poured into 200 ml of ice water and 40 ml of acetic acid. This solution was then extracted with three 200 ml portions of ether, the combined ethereal extracts washed with brine, dried over sodium sulfate and concentrated in vacuo. Toluene (100 ml) was added and the mixture evaporated again to remove acetic acid. This residue was chromatographed on 300 g of silica gel, eluting with a gradient of 5-20% ethyl acetate-hexane (v/v) to yield 0.986 g (60%) of prostaglandin 20, R = CH_3. A small sample of 20, R = CH_3 was evaporatively distilled for spectral analysis: ir (CCl_4) 1750 cm^{-1} (CO_2CH_3 and C=O); nmr δ 5.4 (m, 4, CH=CH), 3.65 (s, 3, OCH_3), and 0.89 ppm (t, 3, CH_3); mass spectrum (70 eV) m/e (rel intensity) 334 (2), 303 (3), 194 (20) and 109 (100).

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Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.14; H, 10.25.

11,15-Desoxy Prostaglandin E_2 (20, R = H). A solution of 0.227 g of potassium hydroxide, 10 ml of water, 10 ml of tetrahydrofuran, 3 ml of methanol and 0.304 g of keto ester 20, R = CH_3 was stirred under nitrogen for 4 hr. Tlc analysis showed the absence of starting ester and the reaction mixture was diluted with 100 ml of water, extracted twice with 200 ml of ether, acidified to pH2 with concentrated hydrochloric acid, and extracted three times with 100 ml of ethyl acetate. The combined ethyl acetate solution were washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was evaporatively distilled at 150°/0.005 mm to yield 0.248 g of 20, R = H: ir (CCl_4) 1750 (C=O) and 1715 cm^{-1} (CO_2H); nmr δ 8.5 (s, 1, CO_2H), 5.4 (m, 4, CH=CH) and 0.89 ppm (t, 3, CH_3); mass spectrum m/e (rel intensity) 320 (1), 302 (1), 194 (7) and 109 (100).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 75.74; H, 10.12.

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References and Notes

(1) (a) Contribution No. 434 from the Institute of Organic Chemistry, Syntex Research. (b) Studies in Prostaglandins, No. 38. (c) The contents of this paper were the subject of lectures by J. Fried, presented at the University of Southern California (Nov 17, 1972), the University of California, Santa Cruz (Jan 8, 1973), and the Eidgenössische Technische Hochschule (Zurich) (May 9, 1973).

(2) For reviews of conjugate addition of organocuprates, see G. Posner, *Org. React.*, **19**, 1 (1972), and V. F. Nort, *Synthesis*, 63 (1972).

(3) For enolate trapping and alkylation see G. Stork, *Pure Appl. Chem.*, **17**, 393 (1968), and G. Stork, P. Rosen, N. Goodman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965).

(4) A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Amer. Chem. Soc.*, **94**, 7827, 9256 (1972).

(5) C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzotti, and M. Casey, *J. Amer. Chem. Soc.*, **94**, 3643 (1972).

(6) Likewise the use of 4-(*R*)-hydroxycyclopent-2-enone should give PGE_2 as the predominant prostaglandin product.

(7) For other syntheses of 11-deoxyprostaglandin E_2 see (a) E. J. Corey and T. Ravindranathan, *Tetrahedron Lett.*, 4753 (1971); (b) P. Crabbé and A. Guzman, *ibid.*, 115 (1972); (c) J. Bagli and T. Bogri, *ibid.*, 3815 (1972); (d) N. A. Abraham, *ibid.*, 451 (1973); (e) P. A. Grieco and J. J. Reap, *J. Org. Chem.*, **38**, 3413 (1973); (f) F. H. Lincoln, W. P. Schneider, and J. E. Pike, *ibid.*, **38**, 951 (1973).

(8) R. M. Coates and R. L. Sowerly, *J. Amer. Chem. Soc.*, **93**, 1027 (1971), reported the very rapid, regiospecific alkylation of cyclopentanone enolates under similar conditions.

(9) E. J. Corey and D. J. Beames, *J. Amer. Chem. Soc.*, **94**, 7210 (1972).

(10) This reduction was performed by A. Prince in these laboratories.

(11) For another synthesis of 11,15-deoxyprostaglandin E_2 see K. F. Bernady and M. J. Weiss, *Tetrahedron Lett.*, 4083 (1972), and P. A. Grieco and J. J. Reap, *J. Org. Chem.*, **38**, 3413 (1973).

(12) G. Zweifel and C. G. Whitney, *J. Amer. Chem. Soc.*, **89**, 2753 (1967).

Pyrolysis of Spirotrithianes

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Pyrolysis of spirotrithianes **3–7** at reduced pressure gave volatile mixtures consisting almost entirely of cyclic thioketones and their enethiols. At higher temperatures volatile products were mixtures of mercaptans and olefins. The nonvolatile residue of higher temperature pyrolysis of cyclohexanethione trimer contained dibenzothiophene, tetrahydrodibenzothiophene, octahydrodibenzothiophene,and spiro-2,2-pentamethylenebenzodithiolane (**13**). Bicyclo[2.2.1]heptane-2-thione (1) is a further example of a relatively stable thioketone.

Several methods for preparing aliphatic thioketones have been reported recently.[1-5] Each suffers from lack of generality. The absence of a general synthetic method for preparing thioketones, their instability, and the disagreeable odor of their intermediates all have slowed the investigation of the chemistry of the thiocarbonyl group. In the course of synthesis of thiols we prepared norbornanethione (1) by pyrolysis of trithiane **3** in good yield despite previous reports[6,7] that pyrolysis of trithianes is unsatisfactory for preparation of aliphatic thioketones. The results of pyrolyzing the structurally related spirotrithianes **4–7** at reduced pressure are shown in Table I.

These pyrolyses were stopped after generating workable quantities of red distillate and were not necessarily pushed to completion. Thioketone content of products was estimated from the absorption maximum at about 500 nm and enethiol content was estimated from nmr spectra.

Table I
Pyrolyses at Reduced Pressure

Pyrolysis of	Pressure, mm	Pot temp, °C (external)	Time, min	% distilling	Composition of distillate: % thione	Composition of distillate: % enethiol
3	~20	210–293	60	85	91	
3′	10	240–278	198	43	96	<1
4	13	195–247	30	10	>13	34
5	13–17	290–310	10	68	*a*	
6	13	165–210	80	45	>34	12
7	10	180–260	95	23	~33	32

[a] Red liquid distillate rapidly crystallized to give trimer.

Experimental Section

General. - Spectra were recorded using the following instruments: Cary model 14 (vis and uv); Perkin-Elmer model 137 and Beckman acculab 4 (ir); Varian T-60 (nmr), using tetramethylsilane as internal standard; A.E.I. MS-9 mass spectrometer. Vpc analyses were done on an Aerograph A-90-P gas chromatograph using silicone SE-30, 4% on 80-100 mesh chromosorb G (column a), silicone SE-52, 20% on chromosorb W (column b), silicone GE SF-96 (column c), or didecylphthalate, 15% on 60-80 mesh chromosorb W (column d). Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed by Chemalytics, Inc., Tempe, Arizona. Commercially available cycloolefins, bicyclo[2.2.1] heptene, bicyclo[3.2.1]-2-octene, cyclohexanethiol, dibenzothiophene, and thianthrene were used as standards in identifying pyrolysis products. 2,4-Dinitrophenyl derivatives were prepared by the method of Bost,[17] except that 2,4-dinitrofluorobenzene (FDNB) was used rather than 2,4-dinitrochlorobenzene.

1,3,5-Trithianes. - H_2S and HCl were bubbled simultaneously through alcoholic solutions of the ketones cooled with ice H_2O baths.[15,18] To make efficient use of H_2S, several preparations were carried out in series on a gas train. A 40% NaOH solution was used as a final trap. Gas flow through each reaction mixture was maintained until the maximum amount of white solid had formed. Reaction times in the gas train varied between 4 and 8 hr. The crude white solids were collected, washed with alcohol, vacuum dried to constant weight over NaOH, and recrystallized from $CHCl_3$-EtOH.

Recrystallized 4 had mp 98.1-99.5°;[15] recrystallized 5 had mp 100.3-101.5°;[15] recrystallized 6 had mp 74-75°.[18] Base-washed 5 and 6 were prepared as described for 3'.

tris-Bicyclo[3.2.1]octane-2-thione (7). - Bicyclo[3.2.1]-octan-2-one (9.3 g, 0.075 mol) in 30 ml of methanol was reacted by simultaneous bubbling of H_2S and HCl. An orange oil separated after 30 min, becoming quite viscous after 2 hr. Some ethanol (10 ml) was added after 2 hr, and the gas flow was maintained for 3 more hr. A crude white solid was obtained, 9.82 g (93% yield). Recrystallization from $CHCl_3$-EtOH gave 7.38 g of white crystals, mp 176.5-178.8°; nmr (CCl_4) all signals 0.8 - 3.03 ppm. Recrystallization from EtOH gave an analytical sample, mp 180.2-182.2°; mass spectrum (50 eV) m/e (rel intensity) 420.1956 (420.1979 calcd for $C_{21}H_{36}S_3^+$) (1), 280 (dimer$^+$) (37), 140 (monomer$^+$) (100).

Anal. Calcd for $C_{21}H_{36}S_3$: C, 68.51; H, 8.62; S, 22.86. Found: C, 68.62; H, 8.74; S, 21.79.

Oligomeric 2-Norbornanethione (3'). - 2-Norbornanone (22.0 g, 0.2 mol) in 180 ml of EtOH was reacted by simultaneous bubbling of H_2S and HCl to give 22.41 g (89% yield) of crude white solid, broad mp beginning at 135.5°. Three recrystallizations of a 5 g portion from $CHCl_3$-EtOH gave a highly crystalline sample[19] (2.73 g), mp 145-175°; mass spectrum (47 eV) m/e (rel intensity) 378 (1), 252 (18), 220 (8), 126 (100).

A $CHCl_3$ solution of 14.5 g of the crude white solid was washed first with 5% $NaHCO_3$ and then repeatedly with H_2O, dried (Na_2SO_4), and evaporated. Recrystallization from $CHCl_3$-EtOH provided 12.96 g of base-washed 3', broad mp beginning at 133°; the nmr spectrum was nearly identical to that of 3.

tris-2-Norbornanethione (3). Liquid H_2S procedure. - A solution of 11.02 g of 2-norbornanone (0.1 mol) in 100 ml of EtOH was added slowly to approximately 30 ml of liquid H_2S maintained at -55° by a dry ice-acetone bath. Hydrogen chloride gas was bubbled through the reaction solution for 1 hr. The reaction mixture was maintained at -55° for 2 more hr, and became opaque with crystal formation. The mixture was warmed cautiously (H_2S evolution) and partitioned between ice H_2O (500 ml) and petroleum ether (500 ml). The petroleum ether phase was washed with H_2O (6 x 100 ml) until the H_2O washes were neutral, dried (Na_2SO_4), and evaporated to dryness. A portion of the crude product (95% yield) was recrystallized from EtOH and gave an analytical sample, white crystals, mp 127-128° (82% yield); nmr (CCl_4) all signals 0.75-2.90 ppm; mass spectrum (70 eV) m/e 378.1484 (378.1510 calcd for $C_{21}H_{30}S_3^+$), 252 (dimer$^+$), 220, 127, 126 (monomer$^+$), 93, 67, 66.

Anal. Calcd for $C_{21}H_{30}S_3$: C, 66.61; H, 7.99; S, 25.40. Found: C, 66.87; H, 8.22; S, 24.71.

Trithiane Pyrolyses at Reduced Pressure. General Methods. - The trithianes were pyrolyzed with an equal weight of ordinary dry sand, except where stated otherwise.

Method A. - The still pot was equipped with a short path distillation apparatus. Reduced pressure was provided by a H_2O aspirator.

Method B. - A short glass tube, heated by an electrical heating tape, was used to connect the still pot with the receiver. A regulated partial vacuum (P) was established for the system, a dry ice-acetone bath was used to chill the receiver, and a steady temperature (T_1) was established for the glass tube. The temperature (T_2) of the still pot heater was monitored. The pyrolyses were often stopped after 1 or 2 hr, and were not necessarily pushed to completion.

Method C. - The still pot, containing a bed of sand, was heated to an externally measured temperature of 300 ± 10° and maintained there throughout the pyrolysis. Molten 5 was injected onto the sand. A room temperature or ice-chilled receiver was used.

Trithiane Pyrolyses at Atmospheric Pressure. Method D. - In a still pot equipped with a H_2O-cooled short path distillation apparatus, mixed trithiane and an equal weight of ordinary dry sand were pyrolyzed completely until no more distillate was collected (receiver at room temperature). Heating times varied from 50 to 120 min. The maximum temperatures attained by the still pot heater varied from 341 to 358°. The temperature at the still head was monitored.

Pyrolysis of tris-2-Norbornanethione (3) by Method A. - 3 (18.94 g, 0.05 mol) and an equal weight of dry sand were heated under reduced pressure. Red liquid (16.08 g) was collected in the still pot temperature range 210-293° over a period of 1 hr. Vpc analysis (column a, 162°) of the red liquid was done 90 min after collecting the product and showed 3 peaks with relative areas 91:8.5:0.5. The 8.5% component had approximately the same retention time as 2-norbornanethiol. Yield of 1 (based on 91% thioketone content, and minimal enethiol content) was 14.63 g, 77%. Mass spectrum (70 eV) of the red liquid, m/e 126.0482 (126.0503 calcd for $C_7H_{10}S^+$).

2-Norbornanethiol. - Following a procedure for the reduction of thioketones,[20] 6.32 g of the red liquid (crude 1) was reduced with $NaBH_4$ and gave 1.63 g of colorless liquid, bp 68.5-70.2° (15 mm); nmr (CCl_4)δ 0.65-2.4 (complex), 2.4-2.95 (very small signals), 2.95-3.45 (1 H), no signals downfield from 3.45 ppm. The nmr shows that the reduced product is predominantly the endo thiol.

Following a procedure describing the use of sodium cyanoborohydride,[21] 2.50 g of crude 1 was reduced with $NaBH_3CN$ using bromocresol green as the color indicator and dropwise additions of 2 N HCl in MeOH to maintain the pH. There was obtained 0.7 ml of colorless liquid, bp 75-81° (23 mm); nmr (CCl_4)δ 0.65-2.4 (complex), 2.4-2.95 (much less than 1 H), 2.95-3.45 (almost 1 H), no signals downfield from 3.45 ppm. The nmr shows that the reduced product is predominantly the endo thiol. Ir (neat liquid) 1755 (weak, C=O due to a trace of norbornanone), 2570 cm^{-1} (strong, SH); mass spectrum (70 eV) m/e 128.0626 (128.0660 calcd for $C_7H_{12}S^+$).

Pyrolysis of Oligomeric 2-Norbornanethione (3') by Method B. - With T_1 = 102° and P = 10 mm, base-washed 3' (3.79 g, equivalent to 0.01 mol of 3) was heated starting from room temperature. Red-orange liquid (1.64 g) was collected in the T_2 temperature range 240-278° over a period of 3.3 hr, leaving 2.06 g of dark brown residue in the still pot, nmr (CCl_4) identical to that of 3'.

The red-orange liquid was warmed to room temperature and portions were promptly removed and characterized: uv-vis (heptane) max 217 nm (ε 5700), 239 (9900), 313 (12.9), 460 (sh), 497 (11.8), 561 (1.5)[22] - no decrease of absorbance was observed in the vis spectrum when it was recorded again 3.8 hr and 4 days later; nmr (CCl_4)δ 1.1-2.1 (complex, 6 H), 2.35 (2 H), 2.78 (1 H), 3.33 (1 H), 5.96 (<<1% of total integration) - no change was observed in this nmr spectrum when it was recorded again 4 days later; ir (neat film) no bands at or near 1640 (C=C), 1755 (C=O), 2550 (SH), 3020 cm^{-1} (=C-H); ir (neat liquid in cavity cell) still no bands were observable at 1640, 1755, 2550, or 3020 cm^{-1}; vpc (column b, 162°) showed 2 peaks with relative areas 96:4. The 4% component had the same retention time as 2-norbornanethiol. The above characterization was completed within 4 hr, except for recording the uv spectrum and re-recording of spectra.

The remaining neat red-orange liquid was stored at room temperature for 5 to 6 days and portions were again removed and characterized. At this time the red-orange liquid contained 64% thioketone (calculation based on ε_{497} = 11.8). The nmr spectrum was nearly unchanged. The vinyl signal at δ 5.96 now accounted for about 0.7% of the total integration (7% enethiol). The ir spectrum was nearly unchanged except for a new band at 1755 cm^{-1} (weak, C=O due to norbornanone). No bands were observable at 1640, 2550, or 3020 cm^{-1}. Vpc (column b, 150°) was unchanged except for a new peak (5%) which had the same retention time as norbornanone.

Pyrolysis of tris-Cyclopentanethione (4) by Method B. - With T_1 = 69° and P = 13 mm, 4 (3.0 g, 0.01 mol) was heated starting from room temperature. Red liquid (0.31 g) was collected in the T_2 temperature range 195-247° over a period of 30 min, leaving an amber liquid in the still pot which solidified rapidly on cooling to off-white crystals, 2.66 g, mp 92-98°; nmr (CCl_4) identical to that of 4.

The red liquid was warmed to room temperature and portions were promptly removed and characterized: dilutions for vis and nmr spectra were made 15 to 20 min after the red liquid was warmed to room temperature; vis (heptane) max 512 nm (with shoulders at 445, 473, 496, 520), 542, 579.[7] An 11% decrease of absorbance at 512 nm was observed in this vis spectrum when it was recorded again 5 hr later. Nmr (CCl_4) δ 1.4-2.9 (complex), 2.9-3.7 (impurity), 5.52 and 5.87 (4.2% of total integration, 34% enethiol). There was no measurable change in this nmr spectrum when it was recorded again 2.5 hr later. The ir (neat) spectrum was recorded 25 min after the red liquid was warmed to room temperature and showed bands at 1593 (C=C), 2520 (SH), and 3030 cm^{-1} (=C-H). Vpc analysis was done 70 min after warming the product to room temperature. By this time the red color of the liquid had faded to pale pink. No cyclopentene was present.

Pyrolyses of tris-Cyclohexanethione (5) by Method C. - 5 (3.38 g) was delivered onto 3.43 g of sand at 13 mm. There was an immediate collection of red liquid distillate, with the collection rate becoming quite slow by 10 min after injection, at which time the red distillate (2.30 g) began to crystallize rapidly to a white solid still bearing some orange color. The residual colored liquid was dissolved in heptane, vis max (main peak) centered at 507 nm (with shoulders at 453, 462, 526), 569.[7] A 6% decrease of absorbance at 507 nm was observed when this spectrum was re-recorded 90 min later. A portion of the largely solidified distillate was recrystallized from $CHCl_3$-EtOH, mp 99-100.5°.

Base-washed 5 (1.64 g) was delivered onto 1.71 g of sand at 15 mm. There was an immediate collection of red liquid distillate. The system was opened 4 min after injection, at which time white solid formed rapidly in the receiver.

Pyrolysis of tris-Cycloheptanethione (6) by Method B. - With T_1 = 105° and P = 13 mm, base-washed 6 (3.85 g, 0.01 mol) was heated starting from room temperature. Red liquid (1.72 g) was collected in the T_2 temperature range 165-210° over a period of 80 min, leaving a brown-amber residue in the still pot.

The red liquid was warmed to room temperature and portions were promptly removed and characterized (within 2 hr): vis (heptane) max 510 nm (with shoulders at 575, 585)[7]; nmr (CCl_4) δ 1.3-2.7 (complex), 3.0-3.25 (broad), 5.67-6.03 (not observed in an earlier and lower temperature pyrolysis of 6), 6.06-6.40 (1% of total integration, 12% enethiol). The neat liquid was still red after 24 hr at room temperature.

Pyrolysis of tris-Bicyclo[3.2.1]octane-2-thione (7) by Method B. - With T_1 = 112° (later increased to 150°) and P = 10 mm, 7 (3.15 g, 0.0075 mol) was heated starting from room temperature. Orange liquid (0.74 g) was collected in the T_2 temperature range 180-260° over a period of 95 min, leaving 2.35 g of pale amber solid (after cooling) in the still pot, nmr (CCl_4) identical to that of 7.

The orange liquid was warmed to room temperature and portions were promptly removed and characterized: uv-vis (heptane) max 219 nm, 231, 498 (main vis peak with shoulders 460, 505, 522), 563 - the vis spectrum for the same solution was recorded again after 2 hr and showed no decay of absorbance; ir (neat) 1630 (C=C), 2550 (SH), and 3020 cm^{-1} (=C-H); nmr (CCl_4) δ 1.0-3.3 (complex), 3.6 (broad, 1% of total integration), 5.25-5.43 (2.7% of total integration, 32% enethiol). The above spectral characterization was completed within 2 hr, except for recording the uv spectrum. The neat liquid still retained some of its orange color after 24 hr at room temperature.

Pyrolysis of Oligomeric 2-Norbornanethione (3') by Method D. - Pyrolysis of 5.79 g of base-washed 3' gave 2.64 g of hard black residue and 1.74 g of light orange liquid distillate, bp 132-180°. Vpc (column d, 160°) showed 2 major peaks (relative areas 45:55) with retention times coincident with those of 2-norbornanethiol and norbornene respectively. Nmr (CCl_4) signals at δ 2.84 and 5.97 showed the presence of norbornene.[23] After further manipulation of the distillate, a trace of norbornanone was detected by vpc and by ir (neat liquid) 1755 cm^{-1} (C=O). A band was also observed at 2550 cm^{-1} (SH).

A portion of fresh distillate (1.22 g) was reacted with FDNB (0.005 mol) and, after work-up and two recrystallizations from EtOH, gave two types of yellow crystals (I and II). Physical separation with a spatula gave 0.85 g of I, mp 110-112°, and 30 mg of II, mp 120-122.5°. Nmr for II ($CDCl_3$) δ 1.0-2.75 (complex, 10 H), 3.11-3.45 (complex, ~ 0.5 H), 3.45-3.9 (complex, ~ 0.5 H), 7.62, 8.37, and 9.04 (3 Ar H), no vinyl signals were observed. I was recrystallized 4 more times to give an analytical sample (0.41 g of homogeneous appearing yellow crystals), mp 112-112.8°; nmr ($CDCl_3$) δ 1.0-2.75 (complex, 10 H), 3.11-3.45 (complex, ~ 0.7 H), 3.45-3.9 (complex, ~ 0.3 H), 7.62, 8.37, and 9.04 (3 Ar H), no vinyl signals were observed. The nmr spectrum of this material, containing ~ 70% of the exo-2-DNP derivative and ~ 30% of the endo-DNP derivative, was very nearly identical to the spectrum of the pure exo-2-DNP derivative.

Anal. Calcd for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79; S, 10.89. Found: C, 52.85; H, 4.95; S, 10.14.

Pyrolysis of tris-Cyclopentanethione (4) by Method D. - Pyrolysis of 3.0 g of 4 (0.01 mol) gave 1.04 g of black charred solid residue and 1.18 g of extremely pale pink liquid distillate, bp 115-133°.

Vpc (column b, 152° and column c, 133°) showed 2 peaks with relative areas 75:25. The 25% component had the same retention time as cyclopentene. Nmr (CCl_4) signals at δ 2.22, 2.33, and 5.7 showed the presence of cyclopentene. Redistillation of 1.0 g of the liquid at 1 atm gave a 0.24 g center fraction, colorless liquid, bp 125–129° [cyclopentanethiol lit. bp 132.2°];[24] ir (neat) showed all the bands of cyclopentanethiol. A combined fraction (0.24 g) of the redistilled colorless liquid [estimated by vpc to contain 0.2 g of cyclopentanethiol (0.002 mol) and 0.04 g of cyclopentene] was reacted with FDNB (0.002 mol) and gave yellow crystals, mp 96–97°. Recrystallization (EtOH) provided an analytical sample, 0.32 g (60% yield), mp 96–97°; nmr (CCl_4) δ 1.5–2.5 (8 H), 3.5–3.95 (1 H), 7.62, 8.34, and 9.00 (3 Ar H), no vinyl signals were observed in the nmr spectrum.

Anal. Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.25; H, 4.51; S, 11.95. Found: C, 49.30; H, 4.60; S, 11.61.

Pyrolysis of tris-Cyclohexanethione (5) by Method D. - Pyrolysis of 3.43 g of 5 (0.01 mol) gave an uncharred, light-yellow liquid residue and 2.13 g of colorless liquid distillate, bp 145–177°. Ir (neat) was identical to that of cyclohexanethiol. Nmr (CCl_4) was very similar to that of cyclohexanethiol except for extra signals at δ 5.6 (<2% of total integration, 12% cyclohexene) and δ 7.2 (also <2% of total integration).

Pyrolysis of tris-Cycloheptanethione (6) by Method D. - Pyrolysis of 3.85 g of base-washed 6 (0.01 mol) gave 1.45 g of hard brown-black residue and 1.66 g of colorless liquid distillate, bp 96–159°. Vpc (column a, 160°) showed 2 peaks with relative areas 84:16. The 84% component had the same retention time as cycloheptene. Redistillation of 1.39 g of the liquid at 1 atm gave 0.89 g of colorless cycloheptene (>99% pure by vpc); bp (of center portion) 105–106°; ir (neat) and nmr (CCl_4) spectra were identical to those of authentic cycloheptene.

Pyrolysis of tris-Bicyclo[3.2.1]octane-2-thione (7) by Method D. - Pyrolysis of 2.10 g of 7 (0.005 mol) gave 1.15 g of hard black residue and 0.45 g of colorless distillate which solidified on cooling, bp ~105–125°. Nmr (CCl_4) strong signals centered at δ 1.6, 1.7, 1.77, 2.31, 5.33 (d, broad), and 5.88 (t, broad) indicated the presence of bicyclo[3.2.1]-2-octene, but other signals were observed including a vinyl signal centered at δ 6.24.

Non-volatile Pyrolysis Products from tris-Cyclohexanethione (5). - 5 (6.85 g, 0.02 mol) was heated without sand in a still pot equipped with a H_2O-cooled reflux condenser and drying tube. A reflux of colorless liquid was established (oil bath 240°). Heating was stopped after 7.5 hr. Distillation of the resulting yellow liquid at 1 atm gave 3.86 g of colorless liquid, bp 74–190°, and left 2.27 g of high boiling yellow liquid residue in the still pot. Redistillation of the colorless liquid at 1 atm gave an initial fraction containing cyclohexene, and a center fraction (1.28 g), bp 155–157°. Ir (neat) and nmr (CCl_4) spectra of this fraction were identical to those of cyclohexanethiol except for a small signal at δ 7.2.

Vacuum distillation of 2.0 g of the pot residue gave 1.38 g of light yellow liquid, bp 108–152° (1 mm). A portion, distilled twice more using a micromolecular still, gave a colorless liquid distillate, bp ~100° (1 mm). The colorless liquid (146 mg) was chromatographed on preparative layers of silica gel HF_{254} (E. Merck) using heptane as the developing solvent (3 passes) giving approximately 84 mg of pale yellow oil (faster band) and 23 mg of pale yellow oil (slower band).

Spiro-2,2-pentamethylenebenzodithiolane (13). - Slower band, nmr (CCl_4) δ 1.3–1.92 (broad, 6 H), 1.92–2.35 (broad, 4 H), 6.8–7.33 (complex, 4 Ar H); mass spectrum (70 eV, 200°) m/e (rel intensity) 224 (4), 223 (7), 222 (47), 193 (8), 181 (10), 180 (13), 179 (100), 166 (15), 153 (8); mass spectrum (chem ionization with isobutane, 200°) base peak m/e 223; uv (heptane) max 237 nm, 274 (ε 28500, 8600); tlc (Eastman silica gel chromagram sheet with fluorescent indicator) with heptane as the solvent showed only a trace of contamination in this sample.

Octahydrodibenzothiophene (9). - The 84 mg sample (faster band on silica gel) was further chromatographed on a preparative layer of aluminum oxide HF_{254} using heptane as the developing solvent (2 passes) giving three bands (A, B, C). The fastest moving band (A) contained 4.9 mg of a cloudy glass; nmr (thick-walled tube, CCl_4) no signals observed downfield from δ 2.85; mass spectrum (chem ionization with isobutane) main peaks m/e 207, 193.

1,2,3,4-Tetrahydrodibenzothiophene (10). - Intermediate tlc band B contained 54.3 mg of colorless oil; nmr (CCl_4) δ 1.64–2.14 (broad, 4 H), 2.5–3.0 (broad, 4 H), 7.0–7.8 (complex, 4 Ar H); mass spectrum (70 eV, 175°) m/e (rel intensity) 190 (11), 189 (30), 188 (100), 187 (42), 161 (17), 160 (100), 147 (17), 115 (27), 43 (75), 42 (28), 41 (32), 40 (11), 39 (15); mass spectrum (chem ionization with isobutane, 175°) m/e (rel intensity) 245 (29), 189 (100); ir (neat) was identical to that of 10;[25] uv (heptane) max 232 nm (log ε 4.44), 264 (3.76), 270 (3.76), 288 (3.42), 298 (3.37).[26]

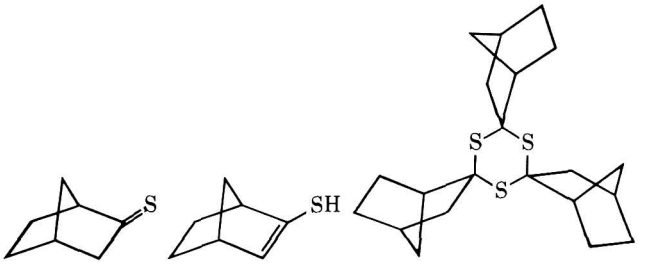
1,2,3,4-Tetrahydrodibenzothiophene-9,9-dioxide. - Following a procedure for the conversion of 10 to its sulfone,[27] about 40 mg of 10 was oxidized with 30% H_2O_2 to give white crystals (from EtOH), mp 185–187°. Ir (KBr) 1144 and 1289 cm^{-1} (SO_2).

Dibenzothiophene (11). - Slow moving tlc band C contained 22.7 mg of white crystals, mp 96.5–98°. Nmr (CCl_4) δ 7.2–7.6 (complex, 4 Ar H), 7.6–8.23 (complex, 4 Ar H), identical to that of authentic dibenzothiophene.

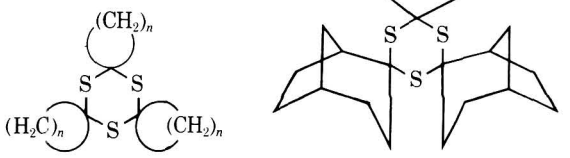
exo-2-Norbornanethiol. - S-Acetyl exo-2-norbornanethiol, bp 48–53° (0.06–0.15 mm), was prepared by addition of thioacetic acid to norbornene.[28] The thioacetate (68.11 g, 0.4 mol) was refluxed for 1 hr with 1 liter of alcoholic KOH (95% EtOH and 10% KOH in equal volumes). The reaction flask was cooled, and 5 N HCl was added to adjust to pH 7, causing the product to oil. The mixture was extracted with ether (900, 500, 250 ml), and the combined ether extracts were washed with H_2O (5 x 100 ml), dried (Na_2SO_4), and concentrated. Distillation gave 31.84 g (62% yield) of colorless liquid, bp 64.5–69.5° (13 mm); ir (neat liquid in cavity cell) 2570 cm^{-1} (SH). A portion was redistilled, bp (center fraction) 71.5° (19.3 mm); mass spectrum (70 eV) m/e 128; nmr (CCl_4) δ 1.0–2.4 (complex, 11 H), 2.6–3.0 (complex, 1 H).

2,4-Dinitrophenyl Derivative of exo-2-Norbornanethiol. - The exo thiol (1.28 g, 0.01 mol) was reacted with 1.86 g of FDNB (0.01 mol). Work-up and recrystallization from EtOH gave 2.66 g (90% yield) of yellow crystals, mp 117.3–118.3°. Two more recrystallizations gave an analytical sample (2.08 g), mp 118–118.9°; nmr ($CDCl_3$) δ 1.05–2.25 (complex, 8 H), 2.25–2.53 (complex, 2 H), 3.11–3.45 (complex, 1 H), 7.62, 8.37, and 9.04 (3 Ar H).

Anal. Calcd for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79; S, 10.89. Found: C, 53.18; H, 4.75; S, 10.99.



1 2 3, 3′



4, $n=4$
5, $n=5$
6, $n=6$

7

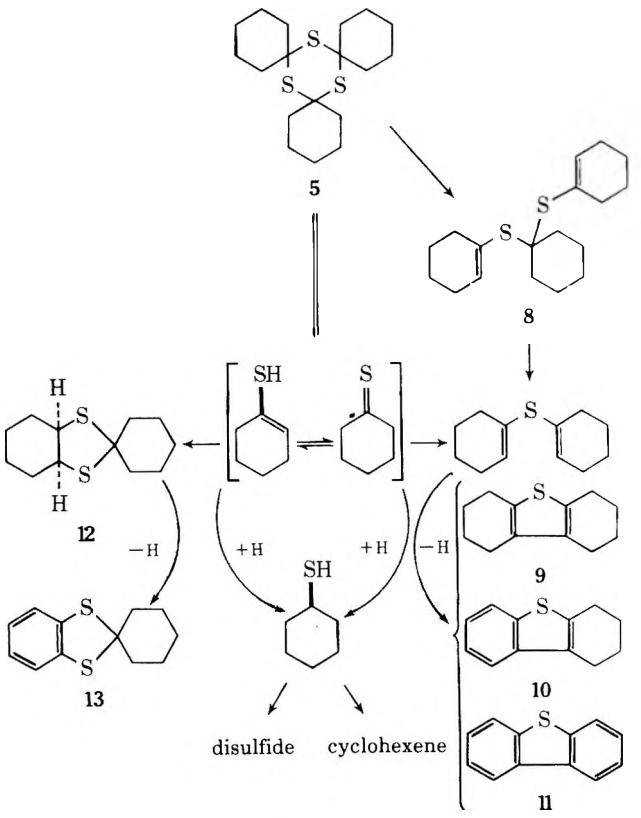
Two oligomers of norbornanethione, both evidently trimers from mass spectra, gave good yields of monomeric thioketone on pyrolysis at reduced pressure. Monomeric norbornanethione was found to be a remarkably stable thioketone. When initially generated it contained less than 1% (nmr) enethiol **2**, and after 5 days at room temperature 7% enethiol with 64% (visible) of the neat liquid surviving as the thioketone. In contrast to this stability, injection of molten cyclohexanethione trimer (**5**) onto sand at 300° instantly produced a red liquid (thioketone) in the condenser which became crystalline and colorless within minutes. The crystals were indistinguishable from the starting trimer.

The few previously reported stable thioketones involve heavily α-substituted rigid skeletons. Thiofenchone,[8,9] 2,2,4,4-tetramethyl-1,3-cyclobutanedithione,[10] and adamantanethione[11] are all rigid, highly hindered, nonenolizable thioketones. Thiocamphor[7,8] and thioketo steroids[12] possess rigidity and some quaternary α carbons. The trimer of adamantanethione is known, but no trimers have been prepared from any of the other stable thioketones. From the relative stability of norbornanethione it appears that the hindrance or conformation provided by the bicyclo[2.2.1]heptane skeleton is sufficient to stabilize the thioketone without the encumbering methyl groups of thiocamphor or thiofenchone. The thioketone stabilizing effect does not extend to its homolog, bicyclo[3.2.1]octane-2-thione. The qualitative order of stability of neat thioketones studied at room temperature is norbornanethione (days) > cycloheptanethione (days) > cyclopentanethione (hours) > cyclohexanethione (minutes). The major causes of fading of the red color are enolization and trimerization.

Freshly generated norbornanethione contained 4% (vpc) of a mixture of *exo*- and *endo*-2-norbornanethiol. These thiols were major products of atmospheric pressure pyrolysis. The appearance of a small amount of norbornanone was observed in several instances by ir, vpc, and mass spectrum after norbornanethione was manipulated or stored for prolonged periods at room temperature. Assuming that the fresh pyrolysis distillate contains 96% norbornanethione, as suggested by its nmr and vpc, pure norbornanethione has λ_{max} (heptane) 497 nm (ε 11.8). This value is close to that observed for other relatively stable thioketones.[7,8,11]

Cracking of trithianes at atmospheric pressure produced no thioketones but only pyrolysis products of thioketones which are characterized by hydrogen disproportionation and H_2S elimination. Pyrolyses of **3′**–**7** were pushed until no more distillate was collected, by which time the heating bath temperature was about 350°. Hard black residues were left after pyrolysis of **3′**, **4**, **6**, and **7**, while the residue from pyrolysis of cyclohexanethione trimer was a yellow oil. The distillates had the following compositions: from **3′**, 45% 2-norbornanethiol and 55% norbornene; from **4**, 75% cyclopentanethiol and 25% cyclopentene; from **5**, 88% cyclohexanethiol and 12% cyclohexene; from **6**, 84% cycloheptene; and bicyclo[3.2.1]-2-octene as the major product from **7**.

Scheme I



Cyclopentanethiol and 2-norbornanethiol were characterized as crystalline 2,4-dinitrophenyl (DNP) derivatives. The 2,4-dinitrophenyl-2-norbornyl sulfide was a mixture of endo and exo isomers which could not be completely separated by recrystallization. However, integration of the unique methine nmr signal showed that the major pyrolysis product was *exo*-2-norbornanethiol. Pure *exo*-2-norbornanethiol was prepared by addition of thioacetic acid to norbornene followed by saponification of *exo*-2-norbornyl thioacetate. *endo*-2-Norbornanethiol, containing some exo isomer, was prepared by $NaBH_4$ reduction of 2-norbornanethione. *endo*-2-Norbornanethiol is distinguished from the exo isomer by its exo methine proton resonance at 2.95–3.45 ppm in CCl_4; this methine resonance occurs at 2.6–3.0 ppm in *exo*-2-norbornanethiol. In the endo-DNP derivative the methine resonance occurs at 3.45–3.9 ppm and in the exo-DNP derivative at 3.11–3.45 ppm.

Distillation products from atmospheric pressure pyrolyses were generally more hydrogenated than the starting trithianes. Pot residues must then be relatively dehydrogenated. The dehydrogenation products of triscyclohexanethione, which appeared to give the least polymeric pot residue, were fractionated by molecular distillation followed by preparative tlc. Major components were identified as 1,2,3,4-tetrahydrodibenzothiophene (**10**), characterized as its crystalline sulfone, crystalline dibenzothiophene (**11**), 1,2,3,4,5,6,7,8-octahydrodibenzothiophene (**9**), and liquid spiro-2,2-pentamethylenebenzodithiolane (**13**).

Dehydrogenation product **13** had a chemical ionization mass spectral ion at *m/e* 223 (M + 1) with isotopic peak intensities expected for natural abundance ^{34}S and ^{13}C in a $C_{12}H_{14}S_2$ compound. It had a uv spectrum compatible with an *o*-dithiobenzene derivative.[13] Spiro structure **13** was assigned primarily on the basis of a four-proton multiplet at 1.9–2.3 ppm rather than a two-proton multiplet in this region required for the conceivable isomer hexahydrothianthrene. Under the dehydrogenative conditions hexahydrothianthrene, if present, could have been expected to undergo extensive dehydrogenation to thianthrene. Pyrolysis of thianthrene is known to give dibenzothiophene.[14] However, no thianthrene could be detected in any fractions. Further, the presence of hydrodibenzothiophenes suggests that the route to dibenzothiophene is one of those shown in Scheme I rather than *via* thianthrene. Fromm investigated the pyrolysis of triscyclohexanethione under similar conditions.[15] He did not examine the pot residue but did isolate a major volatile component to which he assigned structure **8** based on elemental analysis and the decolorization of bromine. Although the structural evidence is not compelling, compound **8** could be an intermediate between trimer **5** and dibenzothiophene. Katritzky and coworkers observed the formation of spiro dimer **12** on treatment of an ethereal ethanolic solution of cyclohexanethione monomer, from which the red color had faded, with diazomethane at 25°.[16] Since **13** was probably formed *via* **12**, the diazomethane used by Katritzky and coworkers is probably not necessary in the conversion of cyclohexanethione into its dithiolane dimer.

Although reduced pressure pyrolysis of trithianes is not necessarily a general method of preparing thioketones, it has some range of utility and is a very good method of preparation of 2-norbornanethione. The stability of norbornanethione compares favorably with the most stable thioketones known. Thus norbornanethione provides a good model for investigation of thioketone chemistry beyond enthiolization and trimerization.

Registry No.—**1**, 51849-44-6; **3**, 51849-42-4; **4**, 177-61-7; **5**, 177-58-2; **6**, 177-54-8; **7**, 51849-43-5; **9**, 15869-74-6; **10**, 16587-33-0; **10** sulfone, 51849-45-7; **11**, 132-65-0; **13**, 7127-65-3; bicyclo[3.2.1]octan-2-one, 5019-82-9; 2-norbornanone, 497-38-1; *endo*-2-norbornanethiol, 51849-46-8; *exo*-2-norbornanethiol 2,4-dinitrophenyl derivative, 51849-47-9; *endo*-2-norbornanethiol 2,4-dinitrophenyl derivative, 51849-48-0; cyclopentanethiol 2,4-dinitrophenyl derivative, 51849-49-1; *exo*-2-norbornanethiol, 51849-50-4.

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References and Notes

(1) M. Demuynck and J. Vialle, *Bull. Soc. Chim. Fr.*, 2748 (1967).
(2) R. Mayer and H. Berthold, *Chem. Ber.*, **96**, 3096 (1963).
(3) D. Paquer and J. Vialle, *Bull. Soc. Chim. Fr.*, 3595 (1969).
(4) J. W. Greidanus and W. J. Schwalm, *Can. J. Chem.*, **47**, 3715 (1969).
(5) O. G. von Ettinghausen and E. Kendrick, *Polymer*, **7**, 469 (1966); O. G. von Ettinghausen, French Patent 1,425,651; *Chem. Abstr.*, **65**, 17082*h* (1966).
(6) E. Campaigne, "The Chemistry of the Carbonyl Group," S. Patai, Ed., Interscience, New York, N. Y., 1966, Chapter 17.
(7) R. Mayer, J. Morgenstern, and J. Fabian, *Angew. Chem., Int. Ed. Engl.*, **3**, 277 (1964).
(8) J. Fabian and R. Mayer, *Spectrochim. Acta*, **20**, 299 (1964).
(9) C. N. R. Rao and R. Venkataraghavan, *Spectrochim. Acta*, **18**, 541 (1962).
(10) E. U. Elam and H. E. Davis, *J. Org. Chem.*, **32**, 1562 (1967).
(11) J. W. Greidanus, *Can. J. Chem.*, **48**, 3530 (1970).
(12) F. O. Bobbio and P. A. Bobbio, *Chem. Ber.*, **101**, 4241 (1968); C. Djerassi and D. Herbst, *J. Org. Chem.*, **26**, 4675 (1961).
(13) W. E. Parham, T. M. Roder, and W. R. Hasek, *J. Amer. Chem. Soc.*, **75**, 1647 (1953).
(14) G. M. Badger, P. Cheuychit, and W. H. F. Sasse, *Aust. J. Chem.*, **17**, 353 (1964); J. Aitken, T. Heeps, and W. Steedman, *Fuel*, **47**, 353 (1968).
(15) E. Fromm, *Chem. Ber.*, **60**, 2090 (1927).
(16) A. R. Katritzky, R. Mayer, J. Morgenstern, and M. J. Sewell, *J. Chem. Soc.*, 5953 (1965).
(17) R. W. Bost, J. O. Turner, and R. D. Norton, *J. Amer. Chem Soc.*, **54**, 1985 (1932).
(18) E. Campaigne and B. E. Edwards, *J. Org. Chem.*, **27**, 3760 (1962).

(19) This sample is probably a mixture of isomers. Several isomeric trimers have subsequently been isolated in reactions of norbornanethione.
(20) J. W. Greidanus, *Can. J. Chem.*, **48**, 3593 (1970).
(21) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Amer. Chem. Soc.*, **93**, 2897 (1971).
(22) Molar extinction coefficients based on 96% thioketone and no enethiol.
(23) The relative amounts of exo and endo thiol could not be estimated from the nmr because of the interfering signal of norbornene at 2.84 ppm.
(24) W. J. Lanum and J. C. Morris, *J. Chem. Eng. Data*, **14**, 93 (1969).
(25) D. Cagniant, P. Faller, and P. Cagniant, *Bull. Soc. Chim. Fr.*, 2410 (1961).
(26) D. Cagniant, P. Cagniant, and J. Trierweiler, *Bull. Soc. Chim. Fr.*, 601 (1969); R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res., Sect. B*, **15**, 497 (1956); *Chem. Abstr.*, **51**, 5785*g* (1957).
(27) J. D. Loudon, L. B. Young, and A. A. Robertson, *J. Chem. Soc.*, 591 (1964).
(28) D. I. Davies, L. T. Parfitt, C. K. Alden, and J. A. Claisse, *J. Chem. Soc. C*, 1585 (1969).

Decomposition of Sulfonyl Azides and *tert*-Butyl Azidoformate By Transition Metal Carbonyls

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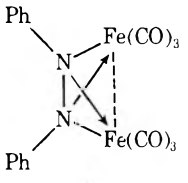
Iron and cobalt complexes $[Fe(RSO_2N)_2CO{\cdot}H_2O]_n$ and $[Co(RSO_2N)_2CO{\cdot}\frac{1}{2}H_2O]_n$ which are deficient of terminal and bridging metal carbonyls have been isolated from the reaction of methane-, benzene-, and *p*-toluenesulfonyl azide with iron pentacarbonyl, diiron nonacarbonyl, and dicobalt octacarbonyl. Hydrolysis of these with dilute hydrochloric acid leads to the corresponding *N,N'*-bis(sulfonyl)urea. Possible structures for the complexes involving coordination of a sulfonyl oxygen to the metal are presented and supporting evidence for such coordination is given. Free singlet sulfonyl nitrenes are not formed in these decompositions. The decomposition of *tert*-butyl azidoformate with iron pentacarbonyl and diiron nonacarbonyl gave impure complexes, still containing terminal and bridging carbonyls, which could be hydrolyzed to give mainly *tert*-butyl carbamate, di-*tert*-butyl iminodicarboxylate, and *N,N*-bis(*tert*-butoxycarbonyl)urea.

Despite the large volume of information available on the thermal and photochemical decomposition of organic azides,[1b,2-4] studies pertaining to the decomposition of organic azides by transition metal carbonyls have only recently appeared. Phenyl azide, which thermolyzes only above 120°, decomposes at room temperature in the presence of diiron nonacarbonyl to give a low yield of the nitrene product, azobenzene. The main product is the complex **1**, which decomposes spontaneously in solution to the urea complex **2**.[5]



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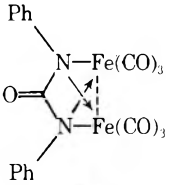

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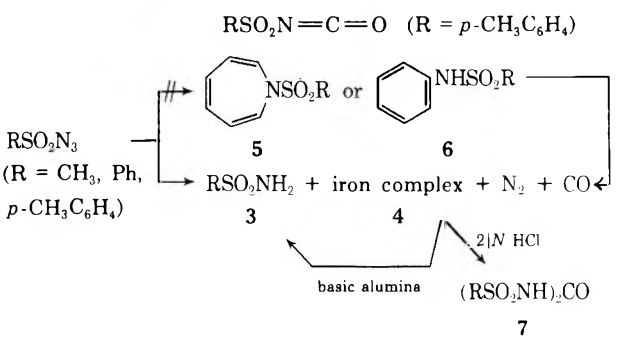
A similar complex was obtained from 2-azidobiphenyl, together with the urea and nitrene-derived products.[6] As part of our interest in generating sulfonyl nitrenes under mild conditions to study their behavior with aromatic compounds under kinetic control conditions,[3,7] we now report the results for the decomposition of sulfonyl azides and *tert*-butyl azidoformate by transition metal carbonyls.

Results and Discussion

The decomposition of excess methane-, benzene-, and *p*-toluenesulfonyl azide and *p*-toluenesulfonyl isocyanate with diiron nonacarbonyl at room temperature (heterogeneous) or iron pentacarbonyl at 60–65° (homogeneous) in benzene gave a low yield of the corresponding sulfonamide (**3**) and a high-melting amorphous iron complex (**4**) devoid of both terminal and bridging iron carbonyls. *N*-Sulfonylazepines (**5**), the expected aromatic addition products if discrete nitrenes were formed, were not detected nor were the corresponding sulfonanilides (**6**). Thus, no free singlet sulfonylnitrenes are generated in these catalyzed decompositions.



The nmr spectra of these complexes could not be obtained owing to their paramagnetic nature (*vide infra*) and their insolubility in solvents that did not effect their decomposition, and the mass spectra could not be determined owing to their insufficient volatility. Elemental analyses (reproducible from run to run) satisfied an empirical formula corresponding to $Fe(RSO_2N)_2CO{\cdot}H_2O$. Hydrolysis of these complexes with dilute hydrochloric acid gave the corresponding *N,N'*-bis(sulfonyl)urea (**7**) in high yield (70–80%), while chromatography on basic alumina gave the corresponding sulfonamide (80%). The crystal structure of the complexes obtained in this study could not be determined because of our inability to obtain them crystalline. They gave blue solutions in dimethyl sulfoxide from which the complex could not be recovered.

The stoichiometry of the reaction was found to be azide: $Fe_2(CO)_9$ = 4. For the decomposition of methanesulfonyl azide with diiron nonacarbonyl, the molar ratio of nitrogen to carbon monoxide evolved was 0.68. The calculated molar ratio, in which seven molecules of carbon monoxide are lost from diiron nonacarbonyl and four molecules of nitrogen are evolved from methanesulfonyl azide, is 0.57. The observed ratio is expected to be higher since a low yield of methanesulfonamide was also formed.

The decomposition of methanesulfonyl azide with dicobalt octacarbonyl in benzene at room temperature gave a

Table I
^{57}Fe Mössbauer Data of Some Iron(III) Complexes

Compd	Temp, °K	Isomer shift, δ	Quadrupole splitting, ΔE
4, R = CH_3	78	0.459 ± 0.023	0.863 ± 0.008
$HFe(H_2O)EDTA$[a]	78	0.457	0.422
$Fe(terpy)_3Cl_3$[b]	77	0.46	0.54
$[Fe(phen)_2Cl_2]ClO_4$[c]	80	0.39	0.05
$Sr_3[Fe(C_2O_4)_3]_2 \cdot 2H_2O$[d]	78	0.45	0.00

[a] Reference 12. [b] Reference 13. [c] Reference 14. [d] Reference 15.

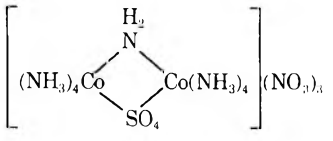
cobalt complex (8), also devoid of terminal and bridging metal carbonyls, as the major product and a low yield of methanesulfonamide. Elemental analysis (also reproducible) satisfied an empirical formula corresponding to $Co(CH_3SO_2N)_2CO \cdot \frac{1}{2}H_2O$ for the complex.

It is suggested that coordination of one of the sulfonyl oxygen atoms to the metal is the stabilizing factor which accounts for the absence of both bridging and terminal metal carbonyls in these complexes. Possible structures considered initially for the iron complexes were iron(II) dimeric and polymeric structures. The observed magnetic moment for the iron complex (4, R = CH_3) was found to be 5.93 BM, however, and this corresponds to an iron(III) high-spin complex. Magnetic moments for iron(III) high-spin complexes vary from 5.7 to 6.0 BM.[8] A metal–metal bond is unlikely in these complexes, since the observed magnetic moment approaches zero for binuclear complexes with metal–metal bonds.[9] It is not surprising that these complexes are high spin if the sulfonyl oxygen is coordinating to the metal because ligands having donor atoms of high electronegativity, especially oxygen and nitrogen, form high-spin complexes.[10,11]

The Mössbauer data for the iron complex (4, R = CH_3) and some related iron(III) complexes are listed in Table I. The observed isomer shift (δ 0.489) is in excellent agreement with that of other iron(III) complexes. Since the quadrupole splitting (ΔE) is high, the iron is clearly in a very unsymmetrical environment.

The infrared spectra of these iron and cobalt complexes exhibited a number of intense absorptions. The strong absorptions at *ca.* 3500–3200 and perhaps that at 1625 cm^{-1} could be due to either "lattice" water or coordinated water. If "lattice" water, it should have been lost on vacuum drying at 100° but was not. The intense absorption at 1625 cm^{-1} is more probably due to a >C=N– moiety and/or less likely to a perturbed organic carbonyl function.

The two sets of absorptions at 1340, 1360, 1255 and 1150, 1115, 1080 cm^{-1} for the cobalt complex are assigned respectively to the asymmetric and symmetric stretching modes of two different sulfonyl groups. If a sulfonyl oxygen is coordinated to cobalt or iron through oxygen, the two oxygen atoms of the sulfonyl groups are no longer equivalent and the degenerate vibrations are expected to be split. For the binuclear complex **9**, in which the sulfate group is a



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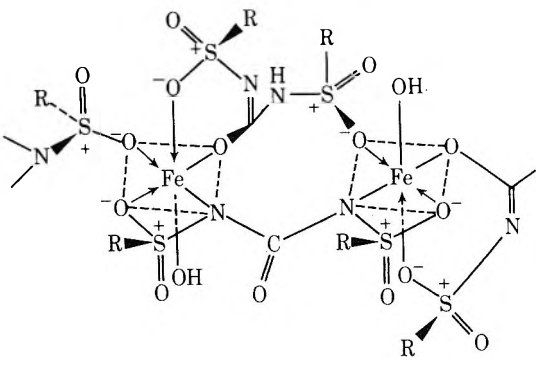
bidendate bridge, the sulfate absorptions are observed as two sets of bands at 1170, 1105, 1060, and 641, 571 cm^{-1}.[16] In comparison, the free sulfate ion exhibits only strong absorption at 1104 and 613 cm^{-1}. Similarly, the iron complexes exhibited two sets of absorptions at 1345, 1310, 1270 and 1165, 1130, and 1070 cm^{-1}.

Possible structures for these complexes are suggested in **10** and **11**, which fit all the known properties of these molecules. It is appreciated, of course, that numerous variants on stereochemistry and positional isomerism are possible, and these structures are presented only as a basis for future discussion. The polymeric nature of these complexes is suggested by their amorphous character and their insolubility. Of the two possibilities we would tend to favor **11** in view of the absence of a normal urea $\nu_{C=O}$ in the infrared spectra.



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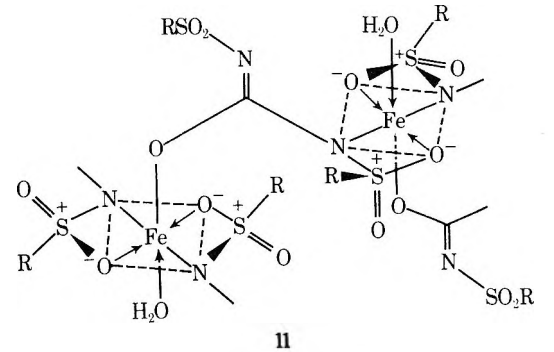

11

No reaction occurred between methanesulfonamide or *N,N'*-bis(methanesulfonyl)urea and diiron nonacarbonyl in benzene at room temperature or between methanesulfonyl azide and diiron nonacarbonyl in aqueous ethanol.

Since aryl azides form iron complexes still retaining terminal and bridging carbonyls,[5,6] we tested the suggestion of sulfonyl oxygen coordination with the metal by studying the decomposition of o-azidophenyl methyl sulfone (**12**) with metal carbonyls. The azide **12** was synthesized from o-aminophenyl methyl sulfone.[17]

The heterogeneous decomposition of an excess of **12** with diiron nonacarbonyl gave an impure iron complex exhibiting weak residual metal carbonyls. Attempted purification *via* Soxhlet extraction with benzene resulted in its decomposition to o-methanesulfonylaniline and *N,N'*-bis(o-methanesulfonylphenyl)urea. The decomposition of an excess of **12** with dicobalt octacarbonyl resulted in the formation of a cobalt complex completely devoid of terminal metal carbonyls, but whose infrared spectrum exhibited strong absorptions at 1605–1598, 1340, 1305, 1265, and 1145, 1125, 1060 cm^{-1}. Elemental analysis corresponded to the empirical formula $Co_2(C_7H_7NO_2S)_2CO \cdot H_2O$. The stoichiometry of the reaction, determined from the relative amount of unconsumed azide, appeared to be azide: $Co_2(CO)_8$ = 2, in contrast to the sulfonyl azide reaction, when the stoichiometric ratio was 4. It is difficult to assign a plausible structure to fit the formula $Co_2(C_7H_7NO_2S)_2CO \cdot H_2O$ without invoking a metal–metal bond. It is clear from the infrared spectrum, however, that a car-

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Experimental Section

General. All decompositions of azides with transition metal carbonyl were carried out with oven-dried (120°) glassware in a dry box under an atmosphere of dry nitrogen. Infrared spectra were determined on a perkin-Elmer 257 grating infrared spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian HA-100 or Perkin Elmer R-20B spectrometer using tetramethylsilane as the internal standard. Mass spectra were recorded on a CEC 21-104 spectrometer. Molecular sieve pellets (Fisher Scientific Co., type 4A, M-237), which were employed for the separation of nitrogen and carbon monoxide, were ground up to 35-48 mesh and activated at 240° for 20 hr in a gas chromatograph (Varian Aerograph A-90-P) using a helium flow rate of 30 ml/min.

o-Azidophenyl methyl sulfone. A mixture of o-aminophenyl methyl sulfone (1.8 g, 10.5 mole) (prepared by the method of Cava and Blake[17]) in distilled water (20 ml) and concentrated hydrochloric acid (2.7 ml) was heated on a steam bath until the solution became homogeneous, cooled to 0° and sodium nitrite (0.80 g, 12 mmole) in water (15 ml) added dropwise such that the temperature did not exceed 5°. Sodium azide (0.80 g, 12 mmole) in water (10 ml) was then added dropwise, while the temperature was maintained between 0-5°. The solution was stirred for a further 30 min, poured into ice-water, and the product recrystallized from aqueous ethanol (1:1 v/v) to give o-azidophenyl methyl sulfone (1.8 g, 80%) mp 93-94°; ir (KBr) 2140 (N_3), 1305 (SO_2), and 1130 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 8.07 (m, 1H), 7.90-7.17 (m, 3H), 3.26 (s, 3H); mass spec. (70 eV) 197 ($M^{+\cdot}$, 10).

Anal. Calcd for $C_7H_7N_3O_2S$: C, 42.68; H, 3.56. Found: C, 42.76; H, 3.67.

Decompositions of methanesulfonyl azide.

(a) With di-iron nonacarbonyl- Di-iron nonacarbonyl (0.576 g, 1.59 mmole) was added in one portion to a stirred solution of methanesulfonyl azide (1.004 g, 8.31 mmole) in dry benzene (20 ml) at room temperature. The resulting light yellow heterogeneous reaction mixture was stirred at room temperature for a further 8 hr, after which time gas evolution has ceased and it had turned dark brown in color. It was filtered under nitrogen and washed with dry benzene (30 ml) to give a tan amorphous *iron complex* (0.81 g), mp > 300°. Careful sublimation of the material under vacuum (0.02 torr) at an oil bath temperature of 115-120° gave methanesulfonamide (0.088 g, 15%) whose spectrum was identical to that of authentic material. The

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unsublimed material was washed and analyzed; ir (KBr) 3520-3260, 2930, 1625, 1430, 1400, 1345, 1310, 1270, 1250, 1165, 1130, 1075-10, 970, 845, and 785-770 cm^{-1}.

Anal. Calcd for $C_3H_6FeN_2O_5S_2 \cdot H_2O$: C, 12.51; H, 2.78; N, 9.72; S, 22.21; Fe, 19.37. Found: C, 12.47; H, 2.94; N, 9.79; S, 21.92; Fe, 19.23.

The original benzene filtrate was chromatographed on silica gel (100 g). Elution with ether (150 ml) gave a colorless oil (0.22 g, 1.9 mmole) whose ir spectrum was identical with that of methanesulfonyl azide. No other compounds were eluted.

The unsublimed material (0.75 g) was added to 2N HCl (12 ml) and stirred for ca. 15 min at room temperature, whereupon N,N'-bis(methanesulfonyl)urea (0.41 g, 72%), mp 199-200° (lit[20] 200-204°) separated and was washed with water; ir (KBr) 3250 and 3220 (NH), 1715 (CO), 1315 (SO_2), and 1125 cm^{-1} (SO_2); nmr (DMSO-d_6): δ 9.45 (NH, 2H, D_2O exchange), 3.30 (s, 6H).

Repetition of this experiment and column chromatography on basic alumina (120 g) of the iron complex from methanesulfonyl azide (5.8 mmole) and di-iron nonacarbonyl (3.35 mmole) gave methanesulfonamide (0.48 g, 80%) on elution with ether-methanol (1:1 v/v, 150 ml).

(b) With iron pentacarbonyl. Iron pentacarbonyl (0.400 g, 2.04 mmole) was added to a stirred solution of methanesulfonyl azide (0.803 g, 6.63 mmole) in dry benzene (25 ml). The resulting homogeneous yellow solution was heated at ca. 60-65° with vigorous stirring for 6 hr, after which time the reaction mixture was dark brown. It was cooled to room temperature, filtered under nitrogen, and the solids washed with benzene (30 ml) to give the crude tan amorphous iron complex (0.55 g), mp > 300°. Careful sublimation of this material gave methanesulfonamide (0.03 g, 7%). The unsublimed material had an ir spectrum identical to that of the iron complex prepared as under (a).

Anal. Calcd for $C_3H_6FeN_2O_5S_2 \cdot H_2O$: C, 12.51; H, 2.78. Found: C, 12.71; H, 2.73.

The original benzene filtrate was chromatographed on silica gel (100 g). Elution with ether (175 ml) gave a colorless oil (0.30 g, 2.5 mmole) whose ir spectrum was identical to that of starting methanesulfonyl azide. No other compounds were eluted.

The unsublimed material (0.51 g) was added to stirred 2 N HCl (14 ml). After stirring for ca. 15 min, N,N'-bis(methanesulfonyl)urea (0.30 g, 99%) was obtained.

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(c) With dicobalt octacarbonyl. Dicobalt octacarbonyl (1.04 g, 3.03 mmole) was added to a stirred solution of methanesulfonyl azide (2.955 g, 24.4 mmole) in dry benzene (50 ml). The resulting wine-colored homogeneous reaction mixture was stirred at room temperature for 7 hr, filtered under nitrogen, and the solid washed with benzene (25 ml) to give a light blue solid (1.64 g, 96%), mp > 300°. Sublimation of part of this material (0.14 g) as in (a) gave methanesulfonamide (ca. 4-5 mg). The material which did not sublime was analyzed; ir (KBr) 3540-3180, 2920, 1625, 1560-1535, 1405, 1340, 1310, 1255, 1195, 1150, 1115, 1080, 960, 935, 845, and 765 cm^{-1}.

Anal. Calcd for $C_3H_6CoN_2O_5S_2 \cdot 1/2H_2O$: C, 12.87; H, 2.50. Found: C, 12.70; H, 2.65.

The benzene filtrate was evaporated under vacuum to give a colorless oil (1.34 g, 11.1 mmole) whose ir spectrum was identical to that of starting methanesulfonyl azide.

The unsublimed material (1.50 g) was added to 2N HCl (14 ml). After stirring for ca. 35 min, N,N'-bis(methanesulfonyl)urea (0.89 g, 77%) was obtained.

Decompositions of benzenesulfonyl azide

(a) With di-iron nonacarbonyl. By a procedure similar to that described above, di-iron nonacarbonyl (0.713 g, 1.96 mmole) and benzenesulfonyl azide (2.11 g, 11.6 mmole) gave a tan amorphous iron complex (1.41 g, 88%), mp > 300°; ir (KBr) 3500-3300, 3060, 1590, 1570, 1480, 1450, 1405, 1350-1260, 1165, 1130, 1070, 1025, 1000, 920, 840-830, 755, 725, and 680 cm^{-1}.

Anal. Calcd for $C_{13}H_{10}FeN_2O_5S_2 \cdot H_2O$: C, 37.82; H, 2.92; N, 6.79. Found: C, 38.01; H, 3.09; N, 6.70.

Hydrolysis of this material (1.30 g) as before with 2N HCl gave N,N'-bis(benzenesulfonyl)urea monohydrate (0.84 g, 78%). The latter was dehydrated in a dry pistol at 100°/0.02 mm to N,N'-bis(benzenesulfonyl)urea, mp 155-157° (lit.[20] 155-156°).

(b) With iron pentacarbonyl. By a procedure similar to that described above, iron pentacarbonyl (0.395 g, 2.01 mmole) and benzenesulfonyl azide (1.21 g, 6.51 mmole) gave a tan amorphous iron complex (0.81 g, 98%), mp > 300°, whose ir spectrum was identical to that of the iron complex obtained in (a).

Hydrolysis of part of this material as before gave N,N'-bis(benzenesulfonyl)-urea monohydrate (80%).

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Decomposition of p-Toluenesulfonyl Azide With Excess Iron Pentacarbonyl.- By a procedure similar to that described above, iron pentacarbonyl (0.525 g, 2.68 mmole) and p-toluenesulfonyl azide (0.976 g, 4.96 mmole) gave a tan amorphous iron complex. Careful sublimation of this material gave p-toluenesulfonamide (0.040 g, 5%). Hydrolysis of the unsublimed material as before with 2N HCl gave N,N'-bis(p-toluenesulfonyl)urea monohydrate. Recrystallization from aqueous ethanol (1:1 v/v) and dehydration in a drying pistol at 100°/0.02 mm gave N,N'-bis(p-toluenesulfonyl)urea, mp 155-156° (lit[20] 155-159.5°).

Decomposition of p-Toluenesulfonyl Isocyanate with Di-iron Nonacarbonyl.- Di-iron nonacarbonyl (0.23 g, 0.062 mmole) was added in one portion to a stirred solution of p-toluenesulfonyl isocyanate (1.35 g, 6.87 mmole) in dry benzene (20 ml). This was stirred at room temperature for 12 hr, filtered under nitrogen, and washed with benzene to give a tan colored solid (ca. 0.29 g), mp > 300°. The filtrate was concentrated under vacuum to give a colorless oil. Upon the addition of water to this material, a white solid precipitated (0.76 g, 4.4 mmole) which had an ir spectrum identical to that of authentic p-toluenesulfonamide.

Hydrolysis of the iron complex with 2N HCl as before gave N,N'-bis(p-toluenesulfonyl)urea monohydrate (0.079 g).

Decomposition of o-Azidophenyl Methyl Sulfone

(a) With di-iron nonacarbonyl. Di-iron nonacarbonyl (0.71 g, 1.9 mmole) was added in one portion to a stirred solution of o-azidophenyl methyl sulfone (0.94 g, 4.8 mmole) in dry benzene (50 ml). As the reaction mixture was stirred at room temperature it became wine-colored (ca. 2 hr), and then dark brown (26 hr). The reaction mixture was filtered and washed with benzene (50 ml) to give a light brown impure complex (0.21 g), decomp. 155°. This material was placed in a Soxhlet extractor and extracted continuously for 54 hr with benzene (30 ml). A white crystalline solid separated and was identified as *N,N'-bis(o-methanesulfonylphenyl)urea* (0.06 g), mp 258-259°; ir (KBr) 3280 (NH), 1675 (CO), 1310 (SO_2), and 1160 cm^{-1} (SO_2); nmr (DMSO-d_6) δ 9.68 (NH, 2H, D_2O exchange), 8.40 (d, H_3 and H_6, $J_{3,4} = J_{5,6}$ = 8.5 Hz), 8.21 (t, H_5, $J_{4,5}$ = 6.5 Hz), 7.88 (t, H_4), 3.82 (s, 3H).

Anal. Calcd for $C_{15}H_{16}N_2O_5S_2$: C, 48.90; H, 4.38. Found: C, 49.06; H, 4.51.

The benzene extract from the Soxhlet extraction was chromatographed on silica gel (100 g). Benzene-ether (1:1 v/v, 150 ml) and ether (75 ml) eluted o-methanesulfonylaniline (0.03 g). No other compounds were eluted.

The original benzene filtrate was chromatographed on silica gel (150 g). Benzene-ether (1:1 v/v, 150 ml) gave o-azidophenyl methyl sulfone (0.17 g, 0.86 mmole). Benzene-ether (1:4 v/v, 100 ml) and ether (150 ml) eluted o-methanesulfonylaniline (0.18 g, 27%). No other compounds were detected.

(b) With dicobalt octacarbonyl. By a procedure similar to that described above, dicobalt octacarbonyl (0.497 g, 1.16 mmole) and o-azidophenyl methyl

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sulfone (1.67 g, 8.48 mmole) gave a grey cobalt complex (0.43 g), decomp. 160-165°.

Anal. Calcd. for $C_{15}H_{14}Co_2N_2O_5S_2 \cdot H_2O$: C, 35.85; H, 3.21; N, 5.59. Found: C, 36.19; H, 3.40; N, 5.41.

The benzene filtrate was chromatographed on silica gel (100 g). Benzene-ether (1:1 v/v, 250 ml) eluted starting o-azidophenyl methyl sulfone (1.19 g, 6.04 mmole). Benzene-ether (1:4 v/v, 100 ml) and ether (75 ml) eluted o-methanesulfonylaniline (0.12 g, 8.5%). No other compounds were detected.

Decomposition of tert-Butyl Azidoformate

(a) Di-iron nonacarbonyl and excess azidoformate. Di-iron nonacarbonyl (0.486 g, 1.35 mmole) was added in one portion to a stirred solution of freshly distilled tert-butyl azidoformate (bp 96-97°/42 mm; 1.19 g, 8.34 mmole) in dry benzene (25 ml). The resulting heterogeneous reaction mixture was stirred at room temperature for a further 10 hr, filtered under nitrogen, and washed with dry benzene (20 ml) to give a rust-colored solid (0.65 g), decomp. 270°; ir (KBr) 2205 (N=C=O), 2055 and 1980 cm^{-1} (terminal CO). Sublimation of this material at 120°/0.02 mm caused its decomposition; ir (KBr) 2205 (N=C=O) cm^{-1}.

Evaporation of the filtrate under vacuum gave a light yellow oil whose ir spectrum was identical to that of starting tert-butyl azidoformate.

(b) With excess di-iron nonacarbonyl. Di-iron nonacarbonyl (1.572 g, 4.31 mmole) was added in one portion to a solution of freshly distilled tert-butyl azidoformate (1.557 g, 10.83 mmole) in dry benzene (20 ml). The resulting heterogeneous reaction mixture was stirred at room temperature overnight, filtered under nitrogen, and washed with dry benzene to give a rust-colored solid. The filtrate was evaporated under vacuum but no organic material remained. The solid was chromatographed on basic alumina (175 g). Benzene-ether (4:1 v/v, 150 ml) eluted di-tert-butyl iminodicarboxylate (0.133 g, 11%), mp 118-119° (from hexane) (lit[21] 119-121°); ir (KBr) 3260 (NH), 1795, 1775, and 1760 cm^{-1} (urethane CO); nmr ($CDCl_3$), δ 6.80 (s, NH, 1H, D_2O exchange), 1.47 (s, 18H).

Anal. Calcd for $C_{10}H_{19}NO_4$: C, 35.35; H, 8.76. Found: C, 35.41; H, 8.98.

Benzene-ether (1:1 v/v, 150 ml) eluted tert-butylcarbamate (0.108 g, 8.5%), mp 104-106° (hexane) (lit[22] 108-109.5°); ir (KBr) 3440, 3320, 3250, 3200 and 1675 cm^{-1} (urethane CO); nmr ($CDCl_3$) δ 4.65 (s, NH_2, 2H, D_2O exchange), 1.42 (s, 9H). Ether (250 ml) and ether-methanol (10:1 v/v, 150 ml) eluted *N,N'-bis(tert-butoxycarbonyl)urea* (0.56 g, 40%), mp 122-124° (hexane); ir (KBr) 3220 (NH), 1790 (urethane CO), and 1725 cm^{-1} (urea CO); nmr ($CDCl_3$) δ 8.82 (NH, 2H, D_2O exchange), 1.47 (s, 18H); mass spec. (70 eV): no parent ion at m/e 260.

Anal. Calcd for $C_{11}H_{20}N_2O_5$: C, 50.77; H, 7.69. Found: C, 51.06; H, 7.81.

No other compounds were eluted.

6

(c) With excess iron pentacarbonyl. A solution of freshly distilled tert-butyl azidoformate (2.55 g, 17.8 mmole) and iron pentacarbonyl (3.74 g, 19.0 mmole) in dry benzene (70 ml) was boiled under reflux for 12 hr with vigorous stirring. The reaction mixture was cooled to room temperature, filtered under nitrogen, and washed with benzene (50 ml) to give a rust-colored solid (ca. 2.46 g); ir (KBr) 2205 (N=C=O) cm^{-1}. This was added to 2N HCl (20 ml) with vigorous stirring at room temperature. The resulting homogeneous yellow solution was stirred for a further 10 min, and then extracted with ether (2 x 250 ml). The combined ether extracts were dried ($MgSO_4$), and evaporated under vacuum to give a light yellow oil which was chromatographed on basic alumina (150 g). Benzene-ether (3:1, v/v, 175 ml) gave a white solid (0.48 g, 25%), mp 115-116°, whose ir spectrum was identical to that of di-tert-butyl iminodicarboxylate. Benzene-ether (1:1 v/v, 150 ml) eluted a white solid (0.106 g, 5.1%), mp 104-105°, whose ir spectrum was identical to that of tert-butylcarbamate. Ether (150 ml) eluted a white solid (0.07 g, 3%) whose ir spectrum was identical to that of N,N'-bis(tert-butoxycarbonyl)urea. Ether-methanol (10:1 v/v, 100 ml) eluted an oily solid (0.075 g, 5%) which crystallized with difficulty from benzene-hexane (1:2 v/v) to give white plates of a compound tentatively identified as *N-tert-butoxycarbonyl urea*, mp 185-187°; ir (KBr) 3385, 3360, 3230, 1715 (urethane CO), 1690 cm^{-1} (urea CO).

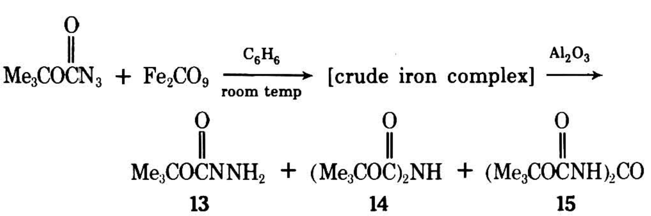
Anal. Calcd for $C_6H_{12}N_2O_3$: C, 45.00; H, 7.55; N, 17.48. Found: C, 45.06; H, 7.66; N, 17.25.

The original benzene filtrate was evaporated under vacuum to give a light yellow oil which was chromatographed on basic alumina (100 g). Benzene-ether (4:1 v/v, 150 ml) eluted di-tert-butyl iminodicarboxylate (0.107 g, 5.5%). Elution with ether (100 ml) gave tert-butylcarbamate (0.055 g, 2.6%), and further elution with ether gave N,N'-bis(tert-butoxycarbonyl)urea (0.054 g, 2.4%). Ether-methanol (10:1 v/v, 125 ml) eluted an oily solid (0.040 g) which crystallized with difficulty from hexane. Sublimation of this material at 65°/0.05 mm gave 5,5-dimethyloxazolidone, mp 77-79° (lit[23] 80°); ir (KBr) 3250 (NH), 1720 cm^{-1} (C=O); mass spec. (70 eV) m/e 115 ($M^{+\cdot}$, 10). No other compounds were eluted.

Gas Analysis of the Decomposition of Methanesulfonyl Azide with Di-iron Nonacarbonyl. - The apparatus consisted of a mercury bubble trap, a three-way glass stopcock, rubber tubing (2 in), a glass tube, a rubber septum and a round-bottomed flask (50 ml). A solution of methanesulfonyl azide to be decomposed in degassed benzene (20 ml) was frozen in a dry ice-acetone bath and then the appropriate amount of di-iron nonacarbonyl was added. The system was evacuated to 0.02 mm, and the frozen reaction mixture was then allowed to warm to room temperature. It was then stirred at room temperature and the evolved gases were analyzed by g.l.c. using a 5 ft x 1/4 in 4A molecular sieve (35-48 mesh) column at an oven temperature of 72° and a helium flow rate of 30 ml/min. The ratio of N_2/CO was found to be 0.68.

bonyl group, if present in this complex, must be seriously perturbed by the metal. The structure of this complex remains to be determined as well.

Since the >S=O ↔ >+S–O− bond is more polar than a carbonyl function, it was expected that the latter might not function as efficiently as the former in displacing metal-bonded carbonyl groups. This, indeed, appears to be the case. The decomposition of *tert*-butyl azidoformate by di-iron nonacarbonyl gave an iron complex which did exhibit terminal metal carbonyl absorptions at 2055 and 1980



13 14 15

cm^{-1}. This material was thermally unstable when heated to 120° under high vacuum. Chromatography of the complex on basic alumina gave *tert*-butyl carbamate (**13**), di-*tert*-butyl iminodicarboxylate (**14**), and *N,N'*-bis(*tert*-butoxycarbony l)urea (**15**) in 11, 9, and 40% yields, respectively.

The decomposition of *tert*-butyl azidoformate with iron pentacarbonyl at *ca.* 65° in benzene gave an impure iron-containing material devoid of both bridging and terminal metal carbonyls. Dilute acid hydrolysis followed by chromatography on basic alumina gave **13, 14, 15,** and *N-tert*-butoxycarbonylurea in 5, 25, 3, and 5% yields, respectively. If the filtrate was chromatographed on basic alumina without prior acid hydrolysis, the following products were obtained: **13** (2.6%), **14** (5.5%), **15** (2.4%), and 5,5-dimethyloxazolidone (2%).

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Registry No.—Diiron nonacarbonyl, 15321-51-4; iron pentacarbonyl, 13463-40-6; dicobalt octacarbonyl, 10210-68-1; methanesulfonyl azide, 1516-70-7; methanesulfonyl azide iron complex, 51779-40-9; methanesulfonyl azide cobalt complex, 51898-91-0; benzenesulfonyl azide, 938-10-3; benzenesulfonyl azide iron complex, 51779-42-1; *p*-toluenesulfonyl azide, 941-55-9; *p*-toluenesulfonyl isocyanate, 4083-64-1; o-aminophenyl methyl sulfone, 2987-49-7; o-azidophenyl methyl sulfone, 51779-31-8; *N,N'*-bis(o-methanesulfonylphenyl)urea, 51806-01-0; *tert*-butyl azidoformate, 1070-19-5; di-*tert*-butyl iminodicarboxylate, 51779-32-9; *tert*-butyl carbamate, 4248-19-5; *N,N'*-bis(*tert*-butoxycarbonyl)urea, 51779-33-0; *N*-*tert*-butoxycarbonylurea, 31598-86-4.

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References and Notes

(1) (a) NSF Undergraduate Participant, summer 1970. (b) R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 149 (1964).
(2) L. Horner and A. Christmann, *Angew. Chem., Int. Ed. Engl.*, **2**, 599 (1963).
(3) R. A. Abramovitch and R. G. Sutherland, *Fortschr. Chem. Forsch.*, **16**, 1 (1970).
(4) W. Lwowski, Ed., "Nitrenes," Interscience, New York, N. Y., 1970.
(5) M. Dekker and G. R. Knox, *Chem. Commun.*, 1243 (1967).
(6) C. D. Campbell and C. W. Rees, *Chem. Commun.*, 537 (1969).
(7) (a) R. A. Abramovitch and V. Uma, *Chem. Commun.*, 797 (1968); (b) R. A. Abramovitch, T. D. Bailey, T. Takaya, and V. Uma, *J. Org. Chem.*, **39**, 340 (1974).
(8) B. N. Figgis and J. Lewis in "Modern Coordination Chemistry," J. Lewis and R. G. Wilkens, Ed., Interscience, New York, N. Y., 1960.
(9) L. Sacconi and I. Bertini, *J. Amer. Chem. Soc.*, **90**, 5443 (1968).
(10) L. Sacconi, M. Ciampolini, and G. P. Speroni, *Inorg. Chem.*, **4**, 1116 (1965).
(11) L. Sacconi and I. Bertini, *J. Amer. Chem. Soc.*, **88**, 5182 (1966).
(12) J. J. Spijkerman, L. H. Hall, and J. L. Lambert, *J. Amer. Chem. Soc.*, **90**, 2039 (1968).
(13) W. M. Reiff, W. A. Baker, and N. E. Erickson, *J. Amer. Chem. Soc.*, **90**, 4794 (1968).
(14) R. R. Barrett, B. W. Fitzsimmons, and A. Owusu, *J. Chem. Soc. A*, 1575 (1968).
(15) P. K. Gallagher and C. R. Kurkjian, *Inorg. Chem.*, **5**, 214 (1966).
(16) K. Nakemota, J. Fugita, S. Taneka, and M. Kobayashi, *J. Amer. Chem. Soc.*, **79**, 4904 (1957).
(17) M. P. Cava and C. E. Blake, *J. Amer. Chem. Soc.*, **78**, 5444 (1956).
(18) R. A. Abramovitch, J. Roy, and V. Uma, *Can. J. Chem.*, **43**, 3407 (1965).
(19) O. C. Dermer and M. T. Edmison, *J. Amer. Chem. Soc.*, **77**, 70 (1955).
(20) L. Field and F. A. Grunwald, *J. Amer. Chem. Soc.*, **75**, 934 (1953).
(21) L. A. Carpino, *J. Org. Chem.*, **29**, 2820 (1964).
(22) B. Loev and M. F. Kormendy, *J. Org. Chem.*, **28**, 3421 (1963).
(23) W. J. Close, *J. Amer. Chem. Soc.*, **73**, 95 (1951).

Synthesis of Dihalomethyl and α-Haloalkyl Sulfones by the Halogenative Decarboxylation of α-Aryl- and α-Alkylsulfonylalkanecarboxylic Acids

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The synthesis by brominative decarboxylation of meta- and para-substituted bromomethyl and α-bromobenzyl benzyl sulfones is described. Included are nine $ArCH_2SO_2CH_2Br$, four $PhCHBrSO_2CH_2Ar$, and five $ArCHBrSO_2CH_2Ph$ types. The nine bromomethyl benzyl sulfones were prepared from the dibromomethyl benzyl sulfones by reduction. Halogenative decarboxylations of α-cyclopropylsulfonyl-α-phenylacetic acid and phenylsulfonylacetic acid in refluxing carbon tetrachloride using *N*-halosuccinimides are described. Phenylthioacetic acid with *N*-chlorosuccinimide in CCl_4 gave mainly phenylthio-α-chloroacetic acid at 25° and mainly phenyl chloromethyl sulfide at 77°. Mechanisms for these reactions are discussed.

The halogenative decarboxylation of α-carboxyalkyl sulfones has been used as a preparative method for haloalkyl and dihalomethyl sulfones since before the turn of the century.[1] Sulfone carboxylic acids of the type $ArSO_2CH_2CO_2H$ give aryl dihalomethyl sulfones, $ArSO_2CHX_2$ (X = Cl, Br, or I), whereas $ArSO_2CHRCO_2H$ types give $ArSO_2CHXR$.[1] Since the corresponding sulfides, $ArSCH_2CO_2H$, $ArSCHRCO_2H$, $RSCH_2CO_2H$, and $RSCHR'CO_2H$, are readily available from reactions of ArSNa or RSNa with $ClCH_2CO_2H$ or $ClCHRCO_2H$ or from reactions of RX with $HSCH_2CO_2Na$ or $HSCHRCO_2Na$, these provide convenient starting materials. The corresponding sulfone carboxylic acids are obtained in high yield by oxidation. The latter react readily with halogens in aqueous acetic acid solution to give good yields, *e.g.*, of dihalomethyl aryl or alkyl sulfones.[1,2] It is often convenient to carry out the preparation of the sulfide, oxidation, bromination, and decarboxylation all in a single reaction vessel, as in the preparation of bis-α-bromobenzyl sulfone.[3] In the present study this method has been extended to the preparation of a number of other α-halo sulfones, *e.g.*

$$ArCH_2X \xrightarrow[\text{2. excess } 30\%\ H_2O_2 \\ \text{3. NaBr}]{\text{1. } HSCH_2CO_2Na} ArCH_2SO_2CHBr_2$$

Use of excess hydrogen peroxide in step 2 ensures complete oxidation of the sulfide and serves to generate bromine in the halogenation step.

This method can also serve as a route to bromomethyl alkyl or aryl sulfones, since the dibromomethyl sulfones are readily reduced to bromomethyl sulfones by sulfite ion[2] (see Experimental Section).

$$ArCH_2SO_2CHBr_2 + SO_3^{2-} + 2H_2O \xrightarrow{H_2O-EtOH} ArCH_2SO_2CH_2Br + SO_4^{2-} + Br^- + H_3O^+$$

A number of types of α-bromobenzyl benzyl sulfones have now been prepared by this general route.

Table I
Halogenative Decarboxylations of Sulfone Carboxylic Acids by *N*-Halosuccinimides (1 Equiv) in Refluxing Carbon Tetrachloride

Substrate	Halogen source	Time, hr	Product	Yield,[a] %
$PhSO_2CH_2CO_2H$ (1)	NCS[b]	12	$PhSO_2CHCl_2$	73
			$PhSO_2CH_2Cl$	15
c-$PrSO_2CH(Ph)CO_2H$ (2)	NCS[b]	5.5	c-$PrSO_2CHClPh$	80
			c-$PrSO_2CCl_2Ph$	20
c-$PrSO_2CH(Ph)CO_2H$ (2)	NBS[c]	5.5	c-$PrSO_2CHBrPh$	87 (63)[d]
c-$PrSO_2CH(Ph)CO_2H$ (2)	NIS[e]	6	c-$PrSO_2CHIPh$	32
$PhSO_2C(Me)(Ph)CO_2H$ (3)	NCS[b]	18	None	
$PhSO_2C(Me)(Ph)CO_2H$ (3)	NCS[b]	19[f]	$PhSO_2CH(Me)Ph$	Low
$PhSCH_2CO_2H$	NCS[b]	4	$PhSCH_2Cl$	(80)[g]
$PhSCH_2CO_2H$	NCS[b]	18[h]	$PhSCHClCO_2H$	71

[a] By nmr. [b] *N*-Chlorosuccinimide. [c] *N*-Bromosuccinimide. [d] Isolated yield. [e] *N*-Iodosuccinimide. [f] In chlorobenzene at 140°. [g] Isolated as the sulfone after oxidation; nmr analysis showed 84% of $PhSCH_2Cl$ and 16% of $PhSCH(Cl)CO_2H$. [h] At 25°.

We also report an alternative procedure for carrying out halogenative decarboxylations using *N*-halosuccinimides as the halogen source and comment on the mechanism and possible extension of the reaction to related systems.

Results

Examples of brominative decarboxylations used in the preparation of bromo sulfones of the types $ArSO_2CHBr_2$, $ArCH_2SO_2CHBr_2$, $ArCHBrSO_2R$, $PhCHBrSO_2CH_2Ar$, and $ArCHBrSO_2CH_2Ph$ are given in the Experimental Section.

The halogenative decarboxylations using *N*-halosuccinimides (NCS, NBS, and NIS) as a source of halogen were carried out in refluxing carbon tetrachloride solution. Phenylsulfonylacetic acid ($PhSO_2CH_2CO_2H$, **1**), α-cyclopropylsulfonyl-α-phenylacetic acid [c-$PrSO_2CH(Ph)CO_2H$, **2**], and α-phenyl-α-methyl-α-phenylsulfonylacetic acid [$PhSO_2C(Me)(Ph)CO_2H$, **3**] were used as typical substrates containing two, one, and zero enolizable hydrogen atoms, respectively. The results are summarized in Table I.

Examination of Table I shows that halogenative decarboxylation is successful when either one or two enolizable hydrogen atoms is present, but fails when an enolizable hydrogen atom is absent.

It seems likely that electrophilic reagents other than halogens may be used in electrophile decarboxylations. Attempts to substitute a PhS group into $PhSO_2CH_2CO_2H$ under the halogenative decarboxylation conditions using PhSCl, $PhSSO_2C_6H_4Me$-*p*, *N*-PhS-phthalimide, or *N*-PhS-phthalimide and F_3CCO_2H have thus far been unsuccessful, however.

Discussion

It is significant that in all the preparative halogenative decarboxylations of sulfone carboxylic acids reported to date one or two hydrogen atoms are present on the carbon atom bearing the RSO_2 and CO_2H groups.[1-3] The failure of $PhSO_2C(Me)(Ph)CO_2H$ (**3**) to undergo halogenative decarboxylation, even under strenuous conditions (Table I), emphasizes the requirement of the presence of at least one enolizable hydrogen atom. Judging from these preparative studies and earlier kinetic studies on the decarboxylation of sulfone carboxylic acids and halo sulfone carboxylic acids, a mechanism involving rate-limiting enolization followed by rapid halogenation and subsequent rapid decarboxylation becomes highly probable, *e.g.*[4]

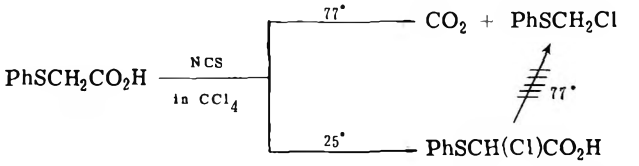
$$PhSO_2CHRCO_2H \xrightarrow{slow} PhSO_2CH{=}C(OH)_2 \xrightarrow{fast}$$

$$PhSO_2C(X)(R)CO_2H \xrightarrow{fast} PhSO_2CHXR + CO_2$$

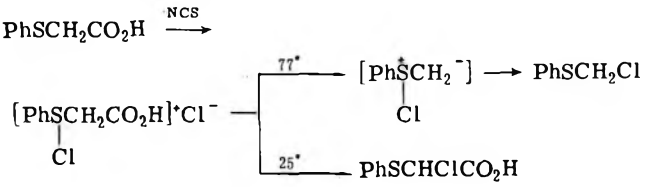
N-Halosuccinimides no doubt serve merely as a convenient source of low concentrations of X_2, a role that has been demonstrated in other types of halogenations, including allylic halogenation.[6] If two enolizable hydrogen atoms are present, enolization of the intermediate halo sulfone carboxylic acid, *e.g.*, $PhSO_2CHXCO_2H$, competes favorably with decarboxylation, and the major product is the dihalomethyl sulfone, *e.g.*, $PhSO_2CHX_2$.

Evidence for rate-limiting enolization in the bromination of α-sulfonylcarboxylic acids comes from the early work of Ramberg and his students, who demonstrated, using several optically active systems, *e.g.*, $EtSO_2CH(Me)CO_2H$ and $PhSO_2CH(Me)CO_2H$, that in acidic solutions in the presence of excess bromine the (pseudo-first-order) rates of bromination and racemization were essentially identical.[7] The order of ease of decarboxylation rates $RSO_2CX_2CO_2H$ > RSO_2CHXCO_2H > $RSO_2CH_2CO_2H$ was established in early preparative studies,[1] as was the more rapid decarboxylation of the carboxylate salts as compared to the free acids.[1,9]

It is clear from the above discussion that halo or dihalo sulfone carboxylic acids are intermediates in the halogenative decarboxylation of α-alkylsulfonyl- or α-arylsulfonylcarboxylic acids. A different route is followed, however, in the conversion of α-phenylthioacetic acid to phenyl chloromethyl sulfide by the action of NCS in refluxing CCl_4. Here phenylthiochloroacetic acid can be isolated from a chlorination run at 25°, but it does not decarboxylate to phenyl chloromethyl sulfide under the reaction conditions (Table I).



A chlorosulfonium salt is probably formed as the initial product. At 25° it rearranges to phenylthiochloroacetic acid,[11] but at higher temperatures decarboxylation of the sulfonium salt competes favorably with rearrangement.[12]



It seems likely from these mechanistic considerations that halogenative decarboxylations will be successful in general for systems of the type $EWGCH_2CO_2H$ and $EWGCH(R)CO_2H$, where EWG is a strongly electron-withdrawing group ($ArSO_2$, RSO_2, CN, NO_2, COR, CO_2R, SR_2^+, NR_3^+, and the like) and R is either an alkyl or an aryl group.

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Experimental Section

Nmr spectra were run on Varian T60 and Perkin-Elmer-Hitachi R-20B spectrometers (60 MHz). Chemical shifts are reported in δ units (parts per million downfield from TMS) and were determined in chloroform solution. Melting points are uncorrected. Microanalyses are by Micro-Tech, Skokie, Illinois.

Dibromomethyl Benzyl and Aryl Sulfones. The preparation of dibromomethyl 3-nitrobenzyl sulfone starting from 3-nitrobenzyl chloride and mercaptoacetic acid is typical of the preparations of dibromomethyl benzyl sulfones (Table II).[14] Dibromomethyl aryl sulfones can be prepared by a similar procedure starting with arenethiols and chloroacetic acid.[1]

Table II. Melting Points and Carbon and Hydrogen Analyses for Dibromomethyl Benzyl Sulfones, $ArCH_2SO_2CHBr_2$.

Substituent	MP °C[a]	Molecular Formula	Calcd. C	Calcd. H	Found C	Found H
3-NO_2	138-140.2	$C_8H_7Br_2NO_4S$	25.76	1.89	25.90	2.04
4-Me	122-123.8	$C_9H_{10}Br_2O_2S$	31.60	2.95	31.79	3.01
4-Cl	121.2-122.6	$C_8H_7Br_2ClO_2S$	26.51	1.95	26.69	2.05
3-Me	145-146	$C_9H_{10}Br_2O_2S$	31.60	2.95	31.55	2.95
3-F	100.8-101.3	$C_8H_7Br_2FO_2S$	27.77	2.04	27.92	2.18
4-NO_2	149-149.5	$C_8H_7Br_2NO_4S$				
3-Br	148.8-150.2	$C_8H_7Br_3O_2S$	23.61	1.73	23.87	1.82
4-MeO	140-141.2	$C_9H_9Br_3O_3S$	24.74	2.08	25.02	2.17

[a]Uncorrected.

In a 250-ml flask equipped with a condenser and stirrer was placed 8.60 g (0.0602 mole) of 3-nitrobenzyl chloride (Eastman) dissolved in 75 ml of 95% EtOH. A solution prepared from 6 ml (0.052 mole) of an 80% aqueous solution of mercaptoacetic acid (Eastman) and 50 ml of aqueous sodium hydroxide (0.15 mole) was added in one portion. After the initial reaction had subsided, the solution was heated at reflux for 1 hr and stirred overnight at room temperature. Most of the ethanol was removed by rotary evaporation and the residue was diluted with 125 ml of water. The solution was acidified to Congo Red paper with 3 N HCl, and the oily layer taken up in ether(2 125-ml extracts). After washing with water the combined ethereal extracts were

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evaporated to give crude 3-nitrobenzylthioacetic acid. To a solution of the crude acid in 75 ml of glacial acetic acid was added 30 ml (0.26 mole) of 30% H_2O_2 over a 30 min period. After a 15 min reflux the solution was allowed to come to room temperature (1 hr) and an aqueous solution of potassium bromide was added until the evolution of bromine ceased. Rapid decolorization of bromine occurred and carbon dioxide was evolved. An additional 6 ml of Br_2 was added to complete the reaction. (If sufficient H_2O_2 and KBr are used this is unnecessary.) The reaction mixture was diluted with water and washed with aqueous bisulfite to remove excess bromine. The solid was collected on a filter and then recrystallized from 95% ethanol; pale yellow crystals, mp 138.8-140.2°; nmr 7.3-8.4 (m, 4H), 6.13 (s, 1H), 4.84 (s 2H). The other dibromomethyl benzyl sulfones for which analytical data are reported in Table II had similar nmr spectra. The sample of dibromomethyl 3-bromo-4-methoxybenzyl sulfone was obtained in a reaction where p-methoxybenzyl alcohol (anisyl alcohol) was the starting material. (Bromination of the benzene ring occurred during the reaction.)

Bromomethyl Benzyl Sulfones. These were prepared from the dibromomethyl benzyl sulfones in average yields of about 75% by reduction with a slight excess of potassium sulfite in aqueous ethanol (7 hr reflux). The nmr spectrum for bromomethyl 3-nitrobenzyl sulfone is typical:[14] 7.6-8.4 (m, 4H); 4.62 (s, 2H); 4.30 (s, 2H).

Table III. Melting Points and Carbon and Hydrogen Analyses for Bromomethyl Benzyl Sulfones, $ArCH_2SO_2CH_2Br$.

Substituent	MP °C[a]	Molecular Formula	Calcd. C	Calcd. H	Found C	Found H
3-NO_2	114-115	$C_8H_8BrNO_4S$	32.67	2.72	32.62	2.76
4-Me	169.5-170.5	$C_9H_{11}BrO_2S$	41.08	4.21	41.00	4.42
4-Cl	195.5-196	$C_8H_8BrClO_2S$				
3-Me	90-90.5	$C_9H_{11}BrO_2S$	41.08	4.21	41.27	4.14
3-F	95-95.8	$C_8H_8BrFO_2S$	35.97	3.02	35.73	3.04
4-NO_2	214-215.8	$C_8H_8BrNO_4S$	32.67	2.72	33.08	2.88
3-Br						
4-MeO	146.5-147.2	$C_9H_{11}Br_2O_3S$	30.19	2.82	30.30	2.16
3-Br	117-117.9	$C_8H_8Br_2O_2S$	29.29	2.46	29.40	2.48

[a]Uncorrected

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α-Bromobenzyl Methyl Sulfone. The procedure was similar to that described for dibromomethyl 3-nitrobenzyl sulfone except that no additional bromine was added. α-Bromophenylacetic acid, 6.7 g (0.0312 mole) in MeOH was treated with a methanol solution containing 0.0312 mole of methanethiol. Oxidation of the sulfide was effected with 20 ml (0.176 mole) of 30% H_2O_2. The yield of sulfone was 68%; mp 96-97°; nmr: 7.3-7.7 (m, 5H); 5.73 (s, 1H); 3.00 (s, 3H). Anal. Calcd for $C_8H_9BrO_2S$: C, 38.37; H, 3.64. Found: C, 38.53; H, 3.60.

α-Bromobenzyl Benzyl Sulfones. Arylmethanethiols were prepared in situ by the action of m- or p-substituted benzyl chlorides with thiourea in 95% ethanol and subsequent treatment with aqueous sodium hydroxide. The crude thiols were condensed with α-bromophenylacetic acid and the resulting α-carboxybenzyl substituted benzyl sulfides were oxidized and subjected to brominative decarboxylation, as above.[14]

Table IV. Melting Points and Carbon and Hydrogen Analyses for α-Bromobenzyl Benzyl Sulfones, $PhCHBrSO_2CH_2Ar$.

Substituent	MP °C[a]	Molecular Formula	Calcd C	Calcd H	Found C	Found H
4-Me	129-129.5	$C_{15}H_{15}BrO_2S$	53.11	4.46	53.03	4.59
4-Cl	175.9-176.1	$C_{14}H_{12}BrClO_2S$	46.75	3.36	47.05	3.57
3-F	110.6-111.3	$C_{14}H_{12}BrFO_2S$	48.99	3.52	48.92	3.52
3-Me	120.4-121.1	$C_{15}H_{15}BrO_2S$	53.11	4.46	53.22	4.58

[a]Uncorrected

The isomeric m- and p-substituted α-bromobenzyl benzyl sulfones were prepared starting from m- and p-substituted mandelic acids. Treatment with PBr_3 followed by methanol gave the bromo esters, $ArCHBrCO_2Me$, which were condensed with phenylmethanethiol to give the sulfides; the latter were subjected to hydrolysis, oxidation and brominative decarboxylation, as above.[14]

Table V. Melting Points and Carbon and Hydrogen Analyses for α-Bromobenzyl Benzyl Sulfones, $ArCHBrSO_2CH_2Ph$.

Substituent	MP °C	Molecular Formula	Calcd C	Calcd H	Found C	Found H
4-Me	124.8-125.2	$C_{15}H_{15}BrO_2S$	53.11	4.46	53.22	4.58
4-Cl	140.2-140.7	$C_{14}H_{12}BrClO_2S$	46.75	3.36	46.78	3.57

Continued...

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3-Cl	117-117.3	$C_{14}H_{12}BrClO_2S$	46.75	3.36	47.00	3.63
4-F	115-115.3	$C_{14}H_{12}BrFO_2S$	48.99	3.52	49.16	3.81
3-Me	83-84	$C_{15}H_{15}BrO_2S$	53.11	4.46	53.08	4.47

[a]Uncorrected

α-Cyclopropylsulfonyl-α-phenylacetic Acid (2). Benzyl cyclopropyl sulfone[15] (1.0 g, 5.1 mmol) was dissolved under nitrogen in 100 ml of anhydrous ethyl ether. Butyllithium (2.91 ml of 2.1 M in hexane) was added with a syringe while the mixture was maintained at 0°. The mixture was warmed to 32° for ½ hr, then dry carbon dioxide (5 g) was bubbled in. The salt precipitated. Ether was removed by rotary evaporation, 100 ml of water was added, and the water extracted with 2 50 ml portions of ether. The solution was acidified to Congo Red, then extracted with 3 30 ml portions of chloroform. The chloroform was dried with sodium sulfate and the solvent removed to give 920 mg (75% yield) of a clear colorless oil which solidified on standing. Recrystallization from chloroform/hexane gave white crystals, mp 133-135°. Nmr: 0.84-1.31 (m, 4H); 2.57 (m, 1H); 5.10 (s, 1H); 7.16-7.80 (m, 5H); 8.57 (s, 1H). Anal. Calcd for $C_{11}H_{12}O_4S$: C, 54.98; H, 5.04. Found: C, 55.03; H, 5.15.

Cyclopropylsulfonylphenylacetic acid was recovered unchanged after refluxing in carbon tetrachloride solution for 5.5 hr.

Treatment of α-Cyclopropylsulfonyl-α-phenylacetic Acid (2) with NBS and NCS in CCl_4. A 566 mg (2.36 mmol) portion of 2 was added to 6.55 mg (3.67 mmol) of NBS in 10 ml of carbon tetrachloride and the mixture refluxed for 5.5 hr. Removal of solvent gave a mixture of oil and solid. Nmr analysis indicated the presence of α-bromobenzyl cyclopropyl sulfone, succinimide and NBS. Chromatography of the mixture on 20 g of acidic alumina, grade II, with column dimensions 2 x 20 cm using 20% ether hexane eluent (changing to 25% ether hexane after 500 ml of solvent was used) collecting 80 ml fractions gave 410 mg (63%) of α-bromobenzyl cyclopropyl sulfone in fractions 4-6. Recrystallization from hexane gave the analytical sample, mp 67-68°. Nmr: 1.11 (m, 4H); 2.63 (m, 1H); 5.71 (s, 1H); 7.43 (m, 5H). Ir (max): 7.55, 8.81. Anal. Calcd for $C_{11}H_{11}BrO_2S$: C, 43.64; H, 4.03. Found: C, 43.70; H, 4.05.

This procedure is representative of those carried out in the other halogenative decarboxylations. (See Table I for a summary of the results.)

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α-Cyclopropylsulfonyl-α-phenylacetic acid (2.6 g, 0.0108 mole crude) was refluxed for 4 hr in 100 ml of CCl_4 containing 2.0 g NCS and a crystal of benzoyl peroxide. After standing overnight, 50 ml of water was added and the organic phase washed twice with $NaHCO_3$. Drying and removal of solvent gave 1.83 g of oil, by nmr analysis 80% $PhCH(Cl)SO_2CH(CH_2)_2$ and 20% $PhC(Cl)_2SO_2CH(CH_2)_2$. Evaporative distillation (0.05 mm, 120°) did not change the composition. Chromatography of 520 mg of this material was done on 30 g silica gel. Elution with 15% ether/hexane gave, in the early fractions, 84 mg of α,α-dichlorobenzyl cyclopropyl sulfone; 0.96-1.30 (m, 4H); 2.43-2.92 (m, 1H); 7.31-7.61 (m, 3H); 7.76-8.13 (m, 2H). Anal. Calcd for $C_{10}H_{12}Cl_2O_2S$: C, 45.29; H, 3.80. Found: C, 45.23; H, 3.77.

Elution with 20% ether/hexane gave 460 mg of α-chlorobenzyl cyclopropyl sulfone, which was contaminated with the dichloride. Nmr: 0.92-1.35 (m, 4H); 2.26-2.74 (m, 1H); 5.70 (s, 1H); 7.30-7.78 (m, 5H). With the exception of the chemical shift of the benzyl proton, the nmr spectrum of this material is the same as that of the bromo compound prepared analogously. Analysis indicated the presence of about 20% of the dichloride. Anal. Calcd for $C_{10}H_{11}ClO_2S$: C, 52.05; H, 4.80. Found: C, 50.85; H, 4.65.

Treatment of Phenylthioacetic Acid with NCS in CCl_4 at Reflux. Phenylthioacetic acid (167 mg, 1 mmol) was added to 10 ml of carbon tetrachloride containing NCS (136 mg, 1 mmol). The mixture was refluxed for 4 hr, cooled, filtered and solvent removed to give an oil. The nmr of this material showed it to be a mixture of chloromethyl phenyl sulfide (identified by comparison with the spectrum of the known compound) and phenylthiochloroacetic acid (nmr: 5.50, CH; 7.35, aromatic; 10.61, OH) in a 6 to 1 ratio respectively. This material was not characterized further but was oxidized by dissolving in 10 ml of dichloromethane and adding m-chloroperoxybenzoic acid (500 mg) and refluxing for 1 hr. The dichloromethane solution was washed with sodium sulfite, then sodium bicarbonate. Drying and removal of solvent gave 153 mg of oil which solidified on seeding with chloromethyl phenyl sulfone. The nmr was identical to that of chloromethyl phenyl sulfone; yield: 80.3%.

Treatment of Phenylthioacetic acid with NCS in CCl_4 at 25°. Phenylthioacetic acid (1 mmol) was stirred for 18 hr at 25° with NCS (1 mmol). (Succinimide was floating on top after 3 hr.) The mixture was filtered and the solvent removed to give 247 mg of an oil. Nmr analysis showed phenylthio-

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chloroacetic acid (71%) and starting material (7%). Integration of the acid proton relative to the aromatic protons was 1:5, indicating that the remainder of the material was a phenyl-substituted carboxylic acid, presumably phenylthiodichloroacetic acid. A sample of this mixture was heated at reflux in CCl_4. Although some decomposition occurred, no chloromethyl phenyl sulfide was detected in the nmr spectrum. The remainder of the material was oxidized with 2 equiv. of m-chloroperoxybenzoic acid in dichloromethane at 25° for 24 hr. After washing with bicarbonate, drying and removal of the solvent, 20 mg of product was obtained. Nmr analysis showed it to be a mixture of chloromethyl phenyl sulfone and dichloromethyl phenyl sulfone in a 1 to 3 ratio. Acidification of the bicarbonate washes led only to the recovery of m-chlorobenzoic acid. No other carboxylic acids remained.

14. Additional experimental details may be found in the Ph.D. Dissertation of M. D. Wolfinger, Northwestern University, June, 1968.

15. W. E. Truce and L. B. Lindy, J. Org. Chem., 26, 1463 (1961). We found cyclization of $PhCH_2SO_2CH_2CH_2CH_2Cl$ with t-BuOK in t-BuOH to be a more convenient preparative method.

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Registry No.—**1**, 3959-23-7; **2**, 51416-85-4; **3**, 51416-86-5; $PhSCH_2CO_2H$, 103-04-8; NCS, 128-09-6; NBS, 128-08-5; NIS, 516-12-1; $PhSO_2CHCl_2$, 7205-98-3; c-$PrSO_2CHClPh$, 51416-87-6; c-$PrSO_2CCl_2Ph$, 51416-88-7; c-$PrSO_2CHBrPh$, 51416-89-8; c-$PrSO_2CHIPh$, 51416-90-1; $PhSO_2CH(Me)Ph$, 24422-78-4; $PhSCH_2Cl$, 7205-91-6; $PhSCHClCO_2H$, 51416-91-2; 3-$NO_2C_6H_4CH_2SO_2CHBr_2$, 51416-92-3; 4-$MeC_6H_4CH_2SO_2CHBr_2$, 31355-33-6; 4-$ClC_6H_4CH_2SO_2CHBr_2$, 51416-93-4; 3-$MeC_6H_4CH_2SO_2CHBr_2$, 31355-35-8; 3-$FC_6H_4CH_2SO_2CHBr_2$, 51416-94-5; 4-$NO_2C_6H_4CH_2SO_2CHBr_2$, 31355-36-9; 3-$BrC_6H_4CH_2SO_2CHBr_2$, 31355-30-3; 4-$MeOC_6H_4CH_2SO_2CHBr_2$, 31355-37-0; 3-$NO_2C_6H_4CH_2SO_2CH_2Br$, 51416-95-6; 4-$MeC_6H_4CH_2SO_2CH_2Br$, 51416-96-7; 4-$ClC_6H_4CH_2SO_2CH_2Br$, 51416-97-8; 3-$MeC_6H_4CH_2SO_2CH_2Br$, 51416-98-9; 3-$FC_6H_4CH_2SO_2CH_2Br$, 51416-99-0; 4-$NO_2C_6H_4CH_2SO_2CH_2Br$, 51417-00-6; 4-$MeOC_6H_4CH_2SO_2CH_2Br$, 51417-01-7; 3-$BrC_6H_4CH_2SO_2CH_2Br$, 51417-02-8; 4-$MeC_6H_4CHBrSO_2Ar$, 51417-03-9; 4-$ClC_6H_4CHBrSO_2Ar$, 51417-04-0; 3-$FC_6H_4CHBrSO_2Ar$, 51417-05-1; 3-$MeC_6H_4CHBrSO_2Ar$, 51417-06-2; 4-$MeC_6H_4CHBrSO_2CH_2Ph$, 51417-07-3; 4-$ClC_6H_4CHBrSO_2CH_2Ph$, 51417-08-3; 3-$ClC_6H_4CHBrSO_2CH_2Ph$, 51417-09-5; 4-$FC_6H_4CHBrSO_2CH_2Ph$, 51417-10-8; 3-$MeC_6H_4CHBrSO_2CH_2Ph$, 51417-11-9; 3-nitrobenzyl chloride, 619-23-8; mercaptoacetic acid, 68-11-1; α-bromobenzyl methyl sulfone, 23211-69-0; α-bromophenylacetic acid, 4870-65-9; methanethiol, 74-93-1; benzyl cyclopropyl sulfone, 51417-12-0.

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References and Notes

(1) See C. M. Suter, "The Organic Chemistry of Sulfur," Wiley, New York, N. Y., 1940, reprinted in 1969 by Intra-Science Foundation, Santa Monica, Calif., pp 678–680.

(2) See, *e.g.*, the preparation of $Ph_2CHSO_2CHBr_2$ from $Ph_2CHSO_2CH_2CO_2H$ and the preparation of $PhSO_2CHBr_2$ from $PhSO_2CH_2CO_2H$ described by F. G. Bordwell, E. B. Hoyl, Jr., B. B. Jarvis, and J. M. Williams, Jr., *J. Org. Chem.*, **33**, 2030 (1968).

(3) F. G. Bordwell and B. B. Jarvis, *J. Amer. Chem. Soc.*, **95**, 3585 (1973).

(4) Enols or enolate ions have also been impliated as intermediates in the bromination of diethyl malonate and of methyl methanetricarboxylate.[5]

(5) R. P. Bell and D. J. Rawlinson, *J. Chem. Soc.*, 726 (1961).

(6) A. Nechvatal, *Advan. Free Radical Chem.*, **4**, 175 (1972).
(7) L. Ramberg and A. Mellander, *Ark. Kemi, Mineral. Geol.*, **11B**, No. 31 (1934); L. Ramberg and I. Hedlund, *ibid.*, **11B**, No. 41 (1934). When bromine was not in excess the reaction was found to display a component for bromine in the rate expression.[8]
(8) See R. P. Bell and B. G. Cox, *J. Chem. Soc. B*, 652 (1971), for a recent discussion.
(9) See also J. E. Taylor and F. H. Verhoek, *J. Amer. Chem. Soc.*, **81**, 4537 (1959). The authors observed a base-catalyzed decarboxylation of (−)-$PhSO_2C(Me)(Et)CO_2H$ to (+)-$PhSO_2CH(Me)Et$. Their conclusion that formation of an optically active decarboxylation product ruled out the presence of a carbanion intermediate has been invalidated, however, by later work.[10]
(10) E. J. Corey and T. H. Lowry, *Tetrahedron Lett.*, **No. 13**, 808 (1965).
(11) For precedents see F. G. Bordwell and B. M. Pitt, *J. Amer. Chem. Soc.*, **77**, 572 (1955); D. L. Tuleen and T. B. Stephens, *J. Org. Chem.*, **34**, 31 (1969).
(12) Decarboxylation of sulfonium salts of the type $[R_2SCH_2CO_2H]^+X^-$ is known to occur readily in refluxing acetone.[13]
(13) D. M. Burness, *J. Org. Chem.*, **24**, 849 (1959).

Facilitation of Deuterium Exchange in a Sulfone by a γ-Halogen Atom in a Ramberg–Bäcklund Reaction

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Observation of deuterium exchange occurring during 1,3-dehydrobromination of $Me_2CHSO_2CHBrPh$ in NaOMe–MeOD and of a low k^H/k^D isotope effect (1.2) for 1,3-dehydrobromination in 40% aqueous dioxane shows that this reaction is occurring by a two-stage, carbanion mechanism, rather than a one-stage, concerted mechanism. Deuterium exchange at the methine position of $Me_2CHSO_2CHClPh$ was found to be over 1000 times as rapid as that in the parent sulfone, $Me_2CHSO_2CH_2Ph$. It is postulated that the chlorine atom accelerates exchange not only by an inductive effect but also by facilitating solvent exchange at the initially formed singly solvated carbanion.

In a previous paper we reported some surprising differences for the effect of methyl substitution on deuterium exchange α to a sulfonyl group *vs.* removal of a similarly situated proton in a Ramberg–Bäcklund reaction. Each substitution of a methyl group in the series $PhCH_2SO_2CH_3$ (**1**), $PhCH_2SO_2CH_2Me$ (**2**), $PhCH_2SO_2CHMe_2$ (**3**) caused a decrease in methoxide-catalyzed deuterium exchange rate of about 100-fold.[1] The rate-limiting step in such exchanges has been shown by Cram to be the rate of solvent exchange between the initially solvated carbanion and bulk solvent (k_s).[2]

$$MeO^- + HCR_2SO_2CH_2Ph \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} MeOH\cdots{}^-CR_2SO_2CH_2Ph$$

$$MeOH\cdots{}^-CR_2SO_2CH_2Ph \xrightarrow{MeOD} MeOD\cdots{}^-CR_2SO_2CH_2Ph \quad (k_s)$$

$$MeO^- + DCR_2SO_2CH_2Ph \xleftarrow{k_{-1}} MeOD\cdots{}^-CR_2SO_2CH_2Ph$$

Methyl substitution probably decreases k_1 by an inductive effect, and may also decrease k_s. Since k_{-1} (internal return) is extremely fast—perhaps even faster than a diffusion-controlled rate—it will be affected to a much lesser extent. Let us assume that the 10^4 rate decrease from **1** to **3** results from a tenfold decrease in k_1 and also in k_s for each methyl substitution. An overall decrease in rate of ~100-fold would then be expected in analogous Ramberg–Bäcklund reactions in the series $PhCHBrSO_2CH_3$ (**4**), $PhCHBrSO_2CH_2Me$ (**5**), $PhCHBrSO_2CHMe_2$ (**6**), since a tenfold retardation in k_1 should be observed on each methyl substitution.

$$MeO^- + HCR_2SO_2CHBrPh \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}$$

4, **5**, **6**
(R = H or Me)

$$MeOH\cdots{}^-CR_2(SO_2)CHBrPh \xrightarrow{k_2} R_2C(SO_2)CHPh + Br^-$$

Instead, the overall rate is affected but little by methyl substitution, the relative rates for **4**:**5**:**6** being (1.0):1.7:0.62.[1] One way to account for these results is to assume that competition between k_2 and k_{-1} has decreased the relative amount of internal return.[1] Another possibility is that there is a change in mechanism along the series; for example, the reaction of **4** (R = R = H) might occur in two stages, as indicated by the equations, whereas the reaction of **6** (R = R = Me) might occur in one stage (concerted mechanism). Additional experiments have now been carried out in an attempt to choose between these two possibilities.

Ordinarily, because of internal return, one observes low or even inverse k^H/k^D isotope effects for exchange of protons α to sulfonyl groups.[2] On the other hand, in a concerted reaction one might expect to observe a sizable k^H/k^D isotope effect. The isotope effect for **6** was therefore examined. Since the two-stage Ramberg–Bäcklund reaction is known to have a large k^{Br}/k^{Cl} leaving-group effect,[3] it was also of interest to examine the behavior of the chloro analog of **6**, $PhCHClSO_2CHMe_2$ (**7**).

Results

The desired α-bromobenzyl isopropyl sulfone and its deuterated analog were obtained by methods reported in the literature. The rates of hydroxide- or methoxide-initiated dehydrobromination were measured spectrophotometrically in 40% aqueous dioxane and methanol solutions, respectively (Table I).

The k^H/k^D of 1.0 in methanol indicated that prior exchange was occurring, and this was supported by quenching experiments. In an experiment run with **6** at 25° in methanol-*O*-*d* the starting material was 37% deuterated at the methine position after the reaction was only 18% complete. Some exchange at the methine position occurred also in 40% aqueous dioxane, but the amount was not sufficient to affect the rate data, as may be judged by the high correlation coefficients obtained from a least-squares plot in the rate calculations (r = 0.9992 for the deuterium compound and 0.9999 for the hydrogen compound). We believe, therefore, that the k^H/k^D of 1.2 at 50° is reasonably accurate; at 25° one would expect the ratio to increase slightly.

Table I
Spectrophotometric Rate Constants for the Reaction of $PhCDBrSO_2CD(CH_3)_2$ and $PhCHBrSO_2CH(CH_3)_2$ with Sodium Hydroxide in 40% Dioxane–Water and with Sodium Methoxide in Methanol at 50°

Compd	[NaOH]	k_2, l. mol^{-1} sec^{-1}	k^H/k^D
H	0.252	$3.56 \pm 0.02 \times 10^{-3}$	1.21
D	0.252	$2.94 \pm 0.05 \times 10^{-3}$	
H	0.252	$3.58 \pm 0.01 \times 10^{-3}$ [a]	1.18
D	0.252	$3.03 \pm 0.05 \times 10^{-3}$ [a]	
H	0.1155	3.53[b]	
Compd	**[NaOMe]**	**k_2, l. mol^{-1} sec^{-1}**	**k^H/k^D**
D	0.261	$4.17 \pm 0.08 \times 10^{-4}$	
D	0.261	$3.82 \pm 0.09 \times 10^{-4}$	
H	0.261	$4.33 \pm 0.08 \times 10^{-4}$	1.0
H	0.261	$4.17 \pm 0.08 \times 10^{-4}$	

[a] Calculated by the infinity method. All others are calculated by the Guggenheim method. [b] Single run; this indicates that the reaction is second order in hydroxide ion.

The relatively slow rate of release of halide ion from α-chlorobenzyl isopropyl sulfone (7) allowed a direct measurement of the rate of exchange of the methine hydrogen in D_2O–dioxane by quenching experiments. The results are summarized in Table II.

Discussion

The observation of 37% exchange at the Me_2CH proton of $Me_2CHSO_2CHBrPh$ (6) with NaOMe in MeOD at 18% reaction together with a k^H/k^D isotope effect of 1.0 (Table I) shows that $k_s > k_2$ and that 6 is reacting by a two-stage, carbanion mechanism and not by a one-stage, concerted mechanism. In 40% aqueous dioxane no exchange was observable. This does not mean, however, that a change to a concerted mechanism has occurred. A more reasonable interpretation would be that now k_2 has become larger than k_s. The low k^H/k^D isotope effect (1.2) is consistent with a two-stage mechanism with extensive internal return ($k_{-1} \gg k_2$). This interpretation is strongly supported by the kinetic data for the chloro analog, $Me_2CHSO_2CHClPh$ (7). Now k_2 would be expected to be slower by a factor of at least 100,[3] and k_s should be larger than k_2. This is what is observed (Table II). It is amusing to note that if one looks only at the relative rates of reaction with NaOMe in MeOD of $Me_2CHSO_2CHBrPh$ (Ramberg–Bäcklund) and $Me_2CHSO_2CH_2Ph$ (exchange of the methine proton), which are 560:(1.0), and at the failure of exchange in $Me_2CHSO_2CHBrPh$ to occur during reaction in 40% aqueous dioxane, one could make a strong case for a concerted reaction. It is only by a careful examination of additional aspects that the two-stage mechanism is revealed.[4]

The most surprising result of the present investigation was the greater than 1000-fold increase in exchange rate on substitution of a chlorine atom for a hydrogen atom in the γ position of 3 (Table II). An effect of comparable size

$$\overset{\gamma}{PhCH_2}\overset{\beta}{SO_2}\overset{\alpha}{CHMe_2}$$

3

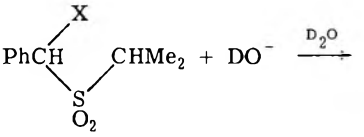
is also apparently operative for γ-bromine atom substitution. This acceleration is remarkable when one considers that chlorine substitution at the α position of $PhSO_2CH_3$ causes only a slightly larger effect.[6] Also, the result contrasts sharply with that in ketones where an α-chlorine atom has been reported to cause an 800-fold acceleration in exchange rate for acetone,[7] whereas a γ-chlorine atom causes only about a tenfold increase for

Table II
Effect of an α-Chlorine Atom on the Deuteroxide-Catalyzed Exchange of the α′-Hydrogen Atom in 40% Dioxane–D_2O at 50°

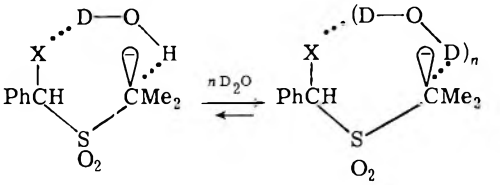
Compd	[NaOD]	k_2, l. mol sec	k_{rel}
$PhCH(Cl)SO_2CH(CH_3)_2$ (7)	0.0355	$(7.19 \pm 0.02) \times 10^{-3}$ [a]	1035
$PhCH_2SO_2CH(CH_3)_2$ (3)	0.518	$(6.94 \pm 0.4) \times 10^{-6}$ [a,b]	(1.0)

[a] Average of two runs. [b] M. D. Wolfinger reports 7.21×10^{-6} (single run): Ph.D. Dissertation, Northwestern University, 1968, p 78.

$PhCHClCOCHMe_2$ *vs.* $PhCH_2COCHMe_2$.[8] Our previous estimate of a fivefold increase in the exchange rate due to the inductive effect of a γ-bromine (or γ-chlorine) atom[1] can be raised to *ca.* tenfold, since the transmission of electronic effects "through" an SO_2 group appears to be more efficient than "through" a methylene group.[9] Nevertheless, a factor of *ca.* 100 remains to be accounted for. It seems likely that an increase in the rate of exchange of external solvent with the initially formed solvated carbanion (k_s) is responsible for the unexpected increase in rate of exchange. A pictorial representation is shown.[11]



6 or 7



8 9

For bromide 6 the exchange data show that deuterium exchange rate and intramolecular displacement rate are competitive. In contrast, for $PhCHBrSO_2CH_3$ deuterium exchange at methyl is much faster than intramolecular displacement. In view of the strong accelerating effect of the γ-halogen atom on the exchange rate, it seems likely that this rate may remain relatively constant on methyl substitution in the series $PhCHBrSO_2CH_3$, $PhCHBrSO_2CH_2Me$, $PhCHBrSO_2CHMe_2$, in sharp contrast to the 10^4 retardation observed in the parent series (hydrogen replaces bromine). If k_s does remain constant, then the rate of intramolecular displacement (k_2) along the series must increase progressively in order for the change $k_s \gg k_2$ to $k_s \simeq k_2$ with methyl substitution to be observed. The constancy in the rate of Ramberg–Bäcklund reaction along this series must then be due to a balance of effects. Methyl substitution decreases k_1 and thereby decreases the equilibrium concentration of carbanion, but this effect is offset by an increase in the rate of k_2.[12]

Experimental Section

Deuterium Exchange Kinetics. Hydrogen–deuterium exchange rates were measured by integration of the remaining proton signal in the pmr spectrum. A typical procedure is as follows. The sulfone (600 mg) was dissolved in 10 ml of purified dioxane (thermostatted to 50.04 ± 0.02°) and added to 15 ml of D_2O, 0.0527 *M* in NaOD (thermostatted). Aliquots (5 ml) were withdrawn at appropriate intervals and quenched with 0.15 *M* HNO_3

(20 ml). The suspension was extracted with carbon tetrachloride (2 × 10 ml) and the carbon tetrachloride layers were washed with water and dried. Solvent was removed by rotary evaporation. Residual dioxane was removed by pumping on the samples (0.1 mm, 48 hr). Samples were dissolved in 500 μl of $CDCl_3$ and the exchangeable hydrogen was integrated. The aromatic protons were used as an internal standard. Four integrations of the proton and standard were performed in each case. Rate constants were determined by plotting the natural logarithm of the remaining proton against time, using a least-squares method. Second-order rate constants were determined by dividing the first-order rate constants by the base strength.

The validity of the integration method was checked by preparation of a calibration curve for α-chlorobenzyl isopropyl sulfone. Mixtures of 0, 25, 50, and 75 deuterated material were prepared by mixing together appropriate weights of undeuterated and fully deuterated (at the site of exchange) substrate. These mixtures were then dissolved in 500 μl of chloroform-*d* and integrated in a manner identical with that used in the rate determinations. The per cent of deuterium in the sample (by weight) was plotted against the per cent of deuterium in the sample by integration to give a straight line ($r = 0.997$) of slope 1.06 ± 0.05.

Acknowledgment. We are grateful to the National Science Foundation (GP-29539X) for support of this investigation.

Registry No.—**3**, 34009-00-2; **7**, 51392-16-6; $PhCDBrSO_2CD(CH_3)_2$, 51392-17-7; $PhCHBrSO_2CH(CH_3)_2$, 35500-99-3.

References and Notes

(1) F. G. Bordwell and M. D. Wolfinger, *J. Amer. Chem. Soc.*, **93**, 6303 (1971). J. R. Jones (private communication) has found relative rates of about (1.0):10^2:10^4 in the rates of tritium exchange in NaOMe–MeOH for the series p-$ClC_6H_4SO_2CHMe_2$, p-$ClC_6H_4SO_2CH_2Me$, p-$ClC_6H_4SO_2CH_3$. Experimental details are given in the Ph.D. Dissertation of Mark D. Wolfinger, Northwestern University, 1968.

(2) D. J. Cram, D. A. Scott, and W. D. Nielsen, *J. Amer. Chem. Soc.*, **83**, 3696 (1961).

(3) (a) F. G. Bordwell and J. M. Williams, Jr., *J. Amer. Chem. Soc.*, **90**, 435 (1968); (b) see F. G. Bordwell and M. D. Wolfinger, *J. Org. Chem.*, **39**, 2521 (1974), for additional examples.

(4) We have commented elsewhere on the rarity of the one-stage mechanism for 1,3-eliminations.[5]

(5) (a) F. G. Bordwell, *Accounts Chem. Res.*, **3**, 281 (1970); (b) F. G. Bordwell and B. B. Jarvis, *J. Amer. Chem. Soc.*, **95**, 3585 (1973). See also F. G. Bordwell and E. Doomes, *J. Org. Chem.*, **39**, 2531 (1974).

(6) D. A. Schexnayder, Ph.D. Dissertation, Northwestern University, 1968, observed ca. a 1400-fold increase in the rate of exchange of $PhSO_2CH_2Cl$ *vs.* $PhSO_2CH_3$ in NaOMe–MeOD at 25°.

(7) R. P. Bell and A. Lidwell, *Proc. Roy. Soc., Ser. A*, **176**, 88 (1950).

(8) F. G. Bordwell and J. Almy, *J. Org. Chem.*, **38**, 575 (1973).

(9) The ρ for $ArSO_2CH_2CO_2H$ is 0.253,[10] as compared to 0.237 for $ArCH_2CH_2CO_2H$.[10] (Our earlier estimate was based on a transmission coefficient of 2.8 for SO_2.)

(10) D. J. Pasto, D. McMillan, and T. Murphy, *J. Org. Chem.*, **30**, 2688 (1965).

(11) An alternative possibility, which we believe to be less likely, is facilitation of ionization and solvent exchange at the methine position by a 1,3 proton shift of the type $PhC\bar{C}ClSO_2CHMe_2 \rightarrow PhCHClSO_2CMe_2$.

(12) See ref 3b for additional data on the effects of methyl substitution on the rate of Ramberg–Bäcklund reactions.

Solvent and Substituent Effects in the Ramberg–Bäcklund Reaction

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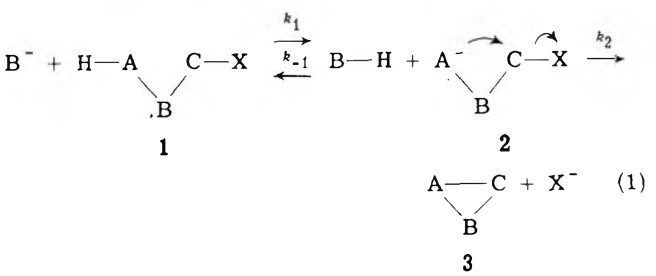
The effects of increasing the proportion of nonaqueous solvent on the rate of reaction of $PhCHBrSO_2CH_2Ph$ with lyate ion in mixtures of water with 1,2-dimethoxyethane, dioxane, ethanol, or methanol have been found to be remarkably similar to those observed earlier under similar conditions with ethylene chlorohydrin. Deuterium exchange studies indicate that with $ArCH_2SO_2CH_2X$ (**4**) and $ArCHXSO_2CH_3$ (**5**), as well as with $ArCHXSO_2CH_2Ar$ (**6**), equilibrium concentrations of α′ carbanions are formed prior to halide loss. The overall ρ values for alkene formation from **4**, **5**, and **6** range from +1.29 to +3.43. Analysis shows that ρ for halide ion loss is negative for **4** and slightly positive for **5** and **6**. Methyl substitution at the α position of **4** or the α′ position of **5** causes surprisingly little change in the overall rate of alkene formation. The k^{Br}/k^{Cl} leaving group effects for **4**, **5**, and **6** in 40% aqueous dioxane ranged from 169 to 207. All of these observations are shown to be consistent with a mechanism wherein equilibrium concentrations of α′ carbanions are formed in the first step and these carbanions participate in a nucleophilic displacement in a second, rate-limiting step.

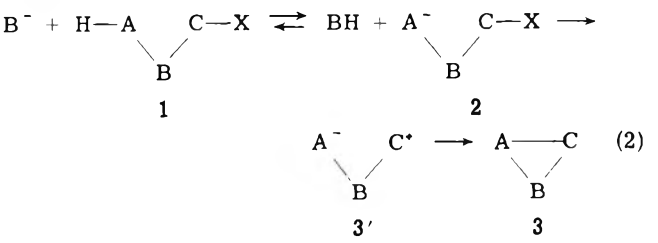
A variety of stepwise mechanisms can be visualized for base-promoted 1,3-elimination of H–X from a system H–A–B–C–X with consequent formation of a three-membered ring.[2] In the most common mechanism (1), deprotonation by a base, B^-, generates an anion (**2**) from which X^- is eliminated by an intramolecular nucleophilic displacement initiated by atom A. (Either k_1 or k_2 can be rate limiting, depending on the system.)



1 **2** **3** (1)

Numerous examples are known where A is O, N, C, S, P, etc., and B and C are carbon atoms.[3,4]

The presence of a negative charge in **2** would be expected to enhance greatly the tendency for X to ionize without direct participation by the nucleophilic atom A^-. If one or more groups capable of stabilizing a carbonium ion, such as Ar, R, or RO, are present on the atom holding X, it would not be surprising, then, to find that the mechanism has changed to one where a dipolar ion intermediate (**3′**) is produced in the second step (mechanism 2).



1 **2** **3′** **3** (2)

Examples where the evidence indicates that a type 2 mechanism obtains, at least in some instances, include (a) α-lactone formation by solvolysis of $ArCHXCO_2H$ in

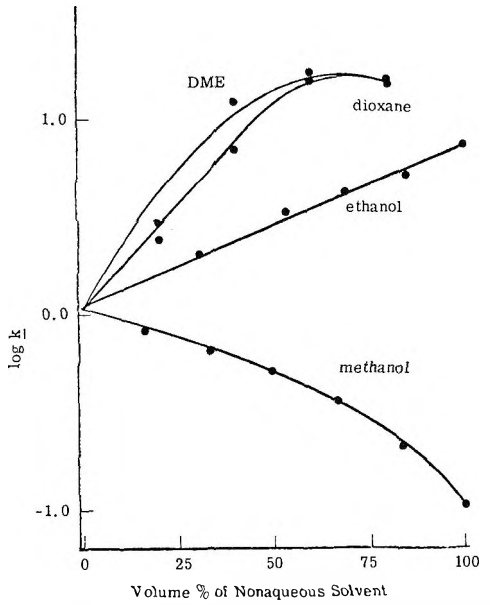


Figure 1. Plot of log k for the reaction of α-bromobenzyl benzyl sulfone with lyate ion in various solvent media *vs.* the volume per cent of nonaqueous solvent.

aqueous base[5] and (b) cyclopropanone formation during Favorskii rearrangements of $ArCH_2COCHXCH_3$, $Ar_2CXCOCH_3$, and the like.[6]

The reaction of 2-haloalkanols with aqueous alkali to form epoxides probably utilize both types of mechanisms. When the halogen is primary or secondary the evidence points to participation by the oxide ion.[7] When the halogen is tertiary, however, the rates calculated for ionization under the influence of the negative charge of the oxide ion are 1 to 3 orders of magnitude faster than the observed rates.[8] Mechanism 2 appears likely, therefore, when the halogen is tertiary.

In earlier studies we have shown that 1,3-dehydrohalogenation of an α-halo sulfone of the type $PhCH_2SO_2CHXPh$ by a base such as sodium methoxide in methanol (Ramberg–Bäcklund reaction) usually occurs by mechanism 1 with k_2 (episulfone formation) being rate limiting.[10] It was of interest to use additional probes to test this mechanism and at the same time to investigate its generality. To this end we have (a) determined the effect of solvent changes on the rates for $PhCH_2SO_2CHXPh$ (X = Cl and Br), (b) determined the effects of meta and para substituents on the rates for $ArCH_2SO_2CH_2X$ (4), $ArCHXSO_2CH_3$ (5), and $ArCHXSO_2CH_2Ar'$ (6), and (c) determined the effect on the rates of methyl substitution α to the halogen in 4 and 5 and α to the phenyl group (α' position) in 5.

Results

Solvent effects on the rates of reaction of α-bromobenzyl benzyl sulfone were determined in basic aqueous 1,2-dimethoxyethane (DME), dioxane, ethanol, and methanol solutions containing amounts of nonaqueous solvent ranging from 100% down to as low as 16% by volume. The results are summarized in Figure 1.[11] α-Chlorobenzyl benzyl sulfone responded similarly to these solvent changes, except that the aqueous DME and dioxane mixtures showed a more nearly linear increase in rate with increasing volume per cent of nonaqueous solvent.[11]

The desired substituted-benzyl bromomethyl sulfones, $ArCH_2SO_2CH_2Br$ (4), were prepared from the benzyl chlorides *via* the arylmethylsulfonylacetic acids, $ArCH_2SO_2CH_2CO_2H$. The latter were subjected to brominative decarboxylation[12] and the resulting benzyl dibromomethyl sulfones were reduced with potassium sulfite.[12,13] This method was used also to prepare α-bromobenzyl benzyl sulfones of the type $ArCHBrSO_2CH_2Ph$ and $PhCH_2SO_2CHBrAr$, and for $PhCHBrSO_2CH_3$.[12] The remaining α-halo sulfones were prepared by halogenation of the appropriate sulfides, followed by oxidation (see Experimental Section).

Rates for $ArCH_2SO_2CH_2Br$ (4), $ArCHBrSO_2CH_3$ (5), and $ArCHBrSO_2Ar'$ (6) reacting with hydroxide ion in 40% (v/v) dioxane–water or methoxide in methanol were determined spectrophotometrically and/or titrimetrically by methods described earlier.[10] The results are summarized in Table I.

Spectrophotometric rates for some members in series 4 and 5 were difficult to determine because the change in absorption between starting sulfone and styrene product was small. For this reason the rates in methanol were determined titrimetrically. Spectrophotometric rate constants for 4 with Ar = $3\text{-}BrC_6H_4$, $3\text{-}FC_6H_4$, and C_6H_5 were found to be 11% higher, 5.6% higher, and 6% lower, respectively, than the corresponding titrimetric rates.

The calculated σ constant for $p\text{-}NO_2$ in series 4, based on the rate constant and using the line defined by the other points, was 1.21, which agrees well with $\sigma^-_{p\text{-}NO_2}$ (1.27).

The rate for 3-bromo-4-methoxybenzyl bromomethyl sulfone was somewhat slower than anticipated by assum-

Table I
Second-Order Rate Constants for the Reaction of $ArCH_2SO_2CH_2Br$ (4), $ArCHBrSO_2CH_3$ (5), and $ArCH_2SO_2CHXAr'$ (6) with Base in 60% (v/v) Dioxane–Water or Methanol

Halo sulfone	Temp, °C	Solvent–base	k_H,[a] M^{-1} sec^{-1}	ρ_{obsd}	r
$ArCH_2SO_2CH_2Br$	25.1	40% dioxane–H_2O	$8.08 \pm 0.04 \times 10^{-2}$	1.47[b,c]	0.992
$ArCH_2SO_2CH_2Br$	25.0	Methanol	$1.35 \pm 0.04 \times 10^{-3}$	1.47[c,d]	0.999
$ArCHBrSO_2CH_3$	50.0	40% dioxane–H_2O	$2.54 \pm 0.05 \times 10^{-3}$	1.29[b,e]	0.978[f,g]
$ArCHBrSO_2CH_3$	25.0	40% dioxane–H_2O	1.24 ± 10^{-4} (calcd)		
$ArCHBrSO_2CH_3$	50.0	Methanol	$1.83 \pm 0.12 \times 10^{-4}$	1.29[d,e]	0.996[f]
$ArCH_2SO_2CHBrPh$	24.9	Methanol	$6.79 \pm 0.06 \times 10^{-2}$	2.31[b,h]	0.993
$ArCHBrSO_2CH_2Ph$[n]	24.9	Methanol	$6.79 \pm 0.06 \times 10^{-2}$	1.51[b,i]	0.990[f,i]
$ArCH_2SO_2CHClPh$	25.0	40% dioxane–H_2O	$2.65 \pm 0.01 \times 10^{-2}$	2.19[b,k]	0.995
$ArCHClSO_2CH_2Ph$	25.0	40% dioxane–H_2O	$2.65 \pm 0.01 \times 10^{-2}$	1.64[b,l]	0.993[f]
$ArCHClSO_2CHAr$	25.0	40% dioxane–H_2O	$2.65 \pm 0.01 \times 10^{-2}$	3.43[b,m]	0.990[f]
$ArCHClSO_2CH_2Ar$	38.9	Methanol	$2.40 \pm 0.03 \times 10^{-3}$	3.32[b,m]	0.993[f]

[a] Rate for Ar = Ph. [b] Spectrophotometric rates. [c] $3\text{-}NO_2$, 3-Br, 3-F, 4-Cl, 3-Br-4-OCH_3, $3\text{-}CH_3$, and $4\text{-}CH_3$ substituents. [d] Titrimetric rates. [e] $3\text{-}NO_2$, 3-F, 4-Cl, $3\text{-}CH_3$, and $4\text{-}CH_3$ substituents. [f] σ normal values were used. [g] Omission of the 4-Cl point gave $\rho = 1.27$ with $r = 0.998$. [h] 3-F, 4-Cl, $3\text{-}CH_3$, and $4\text{-}CH_3$ substituents. [i] $4\text{-}NO_2$, $3\text{-}NO_2$, 3-Cl, 4-Cl, 4-F, $3\text{-}CH_3$, and $4\text{-}CH_3$ substituents. [j] Omission of 4-F point gave $\rho = 1.55$ with $r = 0.999$. [k] 3-F, 4-Cl, and $4\text{-}OCH_3$ substituents. [l] $4\text{-}NO_2$, $3\text{-}NO_2$, 3-F, and 4-Cl substituents were used. [m] $4\text{-}NO_2$, $3\text{-}NO_2$, 3-F, 3-Cl, $3\text{-}CH_3$, $4\text{-}CH_3$ and $4\text{-}OCH_3$ substituents. [n] Registry no., 19217-59-5.

ing additive 3-Br and 4-OCH_3 σ constants. The additive value is 0.28 when the σ^n constant is used for p-OCH_3 (−0.111),[14] 0.12 when the Hammett σ constant is used, and −0.39 when the σ^+ constant is used for p-OCH_3. A value of 0.05 is needed to fit the rate of the line.

α-Bromobenzyl methyl sulfone (**5**) underwent complete exchange at the α' position in 200 sec. Under these conditions the Ramberg-Bäcklund reaction was less than 15% complete, indicating that a preequilibrium is established.

Discussion

Solvent Effects. The effects of increasing the proportion of nonaqueous solvent on the rates of reaction of $PhCHBrSO_2CH_2Ph$ with lyate ion brought out in Figure 1 are remarkably similar to the effects of similar solvent changes observed for the reaction of $ClCH_2CH_2OH$ with lyate ion under similar conditions.[15] The similarity in behavior of the two systems with changing solvents suggests a similarity in mechanism, supporting the assignments of mechanism 1 in each system that have been made previously.[7,10] The increased rate observed on increasing the concentration of 1,2-dimethoxyethane or dioxane in the solvent is presumably due to a decrease in solvation of anion **2** by water and a consequent increase in nucleophilicity of this oxide ion or carbanion. The progressive decrease in rate with increasing methanol concentration conceivably could be due to a greater acidity of methanol than water,[16] but additional factors are no doubt also involved.

Influence of Phenyl and Aryl Substituents. Earlier work has shown that in MeONa–MeOD deuterium exchange at the α' position is essentially complete for $PhCH_2SO_2CHBrPh$ (**6**, Ar = Ph) prior to loss of Br^-.[10] A preequilibrium involving the α' position is clearly established here and this must be true for $PhCH_2SO_2CH_2Br$ (**4**), where bromide ion release is 50-fold slower at 25° than for **6** (Table I). Proton abstraction from the α' (methyl) position of $PhCHBrSO_2CH_3$ (**5**) is *ca.* 10^4 slower than from the α' (benzylic) positions of **4** or **6**.[17] Nevertheless, the present study shows that deuterium exchange is essentially complete at the α' position, prior to loss of Br^-, in this instance also. The correspondence between titrimetric and spectrophotometric rates for **4** shows the halide loss, and not episulfone decomposition, is rate limiting. Comparable data have been obtained with **6**.[10]

Information concerning the step in mechanism 1 wherein halogen is lost (k_2) can be gleaned from relative rates and substituent effects for isomers **4** and **5**. According to mechanism 1, when k_2 is rate limiting, the rate ratio for halogen loss from **4** and **5** should be given by

$$k_2^{(4)}/k_2^{(5)} = K_{eq}^{(5)}/K_{eq}^{(4)} \times k_{obsd}^{(4)}/k_{obsd}^{(5)}$$

where $K^{(4)}_{eq}$ and $K^{(5)}_{eq}$ are the equilibrium constants for the first (equilibrium) step. The pK for $PhCH_2SO_2CH_3$ in dimethyl sulfoxide (DMSO) is *ca.* 4 units higher than for $PhCH_2SO_2CH_3$.[19] Assuming a similar difference for **5** and **4** gives a $K^{(5)}_{eq}/K^{(4)}_{eq}$ ratio of 10^4. Using the $k^{(4)}_{obsd}/k^{(5)}_{obsd}$ ratio of 650 reported in Table I (reactions in 40% dioxane at 25°) gives a $k_2^{(4)}/k_2^{(5)}$ value of 1/15. This indicates that intramolecular displacement of bromine by the carbanion in $PhCHBrSO_2CH_2^-$ is *ca.* 15 times as rapid as in $PhCHSO_2CH_2Br$. The difference is probably due to a combination of a greater nucleophilicity of the carbanion in $PhCHBrSO_2CH_2^-$ and a greater susceptibility of the C–Br bond in this series to cleavage (phenyl activation; phenyl activation is well established for intermolecular nucleophilic displacements).

According to mechanism 1 the ρ values in Table I are a composite of K_{eq} for step 1 and ρ_{k_2} for step 2, *i.e.*

$$\rho_{obsd} = \rho_{K_{eq}} + \rho_{k_2}$$

Judging from the ρ value for the equilibrium constant of $ArCH_2SO_2CH_3$ in DMSO (ρ = 5.0[19]) ρ_{Keq} for $ArCH_2SO_2CH_2Br$ in MeOH will be *ca.* 4. Using this value and ρ_{obsd} of 1.47 (Table I) gives $\rho_{k_2} \cong -2.5$ in 40% dioxane or methanol. In other words, electron-releasing groups strongly accelerate step 2 (*i.e.*, increase k_2). This is understandable for mechanism 1 on the basis of increased nucleophilicity of the carbanion, or for mechanism 2 on the basis of enhancement of the rate of ionization through an electrostatic effect. A similar analysis of ρ_{obsd} for $ArCHBrSO_2CH_3$ (1.29), $ArCHBrSO_2CH_2Ph$ (1.51), and $ArCHClSO_2CH_2Ph$ (1.64) systems favors interpretation by mechanism 1. In these systems the Ar group is separated from the acidic hydrogen atom by two additional atoms. Judging from the equilibrium ρ values in water of 1.00 for $ArCO_2H$, 0.562 for $ArCH_2CO_2H$, and 0.237 for $ArCH_2CH_2CO_2H$,[20a] and ρ = 0.253 for $ArSO_2CH_2CO_2H$,[20b] the ρ value for $ArCH_2SO_2CH_3$ (or **5**) should be about one-fourth that observed for $ArCH_2SO_2CH_3$ or *ca.* 1.0. The ρ values for the other two systems (**6**) should be somewhat smaller. This analysis then makes ρ_{k_2} for the $ArCHBrSO_2CH_3$, $ArCHBrSO_2CH_2Ph$, and $ArCHClSO_2CH_2Ph$ systems small and positive. A positive ρ value for k_2 is of course inconsistent with mechanism 2, since one would expect a negative ρ for the step

$$ArCHBrSO_2CH_2^- \longrightarrow Br^- + Ar\overset{+}{C}HSO_2CH_2^-$$

On the other hand, a small positive ρ for an intramolecular nucleophilic displacement of a benzylic halide seems reasonable, since intermolecular nucleophilic displacements with benzylic halides often have small positive ρ values.[21]

The smaller negative ρ (*ca.* −1.7) calculated (as above) for $ArCH_2SO_2CHBrPh$, as compared to $ArCH_2SO_2CH_2Br$, is consistent with the reaction becoming less sensitive to the nucleophilicity of the carbanion as cleavage of the C–Br bond becomes more facile (owing to phenyl activation).

It is amusing to compare the results with the $ArCH_2SO_2CH_2Br$ system with those of the $ArCH_2COCH_2Cl$ system, where ρ for loss of chloride ion is *ca.* −5.[22] The large negative ρ for the chloro ketone system has been interpreted as indicating ionization to form a dipolar ion.[22] The formation of dipolar ion intermediates in such Favorskii rearrangements is supported by the marked rate acceleration of halide loss observed with methyl substitution ($ArCH_2COCHClCH_3$) system,[6a] the formation in some systems of unusual cyclization products,[6b] and the changes in stereochemistry observed with changing conditions.[6c,23] As will be brought out below, the effect of methyl substitution in the $ArCH_2SO_2CH_2Br$ system argues *against* the dipolar intermediate; the observation of a high degree of stereoselectivity in the Ramberg–Bäcklund reaction provides additional evidence against the dipolar mechanism.[24]

Effect of Methyl Substitution. The effect of methyl substitution at the α or the α' positions of $ArCH_2SO_2CH_2X$ (**4**) and $ArCHXSO_2CH_3$ (**5**) systems are summarized in Table II.

Examination of Table II shows that substitution of one or two methyl groups α to the halogen atom in **4** has surprisingly little effect on the rate of activation parameters. (Note the comparisons for the first five items in Table II.)

Table II
Effects of Methyl Substitution on the Rates of Reaction of $PhCH_2SO_2CH_2X$ (4) and $PhCHXSO_2CH_3$ (5) in 40% (v/v) Dioxane–Water

Registry no.	Halo sulfone	Temp, °C	k, M^{-1} sec^{-1}	k_{rel}	E_a, kcal/mol	ΔS^* (25°), eu
5335-44-4	$PhCH_2SO_2CH_2Cl$	35.0	$1.58 \pm 0.05 \times 10^{-3}$	(1.00)		
		49.57	$1.04 \pm 0.04 \times 10^{-2}$			
		25.0	3.90×10^{-4} (calcd)		25.6	+9.6
51392-35-9	$PhCH_2SO_2CHClMe$	35.0	$1.74 \pm 0.02 \times 10^{-3}$	1.10		
		49.95	$1.17 \pm 0.02 \times 10^{-2}$			
		25.0	4.37×10^{-2} (calcd)		25.2	+8.7
51392-36-0	$PhCH_2SO_2CClMe_2$	35.0	$1.80 \pm 0.04 \times 10^{-3}$	1.14		
		49.65	$1.15 \pm 0.05 \times 10^{-2}$			
		25.0	4.54×10^{-4} (calcd)		25.1	+8.5
19217-58-4	$PhCH_2SO_2CH_2Br$	25.04	$8.08 \pm 0.04 \times 10^{-2}$	(1.00)		
		49.60	1.18 ± 0.05		20.9	+4.5
51392-37-1	$PhCH_2SO_2CHBrMe$	25.07	$1.08 \pm 0.003 \times 10^{-1}$	1.34		
		49.60	1.63 ± 0.07		21.2	+6.0
23211-69-0	$PhCHBrSO_2CH_3$	34.97	$4.39 \pm 0.14 \times 10^{-4}$			
		49.96	$2.54 \pm 0.05 \times 10^{-3}$			
		25.00	1.24×10^{-4} (calcd)	(1.00)	23.2	−0.7
35501-00-9	$PhCHBrSO_2CH_2Me$	34.96	$1.18 \pm 0.07 \times 10^{-3}$			
		49.91	$6.93 \pm 0.07 \times 10^{-3}$			
		25.00	3.29×10^{-4} (calcd)	2.65	23.4	+2.1
35500-99-3	$PhCHBrSO_2CHMe_2$	38.69	$1.15 \pm 0.04 \times 10^{-3}$			
		50.00	$4.04 \pm 0.23 \times 10^{-3}$			
		25.00	2.21×10^{-4} (calcd)	1.78	22.3	−2.6
38009-86-8	$PhCHClSO_2CH_3$	50.0	(1.4×10^{-5})[a]	(1.00)		
51392-16-6	$PhCHClSO_2CHMe_2$	50.0	4.60×10^{-5}	3.3		
	$PhCH_2SO_2CHBrMe$	49.60	1.63 ± 0.07			
	$PhCH_2SO_2CHBrMe$	25.07	$1.08 \pm 0.03 \times 10^{-1}$	21.8	21.2	+6.0
51392-38-2	$PhCHMeSO_2CHBrMe$	25.04	$4.95 \pm 0.07 \times 10^{-3}$	(1.00)		

[a] F. G. Bordwell and G. D. Cooper, *J. Amer. Chem. Soc.*, **73**, 5187 (1951).

This is in sharp contrast to the $PhCH_2COCH_2X$ system, where α-methyl substitution brings about a minimum rate acceleration of 220-fold. (The actual rate enhancement could be much greater.)[6a] The results with 4 also differ from those observed in base-promoted epoxide formation from 2-chloroalkanols, where methyl substitution in the series $HOCH_2CH_2Cl$, $HOCH_2CH(Me)Cl$, $HOCH_2C(Me)_2Cl$ leads to relative rates of (1.0):5.5:250.[25] These rate accelerations find a logical explanation in that α-methyl groups are known to strongly stabilize carbonium ions.[6a,7,26] Evidently the amount of ionic character for the C–X bond developed in the transition state for the reactions of $PhCH_2SO_2CH(Me)Br$ and $PhCH_2SO_2C(Me)_2Br$ are far less than in epoxide formation from $^-OCH_2C(Me)_2Cl$ or in the Favorskii rearrangement of $PhCHCOCH(Me)Cl$. In other words, for reactions of 4 and its α-methyl derivatives there is no evidence for either a dipolar ion transition state or a dipolar ion intermediate.

Examination of Table II shows that methyl substitution at the α' position in $ArCHBrSO_2CH_3$ (5) (items 6–10) also has very little effect on the rate. This again contrasts with epoxide formation, where the relative rates in the series $HOCH_2CH_2Cl$, $HOCH(Me)CH_2Cl$, $HOC(Me)_2CH_2Cl$ are (1.0):21:250.[25] Accelerations by β-methyl groups in such instances have been explained by assuming the development of positive charge at the β-carbon atom in the transition state,[7] and by an entropy effect wherein methyl substitution lowers the ground-state entropy, making entropy loss less for more crowded systems in going from ground state to transition state.[28] Only the latter effect would be expected to apply in the present instance. Evidently, it is counteracted by some other factor or factors. One such could be decreased equilibrium concentrations of carbanions with successive methyl substitution.[19] This effect will be at least partially counteracted by increased carbanion nucleophilicity.

The large k^{Br}/k^{Cl} leaving group effects in the Ramberg–Bäcklund reaction found earlier in methanol have been substantiated and augmented in the present study (Table III). It should be noted that the k^{Br}/k^{Cl} rate ratios decrease rather markedly with increasing temperature because the activation energies for chloro sulfones are *ca.* 4 kcal/mol higher than those of bromo sulfones (Table II).

Table III
Relative Rate Ratio for α-Bromo and α-Chloro Sulfones in the Ramberg–Bäcklund Reaction in 40% Dioxane–Water at 25°

α-Halo sulfone	k^{Br}/k^{Cl}
$PhCH_2SO_2CH_2X$	207[a]
$PhCH_2SO_2CH(Me)X$	247
$PhCH_2SO_2CH(Ph)X$	169[b]
$CH_3SO_2CH(Ph)X$	181[c]
$Me_2CHSO_2CH(Ph)X$	88[c]

[a] At 50° the ratio is 133; in MeOH at 50° it is 128. [b] At 25° in MeOH the ratio is 280. [c] At 50°.

Experimental Section

Substituted α-Chlorobenzyl Benzyl Sulfones. The corresponding meta- or para-substituted benzyl sulfides were chlorinated and the resulting chloro sulfides were oxidized *in situ*, as in the following procedure.[11] A solution of 8.47 g (0.0628 mol) of sulfuryl chloride in 60 ml of dry CCl_4 was added dropwise over 100 min to a stirred solution (under nitrogen) of 15.1 g (0.0621 mol) of bis(4-methylbenzyl) sulfide dissolved in 80 ml of dry CCl_4 kept at reflux. After an additional 1 hr of reflux the solution was cooled to 0° and treated with a solution of 28.6 g (0.166 mol) of 80% *m*-chloroperoxybenzoic acid in 250 ml of dry CH_2Cl_2. After allowing it to warm to room temperature over a 4-hr period the reaction mixture was diluted with 100 ml of $CHCl_3$ and washed successively with aqueous $NaHSO_3$, saturated $NaHCO_3$, and water. After drying ($MgSO_4$) the solvent was evaporated and the chloro sulfone was crystallized from 95% ethanol, mp 160.8–161.7°. The yields in these preparations averaged 70%. Nmr: 7.3–7.7 (m, 8 H), 5.49 (s, 1 H), AB quartet, ν_A = 4.73, ν_B = 4.34 (J_{AB} = 14.7 Hz, 2 H), 2.43 (s, 3 H), 3.40 ppm (s, H).

The other chloro sulfones had similar nmr spectra. Analytical data are summarized in Table IV.

Table IV
Melting Points and Analytical Data[a] for α-Chlorobenzyl Benzyl Sulfones, $ArCHClSO_2CH_2Ar$

Registry no.	Substituent	Mp, °C[b]	Molecular formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
51392-39-3	4-Methyl	160.8–161.7	$C_{16}H_{17}ClO_2S$	62.23	5.55	62.31	5.35
51392-40-6	3-Methyl	75.2–77	$C_{16}H_{17}ClO_2S$	62.23	5.55	62.23	5.60
51392-41-7	4-Nitro	190–191	$C_{14}H_{11}ClN_2O_6S$	45.34	2.99	45.22	3.09
51392-42-8	3-Nitro	160.5–162.8	$C_{14}H_{11}ClN_2O_6S$	45.34	2.99	45.61	3.05
51392-43-9	3-Fluoro	95–96.5	$C_{14}H_{11}ClF_2O_2S$	53.09	3.50	53.15	3.47
51392-44-0	4-Methoxy[c]	145.5–146.5	$C_{16}H_{17}ClO_4S$	56.39	5.03	56.16	5.06

[a] Micro-Tech, Skokie, Ill. [b] Uncorrected. [c] Prepared using *N*-chlorosuccinimide.

Table V
Melting Points and Analytical Data[a] for α-Bromobenzyl Methyl Sulfones, $ArCHBrSO_2CH_3$

Registry no.	Substituent	Mp, °C[b]	Molecular formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
51392-45-1	4-Methyl	104–105	$C_9H_{11}BrO_2S$	41.08	4.21	40.91	4.18
51464-53-0	3-Methyl	64.4–67	$C_9H_{11}BrO_2S$	41.08	4.21	41.02	4.15
51392-46-2	4-Nitro[c]	160–160.7	$C_8H_8BrNO_4S$	32.67	2.74	32.99	2.90
51392-47-3	3-Nitro	159–160	$C_8H_8BrNO_4S$	32.67	2.74	32.9;	2.92
51392-48-4	3-Fluoro	63–64	$C_8H_8BrFO_2S$	35.97	3.02	35.79	3.09
51392-49-5	4-Chloro	119–119.9	$C_8H_8BrClO_2S$	33.88	2.84	34.09	2.90

[a] Micro-Tech, Skokie, Ill. [b] Uncorrected. [c] Bromine was used as the brominating agent.

α-Bromobenzyl Methyl Sulfones. These bromo sulfones (Table V) were prepared from the corresponding sulfides by a method similar to that described above using *N*-bromosuccinimide as the brominating agent. Chromatography over silica gel was required to obtain pure samples of all but the 3-nitro derivative.[11]

Acknowledgment. We are grateful to the National Science Foundation (GP-29539X) for support of this work.

Registry No.—Bis(4-methylbenzyl) sulfide, 13250-88-9; bis(3-methylbenzyl) sulfide, 25033-32-3; bis(4-nitrobenzyl) sulfide, 1835-71-8; bis(3-nitrobenzyl) sulfide, 51392-50-8; bis(3-fluorobenzyl) sulfide, 51392-51-9; bis(4-methoxybenzyl) sulfide, 34106-64-4; methyl 4-methylbenzyl sulfide, 5925-57-5; methyl 3-methylbenzyl sulfide, 51392-52-0; methyl 4-nitrobenzyl sulfide, 51392-53-1; methyl 3-nitrobenzyl sulfide, 51392-54-2; 3-fluorobenzyl methyl sulfide, 50396-78-6; 4-chlorobenzyl methyl sulfide, 5925-82-6.

References and Notes

(1) Abstracted in part from the Ph.D. Dissertation of M. D. Wolfinger, Northwestern University, June 1968.
(2) Concerted 1,3-eliminations are also possible but, for reasons given elsewhere,[3] we believe these to be rare if they exist at all.
(3) F. G. Bordwell and B. B. Jarvis, *J. Amer. Chem. Soc.*, **95**, 3585 (1973), and references cited therein.
(4) For a list of references of 1,3-elimination reactions see A. Nickon and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **89**, 3914 (1967).
(5) F. G. Bordwell and A. C. Knipe, *J. Org. Chem.*, **35**, 2956, 2959 (1970).
(6) (a) F. G. Bordwell and M. W. Carlson, *J. Amer. Chem. Soc.*, **92**, 3370 (1970); (b) F. G. Bordwell and R. G. Scamehorn, *ibid.*, **93**, 3410 (1971); F. G. Bordwell and J. G. Strong, *J. Org. Chem.*, **38**, 579 (1973).
(7) S. Winstein and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 828 (1948).
(8) The "observed" rates reported in Table VI of ref 7 should be lowered by a factor of 10^2 since they are based on a calculation where the pK_a of ethanol is assumed to be 18, whereas more recent work has shown the pK_a of ethanol in water to be 16.[9]
(9) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **82**, 795 (1960).
(10) F. G. Bordwell and J. M. Williams, Jr., *J. Amer. Chem. Soc.*, **90**, 435 (1968).
(11) Detailed data are given in the Ph.D. Dissertation of M. D. Wolfinger, Northwestern University, June 1968.
(12) F. G. Bordwell, M. D. Wolfinger, and J. B. O'Dwyer, *J. Org. Chem.*, **39**, 2516 (1974).
(13) F. G. Bordwell, E. B. Hoyt, Jr., B. B. Jarvis, and J. M. Williams, Jr., *J. Org. Chem.*, **33**, 2030 (1968).
(14) H. Van Bekkum, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **78**, 815 (1959).
(15) J. E. Stevens, C. L. McCabe, and J. C. Warner, *J. Amer. Chem. Soc.*, **70**, 2449 (1948).
(16) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, p 292.
(17) In the parent sulfone, $PhCH_2SO_2CH_3$, the rate of deuterium exchange in MeOD catalyzed by MeONa is *ca.* 2×10^4 greater at 25° in the benzylic than in the methyl position.[18]
(18) D. A. Schexnayder, Ph.D. Dissertation, Northwestern University, 1968.
(19) W. S. Matthews, unpublished results.
(20) (a) H. H. Jaffee, *Chem. Rev.*, **53**, 191 (1953); (b) D. J. Pasto, D. McMillan, and T. Murphy, *J. Org. Chem.*, **30**, 2688 (1965).
(21) For S_N2 reactions of $ArCH_2Cl$ with iodide ion in acetone $\rho = 0.81$; with trimethylamine in benzene $\rho = 0.37$; with hydroxide ion in water $\rho = -0.33$.[20a] Benzyl fluorides with lyate ion in 95% ethanol have $\rho = 0.45$.[20a]
(22) F. G. Bordwell, R. G. Scamehorn, and W. G. Sprirger, *J. Amer. Chem. Soc.*, **91**, 2087 (1969).
(23) For evidence pointing to the generation of dipolar ions in related systems see H. E. Zimmerman and G. A. Epling, *J. Amer. Chem. Soc.*, **94**, 3245 (1972).
(24) F. G. Bordwell and E. Doomes, *J. Org. Chem.*, **39**, 2526 (1974).
(25) H. Nilsson and L. Smith, *Z. Phys. Chem., Abt. A*, **166**, 136 (1933).
(26) For *limiting* soivolyses the rate acceleration caused by stabilization of the developing carbonium ion by an α-methyl group can lead to a 10^8 rate acceleration.[27]
(27) J. L. Fry, J. M. Harris, R. C. Bingham, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 2540 (1970).
(28) G. S. Hammond, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 9.

Stereochemistry and Mechanism of the Ramberg–Bäcklund Reaction. Reaction of Diastereomeric α-Halo Sulfones with Base[1]

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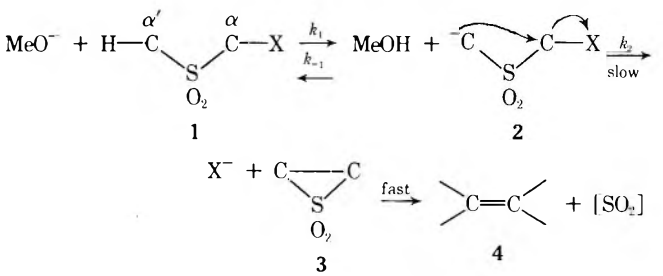
Bromination with *N*-bromosuccinimide of either *meso*- or *dl*-$PhCH(Me)SO_2CH(Me)Ph$ gave a nearly equimolar quantity of diastereomers, $PhCH(Me)SO_2CBr(Me)Ph$. Treatment of the higher melting erythro isomer (**5a**) with NaOMe in MeOH gave *cis*- and *trans*-α,α′-dimethylstilbene in a 93:7 ratio, whereas the threo isomer (**5b**) gave over 95% of *trans*-α,α′-dimethylstilbene. In reactions with **5a** and **5b** run to 10% or less conversion in MeOH the ratio of exchange to epimerization was *ca.* 50–100:1.0. The kinetics with **5a** were second order, but with **5b** they were independent of methoxide ion concentration when the base concentration was above 0.05 *M*. The latter behavior indicated that thermal decomposition of *trans*-2,3-dimethyl-2,3-diphenylthiirane 1,1-dioxide was rate limiting, and this was supported by independent spectroscopic evidence. Reaction of the diastereomers of $PhCH(Me)SO_2CH(Br)CH_3$ with NaOMe–MeOH was also stereoselective, one isomer (presumably threo) giving *cis*- and *trans*-2-phenyl-2-butene in a ratio of *ca.* 70:30 and the other isomer (presumably erythro) giving the opposite ratio. Recovery and nmr analysis of starting materials from incomplete reactions showed that extensive epimerization was accompanying these reactions. Reaction of $PhCBr(Me)SO_2CH_2CH_3$ gave *cis*- and *trans*-2-phenyl-2-butene in a ratio of *ca.* 53:47, which differs appreciably from the equilibrium ratio for these alkenes (83:17). It is suggested that the stereochemistry in such instances is dictated to an appreciable extent by the formation of one of two possible diastereomeric carbanions in a higher equilibrium concentration.

Earlier studies of the Ramberg–Bäcklund reaction in a variety of systems support the stepwise mechanism shown in Scheme I.

Scheme I

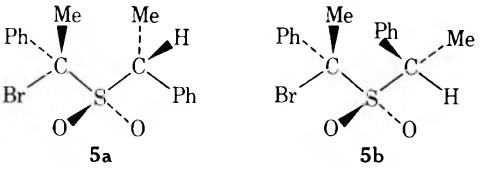


Establishment of an equilibrium between **1** and **2** has been demonstrated for α-halo sulfones of widely differing structures by deuterium exchange studies.[2] Step 2 (thiirane 1,1-dioxide formation), rather than step 3 (alkene formation), has been shown to be rate limiting in these systems by comparisons of titrimetric and spectrophotometric rates,[2] and by studies with thiirane 1,1-dioxides, which show that their rate of decomposition is usually such as to preclude their isolation under the reaction conditions.[3] It is not surprising, then, that prior to the present work[1] there has been no direct evidence for the formation of a thiirane 1,1-dioxide intermediate in these systems. Good indirect evidence was provided, however, from studies of the dehydrobromination of $PhCHBrSO_2CHBrPh$. Here the presence of 2,3-diphenylthiirene 1,1-dioxide as a transient intermediate was detected spectrophotometrically.[4] This intermediate must arise from dehydrobromination of 2-bromo-2,3-diphenylthiirane 1,1-dioxide, and, indeed, the thermal decomposition products, *cis*- and *trans*-2-bromostilbene, from this thiirane 1,1-dioxide are observed as by-products,[4] or, under other conditions, as principal products.[5]

The dehydrobromination and debromination of *dl*- and *meso*-$PhCHBrSO_2CHBrPh$ have been shown to occur stereoselectively with inversion of configuration at each chiral center.[5] The stereoselective dehydrobromination of *erythro*- and *threo*-$PhCBr(Me)SO_2CH(Me)Ph$ (**5a** and **5b**, respectively), which also occurs by a double inversion mechanism, is the principal subject of the present paper.[1] Another aspect of the stereochemistry that has been examined is the preferential formation of cis alkenes from the reaction of α-halo sulfones of the type $RCHXSO_2CHR$.

Results

Treatment of either *meso*- or *dl*-bis-α-methylbenzyl sulfone with *N*-bromosuccinimide in the presence of benzoyl peroxide in refluxing carbon tetrachloride yielded a nearly equimolar mixture of diastereomeric α-bromo-α-methylbenzyl α-methylbenzyl sulfones (**5**). The diastereomers were separated by column chromatography on acidic alumina into monobromides melting at 76 and 112°. Single-crystal X-ray analysis of the 112° isomer identified it as the *dl*-erythro bromo sulfone (**5a**).[6] This requires the 76° isomer to have the *dl*-threo configuration (**5b**). The gross structures of **5a** and **5b** are supported by their ir and nmr spectra and by elemental analysis.



Reaction of **5a** or **5b** with sodium methoxide in methanol yielded α,α′-dimethylstilbenes (**8**) quantitatively and stereoselectively. Thus the *dl*-erythro bromide **5a** gave *cis*- and *trans*-α,α′-dimethylstilbene (**8a** and **8b**) in a 93:7 ratio at 25°, and the *dl*-threo isomer **5b** gave the *trans*-stilbene (**8b**) in excess of 95%. Several experiments were performed in methanol-*O*-*d* at 0° from which the starting material was recovered after partial conversion to alkenes. The recovered mixture from a reaction of **5a** with excess methoxide ion after 62% conversion contained **8a** and **8b** in a *ca.* 9:1 ratio and 38% of the deuterium-exchanged bromo sulfone (**5a**-d_1). When a similar reaction of **5a** was quenched after 10% conversion, exchange was incomplete, however, and the following composition was indicated by nmr analysis of the mixture: *ca.* 10% α,α′-dimethylstilbene (**8a** and **8b**), *ca.* 40% **5a**, and *ca.* 50% **5a**-d_1. These data indicate that the ratio of exchange to epimerization for **5a** is about 50:1 at 0°.[7] A reaction of **5b** which was in-

Table I
Rate Data for the Reaction of *erythro*-PhCBr(Me)SO_2CH(Me)Ph (5a) with Sodium Methoxide in Methanol[a,b]

Temp, °C	[MeO⁻]	$10^2 k$, M^{-1} sec^{-1}
25.0	0.0173	2.0
25.0	0.0518	2.0
25.2	0.0590	2.1[c]
25.2	0.0787	2.2[c]
25.0	0.0944	1.8
25.0	0.0944	1.5[d]
25.0	0.0994	1.3[e]
34.9	0.0118	5.9
34.6	0.0236	6.3
44.8	0.0118	18
44.8	0.0236	19
44.7	0.1180	14
44.7	0.2361	9.2

[a] Unless otherwise indicated the second-order rate constants were determined spectrophotometrically under pseudo-first-order conditions. Runs were usually in triplicate and were reproducible to ±5%. [b] From a plot (r = 0.998) of log k *vs.* $1/T$ at three temperatures, E_a = 21.2 kcal mol^{-1} and ΔS^* = 3 eu (at 25°). [c] Titrimetric rate [d] 0.026 M LiClO added. [e] 0.198 M $LiClO_4$ added.

terrupted after only *ca.* 6% conversion to stilbenes led to the recovery of *ca.* 67% **5b** and 27% sulfone **5b**-d_1 and an exchange to epimerization ratio of *ca.* 90:1. A reaction of **5b** with excess methoxide ion in MeOD which was interrupted after *ca.* 10% conversion to α,α′-dimethylstilbenes led to the recovery of *ca.* 30% unreacted **5b** and *ca.* 60% **5b**-d_1 with an exchange to epimerization ratio of *ca.* 120:1. When the reaction with **5b** was allowed to go to 45% conversion the recovered bromo sulfone had undergone complete exchange. The results show that protonation of the carbanions derived from **5a** or **5b** with methanol occurs about five times as rapidly as does the intramolecular displacement to form the thiirane 1,1-dioxide under these conditions.

The kinetics of the reaction of **5a** with methoxide ion in methanol were found to be first order in methoxide ion over a wide range of concentrations and overall second order (Table I). The second-order rate constants showed a slight decrease with increasing base concentration or upon addition of lithium perchlorate (small negative salt effect). The rate of bromide ion release (titrimetric rate) was found to be equal to the rate of stilbene formation (spectrophotometric rate) within experimental error.

The kinetic behavior of *dl-threo*-PhCH(Me)SO_2CBr(Me)Ph (**5b**) with NaOMe–MeOH was dramatically different from that of the *dl*-erythro isomer **5a**. At base concentrations below *ca.* 0.05 M the pseudo-first-order spectrophotometric rate constants increased with increasing base concentration, but at higher concentrations the rate of α,α′-dimethylstilbene formation became *independent* of base concentration (Table II). On the other hand, the titrimetric rate constants (for bromide ion release) were found to be first order in methoxide ion (k = 2.6 × 10^{-2} M^{-1} sec^{-1} at 25° with methoxide ion concentrations of either 0.0295 or 0.0590 M). With excess base of 0.1 M concentration the rate of pseudo-first-order bromide ion release was *ca.* 3.5 times as fast as the rate of α,α′-dimethylstilbene formation.

The kinetic results with **5b** indicate that in this instance decomposition of the intermediate thiirane 1,1-dioxide is the rate-limiting step. This would require a buildup of the intermediate and, indeed, evidence for such a buildup was obtained by an examination of the absorbancy *vs.* time curve. With methoxide concentrations in the range 0.05–0.118 M the absorbance in the 240–250-nm region due to **5b** was observed to decrease with time. This decrease was followed by an increase in absorbance as *trans*-α,α′-dimethylstilbene (**8b**) began to appear.[8] Excellent first-order plots were obtained from the latter portion of the absorbance *vs.* time curve. An absorbance *vs.* time curve was calculated from the experimentally determined spectrophotometric rate constant (first-order rate constant for thiirane 1,1-dioxide decomposition) and the titrimetric rate constant (second-order rate constant for bromide release) using the following initial conditions: the concentration of **5b** being 1.0 × 10^{-4} M and the methoxide ion concentration being 5.18 × 10^{-2} M at 25°. The plot of concentration *vs.* time for these consecutive reactions showed a maximum buildup of thiirane 1,1-dioxide (**7b**) equaling approximately 50% of the initial concentration of **5b**. Using experimentally determined values for molar absorptivities of **5b** and **8b**, an absorbance *vs.* time curve was also calculated. (The absorbance of **7b** was assumed to be negligible.) This curve was in excellent agreement with the experimental curve for a reaction of **5b** under comparable conditions.

Table II
Kinetic Data for the Reaction of *threo*-PhCBr(Me)SO_2CH(Me)Ph (5b) with Sodium Methoxide in Methanol[a,b]

Temp, °C	[MeO⁻]	$10^4 k$, sec^{-1}
25.0	0.0518	7.4
25.0	0.0944	7.2
25.0	0.0944	7.2[c]
25.0	0.0944	7.2[d]
34.7	0.1180	23
34.7	0.2361	22
44.7	0.1180	73
44.7	0.2361	73

[a] Spectrophotometric rates run at least in triplicate (reproducible to within ±5%). [b] From a plot of log k *vs.* $1/T$ (r = 0.9995), E_a = 22.0 kcal mol^{-1} and ΔS = 1.0 eu. [c] 0.026 M $LiClO_4$ added. [d] 0.198 M $LiClO_4$ added.

Table III
Rate Data for the Reaction of $PhCH_2SO_2CHBrPh$ (5) and Its Derivatives with Sodium Methoxide in Methanol at 25°

α-Bromo sulfone	$10^2 k$,[a] M^{-1} sec^{-1}	k (relative)
$PhCH_2SO_2CHBrPh$ (1)	7.5[b]	1.0
$PhCH_2SO_2C(Me)BrPh$	11.5	1.5
$PhCH(Me)SO_2CHBrPh$	1.5	0.20
$PhCH(Me)SO_2C(Me)BrPh$ (5a)	2.0	0.27
$PhCH(Me)SO_2CHBrCH_3$ (9)	0.025	0.0033

[a] Spectrophotometric rates determined under pseudo-first-order conditions. [b] Reference 2a.

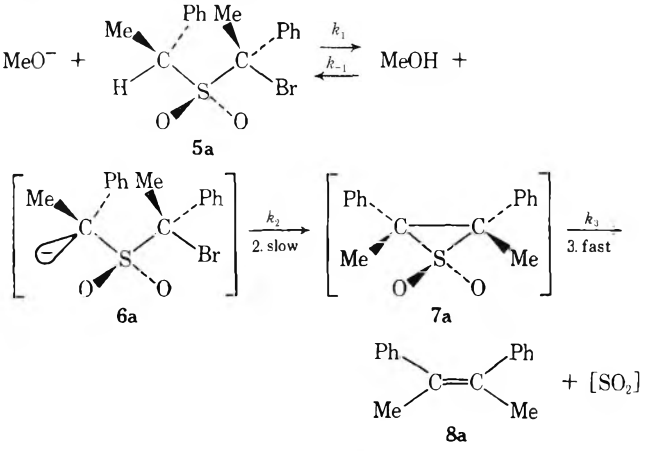
Stereoselectivity was also observed for the Ramberg–Bäcklund reactions of diastereomeric α-methylbenzyl α-bromoethyl sulfones, $PhCH(Me)SO_2CH(Br)CH_3$ (9), with sodium methoxide in methanol. One diastereomer gave a mixture of 2-phenyl-*cis*- and *trans*-2-butene in a 30:70 ratio, whereas with the other diastereomer the ratio was 77:23. Nmr analysis of incomplete reactions of the diastereomer giving mainly cis alkene indicated that epimerization was occurring during the reaction, which is not surprising in view of the presence of two epimerizable reaction sites and a rate of reaction *ca.* 100 times slower than for system **5** (Table III). When *ca.* 17% of unreacted material remained it had been epimerized to the extent of 15%, 85% of the original diastereomer remaining. A comparable experiment with the other isomer showed 31% epimerization.

Reaction of $PhCBr(Me)SO_2CH_2CH_3$ (**10**), a structural isomer of **9**, with 0.62 *M* sodium methoxide in methanol at reflux for 24 hr gave a 57:43 ratio of 2-phenyl-*cis*- and *trans*-2-butene. (Equilibration studies in acetic acid have shown the cis isomer to be favored at equilibrium by a 83:17 ratio.[9]) Recovery of **10** (70%) from a comparable reaction at room temperature showed complete exchange of the α'-hydrogen atoms by deuterium.

The rate studies described above allow an evaluation of the effect of methyl substitution on the rate of thiirane 1,1-dioxide formation (Table III).

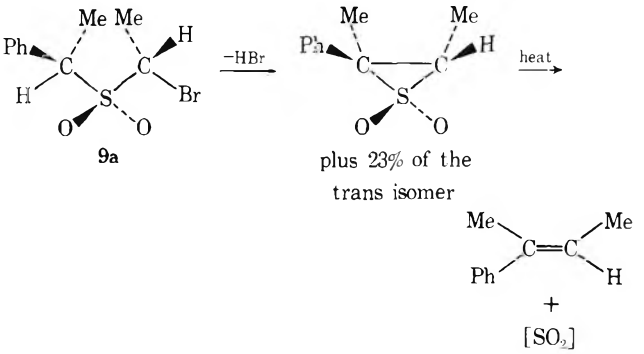
Discussion

Mechanism for the Reaction with 5a, 9a, and 9b. The results indicate that the mechanism for the reaction of the erythro bromo sulfone **5a** is essentially that outlined in Scheme I, except that deuterium exchange experiments show that equilibrium involving the carbanion **6a** is not complete. Evidently the intramolecular nucleophilic displacement (governed by k_2) competes favorably with solvent exchange with the initially formed "singly" solvated carbanion, which is presumably the rate-limiting step for the exchange reaction.[10]



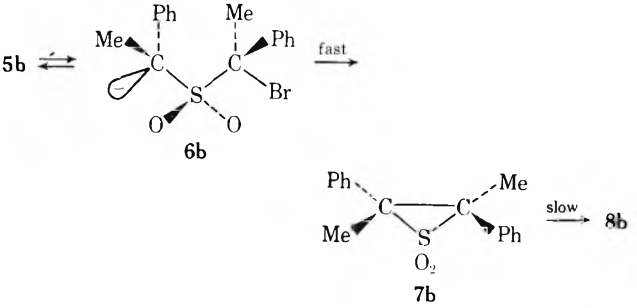
The deuterium exchange experiments show that the rate of the exchange reaction is *ca.* 5 times k_2. Exchange occurs with retention of configuration. [The exchange to epimerization rate ratios in MeOH at 0° of *ca.* 50–100:(1.0) for **5a** and **5b** are of the same order of magnitude as was found previously for $PhCH(Me)SO_2CH(Me)Ph$ (*ca.* 200:1) under comparable conditions.[11]] Reaction of **5a** with methoxide ion involves stereoselective removal of the proton from a conformation wherein it is cis to and flanked by the two sulfonyl oxygen atoms.[11,12] In step 2 inversion occurs at the carbanion carbon and also at the carbon atom holding the bromine atom[1,5] to give *cis*-2,3-dimethyl-2,3-diphenylthiirane 1,1-dioxide (**7a**). The latter cannot epimerize by deprotonation–protonation, as does *cis*-2,3-diphenylthiirane 1,1-dioxide,[2a] because it lacks the necessary α-hydrogen atoms. Stereoselective decomposition of **7a** then occurs to give *cis*-α,α'-dimethylstilbene (**8a**). The experimental results do not exclude double-retention stereochemistry, but we believe this pathway to be unlikely for reasons given earlier.[5] The present results provide further evidence against a dipolar ion mechanism,[2b,13] since one would hardly expect a dipolar ion of the type $^-PhC(Me)SO_2C(Me)Ph^+$ (derived from **5a** or **5b**) to maintain chirality at both the carbanion and carbonium ion centers.

The mechanism for the reactions of the diastereomers of $PhCH(Me)SO_2CH(Br)CH_3$ (**9**) is no doubt similar to that for **5a**. The rate of alkene formation from **9** is about 100 times slower than from **5a**. Since the carbon atoms from which the carbanions are derived are structurally similar for **5a** and **9**, the slower rate must be due primarily to a slower displacement step in **9**.[14] More extensive epimerization of **9a** or **9b** would be expected for this reason, and also because of the presence of a proton on the carbon atom holding the bromine atom.[15] Assuming that double-inversion stereochemistry is being followed, as seems likely, the diastereomer giving mainly 2-phenyl-*cis*-2-butene must be the threo isomer (**9a**), and that giving mainly 2-phenyl-*trans*-2-butene must be the erythro isomer (**9b**).



Effect of Methyl Substitution. Examination of Table III shows that substitution of a methyl group at the α position of **1** causes a 1.5-fold rate acceleration, whereas methyl substitution at the α' position causes a fivefold rate retardation. The effect of α,α'-dimethyl substitution is intermediate. These small methyl effects are comparable to those observed in related systems.[2c] Since a large rate acceleration would be expected for reaction by a dipolar mechanism,[2c] the present results provide additional evidence against this mechanism.

Mechanism for the Reaction with 5b. The nonidentity of the titrimetric and spectrophotometric rates for **5b**, the lack of dependence of the rate of alkene formation on methoxide ion concentration,[17] and the spectrophotometric evidence for a buildup of a thiirane 1,1-dioxide intermediate are all consistent with a change in mechanism from that shown in Scheme I to one where thermal decomposition of *trans*-2,3-diphenyl-2,3-dimethylthiirane 1,1-dioxide (**7b**) has become rate limiting.



This change in mechanism must be caused by a considerably slower rate of decomposition for **7b** than for the corresponding cis isomer **7a**. This conclusion is supported both by the small differences in the rate of formation of **7a** from **5a**, as compared to the rates for comparable substrates wherein thiirane 1,1-dioxide formation is rate limiting (Table III), and by the fact that the rate of first-order decomposition for **7b** in MeOH at 25° is *ca.* 33 times slower than that reported for *trans*-2,3-diphenylthiirane 1,1-dioxide under comparable conditions.[3]

It is noteworthy that the rates of thermal decomposition of thiirane 1,1-dioxides follow the order *trans*-2,3-diphenyl[3] and *cis*-2,3-dimethyl-2,3-diphenyl > *trans*-2,3-dimethyl-2,3-diphenyl > *cis*-2,3-diphenyl[3] > *cis*-2,3-dimeth-

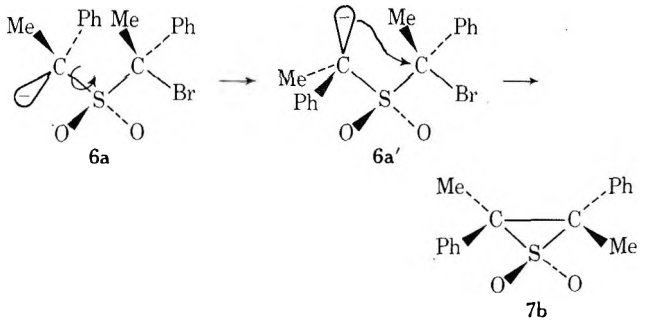
yl,[13] and that the overall difference in rates does not appear to be greater than about two orders of magnitude. The faster rate of decomposition of *trans*-2,3-diphenylthiirane 1,1-dioxide than either its cis isomer or *trans*-2,3-dimethyl-2,3-diphenylthiirane 1,1-dioxide indicates that the stability of the incipient product alkene, rather than steric repulsions in the thiirane 1,1-dioxides, is the more important rate-controlling factor. On the other hand, the opposite conclusion is reached by comparing the rates for **7a** and **7b**. Evidently neither of these factors is very large or is particularly dominant.

Relative Rates of Protonation, Epimerization, and Bromide Ion Expulsion of α-Sulfonyl Carbanions. The rate of deuteration (k_{-1} [MeOD]) of carbanion **6a** and the rate of intramolecular displacement (k_2) of bromide ion by the carbanion are competitive. The experimental data indicate that the rate of formation of deuterated sulfone **5a**-d_1 is *ca.* 5 times as fast as the rate of formation of *cis*-α,α′-dimethylstilbene (**8a**). Assuming a steady-state concentration of **6a** and the mechanistic scheme shown

$$k_{obsd} = \frac{k_1 k_2}{k_{-1}[\mathrm{MeOD}] + k_2} = \frac{k_1 k_2}{5k_2 + k_2} = \frac{k_1}{6}$$

From this relationship we find that $k_1 = 6k_{obsd} \cong 1.2 \times 10^{-1}\ M^{-1}\ \mathrm{sec}^{-1}$ at 25° for $PhCH(Me)SO_2CBr(Me)Ph$ (**5a**). This is *ca.* 100 times the rate of exchange observed for $PhCD(Me)SO_2CD(Me)Ph$ catalyzed by NaOMe in MeOH.[18] Acceleration of the rate of exchange by the γ-bromine atom is, therefore, remarkably large. A similar effect has been observed and commented on elsewhere.[10]

Formation of *ca.* 7% of *trans*-α,α′-dimethylstilbene (**8b**) from **5a** is presumably caused by epimerization of **5a** to some **5b** prior to reaction, rather than by a nonstereoselective decomposition of *cis*-2,3-dimethyl-2,3-diphenylthiirane 1,1-dioxide (**7a**). This view is supported by the similarity of the k_{ex}/k_{ep} ratio calculated on the basis of this assumption with that found under comparable conditions with $PhCH(Me)SO_2CH(Me)Ph$ isomers.[19] Alternatively, **8b** might arise from carbanion **6a′**, a rotamer of **6a**. One can imagine that *ca.* 7% of the **6a** carbanions overcome the rotational barrier to give **6a′** (the inverted form of carbanion **6b**). Ring closure will then give thiirane 1,1-dioxide **7b**, which decomposes to **8b**.



It is also possible that **6a′** might arise directly from **5a** by deprotonation of a conformation in which the H-C bond is anti to the oxygen atoms of the sulfone group.[10,12]

Stereochemistry of the Reaction of $RCHXSO_2CH_2R$ Type Sulfones. In base-initiated 1,3-elimination reaction with $RCHXSO_2CH_2R$, where R is an alkyl group, cis alkenes are formed in considerably greater concentrations than expected from thermodynamic control. Thus, the per cent of *cis*-RCH=CHR is 78% for R = Me, 56% for R = Et, and 52% for R = Pr.[13] At least four explanations have been offered to account for these unusual results: (1) attraction between the methyl groups in the transition state in the nucleophilic displacement step,[13] (a) lesser steric inhibition of solvation in this step,[20] (3) a higher concentration of the carbanion precursor of the cis thiirane 1,1-dioxide caused by a difference in rotational barriers,[21] and (4) preferential formation of a higher equilibrium concentration of the diastereomeric carbanion precursor of the cis thiirane 1,1-dioxide.[22]

Recently it was shown that kinetic control of the stereochemistry is operative even when R = Ph, since as much as 32% of *cis*-stilbene is formed from $PhCHBrSO_2CH_2Ph$ when the base used to initiate the 1,3-elimination is dimethylformamide (DMF).[5] Kinetic control must also be operative in the stereoselective debrominations and dehydrobrominations of *dl*- and *meso*-$PhCHBrSO_2CHBrPh$ by triphenylphosphine and DMF, respectively.[5] The stereoselective dehydrobrominations of the diastereomeric α-bromo sulfones $PhCBr(Me)SO_2CH(Me)Ph$ (**5a** and **5b**) and $PhCH(Me)SO_2CHBrMe$ (**9a** and **9b**) in the present study also appear to be under kinetic control, as does the dehydrobromination of $PhCBr(Me)SO_2CH_2CH_3$ [*ca.* 43% of *trans*-PhC(Me)=$CHCH_3$ formed as compared to *ca.* 17% expected on the basis of thermodynamic control[23]].

The evidence indicating that in some instances there is a preference for two phenyl groups to become cis rather than trans in the thiirane 1,1-dioxide (*e.g.*, the preferential formation of *cis*-2,3-dimethylstilbene from **5a**[23]) and for the preferential formation of a thiirane 1,1-dioxide where a phenyl and a methyl group, rather than two methyl groups, are cis (*e.g.*, the preferential formation of *trans*-α-methylstilbene from one diastereomer of **9**) argues against control of stereochemistry by attractive forces between R groups in the step wherein the thiirane 1,1-dioxide is formed.[13] The evidence points, then, to the carbanion-forming step as that controlling the stereochemistry.

A scheme for stereochemical control through preferential formation of one of two possible diastereomeric carbanions[22] can be illustrated with the reaction of $MeCH_2SO_2CBr(Me)Ph$ (**10**). Deprotonation of **10** by methoxide ion can give either carbanion **10a** or **10a′**, each of which would be expected to maintain its asymmetry for some

Table IV
Summary of Bromination of α-Methylbenzyl Sulfones

Reactant	Mmol	CCl_4, ml	Reaction time, hr	Product	Yield, %
$PhCH(CH_3)SO_2C_2H_5$	50	100	48	**10**	70 (48)[a]
$[PhCH(CH_3)]_2SO_2$	50	100	32	**5**	80 (37)
$PhCH(CH_3)SO_2CH_2Ph$	10	50	18	**11**[b]	75 (41)

[a] Isolated yield is enclosed in parentheses; the other figure represents per cent as determined by nmr analysis. [b] Compound **11** is $PhCH_2SO_2CBr(CH_3)Ph$.[25]

Table V
Physical Data of Bromo Sulfones[a,b]

Compd	Mp, °C	Nmr spectra[c]		
5a	112	1.67	2.13	4.13
5b	76	1.53	2.20	4.80
9a[d]		1.77	1.84	4.24
				4.80
10	67	1.23	2.62	2.94
11	138	2.48	4.20	

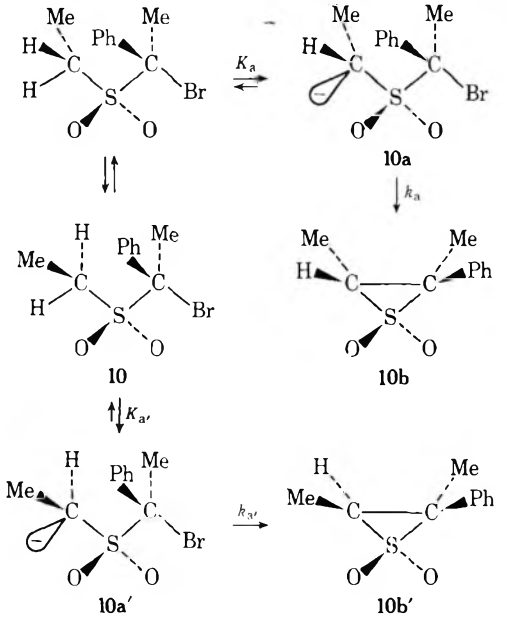
[a] Satisfactory analytical data (±0.4% for C and H) were reported for all new compounds listed in the table: Ed. [b] The sulfones had maxima at *ca.* 7.7 and 7.9 μ. [c] Chemical shifts are reported in δ units relative to TMS as internal standard in dilute chloroform-*d* solution. [d] Recovered as an oil by chromatographing the filtrate obtained from the crystalline isomer **9b**.[27]

Table VI
Methoxide Ion Induced 1,3-Elimination and Deuterium Exchange of 5, 9, and 10

Bromo sulfone	Mmol	$[MeO^-]$[a]	Solvent	Reaction time, hr	Product(s), (yield, %)[b]
5a	0.39	0.063	MeOD	0.35[c]	**5a** (40), **5a**-d_1 (50), **9a** and **8b** (*ca.* 10)
5a	0.57	0.13	MeOD	1.0[c]	**5a**-d_1 (38), **8a** (56), **8b** (*ca.* 6)
5a	0.39	0.19	MeOH	16[d]	**8a** (93), **8b** (7)
5b	0.28	0.090	MeOD	0.05[c]	**5b** (67), **5b**-d_1 (27), **8b** (*ca.* 6)
5b	0.28	0.065	MeOD	0.10[c]	**5b** (30), **5b**-d_1 (60), **8b** (*ca.* 10)
5b	0.38	0.065	MeOD	0.28[c]	**5b**-d_1 (55), **8b** (45)
5b	0.31	0.13	MeOH	12[d]	**8b** (*ca.* 100)
9a	0.74	0.18	MeOH	4[d]	**9a** (59), **9b** (31)[f]
9a	1.1	0.57	MeOH	24[e]	*trans*-PhBu (70), *cis*-PhBu (30)
9b	2.7	0.85	MeOD	4[d]	**9b** (85), **9a** (15)[f]
9b	1.1	0.93	MeOD	24[e]	*trans*-PhBu-d_1 (23), *cis*-PhBu-d_1 (77)
10	1.5	0.18	MeOD	24[d]	**10**-d_2 (70)[g]
10	0.87	0.52	MeOD	24[e]	*trans*-PhBu-d_1 (43), *cis*-PhBu-d_1 (57)

[a] In each experiment excess sodium methoxide was used. Millimoles of methoxide ion may be calculated by multiplying the given concentration by volume used (20 ml in each case). [b] Product ratios were determined by nmr and were checked by vpc for products derived from **9** and **10**. The deuterated bromo sulfones (**5a**-d_1, **5b**-d_1, and **10**-d_2) were isolated and identified by ir and melting point. [c] At 0°. [d] Room temperature. [e] Reflux temperature. [f] Also contained *ca.* 85% 2-phenyl-*cis*- and *trans*-2-butene (*cis*-PhBu and *trans*-PhBu, respectively). [g] Isolated sulfone.

time in methanol solution. Carbanion **10a** will react by double inversion to form thiirane 1,1-dioxide **10b**, which gives rise to the more stable alkene, *cis*-2-phenyl-2-butene; similarly **10a**′ forms **10b**′ and *trans*-2-phenyl-2-butene. The rates of formation of the cis and trans alkenes, assuming rate-limiting thiirane 1,1-dioxide formation, will be $k_{cis} = K_a k_a$ and $k_{trans} = K_{a'} k_{a'}$. Presumably the rate constant k_a will be larger than $k_{a'}$, but this factor favoring formation of **10b** over **10b**′ can be counteracted, or even overshadowed if K_a is substantially larger than $K_{a'}$. In this particular example the two factors approximately balance one another, since the cis:trans alkene ratio is *ca.* 53:47. (In other instances the relative size of the equilibrium constants appears to play the dominant role.) Unfortunately at present we have little insight as to the reason why the equilibrium constant K_a is larger than $K_{a'}$. Presumably **10a** is more stable than **10a**′ because of differences in solvation.



Experimental Section[24]

Bromination of α-Methylbenzyl Sulfones. The parent sulfone, *N*-bromosuccinimide (between 1 and 2 equiv) and a catalytic amount of benzoyl peroxide were heated at reflux temperature for the indicated periods (Table IV).

Product Studies. The α-bromo sulfones (Table V) were allowed to react with excess sodium methoxide in methanol (or methanol-d_1). The reaction mixture was either quenched with nitric acid and/or diluted with water and extracted with dichloromethane or pentane. The organic layer was dried ($MgSO_4$), the solvent was removed under reduced pressure, and the products were analyzed (Table VI).

Kinetic Method. The spectrophotometric and titrimetric rates were determined by previously reported methods.[2,3]

Acknowledgment. We are grateful to the National Science Foundation (GP-29539X) for support of this work.

Registry No.—**1**, 19217-59-5; **5a**, 51380-66-6; **5b**, 51380-67-7; **9a**, 51392-55-3; **9b**, 51392-56-4; **10**, 51392-57-5; **11**, 51392-58-6; PhCH(Me)SO_2CHBrPh, 51392-59-7; PhCH(CH_3)$SO_2C_2H_5$, 51392-60-0; [PhCH(CH_3)]$_2SO_2$, 16907-49-6; PhCH(CH_3)SO_2CH_2Ph, 36611-88-8.

References and Notes

(1) For a preliminary account of this work, see F. G. Bordwell, E. Doomes, and P. W. R. Corfield, *J. Amer. Chem. Soc.*, **92**, 2591 (1970).
(2) (a) F. G. Bordwell and J. M. Williams, Jr., *J. Amer. Chem. Soc.*, **90**, 435 (1968); (b) F. G. Bordwell and J. B. O'Dwyer, *J. Org. Chem.*, **39**, 2519 (1974); (c) F. G. Bordwell and M. D. Wolfinger, *ibid.*, **39**, 2521 (1974).
(3) F. G. Bordwell, J. M. Williams, Jr., E. B. Hoyt, Jr., and B. B. Jarvis, *J. Amer. Chem. Soc.*, **90**, 429 (1968).
(4) F. G. Bordwell, J. M. Williams, Jr., and B. B. Jarvis, *J. Org. Chem.*, **33**, 2026 (1968).
(5) F. G. Bordwell and B. B. Jarvis, *J. Amer. Chem. Soc.*, **95**, 3585 (1973).
(6) P. W. R. Corfield, unpublished results. The conformation shown for **5a** is that found in the crystal.
(7) The exchange to epimerization ratio was calculated from the expression k_{ex}/k_{ep} = % exchange/[(% conversion)(fraction epimerized)] = 50/[(10)(10/90)] = 55. An average of three runs gave an average k_{ex}/k_{ep} = 50.
(8) The length of the induction period and the magnitude of the decrease in absorption depended on the initial concentration of methoxide ion. With 2 *M* NaOMe the disappearance of adsorption due to **5b** was immediate.
(9) D. J. Cram and M. R. V. Sahyun, *J. Amer. Chem. Soc.*, **85**, 1257 (1963).
(10) See the discussion in ref 2b.
(11) F. G. Bordwell, D. D. Phillips, and J. M. Williams, Jr., *J. Amer. Chem. Soc.*, **90**, 426 (1968).
(12) (a) E. J. Corey and T. H. Lowry, *Tetrahedron Lett.*, 803 (1965); (b) S. Wolfe, *Accounts Chem. Res.*, 5, 102 (1972).
(13) N. P. Neureiter, *J. Amer. Chem. Soc.*, **88**, 558 (1966).
(14) Evidence for acceleration of the displacement step by phenyl has been noted previously (see ref 2b and references cited therein).
(15) An α-bromine atom in a sulfone has been shown to accelerate ex-

change at the α position by a factor of ca. 10^3.[16] Epimerization of *cis*- or *trans*-2,3-dimethyl-2-phenylthiirane 1,1-dioxide is unlikely, since *cis*-2,3-dimethylthiirane 1,1-dioxide, which has an acidic proton of a comparable type, does not epimerize under these conditions.[13]

(16) D. A. Schexnayder, Ph.D. Dissertation, Northwestern University, June 1968.

(17) This result is more definitive than the rough kinetic studies of the decomposition of the unstable thiirane 1,1-dioxides themselves.[3] Furthermore, reexamination of the earlier data[3] makes us doubtful as to the reality of the small accelerations in rates observed with increasing methoxide concentration. Our present view is that the decomposition of thiirane 1,1-dioxides is *not* accelerated by low concentrations of bases.

(18) The rate constant k_{-1} probably refers in actual practice to solvent exchange rather than protonation, since the rate-limiting step in these exchanges is probably solvent exchange.[10] Corrections for statistical factors and isotope effects need also to be made, but the 100-fold figure should be of the right order of magnitude.

(19) F. G. Bordwell, D. D. Phillips, and J. M. Williams, Jr., *J. Amer. Chem. Soc.*, **90**, 426 (1968).

(20) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 254–255.

(21) L. A. Paquette, *Accounts Chem. Res.*, **1**, 209 (1968). It is true that this carbanion (labeled **24** in the paper) may be formed faster than that leading to the trans thiirane 1,1-dioxide (**25**) because of a lower rotational barrier, but it is also true that **24** will revert faster to its rotamer (I). There is no reason to believe, then, that the equilibrium concentration of **24** will be higher than that of **25** for this reason, as was assumed.

(22) F. G. Bordwell, B. B. Jarvis, and P. W. R. Corfield, *J. Amer. Chem. Soc.*, **90**, 5298 (1968).

(23) It is assumed that the relative equilibrium concentrations of cis and trans 2,3-, 2,2,3-, and 2,2,3,3-substituted thiirane 1,1-dioxides will not differ greatly from those of the corresponding cis and trans alkenes. This assumption is supported by the formation of a near-equilibrium concentration of *cis*- and *trans*-2-butene from *cis*-2,3-dimethylthiirane 1,1-dioxide when equilibration is effected with *t*-BuOK–*t*-BuOH,[13] and by the formation of only *trans*-stilbene from *cis*-2,3-diphenylthiirane 1,1-dioxide when equilibration is effected with NaOMe–MeOH.[3]

(24) Nmr spectra were determined on a Varian A-60 spectrometer (60 MHz). Infrared spectra were run on a Beckman IR-5 spectrophotometer in KBr disks. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(25) Compound **11** was formed to the exclusion of $PhCHBrSO_2CH(CH_3)Ph$. Data obtained in these experiments indicate that free-radical brominations α to the sulfone group are effective when the hydrogen atom being replaced is both benzylic and tertiary. In fact, it was found previously that simple benzyl and allyl sulfones do not undergo free-radical bromination under comparable conditions.[26]

(26) See H. J. Baker, W. Steven, and N. Dost, *Recl. Trav. Chim. Pays-Bas*, **67**, 451 (1948); *Chem. Abstr.*, **43**, 559 (1949).

(27) M. D. Wolfinger, Ph.D. Dissertation, Northwestern University, June 1968, p 240.

Concerning Driving Forces for 1,3-Elimination Reactions. Dehydrohalogenation of 1-Halo-2-thia-2,3-dihydrophenalene 2,2-Dioxides in a Ramberg–Bäcklund Reaction

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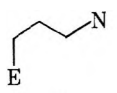
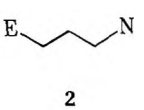
Data obtained for the reaction of 1-bromo-2-thia-2,3-dihydrophenalene 2,2-dioxide (**8**) with NaOMe and MeOH, including deuterium exchange, kinetic order, kinetic salt effects, and kinetic activation parameters, are shown to be remarkably similar to data obtained under similar conditions in a study of an open-chain analog, $PhCHBrSO_2CH_2Ph$ (**9**). The evidence points to a two-stage (carbanion) mechanism for **8**, despite the presence of a geometry that would appear to favor a one-stage (concerted) mechanism. It is concluded that the concerted mechanism for 1,3-elimination has relatively little driving force.

The stereochemistry of two-stage 1,3-elimination reactions involving carbanion intermediates is dictated primarily by the necessity of inversion at the nucleofugal center (N).[1] In acyclic systems this requires removal of the electrofugal atom or group (E) from either conformation **1** (exo-sickle) or conformation **2** (W). Concerted 1,3-elimination reactions could also presumably utilize transition states with geometries corresponding to **1**, **2**, or one of three other possibilities (endo-S, apo-S, or U).[2]

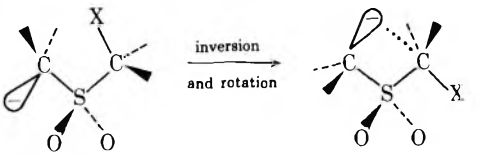


1



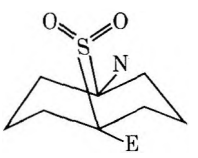
2

1,3-Dehydrobromination of $PhCH(Me)SO_2CBr(Me)Ph$ (**3**)[3] and 1,3-debromination of $PhCHBrSO_2CHBrPh$ (**4**)[1] have been found to involve carbanion intermediates and to prefer overall W geometry (**2**). Here the preference of W over exo-S geometry is believed to be dictated by preferred deprotonation (of **3**) or removal of Br^+ (from **4**) from a conformation in which these electrofugal atoms are flanked by the two oxygen atoms of the sulfonyl group.[1,3] The resulting carbanion (*e.g.*, **5**) is prevented for steric reasons from effecting ring closure. The transition state required for ring closure is **6** wherein carbanion **5** has inverted its configuration and rotation has occurred around the O_2S–CX bond so as to permit inversion of configuration when the nucleofugal group X departs.[1] (Rotation around O_2S–C^- would give the wrong stereochemical result: a barrier to this rotation is assumed.)



5 **6**

If this representation of the reaction is correct, one would expect 1,3-eliminations of this type to be particularly facile in cyclic analogs such as 1-halo-9-thiabicyclo[3.3.1]nonane 1,1-dioxides (**7**), where the E and N atoms



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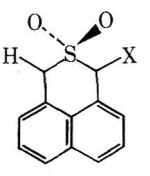
(E = H; N = X)



8

are fixed in the W configuration and the E atom is flanked by the oxygen atoms of the sulfonyl group, or 1-

Table I
Rate Data for the 1,3-Elimination Reaction of 1-Bromo-2-thia-2,3-dihydrophenalene 2,2-Dioxide (8, X = Br)[a-c]

Runs	Temp, °C	[CH_3ONa]	k_{obsd}, sec^{-1}	k_2, M^{-1} sec^{-1}
3	25.0	2.36×10^{-1}	2.63×10^{-3}	1.12×10^{-2}
1	25.0	2.48×10^{-1}	2.73×10^{-3}	1.10×10^{-2}
2	25.0	1.24×10^{-1}	1.04×10^{-3}	0.85×10^{-2}
3	25.0	1.18×10^{-1}	1.05×10^{-3}	0.89×10^{-2}
2	25.0	1.06×10^{-1}	0.98×10^{-3}	0.92×10^{-2}
3	35.0	1.18×10^{-1}	4.34×10^{-3}	3.62×10^{-2}
2	34.9	5.90×10^{-2}	1.95×10^{-3}	3.30×10^{-2}
2	34.9	5.90×20^{-2} [d]	1.73×10^{-3}	2.94×10^{-2}
2	43.0	5.90×10^{-2}	5.76×10^{-3}	0.98×10^{-1}
2	42.5	5.90×10^{-2} [d]	5.00×10^{-3}	0.85×10^{-1}
3	42.5	1.18×10^{-1}	1.30×10^{-2}	1.10×10^{-1}

[a] Correlation coefficients for all runs were at least 0.999. [b] In no case did rate constants (which were averaged) differ by more than 5% from the mean value. [c] E_a = 25.5 kcal/mol^{-1} and ΔS^* = 16 eu (r = 0.9999) from reactions involving 0.118 M sodium methoxide. [d] This solution was 0.064 M in $LiClO_4$.

Table II
Rate Data for the 1,3-Elimination Reaction of $C_6H_5CHBrSO_2CH_2C_6H_5$ (9)

Runs	Temp, °C	[CH_3ONa]	k_{obsd}, sec^{-1}	k_2, M^{-1} sec^{-1}
2	25.0	1.24×10^{-1}	1.17×10^{-2}	9.4×10^{-2}
2	25.0	4.97×10^{-2}	3.80×10^{-3}	7.6×10^{-2}
2	25.0	4.97×10^{-2} [a]	3.23×10^{-4}	6.5×10^{-2}
	25.0	1.55×10^{-2} [b]		7.5×10^{-2}

[a] This solution was 0.093 M in $LiClO_4$. [b] Taken from F. G. Bordwell and J. M. Williams, Jr., *J. Amer. Chem. Soc.*, **90**, 435 (1968).

halo-2-thia-2,3-dihydrophenalene 2,2-dioxides (8), where this geometry is either preferred or easily attained.

Recent studies have indeed shown that 7 and 8 do undergo Ramberg–Bäcklund type reactions. Reaction of 7 (X = Br) with sodium *tert*-pentoxide in tetraglyme at 70° for 1 hr gave an 81% yield of $\Delta^{1,5}$-bicyclo[3.3.0]octane,[4] and a 75% yield was obtained from 7 (X = Cl) when treated with aqueous potassium hydroxide at 100° for 48 hr.[5] Also, the parent sulfone 8 (X = H) is readily converted to acenaphthylene by reaction with KOH-CCl_4 under conditions where the evidence points to the chloro sulfone (8, X = Cl) as the intermediate.[6] Since the favored W geometry is readily available to 8, it seemed likely that proton removal, inversion at that carbon atom, and intramolecular displacement of X (with inversion) would all occur in a single transition state (concerted mechanism). The concerted mechanism would be expected to be preferred in this instance, since the conformation of the ground state is already constricted, which should lead to a more positive entropy of activation than for the acyclic analog. We therefore decided to study the Ramberg–Bäcklund reaction of 8 as a model for the concerted mechanism.

Results

The desired α-halo sulfones (8, X = Br or Cl) were prepared by halogenating the corresponding sulfide followed by oxidation. The four benzylic protons of the parent sulfone appear as a singlet in the nmr spectrum. Since examination of molecular models indicates that the ring containing the sulfone bridge is puckered, the nmr data suggest that ring inversion is rapid on the nmr time scale. The nmr spectra of the halo sulfones 8 show a large downfield shift (1 ppm) of one of the methylene protons relative to the other, indicating that the system is mobile, allowing considerable 1,3-diaxial interaction between one of the methylene protons and the halogen.

Reaction of 8 (X = Br or Cl) with sodium methoxide in methanol gave acenaphthylene in high yield, and as the only detectable product. Treatment of 8 (X = Br or Cl) with NaOMe–MeOD gave dideuterioacenaphthylene. Recovery of the bromo sulfone from a run after about 1 half-life showed that the α and α' protons had been completely exchanged by deuterium.

Excellent first-order plots were obtained from spectrophotometric rate measurements made under pseudo-first-order conditions. Small increases in second-order rate constants were observed with increasing concentrations of sodium methoxide (Table I). Surprisingly enough, the rate constants *decreased* slightly, but significantly, in the presence of lithium perchlorate. Examination of the rates for the reaction of sodium methoxide in methanol with and without added lithium perchlorate for $PhCH_2SO_2CHBrPh$ (9), an open-chain analog of 8, revealed comparable effects (Table II).

Data were also obtained for chloride 8 at 25° (k_2 = 0.87, 0.93, and 0.93 $\times 10^{-4}$ M^{-1} sec^{-1} with 0.248 M NaOMe) and 39.7° (k_2 = 0.93, 1.00, and 1.09 $\times 10^{-3}$ M^{-1} sec^{-1} with 0.248 M NaOMe; 0.83, 0.83, and 0.71 $\times 10^{-3}$ M^{-1} sec^{-1} with 0.124 M NaOMe); E_a = 30.3 kcal/mol for the runs with 0.248 M base.

Discussion

It is significant that the rate data accumulated for the 1-halo-2-thia-2,3-dihydrophenalene 2,2-dioxide system (8) bear a remarkable resemblance to the data obtained for a open-chain analog, $PhCHXSO_2CH_2Ph$ (9).[7] In each instance methoxide-catalyzed deuterium exchange is much faster than intramolecular nucleophilic displacement to form the thiirane 1,1-dioxide ring. Both reactions show slight increases in rate constants for alkene formation with increasing methoxide concentrations and slight decreases in these rate constants with increasing lithium perchlorate concentration (Tables I and II). Both reactions exhibit large k^{Br}/k^{Cl} leaving group effects (121 at 25° for 8 and 280 for 9). The overall rate of alkene formation from 9 (X = Br) is *ca.* 11 times faster at 25° than that from 8 (X = Br), but the activation parameters are the same within the experimental error of the measurements (E_a = 25.5 kcal/mol and ΔS^* = 16 eu at 25° for 8 as compared to 25 kcal/mol and 17 eu at 25° for 9). The data point strongly to reaction of 8 and 9 by similar mechanisms. For 9, numerous lines of evidence point to (1) re-

versible carbanion formation as the initial step, (2) rate-limiting intramolecular nucleophilic displacement to form a thiirane 1,1-dioxide as the second step, and (3) rapid thermal decomposition of the thiirane dioxide to an alkene as the third step.[7-9] There appears to be every reason to accept this mechanism also for the Ramberg–Bäcklund reaction of 8.

Table III
Methoxide Ion Induced 1,3-Eliminations and Deuterium Exchange of 2-Thia-2,3-dihydrophenalene 2,2-Dioxides (8)

Compd	Quantity, mmol	MeO^-, mmol	Solvent (ml)	Reaction time	Product
8 (X = Br)	0.50	3.7	MeOH (15)	12 hr	AN-H_2[a]
8	0.26	3.7	MeOD (10)	4 hr	AN-d_2[a]
8	0.09	0.18	MeOD (4)	50 sec	**1c-d$_3$**[b]
8 (X = Cl)	0.45	2.1	MeOD (10)	36 hr	AN-d_2[a]

[a] AN-H_2 is acenaphthylene. [b] Characterized by ir, nmr, and melting point.

where one might have expected bond making to aid bond breaking in a concerted fashion.[16] The conclusion concerning the rarity of the one-stage mechanism for 1,3-eliminations is supported in a general way by evidence that in similar reactions where two bonds are formed and two bonds are broken, such as S$_N$2′ reactions[8] and 1,2-elimination reactions,[17] two-stage mechanisms are much more common than one-stage mechanisms. Aside from the entropy factor mentioned previously, the most important factor dictating the preference for the two-stage mechanism in these reactions is probably the greater degree to which solvation forces can be utilized in providing the energy necessary for rehybridization of the two carbon atoms and in the cleavage of the C–X bond. In addition to these factors, the one-stage mechanism has a particular handicap in 1,3-eliminations in that a highly strained three-membered ring is being formed. As a result the amount of energy released during formation of the new C–C bond in a 1,3-elimination is appreciably less, for example, than during formation of the new C=C bond in a 1,2-elimination. This makes the concerted mechanism less attractive in a 1,3- than in a 1,2-elimination process.

Table IV
Nmr Data for 2-Thia-2,3-dihydrophenalene Derivatives[a]

Compd	Methylene	Methine	Aromatic
8 (X = H)	4.60 (s, 4 H)		~7.7 (m, 6 H)
8 (X = Br)	4.43 (d, d, J = 16, 3 Hz, 1 H) 5.42 (d, J = 16 Hz, 1 H)	6.03 (d, J = 3 Hz, 1 H)	~7.7 (m, 6 H)
8 (X = Cl)	4.45 (d, d, J = 16, 3 Hz, 1 H) 5.32 (d, J = 16 Hz, 1 H)	5.93 (d, J = 3 Hz, 1 H)	~7.7 (m, 6 H)
10[b]	4.00 (s, 4 H)		~7.4 (m, 6 H)

[a] Chemical shifts are reported in δ units downfield from tetramethylsilane as internal standard. [b] Mp 95–97° (lit.[19] mp 102°).

Table V
Melting Points and Carbon–Hydrogen Analyses for 2-Thia-2,3-dihydrophenalene 2,2-Dioxides[a]

Compd[b]	Mp, °C	Molecular formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
8 (X = H)	244–245	$C_{12}H_{10}SO_2$	66.03	4.62	65.83	4.55
8 (X = Br)	197–198	$C_{12}H_9BrSO_2$	48.50	3.05	47.83	2.99
8 (X = Cl)	167–168	$C_{12}H_9ClSO_2$	56.80	3.57	56.76	3.70

[a] The characteristic ir absorptions at 7.6 and 8.9 μ were observed for the sulfones; crystallized from dichloromethane–hexane.

The failure of 8 to take advantage of the concerted pathway indicates that the concerted mechanism can provide but little driving force in this instance. Apparently stepwise ionic processes, wherein maximum advantage can be taken of solvation forces, provide a lower energy pathway.[13]

The present evidence indicates that, even under what appear to be the most favorable circumstances for a concerted pathway, the Ramberg–Bäcklund reaction occurs by a two-stage rather than a one-stage mechanism. Previously we surveyed the stereochemical evidence that has accumulated with regard to 1,3-elimination reactions and concluded that concerted 1,3-eliminations are rare, if they exist at all.[1,15] This conclusion was based on the premise that, if the one-stage mechanism is favored energetically, examples where a high degree of stereoselectivity is observed should be common and one preferred stereochemical pathway would be likely to emerge. Instead, many 1,3-eliminations exhibit little or no selectivity, and no one stereochemical pathway has emerged as dominant. One example of U geometry being preferred to endo-S has been found,[2] but in most instances the preferred geometry is either exo-S or W. These latter geometries are those expected for two-stage pathways. To this evidence we now add the failure of a driving force to emerge in an example

Experimental Section

Nmr spectra were determined on a Varian T-60 spectrometer (60 MHz). Chemical shifts are reported in δ units (parts per million downfield from TMS) and were determined in chloroform-d solution. Infrared spectra were run on a Beckman IR-5 spectrophotometer in KBr disks. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Melting points are uncorrected.

Preparation of Sulfones. Chlorination (and bromination) of 2-thia-2,3-dihydrophenalene (**10**) was carried out according to the procedure of Tuleen.[18] The crude halo sulfides were oxidized to sulfones (8) with m-chloroperoxybenzoic acid (MCPBA). The isolated yields of **8b** (X = Cl) 52 and **8c** (X = Br) were 52 and 59%, respectively. The known sulfone **8a** (X = H) was obtained from **10** in 64% yield upon oxidation of the latter with MCPBA.

Product Studies. The halo sulfones **8b** and **8c** were allowed to react with excess sodium methoxide in methanol or methanol-d_1. The product, acenaphthylene, was identified by its ultraviolet and nmr spectra and melting point. See Table III for a summary of representative product study experiments, and Tables IV and V for data supporting structures of substrates used in kinetic studies.

Kinetic Method. See previous reports from this laboratory for the spectrophotometric determination of rates.[7] The appearance of acenaphthylene was measured at 320 mμ, and the rates were followed through at least 5 half-lives.

Acknowledgment. This work was supported by the National Science Foundation (GP-29539X).

Registry No.—8 (X = H), 29376-61-2; 8 (X = Br), 51392-61-1; 8 (X = Cl), 51392-62-2; **9**, 19217-59-5; **10**, 203-85-0.

References and Notes

(1) For pertinent references and a discussion see F. G. Bordwell and B. B. Jarvis, *J. Amer. Chem. Soc.*, **95**, 3585 (1973).
(2) A. Nickon and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **89**, 3914 (1967).
(3) F. G. Bordwell, E. Doomes, and P. W. R. Corfield, *J. Amer. Chem. Soc.*, **92**, 2581 (1970).
(4) E. J. Corey and E. Block, *J. Org. Chem.*, **34**, 1233 (1969).
(5) L. A. Paquette and R. W. Houser, *J. Amer. Chem. Soc.*, **91**, 3870 (1969).
(6) C. A. Meyers, A. M. Malte, and W. S. Matthews, *J. Amer. Chem. Soc.*, **91**, 7510 (1969).
(7) F. G. Bordwell and J. M. Williams, Jr., *J. Amer. Chem. Soc.*, **90**, 435 (1968).
(8) F. G. Bordwell, *Accounts Chem. Res.*, **3**, 281 (1970).
(9) The evidence indicates that this is the most common mechanism,[10] but that sometimes deuterium exchange and thiirane dioxide formation are competitive:[11] one example is known where thiirane dioxide decomposition is rate limiting.[3,12]
(10) F. G. Bordwell and M. D. Wolfinger, *J. Org. Chem.*, **39**, 2521 (1974).
(11) F. G. Bordwell and J. B. O'Dwyer, *J. Org. Chem.*, **39**, 2519 (1974).
(12) F. G. Bordwell and E. Doomes, *J. Org. Chem.*, **39**, 2526 (1974).
(13) One could also argue that the axial proton **8** is removed preferentially because this allows maximum overlap with the naphthalene ring (stereoelectronic control). The evidence that stereoelectronic control provides much in the way of driving force for deprotonation is also slight, however.[14]
(14) F. G. Bordwell and R. G. Scamehorn, *J. Amer. Chem. Soc.*, **90**, 6749 (1968).
(15) For an example where superficial examination of a Ramberg–Backlund reaction suggested a concerted mechanism, but more careful examination revealed a two-stage mechanism; see ref 11.
(16) A driving force has failed to emerge in a 1,2-elimination where one might have been expected; see F. G. Bordwell, D. A. R. Happer, and G. D. Cooper, *Tetrahedron Lett.*, 2759 (1972).
(17) F. G. Bordwell, *Accounts Chem. Res.*, **5**, 374 (1972).
(18) D. L. Tuleen, *J. Org. Chem.*, **32**, 4006 (1967).
(19) R. H. Schlessinger and I. S. Ponticello, *J. Amer. Chem. Soc.*, **89**, 3614 (1967).

Ion Radicals. XXIX. Reaction of Thianthrene Cation Radical Perchlorate with Some Benzene Derivatives[1,2]

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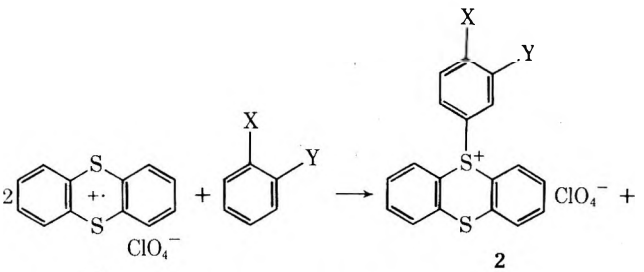
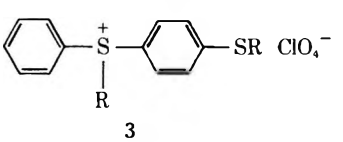
Thianthrene cation radical perchlorate ($Th\cdot^+ClO_4^-$, 1) reacted in acetonitrile solution with acetanilide, phenol, o-chlorophenol, o-*tert*-butylphenol, and *N,N*-dimethylaniline to give 5-arylthianthrenium perchlorates ($ThAr^+ClO_4^-$) in which bonding is presumed to have occurred at the aryl position para to the functional group. Excellent yields were obtained, except in the case of *N,N*-dimethylaniline, which also underwent oxidative dimerization to *N,N,N′,N′*-tetramethylbenzidine. Thianthrene (Th) was formed along with the formation of the 5-arylthianthrenium perchlorates, according to the anticipated stoichiometry $2Th\cdot^+ + ArH \rightarrow Th + ThAr^+ + H^+$. Reaction of 1 with hydrazobenzene caused both oxidation to azobenzene and rearrangement (by concurrently formed acid) to benzidine monoperchlorate. Kinetics of reaction of 1 with phenol and acetanilide in acetonitrile were followed by use of the Durrum-Gibson stopped-flow spectrophotometer. Kinetics of reaction with anisole were reexamined by the same technique, allowing in each case the use of $[1]_0$ in the range 10^{-6}–10^{-5} *M*. Reactions were second order in $Th\cdot^+$ and inverse order in thianthrene. Difficulties with a mechanism of reaction involving the thianthrene dication, formed in the first-stage disproportionation of the thianthrene cation radical, are discussed. No other suitable mechanism is found.

Results and Discussion

Products. The substitution reactions of organic cation radicals with aromatic substrates are not well explored. Anodic dimerizations, particularly of aromatic amines and phenols, are well known,[5] but we exclude them from the class of substitution reactions we have in mind. An earlier report[6] showed that thianthrene cation radical perchlorate (**1**) reacted with anisole to form 5-(*p*-anisyl)thianthrenium perchlorate (**2a**) according to the stoichiometry of eq 1. Compounds of this class are not well known. They may be formed in some cases (*e.g.*, X = Y = H) by reaction of thianthrene oxide with the aromatic and aluminum chloride.[6,7] Recently, analogous examples (**3**) have been made by the anodic dimerization of the sulfides C_6H_5SR (R = phenyl and alkyl).[8] We have now found that reaction of **1** with acetanilide and three phenols occurs very readily in good yield according to eq 1. Reaction with *N,N*-dimethylaniline also occurred, but in poorer yield (21%), being overshadowed by oxidative dimerization to *N,N,N′,N′*-tetramethylbenzidine (TMB) and the latter's oxidation to the corresponding cation radical ($TMB\cdot^+$). Reaction of **1** with hydrazobenzene led not only to the formation of thianthrene and azobenzene but also to benzidine; benzidine rearrangement must without doubt have occurred from the acid liberated in the redox reaction.



	a	b	c	d	e	f	g
X	OMe	NHAc	OH	OH	OH	NMe_2	NH_2
Y	H	H	H	Cl	*t*-Bu	H	H



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Kinetics and Mechanism. In the earlier report the reaction of **1** with anisole was found to be second order in

Table I
Kinetic Data for the Reaction of Thianthrene Cation Radical Perchlorate (1) with Phenol, Acetanilide, and Anisole in Acetonitrile Solution at 25°

Aromatic (Ar)	10^2 [Ar]$_0$, M	10^6 [1]$_0$, M	10^4 [Th]$_0$, M	k_{obsd}, M^{-1} sec^{-1}	r^a	k, M^{-1} sec^{-1}
Phenol	4.6	47	7.6	7.9×10^4	0.957	1.3×10^3
Phenol	4.6	47	7.6	6.8×10^4	0.995	1.1×10^3
Acetanilide	1.3	2.1	16	4.3×10^3	0.991	5.4×10^2
Acetanilide	1.3	4.8	16	2.2×10^3	0.994	2.8×10^2
Acetanilide	1.3	17	16	9.7×10^2	0.997	1.2×10^2
Acetanilide	1.9	3.7	4.0	1.7×10^4	0.999	3.7×10^2
Acetanilide	1.9	20	4.0	4.8×10^3	0.986	1.1×10^2
Anisole	0.87	28	8.7	5.9×10	0.980	5.9
Anisole	12	27	8.7	3.4×10^2	0.999	2.5
Anisole	12	59	8.7	3.3×10^2	0.999	2.4
Anisole	180	13	28	2.4×10^3	0.991	3.7
Anisole	180	3.2	28	1.7×10^3	0.989	2.6
Anisole	40	1.4	5.2	3.6×10^3	0.974	4.7
Anisole	83	8.1	5.2	1.6×10^3	0.989	1.0

[a] Correlation coefficient.

Th·$^+$ and inverse order in thianthrene. We have repeated these kinetics and also run those with acetanilide and phenol with the use of a Durrum-Gibson stopped-flow spectrophotometer, allowing us to use much lower concentrations (10^{-6}–10^{-5} M) of 1 than were possible in the earlier conventional vacuum-line spectrophotometric technique. Although the use of lower concentrations made kinetic measurements more subject to error, the new results duplicate the older ones quite well. Conventional first- and second-order rate plots indicated clearly that the reactions were second order in Th·$^+$. We have treated the rate data according to eq 2 and 3, and have calculated the

$$2\text{Th}^{\cdot+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{Th} + \text{Th}^{2+} \qquad (2)$$

$$\text{Th}^{2+} + \text{ArH} \xrightarrow{k_2} \text{ThAr}^{+} + \text{H}^{+} \qquad (3)$$

second-order rate constants (k_{obsd}) by least-squares treatment, from which we have also calculated the rate constants, $k = k_{obsd}[\text{Th}]_0/[\text{ArH}]_0$. For the anisole case the new results gave an average value of $k = 3.3 \pm 1.3$ M^{-1} sec^{-1}, while the earlier results gave $k = 2.4 \pm 0.34$ M^{-1} sec^{-1}, which we feel is a reasonable agreement. The relevant data are given in Table I. Similar work with acetanilide and phenol gave the data in Table I.

These and the earlier results show that the reaction of 1 with these aromatics is an aromatic substitution reaction in that reaction occurs easily when X in ArX is an electron donor.[6] At the same time, the rates for the three aromatics do not parallel the σ^+ constants for the substituents as one might have expected. Recently, the σ^+ constant for the *p*-acetamido group has been found to be somewhat more negative (−0.69)[9] than indicated earlier.[10] The value for the *p*-hydroxy group remains at −0.92. A new value for *p*-methoxy has not been determined,[9] but there is no reason to believe that the old ones, averaging −0.77,[10] are likely to be in error. Thus, our rate data have substituent effects in the order OH > NHAc > OMe rather than in the σ^+-constant order of OH > OMe > NHAc. Furthermore, the rate for the anisole reaction is particularly low in comparison with the other two. The data for phenol and acetanilide gave a ρ value of −2.7, which is reasonable for attack of an electrophile on the aromatics, but the data for phenol and anisole lead to a ρ value of −16.7, which is entirely unreasonable. Consequently, it may be that reaction of 1 with anisole follows a quite different mechanism from reaction with phenol and acetanilide.

Criticisms of our interpretation (eq 2 and 3) of the aromatic substitution reaction and the analogous water reaction have been made,[11] particularly on the basis that the disproportionation constant (K, eq 2) is so small that substitution rates (eq 3) must approach those of diffusion control to satisfy the rate data. Values of K have been determined from half-wave potentials for the oxidation of thianthrene to the cation radical and dication and found to be about 10^{-9}.[12,13] This requires the rate constant k_2 to be of the order 10^9–10^{12} for the three aromatics studied. These are, of course, decidedly difficult to accept. Nevertheless, no satisfactory alternative mechanism of reaction has been proposed for reactions of thianthrene cation radical which are second order in cation radical and inverse order in thianthrene. A two-step reaction analogous to parts of an electrochemical ECE process (eq 4 and 5) is

$$\text{Th}^{\cdot+} + \text{ArH} \longrightarrow \text{ThAr}^{\cdot} + \text{H}^{+} \qquad (4)$$

$$\text{ThAr}^{\cdot} + \text{Th}^{\cdot+} \longrightarrow \text{ThAr}^{+} + \text{Th} \qquad (5)$$

unattractive because the electron-transfer reaction (eq 5) would have to be rate determining and reversible, neither of which is known to be valid. Recently, Parker proposed for the water reaction that the thianthrene dimer dication may be responsible (eq 6 and 7, in which ThO represents

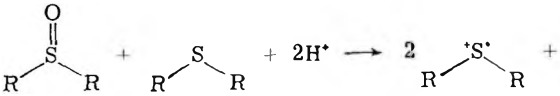
$$2\text{Th}^{\cdot+} \rightleftharpoons (\text{Th}^{\cdot+})_2 \qquad (6)$$

$$(\text{Th}^{\cdot+})_2 + \text{H}_2\text{O} \longrightarrow \text{ThO} + \text{Th} + 2\text{H}^{+} \qquad (7)$$

thianthrene 5-oxide).[14] Kinetics of the water reaction and the aromatic substitution reactions require in that case that eq 7 and analogous eq 8 be reversible. It is known

$$(\text{Th}^{\cdot+})_2 + \text{Ar} \longrightarrow \text{ThAr}^{+} + \text{Th} + \text{H}^{+} \qquad (8)$$

that a mixture of a sulfide and sulfoxide in acid solution will give the cation radical (eq 9). In fact, this is the way



(9)

in which Rundel and Scheffler[15] make 1. On the other hand, the kinetics of the water reaction are not affected by addition of ThO and modest amounts of perchloric acid.[16] Whether or not eq 10 is valid is also not known.

$$\text{ThAr}^{+} + \text{Th} + \text{H}^{+} \longrightarrow 2\text{Th}^{\cdot+} + \text{Ar} \qquad (10)$$

Furthermore, although 1 is known to produce a dimer [*i.e.*, $(\text{Th}^{\cdot+}\text{ClO}_4^-)_2$] in propionitrile and trifluoroacetic anhydride–trifluoroacetic acid,[17] no evidence for that tet-

rameric aggregate has been found in acetonitrile solution.[18] Therefore, although the kinetic data for an aromatic substitution reaction may be satisfied by eq 6 and 8, there are no supporting data for them. An entirely satisfactory solution to all aspects of the mechanism of substitution is, therefore, still needed.

Experimental Section

Materials. Thianthrene cation radical perchlorate (1) was prepared by oxidizing thianthrene with perchloric acid.[4] Solvent acetonitrile was Eastman Kodak Spectrograde (<0.01% water) and was kept over molecular sieve in a septum-capped bottle. Phenol, o-chlorophenol, *o-tert*-butylphenol, and *N,N*-dimethylaniline were distilled under vacuum. Acetanilide was crystallized from hot water, hydrazobenzene was crystallized from aqueous ethanol, and *N,N,N',N'*-tetramethylbenzidine was crystallized from ethanol after decolorizing in benzene with charcoal.

Reaction of 1 with Acetanilide. To a solution of 1.13 g (3.6 mmol) of 1 in 30 ml of acetonitrile was added 0.60 g (4.4 mmol) of solid acetanilide. As the acetanilide dissolved the purple color of the solution slowly faded to pale pink, and a white solid precipitated. This was filtered, the solution was rinsed from the flask with solvent acetone and evaporated to dryness at reduced pressure, and all solids were combined for chromatography on a column of silica gel (Merck, 30-70 mesh, 16 × 2.4 cm). Elution with benzene gave 317 mg (1.5 mmol, 83%) of thianthrene. Elution with acetone gave 362 mg (2.7 mmol) of acetanilide. Elution with ethanol gave 795 mg (1.8 mmol, 100%) of the monohydrate of 5-(*p*-acetamidophenyl)thianthrenium perchlorate (**2b**), mp 136-137° (aqueous ethanol), ultraviolet λ_{max} (acetonitrile) 282.6 nm (ϵ 1.6 × 10^4).

Anal. Calcd for $C_{20}H_{16}NS_2ClO \cdot H_2O$: C, 51.3; H, 3.87; N, 2.99; S, 13.7; Cl, 7.57. Found: C, 51.7; H, 3.93; N, 3.01; S, 13.11; Cl, 8.06.

Hydrolysis of 5-(*p*-Acetamidophenyl)thianthrenium Perchlorate (2b). A solution of 175 mg of **2b** in 10 ml of ethanol was refluxed for 24 hr after 4 drops of 30% sodium hydroxide was added. The solution was evaporated and the white solid was washed with water and benzene and dried, giving 125 mg (0.3 mmol) of crude 5-(*p*-aminophenyl)thianthrenium perchlorate (**2g**), mp 242-243° (methanol), ultraviolet λ_{max} (acetonitrile) 299 nm (10^{-3} ϵ 2.3), 265 (1.6).

Anal. Calcd for $C_{18}H_{14}NS_2ClO_4$: C, 53.0; H, 3.45; N, 3.43; S, 15.7; Cl, 8.69. Found: C, 52.7; H, 3.60; N, 3.33; S, 15.7; Cl, 8.40.

Reaction of 1 with Phenol. The reactants were 619 mg (2.0 mmol) of 1 in 30 ml of acetonitrile and 190 mg (2.0 mmol) of phenol. After work-up the residue was chromatographed and gave with benzene 217 mg (1.0 mmol, 100%) of thianthrene, with ether 68.2 mg (0.3 mmol, 15.0%) of thianthrene 5-oxide, and with acetone 572 mg of solids from which a quantitative yield of 5-(*p*-hydroxyphenyl)thianthrenium perchlorate (**2c**) was obtained by crystallization from ethanol, mp 256.5-257.5°, ultraviolet λ_{max} (acetonitrile) 316 nm (broad, 10^{-4} ϵ 2.4), 267 (sh, 1.0).

Anal. Calcd for $C_{18}H_{13}S_2ClO_5$: C, 52.9; H, 3.20; S, 15.7; Cl, 8.67. Found: C, 53.1; H, 3.37; S, 16.0; Cl, 8.98.

Reaction of 1 with *o*-Chlorophenol. The reactants were 600 mg (1.90 mmol) of 1 in 20 ml of acetonitrile and 1 ml (9.6 mmol) of o-chlorophenol. Work-up gave a purple, liquid residue. Chromatography gave with benzene 216 mg (1.0 mmol, 107%) of thianthrene, with ether 46.9 mg (0.20 mmol, 10.5%) of thianthrene 5-oxide, and with acetone 395 mg of solids from which crystallization from ethanol gave 5-(3-chloro-4-hydroxyphenyl)thianthrenium perchlorate (**2d**), mp 229-230°, ultraviolet λ_{max} (acetonitrile) 316 nm (10^{-4} ϵ 0.85), 289 (1.0), 250 (1.5).

Anal. Calcd for $C_{18}H_{12}S_2Cl_2O_5$: C, 48.7; H, 2.7; S, 14.5; Cl, 16.0. Found: C, 48.7; H, 2.8; S, 14.9; Cl, 15.8.

Reaction of 1 with *o-tert*-Butylphenol. Reactants were 757 mg (2.4 mmol) of 1 in 25 ml of acetonitrile and 0.5 ml (2.6 mmol) of o-*tert*-butylphenol. The pale blue solution gave a mixture of white and dark solids. Chromatography gave with benzene 343 mg of thianthrene wet with *o-tert*-butylphenol, with ether 59.7 mg (0.30 mmol, 12.5%) of thianthrene 5-oxide, and with acetone 511 mg of solids from which crystallization from aqueous ethanol gave quantitatively 5-(3-*tert*-butyl-4-hydroxyphenyl)thianthrenium perchlorate (**2e**), mp 205-106°, ultraviolet λ_{max} (acetonitrile) 313 nm (10^{-4} ϵ 0.67), 283 (1.1), 256 (1.5).

Anal. Calcd for $C_{22}H_{21}S_2ClO_5$: C, 56.8; H, 4.55; S, 13.8; Cl, 7.62. Found: C, 56.5; H, 4.65; S, 14.1; Cl, 8.11.

Reaction of 1 with Hydrazobenzene. Reactants were 919 mg (2.9 mmol) of 1 in 30 ml of acetonitrile and 570 mg (3.1 mmol) of hydrazobenzene. The purple solution turned yellow immediately when the hydrazobenzene was added. Elution of the silica gel column with benzene gave a mixture of thianthrene and azobenzene. Elution with ethanol gave 405 mg of the monoperchlorate of benzidine. The mixture of thianthrene and azobenzene was separated on a column of Florisil (100-200 mesh, Sigma Chemical Co.) using methanol as eluent, giving 631 mg (2.9 mmol, 100%) of thianthrene and 313 mg (1.7 mmol) of azobenzene. The amount of azobenzene corresponded with quantitative reduction of the cation radical, while the amount of benzidine monoperchlorate represents the relatively slower rearrangement of remaining hydrazobenzene, catalyzed by protons liberated in the reduction of the cation radical. Identification of benzidine monoperchlorate was made by comparing the melting point (234-245°), ultraviolet spectrum (λ_{max} 292, 242, 237 nm in acetonitrile), and the change in spectrum on adding both excess of sodium hydroxide (λ_{max} 287.5 nm) and excess of perchloric acid (λ_{max} 243 nm) with those of authentic compound.

Reaction of 1 with *N,N*-Dimethylaniline. On adding 0.8 ml (6.3 mmol) of *N,N*-dimethylaniline to a solution of 1.87 g (5.9 mmol) of 1 in 40 ml of acetonitrile, the solution turned dark green immediately, and a copious mixture of green and white solids separated. The solids were filtered and washed with benzene, whereupon the white solid dissolved. The mixed benzene and acetonitrile solutions were evaporated and the residue was chromatographed. Elution with benzene gave 937 mg (4.3 mmol, 147%) of thianthrene. Elution with ether gave 16.5 mg (0.10 mmol, 1.7%) of thianthrene 5-oxide, and elution with acetone gave 283 mg (0.60 mmol, 21%) of the dihydrate of 5-(*p*-*N,N*-dimethylaminophenyl)thianthrenium perchlorate (**2f**), mp 115-116° (aqueous ethanol), ultraviolet λ_{max} (acetonitrile) 316 nm (10^{-4} ϵ 3.2), 223 (5.2).

Anal. Calcd for $C_{20}H_{18}NS_2ClO_4 \cdot 2H_2O$: C, 49.6; H, 4.58; N, 2.89; S, 13.2; Cl, 7.32. Found: C, 50.0; H, 4.93; N, 2.98; S, 13.09; Cl, 7.10.

The green, benzene-insoluble solid was identified as tetramethylbenzidine cation radical perchlorate (**10**) by comparison with authentic **10** (see below).

Reaction of 1 with *N,N,N',N'*-Tetramethylbenzidine (TMB). To a solution of 1.00 g (3.20 mmol) of 1 in 30 ml of acetonitrile was added 1.20 g (5.00 mmol) of TMB. The solution immediately turned dark green, and during 10 min of stirring a dark green solid separated. This was filtered and washed with benzene and ether, giving 1.14 g (3.40 mmol, 106%) of TMB cation radical perchlorate (**10**), with ultraviolet spectrum in nitromethane identical with that in the literature.[19] The behavior of **10** was also consistent with the literature. Thus, attempts to crystallize **10** from aqueous DMSO caused its reduction to TMB. Attempts to crystallize **10** from ethanol led also to reduction and the formation of impure $TMBH^+ClO_4^-$, identified by its ultraviolet spectrum.

Authentic samples of $TMBH^+$, ClO_4^-, and $TMB2H^{2+}2ClO_4^-$ were prepared. The former, a pale yellow solid, had mp 245-247° dec (ethanol), λ_{max} (acetonitrile) 312, 242, and 239 nm. The latter, yellow needles, had mp 280-281° dec (ethanol), λ_{max} (acetonitrile) 243 nm (broad).

Kinetics. Phenol was distilled from calcium chloride, anisole was distilled, and acetanilide was recrystallized from ethanol. Solutions of 1 and solutions of nucleophiles of known concentration were prepared on a vacuum line in septum-capped flasks from which samples could be withdrawn directly for use in the syringes of the stopped-flow apparatus. The solvent acetonitrile was used for these solutions was Eastman Kodak Spectrograde quality, and was finally dried on the vacuum line by distillation from a solution of 1.

Kinetics were measured on a Durrum-Gibson Model D-110 stopped-flow spectrometer connected to a Tetronix Model 5103N storage oscilloscope. Solutions were transferred from the storage flasks to the spectrometer with 10-ml syringes. The injection block and cell were water jacketed at 25°. The photomultiplier voltage was adjusted to provide an output of 10.0 V when a solution of zero absorbance was in the cell. All measurements were made with the spectrometer amplifier in the absorbance mode and the oscilloscope set for as nearly full-scale output as possible. Oscilloscope traces were photographed for later data reduction. In most cases about 20 points were taken for each run and the results were analyzed by least-squares and graphic techniques. All data given in Table I are from least-squares treatment. The ex-

tinction coefficient of the cation radical at 542 nm were assumed to be 8.5×10^3.[4]

Registry No.—**1**, 212999-20-7; **2b**, 51608-82-3; **2c**, 51608-83-4; **2d**, 51608-85-6; **2e**, 51608-87-8; **2f**, 51608-89-0; **2g**, 51608-91-4; acetanilide, 103-84-4; phenol, 108-95-2; anisole, 100-66-3; o-chlorophenol, 95-57-8; *o-tert*-butylphenol, 88-18-6; hydrazobenzene, 122-66-7; *N,N*-dimethylaniline, 121-69-7; *N,N,N',N'*-tetramethylbenzidine, 366-29-0.

References and Notes

(1) Part XXVII: H. J. Shine and K. Kim, *Tetrahedron Lett.*, 99 (1974). Part XXVIII: H. J. Shine and L. R. Shade, *J. Heterocycl. Chem.*, **11**, 139 (1974).
(2) Supported by the National Science Foundation, Grant GP-25989X.
(3) Postdoctoral Fellow.
(4) Y. Murata and H. J. Shine, *J. Org. Chem.*, **34**, 3368 (1969).
(5) See, *e.g.*, M. M. Baizer, Ed., "Organic Electrochemistry," Marcel Dekker, New York, N. Y., 1973.
(6) J. J. Silber and H. J. Shine, *J. Org. Chem.*, **36**, 2923 (1971).
(7) G. H. Wieland and W. E. McEwen, *J. Org. Chem.*, 33, 2671 (1968).
(8) S. Torii, Y. Matsuyama, K. Kawasaki, and K. Uneyama, *Bull. Chem. Soc. Jap.*, **46**, 2912 (1973).
(9) S. Clementi and P. Linda, *J. Chem. Soc., Perkin Trans. 2*, 1887 (1973).
(10) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).
(11) V. D. Parker and L. Eberson, *J. Amer. Chem. Soc.*, **92**, 7488 (1970).
(12) O. Hammerich and V. D. Parker, *Electrochim. Acta*, **18**, 537 (1973).
(13) K. W. Fung, J. Q. Chambers, and G. Mamantov, *J. Electroanal. Chem.*, **47**, 81 (1973).
(14) O. Hammerich and V. D. Parker, 5th Organosulfur Symposium, Ronneby Brun, Sweden, June 1972.
(15) W. Rundel and K. Scheffler, *Tetrahedron Lett.*, 993 (1963).
(16) Unpublished work of Dr. V. J. Hull.
(17) M. de Sorgo, B. Wasserman, and M. Szwarc, *J. Phys. Chem.*, **76**, 3468 (1972).
(18) Private communication from Professor Szwarc.
(19) M. Vernois, G. Friedmann, M. Brini, and P. Federlin, *Bull. Soc. Chim. Fr.*, 1793 (1973).

Ion Radicals. XXX. Reactions of Thianthrene Cation Radical Perchlorate with Amino Compounds[1,2]

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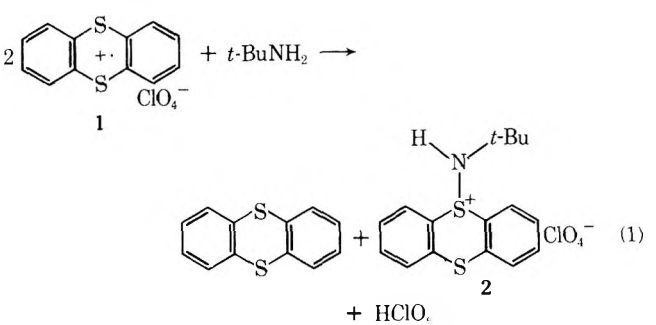
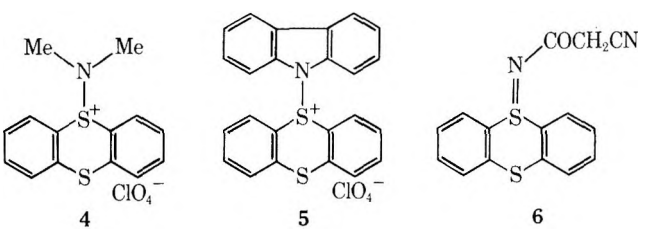
Reaction of thianthrene cation radical perchlorate (1) with *tert*-butylamine in acetonitrile solution gave equimolar amounts of thianthrene and 5-(*tert*-butylamino)thianthrenium perchlorate (2) in quantitative yields. Similarly, dimethylamine, carbazole, and cyanoacetamide gave, respectively, 5-(dimethylamino)- (4) and 5-carbazol-9-ylthianthrenium perchlorate (5) and 5-[(cyanoacetyl)imino]-5,5-dihydrothianthrene (6). Reaction of 1 with methylamine, ethylamine, propylamine, and cyclohexylamine gave thianthrene and 5,5-dihydro-5-(5-thianthreniumylimino)thianthrene perchlorate (7) in good yields. Compound 7 is ordinarily obtained by reaction of 1 with ammonia. Precautions were taken to eliminate the presence of ammonia in the amines used, and the way in which they give rise to 7 is being sought.

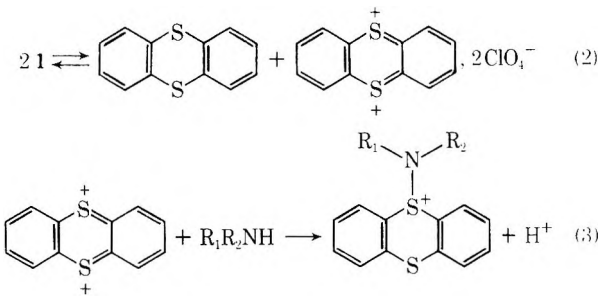
Very few reactions of organic cation radicals with amines are known. For the most part reactions have been of aromatic cation radicals with pyridine and methylpyridines, and many of these have been carried out electrochemically.[3-9] We have reported the reaction of the thianthrene and phenothiazine cation radicals with pyridine,[10] and the reaction of the thianthrene cation radical with ammonia.[11] There are in the literature, particularly the electrochemical, examples of oxidative dimerization of aromatic amines which may be interpreted as involving in one of the steps the reaction of the arylamine with its cation radical.[12]

As far as we know, however, reactions of cation radicals with aliphatic amines and amino compounds have not been reported. We have now found that some amines react quantitatively with the thianthrene cation radical perchlorate (1) to give sulfilimine derivatives. The overall stoichiometry is given for *tert*-butylamine in eq 1. The reaction occurred rapidly (too rapidly for stopped-flow kinetic measurements), and gave 5-(*tert*-butylamino)thianthrenium perchlorate (2). Analogous reactions with dimethylamine, carbazole, and cyanoacetamide gave the compounds **4**, **5**, and **6**.





The mechanism of these reactions is not known. We have previously interpreted the reaction of 1 with ammonia as involving the thianthrene dication, formed by disproportionation of the cation radical, but we have not been able to verify this kinetically. Reactions of 1 with ammonia, *tert*-butylamine, and dimethylamine have been too fast for us to follow even with stopped-flow techniques. Attempts to overcome the problem by going to very low concentrations of 1 ($<10^{-6}$ *M*) were made unreliable by competitive reaction of 1 with residual water in the dried solvents. By analogy with our interpretation of the ammonia reaction, the present reactions would follow eq 2 and 3, leading to the compounds **2**, **4**, **5**, and **6**, depending on whether R_1 = H or not. It is noteworthy that

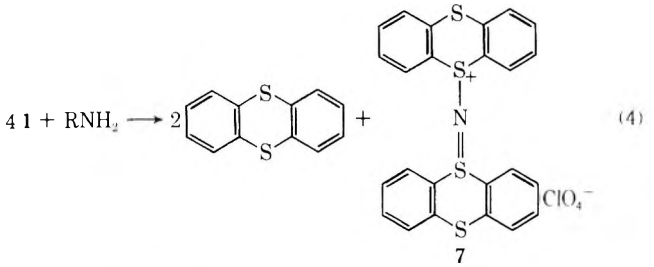


(2)

(3)

the sulfilimine 3 must be significantly basic, since the product isolated from reaction with *tert*-butylamine is protonated 3 (*i.e.*, 2).

We are surprised that reaction with so weak a base as cyanoacetamide occurs. We were also surprised to find that reaction with methylamine, ethylamine, propylamine, and cyclohexylamine gave not analogs of 2 and 4 but the dealkylated product 5,5-dihydro-5-(5-thianthreniumylimino)thianthrene perchlorate (7), eq 4. We have



(4)

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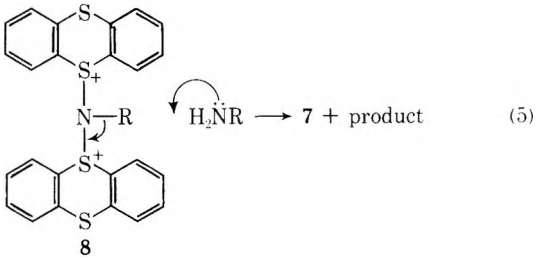
tried to eliminate the likelihood that 7 was formed from reaction with ammonia as an impurity in the amines. The amines were stored over ammonia-absorbing molecular sieve, methylamine was used directly from a commercial supply and also generated from its recrystallized hydrochloride, and propylamine and cyclohexylamine were redistilled. It is possible that the product of reaction of these amines with 1 has initially the structure 8, from which the alkyl group is eliminated, as shown in eq 5, as



(5)

8

an olefin or dialkylamine. Searches for dimethylamine, dicyclohexylamine, and cyclohexene as products in the appropriate cases, however, have been so far unsuccessful.

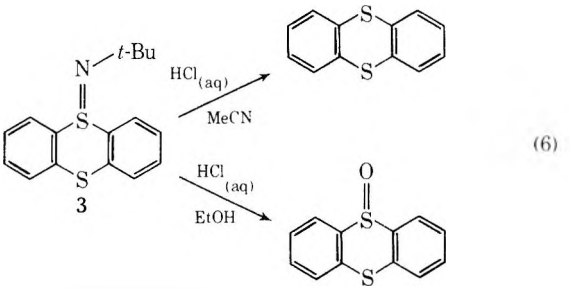
Reaction of 1 with carbazole gave not only 5 but also a green solid which gave an esr signal and is thought to be the cation radical perchlorate of a carbazole dimer. This product was not examined further.

Reaction of 1 with urea gave a product whose identity is still unknown to us.

Compound 2 was deprotonated by sodium hydroxide, giving the *tert*-butylsulfilimine 3.

Reaction of 3 (and 2) in acetonitrile solution with cold dilute hydrochloric acid gave thianthrene, while warming 3 in ethanol with concentrated hydrochloric acid gave 90% of thianthrene 5-oxide and only 8% of thianthrene (eq 6).

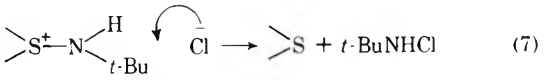
Alkyl-substituted sulfilimines are not readily made[13] and their chemistry has not been explored very much.[14] Diethylsulfilimine is reported to form *N*-chlorodiethylsulfilimine when treated with 0.1 *N* hydrochloric acid,[15] and diphenylsulfilimine to be hydrolyzed to diphenyl sulfoxide



(6)

3

when heated with 20% sulfuric acid.[16] Our present experience suggests that displacement of thianthrene from the protonated sulfilimine by chloride ion may occur (eq 7), and we are exploring this possibility.



(7)

Experimental Section

Thianthrene cation radical perchlorate (1) was prepared as described earlier.[17] Acetonitrile was Eastman Kodak Spectrograde and was stored over Linde 4A molecular sieve in a septum-capped bottle. Nitromethane was Eastman Kodak Spectrograde and was also stored over molecular sieve after drying over phosphorus pentoxide and distilling twice. Methylamine, dimethylamine, and ethylamine were Matheson anhydrous gases. Propylamine (98%), *tert*-butylamine (99+%), and carbazole (99+%) were from Aldrich. Cyclohexylamine and cyanoacetamide were from Eastman Organic Chemicals.

All column chromatography was performed with Merck silica gel either 30–70 ASTM mesh, 0.2–0.5 mm (Cat. No. 7733), or 70–325 ASTM mesh, 0.05–0.2 mm (Cat. No. 7734).

Reaction of 1 with *tert*-Butylamine. To a stirred solution of 1.37 g (4.30 mmol) of 1 in 40 ml of acetonitrile, protected by a drying tube, was added 1 ml (*ca.* 9.52 mmol) of *tert*-butylamine. The purple solution became pale yellow immediately and thianthrene precipitated. After 5 min the solution was rinsed from the flask with solvent acetone and evaporated, and the residue was chromatographed. Elution with benzene gave 480 mg (2.2 mmol, 102% of theory) of thianthrene. Elution with ether gave 10 mg (0.043 mmol, 1%) of thianthrene 5-oxide. Elution with acetone gave 820 mg (2.1 mmol, 100% of theory) of 5-(*tert*-butylamino)thianthrenium perchlorate (2), mp 203.5–204.5° (aqueous ethanol), ultraviolet λ_{max} (acetonitrile) 224 nm (10^{-4} ϵ 2.0), 254 (1.0), 289 (0.54), and 326 (0.34).

Anal. Calcd for $C_{16}H_{18}NS_2ClO_4$: C, 49.5; H, 4.67; N, 3.71; S, 16.5; Cl, 9.14. Found: C, 49.6; H, 4.81; N, 3.69; S, 16.3; Cl, 9.21.

Reaction of 2 with Base. Formation of 5-(*tert*-Butylimino)-5,5-dihydrothianthrene (3). A mixture of 98 mg (0.25 mmol) of 2 in 10 ml of ethanol and 3 ml of 30% aqueous sodium hydroxide was refluxed for 5 hr. Concentration gave a white solid, which was filtered, washed with water, and dried to give 72 mg (0.25 mmol, 100%) of 3: mp 148–149° (aqueous DMSO); parent mass peak *m/e* 287.08; ultraviolet λ_{max} (acetonitrile) 249 nm (ϵ 1.8×10^3), 288 (weak, broad).

Anal. Calcd for $C_{16}H_{17}NS_2$: C, 66.8; H, 5.96; N, 4.87; S, 22.3. Found: C, 66.9; H, 6.16; N, 4.88; S, 22.1.

Reaction of 3 with Acids. Addition of 1 drop of concentrated hydrochloric acid to a 3-ml cuvette containing 3 in acetonitrile (4.23×10^{-5} *M*) caused within the time of recording the spectrum a change of the spectrum from that of 3 (249 nm) to that of thianthrene (256 nm). Addition of 1 drop of 1.2% hydrochloric acid to a similar solution caused the spectrum to become immediately that of protonated 3 (*cf.* 2) and then to change slowly to that of thianthrene, going through an isosbestic point at 236 nm. Addition of 1 drop of 70% perchloric acid to a similar solution caused the spectrum to change to that of 2. Addition of 1 drop of 0.15% hydrochloric acid gave also the spectrum of the protonated ion (2), namely λ_{max} 225, 255, 289, and 326 nm. In contrast, a solution of 58 mg (0.20 mmol) of 3 in 15 ml of ethanol containing 10 drops of concentrated hydrochloric acid was warmed for 20 min on the water bath. The solution was then evaporated in the rotary evaporator at reduced pressure, and the white solid residue was washed with water several times, dried, and chromatographed on silica gel to give 3.7 mg (0.017 mmol, 8%) of thianthrene and 43.4 mg (0.19 mmol, 95%) of thianthrene 5-oxide, identified by its ultraviolet spectrum and mp 140–143°.

Reaction of 1 with Dimethylamine. A stream of dry dimethylamine was bubbled into a solution of 1.65 g (5.2 mmol) of **1** in 80 ml of acetonitrile. The purple solution became pale yellow almost instantly. The reaction mixture was worked up as before to give 834 mg (3.9 mmol, 156%) of thianthrene, 70 mg (0.3 mmol, 5.8%) of thianthrene 5-oxide, and 465 mg (1.3 mmol, 57%) of 5-(dimethylamino)thianthrenium perchlorate (**4**), mp 139–140° (aqueous ethanol), ultraviolet λ_{max} (acetonitrile) 226 nm (10^{-3} ϵ 0.29), 259 (9.0), 300 (7.0), 332 (4.0).

Anal. Calcd for $C_{14}H_{14}NS_2ClO_4$: C, 46.7; H, 3.92; N, 3.89; S, 17.8; Cl, 9.85. Found: C, 46.4; H, 4.01; N, 4.07; S, 17.9; Cl, 9.97.

Reaction of 1 with Carbazole. To a solution of 1.01 g (3.2 mmol) of **1** in 30 ml of acetonitrile was added 552 mg (3.3 mmol) of solid carbazole. The solution turned green immediately and a copious dark green precipitate formed. This was filtered after stirring for 10 min and washed with benzene. The green solid (178 mg) gave a single-line esr spectrum. Evaporation of filtrate and washings gave a yellow-green residue. Chromatography gave with benzene 766 mg of a mixture of thianthrene and carbazole which could not be separated; with ether 19 mg (0.08 mmol, 2.5%) of thianthrene 5-oxide; and with acetone 932 mg (1.9 mmol, 121%) of crude 5-carbazol-9-ylthianthrenium perchlorate (**5**), mp 264–265° dec (methanol), ultraviolet λ_{max} (acetonitrile) 275 nm (10^{-3} ϵ 43), 318 (sh, 6.4).

Anal. Calcd for $C_{24}H_{16}NS_2ClO_4$: C, 59.6; H, 3.34; N, 2.91; S, 13.3; Cl, 7.35. Found: C, 59.6; H, 3.73; N, 3.06; S, 13.7; Cl, 7.23.

Reaction of 1 with Cyanoacetamide. A solution of 1.03 g (3.3 mmol) of **1** in 30 ml of acetonitrile and 340 mg (4.0 mmol) of solid cyanoacetamide were used. The purple color of the solution became pale purple only after 40 min of stirring. Much white solid formed. Evaporation gave a mixture of white and purple solids, which became pale yellow on trituration with acetone. Chromatography gave, with benzene, 381 mg (1.8 mmol, 110%) of thianthrene; with ether, 17.7 mg (0.076 mmol, 3%) of thianthrene-5-oxide; with ether–acetone (1:1) 162 mg (1.9 mmol) of cyanoacetamide; and with acetone 508 mg (1.6 mmol, 103%) of 5-[(cyanoacetyl)imino]-5,5-dihydrothianthrene (**6**): mp 214–215° dec (DMSO); ultraviolet λ_{max} (acetonitrile) 282 nm (ϵ 4.0×10^3); parent mass peak *m/e* 282.02.

Anal. Calcd for $C_{15}H_{10}N_2S_2O$: C, 58.4; H, 3.26; N, 9.08; S, 20.8. Found: C, 58.8; H, 3.68; N, 9.05; S, 21.2.

Compound **6** was recovered quantitatively after being refluxed for 24 hr in 10 ml of ethanol containing 1 ml of 30% sodium hydroxide. In contrast, treatment of 3 ml of a solution of **6** in acetonitrile with 1 drop of 10% hydrochloric acid caused the rapid appearance of the thianthrene ultraviolet spectrum.

Reaction of 1 with Methylamine. A. Methylamine gas (Matheson), dried by passage through calcium chloride, was bubbled into a solution of 601 mg (1.9 mmol) of **1** in 50 ml of acetonitrile until the purple color was gone. Work-up and chromatography gave 247 mg (1.1 mmol, 118%) of thianthrene; 30.4 (0.1 mmol, 5.3%) of thianthrene 5-oxide; and 437 mg (0.80 mmol, 94%) of 5,5-dihydro-5-(5-thianthreniumylimino)thianthrene perchlorate (**7**), mp 239–240° dec (aqueous DMSO).

Anal. Calcd for $C_{24}H_{16}NS_4ClO_4$: C, 52.8; H, 2.93; N, 2.56; S, 23.5; Cl, 6.49. Found: C, 52.7; H, 2.94; N, 3.14; S, 23.4; Cl, 6.56.

B. Methylamine gas was generated by addition of 50% sodium hydroxide solution to solid methylamine hydrochloride, dried by passage through calcium sulfate, and used as above with 1.06 g (3.40 mmol) of **1** in 80 ml of acetonitrile. Work-up gave with benzene 389 mg (1.80 mmol) of thianthrene, with chloroform 37.1 mg (0.16 mmol) of thianthrene 5-oxide, and with acetone 575 mg (1.10 mmol) of **7**.

Reaction of 1 with Ethylamine. Ethylamine gas (Matheson) was used as above with 1.44 g (4.6 mmol) of **1** in 50 ml of nitromethane. Work-up gave 570 mg (2.6 mmol, 114%) of thianthrene, 47.1 mg (0.20 mmol, 4.3%) of thianthrene 5-oxide, and 611 mg (1.1 mmol, 52%) of **7**.

Reaction of 1 with Propylamine. Propylamine, 0.106 g (1.8 mmol), was added to a solution of 2.19 g (6.9 mmol) of **1** in 75 ml of acetonitrile. The purple color disappeared only slowly. Work-up gave 1.05 g (4.9 mmol, 143%) of thianthrene, 21.4 mg (0.09 mmol, 1.5%) of thianthrene 5-oxide, and 1.13 g (2.1 mmol, 63%) of **7**.

Reaction of 1 with Cyclohexylamine. A. Reaction of 572 mg (1.8 mmol) of **1** in 30 ml of nitromethane with 0.8 ml (*ca.* 7.0 mmol) of cyclohexylamine gave immediately a pale yellow solution. Work-up gave 226 mg (1.0 mmol, 111%) of thianthrene, 7.2 mg (0.03 mmol, 1.7%) of thianthrene 5-oxide, and 326 mg (0.6 mmol, 69%) of **7**.

B. Cyclohexylamine was redistilled and passed through a column packed with Linde molecular sieve (Type 4A). Enough of the amine was added to a solution of 1.1 g (3.5 mmol) of **1** in 25 ml of acetonitrile until the color of the solution was discharged. The solution was evaporated under vacuum and the pale brown residue was chromatographed on silica gel. Elution with benzene gave 514 (2.4 mmol) of thianthrene; elution with ether gave 34 mg (0.1 mmol) of thianthrene 5-oxide; and elution with acetone gave 707 mg (1.3 mmol) of **7**.

Registry No.—**1**, 35787-71-4; **2**, 51608-74-3; **3**, 51608-75-4; **4**, 51608-77-6; **5**, 51608-79-8; **6**, 51608-80-1; **7**, 35612-51-2; *tert*-butylamine, 75-64-9; dimethylamine, 124-40-3; carbazole, 86-74-8; cyanoacetamide, 107-91-5; methylamine, 74-89-5; ethylamine, 75-04-7; propylamine, 107-10-8; cyclohexylamine, 108-91-8.

References and Notes

(1) Part XXIX: K. Kim, V. J. Hull, and H. J. Shine, *J. Org. Chem.*, **39**, 2534 (1974).
(2) Supported by the National Science Foundation, Grant GP-25989X.
(3) J. Rochlitz, *Tetrahedron*, **23**, 3043 (1967).
(4) V. D. Parker and L. Eberson, *Acta Chem. Scand.*, **24**, 3542 (1970).
(5) G. Cauquis, J.-L. Gros, and M. Genies, *Bull. Soc. Chim. Fr.*, 3765 (1971).
(6) L. Marcoux, *J. Amer. Chem. Soc.*, **93**, 537 (1971).
(7) H. N. Blount, *J. Electroanal. Chem.*, **42**, 271 (1973).
(8) U. Svanholm and V. D. Parker, *Acta Chem. Scand.*, **27**, 1454 (1973).
(9) M. D. Johnson and M. Calvin, *Nature (London)*, **241**, 271 (1973).
(10) H. J. Shine, J. J. Silber, R. J. Bussey, and T. Okuyama, *J. Org. Chem.*, **37**, 2691 (1972).
(11) H. J. Shine and J. J. Silber, *J. Amer. Chem. Soc.*, **94**, 1026 (1972).
(12) See, for example, M. M. Baizer, Ed., 'Organic Electrochemistry,' Marcel Dekker, New York, N.Y., 1973.
(13) Y. Tamura, K. Sumoto, J. Minamikawa, and M. Ikeda, *Tetrahedron Lett.*, 4137 (1972).
(14) Y. Tamura, K. Sumoto, H. Matsushima, H. Taniguchi, and M. Ikeda, *J. Org. Chem.*, **38**, 4324 (1973).
(15) R. Appel and W. Büchner, *Chem. Ber.*, **95**, 849 (1962).
(16) N. Furukawa, T. Omata, T. Yoshimura, T. Aida, and S. Oae, *Tetrahedron Lett.*, 1619 (1972).
(17) Y. Murata and H. J. Shine, *J. Org. Chem.*, **34**, 3368 (1969).

Preparation and Reactions of *N*-Ethoxycarbonylthiophene-2-carboxamide and *N*-Ethoxycarbonylthiophene-2-thiocarboxamide

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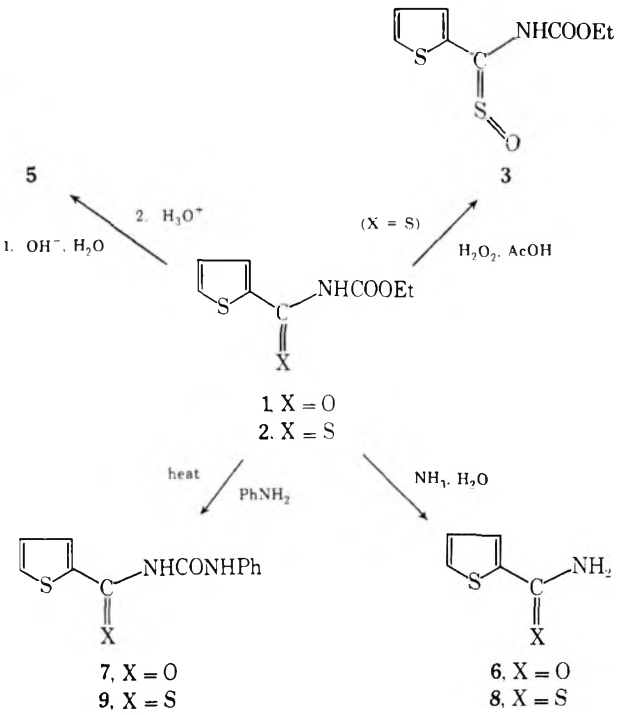
In the presence of anhydrous stannic chloride, thiophene reacts with ethoxycarbonyl isocyanate and isothiocyanate to yield the title compounds, which exhibit considerable reactivity toward nucleophilic reagents at both carbonyl and thiocarbonyl groups.

The reactions of pyrrole with ethoxycarbonyl isocyanate and isothiocyanate proved to be convenient sources of a variety of 2-pyrrolyl derivatives.[1] Some of these compounds were found to undergo cyclization reactions resulting in the formation of a new five-membered ring fused to the original pyrrole ring at positions 1 and 2. In no case, however, was ring closure observed to occur between positions 2 and 3 of the pyrrole ring. It was of interest to investigate the chemistry of the corresponding derivatives of thiophene, which, like pyrrole, reacts with isocyanates at position 2.[2,3] Cyclization of an initially formed 2-thienyl derivative, if it occurred, would have to involve position 3 of the ring.

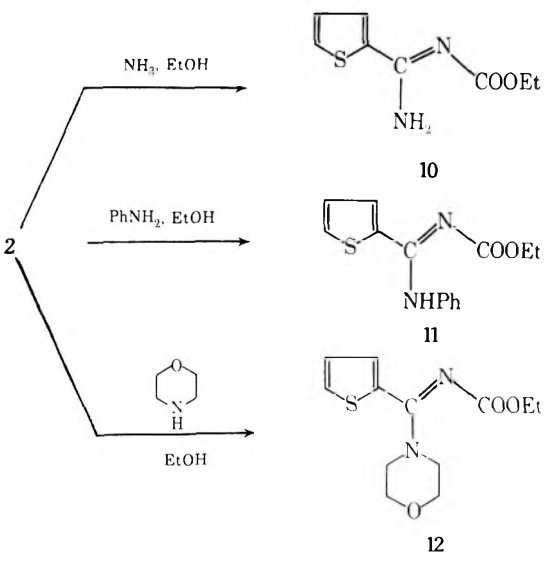
The reactivity of thiophene toward ethoxycarbonyl isocyanate and isothiocyanate has been found to be much less pronounced than that of pyrrole. A mixture of thiophene with either reagent remains unchanged for several days. However, the anticipated reactions occur at a convenient rate in the presence of anhydrous stannic chloride and yield *N*-ethoxycarbonylthiophene-2-carboxamide (**1**) and *N*-ethoxycarbonylthiophene-2-thiocarboxyamide (**2**), respectively. The reaction with the isocyanate appears to proceed more slowly, in spite of the otherwise greater reactivity of this reagent compared with the isothiocyanate. The structures assigned to the products of these reactions are in complete agreement with their ir and nmr spectra and are supported by the oxidation of **2** to **1** by alkaline hydrogen peroxide in ethanol. It is interesting to note that hydrogen peroxide in acetic acid oxidizes **2** to *N*-ethoxycarbonylthiophene-2-thiocarboxamide *S*-oxide (**3**), just as observed in the case of the corresponding derivative of pyrrole.[1b]

In contrast to the behavior of *N*-ethoxycarbonylpyrrole-2-carboxamide (**4a**) and *N*-ethoxycarbonylpyrrole-2-thiocarboxamide (**4b**), neither **1** nor **2** undergo cyclization upon treatment with boiling quinoline, but yield instead tarry materials. Other than that, the reactions of thiophene derivatives **1** and **2** are similar to those of the corresponding pyrrole derivatives. However, it is more difficult to cause nucleophilic attack to occur selectively at the ester carbonyl of **1** or **2** than for the pyrrole compounds, where the reactivity of the carbonyl or thiocarbonyl attached to the ring is decreased considerably by the nucleophilic character acquired by the pyrrole ring following loss of the NH proton.[4] Thus, partial hydrolysis of **4a** to pyrrole-2-carboxamide and **4b** to pyrrole-2-thiocarboxamide is brought about easily by the action of hot aqueous sodium hydroxide.[1] In the present case, the alkaline hydrolysis of **1** or **2** cannot be stopped effectively at the amide or thio amide stage and thiophene-2-carboxylic acid (**5**) is the isolated product. Thiophene-2-carboxamide (**6**) is nevertheless obtained from **1** by the action of hot, aqueous ammonia, under pressure. A similar treatment of **2** results in the formation of thiophene-2-thiocarboxamide

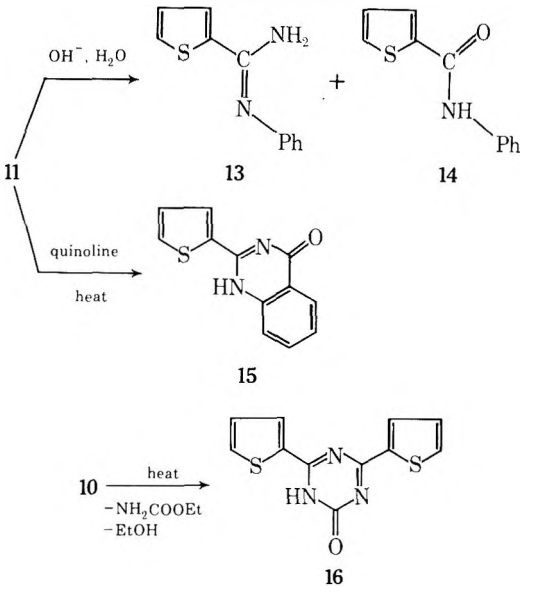


(**8**). Momentary boiling with aniline causes reaction to occur at the ester carbonyl and converts **1** into *N*-phenylcarbamoylthiophene-2-carboxamide (**7**) and **2** into the corresponding thiocarboxamide derivative **9**. The evolution of H_2S, in the latter case, is indicative of a competing reaction occurring at the thiocarbonyl, as described below. Alkaline hydrogen peroxide oxidizes the thio amides **8** and **9** to the amides **6** and **7**, respectively.

As in the case of the corresponding pyrrole derivative **4b**,[1b] the thiocarbonyl group of **2** shows considerable reactivity toward ammonia and primary or secondary amines. Thus **2** reacts with hot, alcoholic ammonia, under pressure, to yield *N'*-ethoxycarbonylthiophene-2-carboxamidine (**10**). Treatment with aniline at room temperature or with a hot, dilute solution of aniline in ethanol converts **2** into *N'*-ethoxycarbonyl-*N*-phenylthiophene-2-carboxamidine (**11**). Similarly, the morpholine derivative **12** is obtained when **2** is boiled briefly with a solution of morpholine in ethanol. The fact that the carbonyl stretching band in the ir spectra of **11** and **12** appears at nearly the same place (1660 cm^{-1} for **11** and 1680 cm^{-1} for **12**) supports the α,β-unsaturated ester structure for **11** rather than the isomeric carbamate structure. Hot, dilute hydrochloric acid hydrolyzes the amidines **10**, **11**, and **12** to *N*-ethoxycarbonylthiophene-2-carboxamide (**1**). Hydrolysis of **10** and **12** under alkaline conditions proceeds as expected to form thiophene-2-carboxylic acid, but a similar treatment of **11** yields, instead, *N'*-phenylthiophene-2-carboxamidine



(13) together with a smaller amount of *N*-phenylthiophene-2-carboxamide (14). Since further refluxing of amidine 13 with aqueous sodium hydroxide does not convert it to anilide 14, it may be concluded that the former is not an intermediate in the formation of the latter.



In complete analogy with the behavior of the corresponding pyrrole derivative,[1b] when heated above its melting point amidine 11 undergoes a cyclization reaction involving the benzene ring to yield 2-(2-thienyl)quinazolin-4(1*H*)-one (15), or its 3*H* tautomer. On the other hand, a condensation reaction involving two molecules of amidine 10 occurs when this compound is heated at 160–180°. Ethyl carbamate and ethanol are eliminated and a high-melting compound is produced which is formulated as 4,6-bis(2-thienyl)-1,3,5-triazin-2(1*H*)-one (16). The ir spectrum of this product, which contains a strong absorption band at 1680 cm^{-1}, is consistent with an α,β-unsaturated carbonyl group and more in keeping with the structure of the 1*H* than the symmetrical 5*H* tautomer, because of its rather complex appearance. The nmr spectrum displays only the typical signals of the ring protons of a 2-substituted thiophene. No signal for the NH proton has been detected, probably as a result of the low concentration of the solution used, due to the low solubility of the compound.

Further support for structure 16 is found in the analogous formation of 4,6-diphenyl-1,3,5-triazin-2(1*H*)-one, together with ethyl carbamate and ethanol, upon heating of *N'*-ethoxycarbonylbenzamidine at about 150°.[5]

Experimental Section[6]

***N*-Ethoxycarbonylthiophene-2-carboxamide (1).** A mixture of 8.4 g (0.10 mol) of thiophene, 11.5 g (0.10 mol) of ethoxycarbonyl isocyanate,[7a] and 10 ml of anhydrous stannic chloride was allowed to stand for 24 hr[8] and the resulting solid was ground into a powder and thoroughly mixed with dilute hydrochloric acid. Filtration followed by washing of the precipitate first with dilute hydrochloric acid and then with water yielded 15.5 g (78%) of crude 1, mp 130–135°. The pure compound was obtained by recrystallization from carbon tetrachloride–ethyl acetate (1:1) in the form of colorless crystals: mp 142–143°; ir 3260 (NH), 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.3 (t, 3, $-CH_3$), 4.2 (q, 2, $-OCH_2-$), 7.0 (m, 1, ring C-4 proton), 7.5 (m, 1, ring C-5 proton), 7.7 (m, 1, ring C-3 proton), and 8.5 ppm (s, 1, NH).

Anal. Calcd for $C_8H_9O_3NS$: C, 48.23; H, 4.55; N, 7.03. Found: C, 48.38; H, 4.65; N, 6.99.

***N*-Ethoxycarbonylthiophene-2-thiocarboxamide (2).** A mixture of 8.4 g (0.10 mol) of thiophene, 13.1 g (0.10 mol) of ethoxycarbonyl isothiocyanate,[7b] and 10 ml of anhydrous stannic chloride solidified completely when allowed to stand for 4 hr.[8] The product was worked up as for 1 to yield 17.5 g (81%) of crude 2, mp 101–103°. Recrystallization from carbon tetrachloride yielded the pure compound as dark red crystals: mp 107–108; ir 3250 (NH), 1730 (C=O), 1190 cm^{-1} (C=S); nmr ($CDCl_3$) δ 1.3 (t, 3, $-CH_3$), 4.2 (q, 2, $-OCH_2-$), 6.9 (m, 1, ring C-4 proton), 7.4 (m, 2, ring C-3 and C-5 protons), and 9.1 ppm (s, 1, NH).

Anal. Calcd for $C_8H_9O_2NS_2$: C, 44.63; H, 4.21; N, 6.51. Found: C, 44.81; H, 4.03; N, 6.45.

***N*-Ethoxycarbonylthiophene-2-thiocarboxamide *S*-Oxide (3).** Hydrogen peroxide (30%, 3 ml) was added to a solution of 0.50 g of 2 and 1.5 g of sodium acetate in 6 ml of acetic acid and the resulting mixture was let stand for 30 min. Dilution with water and filtration yielded 0.40 g (75%) of 3, mp 118–119° dec. The pure compound was obtained as yellow crystals by recrystallization from ethyl acetate: mp 120–121° dec; ir 3160 (NH), 1720 (C=O), 990 cm^{-1} (S=O); nmr δ 1.3 (t, 3, $-CH_3$), 4.2 (q, 2, $-OCH_2-$), 7.2 (m, 1, ring C-4 proton), 7.9 (m, 2, ring C-3 and C-5 protons), and 10.5 ppm (broad s, 1, NH).

Thiophene-2-carboxylic Acid (5). A. From 1. A mixture of 0.50 g of 1 and 10 ml of 10% aqueous sodium hydroxide was heated on the steam bath for 30 min. Following a cooling treatment, acidification of the solution yielded 0.25 g (78%) of 5, mp 126–127°. Recrystallization from water raised the melting point to 128–129° (lit.[9] mp 129–130°): ir 1690 cm^{-1} (C=O); nmr δ 6.9 (m, 1, ring C-4 proton), 7.5 (m, 2, ring C-3 and C-5 protons), and 11.5 ppm (broad s, 1, $-COOH$).

B, From 2. Acidification of the solution obtained by refluxing 1.0 g of 2 and 25 ml of 10% aqueous sodium hydroxide for 15 min yielded 0.40 g of 5, mp 120–125°.

Thiophene-2-carboxamide (6). A mixture of 1.0 g of 1, 5 ml of concentrated aqueous ammonia, and 5 ml of water was placed in a pressure bottle and heated on a steam bath for 30 min. The resulting solution was cooled and let stand in an open flask overnight to yield 0.40 g (63%) of 6, mp 172–175°. Recrystallization from water raised the melting point to 179–180° (lit.[10] mp 179–180°): ir 3360, 3160 (NH), 1650 cm^{-1} (C=O); nmr δ 7.0 (m, 1, ring C-4 proton) and 7.6 ppm (m superimposed on broad signal, 4, ring C-3 and C-5 protons, $-NH_2$).

***N*-Phenylcarbamoylthiophene-2-carboxamide (7).** After a mixture of 0.50 g of 1 and 2 ml of aniline had been boiled for a few moments, it was cooled and diluted with ethanol to yield 0.50 g (81%) of pure 7 as colorless crystals: mp 222–223° (lit.[11] mp 206°); ir 3240 (NH), 1700 (C=O), 1660 cm^{-1} (C=O); nmr δ 7.0–7.5 (m, 6, C-4 thienyl and phenyl protons), 7.9 (m, 1, C-5 thienyl proton), 8.2 (m, 1, C-3 thienyl proton), 10.5 (s, 1, NH), and 10.7 ppm (s, 1, NH).

Anal. Calcd for $C_{12}H_{10}O_2N_2S$: C, 58.52; H, 4.09; N, 11.38. Found: C, 58.62; H, 4.11; N, 11.34.

Thiophene-2-thiocarboxamide (8). A mixture of 1.0 g of 2 and 10 ml of concentrated aqueous ammonia was placed in a pressure bottle and heated on a steam bath for 1 hr. After it had been cooled, the resulting solution was acidified to yield 0.20 g (30%) of crude 8, mp 98–100°. Recrystallization from benzene yielded the pure compound in the form of yellow crystals: mp 107–109° (lit.[12] mp 108°); ir 3380 3270, 3170 (NH), 1050 cm^{-1} (C=S); nmr δ 7.0

(m, 1, ring C-4 proton), 7.5 (m, 2, ring C-3 and C-5 protons), and 9.3 ppm (broad, partly resolved d, 2, $-NH_2$).

***N*-Phenylcarbamoylthiophene-2-thiocarboxamide (9).** As for **7**, from 0.50 g of **2** and 2 ml of aniline, there was obtained 0.20 g (33%) of crude **9**, mp 203–205° dec. Recrystallization from ethanol yielded the pure compound in the form of yellow crystals: mp 225–226° dec; ir 3260 (NH), 1690 cm^{-1} (C=O); nmr δ 6.9–7.5 (m, 6, phenyl and C-4 thienyl protons), 7.8 (m, 2, C-3 and C-5 thienyl protons), 10.6 (s, 1, NH), and 10.1–11.8 ppm (very broad, diffuse signal, 1, NH).

Anal. Calcd for $C_{12}H_{10}ON_2S_2$: C, 54.94; H, 3.84; N, 10.68. Found: C, 55.09; H, 3.66; N, 10.62.

***N'*-Ethoxycarbonylthiophene-2-carboxamidine (10).** A solution of 5.0 g of **2** in 30 ml of ethanol saturated with ammonia at 0° was placed in a pressure bottle and heated on a steam bath for 35 min. Following a cooling treatment, dilution with water yielded 3.5 g (76%) of **10**, mp 150–152°. The pure compound was obtained by recrystallization from aqueous ethanol as colorless crystals: mp 153.5–154.5°; ir 3370 (NH), 3200–3300 (NH), 1660 cm^{-1} (C=O); nmr δ 1.2 (t, 3, $-CH_3$), 4.0 (q, 2, $-OCH_2-$), 7.0 (m, 1, ring C-4 proton), 7.6 (m, 1, ring C-5 proton), 7.9 (m, 1, ring C-3 proton), and 8.9 ppm (s, 2, $-NH_2$).

Anal. Calcd for $C_8H_{10}O_2N_2S$: C, 48.47; H, 5.09; N, 14.13. Found: C, 48.64; H, 4.98; N, 14.16.

***N'*-Ethoxycarbonyl-*N*-phenylthiophene-2-carboxamidine (11).** A solution of 3.0 g of **2** and 6 ml of aniline in 50 ml of ethanol was heated on a steam bath until the initial red color had been discharged (about 2 hr). Following filtration to remove a small amount of insoluble material (**9**), steam distillation of the filtrate left a gummy residue which was crystallized from aqueous ethanol to yield 2.6 g (68%) of **11**, mp 98–101°. Recrystallization from the same solvent afforded the pure compound as colorless crystals: mp 101–102°; ir 3310 (NH), 1660 cm^{-1} (C=O); nmr δ 1.0 (t, 3, $-CH_3$), 3.7 (q, 2, $-OCH_2-$), 6.6–7.4 (m, 7, thienyl C-4, C-5, and phenyl protons), 7.6 (m, 1, thienyl C-3 proton), and 9.6 ppm (s, 1, NH).

Anal. Calcd for $C_{14}H_{14}O_2N_2S$: C, 61.30; H, 5.14; N, 10.21. Found: C, 61.47; H, 4.96; N, 10.29.

Hydrolysis of 11. Refluxing for 2 hr of a mixture of 2.0 g of **11** and 20 ml of 10% aqueous sodium hydroxide, followed by cooling and filtration, yielded 1.2 g of a solid, mp 106–136°. This was mixed thoroughly with dilute hydrochloric acid and the mixture was filtered to give 0.40 g (27%) of crude **14**. The melting point of this product, initially 130–133°, became 143–145° after recrystallization from aqueous ethanol and was undepressed upon admixture with independently prepared **14** (lit.[13] mp 144–145°). Further, its ir and nmr spectra were superimposable on those of authentic **14**: ir 3300 (NH), 1625 cm^{-1} (C=O); nmr δ 7.0–7.7 (m, 7, thienyl C-4, C-5, and phenyl protons), 7.9 (m, 1, thienyl C-3 proton), and 10.1 ppm (s, 1, NH). When the filtrate from the separation of **14** was made alkaline by addition of 10% aqueous sodium hydroxide, a precipitate was formed and filtration yielded 0.70 g (47%) of **13**, mp 140–142°. Recrystallization from aqueous ethanol yielded the pure compound as colorless crystals: mp 143–144° (lit.[14] mp 144–145°); ir 3425, 3300, 3150, 1625, 1600, 1580 cm^{-1}; nmr δ 6.2 (s, 2, $-NH_2$), 6.6–7.6 ppm (m, 8, thienyl and phenyl protons).

Anal. Calcd for $C_{11}H_{10}N_2S$: C, 65.32; H, 4.98; N, 13.85. Found: C, 65.50; H, 5.26; N, 13.91.

Amidine **13** was recovered unchanged after it had been refluxed with 10% aqueous sodium hydroxide for 2 hr. Similarly, treatment with hydrochloric acid under a variety of conditions, followed by neutralization, led to recovery of the original compound.

***N'*-Ethoxycarbonyl-*N,N*-oxybis(ethylene)thiophene-2-carboxamidine (12).** A solution of 1.0 g of **2** and 2 ml of morpholine in 5 ml of ethanol was boiled for 3 min, then cooled and diluted with water to yield 0.90 g (73%) of **12**, mp 84–86°. The pure compound was obtained in the form of colorless crystals by recrystallization from cyclohexane: mp 85.5–87°; ir 1680 (C=O), 1580 cm^{-1} (C=N); nmr δ 0.9 (t, 3, $-CH_3$), 3.5 (m, 8, morpholine CH protons), 3.8 (q, 2, $-OCH_2-$), 7.0 (m, 2, thienyl C-4 and C-5 protons), and 7.6 ppm (m, 1, thienyl C-3 proton).

Anal. Calcd for $C_{12}H_{16}O_3N_2S$: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.84; H, 5.91; N, 10.30.

2-(2-Thienyl)quinazolin-4(1*H* or 3*H*)-one (15). A mixture of 1.0 g of **11** and 5 ml of quinoline was boiled briefly, then cooled and diluted with petroleum ether (bp 65–75°) to yield 0.60 g (73%) of pure **15** as colorless crystals: mp 285–286° (sealed capillary); ir 3170 (NH), 1670 (C=O), 1590 (C=N), 770 cm^{-1} (ortho-disubstituted benzene ring); nmr δ 7.0–8.1 (m, 7, thienyl and phenyl protons) and 12.3 ppm (s, 1, NH).

Anal. Calcd for $C_{12}H_8ON_2S$: C, 63.14; H, 3.53; N, 12.27. Found: C, 63.28; H, 3.36; N, 12.18.

4,6-Bis(2-Thienyl)-1,3,5-triazin-2(1*H*)-one (16). When 1.0 g of **10** had been heated at 180–200° for about 10 min, initial melting of the substance was accompanied by decomposition, resolidification, and formation of a condensate which was identified as ethyl carbamate on the basis of its ir and nmr spectra. The residue (0.60 g, 91%) was recrystallized from 1-butanol to yield pure **16** as colorless crystals: mp >300°; ir 1680 (C=O), 1560, 1540, 1500 cm^{-1}; nmr δ 7.3 (m, 1, thienyl C-4 proton), 8.0 (m, 1, thienyl C-5 proton), 8.2 ppm (m, 1, thienyl C-3 proton).

Anal. Calcd for $C_{11}H_7ON_3S_2$: C, 50.56; H, 2.70; N, 16.08. Found: C, 50.75; H, 2.74; N, 15.87.

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Registry No.—**1**, 51774-58-4; **2**, 51774-59-5; **3**, 51774-60-8; **5**, 527-72-0; **6**, 5813-89-8; **7**, 19382-27-5; **8**, 20300-02-1; **9**, 51774-61-9; **10**, 51774-62-0; **11**, 51774-63-1; **12**, 51774-64-2; **13**, 3737-39-1; **14**, 6846-13-5; **15**, 51774-65-3; **16**, 51774-66-4; thiophene, 110-02-1; ethoxycarbonyl isocyanate, 19617-43-7; ethoxycarbonyl isothiocyanate, 16182-04-0.

References and Notes

(1) (a) E. P. Papadopoulos, *J. Org. Chem.*, **37**, 351 (1972); (b) *ibid.*, **38**, 667 (1973).
(2) R. Leuckart and M. Schmidt, *Chem. Ber.*, **18**, 2333 (1885).
(3) R. Graf, *Justus Liebigs Ann. Chem.*, **661**, 111 (1963).
(4) A. Treibs and W. Ott, *Justus Liebigs Ann. Chem.*, **577**, 119 (1952).
(5) A. Pinner, *Chem. Ber.* **23**, 2919 (1890).
(6) Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer using mineral oil mulls. Nmr spectra were obtained on a Varian EM 360 spectrophotometer using solutions in hexadeuteriodimethyl sulfoxide, unless otherwise specified, with tetramethylsilane as internal standard. Hydrolysis and oxidation products were identified by comparison of their ir and nmr spectra with those of authentic samples, as well as by mixture melting point determination.
(7) (a) R. W. Lamon, *J. Heterocycl. Chem.*, **6**, 261 (1969); (b) *ibid.*, **5**, 837 (1968).
(8) The reaction flask was cooled occasionally during the early stage of the reaction to prevent overheating of the reacting mixture.
(9) H. D. Hartough and L. G. Conley, *J. Amer. Chem. Soc.*, **69**, 3096 (1947).
(10) J. A. Blanchette and E. V. Brown, *J. Amer. Chem. Soc.*, **73**, 2779 (1951).
(11) V. Meyer, *Justus Liebigs Ann. Chem.*, **236**, 200 (1886).
(12) M. Berçot-Vatteroni, *Ann. Chim. (Paris)*, [13] **7**, 303 (1962).
(13) G. M. Badger, R. T. Howard, and A. Simons, *J. Chem. Soc.*, 2849 (1952).
(14) S. Robev, *Chem. Ber.*, **91**, 244 (1958).

Arylsulfonoxylation of Aromatic Compounds. V. An Oxygen-18 Tracer Study of the p-Nitrophenylsulfonoxylation of Arenes[1]

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p-Nitrobenzenesulfonyl peroxide labeled with oxygen-18 in the sulfonyl oxygens was used to arylsulfonoxylate *p*-xylene and benzene to produce aryl *p*-nitrobenzenesulfonates in which the labeling of the phenolic oxygens was determined by mass spectral studies of the esters themselves or their hydrolysis products. From substitutions previously established to be kinetically clean first order with respect to arene (*p*-xylene in ethyl acetate solution and benzene in methylene chloride) the phenolic oxygens of the arylsulfonates arose exclusively from the peroxidic oxygens of the peroxide. Arylsulfonoxylation of benzene in ethyl acetate solution, which has previously been kinetically established to proceed 35% by a competing zero-order process, now from labeling experiments is found to give 41% of product incorporating sulfonyl oxygen of the peroxide as phenolic oxygen of the ester. In neat benzene, *p*-nitrophenylsulfonoxylation produces an ester arising 30.3% from the sulfonyl oxygens of the reagent. Possible mechanisms for these reactions are discussed.

The reaction of aromatic compounds with substituted benzenesulfonyl peroxides to give the corresponding aryl nitrobenzenesulfonates has been classified as an electrophilic substitution[2-7] on the basis of partial rate factors for the nitrophenylsulfonoxylationof monosubstituted benzenes, esr measurements of the reacting solutions, and the lack of side-chain hydrogen abstraction from alkylbenzenes.

Kinetic studies[4,5] have revealed that benzene derivatives behave identically upon arylsulfonoxylation in that a clean first-order rate dependence on arene concentration is observed in both ethyl acetate and methylene chloride as solvents. The arylsulfonoxylation of benzene itself, in contrast, exhibits a first-order dependence with respect to the aromatic only in methylene chloride; in ethyl acetate a partial (0.66–0.70) order is obtained. This fractional order results from a competition to the familiar first-order reaction by a reaction zero order with respect to benzene.[4]

Three possible mechanisms involving the introduction of electropositive oxygen into the nucleus of an aromatic substrate and one for a radical substitution are given in Chart I. Which of these four mechanisms is operative might be established by nitrophenylsulfonoxylatingarenes with a peroxide labeled with oxygen-18 in one of each pair of sulfonyl oxygens and determining the amount of incorporation of the oxygen-18 label in the phenolic oxygen of the resultant ester. If the reaction proceeds through **1**, the phenolic oxygen of **5** will contain no oxygen-18. If the mechanism involves **2**, the percentage of oxygen-18 in the phenolic oxygen of **5** should be one-half that of a labeled sulfonyl oxygen of the peroxide. If the ion pair **3** or radical **4** is the

Chart I

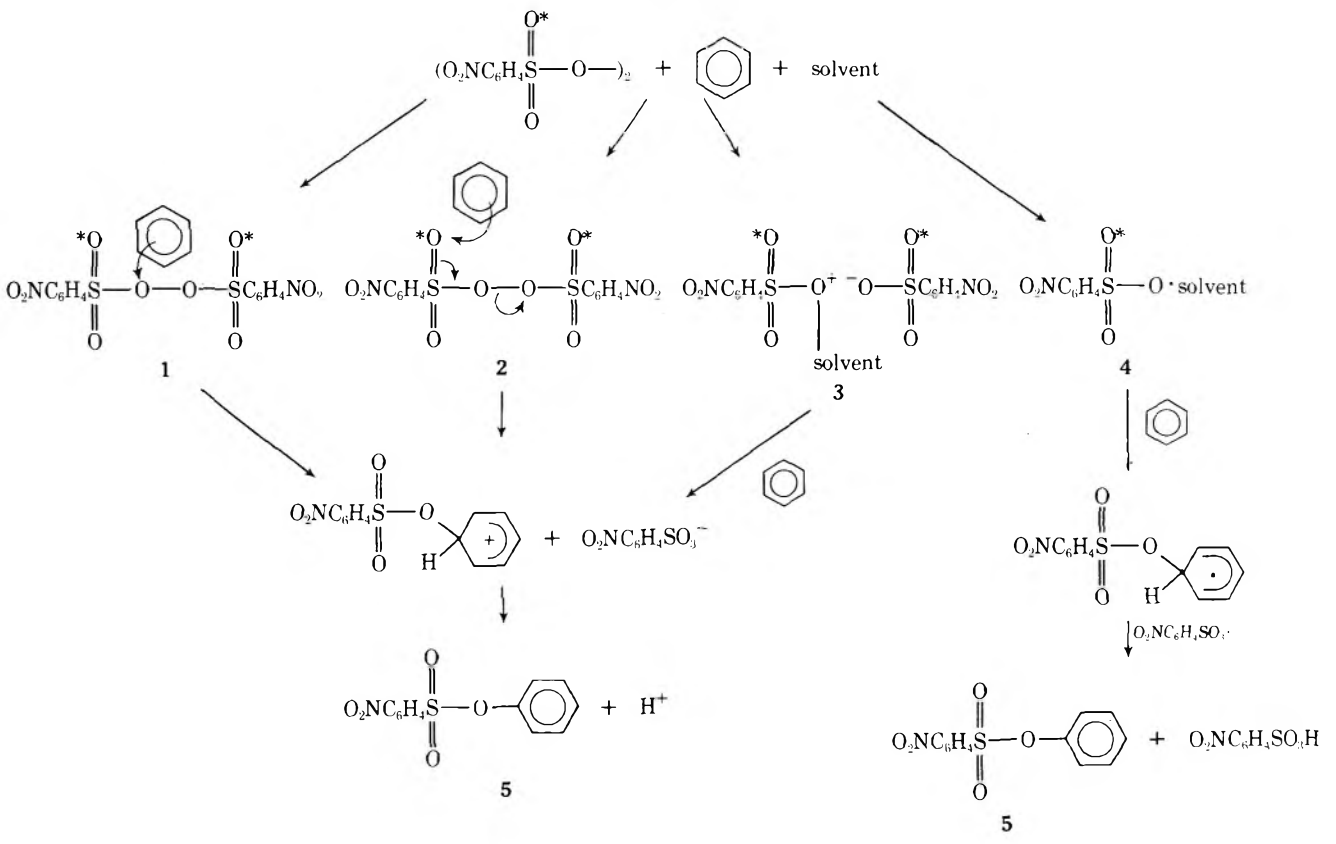


Table I
Mass Spectral Data and Isotope Ratios for the Reagents and Products

Expt	Comp	Registry no.	Ion	Number of scans	(M + 2)/M	% oxygen-18 excess[a]
1[b]	*p*-Xylyl *p*-nitrobenzenesulfonate	51821-10-4	$O_2NC_6H_4SO_3C_8H_7^+$	15[i]	0.1075[c]	4.02
1[b]	*p*-Xylyl *p*-nitrobenzenesulfonate		$O_2NC_6H_4SO_2^+$	16[i]	0.0984[d]	4.13
2	*p*-Nitrobenzenesulfonyl chloride	98-74-8	$O_2NC_6H_4SO_2^+$	10[i]	0.0907[f]	3.97
2[e]	Phenyl trimethylsilyl ether	1529-17-5	$C_6H_5SO_3Si(CH_3)_3^+$	11[i]	0.0455[g]	−0.003
3	*p*-Nitrobenzenesulfonyl chloride		$O_2NC_6H_4SO_2Cl^+$	2[k]	0.4380[d]	5.58
3[b]	Phenyl trimethylsilyl ether		$C_6H_5OSi(CH_3)_3^+$	8[i]	0.0552[g]	1.13
4[b]	Phenyl *p*-nitrobenzenesulfonate	32337-46-5	$O_2NC_6H_4SO_3C_6H_5^+$	8[i]	0.1274[h]	6.02
4[b]	Phenyl *p*-nitrobenzenesulfonate		$O_2NC_6H_4SO_2^+$	8[i]	0.1051[d]	4.77
5[i]	Phenyl *p*-nitrobenzenesulfonate		$O_2NC_6H_4SO_3C_6H_5^+$	13[j]	0.1236[h]	5.68
5[i]	Phenyl *p*-nitrobenzenesulfonate		$O_2NC_6H_4SO_2^+$	13[j]	0.1056[d]	4.82

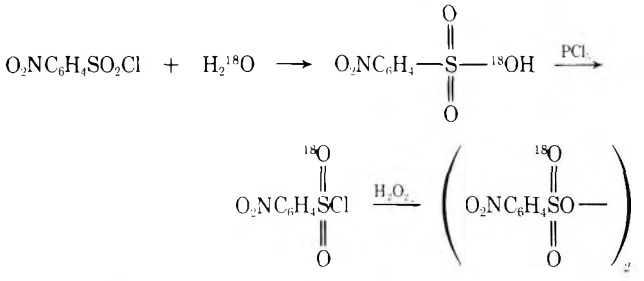
[a] Calculated for excess oxygen-18 in one oxygen only. [b] Reaction run in ethyl acetate solution. [c] Statistical value 0.0651 without labeling. [d] Statistical value 0.0550. [e] Reaction run in methylene chloride. [f] Statistical value 0.3789. [g] Statistical value 0.0438. [h] Statistical value 0.0634. [i] Reaction run in neat benzene. [j] Reference 9. [k] Reference 10.

proper intermediate, the phenolic oxygen of **5** should have one-third of the oxygen-18 concentration originally present in the peroxide's labeled sulfonyl oxygen.

In the present work labeling experiments were planned to clarify the mechanisms of the sulfonoxylation first order with respect to arenes and also the reaction in ethyl acetate zero order with respect to benzene.

Results and Discussion

Labeling of the Peroxide. Hydrolysis of *p*-nitrobenzenesulfonyl chloride with water enriched in oxygen-18 and treatment of the resultant acid with phosphorus pentachloride regenerated the sulfonyl chloride with one of its two oxygens labeled with oxygen-18. The acid chloride was converted to the peroxide as described in the literature.[3]



The labeling of the peroxide was measured by one of two methods in the present work. In some cases, after an arene had been arylsulfonoxylated, the resulting aryl *p*-nitrobenzenesulfonate was subjected directly to mass spectral analysis and the amount of oxygen-18 label present (as determined from the parent peak) was taken to be identical with the labeling of the peroxide. Alternatively, the oxygen-18 enrichment of the precursor sulfonyl chloride was measured by mass spectrometry and assumed to persist in the sulfonyl oxygens of the peroxide. This assumption was later proved correct when some reaction products were isolated which proved that scrambling of the oxygen-18 label in the peroxide had not occurred. Confirmation has also recently been reported by Yokoyama, *et al.*,[8] who treated the analogous labeled *m*-nitrobenzenesulfonyl peroxide with triphenylphosphine and found none of the oxygen-18 label in the triphenylphosphine oxide produced.

Substitution of *p*-Xylene in Ethyl Acetate Solution. Kinetic studies[4,5] of the arylsulfonoxylations of several benzene derivatives in ethyl acetate solution have demonstrated the substitutions to be first order with respect to the aromatic substrates. From the aromatics already proved to react by clean first-order kinetics,[4] *p*-xylene was selected for study in the present work because it yields only one monosubstitution product.

Oxygen-18 labeled *p*-nitrobenzenesulfonyl peroxide was added to *p*-xylene in ethyl acetate and the resultant 2,5-dimethylphenyl *p*-nitrobenzenesulfonate was isolated and subjected to mass spectral analysis.[9] From the parent peak, the labeling in one of the oxygens (necessarily corresponding to one of the sulfonyl oxygens of the peroxide) was 4.02% above natural abundance (Table I, expt 1). From the peak corresponding to the *p*-nitrobenzenesulfonyl ion ($O_2NC_6H_4SO_2^+$), the labeling of one of the sulfonyl oxygens was 4.13% above natural abundance. Therefore, within the limits of experimental error the sulfonyl label was unchanged and the phenoxy oxygen of the ester arose exclusively from the peroxy oxygens of the peroxide (intermediate **1**).

Substitution of Benzene in Methylene Chloride. The substitution of benzene in methylene chloride solution has also been proved to be clean first order with respect to the arene.[4] The substitution of benzene in this solvent with *p*-nitrobenzenesulfonyl peroxide labeled with oxygen-18 (3.97% above natural abundance in one of the sulfonyl oxygens from the mass spectrum of the precursor sulfonyl chloride) produced a phenyl sulfonate which after isolation was cleaved with sodium–naphthalene and the resultant phenol was converted to the trimethylsilyl ether. Mass spectral analysis of this ether showed that its oxygen had zero enrichment of oxygen-18 (−0.003%, Table I, expt 2), which corresponds to its formation also *via* intermediate **1**. Arylsulfonoxylation of an aromatic *via* a process first order with respect to arene therefore exclusively involves incorporation of the peroxidic oxygens as phenolic oxygens of the product ester.

The complete absence of oxygen-18 in the phenolic oxygen of the ester is also proof that in the conversion of the labeled sulfonyl chloride to the corresponding peroxide, no scrambling of the labeled oxygen occurred.

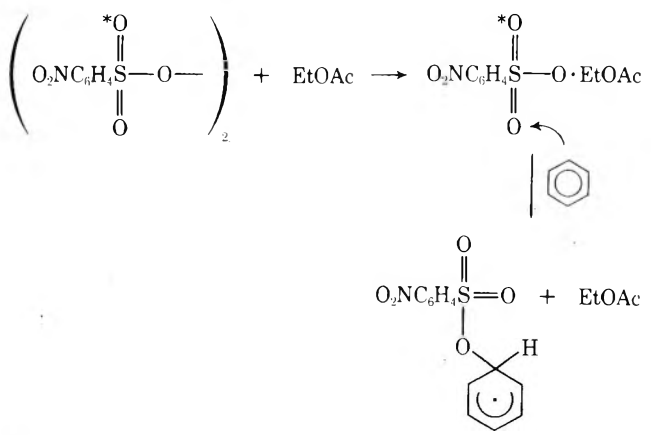
Substitution of Benzene in Ethyl Acetate. *p*-Nitrobenzenesulfonyl peroxide labeled in one-half of the sulfonyl oxygens (5.58%[10] above natural abundance of oxygen-18 in each of the labeled oxygens by measurement of the precursor sulfonyl chloride, Table I, expt 3) was added to benzene in ethyl acetate solution. The phenyl *p*-nitrobenzenesulfonate was cleaved by sodium–naphthalene;[11] the resultant phenol was converted to the trimethylsilyl ether, and the ether's oxygen-18 content (1.13% above natural abundance) was determined.[9] These analytical values, taking into account that the labeled and unlabeled sulfonyl oxygens are equivalent, correspond to 40.5% of the phenolic oxygens arising from sulfonyl oxygens, 59.5% from the peroxidic oxygens. In an alternate experiment (Table I, expt 4), the labeling of the peroxide was determined from the parent ion of the phenyl *p*-nitrobenzenesulfonate pro-

duced (6.02% oxygen-18 above natural abundance in one of the sulfonyl oxygens) and the labeling of the sulfonyl oxygens of the ester from p-nitrobenzenesulfonyl ion (4.77% oxygen-18 above natural abundance). From this alternate experiment, 41.6% of the phenolic oxygens arose from sulfonyl oxygens. The two procedures therefore check quite well with an average value of 41.0 ± 0.6%.

This partial labeling of the phenolic oxygen is not surprising because kinetic studies[4] have already shown that in ethyl acetate the reaction first order with respect to benzene (which should yield exclusive peroxidic oxygen incorporation in the phenol) competes with a reaction zero order with respect to aromatic. The present labeling experiment proves that the zero-order process also results in arylsulfonoxylation and must involve either exclusive sulfonyl oxygen attack or a symmetrical intermediate leading to a scrambling of oxygens prior to formation of the phenol. The rate constants reported for the k_0 and k_1 processes, unfortunately, are of limited accuracy because they must be derived from plots of experimentally determined pseudo-first-order rate constants. Correcting these reported rate constants[4] at 20° to room temperature (22°) and adjusting for the concentration of benzene (1.18 *M*) used in the present work gives the following rates: k_0, 3.2×10^{-5} mol l.$^{-1}$ sec^{-1}; k_1, 5.9×10^{-5} mol l.$^{-1}$ sec^{-1}. From these corrected values the zero-order process should account for 35% of the reaction. The kinetic (35%) and labeling (41%) values are reasonably close under the circumstances, and correspond only to exclusive attack on the sulfonyl oxygen (intermediate **2**).

For the zero-order mechanism to proceed *via* an intermediate in which three oxygens equilibrate (**3** or **4**) and give the observed 1.13% oxygen-18 label, it would be necessary for the zero-order reaction to produce 61% of the ester product. The reported k values admittedly have some limitations in accuracy, but not of such magnitude to permit the zero-order rate to be 1.5 times as great instead of one-half as great as the first-order process. Only exclusive sulfonyl oxygen attack for the zero-order process is therefore compatible with the data.

A solvolytic dissociation of the peroxide (probably homolytic **4** and not heterolytic **3** from the entropy of activation) has been suggested for the reaction zero order with respect to benzene[4] because it is solvent dependent. If solvation of the peroxidic oxygen promotes the homolytic dissociation, then the solvating molecule(s) might sterically prevent approach of the benzene to this peroxidic oxygen site, leading to exclusive attack on the sulfonyl oxygens.



A reaction of the labeled peroxide with an ethyl acetate solution of benzene was undertaken in the presence of galvinoxyl. It was expected that the zero-order process (if homolytic) would be inhibited and only the first-order reaction would occur with a complete absence of incorporation of oxygen-18 in the phenolic oxygen of the resultant ester. Unfortunately, the peroxide reacted primarily with the galvinoxyl (probably *via* nuclear substitution) and too little phenyl p-nitrobenzenesulfonate was produced to permit isolation and sufficient purification for a mass spectral analysis.

p-Nitrophenylsulfonoxylation of Neat Benzene. If the observed zero-order reaction with benzene in ethyl acetate is the result of a solvolytic dissociation of the peroxide, in neat benzene a clean first-order reaction yielding exclusive attack on peroxidic oxygen might be expected. A kinetic dependence in the neat solvent cannot be established, but a labeling experiment should be elucidating.

The reaction of the labeled peroxide with neat benzene has now been used to produce phenyl p-nitrobenzenesulfonate (5.68% oxygen-18 above natural abundance in one oxygen from the parent ion peak of the mass spectrum of the ester, Table I, expt 5). The p-nitrobenzenesulfonyl ion peak (4.82% oxygen-18 above natural abundance in one sulfonyl oxygen) in the mass spectrum showed that 30.3% of the phenolic oxygen arose from sulfonyl oxygen attack. Similarly the reaction of labeled m-nitrobenzenesulfonyl peroxide in neat benzene has recently[8] been reported to produce phenyl m-nitrobenzenesulfonate with 35–36% of the phenolic oxygen arising from sulfonyl oxygens. These low percentages do not correspond to any single intermediate and must arise from competing reactions.

These data are difficult to interpret. It is known, however, that coordination of the peroxide with the aromatic precedes electrophilic substitution[5] and that with some polynuclear hydrocarbons at normal concentrations in ethyl acetate[7] arylsulfonoxylation is second order with respect to arene. In neat benzene it is conceivable that the transition state might involve two or more arene molecules coordinated to different oxygen atoms. Such a transition state could produce the partial scrambling of the oxygen-18 label because any one of the coordinated arene molecules might produce the aryl ester product.

Experimental Section

Boiling points and melting points are uncorrected.

Materials. The $H_2{}^{18}O$, about 10 atom % enriched, was obtained from Yeda R. and D. Co. or Thompson and Packard, Inc., and used directly. Hexamethyldisilazane (Peninsular ChemResearch Inc.) and p-nitrobenzenesulfonyl chloride (Eastman Kodak) were used as received. Benzene (Matheson Coleman and Bell, spectroquality) was fractionally distilled and ethyl acetate (J. T. Baker, analyzed reagent) was purified[12] before use.

***p*-Nitrobenzenesulfonyl Chloride-*sulfonyl*-^{18}O.** Oxygen-18 enriched water (2.1 g, 0.117 mol), p-nitrobenzenesulfonyl chloride (22.3 g, 0.1 mol) and dry dioxane (2 g) were heated to 100° for 19 hr in an aerosol compatibility tube. The tube was then cooled, the evolved hydrogen chloride was allowed to escape, methylene chloride (30 ml) was added, and the precipitate (12.8 g, 63%) which formed was collected by filtration to yield crude p-nitrobenzenesulfonic acid which melted at 85–90° (lit.[13] mp 90°). To the crude acid was added phosphorus pentachloride (25.6 g, 0.122 mol) and dry dioxane (3 g). After the vigorous evolution of hydrogen chloride had ceased, the mixture was warmed on a steam bath for 10 min and then poured over crushed ice, and the product was extracted with three 50-ml portions of chloroform. The combined chloroform extracts, after drying with magnesium sulfate, were evaporated to dryness *in vacuo*. Addition of heptane (20 ml) to the residue produced crystalline p-nitrobenzenesulfonyl chloride (10.25 g, 73%) which melted at 73–75° (lit.[14] mp 77°). Reduction in volume of the heptane filtrate gave a second crop of crystals (0.2 g) which melted at 77°.

***p*-Nitrobenzenesulfonyl Peroxide-*sulfonyl*-^{18}O.** In a conventional synthesis,[3] hydrogen peroxide (30%, 18.2 g) was added at −20° to potassium carbonate (7.8 g) in 2:1 water–ethanol (180 ml) in a Waring blender cup. p-Nitrobenzenesulfonyl chloride-*sulfonyl*-^{18}O (10 g) in chloroform (20 ml) was added and the mixture

was agitated at full power for 1 min. The resulting precipitate was collected by filtration, washed with water, and dried by drawing air through it. The crude peroxide was dissolved in acetone (180 ml), the solution was filtered, and after reduction in volume to 90 ml the filtrate was cooled in Dry Ice. The *p*-nitrobenzenesulfonyl peroxide-*sulfonyl*-^{18}O (4.6 g, 46% yield) which precipitated, after collection on a filter and drying *in vacuo*, melted at 125° (lit.[2] mp 127°).

p-Nitrophenylsulfonoxylation of p-Xylene. *p*-Nitrobenzenesulfonyl peroxide-*sulfonyl*-^{18}O (0.202 g, 0.5 mmol) in ethyl acetate (50 ml) and *p*-xylene (5.3 g, 0.05 mol) was stirred at room temperature for 24 hr. The mixture was washed successively with 5% aqueous potassium hydroxide (25 ml), 5% hydrochloric acid (25 ml), and water (40 ml) and dried with magnesium sulfate, and the solvent was removed *in vacuo*. Recrystallization of the residue from 1:1 benzene–heptane gave *p*-xylyl *p*-nitrobenzenesulfonate (0.083 g, 54%) which had an infrared spectrum identical with that of an authentic sample. This ester was subjected to mass spectral analysis (Table I, expt 1).

p-Nitrophenylsulfonoxylation of Benzene in Methylene Chloride. A mixture of labeled peroxide (3.1 g) in benzene (9.3 g) and methylene chloride (89 ml) was stirred at room temperature for 85 hr. A procedure identical with that above gave phenyl *p*-nitrobenzenesulfonate, mp 114–116° (lit.[15] mp 114°). The infrared spectrum was identical with that of an authentic sample. A portion of this ester, by the procedure given below, was converted to the trimethylsilyl ether, which was subjected to mass spectral analysis (Table I, expt 2).

Reaction of p-Nitrobenzenesulfonyl Peroxide-*sulfonyl*-^{18}O with Benzene in Ethyl Acetate Solution. A solution of *p*-nitrobenzenesulfonyl peroxide-*sulfonyl*-^{18}O (2.6 g, 6.5 mmol) in ethyl acetate (75 ml) and benzene (7.8 g, 0.1 mol) was stirred at room temperature for 70 hr. By a procedure identical with that previously described, phenyl *p*-nitrobenzenesulfonate was isolated and subjected directly to mass spectral analysis (Table I, expt 4).

In a duplicate run this ester was cleaved to phenol, which was converted to the trimethylsilyl ether, which was then analyzed by mass spectrometry. Phenyl *p*-nitrobenzenesulfonate (0.73 g, 2.62 mmol) labeled with oxygen-18 and tetrahydrofuran (10 ml) were placed in a flask fitted with a rubber septum and purged with nitrogen for 5 min. Sodium–naphthalene in tetrahydrofuran[8] (0.6 *M*, 30 ml) was added *via* a syringe and after 3 min of stirring, water (0.5 ml) was added to quench the excess sodium–naphthalene. The mixture was filtered through a fritted glass funnel and the tetrahydrofuran was removed using a rotary evaporator. The residue was dissolved in ether (30 ml) and extracted with three 40-ml portions of 0.1 *M* KOH. The combined alkaline solutions were acidified with 3 *M* HCl and extracted with ether (three 50-ml portions). The combined ether extracts, after drying with magnesium sulfate, were evaporated *in vacuo*. To the residue was added hexamethyldisilazane (5 ml) and a trace of sand, and the mixture was refluxed for 3 hr. Vacuum distillation of the mixture gave a forerun of hexamethyldisilazane and a clear liquid (0.2 ml) whose infrared spectrum was identical with that of an authentic sample of phenyl trimethylsilyl ether. This liquid was subjected to mass spectral analysis (Table I, expt 3).

Reaction of p-Nitrobenzenesulfonyl Peroxide-*sulfonyl*-^{18}O with Benzene (Neat). *p*-Nitrobenzenesulfonyl peroxide-*sulfonyl*-^{18}O (1.0 g, 2.5 mmol) in benzene (50 g, 0.64 mol) was allowed to stand overnight at room temperature. By the procedure already described, phenyl *p*-nitrobenzenesulfonate was isolated and subjected to mass spectral analysis (Table I, expt 5).

Registry No.—*p*-Nitrobenzenesulfonylperoxide, 6209-72-9; *p*-xylene, 106-42-3; benzene, 71-43-2.

References and Notes

(1) (a) Supported in part by the U. S. Army Research Office (Durham) through Grant DA-ARO-(D)-31-124-G720 and by National Science Foundation Grant GP-19018. (b) Taken in part from the dissertation of R. V. Hoffman, submitted to the Graduate School of Case Western Reserve University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Dec 1969. (c) Presented in part at the International Symposium on the Chemistry of Organic Peroxides, Berlin, 1967.
(2) R. L. Dannley and G. E. Corbett, *J. Org. Chem.*, **31**, 153 (1966).
(3) R. L. Dannley, J. E. Gagen, and O. J. Stewart, *J. Org. Chem.*, **35**, 3076 (1970).
(4) R. L. Dannley, J. E. Gagen, and K. A. Zak, *J. Org. Chem.*, **38**, 1 (1973).
(5) R. L. Dannley and W. R. Knipple, *J. Org. Chem.*, **38**, 6 (1973).
(6) F. N. Keeney, Ph.D. Thesis, Case Western Reserve University, Cleveland, Ohio, 1967.
(7) N. T. Kurnath, Ph.D. Thesis, Case Western Reserve University, Cleveland, Ohio, 1969.
(8) Y. Yokoyama, H. Wada, M. Kobayashi, and H. Minato, *Bull. Chem. Soc. Jap.*, **44**, 2479 (1971).
(9) Mass spectrum determined on a Varian M66 mass spectrometer.
(10) Mass spectrum determined by Morgan Schaffer Corp., Montreal, Canada.
(11) W. D. Closson, P. Wriede, and S. Bank, *J. Amer. Chem. Soc.*, **88**, 1581 (1966).
(12) C. D. Hurd and J. S. Strong, *Ind. Eng. Chem., Anal. Ed.*, **23**, 542 (1951).
(13) A. Ekbom, *Chem. Ber.*, **35**, 651 (1902).
(14) A. Rieche and E. Naumann, *J. Prakt. Chem.*, **9**, 109 (1959).
(15) F. Bell, *J. Chem. Soc.*, 2777 (1928).

Reactivity of Aryl Nitrenes. Competition between Carbazole Formation and Internal Bond Reorganization in Biphenylnitrenes

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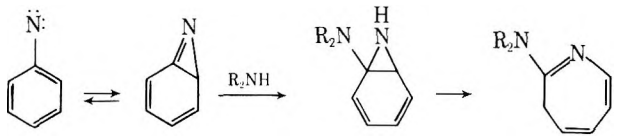
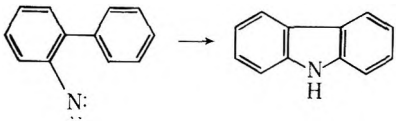
A series of three 3′,5′-disubstituted 2-azidobiphenyls (**1b–d**) has been prepared. The sensitivity of carbazole yield on photolysis to the presence of the nucleophilic trapping agent diethylamine (DEA) has been determined and compared with similar data for the unsubstituted compound **1a**. All four compounds exhibit formation of some 2-diethylamino-3-aryl-3*H*-azepine (**3a–d**) as well as the expected carbazole (**2a–d**) on photolysis in the presence of DEA. For electron-withdrawing substituents (CF_3, CO_2CH_3) the drop in carbazole yield is from ~80 to ~20–30% but for CH_3 and the unsubstituted compound the decrease is somewhat less. Deoxygenations of 2-nitrosobiphenyl and the 3′,5′-bis(trifluoromethyl) analog were studied to provide an alternative source of the presumed nitrene intermediates. These results appear to require revision of previous mechanisms for formation of carbazole from biphenylnitrene to include an azirine intermediate which can be diverted to azepine formation by DEA.

The chemistry of phenylnitrene is dominated by an internal bond reorganization which eventually leads to ring-expanded products in the presence of nucleophilic trapping agents, specifically secondary amines.[1] The initial reaction in this sequence is very rapid and flash-photolysis studies indicate that phenylnitrene has a half-life of 30 μsec or less.[1a] Intermolecular addition and insertion reactions are inefficient processes for phenylnitrene.[2,3] In contrast, arylnitrenes with adjacent sites of unsaturation cyclize with efficiency.[4] Biphenylnitrene, for example, gives carbazole in yields of around 80%.[5] The cause of the general inefficiency of intermolecular reactions of phenylnitrene may lie in the



rapidity of cyclization to the azirine and subsequent decomposition of this intermediate. An alternative view is that unsubstituted arylnitrenes are not as highly electron deficient as necessary to promote typical nitrene reactivity.[6] The two points of view are not mutually exclusive and both factors might contribute to the lack of intermolecular insertion reactions for phenylnitrene. We were interested

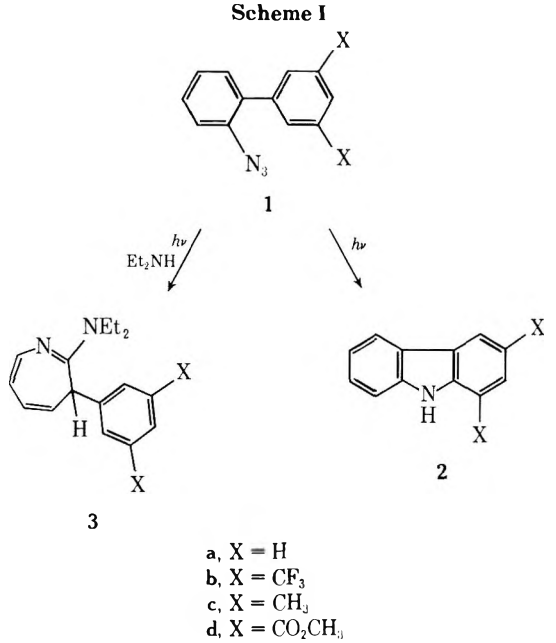


in probing the possibility of competition between the internal bond reorganization process and carbazole formation for biphenylnitrenes. In this paper we report on the generation of such nitrenes in the presence of secondary amines which serve to trap the azirine intermediate formed by internal bond reorganization.

Results

Preliminary experiments involving photolysis of biphenyl azide in THF–DEA mixtures resulted in the formation of 2-diethylamino-3-phenyl-3*H*-azepine and an accompanying decrease in carbazole yield.[7] The deoxygenation of o-nitrobiphenyl, which presumably proceeds through the same nitrene intermediate, also gives rise to this azepine.[8] In order to study this competitive trapping process in more detail, a series of substituted biphenyl azides (**1a–d**, Scheme I) was prepared. 3′,5′-Disubstituted systems were

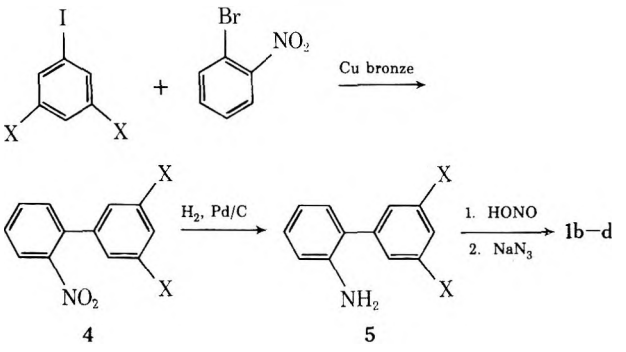
Scheme I



a, X = H
b, X = CF_3
c, X = CH_3
d, X = CO_2CH_3

chosen. The symmetrical substitution results in there being a single possible carbazole product, and the presence of two substituent groups should accentuate any electronic effects on the competition between carbazole and azirine formation. The Ulmann coupling reaction of 3,5-disubstituted iodobenzenes with o-bromonitrobenzene proved to be a generally satisfactory synthetic method. Details of the syntheses, which are outlined in Scheme II, are given in the Experimental Section.

Scheme II



Photolyses of **1a**, **1b**, and **1c** were carried out in THF–DEA mixtures of varying concentration containing 5% by volume of piperylene.[9] The yield of the appropriate carbazole was measured by glpc in each case. Quantitative yield data were also obtained for the azepine in the case of **1a** and **1b**. The carbazole yield data are summarized in Table I. In each of the systems, it was possible to effect a substantial diversion of the nitrene intermediate from carbazole formation at sufficiently high DEA concentration. The effect is quite dramatic in the case of **1b**, the bis(trifluoromethyl) system. The yield of carbazole **2b** drops from >80 to ~20% as DEA is incorporated into the solvent mixture to the extent of 1% (~0.1 *M*). Further addition of DEA up to and including use of DEA as the solvent medium (along with 5% by volume piperylene) causes no further diminution in carbazole yield.

For **1a** and **1c** the concentration required for maximum diversion from carbazole formation is much higher (~50% or ~5 *M*). The amount of nitrene which cannot be diverted to azepine is also substantially higher for **1a** and **1c**, being 40 ± 10%.

The bis(carbomethoxy) compound **1d** proved to be unsuitable for extensive quantitative study but qualitatively resembled the trifluoromethyl system. The substituted carbazole **2d** was formed in 82% yield in the absence of DEA but dropped to 27 ± 1% in solution containing 5, 95 and 100% DEA. The azepine **3d** was formed in 45 ± 1% yield under these conditions.

Azepine **3a** has been previously described.[7,8,12] The nmr spectra of the substituted analogs **3b–d** were very similar. In addition to the peaks expected for the diethylamino group and the 3-aryl groups, each compound showed a doublet (H-7) and multiplet (H-5) near 6.7–6.8 and 6.3–6.5 ppm, respectively. In each case the other azepine ring protons appear as a multiplet at 5.2–5.4 ppm.

Azepine yield data were measured in the experiments with **1a** and **1b**. These data are included in Table I. It is evident that the drop in carbazole yields is largely accounted for by azepine formation.

The extent of internal bond reorganization as measured by azepine formation has been found to be wavelength dependent for *p*-cyanophenyl azide.[10] With 3500-Å light a hydrazine formed by nucleophilic trapping without bond reorganization is the major product while 2537-Å light leads to the azepine and hydrazine in comparable amounts. We photolyzed **1a** and **1b** with both unfiltered 2537-Å and 3000-Å light filtered through Pyrex. The data for **1a** indicate that a wavelength dependence is present. The azepine: carbazole ratio (Table II) is consistently higher and the azepine yield higher with the 2537-Å source than with the longer wavelength source. The data for **1b** exhibit a similar trend. Control experiments in the unsubstituted system indicated that photodestruction of **3a** was not significant

Table I
Product Yields[a] as a Function of Diethylamine Concentration and Light Source

		1a						1b						1c
		Mixed[c]		2537 Å[d]		>2900 Å[e]		Mixed[f]		2537 Å[g]		>2900 Å[h]		Mixed[i]
% DEA	M^b	2a	3a	2a	3a	2a	3a	2b	3b	2b	3b	2b	3b	2c
0	0	86	0	76	0	76	0	81	0	70	0	—	—	81
0.5	0.49							29	49	26	43	45	41	
1.0	0.98							22	55	19	51	35	44	
2.0	0.20							20	63	16	56	31	47	
3.0	0.29							22	69					
5.0	0.48	73	4	71	8			21	70	15	57			76
10.0	0.98	69	9	58	22	64	4	15	68					62
25.0	2.4	64	25	49	37	56	16	15	68					62
50.0	4.8	62	28	41	45	52	18	17	64					51
75.0	7.3	49	30	39	52	47	22	15	66					41
90.0	8.8	53	33					16	63					39
95.0	9.3	49	33	32	43			17	65					40

[a] Yields quoted are averages of at least two separate runs. In most cases duplicate values were within ±3 percentage units of the mean. Occasional instances of wider deviation were checked with additional runs. [b] Calculated assuming additivity of solvent volume. [c] 30-min photolysis; 40–50% azide decomposition; light source was unfiltered irradiation from Southern New England Ultraviolet RPR 3000-Å lamps. [d] 30-min photolysis; 60–70% azide decomposition; light source was unfiltered irradiation from RPR 2537-Å source. [e] 60-min photolysis; 50–55% azide decomposition; RPR 3000-Å source filtered through Pyrex. [f] 120-min photolysis; 75–85% azide decomposition; unfiltered RPR 3000-Å source. [g] 60-min photolysis; >90% azide decomposition; unfiltered RPR 2537-Å source. [h] 120-min photolysis; 75–80% azide decomposition; RPR 3000-Å source filtered through Pyrex. [i] 60-min photolysis; 65–80% azide decomposition; unfiltered RPR 3000-Å source.

over periods of up to 2 hr under the conditions used in collecting the analytical data. There was some photolysis of carbazole evident in the control experiments but this was more significant with the 3000-Å source and therefore cannot be responsible for the lower azepine:carbazole ratio at the longer wavelength.

Deoxygenation of aromatic nitroso compounds provides an alternative method for generation of arylnitrenes in solution near room temperature.[11] Data for deoxygenation of o-nitrosobiphenyl and 2-nitroso-3′,5′-bis(trifluoromethyl)-biphenyl are given in Table III. It is evident that the nitrenes formed by deoxygenation can also be diverted to azepine. The yields in the deoxygenation reactions, however, are lower than in the photolyses. The ratios of these two products are similar for the two alternative sources of the nitrene. Deoxygenation of2-nitroso-3′,5′-bis(trifluor omethyl)biphenyl also results in total azepine and carbazole yields below those obtained in the photolysis. In THF–DEA mixtures, the ratio between azepine and carbazole yields is again similar to those found from the azide. However, in the absence of DEA the **2b** yield is only 47% and some of the azo compound is formed. The possibility of a variety of competing processes in the deoxygenation reaction makes attempts at quantitative comparison of the product ratios with the azide photolysis of dubious value.

Table II
Wavelength Dependence of Azepine:Carbazole Ratio

	:2a			3b:2b	
% DEA	2537 Å	>2900 Å	% DEA	2537 Å	>2900 Å
25	0.76	0.29	0.5	1.6	0.91
50	1.1	0.35	1.0	2.7	1.2
75	1.3	0.47	2.0	3.5	1.5

Table III
Yield Data for Deoxygenation Reactions

2-Nitrosobiphenyl				2-Nitroso-3′,5′-bis(trifluoromethyl)-biphenyl			
% DEA	2a	3a	3a:2a	% DEA	2b	3b	3b:2b
0	67	0		0	47	0	
25	24	15	0.62	0.5	14	32	2.3
50	23	17	0.74	1.0	13	40	3.1
75	12	11	0.92	5.0	12	48	4.0
100	10	10	1.0	50	13	51	3.9

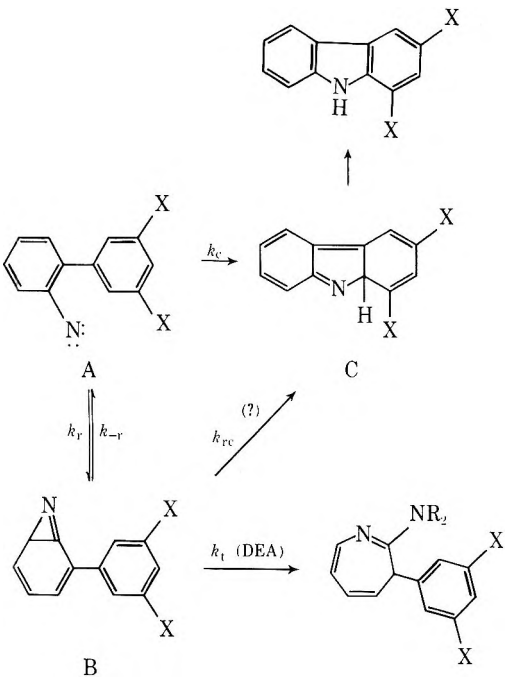
Discussion

These trapping experiments permit several qualitative statements to be made about the biphenylnitrene intermediate. (1) The formation of azepines and concomitant decrease in carbazole yield imply that the rate of internal bond reorganization must be competitive with intramolecular cyclization to a carbazole. (2) Since carbazole yields are high in the absence of secondary amine trapping agents, the formation of the azepine precursor cannot be an irreversible process which prevents subsequent carbazole formation.[13] (3) The extent to which the nitrene can be diverted from carbazole formation is a function of the substitution on the second ring, with electron-attracting substituents favoring the formation of azepine in the presence of DEA. (4) A significant substituent effect also appears in the concentration of DEA required to obtain the maximum diversion to azepine. (5) Finally, there is qualitative similarity between the behavior of biphenylnitrenes generated by deoxygenation and those generated by azide photolysis. Further discussion of these points will be made with reference to a mechanism similar to that proposed in ref 7 and outlined in Scheme III.

We assume that in the high DEA concentration limit the azepine:carbazole yield ratio reflects primarily k_r:k_c. The existence of a fraction of nitrene which cannot be diverted from carbazole then reflects the competition between the cyclization (k_c) and reorganization (k_r) processes. These are seen to be closely balanced in each of the cases studied with $k_r \lesssim k_c$ for **1a** and **1c** but with $k_r \lesssim 4k_c$ for **1b**. This shift in the case of **1b** is in a reasonable direction if the nitrene attack on the adjacent aromatic ring is viewed as being electrophilic in character and therefore impeded by electron-withdrawing substituents. It is possible that k_c represents the sum of two processes. For example, if both singlet and triplet nitrene are generated, as has been observed in other azide photolyses,[14] k_c would represent the composite of the two independent cyclization processes.

The internal bond reorganization process designated by k_r must either be reversible or there must be a route from the azirine intermediate B to carbazole (such a process is

Scheme III



designated by k_{rc} in Scheme III). These conditions are necessary in order to account for the high yield of carbazole in the absence of nucleophilic trapping agent. A direct rearrangement of the azirine B to carbazole precursor C has some analogy in the facile formation of 2-phenylpyrrole from 3-styrylazirine below room temperature.[15]

We have estimates of some of the rates of the reactions in this scheme from ongoing flash-photolysis studies.[1a,16] Work with phenylnitrene indicates that azirine formation is very rapid.[1a] Reactions of the azirines from *o*-alkylphenylnitrenes with amines are in the range 3×10^4 to 8×10^8 l. mol^{-1} sec^{-1} and a rough rate of $\sim 10^6$ l. mol^{-1} sec^{-1} has been measured for formation of azepine **3b**.[1a,16] Rates of carbazole formation have been reported[17] for **1a** (1.1×10^3 at 292°K) and measured[16] for **1b** ($\sim 1.0 \times 10^2$ at 293°K). These rates permit placing some limits on the pathways for azepine and carbazole formation. In the case of **1b**, 0.1 *M* DEA is sufficient to cause maximal carbazole diversion. The trapping of B at this DEA concentration would be occurring at a rate of $\sim 10^5$ sec^{-1}, much faster than carbazole is formed in the absence of DEA. This indicates the existence of two intermediates, one of which cannot be intercepted by DEA. The nondivertable pathway must account for about 20% of the photolyzed azide. The case of **1a** is more uncertain because it is not possible to measure k_t. We estimate that it would be in the range 10^5–10^4 l. mol^{-1} sec^{-1} on the basis of the value for **1b** and the fact that a substantial electronic effect has been noted in this reaction.[1a] Maximal diversion from carbazole in this case requires 5 *M* DEA; so the rate of azepine formation would be $\sim 5 \times 10^5$ to 5×10^4 sec^{-1} in the high DEA concentration range. This is also sufficiently rapid that carbazole formation ($k \approx 1 \times 10^3$ sec^{-1}) would be completely suppressed if a single carbazole precursor which could be diverted to azepine were involved. Analysis in the case of both **1a** and **1b** appears to require formation *of two intermediates* during or very rapidly after the photolysis step. One of these intermediates can be trapped by DEA; the other cannot. The carbazole yield data indicate that the ratio of trappable to nontrappable intermediate is ~1:1 for **1a** and ~4:1 for **1b**. Although there is much less quantitative data on which to rely, it appears that the distribution of intermediates from **1c** is very similar to that from **1a** whereas **1d** resembles the **1b** case.

The maximum formation of azepine occurs at much lower amine concentrations for **1b** and **1d** than for **1a** and **1c**. This can be attributed to the electronic effect on k_t. With k_t large for **1b** (and, presumably, **1d**) the trapping process is able to divert all the azirine at significantly lower DEA concentration. At this stage the competition is with the processes governed by rate constants k_{-r} and/or k_{rc}.

The data from the nitrosobiphenyl deoxygenations seem to imply the existence of both a trappable and a nontrappable carbazole precursor in this system as well. The yields in the deoxygenation reactions are lower and the likely involvement of other reactions which consume nitroso compound, nitrene intermediate, and probably azepine prevent detailed quantitative comparison of the data from the two sources. However, for both 2-nitrosobiphenyl and the bis(trifluoromethyl) derivative some carbazole formation occurs at high DEA concentrations. The limiting ratios of azepine to carbazole in these two systems (~1:1 and ~4:1, respectively) are roughly similar to those noted in the azide photolysis experiments.

There appears to be some wavelength dependence on the azepine:carbazole ratio. These data are summarized in Table III. The tendency toward diminishing azepine yield at longer wavelength parallels the observation of Odum and Wolf[10] using *p*-cyanophenyl azide. The wavelength dependence of the azepine:carbazole ratio implies that partitioning between the trappable and nontrappable intermediates is affected by the energy of the exciting light. Shorter wavelengths irradiation increases the fraction converted to the trappable intermediate.

There have been several prior studies on the mechanism of formation of carbazole after photolysis of *o*-biphenyl azide. Reiser and coworkers examined the reaction in an EPA glass at 77°K. They observed formation of an intermediate which was converted to carbazole by subsequent irradiation.[18] The interpretation was that the intermediate was triplet *o*-biphenylnitrene. Cyclization, which was implied to involve hydrogen abstraction and recombination, was considered to proceed through excitation of the triplet intermediate. A singlet-state species as the reactive intermediate was not considered to have been excluded. Later, this group examined carbazole formation in a polymer matrix at room temperature.[19] Flash photolysis generated an intermediate which decayed at a rate of ~350 sec^{-1} and was considered to be triplet *o*-biphenylnitrene. The rate constant was associated with cyclization to carbazole and was considered to involve intramolecular hydrogen abstraction followed by rapid recombination to give carbazole. Swenton, Ikeler, and Williams[5b] studied the photolysis in benzene near room temperature in the presence of various sensitizers and quenchers. Their results appeared most consistent with a singlet nitrene intermediate but the multiplicity was considered an open question. Lehman and Berry[17] measured the rate of carbazole appearance from a photochemically generated intermediate between 5 and 46° in cyclohexane. The rate constant at 24° is 1.85×10^3 sec^{-1}. They concluded that the rate-determining step is intramolecular addition of triplet *o*-biphenylnitrene to the adjacent aromatic ring, generating a diradical which rapidly goes to carbazole by hydrogen atom migration. The absorption spectrum of the transient species, which is the same as that observed by Reiser,[18,19] was the principal basis for identifying the intermediate as the triplet nitrene.

None of these mechanisms consider the possibility of a reversible intramolecular bond reorganization process. In fact, these mechanisms make it very difficult to account for

the formation of azepines. The species being trapped cannot be singlet biphenylnitrene, since it would not be expected to have sufficient lifetime to permit reaction with DEA to occur over the period of 0.01–1.0 msec during which the trapping reaction occurs.[1a] An addition reaction of triplet biphenylnitrene with DEA is not readily visualized. Neither is a mechanism for formation of the azepine initiated by a hydrogen-abstraction step attractive. The evidence against hydrogen-abstraction processes includes the fact that negligible amounts of *o*-biphenylamines are formed in these reactions. Our data indicate that photodecomposition of biphenyl azides generates two reactive intermediates, only one of which can be diverted by DEA.

We suggest that the trappable carbazole precursor is the azirine B. This type of structure is generally assumed[1b,13] to be the precursor of azepines in aryl azide thermal and photochemical decompositions. Our data do not permit a conclusion on the question of the route of conversion of B to carbazole. This could occur *via* the nitrene A by reversal of the cyclization step or by way of a carbazole precursor such as C.

The assignment of a structure to the nontrappable intermediate is more uncertain. The nontrappable carbazole precursor could be C. If it were irreversibly formed competitively with B, a route to carbazole insensitive to trapping by DEA would exist. If k_{-r} and/or k_{rc} were large relative to conversion of C to carbazole, the concentration of C would rapidly build up. This mechanism would then attribute structure C to the carbazole precursor which has been observed by Reiser and coworkers[18,19] and by Berry and Lehman.[17] Although in contradiction to previous assignments of this intermediate as the triplet nitrene, it should be pointed out that the previous spectral assignments[20] rest on similarity of the spectrum to those of other triplet aryl nitrenes and have not, for example, been corroborated by esr measurements. So far as we have been able to determine there are no recorded spectra of the 8a*H*-carbazole chromophore present in C; so it is an open question as to whether the observed spectrum is compatible with structure C.

Alternatively, the nontrappable intermediate could be considered to be the triplet form of the nitrene, ^{3}A. It would be expected that ^{3}A would not be converted to azirine B and therefore would not be diverted by DEA. Formation of triplet nitrene in photolytic azide decompositions has adequate precedent.[14] Since this is the ground state of the nitrene, ^{3}A could be formed from B by reversal to singlet nitrene followed by spin inversion. In this way B could be converted to ^{3}A and then to carbazole in the absence of DEA. A reservation to assigning ^{3}A as the nontrappable carbazole precursor is the fact that this assignment requires that the triplet nitrene be rather long lived ($t_{1/2}$ for conversion to carbazole ~1 msec) even in the presence of a substantial (0.01 *M*) concentration of piperylene.[16]

The present data do not seem to permit an unambiguous assignment of structure to the nontrappable carbazole precursor but do require that previously postulated mechanisms be modified to account for the ability of DEA to divert some of the nitrene to azepine.

Experimental Section[21]

3′,5′-Bis(trifluoromethyl)-2-nitrobiphenyl (4b). A stirred mixture of 3,5-di(trifluoromethyl)iodobenzene[22] (34.0 g) and 1-bromo-2-nitrobenzene (20.2 g) was heated to 180°. Copper bronze (15 g) was added in portions over 0.5 hr and heating was continued for 3 hr after the addition was complete. The cooled reaction mixture was extracted with hot chloroform and after filtration and concentration the residue was chromatographed on alumina. Ether–hexane (1:4) eluted **4b** and it was recrystallized from ethanol (10.1 g, 30%): mp 76.5–77°; nmr ($CDCl_3$) δ 7.80 (m); mass spectrum *m/e* (rel intensity) 335 (27), 315 (30), 285 (58), 270 (20), 269 (100), 266 (18), 238 (32), 237 (17), 236 (28), 220 (54), 219 (54), 201 (27), 199 (16), 170 (20), 169 (16), 75 (15).

2-Amino-3′,5′-bis(trifluoromethyl)biphenyl (5b). Reduction of **4b** in ethanol over Pd/C proceeded quantitatively to give **5b**, which was recrystallized from hexane, mp 44–45°.

2-Azido-3′,5′-bis(trifluoromethyl)biphenyl (1b). Procedure A of Smith and Brown[23] was used. An ether extract of the azide was washed with dilute HCl, 5% $NaHCO_3$, and water. Drying and evaporation of the ether gave **1b** as a white solid which was recrystallized from 95% ethanol: mp 43–43.5°; nmr ($CDCl_3$) δ 7.29 (4, m), 7.84 (3, s); mass spectrum *m/e* (rel intensity) 331 (2), 303 (24), 284 (32), 283 (100), 234 (48), 233 (19), 214 (17), 213 (17), 75 (19), 69 (46).

3,5-Dimethyliodobenzene. 3,5-Dimethylaniline (5.0 g) was dissolved in 65 ml of 25% sulfuric acid and the solution was cooled to −10°. Aqueous $NaNO_2$ was added until starch–iodide paper indicated the presence of unreacted nitrous acid. A solution of KI (8.0 g) was then added, keeping the reaction mixture below 0°. The solution was kept overnight at room temperature, warmed for 0.5 hr on a steam bath, and finally extracted with ether. Distillation gave the product, bp 51–53 (1 mm), in 52% yield, nmr ($CDCl_3$) δ 2.23 (6, s), 6.90 (1, s), 7.30 (2, s).

2-Amino-3′,5′-dimethylbiphenyl (5c). A mixture of 3,5-dimethyliodobenzene (12.3 g) and 1-bromo-2-nitrobenzene (10.0 g) was heated to 170–180° with stirring and copper bronze (10.0 g) was added in small portions over 30 min. The solution was then maintained at 180° for 3 hr. The reaction mixture was extracted with boiling chloroform, filtered, concentrated, and distilled. After some unreacted iodo compound was recovered, **4c** (6.9 g, 57%) distilled at 130–135° (0.5 mm). Reduction over Pd/C in ethanol for 3 hr at 3 atm hydrogen gave **5c** in quantitative yield after distillation, nmr ($CDCl_3$) δ 2.30 (6, s), 3.7 (2, s), 6.85 (7, m).

2-Azido-3′,5′-dimethylbiphenyl (1c). The azide was prepared following procedure A of Smith and Brown.[23] The crude azide was extracted with ether and washed successively with 2 *N* hydrochloric acid, 5% $NaHCO_3$ solution, and water. After drying and evaporation of the solvent, the residual oil was purified by elution through silica gel with benzene. Evaporation of the benzene left an oil which was pure **1c** as judged by glpc, tlc, and spectral data. The compound decomposed on attempted distillation and no satisfactory analysis was obtained.

Dimethyl 5-Iodoisophthalate. 5-Iodoisophthalic acid was prepared according to the procedure of Grahl[24] and then esterified. The product was recrystallized from 95% ethanol, mp 100–102° (lit.[25] mp 104–105°).

3′,5′-Dicarbomethoxy-2-nitrobiphenyl (4d). The coupling reaction was carried out as for **4b** but the heating period was reduced to 2 hr. Chromatography on alumina using 1:9 ether–benzene gave **4d** (44% yield) which was recrystallized from benzene–hexane: mp 145–147°; nmr ($CDCl_3$) δ 3.92 (6, s), 7.45 (4, m), 8.15 (2, d, J = 1.5 Hz), 8.68 (1, m).

2-Amino-3′,5′-dicarbomethoxybiphenyl (5d). Reduction over Pd/C at 3 atm pressure in 1:1 ethanol–tetrahydrofuran gave **5d** (88% yield): mp 129–131° after recrystallization from 95% ethanol; nmr ($CDCl_3$) δ 3.92 (8, s overlapping exchangeable NH_2 signal), 7.00 (4, m), 8.30 (2, m), and 8.60 (1, m).

2-Azido-3′,5′-dicarbomethoxybiphenyl (1d). The procedure described for **1b** gave **1d** in 71% yield: mp 103–104° after recrystallization from 95% ethanol; nmr ($CDCl_3$) δ 3.92 (6, s), 7.24 (4, m), 8.22 (2, d), 8.60 (1, t).

Preparation of 1,3-Disubstituted Carbazoles. Samples of each of the carbazoles **1b–d** were prepared by thermolysis of the appropriate azides in decalin at 170–190° for 0.5–1.5 hr.

A. 1,3-Bis(trifluoromethyl)carbazole (2b). Chromatography of the pyrolysis solution gave **2b** (eluted by petroleum ether) in quantitative yield: mp 109–111° after recrystallization from benzene; uv (95% ethanol) λ_{max} (log ϵ) 215 (4.59), 241 (4.48), 267 (4.49), 300 (3.96), 331 nm (3.60); nmr (acetone-d_6) δ 7.48 (3, m), 7.92 (1, s), 8.27 (1, d, J = 7 Hz), 8.70 (1, s), 11.1 (1, broad).

B. 1,3-Dimethylcarbazole (2c). After elution from alumina with benzene, recrystallization from Skellysolve gave **2c**: mp 93–95° (lit.[26] mp 95°); uv (95% ethanol) λ_{max} (log ϵ) 227 (4.52), 235 (4.58), 240 (4.63), 250 (4.40), 261 (4.26), 297 (4.23), 331 nm (3.60).

C. 1,3-Dicarbomethoxycarbazole (2d). The carbazole (55% yield) precipitated on cooling the pyrolysis solution to −10° and was recrystallized from methanol, mp 193–193.5°.

Preparation and Characterization of 3-Aryl-2-diethylamino-3*H*-azepines. A. 2-Diethylamino-3-phenyl-3*H*-azepine (3a). This compound has been previously described.[7,8] A sample

Table IV
Control Data[a]

Photolysis time, hr	Yield, %: 2537 Å 2b	2537 Å 3b	>2900 Å 2b	>2900 Å 3b
0.5	52	39	67	15
1.0	44	40	60	15
2.0	45	37	54	18
4.0			48	17

[a] Photolyses were carried out in 25% DEA.

obtained in the present work by photolysis of **1a** in DEA had spectral properties identical with those of the material prepared during the previous work.[7]

B. 2-Diethylamino-3-[3,5-bis(trifluoromethyl)phenyl]-3*H*-azepine (3b). A solution of **1b** (451 mg) in 30 ml of 95:5 DEA–piperylene was deoxygenated by a nitrogen stream and photolyzed for 2.5 hr in a series of quartz test tubes using 3000-Å lights in a Rayonet Model RS photochemical reactor. After photolysis each tube was treated with 5 ml of 1% acetic acid in methanol and allowed to stand overnight to ensure completion of tautomerism to the stable 3*H* isomer.[1b] The solvent was evaporated and the residue was chromatographed on alumina. Ether–hexane containing ~2% methanol eluted the azepine (155 mg, 30%). Further purification by preparative glpc on a 6-ft, 5% FS1265 column at an oven temperature of 170° gave a light yellow oil: $\nu_{C=N,C=C}$ 1560, 1520 cm^{-1}; nmr ($CDCl_3$) δ 2.20 (6, t), 3.46 (4, q), 5.40 (3, m), 6.55, (2, d superimposed on m), 7.52 (3, s).

2-Diethylamino-3-(3,5-dimethylphenyl)-3*H*-azepine (3c). A solution of **1c** (520 mg) in 40 ml of 95:5 DEA–piperylene was photolyzed and processed as described for **3b**. Chromatography gave 248 mg of unreacted **1c** and some of the carbazole **2c** (90 mg, 38%). Ether–hexane containing about 2% methanol eluted **3c** (96 mg, 29%) which was further purified by preparative glpc under the same conditions as for **3b**: $\nu_{C=N,C=C}$ 1570, 1530 cm^{-1}; nmr ($CDCl_3$) δ 1.18 (6, t), 2.18 (6, s), 3.45 (4, q), 5.42 (3, m), 6.7 (5, m).

3-(3,5-Dicarbomethoxyphenyl)-2-diethylamino-3*H*-azepine (3d). A solution of **1d** (232 mg) in 20 ml of 95:5 DEA–piperylene was photolyzed for 2 hr and then worked up as described for **3b**. Addition of ether to the residue from evaporation of solvent resulted in the precipitation of **3d** (25% yield), which was recrystallized from petroleum ether: mp 171–172°; $\nu_{C=N,C=C}$ 1570, 1520 cm^{-1}; nmr ($CDCl_3$) δ 1.20 (6, s), 3.52 (4, q), 3.88 (6, s), 5.40 (3, m), 6.64 (d, superimposed on m), 7.92 (2, s, slightly broadened), 8.35 (1, s, slightly broadened).

Conditions for Photolysis and Quantitative Product Analysis. Accurately weighed amounts (~50 mg) of the azide were placed in quartz test tubes and dissolved in the appropriate solvent mixture. Solvent mixtures were prepared volumetrically by adding 0.50 ml of piperylene and the appropriate amount of DEA to a volumetric flask and then diluting to 10 ml with THF. An aliquot (5.0 ± 0.2 ml) of the solution was then transferred to the test tubes, which were capped with rubber septa and deoxygenated with nitrogen for about 5 min using a hypodermic needle. The tubes were then placed in a merry-go-round apparatus centered in a Rayonet Type RS reactor and photolyzed at 38°.[27] Photolysis times are included in Table I. At the completion of the photolysis 5 ml of 1% acetic acid in methanol was injected into each test tube. The tubes were kept capped overnight at room temperature. The appropriate internal standard was added and analysis for unreacted azide, carbazole, and azepine (except for **3c**) was then carried out under the following conditions: **1a, 2a,** and **3a,** 5% OV-101 column, isothermal at 160° with stilbene internal standard; **1b, 2b,** and **3b,** 5% SE-30 column, 140° until the azide elutes then to 180° at 8°/min with carbazole internal standard; **1c** and **2c,** 5% FS1265, temperature programmed over 140 to 190° at 10°/min beginning at injection with carbazole internal standard. Detection was by flame ionization on Varian Aerograph Model 1800 or 2440 gas chromatographs.

Analysis of the reaction mixtures from **1d** were carried out by evaporating the solvent and dissolving the residue in methylene chloride. The azepine **3d** was extracted by 6 *N* HCl. After neutralization with 8 *N* NaOH the azepine was extracted into methylene chloride and diluted volumetrically. The azepine yield was determined by uv absorbance at 291 nm. The carbazole yield was determined by uv absorbance at 358 nm in the original methylene chloride solution. The yields were corrected for unreacted azide by recovery of the azide by chromatography.

Control Experiments to Determine Product Stability (Table IV). Selected reaction solutions were photolyzed for periods longer than reported in Table I to determine product photosensitivity. Secondary photolysis of the product during the photolysis times used in the analytical experiments was significant only for carbazole.

2-Nitrosobiphenyl (6a). The procedure of Havinga and coworkers[28] was used. After recrystallization from ethanol the compound melted at 112–114°, somewhat higher than previously reported (lit.[11a,28] mp 101°). The nmr was concentration dependent because of dimerization of **6a**. A doublet at δ 5.82 is due to dimer while that at δ 6.16 is due to monomer. Approximate ratios at several molarities in $CDCl_3$ follow: 1.0 *M* 1:1; 0.5 *M*, 2:1; 0.25 *M*, 3:1; 0.13 *M*, large. These ratios indicate that *K* for dimerization = 1.7 ± 0.3 mol^{-1}.

3′,5′-Bis(trifluoromethyl)-2-nitrosobiphenyl (6b). A solution of the amine **5b** (500 mg) in 20 ml of dichloromethane was treated dropwise with *m*-chloroperoxybenzoic acid (0.6 g) dissolved in 20 ml of dichloromethane. The solution was allowed to stir at 0° overnight, warmed to room temperature, and washed several times with 5% $NaHCO_3$ solution. The solution was then dried and evaporated. The residue was dissolved in toluene and eluted through a small alumina column with toluene. The solvent was evaporated at reduced pressure and the residue was recrystallized from ether–benzene to give **6b,** mp 123–124°.

Deoxygenation Reactions. A. Nitrosobiphenyl. A weighed solution of the nitroso compound (~50 mg) in THF (1 ml) was added over a period of 15 min to 20 ml of a cold (−10°) solution of the appropriate THF–DEA mixture containing 0.3 ml of triethyl phosphite. The solution was then kept at room temperature for several hours and then the solvent was removed. Triethyl phosphite was removed using a vacuum pump and the residue was analyzed by glpc.

B. 2-Nitroso-3′,5′-bis(trifluoromethyl)biphenyl. The procedure was identical with that used for nitrosobiphenyl except that the reaction was run at 38°. After removal of the solvent, glpc analysis was carried out. Runs on a 200-mg scale indicated some 2,2′-bis(3,5-trifluoromethylphenyl)azobenzene (**7b**) to be formed (~10%) both in the presence and absence of DEA in addition to **2b** and **3b**.

Acknowledgment. This research was supported by NSF Grant GP-33274.

Registry No.—**1a,** 7599-23-7; **1b,** 51839-01-1; **1c,** 51839-02-2; **1d,** 51888-57-4; **2a,** 86-74-8; **2b,** 51839-03-3; **2c,** 18992-68-2; **2d,** 51839-04-4; **3a,** 24955-75-7; **3b,** 51839-05-5; **3c,** 51839-06-6; **3d,** 51839-07-7; **4b,** 51839-08-8; **4c,** 51839-09-9; **4d,** 51839-10-2; **5b,** 51839-11-3; **5c,** 51839-12-4; **5d,** 51839-13-5; **6a,** 21711-71-7; **6b,** 51839-14-6; 3′,5′-bis(trifluoromethyl)-2-nitrobiphenyl, 328-73-4; 1-bromo-2-nitrobenzene, 577-19-5; 3,5-dimethyliodobenzene, 22445-41-6; 3,5-dimethylaniline, 108-69-0; dimethyl 5-iodoisophthalate, 51839-15-7; 5-iodoisophthalic acid, 51839-16-8.

References and Notes

(1) (a) B. A. DeGraff, D. W. Gillespie, and R. J. Sundberg, manuscript in preparation; (b) R. J. Sundberg, S. R. Suter, and M. Brenner, *J. Amer. Chem. Soc.*, **94,** 513 (1972), and references cited therein.
(2) J. H. Hall, J. W. Hill, and H. Tsai, *Tetrahedron Lett.*, 2211 (1965); J. H. Hall, J. W. Hill, and J. M. Fargher, *J. Amer. Chem. Soc.*, **90,** 5313 (1968).
(3) W. von E. Doering and R. A. Odum, *Tetrahedron*, **22,** 81 (1966).
(4) P. A. S. Smith in "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y., 1970, pp 129–142.
(5) (a) P. A. S. Smith and B. B. Brown, *J. Amer. Chem. Soc.*, **73,** 2435 (1951); (b) J. S. Swenton, T. J. Ikeler, and B. H. Williams, *J. Amer. Chem. Soc.*, **92,** 3103 (1970).
(6) R. A. Abramovitch, S. R. Challand, and E. F. V. Scriven, *J. Org. Chem.*, **37,** 2705 (1972).
(7) R. J. Sundberg, M. Brenner, S. R. Suter, and B. P. Das, *Tetrahedron Lett.*, 2715 (1970).
(8) J. I. G. Cadogan and M. J. Todd, *J. Chem. Soc. C*, 2808 (1969).
(9) The piperylene was added because of Swenton's[5b] results, which indicate that the presence of piperylene maximizes carbazole yields.
(10) R. A. Odum and G. Wolf, *J. Chem. Soc., Chem. Commun.*, 360 (1973).
(11) (a) P. J. Bunyan and J. I. G. Cadogan, *J. Chem. Soc.*, 42 (1953); (b) R. A. Odum and M. Brenner, *J. Amer. Chem. Soc.*, **88,** 2074 (1966); (c) R. J. Sundberg, *ibid.*, **88,** 3781 (1966).
(12) J. I. G. Cadogan and R. K. Mackie, *J. Chem. Soc. C*, 2819 (1969).
(13) R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64,** 149 (1964), have previously suggested that the nitrene–azirine interconversion might be reversible.
(14) J. S. McConaghy, Jr., and W. Lwowski, *J. Amer. Chem. Soc.*, **89,** 4450 (1967); A. Reiser and L. J. Leyshon, *ibid.*, **93,** 4051 (1971).

(15) K. Isomura, M. Okada, and H. Taniguchi, *Chem. Lett.*, 629 (1972).
(16) D. W. Gillespie, research in progress.
(17) P. A. Lehman and R. S. Berry, *J. Amer. Chem. Soc.*, **95**, 8614 (1973).
(18) A. Reiser, H. Wagner, and G. Bowes, *Tetrahedron Lett.*, 2635 (1966).
(19) A. Reiser, F. W. Willets, G. C. Terry, V. Williams, and R. Marley, *Trans. Faraday Soc.*, **64**, 3265 (1968).
(20) A. Reiser, G. Bowes, and R. J. Horne, *Trans. Faraday Soc.*, **62**, 3162 (1966).
(21) Satisfactory microanalyses were obtained for the following new compounds: **1b, 1d, 2b, 2d, 3b, 3c, 3d, 4b, 4d, 5b, 5c, 5d, 6b,** and **7b.**
(22) S. D. Ross, M. Markarian, and M. Schwarz, *J. Amer. Chem. Soc.*, **75**, 4967 (1953).
(23) P. A. S. Smith and B. B. Brown, *J. Amer. Chem. Soc.*, **73**, 2438 (1951).
(24) A. Grahl, *Chem. Ber.*, **28**, 84 (1895).
(25) H. Burton and J. Kenner, *J. Chem. Soc.*, **123**, 1043 (1923).
(26) F. Ulmann, *Justus Liebigs Ann. Chem.*, **332**, 82 (1904).
(27) The equilibrium temperature maintained in the photolysis well by the heat generated from the lamps.
(28) W. J. Mijs, S. E. Hoekstra, R. M. Ulmann, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **77**, 746 (1958).

Mechanism of Cycloaddition of Nitroso Compounds with Diphenylketene

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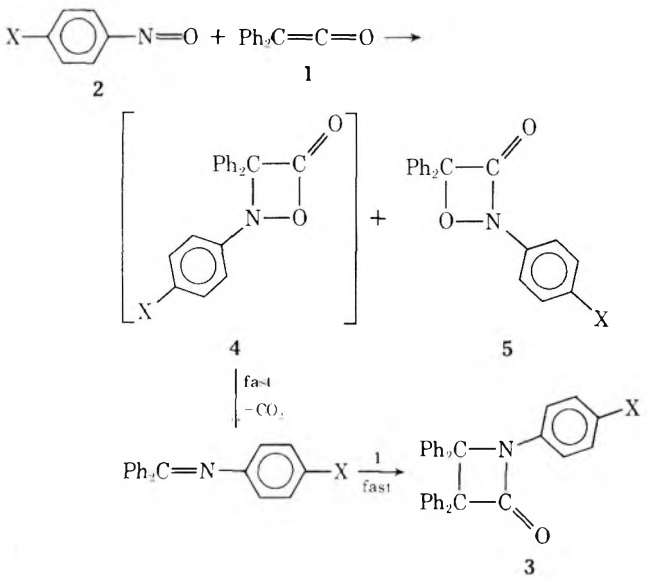
The cycloaddition of aromatic nitroso compounds *p*-X-C_6H_4NO with diphenylketene occurs in all cases rapidly and with relatively low regioselectivity, which is little affected by solvents or substituents. With X = CH_3O, CH_3, H, and CH_3O_2C, the principal product is the 2-aryl-4,4-diphenyl-1,2-oxazetidin-3-one. The isomeric oxazetidin-4-one, the main primary product for X = $(CH_3)_2N$, is unstable in all cases and decomposes to carbon dioxide and a Schiff base, which reacts *in situ* to form an azetidinone. The oxazetidin-3-ones undergo a very facile solvolysis reaction, apparently *via* a nitrenium ion-like intermediate. The cycloaddition results suggest a near-concerted mechanism.

Like most reactions of ketenes, the cycloaddition with nitroso compounds was discovered by Staudinger, who reported in 1911[1] that diphenylketene (**1**) reacted with *p*-dimethylaminonitrosobenzene (**2a**) to yield ultimately the β-lactam **3a** (65%). Staudinger proposed that **3a** arose *via* an unstable oxazetidin-4-one, **4a**, which decomposed to a Schiff base; the latter was shown to give the product **3a** (Scheme I). In contrast to **2a**, nitrosobenzene (**2b**) gave the oxazetidin-3-one **5b** in 63% yield.[1]

Scheme I



a, X = NMe_2
b, X = H
c, X = OMe
d, X = Me
e, X = CO_2Me
f, X = Br
g, X = Cl

These results were extended by Kresze and Trede,[2] who obtained oxazetidin-3-ones **5d, 5f,** and **5g** in 19–48% yields from **2d, 2f,** and **2g,** and the β-lactam **3c** (40%) from reaction of **2c** with **1**. These workers deduced from the effect of the dimethylamino and methoxy groups on the products that the unstable **4** was produced by a dipolar mechanism and **5** by a concerted process.

Mechanisms of ketene cycloadditions have received substantial theoretical[3-5] and experimental study in recent years. Alkenes,[6-10] vinyl ethers,[11,12] and azo compounds[13-15] react with ketenes by essentially concerted [$_\pi2_s$ + $_\pi2_a$] mechanisms, whereas enamines (at least in part),[16-18] imines,[19-21] carbodiimides,[22] and sulfodiimides[23] react *via* dipolar intermediates.

In contrast to these extensive studies on ketene cycloadditions, nitroso compound cycloadditions have been relatively little studied. Nitroso compounds function as dienophiles in Diels–Alder reactions,[24,25] but their involvement in [2 + 2] cycloadditions, despite a number of erroneous early reports,[26-31] is fairly rare. They do yield [2 + 2] adducts (oxazetidines) with highly halogenated[32,33] and methoxylated[34] alkenes, presumably by diradical processes. More recently, the [2 + 2] cycloaddition of nitroso compounds with ketenimines has been reported and studied by Barker.[35] We report here a study of the mechanism of cycloaddition of diphenylketene (**1**) with substituted nitrosobenzenes, **2**.

Results

The principal tool used in this investigation has been the regioselectivity of the cycloaddition, as affected by substituents and solvents. Previous investigators[1,2] had generally reported the formation of *either* **4** *or* **5** from a given nitrosobenzene derivative, which might be taken to imply a completely regiospecific cycloaddition, had the material balances been better.

In our study, the reaction was run by titrating a solution of **1** with a solution of **2** until the end point was indicated by persistent blue or green color of **2** and the complete disappearance of ketene absorption at 2090 cm^{-1} in the ir. (This procedure was made practical by the great speed of the reaction.) In some cases (X = H, CO_2Me) the primary product **5** was stable and was isolated as such; in

Table I
Products of Reaction of 1 with Nitroso Compounds p-XC_6H_4NO[a] (2)

X	σ_p	% 3[b]	% 5[b]	% urethane[b,c]	% urea[b,d]	% Ph_2CO[b]	% 4[e,f]	% 5[f,g]
NMe_2	−0.83	61	0	28	0	36	61 (68)	28 (32)
OMe	−0.27	22	0	81	0	69	22 (21)	81 (79)
Me	−0.17	13	0	0	86	30	13 (13)	86 (87)
H[h]	0.00	13	60	0	10	19	13 (16)	70 (84)
CO_2Me[i]	0.31	(28)	(72)	0	0	0	(28)	(72)

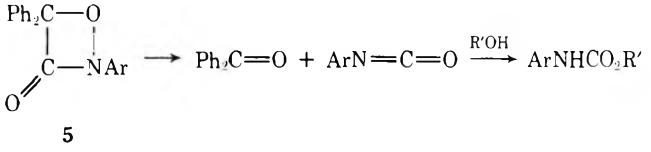
[a] In chloroform at 25°. [b] Isolated yields, based on 2. [c] Formed by addition of ethanol or methanol to the reaction mixture. [d] Formed by hydrolysis of isocyanate (from 5) on chromatography. [e] Based on yield of 3, derived from 4. [f] Yields in parentheses normalized to 100%. [g] Based on combined yields of 5 and products derived therefrom. [h] Diphenylacetic acid (11%) also isolated. [i] Yields by nmr.

Table II
Effect of Solvents in Product Ratio in Reaction of 1 with 2

X	Solvent	E_T[a]	% 3 = % 4[b]	% urethane = % 5[b]	% Ph_2CO[b]
OMe	Hexane	30.9	22 (25)	67 (75)	68
OMe	Chloroform	39.1	22 (21)	81 (79)	69
OMe	Dimethylformamide	43.8	17 (21)	65 (79)	64
OMe	Acetonitrile	46.0	9 (9)	91 (91)	74
NMe_2	Benzene	34.5	78 (79)	21 (21)	32
NMe_2	Chloroform	39.1	61 (68)	28 (32)	35
NMe_2	Acetonitrile	46.0	83 (94)	5 (6)	4

[a] Solvent polarity parameter: ref 36. [b] Isolated yields, based on 2; yields in parentheses normalized to 100%.

others (X = NMe_2, OMe) it decomposed *in situ* to benzophenone and an isocyanate, which was isolated as the urethane or urea. Thus the quantity of 4 formed in the initial



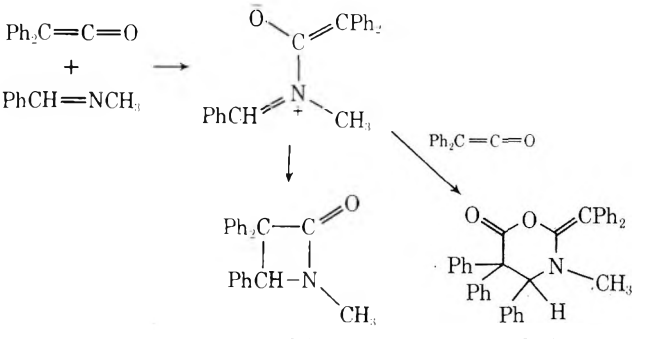
5

cycloaddition was measured by the quantity of β-lactam 3 isolated; the quantity of 5 was measured either directly or from the quantity of urethane or urea. The results are summarized in Table I.

Except for the case of **2a**, the major primary product is the oxazetidin-3-one, whether X is electron donating or electron withdrawing. Moreover, the regioselectivity is in no case very great, ranging from 1:2 to 6:1; both primary products, 4 and 5, are produced and detected in every case. The very strongly electron-donating dimethylamino group, as previously reported,[1] causes 4 to become the predominant primary product, but only by a modest 2:1 ratio. To test Kresze's hypothesis[2] that 4 arises by a dipolar and 5 by a concerted process, the effect of solvents on the product distribution was investigated (Table II) using **2a** and **2c**, which should be most prone to react by a dipolar mechanism, and most sensitive therefore to solvent effects.

It is evident that, for both **2a** and **2c**, the solvent, like the substituent X, has only a modest effect on the product ratio. There is no consistent increase in the amount of 4 with increasing solvent polarity as required by Kresze's proposal. The concept[2] that one primary product, 4, is produced by one mechanism and the other, 5, by a fundamentally different mechanism is not supported by these facts. We therefore conclude for the remainder of the discussion that a common type of mechanism leads to both primary products in every case. This common mechanism might be a dipolar, diradical, or concerted mechanism, as limiting cases (Scheme II).

Dipolar intermediates are well established in some [2 + 2] cycloadditions.[16-23] In these cases, the reactions have been found to be regiospecific, strongly affected by solvents, and prone to formation of 2:1 adducts by reaction of the 1,4-dipolar intermediate with an additional ketone molecule. As between the two possible dipolar intermedi-

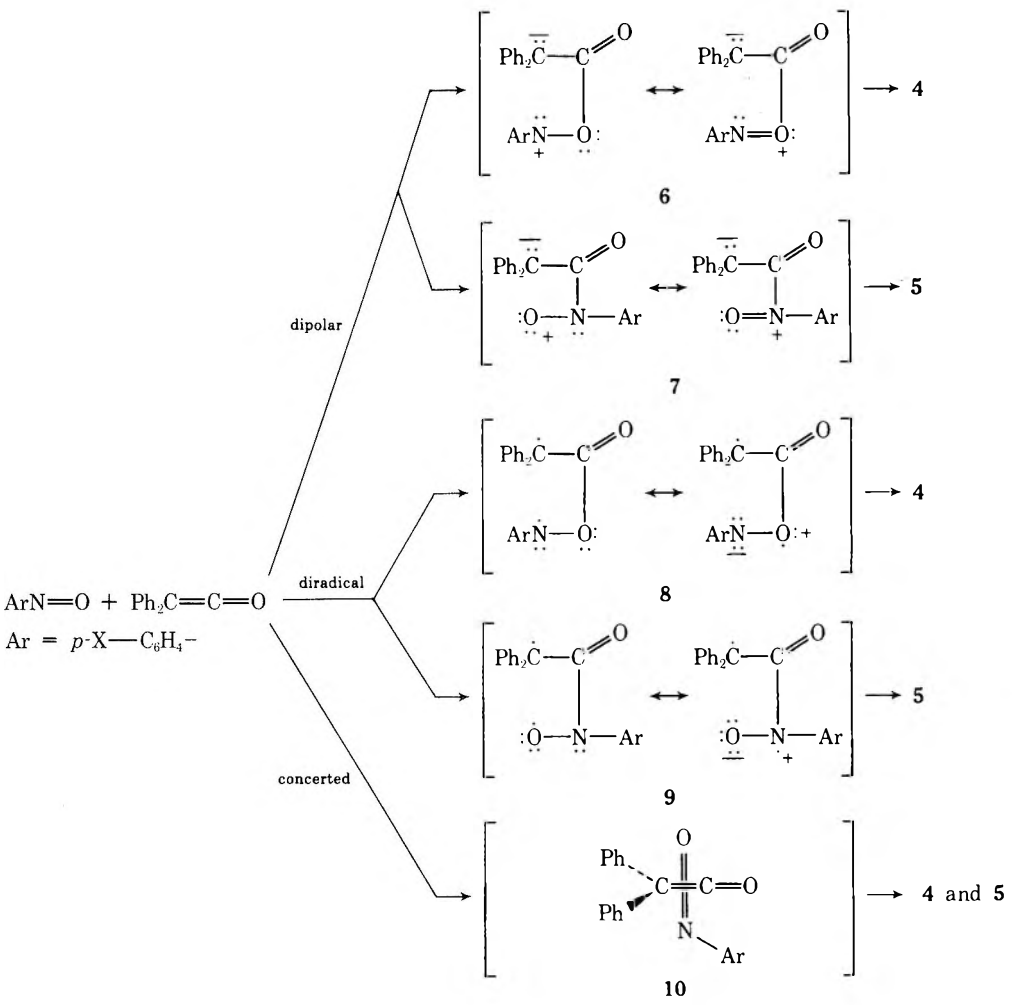


ates, 6 and 7, the nitrenium ion[37] 6 seems less unreasonable than the oxenium ion 7, at least in the absence of strong electron-withdrawing groups X. One would therefore expect 4 to be the predominant primary product in most cases, accompanied by 2:1 adduct(s).

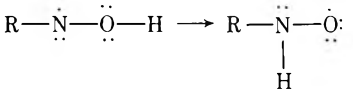
Clearly none of the above expectations for a dipolar mechanism accords with the experimental observations: no 2:1 adducts are detectable in the reaction mixtures, despite the presence of a large excess of ketene 1 in the early stages; the major primary product is generally 5, not 4; and solvent and substituent effects on the regioselectivity are modest. We are therefore led to reject the dipolar mechanism.

In contrast to 6 and 7, diradical intermediates 8 and 9 would appear *a priori* relatively favorable. Nitroxyl radicals (such as 9) are probably the most stable and best characterized of radicals;[38] a number of stable oxaminyl radicals like 8 have also recently been characterized.[39-44] However, addition of radicals to nitroso compounds occurs only at N, to give nitroxyls, rather than at O, in the absence of extraordinary steric hindrance at N.[41,43] This indicates the greater stability of nitroxyls relative to oxaminyls, as does the rearrangement of the latter.[39,40] We

Scheme II

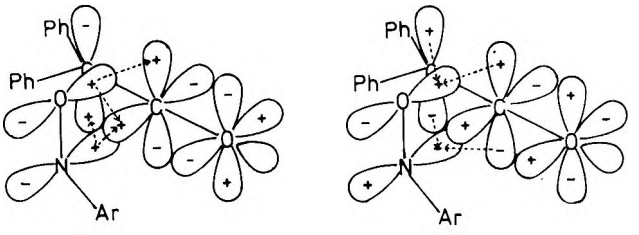


would thus expect the diradical **9** to be substantially more stable than **8**, and thus **5** to be the sole (or at least predominant) primary product. Diradical **9** being the more polar of the two, polar solvents should increase the **5**:**4** ratio relative to nonpolar solvents.[45] Relative substituent effects on **8** and **9** are difficult to predict, however.



The observed preferential formation of **5** over **4** is *qualitatively* consistent with a diradical mechanism; however, the low regioselectivity of the cycloaddition is difficult to reconcile with the normal regiospecificity of radical additions to nitroso compounds, as is the preference for **4a** over **5a**.

However, the experimental observations are consistent with an essentially concerted mechanism, analogous to that proposed by Woodward and Hoffmann[3] for the ketene + alkene cycloaddition. The transition state **10** is quite free of steric hindrance, and is stabilized by interactions of the π_{NO} OMO of the nitroso compound with the π_{CC}^* and π_{CO}^* (UMO) orbitals of the ketene (**10a**), complimented by interaction of the π_{NO}^* LUMO of the nitroso group with the π_{CC} HOMO of the ketene (**10b**). The low-lying nature of the π_{NO}^* LUMO of nitrosobenzene is indicated by its facile electrochemical reduction.[46] In view of the fairly weak N=O double bond and its relationship to singlet oxygen,[47] one may expect a relatively high-lying π_{NO} orbital.[48]

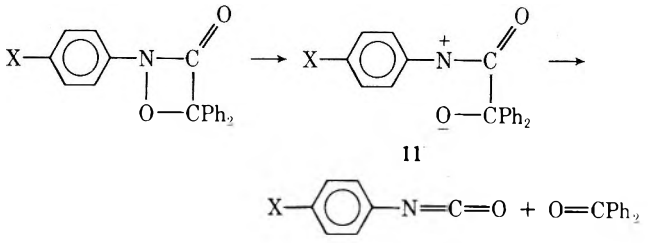


10a 10b

If the regioselectivity is ketene LUMO controlled[49] (as in **10a**), then **4** should be the major primary product, as in fact found with **2a**. In the absence of the strong electron-donating (HOMO- and LUMO-raising) effect of the dimethylamino group of **2a**, however, the reaction must be more nearly ketene HOMO controlled (**10b**), giving a moderate preference for **5** in most cases. The concept of ketene HOMO control is also in full accord with the relative reactivities of various ketenophiles (*e.g.*, ArN=O > ArN=NR ≫ ArCH=CH_2) in concerted reactions, which parallel their reducibilities.

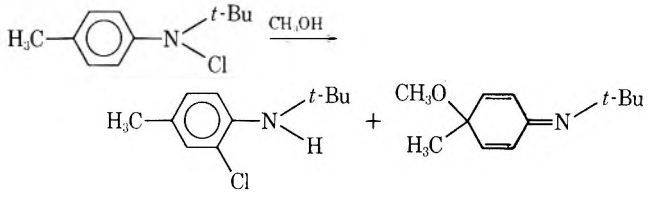
Stabilities of 1,2-Oxazetidin-3-ones. The thermal stabilities of **5a–e** exhibit a marked dependence on the substituents X, ranging from the readily isolable **5e** and **5b** (X = CO_2CH_3, H) through **5d** (X = CH_3), stable in the reaction mixture but not to chromatography, and **5c** (X = OCH_3), in part decomposed in the reaction mixture, to **5a** (X = NMe_2), entirely undetectable except through its decomposition products. Thus, the thermal stabilities of the oxazetidin-3-ones decrease dramatically as X becomes

more electron donating. This is most consistent with thermal decomposition *via* a nitrenium ion-like intermediate, **11**.[50]

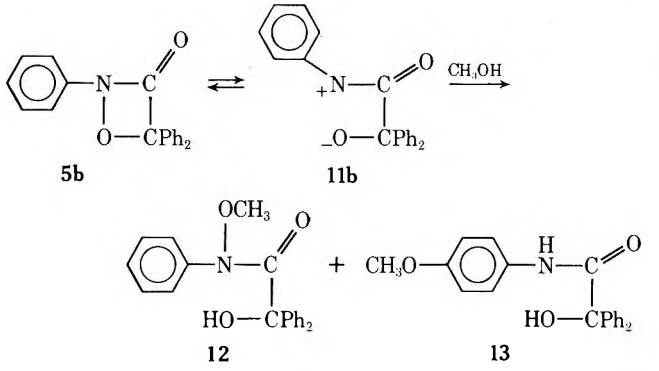


11

Analogous nitrenium ions have been detected in the solvolyses of *N*-chloroanilines, for which a ρ^+ of −6.35 has been measured, by trapping with methanol.[51] Similarly,



addition of methanol to product mixtures from reaction of **1** with **2a** and **2c** resulted in solvolysis of the oxazetidin-3-ones *via* **11**, as shown by the nature of the products formed. Thus, two additional products not present upon completion of the reaction (ir) were isolated from the reaction mixture of **1** with **2b** after adding methanol. One of these, **12**, was a white solid whose ir [2940 (s, br, OH), 1634 (s, amide C=O), 760 and 700 cm^{-1} (s, C_6H_5)], nmr [δ 3.00 (s, 3 H), 7.2 (m, 15 H), 8.5 (br s, 1 H, exchangeable with D_2O)], and analysis indicated the structure *N*-methoxybenzilanilide.[52] The other, **13**, was identified as benzil-*p*-anisidide by its ir [1664 (s, amide C=O), 833 cm^{-1} (s, *p*-C_6H_4)] and nmr data [δ 3.68 (s, 3 H), 6.72 (d, $J \approx 10$ Hz, 2 H), 7.2 (m, 13 H), 8.2 (br s, 1 H)] and comparison with an authentic sample.

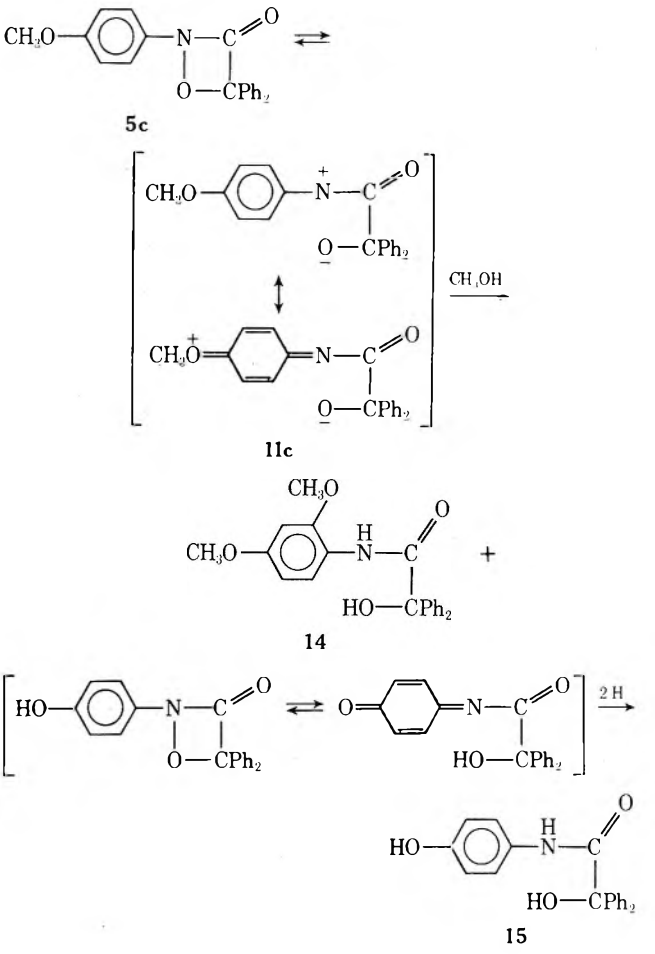


5b 11b

12 13

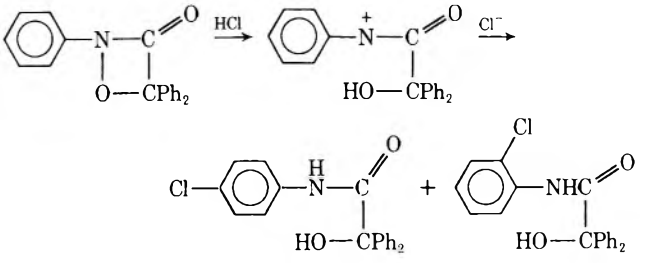
Two additional products (Scheme III) were also obtained from methanolysis of the transient oxazetidin-3-one **5c**. One, **14**, was identified as *N*-(2,4-dimethoxyphenyl)benzilamide by its ir [1669 (s, amide C=O), 909 and 839 (1,2,4-C_6H_3), 752 and 700 cm^{-1} (C_6H_5)] and nmr data [δ 3.65 (s, 3 H), 3.67 (s, 3 H), 3.95 (s, 1 H), 6.41 (m, 2 H), 7.33 (m, 10 H), 8.30[53] (d, $J \approx 9$ Hz, 1 H), 8.89 (br s, 1 H)] and comparison with an authentic sample. The other product, **15**, was identified as *N*-(4-hydroxyphenyl)benzilamide by its ir [1640 (s, amide C=O), 820 cm^{-1} (s, *p*-C_6H_4)], nmr [δ 6.02 (d, $J \approx 10$ Hz, 2 H), 6.45 (d, $J \approx 10$ Hz, 2 H), 7.25 (m, 12 H), 8.24 (s, exchangeable with D_2O, 1 H)], and mass spectra [*m/e* 319 (P^+), 274 (P − OH − CO^+), 194 (Ph_2CCO^+), 183 (Ph_2COH^+), 135 (HO-$C_6H_4NCO^+$), 105 ($PhCO^+$)].

Scheme III



5c 11c 14 15

Related reactions have also been reported by Sheradsky,[54] who isolated ring-chlorinated products on treating **5b** with HCl. The nature of the product in all of these



cases implicates nitrenium ion-like intermediates **11** in the solvolyses and supports their intermediacy in the thermal decompositions to isocyanates and benzophenone.

Experimental Section[55]

Materials. Diphenylketene (**1**),[13] 4-nitrosoanisole (**2c**),[56] 4-nitrosotoluene (**2d**),[57] and methyl 4-nitrosobenzoate (**2e**)[58] were prepared by literature methods. *N,N*-Dimethyl-4-nitrosoaniline, nitrosobenzene, 4-aminophenol, *N,N*-dimethyl-*p*-phenylenediamine, and 2,4-dimethoxyaniline were used as obtained from Aldrich Chemical Co. *p*-Anisidine (Aldrich) was recrystallized from cyclohexane.

Reaction of 2a with 1 in Chloroform. A chloroform solution of *N,N*-dimethyl-4-nitrosoaniline (**2a**, 2.700 g in 25 ml) was added dropwise to a stirred solution of diphenylketene (3.471 g, 17.9 mmol) in 25 ml of chloroform, under a nitrogen atmosphere, until the ketene absorbance at 2090 cm^{-1} in the ir disappeared. The amount of **2a** actually consumed was 1.670 g (11.1 mmol). The ir spectrum indicated isocyanate (2270 cm^{-1}), lactam **3a** (1730 cm^{-1}), and benzophenone (1655 cm^{-1}). Ethanol (10 ml) was added to convert isocyanate to urethane, and after 5 hr the sol-

vents were stripped off. The residue was chromatographed on 65 g of silica gel. Elution with benzene yielded a binary mixture of lactam **3a** and benzophenone (ir). Lactam **3a** was isolated (2.23 g) by dissolving out the benzophenone with hexane–benzene, followed by recrystallization from acetone: mp 191–196° dec (lit.[1] mp 196–200°); nmr ($CDCl_3$) δ 3.17 (s, 6 H), 6.79 (d, $J \approx 10$ Hz, 2 H), 7.28 (m) and 7.60 (d, $J \approx 10$ Hz) (combined integral 22 H); mass spectrum *m/e* (rel intensity) 494 (0.1, P), 300 (100, $Ph_2C{=}NC_6H_4NMe_2$), 223 (34, $PhC{\equiv}NC_6H_4NMe_2$), 194 (26, Ph_2CCO), 165 (59, $C_{12}H_9$). The hexane–benzene filtrate left 1.81 g residue upon evaporation, which was dissolved in ethanol and treated with excess 2,4-dinitrophenylhydrazine reagent[59] to precipitate the 2,4-dinitrophenylhydrazone derivative of benzophenone (1.43 g, 3.95 mmol), which indicated the residue to have contained 3.95 mmol (0.72 g, 36%) of benzophenone and 1.09 g of lactam **3a**, for a total of 3.32 g (6.72 mmol, 61%) of the latter.

Elution of the column with 60% ether–benzene gave 0.651 g (3.13 mmol, 28%) of a green solid, mp 71–73°, which afforded a white solid, mp 77–78°, upon recrystallization from hexane, identical (ir, nmr, mixture melting point) with authentic ethyl 4-(*N,N*-dimethylamino)carbanilate. The latter was prepared from ethyl chloroformate and *N,N*-dimethyl-*p*-phenylenediamine: mp 79–81°; ir (KBr) 3210 (s), 2860 (s, br), 1670 (s), 1640 (s, br), 943 (m, br). 813 (s), and 758 cm^{-1} (m); nmr ($CDCl_3$) δ 1.30 (t, $J \approx 8$ Hz, 3 H), 2.90 (s, 6 H), 4.23 (q, $J \approx 8$ Hz, 2 H), 6.74 (d, $J \approx 9$ Hz, 2 H), 7.32 (d, $J \approx 9$ Hz, 2 H).

A previous run of the reaction gave 46% isolated **3a**, 42% benzophenone, and 28% of the urethane. Reactions in acetonitrile and benzene were run as above, with results as in Table II.

Reaction of 2c with 1 in Chloroform. A solution of 1.900 g of 4-nitrosoanisole (**2c**) in 25 ml of chloroform was added dropwise to a stirred solution of **1** (2.764 g, 14.3 mmol) in 25 ml of chloroform in a 250-ml three-neck flask equipped with a reflux condenser and nitrogen inlet tube, until the blue-green color persisted and the ketene absorbance at 2090 cm^{-1} in the ir disappeared. This left 0.40 g of unreacted **2c**, whence the amount consumed was 1.50 g (10.4 mmol). After 2 hr of stirring at room temperature, an ir spectrum showed strong peaks due to oxazetidin-3-one **5c** (1764 cm^{-1}) and lactam **3c** (1730 cm^{-1}), and weak peaks due to isocyanate (2260 cm^{-1}) and benzophenone (1655 cm^{-1}). Refluxing for 4 hr resulted in loss of the oxazetidin-3-one and large increases in the isocyanate and benzophenone peaks. Methanol (10 ml) was added, the solution was stirred for 10 min, and the solvents were stripped off. Methanol (30 ml) was added to the partially crystalline residue, which mixture was then filtered to give 1.07 g of white solid, mp 213–218°. Recrystallization from hexane–benzene gave white crystals of lactam **3c**: mp 226–227° (lit.[2] mp 222–225°); ir (KBr) 1730, 1520, 1350, 1250, and 850 cm^{-1} (all s); nmr ($CDCl_3$) δ 3.62 (s, 3 H), 6.59 (d, $J \approx 10$ Hz), 6.95 (m), 7.27 (d, $J \approx 10$ Hz) (doublets and multiplet, 24 H).

The residue from the methanol filtrate, 3.05 g brown oil, was chromatographed on 60 g of silica gel. Elution with benzene gave a binary mixture of benzophenone and lactam **3c** (ir), 1.485 g. Hexane precipitated 0.10 g of **3c**, mp 212–218°, for a total yield of 1.17 g (2.44 mmol, 22%). The remainder was benzophenone (1.37 g, 7.56 mmol, 69%) by ir.

Elution of the column with 10% ether–benzene afforded methyl 4-methoxycarbanilate (1.60 g, 8.86 mmol, 81%), mp 82–88°. Recrystallization from hexane–benzene gave a white solid: mp 90–91.5° (lit.[60] mp 90°); ir (KBr) 3230 (m), 1740 (s), 1540 (s, br), 1235 (s, br), 1080 (m), and 851 cm^{-1}; nmr ($CDCl_3$) δ 3.65, 3.68 (two singlets, total 6 H), 6.72 (d, $J \approx 10$ Hz, superimposed on br s, total 3 H), 7.16 (d, $J \approx 10$ Hz, 2 H).

Reactions in acetonitrile, dimethylformamide, and hexane were run as above, with results as in Table II.

Reaction of 2d with 1 in Chloroform. The reaction was run as above, using 2.99 g (15.4 mmol) of **1** and 1.25 g (10.3 mmol) of **2d**. An ir spectrum of the reaction mixture at completion showed peaks due to oxazetidin-3-one **5d**[2] (1779 cm^{-1}) and lactam **3d** (1735 cm^{-1}). The chloroform was stripped from the mixture, and 15 ml of hexane was added. Filtration after 18 hr yielded **3d** (0.242 g) as a white solid, mp 186–195°. Crystallization from hexane–benzene gave white crystals: mp 199–205°; ir (KBr) 1735 (s), 1515 (m), 1366 (s), 820 (m), 704 cm^{-1} (br m); nmr ($CDCl_3$) δ 2.21 (s, 3 H), 7.1 (m, 24 H).

The residue from the hexane filtrate, 4.10 g of brown oil, was chromatographed on 65 g of silica gel. Elution with benzene afforded a yellow oil, fractional crystallization of which from hexane yielded first 0.365 g of lactam **3d**, then 0.100 g of a yellow solid, and further recrystallization of which gave a white solid, mp 158–161°, whose spectral data [ir (KBr) 3240 (s), 1670 (vs), 1605 (s), 1518 (s), 700 cm^{-1} (s); nmr ($CDCl_3$) δ 2.30 (s, 3 H), 3.96 (s, 1 H), 5.01 (s, <1 H), 7.40 (m, *ca.* 13 H), 8.31 (d, <1 H, $J \approx 9$ Hz), and 9.08 (s, 1 H)] did not suggest a unique structure.[61] Treatment of the residue from the crystallizations with 2,4-dinitrophenylhydrazine reagent[59] gave 1.63 g (4.50 mmol) of 2,4-dinitrophenylhydrazone derivative, whence the yield of benzophenone was also 4.50 mmol (0.83 g, 44%). Some additional **3d** also contained in the residue could not be isolated. The total isolated amount of **3d** was 0.607 g (1.34 mmol, 13%).

Elution of the column with 50% ether–benzene gave 1.07 g (4.40 mmol, 86%) of crude di-*p*-tolylurea, mp 245–261°. Recrystallization from ether–benzene gave a white solid, mp 270–271° (lit.[62] mp 277°), identical (ir, nmr, mixture melting point) with authentic material.

Reaction of 2b with 1 in Chloroform. The reaction was run as above, using 3.556 g (18.3 mmol) of **1** and 1.240 g (11.6 mmol) of **2b**. An ir spectrum at completion showed large amounts of oxazetidin-3-one **5b** (1776 cm^{-1}) and lactam **3b** (1733 cm^{-1}), and traces of phenyl isocyanate (2240 cm^{-1}) and benzophenone (1655 cm^{-1}). Evaporation of the chloroform left a yellow oil, which on standing for 18 hr in hexane precipitated 0.415 g of lactam **3b**, mp 181–190°. Recrystallization from ethanol gave pure **3b**, mp 189–190° (lit.[63] mp 190–191°), ir identical with that of an authentic[64] sample. The residue from the hexane filtrate (4.40 g) was chromatographed on 65 g of silica gel. Elution with benzene yielded a yellow oil, fractional crystallization (hexane) of which yielded first 0.287 g of **3b**, mp 188–189° (total yield 0.702 g, 1.55 mmol, 13%), then 1.943 g of **5b**: mp 72–73° (lit.[2] mp 73.0–73.5°); ir (KBr) 1773 (s), 1600 (m), 1493 (s), 1360 (s), 763 (s), 747 (s), and 694 cm^{-1} (s). The residue from the recrystallizations (0.539 g), a binary mixture of oxazetidin-3-one **5b** and benzophenone by ir, was treated to obtain the 2,4-dinitrophenylhydrazone of benzophenone[59] (2.15 mmol, 19%), whence an additional 0.148 g of **5b** was also present by difference. The total yield of **5b** was thus 2.017 g (6.90 mmol, 60%).

Elution of the column with 8% ether–benzene gave 0.425 g (2.0 mmol, 11%) of crude diphenylacetic acid, mp 127–140°, mp 142–146° after recrystallization from hexane–benzene (lit.[65] mp 146°). Elution with 50% ether–benzene gave 0.128 g (0.605 mmol, 10%) of 1,3-diphenylurea, mp 219–222°, mp 240–241° after recrystallization from hexane–benzene (lit.[66] mp 237–237.5°).

Reaction of 2e with 1 in Chloroform. The reaction was run as above, using 1.507 g (7.70 mmol) of **1** and 1.065 g (6.50 mmol) of **2e**. The ir spectrum indicated oxazetidin-3-one **5e** (1779 cm^{-1}) and lactam **3e** (1742 cm^{-1}), in addition to the ester groups at 1712 cm^{-1}. No change occurred in the ir after 18 hr. The chloroform was stripped off and the residue, 3.62 g, was chromatographed on silica gel. Elution with benzene yielded a mixture of **3e** and **5e**, which proved inseparable by preparative layer chromatography as well as column chromatography. Fractional crystallization of the mixture from hexane–benzene yielded lactam **3e** as opaque white crystals: mp 195–196°; ir (KBr) 1742 (s), 1712 (s), 1597 (s), 1332 (s), 1271 (s), 1180 (m), 1104 (m), 830 (m, br), 770 (m), 725 (m), and 694 cm^{-1} (m); nmr ($CDCl_3$) δ 3.78 (s, 3 H), 7.10 (br m, 20 H), 7.58 (d, $J \approx 10$ Hz, 2 H), 7.92 (d, $J \approx 10$ Hz, 2 H).

Anal: Calcd for $C_{35}H_{27}NO_3$: C, 82.51; H, 5.31; N, 2.75; Found: C, 82.64; H, 5.35; N, 2.70.

The reaction was rerun as above, using 0.603 g (3.11 mmol) of **1** and 0.364 g (2.21 mmol) of **2e**. The ratio of the products was determined by careful integration of the two methyl ester peaks at δ 3.78 (**3e**) and 3.82 (**5e**), using sweep widths of 108 and 54 Hz. This showed the quantities to be 28% lactam **3e** and 72% oxazetidinone **5e**, ±2%. Fractional crystallization of the mixture from acetone afforded the oxazetidin-3-one **5e** as colorless, transparent crystals: mp 122–123°; ir (KBr) 1770, 1724, 1600, 1372, 1274, 823, 700 cm^{-1} (all strong); nmr ($CDCl_3$) δ 3.82 (s, 3 H), 7.26 (m, 12 H), 7.88 (d, $J \approx 9$ Hz, 2 H).

Anal: Calcd for $C_{22}H_{17}NO_4$: C, 73.54; H, 4.73; N, 3.90. Found: C, 73.75; H, 4.58; N, 3.82.

Reaction of 2b with 1, with Methanolysis of 5b. The reaction was run as previously described, using 4.221 g (21.7 mmol) of **1** and 1.373 g (12.8 mmol) of **2b**. Evaporation of the chloroform left a light brown oil, to which was added 25 ml of methanol. Filtration of the resulting mixture gave solid lactam **3b** (0.694 g, 1.54 mmol, 12%), mp 177–186°. Evaporation of the methanol left 4.86 g of brown oil which was chromatographed as before. Elution with benzene gave a mixture (3.80 g) which contained benzophenone and **5b**; further chromatography yielded 0.737 g (2.4 mmol, 19%) of **5b** from this mixture. Elution with 8% ether–benzene gave first

a white solid (0.705 g), mp 96–96.5° after recrystallization from hexane, whose spectra (see text) and analysis suggested the structure *N*-methoxybenzilanilide (**12**, 2.12 mmol, 17%).

Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.67; H, 5.71; N, 4.20. Found: C, 75.51; H, 5.85; N, 4.19.

Continued elution with 8% ether–benzene gave benzil-*p*-anisidide (**13**), mp 178–179.5° after recrystallization from carbon tetrachloride (0.259 g, 0.78 mmol, 6%); for ir and nmr spectra, see text. The material was identical (ir, nmr, mixture melting point) with an authentic sample, mp 177–179.5° (lit.[67] mp 170–172°), synthesized by reaction of chlorodiphenylacetyl chloride and *p*-anisidine, followed by hydrolysis.[54] Elution of the column with ether gave 0.23 g (1.07 mmol, 5%) of diphenylacetic acid.

Reaction of 2c with 1, with Methanolysis of 5c. The reaction was run as previously described, using 3.27 g (16.9 mmol) of **1** and 2.040 g (14.9 mmol) of **2c**. After removal of the solvent, the residue was taken up in 25 ml of methanol. Filtration gave 1.675 g of lactam **3c**, mp 212–218°. The residue from evaporation of the filtrate, 3.99 g of brown oil, was chromatographed on 65 g of silica gel. Elution with benzene yielded initially a mixture of benzophenone and **3c**; analysis as before indicated 6.1 mmol (41%) of benzophenone and 0.81 g of **3c** (total yield 2.49 g, 5.16 mmol, 35%). Further elution with benzene yielded a green-yellow solid, mp 117–119°, identified as 4,4′-azoxydianisole by ir.[68] Elution with 6% ether–benzene gave a brown oil (0.418 g, 1.15 mmol, 8%), recrystallization of which from hexane–benzene gave a white solid, mp 122.5–123.5°; for spectra, see text. This was identical (ir, nmr, mixture melting point) with authentic *N*-(2,4-dimethoxyphenyl-)benzilamide (**14**), mp 123–124°, synthesized by reaction of chlorodiphenylacetyl chloride with 2,4-dimethoxyaniline, followed by hydrolysis.[54,69]

Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.72; N, 5.80; N, 3.85; O, 17.63. Found: C, 73.12; H, 5.70; N, 3.99; O, 17.20.

Further elution of the column with 6% ether–benzene gave methyl 4-methoxycarbanilate (0.665 g, 3.67 mmol, 25%), mp 90–91.5° after recrystallization from hexane–benzene. Elution with 12% ether–benzene gave **15** as a brown solid (1.28 g, 4.02 mmol, 27%), mp 173–177° after recrystallizations from hexane–benzene; for ir, nmr, and mass spectra, see text. A good carbon analysis could not be obtained on this difficultly purified material.

Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.24; H, 5.33; N, 4.39. Found: C, 77.63, 77.32; H, 4.87, 5.19; N, 3.85, 4.14.

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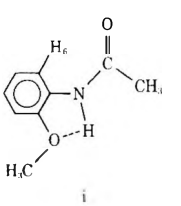
Registry No.—**1**, 525-06-4; **2a**, 138-89-6; **2b**, 586-96-9; **2c**, 1516-21-8; **2d**, 623-11-0; **2e**, 13170-28-0; **3a**, 51751-63-4; **3b**, 14313-14-5; **3c**, 51751-64-5; **3d**, 51751-65-6; **3e**, 51751-66-7; **5c**, 51751-67-8; **5e**, 51751-68-9; **12**, 51751-69-0; **13**, 20594-45-0; **14**, 51751-74-7; **15**, 51751-75-8; ethyl 4-(*N*,*N*-dimethylamino)carbanilate, 41116-23-8; methyl 4-methoxycarbanilate, 14803-72-6.

References and Notes

(1) H. Staudinger and S. Jelagin, *Chem. Ber.*, **44**, 365 (1911).
(2) G. Kresze and A. Trede, *Tetrahedron*, **19**, 133 (1963).
(3) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970, p 163.
(4) R. Sustmann, A. Ansmann, and F. Vahrenholt, *J. Amer. Chem. Soc.*, **94**, 8099 (1972).
(5) N. D. Epiotis, *J. Amer. Chem. Soc.*, **95**, 5624 (1973); A. H. Andrist, *J. Org. Chem.*, **38**, 1772 (1973).
(6) R. Huisgen and L. Feiler, *Chem. Ber.*, **102**, 3391, 3475 (1969).
(7) L. Ghosez, R. Montaigne, H. Vanlierde, and F. Dumay, *Angew. Chem., Int. Ed. Engl.*, **7**, 221, 643 (1968).
(8) W. Weyler, Jr., L. Byrd, M. Caserio, and H. W. Moore, *J. Amer. Chem. Soc.*, **94**, 1021 (1972).
(9) R. De Selms and F. Delay, *J. Org. Chem.*, **37**, 2908 (1972).
(10) J. Baldwin and J. Kapecki, *J. Amer. Chem. Soc.*, **92**, 4868, 4874 (1970).
(11) J. Martin, V. Goodlett, and R. Burpitt, *J. Org. Chem.*, **30**, 4309 (1965).
(12) R. Huisgen, L. Feiler, and P. Otto, *Chem. Ber.*, **102**, 3405, 3460 (1969).
(13) R. C. Kerber, T. J. Ryan, and S. D. Hsu, *J. Org. Chem.*, **39**, 1215 (1974).
(14) A. H. Cook and D. G. Jones, *J. Chem. Soc.*, 184 (1941); G. O. Schenk and N. Engelhard, *Angew. Chem.* **68**, 71 (1956).
(15) R. C. Kerber and T. J. Ryan, *Tetrahedron Lett.*, 703 (1970).
(16) J. C. Martin, P. G. Gott, and H. U. Hostetter, *J. Org. Chem.*, **32**, 1654 (1967).
(17) L. Feiler and R. Huisgen, *Chem. Ber.*, **102**, 3428 (1969).
(18) R. Huisgen and P. Otto, *J. Amer. Chem. Soc.*, **91**, 5922 (1969).
(19) R. Huisgen, B. Davis, and M. Morikawa, *Angew. Chem., Int. Ed. Engl.*, **7**, 826 (1968).
(20) A. Gomes and M. M. Jouille, *Chem. Commun.*, 935 (1967).
(21) H. B. Kagan and J. L. Luche, *Tetrahedron Lett.*, 3093 (1968).
(22) W. T. Brady and E. D. Dorsey, *Chem. Commun.*, 1638 (1968).
(23) T. Minami, K. Yamataka, Y. Ohshiro, T. Agawa, N. Yasuoka, and N. Kasai, *J. Org. Chem.*, **37**, 3810 (1972).
(24) G. Kresze and J. Firl, *Tetrahedron Lett.*, 1043 (1968).
(25) J. Hamer, "1,4-Cycloaddition Reactions," Academic Press, New York, N. Y., 1967, p 420.
(26) C. K. Ingold and S. D. Weaver, *J. Chem. Soc.*, **125**, 1456 (1924).
(27) N. Hepfinger and C. Griffin, *Tetrahedron Lett.*, 1365 (1963).
(28) G. N. Burkhardt and A. Lapworth, *J. Chem. Soc.*, **127**, 1742 (1925).
(29) G. N. Burkhardt, A. Lapworth, and J. Walkden, *J. Chem. Soc.*, **127**, 2458 (1925).
(30) C. K. Ingold, *J. Chem. Soc.*, **125**, 93 (1924).
(31) G. Burkhardt, A. Lapworth, and E. Robinson, *J. Chem. Soc.*, **127**, 2234 (1925).
(32) R. Huisgen and L. Krause, *Justus Liebigs Ann. Chem.*, **574**, 157 (1951).
(33) V. A. Ginsberg, *et al.*, *Dokl. Chem.*, **153**, 796 (1963); *Dokl. Akad. Nauk SSSR*, **153**, 1104 (1963), and references cited therein.
(34) R. W. Hoffmann and H. Hauser, *Angew. Chem., Int. Ed. Engl.*, **3**, 380 (1964).
(35) M. Barker and J. T. Gill, *J. Heterocycl. Chem.*, **7**, 1203 (1970); M. Barker, L. Combs, and J. T. Gill, *ibid.*, **9**, 77 (1972).
(36) C. Reichardt and K. Dimroth, *Fortschr. Chem. Forsch.*, **11**, 22 (1968).
(37) For reviews of nitrenium ion chemistry, see P. G. Gassman, *Accounts Chem. Res.*, **3**, 26 (1970); P. G. Gassman, Abstracts, 22nd National Organic Symposium, June 1971, pp 84–91; P. T. Lansbury in "Nitrenes," W. Lwowski, Ed., Wiley, New York, N. Y., 1970, Chapter 11, pp 405–419.
(38) E. G. Rosantsev, "Free Nitroxyl Radicals," Plenum Press, New York, N. Y., 1970; A. R. Forrester, J. M. Hay, and R. H. Thomson, "Organic Chemistry of Stable Free Radicals," Academic Press, New York, N. Y., 1968, pp 180–246.
(39) J. C. Baird and J. R. Thomas, *J. Chem. Phys.*, **35**, 1507 (1961); H. Chihara, M. Nakamura, and S. Seki, *Bull. Chem. Soc. Jap.*, **38**, 1776 (1965).
(40) P. Smith and W. M. Fox, *Can. J. Chem.*, **47**, 2227 (1969).
(41) S. Terabe and R. Komaka, *J. Chem. Soc., Perkin Trans. 2*, 369 (1973).
(42) N. Negoita, R. Baican, and A. T. Balaban, *Tetrahedron Lett.*, 1877 (1973).
(43) W. Ahrens, K. Wieser, and A. Berndt, *Tetrahedron Lett.*, 3141 (1973).
(44) W. C. Danen, C. T. West, and T. T. Kensler, *J. Amer. Chem. Soc.*, **95**, 5716 (1973).
(45) The dipole moment of diphenylnitroxyl is 3.00 D: E. G. Rosantsev and E. N. Gur'yanov, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 979 (1966). Di-*tert*-butylnitroxyl is well solvated by polar solvents, from epr results: T. Kawamura, S. Matsunami, and T. Yonezawa, *Bull. Chem. Soc. Jap.*, **40**, 1111 (1967).
(46) C. K. Mann and K. K. Barnes, "Electrochemical Reactions in Nonaqueous Systems," Marcel Dekker, New York, N. Y., 1970, p 329.
(47) Singlet oxygen, having both a high-energy π orbital and a low-energy π^* orbital (both nearly nonbonding in character), should be an ideal cycloaddition partner with ketenes.
(48) This is confirmed by the photoelectron spectrum: J. Rabalais, *J. Electron Spectros. Relat. Phenomena*, **1**, 83 (1972).
(49) K. N. Houk, *et al.*, *J. Amer. Chem. Soc.*, **95**, 7287, 7301 (1973); 7301 (1973); *Tetrahedron Lett.*, 897 (1974).
(50) Catalysis by adventitious acid is not excluded.
(51) P. G. Gassman and G. A. Campbell, *J. Amer. Chem. Soc.*, **93**, 2567 (1971).
(52) An isomeric structure, *N*-hydroxydiphenylmethoxyacetanilide, also fits the data but is rejected on mechanistic grounds, and is inconsistent with the other products **13**–**15** formed in these reactions.
(53) This extraordinary low-field absorption is due to H-6 on the 2,4-dimethoxyaniline ring of **14**, evidently strongly deshielded by the amide carbonyl group. The same effect is observed for H-6 of *o*-acetanisidide (i): "Sadtler Standard Spectra," Sadtler Research



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Laboratories, Inc., Philadelphia, Pa., 1966, NMR Spectrum No. 11340.
(54) T. Sheradsky, U. Reichman, and M. Frankel, *J. Org. Chem.*, **33**, 3619 (1968).
(55) All melting points were measured on a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord Model 137 NaCl spectrophotometer. The nuclear magnetic resonance spectra were measured on a Jeol MH-100 or a Varian Model A-60, using tetramethylsilane as an internal reference. The vapor phase chromatographic measurements

were obtained using a Varian Aerograph Series 1200 chromatograph equipped with a flame ionization detector or a Varian Aerograph Model 90-P chromatograph equipped with a thermal conductivity detector. The mass spectra were determined by the Morgan-Schaffer Corp., Montreal, Quebec, Canada, on a Hitachi Perkin-Elmer RMU-6D spectrometer. Elemental analyses were obtained from Galbraith Laboratories, Inc., Knoxville, Tenn., or from Meade Microanalytical Laboratory, Amherst, Mass. The chloroform used in each experiment was distilled from barium oxide, passed through a basic alumina column, and dried over magnesium sulfate just prior to use, except as noted. Benzene and hexane were distilled from phosphorus pentoxide prior to use. Dimethylformamide (DMF) was shaken for 3 days over phosphorus pentoxide and 5 g of fresh phosphorus pentoxide was added each day. The DMF was then decanted, shaken for 5 hr over potassium hydroxide to neutralize any formic acid, decanted again, and distilled from Type 4A molecular sieves under a stream of nitrogen at reduced pressure (bp 56°). All transferring of DMF was done under a nitrogen atmosphere. Acetonitrile was distilled from phosphorus pentoxide directly into the reaction vessel.

(56) J. T. Hays, E. H. de Butts, and H. L. Young, J. Org. Chem., 32, 153 (1967).
(57) R. E. Lutz and M. R. Lytton, J. Org. Chem., 2, 68 (1937).
(58) F. J. Alway and A. B. Walker, Chem. Ber., 36, 2312 (1903).
(59) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1965, p 126.
(60) J. A. Attaway, R. W. Wolford, G. Alberding, and G. Edwards, Anal. Chem., 34, 671 (1962).
(61) The small quantity of this material, which may be a mixture of diphenylaceto-p-toluidide and benzil-p-toluidide, prevented further work.
(62) M. Halmann, J. Chem. Soc., 305 (1959).
(63) W. Kirmse and L. Horner, Chem. Ber., 89, 2759 (1956).
(64) "Sadtler Standard Spectra," Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1966, Spectrum No. 23833.
(65) "Handbook of Chemistry and Physics," 45th ed, R. C. Weast, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1964, p C-93.
(66) Reference 65, p C-591.
(67) P. A. Petyunin, P. A. Bezuglyi, and N. G. Panferova, Khim.-Farm. Zh., 2, 19 (1968); Chem. Abstr., 69, 106404z (1968).
(68) Sadtler IR Spectrum No. 6649; cf. ref 64.
(69) We gratefully acknowledge Mr. Stuart Plotkin's synthesis of this authentic sample.

Addition of Nitrosyl Chloride to Trimethylsilyl Enol Ethers. A New General Method for Nitrosation of Carbonyl Compounds[1]

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Addition of nitrosyl chloride to trimethylsilyl enol ethers 1 in dichloromethane at −10 to −15° gives good yields of α-oximinocarbonyl compounds 2. In the case of aldehydes, these initial products are unstable, but may be trapped by hydroxylamine as the glyoximes 3. The silyl ether of cyclohexanone **1h** yields 2,6-dioximinocyclohexanone (4) upon treatment with excess NOCl, whereas with 1 equiv of NOCl the unstable nitroso dimer 5 is formed. Similarly, the silyl derivatives of esters, lactones, and carboxylic acids are directly converted to α-oximino esters and acids. The results are explained by initial addition of NOCl to the silyl enol ether double bond, followed by elimination of trimethylsilyl chloride and tautomerization to the oxime.

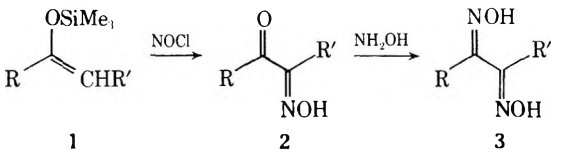
Trimethylsilyl enol ethers are now readily available from ketones or aldehydes,[2a] and their utility as synthetic equivalents of enols[3,4] has recently been demonstrated. Similar derivatives of esters[2b] and acids[2c] have also recently become available. Our interest in the regiospecific and stereospecific introduction of nitrogen functions into organic molecules by additions to double bonds[5] prompted us to study the reaction of silyl enol ethers with nitrosyl chloride. We have found that the reaction is instantaneous at −10 to −15° in dichloromethane and affords good yields of α-oximino carbonyl compounds in a high state of purity.

Results

When the ketone-derived trimethylsilyl enol ethers **1a–c** were treated with excess NOCl for <1 min, good yields of the corresponding α-oximino ketones **2a–c** were formed (Table I). The only by-products were the corresponding ketones, presumably from hydrolysis of **1**. Purification[6] of the NOCl (by removal of HCl, H_2O, and NO_2) led to no improvement in yields or reduction of hydrolysis. If the reaction time was extended to several hours, different products were formed. For instance, when the reaction mixture from **1a** was allowed to stand for 18 hr at −20°, α-oximinophenacyl chloride (**2g**, R = Ph; R′ = Cl) was obtained in 48% yield. Acetophenone (14%) and benzoic acid (21%) were identified as by-products in this reaction. The formation of **2g** is not surprising, since it can also be prepared from acetophenone and excess NOCl in 24.5% yield.[7]

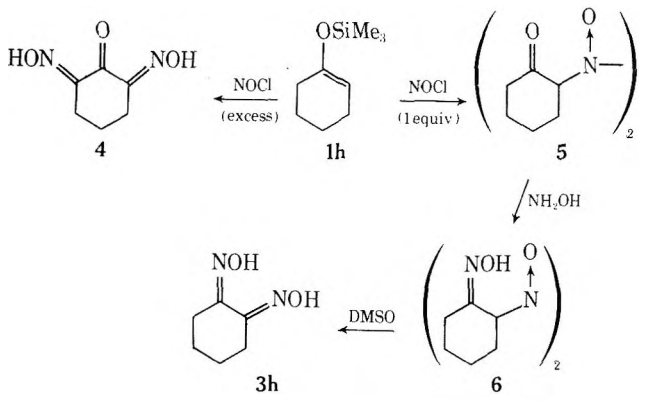
Table I
Oximes from Trimethylsilyl Enol Ethers 1 and Nitrosyl Chloride

Silyl ether	R	R′	Product	Yield, %
1a	Ph	H	**2a**	82
1b	Ph	Me	**2b**	83.5
1c	Et	Me	**2c**	72
1d	H	Et	**3d**	66
1e	H	$PhCH_2$	**3e**	77.5
1f	H	n-C_8H_{17}	**2a**	63



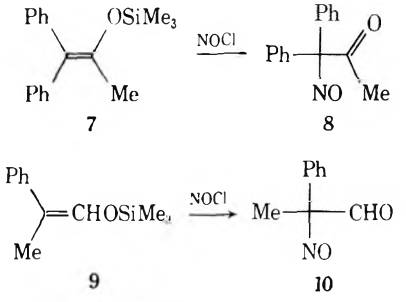
The reaction of the silyl ether of cyclohexanone (**1h**) is somewhat more complicated. With excess NOCl, 2,6-dioximinocyclohexanone (**4**)[8] was obtained in 93% yield. By contrast, treatment with 1 equiv of NOCl yielded the unstable nitroso dimer **5** in quantitative yield. Reaction of the latter with hydroxylamine afforded dimer **6**, which dissociated and tautomerized to dioxime **3h**[9] upon dissolution in dimethyl sulfoxide (DMSO). The establishment of structures **5** and **6** rests upon spectral data and upon the isolation and identification of **3h** (see Experimental Section).

When silyl ethers of aldehydes (**1d–f**) were treated with NOCl, the initially formed α-oximino aldehydes **2d–f** were



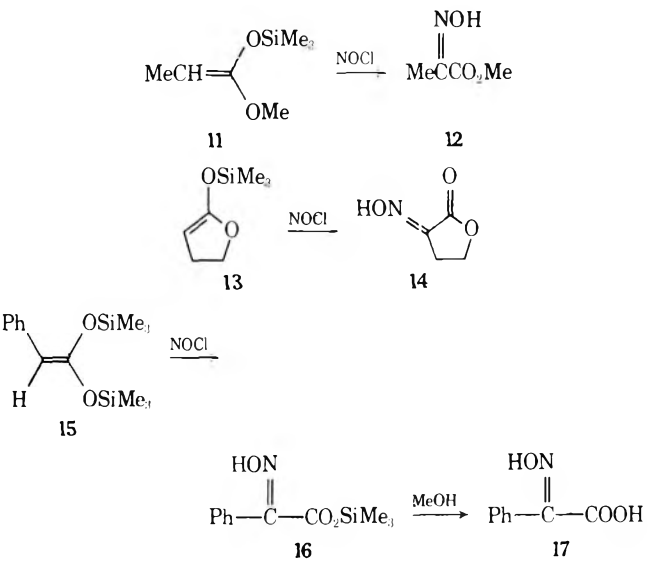
too unstable to be isolated, and polymerized upon warming to ambient temperature. However, they could be trapped in good yield (Table I) as the glyoximes 3d-f by direct addition of a solution of hydroxylamine to the cold reaction mixture. This provides a facile two-step synthesis of this type of compound from simple aldehydes.

Reaction of NOCl with silyl ethers 7 and 9 gave the corresponding α-nitroso compounds 8 and 10. The initial so-



lution containing 8 was intensely green in color, and rapidly faded to pale yellow as 8 dimerized. The nmr of the crude product indicated an approximately 2:1 ratio of 1,1-diphenylacetone to nitroso dimer (See Experimental Section). No attempt was made to separate them. The low yield of 8 here may be largely due to steric problems. Compound 10 produced a deep blue solution, and was apparently quite stable at 0° or lower, slowly dimerizing at room temperature. Various attempts at purification yielded acetophenone as the only isolable compound.

To test the generality of the reaction and its applicability to acid derivatives the nitrosation of some representative ketene alkyl trimethylsilyl[2b] and bis(trimethylsilyl) acetals[2c] was studied. The acetal 11 derived from methyl propionate produced α-oximino ester 12[10] in 63.5% yield,

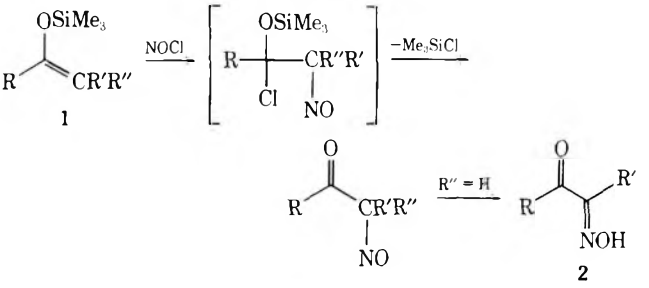


while 13 derived from α-butyrolactone gave 50.5% α-oximino-γ-butyrolactone (14), an important intermediate in the synthesis of methionine.[11] With the bis(trimethylsilyl) acetal 15, the initial product 16 was not isolated, but was hydrolyzed directly by treatment with methanol to α-oximinophenylacetic acid (17)[12] in 68.3% yield.

Discussion

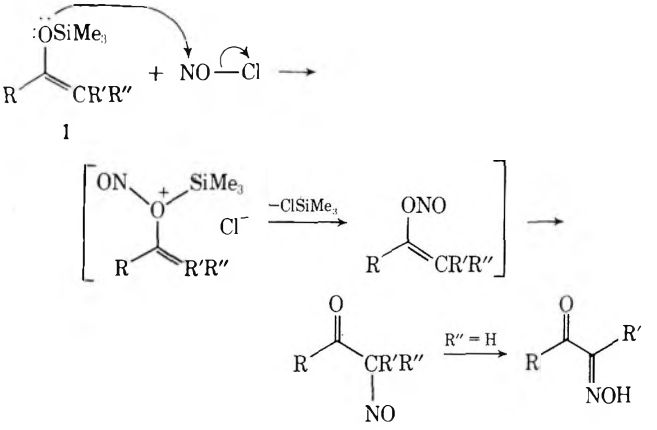
The formation of α-oximino carbonyl products from the silyl ethers could involve initial addition of NOCl to the enol ether double bond (Scheme I). The initial adduct

Scheme I

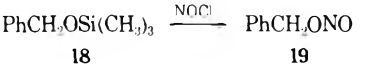


then rapidly eliminates trimethylsilyl chloride and tautomerization to the oxime occurs when an α hydrogen is present. An alternative explanation involves nucleophilic attack of the silyl ether oxygen on NOCl (Scheme II), fol-

Scheme II



lowed by rearrangement of the intermediate vinyl nitrite. The fact that such a reaction might be possible was shown by reaction of the silyl ether[13] of benzyl alcohol (18) with nitrosyl chloride. After 3 hr at room temperature, nmr indicated a 77% conversion to benzyl nitrite (19).[14] How-



ever, the slower rate of this reaction as compared to that of the enol ethers, previous results on additions to silyl enol ethers,[3,4] and the known ease of addition of NOCl to double bonds,[15] make Scheme I more reasonable.

α-Oximino ketones can be readily prepared from ketones under a variety of conditions.[16] The new method is superior in cases where direct nitrosation of the ketone gives (1) low yields, (2) mixtures of products, or (3) only one of two possible isomers (see ref 16 for numerous examples). The real utility of our procedure lies in the nitrosation of aldehydes, since there appears to be no report in the literature of conventional nitrosation procedures.[16] This does not seem surprising in view of the instability noted for oximino aldehydes 2d-f. It was necessary to trap

these products and it is reasonable to assume that other methods of trapping these unstable species can be developed. Since α-oximino ketones have served in the preparation of a large number of difficultly obtainable compounds,[16] the scope of these reactions can now be easily extended to aldehyde derivatives as well. Derivatives of α-keto aldehydes have been obtained previously only through multistep syntheses.[17]

α-Oximino acids and esters, which are important intermediates in the synthesis of α-amino acids and esters, have been available in the past by nitrosation of substituted β-keto esters, malonic acids, and malonic esters.[16] These oximes also provide routes to α-oxo acids and esters, to nitriles, and to hydroxamic acids.[12] The present procedure for their preparation appears to be more economical and desirable, since these α-oximino compounds are attainable directly, in two simple steps and without purification of the intermediate silyl acetals, from the corresponding acids or esters. The entire reaction sequence requires about 2-3 hr. The lower yields of oximes from ketene acetals than from enol ethers are probably a reflection of increased sensitivity of the former toward hydrolysis.

Experimental Section

Melting points (taken on a Fisher-Johns block) and boiling points are uncorrected. Infrared spectra were obtained using a Perkin-Elmer 457 instrument. Nmr spectra were recorded on a Varian A-60A spectrometer with TMS as an internal standard. Mass spectra were taken on a Varian MAT CH-5 instrument.

Trimethylsilyl Enol Ethers. All trimethylsilyl ethers were prepared by the method of House.[2a] Ethers **1a**,[2a] **1b**,[4] **1d**,[2a] and **1h**[2a] have been described previously. The following new silyl ethers were prepared.

1c from 3-Pentanone. Nmr indicated the reaction to be complete after 11.5 hr. Normal work-up[2a] led to partial hydrolysis as evidenced by formation of starting ketone and trimethylsilyl alcohol. Purification by distillation was difficult owing to the high volatility of **1c**, which codistilled with starting ketone. Pure **1c**, along with several fractions containing **1c** and ketone, was obtained in approximately 30% yield as a mixture of *E* and *Z* isomers, bp 130–135° at atmospheric pressure. No attempt was made to improve the yield: ν (neat) 1680 cm^{-1}; nmr (CCl_4) τ 9.84 (s, 9 H), 8.98 and 9.00 (2 t, $J \cong 7$ Hz, 3 H), 8.38–8.62 (m, 3 H), 7.74–P.25 (m, 2 H), 5.30–5.77 (m, 1 H).

1e from Hydrocinnamaldehyde. The time required for complete reaction was 3 hr. **1e** was obtained as a 2:3 mixture of *E* and *Z* isomers: bp 98–102° (5.2 mm); 83.3% yield; ν (neat) 1655 cm^{-1}; nmr ($CDCl_3$) τ 9.83 (s, 9 H), 6.75 (d of d, J = 7.5 and 1.0 Hz, *E* isomer), and 6.54 (d of d, J = 7.5 and 1.50 Hz, *Z* isomer), total of 2 H, 5.27 (d of t, J = 7.5 and 6.0 Hz, *Z*) and 4.79 (d to (d of t, J = 7.5 and 12.0 Hz, *E*), total of 1 H, 3.50–3.75 (m, 1 H), 2.75 (s, 5 H).

1f from Decanal. Reaction time was 4 hr. **1f** was obtained as a 2:3 mixture of *E* and *Z* isomers: bp 115–125° (~15 mm); 64.4% yield; ν (neat) 1655 cm^{-1}; nmr ($CDCl_3$) τ 9.82 (s, 9 H), 9.12 (t, J = 4.5 Hz, 3 H), 8.69 (m, 12 H), 8.07 (m, 2 H), 5.33–5.68 (d of t, J = 7.0 and 5.5 Hz, *Z*) and 4.75–5.22 (d of t, J = 7.0 and 12.0 Hz, *E*), total of 1 H, 3.64–3.93 (m, 1 H).

7 from 1,1-Diphenylacetone. Reaction time was 18 hr. **7** was obtained in 70% yield: bp 115–120° (0.5 mm); ν (neat) 1660 and 1625 cm^{-1}; nmr ($CDCl_3$) τ 9.85 (s, 9), 7.99 (s, 3), 2.64 (m, 5), 2.25–2.50 (m, 3), 1.97–2.18 (m, 2).

9 from 2-Phenylpropionaldehyde. Reaction time was 1.5 hr. **9** was obtained in 91% yield as a 3:1 mixture of *E* and Z isomers: bp 100–105° (7.5 mm); ν (neat) 1645 cm^{-1}; nmr ($CDCl_3$) τ 9.84 and 9.79 (2 s, 9 H), 8.12 and 8.02 (2 d, J = 1.5 Hz, *Z* and *E* 3 H), 3.58 and 3.28 (2 q, J = 1.5 Hz, *Z* and *E*, 1 H), 2.50–2.87 (m) and 2.20–2.42 (m, *Z* isomer), total of 5 H.

Ketene Alkyl Trimethylsilyl and Bis(trimethylsilyl) Acetals. The silyl acetals were prepared according to literature procedures[2b,c] and were used without purification for the subsequent reaction. Acetals **11**[2b] and **15**[2c] were previously described, while **13** was obtained from γ-butyrolactone in 90.6% yield: ν (neat) 1685 cm^{-1}; nmr ($CDCl_3$) τ 9.73 (s, 9 H), 7.38 (d of t, J = 2.0 and 9.0 Hz, 2 H), 6.30 (t, J = 2.0 Hz, 1 H), 5.68 (t, J = 9.0 Hz, 2 H).

General Procedure for Reaction of Silyl Ethers with NOCl. Dichloromethane solutions (10–15 ml) of nitrosyl chloride were prepared at −10 to −15° (Dry Ice–carbon tetrachloride bath) according to the procedure of Hassner and Heathcock.[18] A dichloromethane solution of the silyl ether was added, and the mixture was stirred for ca. 30 sec. Slow concentration of solvent *in vacuo* at ~0° often led to crystallization of relatively pure oxime **2**. In the case of aldehydes, a slight excess of hydroxylamine solution[9] was added directly to the cold reaction mixture. The mixture was then allowed to warm to room temperature, stirred for about 1 hr, washed with water, and dried (Na_2SO_4), and the solvent was removed to give crude dioxime **3**. Variations in the procedure and identification of products are described below.

α-Oximinoacetophenone (2a). Silyl ether **1a** (5 mmol) gave 608 mg (82%) of **2a** as pale yellow crystals, displaying infrared, nmr, and melting point properties identical with those published in Sadtler.

α-Oximinopropiophenone (2b). Silyl ether **1b** (10 mmol) produced 1.28 g of **2b** as colorless crystals: mp 112–113° (lit.[19] mp 111–113°); ν (KBr) 3240, 1660, 1650, 1190, 1020, 1005, 905 cm^{-1}; nmr (acetone-d_6) τ 7.85 (s, 3 H), 2.32–2.64 (m, 3 H), 1.88–2.11 (m, 2 H), −1.29 (br s, 1 H); mass spectrum *m/e* (rel abundance) 163 (41.2), 118 (7.6), 105 (100). Chromatography of the filtrate on alumina gave 126 mg of propiophenone (9.5%) and an additional 80 mg of **2b** (total yield 83.5%)

2-Oximino-3-pentanone (2c). Silyl ether **1c** (9.4 mmol) gave 775 mg (72%) of **2c** as colorless crystals: mp 70–71° (lit.[20] mp 69–72°); ν (KBr) 3300, 1665, 1020 cm^{-1}; nmr ($CDCl_3$) τ 8.87 (t, J = 7 Hz, 3 H), 7.94 (s, 3 H), 7.12 (q, J = 7 Hz, 2 H), 0.23 (br s, 1 H); mass spectrum *m/e* (rel abundance) 115 (9.1), 98 (10.3), 87 (10.7), 58 (14.7), 57 (100), 42 (34.9).

Ethyl Glyoxime (3d). Silyl ether **1d** (3.47 mmol) gave 267 mg (66%) of **3d** as a colorless solid: mp 127–128° (lit.[17a] mp 129°); ν (KBr) 3240 with tailing to about 2500, 1425, 955, 825 cm^{-1}; nmr (DMSO-d_6) τ 8.96 (t, J = 7 Hz, 3 H), 7.47 (q, J = 7 Hz, 2 H), 2.36 (s, 1 H), −1.43 (br s, 2 H); mass spectrum *m/e* (rel abundance) 116 (28.5), 99 (100), 71 (28.8), 55 (29.7), 54 (46.4), 44 (73.3).

Benzyl Glyoxime (3e). Silyl ether **1e** (5 mmol) gave 690 mg (77.5%) of **3e** as a colorless solid: mp 160–161.5° (lit.[17b] mp 163°); ν (KBr) 3290, 3050, 2930, 1430, 970, 940, 875, 755, 710 cm^{-1}; nmr (DMSO-d_6) τ 6.03 (s, 2 H), 2.75 (br s, 5 H), 2.20 (s, 1 H), −1.08 (br s, 1 H), −1.32 (br s, 1 H); mass spectrum *m/e* (rel abundance) 178 (68.8), 161 (11.4), 144 (31.1), 143 (18.2), 117 (71.8), 91 (100).

***n*-Octyl Glyoxime (3f).** Silyl ether **1f** (10 mmol) gave 1.26 g (63.0%) of **3f** as a colorless solid (from acetone–hexane): mp 117–118°; ν (KBr) 3280, 3100, 1465, 1430, 965 cm^{-1}; nmr (DMSO-d_6) τ 9.13 (t, J = 4.5 Hz, 3 H), 8.72 (m, 12 H), 7.50 (m, 2 H), 2.35 (s, 1 H), −1.45 (br s, 2 H); mass spectrum *m/e* (rel abundance) 200 (9.7), 183 (100), 169 (21.3), 112 (35.0), 102 (71.9), 99 (12.2), 98 (73.3), 85 (16.1), 71 (16.7), 69 (25.6), 57 (22.3), 55 (75.2), 43 (59.7).

Reaction of Silyl Ether 1h with NOCl. A. Silyl ether **1h** (10 mmol) under the general reaction conditions gave 1.45 g (93%) of **4** as an unstable pale yellow solid which displayed properties identical with those reported:[8] ν (KBr) 3160, 3070, 1700, 1570, 1435, 1415, 1105, 900 cm^{-1}; nmr (DMSO-d_6) τ 8.23 (p, J = 6.5 Hz, 2 H), 7.25 (t, J = 6.5 Hz, 4 H), 0.92 (br s, 2 H); mass spectrum *m/e* (rel abundance) 156 (100), 139 (17.8), 127 (11.3), 126 (6.5), 111 (37.1), 82 (13.7), 80 (12.1).

B. Alternatively, **1h** (5 mmol) was dissolved in 10 ml of CH_2Cl_2 and placed in a Dry Ice–CCl_4 bath, and 3.5 ml of a NOCl solution[18] was added and stirred for 10 min. Removal of solvent *in vacuo* gave 634 mg (100%) of **5** as a colorless solid, ν (KBr) 1725, 1240, 1210, 1195, 850 cm^{-1}. Since dimer **5** turned yellow and decomposed fairly rapidly on standing, it was treated with 1 equiv of a hydroxylamine solution at room temperature overnight, then placed in the refrigerator for 2 hr. Filtration gave 256 mg (35.6%) of **6** as a colorless solid: ν (KBr) 3280, 1140, 1385, 1330, 1195, 980, 955, 870 cm^{-1}; nmr ($DMSOd_6$) τ 8.70–6.90 (series of m, >18 H), 4.20–4.58 (m, 2 H), −0.90 (br s, 2 H), integration of the upfield multiplet was not accurate owing to partial dissociation (see below); mass spectrum *m/e* (rel abundance) no M^+, 224 (5.4), 207 (2.2), 204 (2.2), 187 (4.0), 142 (21.3), 125 (5.3), 112 (56.7), 94 (34.7), 81 (26.7), 79 (21.3), 67 (100). The filtrate from **6** yielded only polymer on evaporation. Monitoring of the nmr sample of **6** showed complete conversion to 1,2-dioximinocyclohexane (**3h**) after 3 days. The nmr pattern was identical with Sadtler's but shifted somewhat owing to the different solvent: nmr (DMSO-d_6) τ 8.44 (m, 4 H), 7.48 (m, 4 Hz, −1.12 (br s, 2 H). The sample was poured into water, and precipitated **3h** was filtered and identified by comparison of its ir spectrum with Sadtler's. Mass spectrum: *m/e* (rel abundance) 142 (74.2), 125 (15.6), 107 (23.3), 95 (19.0),

94 (16.4), 80 (22.4), 68 (24.2), 67 (70.8), 66 (23.3), 55 (50.0), 41 (100).

Reaction of Silyl Ether 7 with NOCl. Silyl ether 7 (5 mmol) was treated with excess NOCl according to the general procedure to give a deep green solution. While excess NOCl was removed *in vacuo* at 0°, the solution faded to light yellow. Removal of solvent *in vacuo* gave a yellow oil, ν (neat) 1720, 1660, 1285 cm^{-1}. Nmr indicated this to be a 2:1 mixture of 1,1-diphenylacetone and the nitroso dimer [τ 7.62 (s)].

Reaction of Silyl Ether 9 with NOCl. A. Silyl ether 9 (5 mmol) was treated with excess NOCl according to the general procedure for ketones and the solvent was removed *in vacuo* to give 0.83 g of **10** as an intensely blue oil which, upon standing for 30 sec, underwent an exothermic reaction to give the dimer as an orange oil: ν (neat) 1735, 1550, 1495, 1450, 1290, 770, 705 cm^{-1}; nmr ($CDCl_3$) τ 8.02 (s, 3), 2.52 (br s, 5), 0.50 (s, 1). No purification was achieved by chromatography on silica gel–ether, while treatment with 1 equiv of hydroxylamine for 1 hr led to a polymer.

B. The reaction was repeated according to the general procedure for silyl ethers **1d–f**, to yield a yellow oil (largely acetophenone by nmr). Chromatography on alumina–ether gave 365 mg (54.5%) of acetophenone as the only identifiable product.

C. The reaction was repeated as in A, except that the excess NOCl was removed *in vacuo* at 0° to give a deep blue solution, ν (CH_2Cl_2) 1720 and 1570 cm^{-1}. Upon warming to room temperature, the solution slowly turned yellow. Removal of solvent *in vacuo* gave a yellow oil, the nmr of which indicated the presence of the dimer (as in A) as the major product, along with acetophenone and polymer.

Reaction of Acetal 11 with NOCl. Acetal **11** (8.33 mmol), under the general reaction conditions, gave 620 mg (63.5%) of methyl α-oximinopropionate (**12**) as colorless crystals: mp 69° (lit.[10] mp 68–69°); ν (KBr) 3200, 1725, 1440, 1315, 1200, 1160, 1035, 1000, 845, 770, and 750 cm^{-1}; nmr ($CDCl_3$) τ 7.86 (s, 3 H), 6.10 (s, 3 H), −0.20 (br s, 1 H); mass spectrum *m/e* (rel abundance) 117 (71.3), 86 (33.4), 85 (100), 59 (77.3), 58 (95.5), 57 (50.0).

Reaction of Acetal 13 with NOCl. Acetal **13** (20 mmol) gave 1.16 g (50.5%) of α-oximino-γ-butyrolactone (**14**) as a pale yellow solid: mp 184–186° (lit.[11] mp 183–185°); ν (KBr) 3250, 1745, 1660, 1390, 1295, 1265, 1000 cm^{-1}; nmr ($CDCl_3$) τ 7.00 (t, J = 7.0 Hz, 2 H), 5.52 (t, J = 7.0 Hz, 2 H), −0.25 (br s, 1 H); mass spectrum *m/e* (rel abundance) 115 (100), 114 (41.3), 97 (54.4), 85 (59.8), 83 (15.2), 70 (13.6), 57 (68.5), 54 (76.1). The filtrate from **14** was a deep green in color. Upon standing overnight, the color had changed to yellow-orange. Removal of the solvent *in vacuo* gave 1.0 g of orange oil. Nmr indicated that this oil contained γ-butyrolactone, polymer, and perhaps a small amount of nitroso dimer.

Reaction of Acetal 15 with NOCl. Acetal **15** (20 mmol) gave a red-orange oil. This was dissolved in chloroform, excess methanol was added, and after 15 min the solvent was removed *in vacuo* to give 3.65 g of red oil. Repeated fractional crystallization from chloroform gave 2.25 g (68.3%) of α-oximinophenylacetic acid (**17**) as colorless needles, mp 147° dec (lit.[12] mp 144–145° dec). The residue from the recrystallizations was dissolved in ether and extracted twice with 5% aqueous sodium bicarbonate. The ether layer yielded 638 mg of a red polymeric oil. Acidification and reextraction of the bicarbonate layer gave 445 mg (16.3%) of phenylacetic acid.

Reaction of Benzyloxytrimethysilane (18) with NOCl. A solution of **18** (5 mmol) and NOCl was stirred at room temperature and monitored by nmr. After 3 hr, the solvent was removed *in vacuo* to give a pale greenish oil which displayed infrared absorptions identical with those reported[14] for benzyl nitrite. Nmr indicated benzyl nitrite (77%), **18** (10%), and benzyl alcohol (13.2%). A similar reaction with benzyl alcohol (3 hr at room temperature) led to a 60% conversion to benzaldehyde.

Registry No.—**1a**, 13735-81-4; **1b**, 37471-46-8; (*E*)-**1c**, 51425-53-7; (*Z*)-**1c**, 51425-54-8; **1d**, 6651-33-8; (*E*)-**1e**, 51425-55-9; (*Z*)-**1e**, 51425-56-0; (*E*)-**1f**, 51425-57-1; (*Z*)-**1f**, 51425-58-2; **2b**, 119-51-7; **2c**, 32818-79-4; **3d**, 51425-59-3; **3e**, 4732-56-3; **3f**, 51425-60-6; **5**, 51425-61-7; **6**, 51425-62-8; **7**, 51425-63-9; (*E*)-**9**, 51425-64-0; (*Z*)-**9**, 51425-65-1; **11**, 34880-70-1; **12**, 5634-53-7; **13**, 51425-66-2; **14**, 5400-68-0; **15**, 31491-21-1; **18**, 14642-79-6; 3-pentanone, 96-22-0; hydrocinnamaldehyde, 104-53-0; decanal, 112-31-2; 1,1-diphenylacetone, 781-35-1; 2-phenylpropionaldehyde, 93-53-8; γ-butyrolactone, 96-48-0; nitrosyl chloride, 2696-92-6.

References and Notes

(1) Synthetic Methods. VI. For paper V see ref 4.
(2) (a) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969); (b) C. Ainsworth, F. Chen, and Y.-N. Kuo, *J. Organometal. Chem.*, **46**, 59 (1972); (c) C. Ainsworth and Y.-N. Kuo, *ibid.*, **46**, 73 (1972).
(3) S. Murai, Y. Kuroki, T. Aya, N. Sonoda, and S. Tsutsumi, *J. Chem. Soc., Chem. Commun.*, 741 (1972); S. Murai, Y. Kuroki, K. Hasegawa, and S. Tsutsumi, *ibid.*, 946 (1972); Y. Kuroki, S. Murai, N. Sonoda, and S. Tsutsumi, *Organometal. Chem. Syn.*, **1**, 465 (1972).
(4) J. K. Rasmussen and A. Hassner, *Tetrahedron Lett.*, 2783 (1973); R. H. Reuss and A. Hassner, *J. Org. Chem.*, **39**, 1785 (1974).
(5) (a) A. Terada and A. Hassner, *Bull. Chem. Soc. Jap.*, **40**, 1937 (1967), and references sited therein; (b) J. E. Kropp, A. Hassner, and G. J. Kent, *Chem. Commun.*, 906 (1968); (c) A. Hassner, J. E. Kropp, and G. J. Kent, *J. Org. Chem.*, **34**, 2628 (1969); (d) A. Hassner, R. P. Hoblitt, C. Heathcock, J. E. Kropp, and M. Lorber, *J. Amer. Chem. Soc.*, **92**, 1326 (1970); (e) A. Hassner, *Accounts Chem. Res.*, **4**, 9 (1971); (f) J. E. Galle and A. Hassner, *J. Amer. Chem. Soc.*, **94**, 3930 (1972).
(6) E. G. Bozzi, C. -Y. Shiue, and L. B. Clapp, *J. Org. Chem.*, **38**, 56 (1973).
(7) H. Rheinboldt and O. Schmitz-Dumont, *Justus Liebigs Ann. Chem.*, **444**, 113 (1925).
(8) W. Borsche, *Chem. Zentr.*, II, 1549 (1909).
(9) T. A. Geissman and M. J. Schlatter, *J. Org. Chem.*, **11**, 771 (1946).
(10) R. Loquin, *Bull Soc. Chem. Fr.*, **31**, 1068 (1904).
(11) H. R. Snyder, J. H. Andreen, G. W. Cannon, and C. F. Peters, *J. Amer. Chem. Soc.*, **64**, 2082 (1942).
(12) A. Ahmad and I. D. Spenser, *Can. J. Chem.*, **39**, 1340 (1961).
(13) The authors thank Dr. A. H. Andrist for a sample of this compound.
(14) P. Gray, P. Rathbone, and A. Williams, *J. Chem. Soc.*, 3932 (1960).
(15) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 613.
(16) O. Touster, *Org. React.*, **7**, 327 (1953).
(17) (a) W. Reppe, *Justus Liebigs Ann. Chem.*, **596**, 38 (1955); (b) W. Bradley and J. K. Eaton, *J. Chem. Soc.*, 1913 (1937); (c) F. Weygand and H. J. Bestmann in "Newer Methods of Preparative Organic Chemistry," Vol. III, Academic Press, New York, N. Y., 1964, p 460.
(18) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964).
(19) W. Hartung and F. Crossley, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 363.
(20) E. Janecke, *Chem. Ber.*, **32**, 1095 (1899).

Evidence for Different Addition Mechanisms in the Bromochlorination of 3-*tert*-Butylcyclohexene with Bromine Chloride and with Monopyridinebromine(I) Chloride

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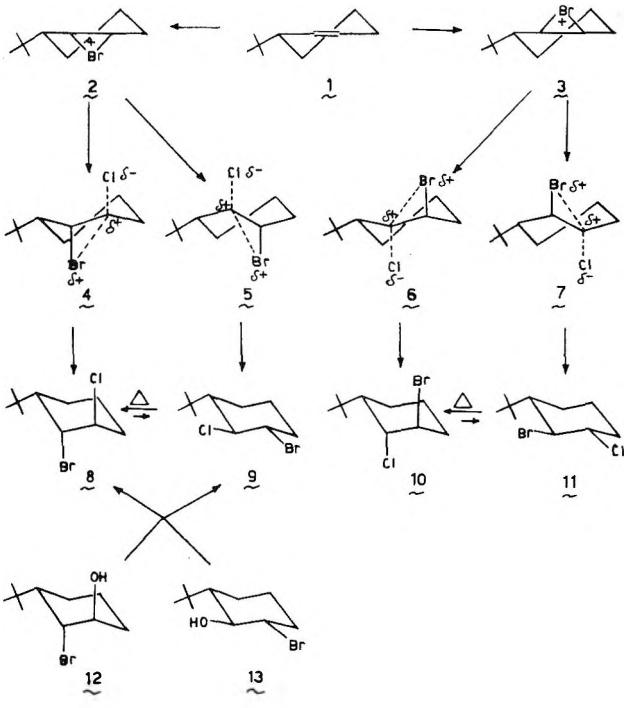
The bromochlorination of 3-*tert*-butylcyclohexene has been investigated in several solvents and with different halogenating reagents. The distribution of the four possible trans bromochlorides, which has been determined through a mixed glpc–ir method of analysis, is in accordance with ionic two-step mechanisms. The stereoselectivity of the electrophilic attack by bromine ranges between 64 and 79% anti to the *tert*-butyl group with preformed bromine chloride, but practically disappears when monopyridinebromine(I) chloride in chloroform is used as the reagent. The nucleophilic attack is directed preferentially at C_1 on both of the bridged intermediates formed in the electrophilic step; however, while the regioselectivity of the attack by chloride syn to the *tert*-butyl group is constant under all examined conditions, that of the anti attack is strongly dependent both on the solvent and on the reagent. The results obtained with bromine chloride are consistent with an addition mechanism involving the rate- and product-determining formation of epibromonium ion intermediates; those found with pyridinebromine chloride suggest instead that the steric course of the addition be controlled mainly during the nucleophilic rather than during the electrophilic step.

Previous work[1-3] on bromine addition to cyclohexene derivatives in low-polarity nonprotic solvents had shown a marked influence of the ring substituents, the solvent, and the brominating agent on the steric course of the halogenation of both nonconjugated and conjugated substrates. While the latter compounds can give both anti and syn dibromo adducts in ratios depending on the reaction conditions,[2] the former ones undergo exclusive anti addition, affording mixtures of diaxial and diequatorial trans dibromides. It was also shown[1] that alkyl substituents in the allylic position favor the formation of the diequatorial adducts, this effect being, however, markedly reduced by a basic solvent like ethyl ether or by the use of pyridine perbromide and pyridinium hydrobromide perbromide as the brominating agents, or even by the mere presence of tertiary amines in the reaction medium. The product distribution of the addition of free bromine in nondonor solvents was rationalized on the basis of the usual bromination mechanism,[4] involving the rate-determining formation of epibromonium ion intermediates followed by a fast nucleophilic anti attack by bromide (or tribromide) ions to give the dibromo adducts. The decrease in the ratio of diequatorial to diaxial dibromides observed when bromine is coordinated by a base was attributed[1] to a change in the rate-determining step of the reaction, which would instead occur through a fast, reversible electrophilic step followed by a slow nucleophilic attack on the intermediates. Under these conditions both the stereo- and the regioselectivity of the addition would be determined mostly by substituent effects during the nucleophilic rather than during the electrophilic step. This type of behavior was actually observed for electrophilic additions to cyclohexene derivatives of several nonsymmetrical reagents such as NBS–H_2O (but not preformed BrOH),[5,6] IOH,[7] IN_3,[7] IOAc,[8] and $Hg(OAc)_2$,[9] which permit us to distinguish between the direction of the electrophilic and that of the nucleophilic attack, but, of course, this approach cannot be directly applied to the addition of bromine, for which only indirect evidence based on the analogy with other reactions could be given.[1,3] The possibility of a mechanism of the latter type has been, however, recently inferred[10] from kinetic evidence for the bromination of acyclic alkenes in trifluoroacetic acid. In order to obtain more significant information about the halogenation mechanisms of cycloalkenes in low-polarity nonprotic solvents, we undertook a study of the addition of an intehalogen, bromine chloride, and chose 3-*tert*-butylcyclohexene (**1**) as the first substrate, since previous work had shown[5,11,12] that an allylic *tert*-butyl group exerts a strong directive effect on both the electrophilic and the nucleophilic step of the additions.

Results

The bromochlorination of 3-*tert*-butylcyclohexene (**1**) was performed with a variety of reagents, including bromine chloride preformed from molecular bromine and chlorine, *N*-bromosuccinimide (NBS) in the presence of hydrogen chloride, and monopyridinebromine(I) chloride. Mixtures of all expected trans bromochlorides **8**–**11** (Scheme I) were obtained in every case, appreciable

Scheme I



amounts of trans dibromides and trans dichlorides being formed only with the first reagent. Column chromatogra-

Table I
Products Distribution, Stereoselectivity, and Regioselectivity Found in the Bromochlorinations of 1

Bromochlorinating reagent (solvent)	Ratio of bromochlorides to dibromides plus dichlorides	Distribution of bromochlorides, % 8	9	10	11	Stereoselectivity of the electrophilic attack syn/anti ratio	Regioselectivity of the nucleophilic attack C_1/C_2 ratio Cis intermediate	Trans intermediate
BrCl (CCl_4)	90:10	16	5	13	66	21:79	76:24	84:16
BrCl ($CHCl_3$)	80:20	18	15	11	56	33:67	55:45	84:16
BrCl (CH_2Cl_2)	80:20	20	16	11	53	36:64	56:44	83:17
BrCl (C_6H_6)	85:15	18	15	10	57	33:67	55:45	85:15
BrCl (Et_2O)	90:10	21	7	12	60	28:72	75:25	83:17
BrCl + HCl (CH_2Cl_2)	85:15	22	9	12	57	31:69	71:29	83:17
NBS + HCl (CH_2Cl_2)	95:5	22	8	12	58	30:70	73:27	83:17
C_5H_5NBrCl (CCl_4)	>95:<5	38	2	10	50	40:60	95:5	83:17
C_5H_5NBrCl ($CHCl_3$)	>95:<5	50	2	8	40	52:48	96:4	83:17

phy of these mixtures allowed isolation of large amounts of pure **11**, while it was not possible to separate **8** and **10** from each other nor to isolate pure **9**. Thermal equilibration of **11** caused its conversion into **10** by 1,2-interchange,[13] the equilibrium being shifted to about 98% in favor of the latter. The other couple of bromochlorides (**8** and **9**) was prepared by treating both bromohydrins **12** and **13** with thionyl chloride; a 70:30 ratio of **8** to **9** was obtained from **12** and a 63:37 ratio from **13**. The 1,2-interchange of halogens occurring in these transformations was not unexpected, since the tendency of vicinal bromine to participate in displacement reactions on bromohydrins through epibromonium ions or SNi′ mechanisms is known.[14] Pure **8** and **9** could be separated from their mixtures, but **8** was more conveniently obtained after thermal equilibration, which changed the ratio of **8** to **9** to about 97:3.

The relative position of bromine and chlorine with respect to the *tert*-butyl group and the relative configurations of these bromochlorides were inferred from the method of obtainment and from their nmr spectra. Thus, both products arising from **12** and **13** must have bromine cis to the *tert*-butyl group as in the starting bromohydrins, this halogen atom being therefore vicinal to the alkyl substituent in the diaxial and in a 1,3 relationship to it in the diequatorial isomer. In the 60-MHz nmr spectrum of the major product obtained from **12** and **13** the two protons α to the halogens gave overlapping narrow signals ($W_{1/2}$ = 4.5 Hz), indicating a diaxial disposition of the two halogen atoms as in **8**; on the other hand, the minor isomer showed for the α protons a broad, complicated pattern of signals at higher field, as expected for **9**. The nmr spectra provided also safe configurational assignments for the other couple of bromochlorides, since the thermodynamically stable isomer and its partner showed patterns respectively very similar to those of **8** and **9** and consistent with the relative configurations **10** and **11**.[15]

A complete analysis of the mixtures of bromochlorides formed in the additions to **1** was not possible by glpc alone, but a mixed glpc–ir method solved the analytical problem (see Experimental Section). The results obtained by this method of analysis are summarized in Table I, which also includes the ratios of bromochlorides to trans dibromides and dichlorides formed in the various conditions.

It can be seen from Table I that the distribution of the individual bromochlorides is affected both by the reagent and by the solvent. Furthermore, the amount of trans dibromides and dichlorides formed in the additions of free bromine chloride depends on the solvent. It must also be observed that the total amounts of the diaxial adducts (**8** + **10**) and those of the diequatorial ones (**9** + **11**) are fairly constant in all mixtures obtained with preformed bromine chloride, but the total percentage of the former compounds increases when pyridinebromine chloride is used as the halogenating agent, in analogy with the results previously reported for the bromination reactions.[1]

Discussion

It is well known[16,17] that bromine is the electrophilic and chlorine the nucleophilic species in the polar additions of bromine chloride to alkenes. A two-stage mechanism, similar to that involved in the bromination, is generally assumed. On this basis, the course of the additions of bromine chloride to **1** can be illustrated as in Scheme I. It must be pointed out that this scheme is a rough simplification, since it does not consider the formation of charge transfer complexes between the interhalogen and the olefin, which, in analogy with the bromine additions,[18-20] could be involved as the precursors of the epibromonium ions **2** and **3**. Furthermore, the latter intermediates, which in the scheme are simply represented as free ions, in the nonpolar solvents employed are very probably ion-paired species, the nature of the negative counterion depending on the reaction order in electrophile.

The stereoselectivity of the electrophilic attack relative to the *tert*-butyl group and regioselectivity of the nucleophilic one on the ionic intermediates in the various additions of bromine chloride to **1** are given in Table I.

The data of Table I show that in the addition of preformed bromine chloride to **1** under all examined conditions the attack by positive bromine is directed preferentially anti to the alkyl substituent. This is consistent with the most generally accepted mechanism of electrophilic additions to alkenes,[21] involving an irreversible, rate-limiting electrophilic step leading to cationic intermediates, followed by a fast nucleophilic attack to give the final adducts. Under these conditions the stereoselectivity of the addition must be determined by steric and electronic effects of the substituents during the electrophilic stage. In the case of additions to **1**, the strong steric effect of the allylic *tert*-butyl group, hindering syn attack, should cause the preferential formation of products arising from anti electrophilic attack by bromine, as is actually found with preformed bromine chloride. The range of anti stereoselectivity observed in the various solvents is possibly due to a different polarization of the interhalogen and/or to slight solvent effects on the rates of attack on the two faces of the double bond.

The regioselectivity of the nucleophilic attack on the trans intermediate **3** is remarkably constant under all examined conditions (Table I) and very similar to that found in other electrophilic additions to **1** involving epibromonium ion intermediates.[5] The high preference for attack on C_1 is consistent with the expectation, supported also by the course of opening reactions of *trans*-3-*tert*-butyl-1,2-epoxycyclohexane,[5,11b] that the strong repulsive interaction between the attacking nucleophile and the *tert*-butyl group[22]

raises the energy of transition state 6 with respect to 7 so much as to reverse the usual preference for antiparallel over parallel opening of cyclohexene epibromonium ions.[23] The nucleophilic attack on the cis intermediate 2 occurs preferentially at C_1, through the chair-like transition state 4; however, in the addition of preformed bromine chloride this regioselectivity is much lower than expected on the basis of other additions to 1 involving electrophilic bromine as well as of opening reactions of *cis*-3-*tert*-butyl-1,2-epoxycyclohexane,[5,11b] surprisingly high percentages of parallel attack on C_2 anti to the *tert*-butyl group being found particularly in chloroform, dichloromethane, and benzene as the solvents. The latter results show that also more subtle factors than direct steric or inductive effects of ring substituents can play a considerable role in determining the mode of opening of cyclohexene epihalonium ions.

The steric course of the addition performed with NBS in the presence of hydrogen chloride is identical with that found when free bromine chloride is added in the presence of the same acid and is completely different from that observed with NBS in DMSO–water,[5] which gives 78% of the diaxial bromohydrin 12 through 2. This difference suggests that in the NBS–HCl reaction, in contrast with the NBS–DMSO–water addition, bromine is not directly transferred from nitrogen to the alkene, but free bromine chloride is formed before the electrophilic attack.

A definite change in product distribution is brought about when pyridinebromine chloride is used as the halogenating reagent. The inspection of Table I shows that this change is due first to an increased syn stereoselectivity of the electrophilic attack by bromine and second to a decreased percentage of parallel opening on C_2 of the cis intermediate formed in the electrophilic step. The unlikely possibility that pyridinebromine chloride acts as a donor of electrophilic chlorine rather than bromine can safely be ruled out, since the trans chloronium ion would give mostly the diequatorial adduct 9, which on the contrary is produced in a very small amount. Also the hypothesis that the coordination of the halogen molecule by the base may reduce the effective size of electrophilic bromine so much as to cause a practically random attack on the two faces of the double bond of 1 in spite of the presence of the bulky alkyl substituent seems very unlikely. In fact, all examined one-step additions (like epoxidation[11a] and hydroboration[12]) and two-step additions involving an irreversible electrophilic step (like addition of preformed hypochlorous and hypobromous acid and acetyl hypobromite[5,11b]) to 1 show a definite preference for anti electrophilic attack, independently of the different sizes of the various reagents. The change in steric course when pyridinebromine chloride is used as the reagent may instead be rationalized by the assumption of a change in the addition mechanism.

The present stage of knowledge about the nature and chemical behavior of this reagent does not allow definite conclusions to be drawn about its addition mechanism. However, it can be observed that both the stereoselectivity and the regioselectivity found in the bromochlorination of 1 with pyridinebromine chloride in chloroform tend to approach those expected from an addition mechanism of the type already proposed for the bromination with pyridine perbromide[1] and other additions showing a preference for syn electrophilic attack to a much higher degree.[6] The latter mechanism would involve a reversible electrophilic step leading to bridged cationic intermediates, followed by a slow, rate-determining nucleophilic attack to give products. Under these conditions, if the nucleophilic attacks are sufficiently slower than the formation of the intermediates 2 and 3 (or some equivalent species) and their reversal to the alkene, the overall steric course of the bromochlorination of 1 would mostly depend on the rates of the four competitive nucleophilic steps leading to the adducts 8–11. Since antiparallel attack on C_1 of the cis intermediate through a chair-like transition state like 4 would be less energy demanding than both antiparallel attack on C_2 of the trans intermediate (a chair-like transition state of type 6 being destabilized by repulsive interaction between the attacking nucleophile and the *tert*-butyl group) and parallel attacks (involving energetically less favorable boat-like transition states like 5 and 7), 8 should therefore be the main product. This actually occurs in the addition of pyridinebromine chloride in chloroform and to a smaller degree in carbon tetrachloride.

In conclusion, while more evidence, particularly of kinetic type, is definitely desirable and is being sought in order to better define mechanistic aspects, the present results fit well with the previously acquired ones into a picture that requires two different ionic mechanisms of addition for different electrophilic reagents.

Experimental Section

Nmr spectra were registered with a Geol C-60 HL spectrometer from *ca.* 30% (w/w) $CDCl_3$ solutions using TMS as internal standard. Glpc analyses were performed on a Fractovap C. Erba instrument, fitted with a 2-m glass column, 2.5 mm i.d., packed with 1% neopentyl glycol succinate on sylanized Chromosorb W 80–100 mesh. Ir spectra were registered on liquid films with a Perkin-Elmer Model 257 double-beam grating spectrophotometer.

3-*tert*-Butylcyclohexene was obtained from 2-*tert*-butylcyclohexanone tosylhydrazone with butyllithium.[11a] Bromine chloride was prepared[24] by mixing equimolar amounts of carbon tetrachloride solutions of bromine and chlorine and used after several hours. Monopyridinebromine(I) chloride was prepared by slowly adding the calculated volume of a carbon tetrachloride solution of bromine chloride to a slight excess of dry pyridine in the same solvent;[25] the white cyrstalline precipitate was immediately used without further purification. Dichloromethane was refluxed over P_2O_5 and rectified. Chloroform was purified by washing with 2 *N* NaOH, concentrated H_2SO_4, and water, drying with K_2CO_3, and distillation and was immediately used. Carbon tetrachloride was Rudi Pont spectroanalyzed reagent grade. Benzene was washed with H_2SO_4, refluxed on sodium, and distilled. Ethyl ether was freed from peroxides by washing with a solution of ferrous sulfate. $MgSO_4$ was always used as the drying agent. Evaporations were made *in vacuo* (rotary evaporator) at 30°. Petroleum ether refers to the fraction of boiling range 40–60°.

***r*-1-Chloro-*t*-2-bromo-*t*-3-*tert*-butylcyclohexane (8) and *r*-1-Bromo-*t*-2-chloro-*c*-3-*tert*-butylcyclohexane (9). A.** Thionyl chloride (7.5 ml) was added at 0° to bromohydrin 13[5] (3.0 g), and the mixture was left in a sealed vessel at room temperature for 2 hr and then poured onto ice and extracted with ether. The extract was washed with water and saturated aqueous $NaHCO_3$, dried, and evaporated to give a crude residue (2.6 g) consisting of a mixture of 8 and 9 in a ratio of 63:37. A portion of this mixture (1.0 g) was chromatographed through a 40 × 1.8 cm column of neutral silica gel (Schuchardt, grade I), petroleum ether being used as the eluent; 25-ml fractions were collected. Fractions 4–8 contained 0.50 g of pure 8: $n^{25}D$ 1.5072; nmr δ 0.96 (*t*-Bu, s, 9 H), 4.60 ppm (–CHBr– and –CHCl–, 2 overlapping m, $W_{1/2}$ = 4.5 Hz, 2 H); ir 665, 680 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}BrCl$: C, 47.36; H, 7.15; Br, 31.50; Cl, 13.98. Found: C, 47.45; H, 7.25; Br, 31.70; Cl, 14.00.

Fractions 12–16 gave 0.28 g of pure 9: $n^{25}D$ 1.5135; nmr δ 1.08 (*t*-Bu, s, 9 H), 3.65–4.32 ppm (–CHBr– and –CHCl–, 2 overlapping m, 2 H); ir 680, 740, 770 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}BrCl$: C, 47.36; H, 7.15; Br, 31.50; Cl, 13.98. Found: C, 47.25; H, 7.10; Br, 31.40; Cl, 13.80.

Another portion (1.0 g) of the above mixture was heated in a sealed vial for 6 hr at 165°. Glpc analysis showed that the original ratio of 8 to 9 was changed to 97:3, which remained unchanged after further heating. Percolation of this crude product through a silica gel column yielded pure 8.

B. Treatment of bromohydrin 12[5] with thionyl chloride as described under A gave a 70:30 mixture of 8 and 9.

The ratios of 8 to 9 obtained from both bromohydrins 12 and 13 did not change after reaction times ranging between 30 min and 48

hr, showing that the products were stable in the reaction conditions.

***r*-1-Chloro-*t*-2-bromo-*c*-3-*tert*-butylcyclohexane (11).** A solution of *N*-bromosuccinimide (6.5 g, 36.5 mmol) in dichloromethane (100 ml) was slowly added to a solution of 1 (4.0 g, 29 mmol) in 100 ml of the same solvent cooled at 0° and saturated with dry hydrogen chloride. The acid was bubbled until the end of the addition. The reaction mixture was then washed with water, saturated aqueous $NaHSO_3$, and water, dried, and evaporated to give 7.0 g of a crude mixture consisting of ~95% of bromochlorides and 5% of trans dibromides and dichlorides. Glpc analysis showed that the bromochlorides consisted of 34% of the diaxial adducts 8 and 10 (unseparated), 58% of 11, and 8% of 9. This mixture was chromatographed on a 65 × 1.8 cm column of neutral silica gel with petroleum ether as the eluent, and 25-ml fractions were collected. Fractions 5 and 6 contained mixtures of 8 and 10 (2.0 g) uncontaminated by the other adducts; ir analysis showed for both of them a 8 to 10 ratio of 64:36. Fractions 8–11 gave 2.5 g of pure 11: n^{25}D 1.5140; nmr δ 1.08 (*t*-Bu, s, 9 H), 3.84–4.37 ppm (–CHBr– and –CHCl–, 2 overlapping m, 2 H); ir 635, 690, 730, 780 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}BrCl$: C, 47.36; H, 7.15; Br, 31.50; Cl, 13.98. Found: C, 47.20; H, 7.05; Br, 31.65; Cl, 14.10.

High yields of pure 11 were also obtained by column chromatography of all mixtures obtained by addition of preformed bromine chloride or pyridinebromine chloride, as described below.

***r*-1-Bromo-*t*-2-chloro-*t*-3-*tert*-butylcyclohexane (10).** A sample of 11 (1.0 g) was heated in a sealed vial for 5 hr at 165°, after which time glpc analysis showed that it was transformed into 10 in a 98% yield. A 2% amount of 11 remained unchanged also after further heating. Percolation of this crude product through a silica gel column gave pure 10: n^{25}D 1.5070; nmr δ 0.96 (*t*-Bu, s, 9 H), 4.62 ppm (–CHBr– and –CHCl–, 2 overlapping m, $W_{1/2}$ = 4.0 Hz, 2 H); ir 650, 695 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}BrCl$: C, 47.36; H, 7.15; Br, 31.50; Cl, 13.98. Found: C, 47.25; H, 7.05; Br, 31.70; Cl, 14.10.

Additions of Bromine Chloride. A. With BrCl. A 10% excess of 1 *M* solution of BrCl in CCl_4 was added dropwise to a stirred solution of 1.0 g of 1 in 25 ml of the appropriate solvent at 0°. After the addition was complete, the reaction mixture was stirred for 10 min, and then washed with saturated aqueous $NaHSO_3$ and water, dried, and evaporated. The reaction in dichloromethane in the presence of hydrogen chloride was performed by bubbling the acid during the addition of the interhalogen.

B. With C_5H_5NBrCl in CCl_4. A 20% excess of solid C_5H_5NBrCl (1.75 g) was added to a solution of 1 (1.0 g) in CCl_4 (20 ml) at 0°. After stirring for 45 min most of the solid was dissolved and the reaction mixture was washed with saturated aqueous $NaHSO_3$, aqueous 2 *N* HCl, and water, dried, and evaporated.

C. With C_5H_5NBrCl in $CHCl_3$. A solution of C_5H_5NBrCl (1.75 g) in 17 ml of $CHCl_3$ was added within 20 min to a stirred solution of 1 (1.0 g) in 20 ml of the same solvent at 0°. After 10 min the reaction mixture was treated as described under B.

Three or more experiments were carried out for every procedure. The crude reaction mixtures were subjected to glpc. Under the conditions employed (column 80°, evaporator 130°, detectors 130°, nitrogen flow 45 ml/min) the bromochlorides, in contrast with the dibromides, did not undergo thermal interconversion on the gas chromatographic columns and the trans dibromides and dichlorides present in some reaction mixtures did not interfere with their determination; however, while the diequatorial adducts 9 and 11 were well separated from each other and from the diaxial isomers 8 and 10, the latter two gave a single peak. The relative retention times of all possible adducts follow: *r*-1,*t*-2-dichloro-*t*-3-*tert*-butylcyclohexane, 1; 8 and 10 (unseparated), 1.75; *r*-1,*t*-2-dibromo-*t*-3-*tert*-butylcyclohexane, 3.05; *r*-1,*t*-2-dichloro-*c*-3-*tert*-butylcyclohexane, 3.60; 11, 4.70; 9, 6.20; *r*-1,*t*-2-dibromo-*c*-3-*tert*-butylcyclohexane, 7.60. Thus, glpc analysis gave the percentage of trans dibromides and dichlorides, the single percentages of the diequatorial bromochlorides (9 and 11), and the total percentage of the diaxial ones (8 and 10). The reaction mixtures were thereafter rapidly chromatographed over silica gel. The first eluted fractions, consisting of mixtures of 8 and 10 free from the other adducts, were subjected to ir analysis utilizing the bands at 650 and 695 cm^{-1}, typical of 10, and those at 665 and 680 cm^{-1}, typical of 8, by comparison with a calibration curve obtained with the pure reference compounds. No fractionation of 8 and 10 occurred, since identical ratios of 8 to 10 were obtained from three or more consecutive fractions. The single percentages of the diaxial bromochlorides were then deduced on the basis of their total percentage obtained by glpc and of the 8 to 10 ratio obtained by ir analysis. The values listed in Table I were reproducible within ±2%.

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Registry No.—1, 14072-87-8; 8, 51821-11-5; 9, 51821-12-6; 10, 51830-05-8; 11, 51830-06-9; 13, 38512-63-9; BrCl, 13863-41-7; C_5H_5NBrCl, 51821-13-7.

References and Notes

(1) P. L. Barili, G. Bellucci, F. Marioni, I. Morelli, and V. Scartoni, *J. Org. Chem.*, **37**, 4353 (1972).
(2) P. L. Barili, G. Bellucci, F. Marioni, I. Morelli, and V. Scartoni, *J. Org. Chem.*, **38**, 3472 (1973).
(3) P. L. Barili, G. Bellucci, G. Berti, M. Golfarini, F. Marioni, and V. Scartoni, *Gazz. Chim. Ital.*, **104**, 107 (1974).
(4) R. C. Fahey, *Top. Stereochem.*, **3**, 286 (1968).
(5) G. Bellucci, M. Ferretti, G. Ingrosso, F. Marioni, A. Marsili, and I. Morelli, *Tetrahedron Lett.*, 3527 (1972).
(6) G. Bellucci, G. Berti, G. Ingrosso, and E. Mastrorilli, *Tetrahedron Lett.*, 3911 (1973).
(7) C. Freppel and J.-C. Richer, *Tetrahedron Lett.*, 2321 (1972).
(8) P. L. Barili, G. Bellucci, B. Macchia, F. Macchia, and G. Parmigiani, *Gazz. Chim. Ital.*, **101**, 300 (1971).
(9) D. J. Pasto and J. A. Gontarz, *J. Amer. Chem. Soc.*, **93**, 6902, 6909 (1971).
(10) M. Rau, P. Alcais, and J.-E. Dubois, *Bull. Soc. Chim. Fr.*, 3336 (1972).
(11) (a) J.-C. Richer and C. Freppel, *Can. J. Chem.*, **46**, 3709 (1968); (b) *Tetrahedron Lett.*, 4411 (1969); (c) *Can. J. Chem.*, **48**, 148 (1970).
(12) D. J. Pasto and F. M. Klein, *J. Org. Chem.*, **33**, 1468 (1968).
(13) P. L. Barili, G. Bellucci, G. Berti, F. Marioni, A. Marsili, and I. Morelli, *J. Chem. Soc., Perkin Trans. 2*, 58 (1972).
(14) G. Bellucci, F. Marioni, and A. Marsili, *Tetrahedron*, **25**, 4167 (1969); G. Bellucci, G. Ingrosso, F. Marioni, A. Marsili, and I. Morelli, *Gazz. Chim. Ital.*, **104**, 69 (1974).
(15) By analogy with *r*-1,*t*-2-dibromo-*c*-3-*tert*-butylcyclohexane, the possibility of a twist form participating in the conformational equilibrium of bromochloride 11 cannot be ruled out: P. L. Barili, G. Bellucci, G. Ingrosso, F. Marioni, and I. Morelli, *Tetrahedron*, **28**, 4583 (1972).
(16) P. B. D. de la Mare and S. Galandauer, *J. Chem. Soc.*, 36 (1958).
(17) H. J. Hageman and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 1141 (1966).
(18) R. E. Buckles, J. L. Miller, and R. J. Thurmaier, *J. Org. Chem.*, **32**, 888 (1967).
(19) F. Garnier and J.-E. Dubois, *Bull. Soc. Chim. Fr.*, 3797 (1968).
(20) C. G. Gebelein and G. D. Frederick, *J. Org. Chem.*, **37**, 2211 (1972).
(21) Reference 4, p 238.
(22) The origin of steric interactions of this type has been thoroughly discussed in a previous paper.[6]
(23) J. Vails and E. Toromanoff, *Bull. Soc. Chim. Fr.*, 758 (1961).
(24) Houben-Weyl, "Methoden der Organischen Chemie," Vol. V/4, Georg Thieme Verlag, Stuttgart, 1960, p 150.
(25) D. M. Williams, *J. Chem. Soc.*, 2783 (1931).

Hydro-1,3-ethanoindeno[2,1-*c*]pyridines

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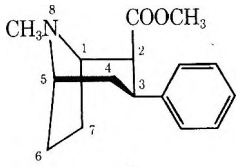
Methyl 3β-phenyl-1αH,5αH-tropane-2β-carboxylate (1) has been cyclized by polyphosphoric acid to form 1,2,3,4,4a,9a-hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-*c*]pyridin-9-one (**2a**). Conversions of this 9-one to the corresponding 9-ols, 9-CH_2, and some unsaturated products are described. Absolute configurations are assigned to all products.

In the course of our studies on the biological properties of rigid phenylalkylamines we prepared a series of tropanes carrying an aromatic ring at C-3 and a carboalkoxyl group at C-2.[1] These compounds are exemplified by structure **1**. Reactions of such compounds with polyphosphoric acid (PPA) gives rise to an even more restricted ring system typified by structure **2a**. The chemistry of these 1,3-ethanoindeno[2,1-*c*]pyridines is the subject of this paper.



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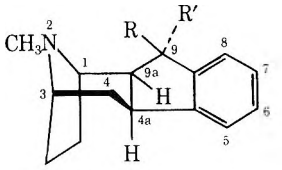


2a, RR′ = O

b, RR′ = 

c, R = R′ = H

d, R = OH; R′ = H

e, R = OAc; R′ = H

f, R = H; R′ = OH

Treatment of tropane ester **1** (cocaine configuration) or its C-2 equatorial epimer[2] with PPA at 150° for 5 hr produced ketone **2a** (76%). Formation of a bisulfite addition complex facilitated separation of the product from 8% of unchanged starting material.

The thermodynamically more stable form of **2a** is that in which the cyclopentanone ring is fused to the tropane moiety in a cis manner. Nmr coupling constants for **2a** substantiated that the compound at hand had this structure.[3] The 4a hydrogen of **2a** originated as a nonepimerizable, α-oriented hydrogen in the starting material **1** and thus controlled which cis isomer was obtained.

It has been observed[1,4] that axial substituents at C-2 in a tropane ring system prevent or significantly inhibit quaternization of the nitrogen atom. In accord with predictions in the present system, the axial carbonyl group at C-9a prevented quaternization with EtI at room temperature (1 hr).

The carboxylic acid corresponding to structure **1**[1] also could be cyclized with PPA to give **2a** (75%). Its 2α epimer[1] gave **2a** in 57% yield. However, ring closure utilizing HF, H_2SO_4 (dioxane), PPA (dioxane), or PPA in hexamethylphosphoramide was not successful.

Since the absolute configuration of tropane ester **1** was known,[1] the configuration of **2a** could be assigned. Chemical and spectral data below then allowed absolute configurational assignments to the other products described here.

Conversion of ketone **2a** to thioketal **2b** followed by desulfurization with Raney nickel afforded the 9-methylene derivative **2c**. Failure of the product to quaternize with EtI indicated that the C-9 methylene was still in an axial configuration with respect to the tropane moiety.

Reduction of ketone **2a** with $NaBH_4$ produced an epimeric mixture of alcohols. The 9β-ol **2d** was readily recognized in that its ir spectrum demonstrated intramolecular hydrogen bonding (3200 cm^{-1}). This value is rather low but is close to that found (3231 cm^{-1}) for a similar case of intramolecular N···H–O bonding in 3β-phenyl-1αH,5αH-tropane-2β-methanol.[1] Incidentally, the acetate ester **2e** of alcohol **2d** was prepared.

The ir spectrum of a 0.001 *M* solution of 9α-ol **2f** in CCl_4 showed hydroxyl stretching bands at 3644 (nonbonded) and 3604 cm^{-1} (H π bonded). Benzyl alcohol shows similar ir bands at 3632 and 3615 cm^{-1}.[5]

Reduction of ketone **2a** by adding it to borane in THF resulted in formation of the 9-methylene derivative **2c** in 40% yield along with 9β-ol **2d** (54%) and 9α-ol **2f** (3%). Inverse addition in this reaction raised the yield of 9-methylene compound to 73% and lowered the yield of 9β-ol **2d** to 23%. No 9α-ol was isolated.

There was indication that a mixture of 9α- and 9β-ols was initially formed and that the 9α-ol was transformed to 9-CH_2 more rapidly than was the 9β-ol. Thus, treatment of a mixture of equal parts of 9α- and 9β-ols with borane gave two parts of 9-CH_2 product and one part of 9β-ol with no 9α-ol remaining.

These observations afford a plausible explanation for the formation of considerably more 9-CH_2 compound **2c** by the *inverse* addition described above. In the initial experiment where the amino ketone was added to the borane, the high relative concentration of the latter produced complexing with the nitrogen[6] and effective blocking of the β face of the ketone. Considerable α-attack then occurred to give 9β-ol **2d**, the epimer which was reduced further only slowly. In the inverse addition, the borane added found less amino ketone in complexed form and was able to attack from the β face to form more 9α-ol **2f**, the epimer which was easily reduced further.

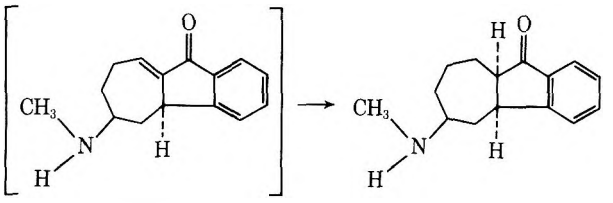
A methoxyl group on either C-6 or C-8 of ketone **2a** dramatically affected the reduction reaction with borane. It considerably activated the benzylic position with the result that the hydroxyl groups of both intermediates were completely cleaved and only the 9-methylene product was isolated. The details of these reactions are reported in a related, biologically oriented paper.[7]

Reduction of aromatic ketones such as xanthone and thioxanthone to the corresponding methylene derivatives has been accomplished by BH_3·THF at 0°.[8] In the present work with mixed aliphatic–aromatic ketones a reflux temperature was necessary for good yields of the methylene derivatives. The mechanism of the reaction was not determined.

Hitherto, all reductions discussed have been chemical in nature. Reduction with Adams catalyst in EtOH afforded a simple mixture (two tlc spots) of 9β-ol **2d** (25%) and 9α-ol **2f** (49%).[9] Although the 9β-ol is a benzylic alcohol, it was not hydrogenolyzed by either Pt or Pd in EtOH in the presence of $HClO_4$. This reaction was not checked with the 9α-ol.

Reduction of ketone **2a** in the form of the free base or its HCl salt with 10% Pd/C in EtOH gave a surprising result. Apparently β-elimination of the amino group occurred followed by hydrogenation of the resulting unsaturated ketone as shown. Ketone **4** (44%) was the only product isolat-

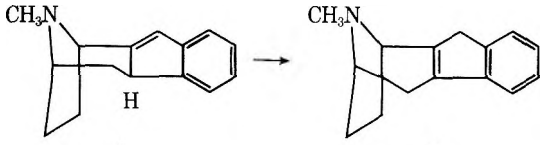
2a →



3 **4**

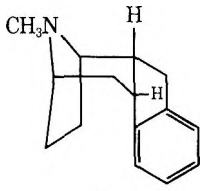
ed but some more-polar products observed by tlc indicated that further reduction occurred.

Dehydration of alcohol **2d** (9β-ol) with $POCl_3$ apparently produced only $\Delta^{9(9a)}$ olefin **5** because immediate hydrogenation of the crude product with Pd/C furnished essentially only the cis–syn compound **2c** (aromatic ring on the same side as the nitrogen). A model shows that the 9–9a double bond is directed toward the β face and that hydrogenation should be expected from the α side. Attempted isolation of this $\Delta^{9(9a)}$ olefin (exposure to NH_4OH) resulted in partial isomerization to $\Delta^{4a(9a)}$ olefin **6** (~7:3 ratio of **5**: **6**). This ratio was little affected by tosyl acid in refluxing



5 **6**

ethanol, but $NaOCH_3$ in CH_3OH caused complete isomerization to **6**.[10] Hydrogenation of this olefin with Pd/C produced cis–anti indenopyridine **7**, resulting from β-side at-



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tack by hydrogen (cis hydrogenation assumed). This compound had no axial substituent on "carbon-2" of the tropane moiety and indeed reacted rapidly with EtI to form a quaternary salt.

Chemical reduction ($Na–NH_3$) of the 70:30 mixture of isomers **5** and **6** produced only the two cis compounds **2c** (38%) and **7** (32%) with no evidence of any trans product; 3% of unreduced material was recovered. Pure olefin **6** was reduced by the same reagent to form only the cis–anti product **7**.

The effect of the double bonds in olefins **5** and **6** on the nmr peak positions of the NCH_3 is worthy of note. The NCH_3 peak in compound **2c** with no styrenic double bond appears at 2.2 ppm. A $\Delta^{4a(9a)}$ double bond (**6**) deshields the methyl group (δ 2.4 ppm). A $\Delta^{9(9a)}$ bond (**5**) has a slight shielding effect (δ 2.1 ppm).

The enantiomers of tropane ester **1** and its 2α epimer were available from earlier work.[1] They were transformed by PPA into the enantiomer of ketone **2a** according to the procedure used for **2a**. Borane (24 hr) reduced this ketone in the expected manner to give the enantiomers of 9β-ol **2d** and 9-methylene compound **2c**. When the reflux time with borane was reduced to 3 hr, some of the enantiomer of 9α-ol **2f** was isolated. Enantiomeric 9-methylene compound **2c** was also formed *via* the thioketal route used for **2c**. As mentioned earlier in this paper, enantiomeric ketone **2a** was reduced by $PtO_2–H_2$ to form a mixture of 9α- and 9β-ols.

Some final comments are related to other than reductive reactions of ketone **2a**. A tendency toward β-elimination in this β-amino ketone was evidenced in the formation of **4**. Yet this ketone was stable to $NaOCH_3$ in boiling THF for 20 min.

An attempted Wittig reaction failed using trimethyl phosphonoacetate and $NaOCH_3$ in DMF and again in DMSO. Starting ketone was recovered. This ketone also failed to react with trimethylsulfoxonium ylide and did not form an enamine with morpholine.

Ketone **2a** reacted with N_2H_4 to form a complex mixture with at least seven components, probably involving β-elimination. Acrylonitrile also produced a complex mixture and acetic anhydride gave other than a simple enol acetate.

The biological activity of the compounds described here together with a considerable number of analogs is being reported in the *Journal of Medicinal Chemistry*.[7]

Experimental Section[11]

(1*R*,3*S*,4a*S*,9a*S*)-1,2,3,4,4a,9a-Hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-c]pyridin-9-one (2a). A 1:3 mixture of methyl (1*R*,2*S*,3*S*,5*S*)-3β-phenyl-1α*H*,5α*H*-tropane-2β-carboxylate (**1**) and its 2α epimer, methyl (1*R*,2*R*,3*S*,5*S*)-3β-phenyl-1α*H*,5α*H*-tropane-2α-carboxylate[1] (370 g, 1.42 mol) was warmed to 100° and added all at once to 3.7 kg (11 mol) of PPA at 100° with stirring. This mixture was stirred at 150° for 5 hr and poured onto a large volume of crushed ice. Concentrated NH_4OH (5.4 kg) was added with cooling and the alkaline mixture was extracted with CH_2Cl_2. Concentration of the dried (Na_2SO_4) extracts gave an oily residue which was extracted multiply with a total of 8 l. of pentane. Partial concentration precipitated 136 g of **2a**, mp 75–78°. The mother liquor residue in 500 ml of MeOH was added to a solution of 440 g of $Na_2S_2O_5$ in 2.2 l. of H_2O. Extraction of this solution with 6 × 500 ml of CH_2Cl_2 separated 31 g (8%) of starting material. The aqueous solution together with some bisulfite adduct which had precipitated was treated with 560 g of solid $NaHCO_3$. Water (200 ml) and CH_2Cl_2 (1.1 l.) were added and the mixture was heated under reflux for 5 hr. The CH_2Cl_2 layer yielded a solid residue which was recrystallized from pentane, giving 85.2 g more of **2a**, mp 75–78° (76% based on I consumed). The analytical sample melted at 78–79° (pentane): $[\alpha]^{25}D$ +13.4°; ir 1712 cm^{-1}; uv max 245 nm (ε 11,600) and 288 (2900); nmr δ 1.30–2.40 (m, 6, CH_2), 2.20 (s, NCH_3), 2.45 (q, C_9 H, $J_{1,9a}$ = 1.8 Hz, $J_{4a,9a}$ = 7.5 Hz), 3.15 (m, C_3 H), 3.52 (q, C_{4a} H), 3.90 (d, C_1 H), 7.20–7.80 ppm (m, 4, aromatic H).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.1; H, 7.6; N, 6.2.

The HCl salt of 2a from CH_3CN showed polymorphism: mp 222–224 and 259° dec (evacuated capillary); $[\alpha]^{25}D$ +39.8°.

Anal. Calcd for $C_{15}H_{17}NO·HCl$: C, 68.30; H, 6.88; Cl, 13.44. Found: C, 68.2; H, 6.9; Cl, 13.6.

Ketone 2a from Tropanecarboxylic acids. Treatment of 3β-phenyltropane-2β-carboxylic acid hydrochloride[1] with PPA at 150° for 5 hr with work-up as above gave a 73% yield of **2a** using preparative tlc (3:97 *i*-$PrNH_2$–Et_2O) for purification. In the same manner the 2α-carboxylic acid[1] gave **2a** in 57% yield.

Nonreaction of Ketone 2a with EtI. A solution of 5 g of **2a** in 150 ml of Et_2O was treated with 3.44 g of EtI at room temperature. After 1 hr there was no evidence of precipitate formation and concentration of the solution *in vacuo* gave only recovered starting material.

(1*R*,3*S*,4a*S*,9a*S*)-1,2,3,4,4a,9a-Hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-c]pyridine Hydrochloride (2c). A solution of 9.35 g (0.040 mol) of ketone **2a** in 250 ml of HOAc was treated with 20 ml of ethanedithiol and 20 ml of boron trifluoride etherate. The next day the precipitate was separated, Et_2O was added to the filtrate, and more solid was collected. The solid residues were washed with fresh Et_2O and then dissolved in H_2O. Dilute NaOH (2 *N*) was added and the free base was separated with Et_2O. Crystallization from pentane gave 6.7 g (55%) of (1*R*,3*S*,4a*S*,9a*S*)-**9,9-ethylenedithio-1,2,3,4,4a,9a-hexahydro-2-methyl-9*H*-1,3-ethano-**

indeno[2,1-*c*]pyridine (2b): mp 102–103°; uv max 262 nm (ε 3400), 271 (3100), and 280 (2800).

Without further purification this product was dissolved in 350 ml of 95% EtOH and refluxed for 12 hr in the presence of 12 tsp of Raney Ni. Removal of catalyst and solvent gave 3.4 g of crude **2c.** A portion (0.5 g) was chromatographed on silica preparative plates (Et_2O–pentane–*i*-$PrNH_2$, 50:47:3) to give pure, oily **2c:** *m/e* 213; nmr δ 1.0–2.7 (m, 6, CH_2), 2.2 (s, NCH_3), 2.7–3.6 (m, 5, NCH, benzylic H), and 7.0–7.3 ppm (m, 4, Ar); R_f 0.55 (SiO_2, 97:3 Et_2O–*i*-$PrNH_2$).

The remainder of the crude **2c** was converted to the **HCl salt:** 2.4 g; mp 301° dec (from acetone); $[\alpha]^{25}D$ +93.5°; total yield 51% from thioketal.

Anal. Calcd for $C_{15}H_{19}N$·HCl: C, 72.13; H, 8.07; N, 5.61. Found: C, 72.3; H, 8.2; N, 5.9.

$NaBH_4$ Reduction of (1*R*,3*S*,4a*S*,9a*S*)-1,2,3,4,4a,9a-Hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-*c*]pyridin-9-one (2a). A solution of 3.13 g (13 mmol) of **2a** in 50 ml of EtOH was treated with 1.5 g (40 mmol) of $NaBH_4$ in 5 ml of H_2O. After 72 hr at room temperature the cooled solution was treated with acetone. More H_2O and Et_2O were added. The Et_2O layer was dried (Na_2SO_4) and concentrated to afford a crude mixture of alcohols **2d** and **2f.** Plate chromatography (3:97 *i*-$PrNH_2$–Et_2O, 11 plates, two solvent passes) gave 1.8 g of a more polar alcohol (**2f**), 57%, mp 98–100°, ir (CCl_4, 0.05–0.001 *M*) 3644 and 3604 cm^{-1}, and 0.25 g of a less polar alcohol (**2d**), 8%, mp 140–142°, ir (CCl_4, 0.05–0.001 *M*) 3200 cm^{-1}.

The HCl salt of 2f (acetonitrile) melted at 285–287° dec. $[\alpha]^{25}D$ + 62.9°.

Anal. Calcd for $C_{15}H_{19}NO$·HCl: C, 67.79; H, 7.59; Cl, 13.34. Found: C, 68.0; H, 7.7; Cl, 13.3.

The HCl salt of 2d melted at 230–231° dec (acetone), $[\alpha]^{25}D$ +74.1°.

Anal. Calcd for $C_{15}H_{19}NO$·HCl: C, 67.79; H, 7.59; Cl, 13.34. Found: C, 67.5; H, 7.6; Cl, 13.6.

(1*R*,3*S*,4a*S*,9*R*,9a*S*)-1,2,3,4,4a,9a-Hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-*c*]pyridin-9-ol Acetate (2e). Alcohol **2d** (10 g, 41 mmol) was treated with 50 ml of pyridine and 40 ml of Ac_2O for 24 hr at room temperature and the product was isolated in the usual manner. Its crude methanesulfonate salt (9.48 g, 89%) melted at 202–205°. Recrystallization from acetone gave mp 214–215°; $[\alpha]^{25}D$ +197°; ir (KBr) 1740 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}NO_2 \cdot CH_3SO_3H$: C, 58.84; H, 6.86; S, 8.73. Found: C, 58.8; H, 6.9; S, 8.5.

Borane Reduction of 2a. A solution of 80 g (0.38 mol) of **2a** in 1.0 l. of THF was added in 1.5 hr to 1.8 l. of 1 *M* BH_3 in THF with stirring under N_2 and cooling by ice. The solution was heated under reflux for 24 hr. After standing at room temperature for 66 hr, 160 ml of H_2O was added dropwise followed by 800 ml of 2 *N* NaOH. Most of the THF was boiled away over a 2.5-hr period. Et_2O was added and the layers were separated. The Et_2O solution was dried (Na_2SO_4) and concentrated to afford 89.4 g of an oily residue that partially crystallized from pentane. The solid was digested with Et_2O to afford 37.3 g of 9β-ol **2d,** mp 138–140°. The combined mother liquors were distilled at 1 mm. The fraction boiling at 116–126° (29.9 g, 40%) was almost pure **2c,** $n^{28}D$ 1.5562. The pot residue crystallized and afforded another 2.4 g of **2d,** mp 139–142° (54% yield). The mother liquor obtained from this solid (5.1 g) appeared to be a 1:1 mixture of α-alcohol **2f** (3% yield) and β-alcohol **2d** by tlc analysis.

Borane Reduction of 2a by Inverse Addition. A solution of 1850 ml of 1 *M* BH_3 in THF was added over 0.5 hr to 80 g (0.38 mol) of **2a** in 940 ml of THF with stirring under N_2 at room temperature. The solution was then heated under reflux for 24 hr. After standing at room temperature for another 66 hr, it was worked up as in the preceding experiment, affording 93.1 g of oily residue. Distillation at 0.7 mm and collection of the fraction that boiled at 110–123° gave 54.9 g (73%) of almost pure **2c.** A fraction that boiled at 123–140° solidified, giving 11.7 g of **2d,** mp 140–142°. The pot residue afforded another 6.9 g of **2d** (from Et_2O), mp 138–140° (23%).

Borane Reduction of a Mixture of α-Alcohol 2f and β-Alcohol 2d. A solution of 9.6 g of mother liquor from an experiment like the above containing an equal mixture of **2d** and **2f** in 160 ml of THF was added to 250 ml of 1 *M* BH_3 in THF at ice-bath temperature. After 18-hr reflux and work-up as above the crude product showed only two components (**2c** and **2d**) by tlc. Distillation gave 3.6 g of **2c,** bp 115–130° (0.7 mm). The pot residue crystallized and afforded 1.8 g of β-alcohol **2d,** mp 138–140°.

(4b*R*,6*S*,9a*R*)-5,6,7,8,9,9a-Hexahydro-6-(methylamino)-benz[*a*]azulen-10(4b*H*)-one (4). A solution of 3.35 g (0.013 mol) of 2a HCl salt in 300 ml of 95% EtOH was hydrogenated at 3.5 kg/cm² in the presence of 0.3 g of 10% Pd/C. Absorption of 1 mol of H_2 required 2 hr. Removal of the catalyst and solvent afforded 3.4 g of a mixture of HCl salts. Liberation of the free bases with 2 *N* NaOH and extraction with Et_2O gave 3.0 g of a mixture which was chromatographed on 12 preparative plates using 3:97 *i*-$PrNH_2$–Et_2O and six solvent passes. A less polar band afforded 1.3 g (44%) of **4.** A mixture of more polar compounds (0.63 g) was poorly resolved and was not investigated further. Amino ketone **4** formed massive prisms: mp 76–78° (Et_2O–acetone); ir (CCl_4) 3423 cm^{-1}; ir (KBr) 1700 cm^{-1}; nmr δ 1.0–2.4 (m, 9 H, CH_2 and NH), 2.4–3.0 (d, 3 H, NCH_3; m, 1 H, CHN; m, 1 H, ArC**H**), 4.6 (m, 1 H, >CHC=O), and 7.0–8.0 ppm (m, 4 H, aromatic); *m/e* 229.

The HCl salt of 4 melted at 262–264° dec (CH_3CN), $[\alpha]^{25}D$ −22.1°.

Anal. Calcd for $C_{15}H_{19}NO$·HCl: C, 67.79; H, 7.59; Cl, 13.34. Found: C, 67.8; H, 7.7; Cl, 13.5.

Similar results were obtained when the free base was reduced with 10% palladium on carbon in EtOH.

Catalytic Hydrogenation of the Kinetic Dehydration Product of 2d. A solution of 9.7 g (0.042 mol) of 9β-hydroxy compound **2d** in 60 ml of $POCl_3$ was heated under reflux for 3 hr. The excess reagent was removed by warming *in vacuo.* The residue was dissolved in 300 ml of EtOH and hydrogenated at 3.5 kg/cm² in the presence of 0.5 g of 10% Pd/C. When the theoretical amount of H_2 had been absorbed the catalyst and solvent were removed and the residue was treated with NH_4OH and Et_2O. Concentration of the Et_2O layer afforded 8.9 g of crude cis–syn amine **2c** which appeared almost entirely as a single tlc spot of R_f 0.55 (silica, 3:97 *i*-$PrNH_2$–Et_2O). Conversion to the HCl salt and recrystallization from acetone afforded 7.5 g (72%) of **2c,** mp 295–297° dec. Glpc of the base from the mother liquors showed 45% of **2c** (retention time 63 min) and six minor peaks, none of which corresponded to the cis–anti amine **7.**

Dehydration of 9β-ol 2d with $POCl_3$ and Rearrangement of the Product to (1*R*,3*S*)-1,2,3,4-Tetrahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-*c*]pyridine (6). β-Hydroxy compound **2d** (26.4 g, 0.12 mol) and 150 ml of $POCl_3$ were refluxed for 3 hr. The excess reagent was removed by heating *in vacuo.* A small aliquot was treated with dilute NH_4OH. Et_2O extraction gave an oil: uv max 260 nm (ε 10,500), 225 (8000), and 217 (11,900); *m/e* 211; tlc on silica gel (97:3 Et_2O–*i*-$PrNH_2$) a more intense band at R_f 0.45 and a less intense band at R_f 0.40 (uv indicator and Dragendorff spray); nmr δ 6.47 (s, 0.7 H, vinyl) and 6.98–7.50 ppm (m, 4 H, aromatic). When this mixture was refluxed with *p*-toluenesulfonic acid in EtOH for 24 hr, tlc indicated no change in composition. The bulk of the oily residue was dissolved in MeOH and treated with 2.5 g of NaOMe. The mixture was heated under reflux for 1.5 hr and filtered free of NaCl. The filtrate was diluted with Et_2O, washed with saturated NaCl, dried ($NaSO_4$), and concentrated to give 20.0 g of almost pure **6** (84%). Distillation at 112–116° (0.5–0.6 mm) yielded 18.0 g of **6** (74%): *m/e* 221; nmr δ 6.80–7.60 (m, 4 H, aromatic), 3.45 (m, 1 H, CHN), 3.62 (m, 1 H CHN), 3.25 (s, 2 H, CH_2 aromatic), 2.95 (m, 1 H, allylic), 2.80 (m, 1 H, allylic), 2.38 (s, 3 H, CH_3N), and 1.00–2.60 ppm (m, 4 H, CH_2); uv max 260 nm (ε 11,700), 225 (8900), and 217 (13,300); tlc (silica, 97:3 Et_2O–*i*-$PrNH_2$) R_f 0.40.

The HCl salt of 6 melted at 268–270° (from acetone), $[\alpha]^{25}D$ +80.7°.

Anal. Calcd for $C_{15}H_{17}N$·HCl: C, 72,71; H, 7.32; Cl, 14.31. Found: C, 72.6; H, 7.4; Cl, 14.2.

Catalytic Hydrogenation of 6 to Form (1*R*,3*S*,4a*R*,9a*R*)-1,2,3,4,4a,9a-Hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-*c*]-pyridine Hydrochloride (7). A solution of 5.0 g (0.02 mol) of the HCl salt of **6** in 300 ml of 95% EtOH was hydrogenated at 3.5 kg/cm² in the presence of 0.5 g of 10% Pd/C. When 1 mol of H_2 was absorbed, the catalyst and solvent were removed. The crystalline residue (5.0 g) was recrystallized from acetone to give 4.0 g (80%) of **7:** mp 306° dec; $[\alpha]^{25}D$ −27.9°; glpc retention time 68 min; tlc (silica, 97:3 Et_2O–*i*-$PrNH_2$) R_f 0.25; nmr compatible with the assigned structure but without sufficient separation of the 4a and 9a hydrogens.

Anal. Calcd for $C_{15}H_{19}N$·HCl: C, 72.13; H, 8.07; N, 5.61. Found: C, 72.0; H, 8.1; N, 5.6.

Reaction of 7 with EtI. A solution of 100 mg of **7** in 1 ml of acetone was treated with 0.2 ml of EtI. There was almost immediate precipitation of a crystalline solid. After 2 hr, Et_2O was added and a quantitative yield of the ethiodide of **7** was collected. The nmr was consistant with this quaternary salt.

Anal. Calcd for $C_{17}H_{24}NI$: C, 55.29; H, 6.55; I, 34.36. Found: C, 55.1; H, 6.6; I, 34.3.

Attempted Reaction of 2c with EtI. A solution of 100 mg of **2c** in 1 ml of acetone was treated with 0.2 ml of EtI. After 2 hr, Et_2O was added. There was no precipitation. Evaporation of the solvent afforded **2c** (tlc confirmation).

Na–NH_3 Reduction of the Dehydration Product from 2d. A solution of 10 g (0.044 mol) of 9β-ol **2d** in 60 ml of $POCl_3$ was heated under reflux for 3 hr. The excess reagent was removed by warming *in vacuo*. Ice–water and dilute NH_4OH were added and the mixture was extracted with Et_2O. The Et_2O was washed (saturated NaCl), dried (Na_2SO_4), and concentrated to afford 9.2 g of dehydrated product. Tlc indicated an approximately 70:30 mixture of kinetic (**5**) to thermodynamic (**6**) product.

This product in 125 ml of THF was added to 1 l. of NH_3 containing 2.3 g (0.1 g-atom) of Na. After the reaction mixture was stirred for 20 min, 7.5 g of NH_4Cl was added. The NH_3 was evaporated and Et_2O and H_2O were added. The Et_2O layer afforded 9.2 g of crude product which was chromatographed on 500 g of silica gel pretreated with 100 ml of *i*-$PrNH_2$ and air dried. A least polar band, eluted with 3:1 pentane–Et_2O, yielded 3.6 g (38%) of cis–syn compound **2c**, which was identical with **2c** described above by glpc, tlc, ir, and nmr. Its HCl salt melted at 298° dec.

A mid band (0.3 g), eluted with 1:1 Et_2O–pentane, was indicated to be starting material by tlc.

A more polar band, eluted by 99:1 Et_2O–*i*-$PrNH_2$, afforded the cis–anti compound **7** (3.0 g, 32%). Its HCl salt melted at 301° dec and a sample of liberated base was identical with **7** described above (glpc, tlc, ir, and nmr).

Na–NH_3 Reduction of 6. Compound **6** (1.8 g, 8.5 mmol) in 25 ml of THF was added to 0.46 g (0.02 g-atom) of Na in 100 ml of liquid NH_3 and the reaction was worked up in the conventional manner. The HCl salt of the crude product was recrystallized from acetone to give 1.2 g of **7** HCl, mp 303° dec, $[\alpha]^{25}D$ – 27.1°. A sample of liberated base was identical with **7** described above (glpc, tlc, ir, and nmr). Tlc analysis of the reaction mother liquor indicated a 1:1 content of **7** and starting material **6** (estimated total yield of **7** was 80%).

(1*S*,3*R*,4a*R*,9a*R*)-1,2,3,4,4a,9a-Hexahydro-2-methyl-9*H*-1,3-ethanoindeno-[2,1-*c*]pyridin-9-one (2a enantiomer) was prepared from a 1:3 mixture of the enantiomer of **1** and its 2α epimer[1] in the same manner used to prepare **2a**. The analytical sample melted at 78–80° (*n*-pentane), $[\alpha]^{25}D$ –13.6°.

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.2; H, 7.5; N, 6.3.

The HCl salt of 2a enantiomer from acetonitrile exhibited polymorphism, melting at 218–220 and 261° dec (evacuated tube), $[\alpha]^{25}D$ –39.4°.

Anal. Calcd for $C_{15}H_{17}NO{\cdot}HCl$: C, 68.30; H, 6.88; Cl, 13.44. Found: C, 68.3; H, 6.9; Cl, 13.5.

(1*S*,3*R*,4a*R*,9a*R*)-1,2,3,4,4a,9a-Hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-*c*]pyridine hydrochloride (2c enantiomer) was prepared from **2a** enantiomer *via* the thioketal method used for conversion **2a** → **2b** → **2c**.

The analytical sample from acetone melted at 298° dec, $[\alpha]^{25}D$ –95.8°.

Anal. Calcd for $C_{15}H_{19}N{\cdot}HCl$: C, 72.13; H, 8.07; N, 5.61. Found: C, 72.2; H, 8.1; N, 5.6.

Borane reduction of ketone 2a enantiomer in the manner described for **2a** (ketone added to the borane) afforded **2c enantiomer**, bp 120–134° (1–1.5 mm), $n^{27}D$ 1.5552. Its **HCl salt** melted at 298° dec, $[\alpha]^{25}D$ – 93.0°.

Also obtained was **2d enantiomer**, mp 138–140°. The **HCl salt** melted at 220° dec, $[\alpha]^{25}D$ –74.7°.

Anal. Calcd for $C_{15}H_{19}NO{\cdot}HCl$: C, 67.79; H, 7.58; Cl, 13.34. Found: C, 67.5; H, 7.7; Cl, 13.0.

In a similar experiment that was heated under reflux for only 3 hr, **2f enantiomer** was also obtained after chromatography.

The **HCl salt** melted at 282° dec, $[\alpha]^{24}D$ – 62.6°.

Anal. Calcd for $C_{15}H_{19}NO{\cdot}HCl$: C, 67.79; H, 7.58; Cl, 13.34. Found: C, 67.6; H, 7.6; Cl, 13.4.

Platinum Oxide Catalyzed Hydrogenation of 2a Enantiomer. A solution of 0.59 g (2.6 mmol) of **2a** enantiomer in 300 ml of 95% EtOH containing 0.25 g of Pt_2O was hydrogenated at 3.5 kg/cm^2. Removal of the catalyst and solvent gave 0.59 g of an epimeric mixture of alcohols which was separated by plate chromatography (97:3 Et_2O–*i*-$PrNH_2$). The less polar band afforded 150 mg (25%) of somewhat impure **2d** enantiomer, mp 128–135°. The more polar band gave 290 mg (49%) of **2f** enantiomer, mp 99–100°. Ir and tlc comparison of these alcohols with their enantiomers confirmed their identity.

Acknowledgment. We thank Dr. R. K. Kullnig, Miss Catherine M. Martini, and their associates for the spectral data presently reported. Also we thank the Analytical Division of this Institute for the measurement of optical rotations.

Registry No.—**1**, 50372-80-0; 1 enantiomer, 50583-05-6; 1 2α epimer, 50370-54-2; **2a**, 51805-79-9; **2a** enantiomer, 51868-65-6; **2a** HCl, 51868-66-7; **2a** enantiomer HCl, 51897-49-5; **2b**, 51805-80-2; **2c**, 51805-81-3; **2c** HCl, 51829-78-8; **2c** enantiomer HCl, 51829-77-7; **2d**, 51805-82-4; **2d** enantiomer, 51829-79-9; **2d** HCl, 51868-72-5; **2d** enantiomer HCl, 51868-67-8; **2e** methanesulfonate salt, 51805-84-6; **2f**, 51829-80-2; **2f** HCl, 51868-68-9; **2f** enantiomer HCl, 51829-81-3; **4**, 51868-73-6; **4** HCl, 51805-85-7; **6**, 51868-74-7; **6** HCl, 51805-86-8; **7** HCl, 51829-82-4; **7** ethiodide, 51805-87-9; 3β-phenyltropane-2β-carboxylic acid hydrochloride, 50373-05-2; 3β-phenyltropane-2α-carboxylic acid hydrochloride, 51829-83-5.

References and Notes

(1) R. L. Clarke, S. J. Daum, A. J. Gambino, M. D. Aceto, J. Pearl, M. Levitt, W. R. Cumiskey, and E. F. Bogado, *J. Med. Chem.*, **16**, 1260 (1973).
(2) The mixture of these C-2 epimers formed in their preparation[1] can be used directly in this cyclization process.
(3) Spin decoupling of the C-9a H from the C-1 H of **2a** resulted in a doublet with a coupling constant $J_{9a,4a}$ = 7.5 Hz. This corresponds roughly to a dihedral angle of 30°, an angle close to that found in a Dreiding model of **2a**. The trans isomer cannot be formed without damage to the models.
(4) I. Weisz, P. Agocs, M. Halmos, and K. Kovacs, *Acta Chir. (Budapest)*, **56** (2), 195 (1968).
(5) P. v. R. Schleyer, D. S. Trifan, and R. Bacskai, *J. Amer. Chem. Soc.*, **80**, 6691 (1958).
(6) R. E. Lyle, K. R. Carle, C. R. Ellefson, and C. K. Spicer, *J. Org. Chem.*, **35**, 802 (1970).
(7) R. L. Clarke, A. J. Gambino, and S. J. Daum, *J. Med. Chem.*, in press.
(8) W. J. Wechter, *J. Org. Chem.*, **28**, 2935 (1963).
(9) This experiment was done on the *enantiomer* of ketone **2a**, which will be described below.
(10) A. Ebnother and J. Bastian, U. S. Patent 3,573,316 (March 1971).
(11) All melting points were determined in capillary tubes and are not corrected. EtOH (95%) was used for uv spectra, $CHCl_3$ for ir spectra, and $CDCl_3$ for nmr spectra. Optical rotation of bases were measured in $CHCl_3$; those of salts were measured in H_2O. Nmr spectra were recorded on a Varian HA-100 pmr spectrometer with an internal TMS standard, spin-decoupling experiments were done with the same instrument using a Hewlett Packard Audio Oscillator-4204A, uv spectra were recorded on a Cary Model 15 spectrometer, ir spectra were recorded on a Perkin-Elmer Model 21 spectrometer, and hydrogen-bonding studies were done using a Beckman IR-7 instrument. The mass spectra were measured with a Joelco JMS-1-OCS mass spectrograph. Preparative plate chromatography was accomplished using 1-mm thick coatings of Brinkmann P_{254} silica gel on 20 × 40 cm glass plates. Glpc data were obtained from a 6-ft 10% Carbowax column at 210°.

Synthesis and Conformation of [2.2](2,5)Furano(2,5)pyridinophane

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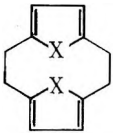
The synthesis of [2.2](2,5)furano(2,5)pyridinophane by a "cross-breeding" reaction between 2,5-dimethylene-2,5-dihydrofuran and 2,5-dimethylene-2,5-dihydropyridine is described. The conformation of the compound is such that the furan ring is essentially perpendicular to the pyridine ring with the oxygen function of the furan ring closer to the C_3–C_4 than to the N–C_6 bond.

Reports describing the syntheses of cyclophanes and studies describing their physical and chemical properties abound.[1] For example, in a series of very elegant papers, Cram and coworkers[2] have shown that in [2.2]paracyclophanes there exist transannular interactions between the benzene rings in these systems. These studies have been extended to include mixed [2.2]paracyclophanes where one ring is pyridinoid and the other is benzenoid.[3]

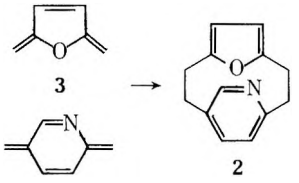
The four isomeric [2.2](2,5)pyridinophanes have also been recently synthesized,[4] as have been the two cyclophanes **1a** and **1b**.[5,6]



1a, X = O
b, X = NCH_3

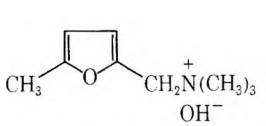
We became interested in preparing the mixed heterocyclophane **2**, since it represents the first example of a mixed heterocyclophane composed of a π-deficient (pyridine) and a π-excessive (furan) ring.

The most reasonable approach to the synthesis of compound **2** appeared to us to be *via* a "cross-breeding" dimerization of compounds **3** and **4**. In this type of reaction, it is,



3 **4** **2**

of course, to be anticipated that the furan dimer **1a**, as well as the isomeric [2.2](2,5)pyridinophanes, will also be formed. Compounds **3** and **4** were generated *in situ* from the quaternary hydroxides **5** and **6**, respectively; the cross-



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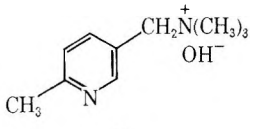

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breeding reaction was carried out in refluxing toluene, and the reaction mixture was subjected to dry-column chromatography. The proportions of the various possible products expected were those reported in Table I. Along with these cyclophanes, a substantial amount of the ether **7**, as ob-

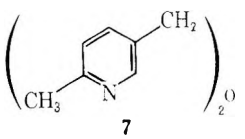

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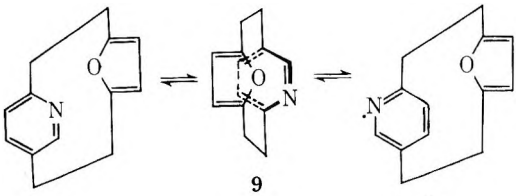
Table I
Reaction Products Distribution

Compd[a]	% of total product
	48
21a	18
Mixture of [2,2](2,5)pyridinophanes[b]	4
7	30

[a] See text for structures. [b] Identified by pmr spectra (*cf.* ref 4).

served in the formation of the pyridinophanes,[4] was obtained.

The desired compound, **2**, was identified by its correct elemental analysis, mass spectrometric molecular weight, and pmr spectrum. It is obvious that compound **2** could exist as conformer **8**, **9**, or **10** or as a rapidly equilibrating mixture of these three conformers. The latter possibility



8 **9** **10**

appears to be a fairly unlikely one in view of the fact that Dreiding models rule out a facile interconversion of the structures. In order to establish the correct structure for this mixed paracyclophane an analysis of its uv and pmr spectra was undertaken.

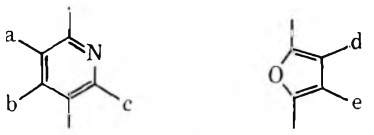
A comparison of the uv spectra of the furanophane **1a** with that of compound **2** shows that the furan absorption in compound **2** (λ_{max} 224 nm) is the same as that found in the furanophane (λ_{max} 222 nm). In the latter instance it has been established that the compound exists in the staggered conformation **11**.

11

Consequently, one can suggest that there is no transannular interaction of the π clouds of the furan ring with those of the pyridine ring in compound **2**.

The furan protons of the furan dimer **1a** (δ 6.05 ppm) are deshielded by 0.25 ppm in comparison to 2,5-dimethylfuran (δ 5.80 ppm), while those of the mixed dimer **2** resonate at δ 5.69 and 5.75 ppm, respectively (see Table II). Thus, in the staggered conformation of the furan dimer **11** the furan protons are subject to a deshielding effect, while in the configuration of the mixed dimer **2**, the protons are experienc-

Table II
Pmr Spectral Data[a]

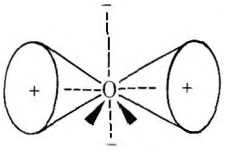


Compd[b]	H_a	H_b	H_c	H_d	H_e
2,5-Dimethylfuran				5.80	
2,5-Dimethylpyridine	7.00	7.34	8.30		
1a[c]				6.05	
2[d]	6.90	7.16	7.72	5.69	5.75

[a] In parts per million (δ). [b] Dilute solutions in $CDCl_3$. [c] See text for structures. [d] The pmr spectrum, in $CDCl_3$ or DMSO, is temperature independent from -50 to 60°, and in C_5D_5N from room temperature to 110°.

ing a slight shielding effect, with respect to the furan protons in 2,5-dimethylfuran. Thus, these protons are not influenced by the pyridine ring anisotropic effects. There are, however, significant shielding effects operating on the pyridine ring of dimer **2** where the α, γ, and δ protons are shielded, with respect to those in 2,5-dimethylpyridine, by 0.58, 0.18, and 0.10 ppm, respectively. Consequently, one must conclude that compound **2** exists neither as conformer **8** nor conformer **10**.

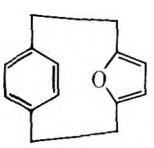
In view of the fact that the pyridine α proton in compound **2** is considerably more shielded than are the γ and δ protons, and keeping in mind that the estimated anisotropic effects in ether-type oxygens are represented by drawing **12**, one can strongly suggest that the correct room-temper-



12

ature configuration for compound **2** in solution is representation **9** with the furan oxygen somewhat more closely situated toward the N_1–C_6 bond than toward the C_4–C_5 bond.

A variable-temperature pmr study of compound **2** (110° in C_5D_5N to room temperature, and room temperature to -50° in $CDCl_3$) showed no spectral changes in this temperature region. This behavior is surprising in view of the report that compound **13** is described as undergoing the type



13

of inversion as indicated for the similar conformers **8** and **10**.[9]

Experimental Section

Nmr spectra were obtained with a Varian HA-100 spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector. The ionizing voltage employed was 80 eV. Elemental analyses were determined by the Analytical Services Laboratory of the University of Alabama Chemistry Department.

6-Methyl-*N,N'*-dimethylnicotinamide. Ethyl 2-methyl-5-ethylnicotinate[8] (25.5 g, 0.15 mol) was stirred at room temperature with an excess of a saturated aqueous solution of dimethylamine. After 30 hr, the clear reaction mixture was extracted with $CHCl_3$ and washed with 50 ml of H_2O and 2 × 50 ml of a saturated aqueous solution of NaCl. The organic layer was dried over anhydrous Na_2CO_3. The reaction mixture was distilled at 115–120° (1 Torr) and 12.5 g (50% yield) of product was collected: mol wt 164 (mass spectrum); pmr spectrum δ_{TMS} ($CDCl_3$) 7.67 (1 H, d of d), 7.18 (1 H, d), 8.54 (1 H, d), 3.05 [6 H, $-N(CH_3)_2$, s], 2.56 (3 H, $-CH_3$, s).

2-Methyl-5-dimethylaminomethylpyridine. 6-Methyl-*N,N'*-dimethylnicotinamide (8.55 g, 0.052 mol) in 100 ml of ether was added dropwise to a slurry of $LiAlH_4$ (1.9 g in 100 ml of ether) and the reaction mixture was refluxed with stirring overnight. Water (2.7 ml) was then added to destroy the excess of $LiAlH_4$. The reaction mixture was then filtered, the filtrate was dried over anhydrous Na_2CO_3, the solvent was evaporated, and the product was distilled at 53–55° (1 Torr). The product, 3.59 g (46.1% yield), was collected: mol wt 150 (mass spectrum); pmr spectrum δ_{TMS} ($CDCl_3$) 8.38 (1 H, d), 7.53 (1 H, 2 d), 7.10 (1 H, 5 d), and singlets at 3.38 (2 H, $-CH_2-$), 2.53 (3 H, $-CH_3$), and 2.22 [6 H, $-N(CH_3)_2$], respectively.

2-Methyl-5-trimethylaminomethylpyridinium Iodide. 2-Methyl-5-dimethylaminomethylpyridine (3.59 g, 0.024 mol) was dissolved in 50 ml of ether, and methyl iodide (4.48 g, 0.031 mol) in 50 ml of ether was added slowly with stirring at room temperature. After stirring overnight, the reaction mixture was filtered and the off-white solid was washed with ether and dried (6.4 g, 91.7% yield).

Anal. Calcd for $C_{10}H_{17}N_2I$: C, 41.11; H, 5.87; N, 9.59. Found: C, 41.00; H, 6.17; N, 9.37.

[2.2](2,5)Furano(2,5)pyridinophane. 2-Methyl-5-trimethylaminomethylpyridinium iodide (1.2 g, 0.004 mol) and 5-methyl-2-furfuryltrimethylammonium iodide (1.1 g, 0.004 mol) were dissolved in 100 ml of water and the resulting solution was stirred with 2.5 g of freshly prepared Ag_2O for a period of 1 hr. The mixture was filtered and the filtrate was freeze-dried. The remaining solid was suspended in 300 ml of toluene, a small amount of hydroquinone was added, the stirred mixture was heated at reflux, and the water that was formed was collected in a Dean-Stark trap. After 2 hr, no more trimethylamine was formed and the reaction was judged complete. The reaction mixture, after cooling to room temperature, was filtered and the filtrate was concentrated *in vacuo* to dryness. The remaining oily material was then subjected to dry-column chromatography (15 × 1 in., neutral alumina, 100–200 mesh, Brockman grade III), using ether as a developing solvent. By examining the behavior of the reaction mixture on tlc (identical conditions with the dry-column chromatogram) (visualization with I_2), the location of the various components on the dry-column chromatogram was ascertained. The various zones were then collected and the compounds were extracted from the alumina with methylene chloride. In this manner four different components were obtained.

These compounds were identified respectively as (1) [2.2](2,5)furanophane (**1a**, 250 mg, 16%, mp 189–191° dec) by comparison with an authentic sample;[6] (2) [2.2](2,5)furano(2,5)pyridinophane [100 mg, 6.3%, mp 86–87° after vacuum sublimation at 60° (1 Torr)] (*Anal.* Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.63; N, 7.05. Found: C, 78.11; H, 6.89; N, 6.78) (*cf.* also pmr and uv data in tables); (3) a mixture of the isomers of [2.2](2,5)pyridinophane (20 mg, 1.2%) by comparison with the reported pmr spectra, and the mass spectrometric molecular weight of 210;[4] (4) the ether **7** (190 mg, 10.3%) by comparison with an authentic sample.[4]

Registry No.—**1a**, 5088-46-0; **2**, 51849-29-7; **7**, 34107-45-4; 6-methyl-*N,N*-dimethylnicotinamide, 51849-30-0; ethyl 2-methyl-5-ethylnicotinate, 22701-39-9; dimethylamine, 124-40-3; 2-methyl-5-dimethylaminomethylpyridine, 51849-31-1; 2-methyl-5-trimethylaminomethylpyridinium iodide, 51849-32-2.

References and Notes

(1) For a review, see F. Voegtle and P. Neumann, *Synthesis*, 85 (1973).
(2) D. J. Cram and D. G. Hefelfinger, *J. Amer. Chem. Soc.*, **93**, 4754 (1971), and numerous earlier papers.
(3) J. Bruhin and W. Jenny, *Chimia*, **26**, 420 (1972).
(4) J. Bruhin and W. Jenny, *Chimia*, **26**, 238 (1971).
(5) J. Bruhin and W. Jenny, *Chimia*, **25**, 310 (1971).
(6) H. E. Winberg, F. S. Fawcett, W. E. Mochel, and C. W. Theobald, *J. Amer. Chem. Soc.*, **82**, 1428 (1960).
(7) H. H. Wasserman and D. T. Bailey, *Chem. Commun.*, 107 (1970).
(8) P. A. Plattner, W. Keller, and A. Boller, *Helv. Chim. Acta*, **37**, 1379 (1954).
(9) (a) J. F. Haley, Jr., and P. M. Keehn, *Tetrahedron Lett.*, 4017, 4021 (1973); (b) G. M. Whitesides, B. A. Pawson, and A. C. Cope, *J. Amer. Chem. Soc.*, **90**, 639 (1968).

Formation of Pyrroles from Dihydro-1,3-oxazines[1]

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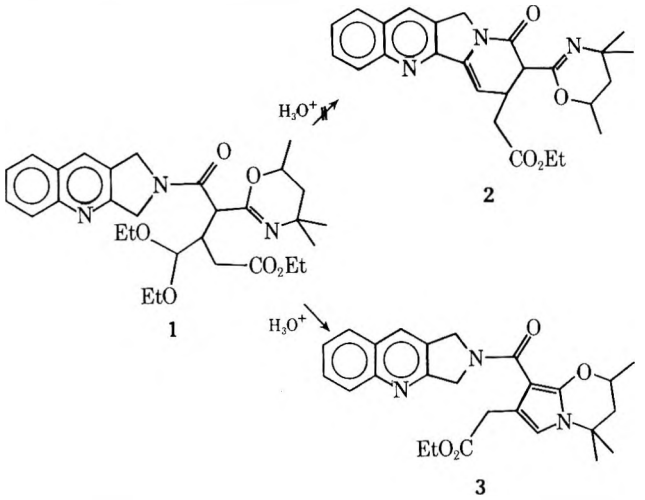
The reaction of carboethoxymethyloxazines with electrophilic aldehydes or olefins leads to a facile approach to polysubstituted pyrroles. The method allows, by appropriate choice of condition, either *N*-alkylpyrroles or fused pyrrolooxazines.

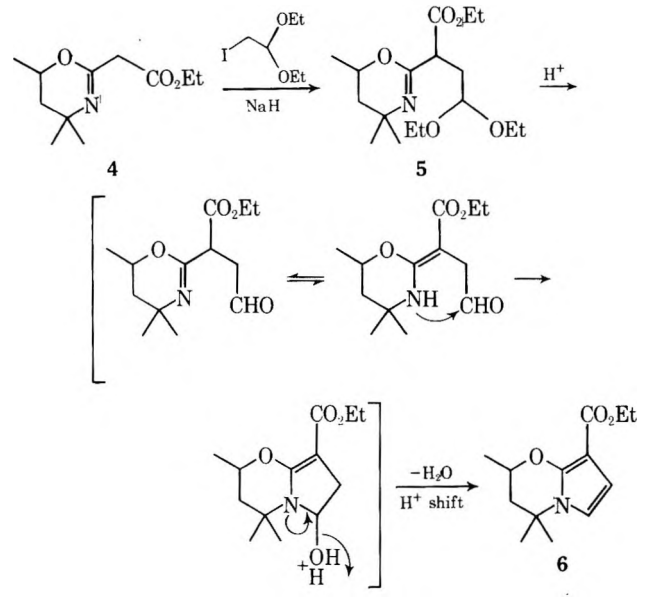
During the course of our total synthesis of camptothecin[3] we observed an unusually facile reaction involving the advanced intermediate **1** when an attempt was made to effect cyclization to the dihydropyridone **2**. Upon acid-catalyzed hydrolysis of **1**, none of the desired fused tetracyclic system could be obtained, although the fused pyrrole **3** was formed in 80% yield. After various attempts to circumvent this



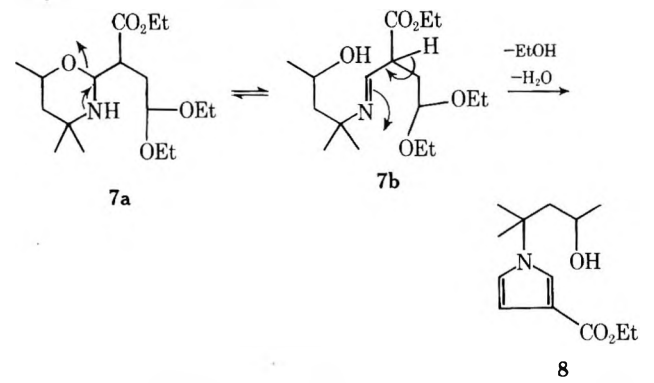
2 **1** **3**

"undesirable" reaction, it soon became clear that **3** was the result of a much more favorable process than that leading to **2**. A study was undertaken to assess the generality of this pyrrole formation utilizing simpler systems and indeed proved that our anticipations were justified.

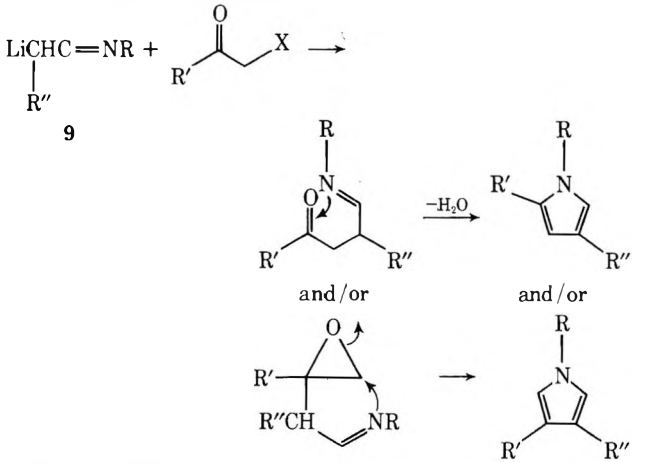
The oxazine ester **4** was employed as a suitable starting material, since it was readily available.[4] Alkylation of oxazine ester **4** with iodoacetaldehyde diethyl acetal in dimethyl sulfoxide using sodium hydride as base afforded the acetal ester **5** in 78% yield. Treatment of the latter with a catalytic amount of trifluoroacetic acid in refluxing toluene, which had not been dried, for 2 hr led to the pyrrolooxazine **6** in 98% yield. None of the intermediates (proposed in brackets) could be isolated or detected in the crude reaction product. It was further found that reduction of the C=N link in **5** with aqueous sodium borohydride (−30°, pH 4–6)[4] gave **7a** in 92% yield as a crystalline product. Treatment of **7a** with a catalytic amount of trifluoroacetic acid in refluxing toluene led to an 83% yield of the *N*-alkyl-3-carboethoxypyrrole **8**. Mechanistically, the pyrrole may be envisioned as arising from the ring–chain tautomerism[4] as shown in intermediates **7a,b** which ultimately undergoes ring closure after releasing the formyl group. This facile pyrrole synthesis is related to that recently reported by Wittig[5] which involves the reaction of lithio imines **9** with α-halo ketones. This reaction, however, may



4 **5** **6**



7a **7b** **8**



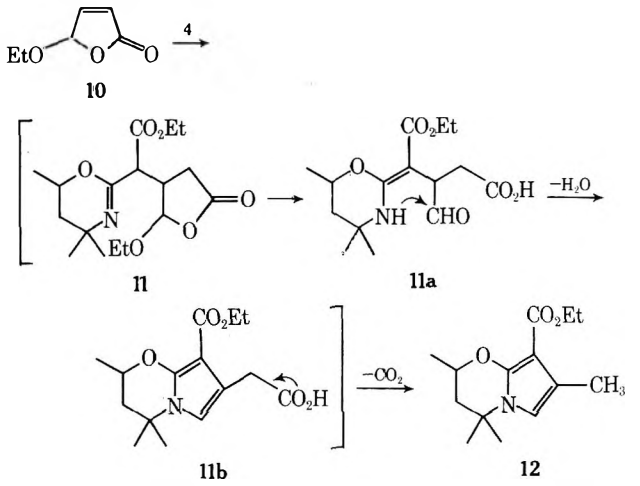
9

give rise to certain mixtures of isomers because of its dual pathway (*via* halide displacement or epoxide formation).

Another interesting reaction which led to pyrrole formation occurred when the ester oxazine **4** was treated with the unsaturated lactone **10** in acetonitrile or ethanol as solvent at 130–150° (sealed tube). No trace of the expected lactone **11** was observed. Instead, the pyrrole **12** was formed in 91% yield.

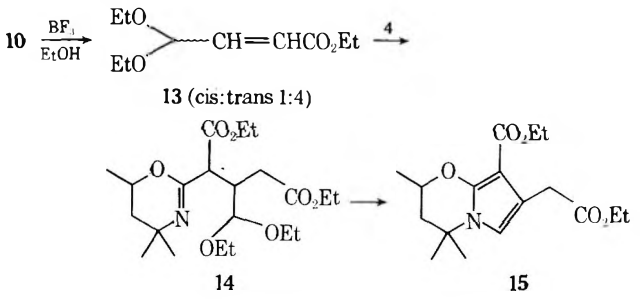
Although lactone **11** could not be detected in the reaction mixture, it most likely is a transient intermediate in the

formation of **12**. Following its formation, traces of water in the reaction mixture (the acetonitrile was not dried) would be expected to hydrolyze the lactone **11** to the aldehyde acid **11a**. With the free aldehyde now present, condensation to the pyrrole **11b** would occur followed by decarboxylation to give the pyrrole **12**. A similar mode of decarboxyla-



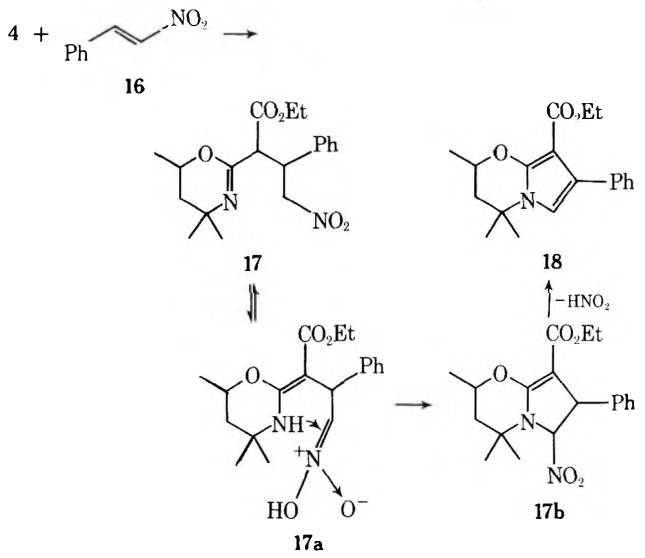
tion was noted for the free acid of **3** producing the corresponding methyl derivative.[3]

When lactone **10** was transformed into the unsaturated ester[3] **13** and treated with oxazine ester **4** (145°, EtOH, OEt^-), the adduct **14** was obtained in 62% yield. Heating



the latter at reflux in toluene containing a trace of trifluoroacetic acid produced the fused pyrrole **15** in 78% yield. Thus, while the free carboxylic group in **11b** is unstable and undergoes decarboxylation to **12**, the carboethoxy group in **14** remains intact en route to the pyrrole diester **15**. This was verified by hydrolysis of **14** in aqueous ethanol containing dilute hydrochloric acid. Under these conditions, a mixture (1:1) of **12** and **15** was indeed obtained.

The most novel and least expected pyrrole formation was



observed when 1 equiv each of the oxazine ester **4** and β-nitrostyrene (**16**) were refluxed in *tert*-butyl alcohol for 20 hr. The crude viscous residue, after chromatography on basic alumina, afforded two products. The major component (63% yield) was the expected Michael addition product **17** while the minor component (28% yield) was fully characterized as the pyrrole **18**.

From a comparison of the infrared spectrum of the crude reaction product with that of the pyrrole **18**, it appears as though **18** was formed as a result of the reaction conditions, and not during the chromatographic separations.

If this is the case, the direct pyrrole formation may be considered to pass through intermediates **17a** and **17b** in an intramolecular Nef-type reaction. No attempt was made to optimize the pyrrole formation *via* the β-nitrostyrene route.

An effort was made to remove the *N*-alkyl group in the monocyclic pyrroles **8**, which would then lead to the unencumbered nucleus. Hydrolytic, photochemical, thermal and retro Michael additions (on the corresponding ketone) all failed to dealkylate **8**.[6]

In summary, a route to monocyclic pyrroles and their fused homologs appears viable from oxazine esters and their derivatives (amide-containing oxazines)[3] which place various substituents at the 1 and/or 2, 3, and 4 positions of the pyrrole nucleus.

Experimental Section[7]

Oxazine Ester Diethyl Acetal 5. To the oxazine **4** (5.0 g, 0.0235 mol) under an atmosphere of nitrogen in 25 ml of dry dimethyl sulfoxide (distilled from calcium hydride) was added sodium hydride (0.57 g, 1.0 g of 57% oil dispersion, 0.0235 mol). After hydrogen evolution had ceased, iodoacetaldehyde diethyl acetal (5.73 g, 0.0235 mol) was added dropwise at room temperature over a period of 10 min. The reaction mixture was then stirred for 16 hr, poured into 100 ml of ice water, and extracted with chloroform. The combined extracts were washed with water several times, dried over anhydrous potassium carbonate, and evaporated *in vacuo* to a yellow oil. Distillation (92–98°, 0.06 mm) afforded 6.0 g (78% yield) of **5** as a colorless oil. The analytical sample was chromatographed on silica gel (tlc, eluted with ether) followed by distillation (90–95°, 0.05 mm): ir (film) 1640, 1675, 1140–1120 cm^{-1}; nmr ($CDCl_3$) δ 4.58 (t, 1 H), 4.19 (t, 2 H, J = 7 Hz), 3.2–3.9 (complex multiplet, 5 H), 2.3–1.4 (m, 3 H), 1.4–1.1 (m, complex, 18 H); *m/e* 329 (molecular ion).

Anal. Calcd for $C_{17}H_{31}NO_5$: C, 61.98; H, 9.48; N, 4.25. Found: C, 61.82; H, 9.61; N, 4.32.

Pyrrolooxazine 6. To the oxazine acetal **5** (0.83 g, 2.52 mmol) in 10 ml of toluene was added trifluoroacetic acid (0.1 ml) and the reaction mixture was fitted with a Dean-Stark trap and refluxed under a nitrogen atmosphere for 2 hr. After cooling, the reaction mixture was washed with 10 ml of saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate and the toluene was removed under vacuum. The pale orange oil crystallized, 0.59 g (98% yield). The analytical sample was recrystallized twice from petroleum ether–ether: mp 82–83°; ir (neat) 1675, 1550 cm^{-1}; nmr ($CDCl_3$) δ 6.44 (d, 1 H, J = 4 Hz), 6.25 (d, 1 H, J = 4 Hz), 4.25 (q superimposed on a multiplet, 2 H, J = 7 Hz, m, 1 H), 1.90 (d, 2 H, J = 6 Hz), 1.47 (d, 3 H, J = 7 Hz), 1.50 (s, 6 H), 1.30 (t, 3 H, J = 7 Hz); *m/e* 237 (molecular ion).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07. Found: C, 65.67; H, 7.90.

Tetrahydro-1,3-oxazine Acetal 7a. To the oxazine acetal **5** (1.64 g, 0.0050 mol) in 8 ml of tetrahydrofuran and 8 ml of ethanol (95%) cooled to −35 to −45° at pH 5 (made acidic at −35° with 9.7% hydrochloric acid solution) was added sodium borohydride solution dropwise (0.19 g, 0.005 mol dissolved in 1.5 ml of water and stabilized with 1 drop of 40% sodium hydroxide solution). During the slow addition of the borohydride solution (~20 min), the pH of the reaction mixture was maintained at 5 by dropwise addition of 9.7% hydrochloric acid solution as needed. After all the borohydride had been added, stirring was continued at −35 to −45° for 1 hr and then the reaction mixture was poured into a two-phase system of water (50 ml) (3 drops of 40% sodium hydroxide solution added) and dichloromethane (50 ml). After several extrac-

tions with dichloromethane, the combined extracts were dried over sodium sulfate, filtered and evaporated *in vacuo* to a pale yellow oil, 1.51 g.

The ir spectrum of the product showed only a very small amount of dihydrooxazine remaining. The product crystallized from pentane in the freezer: mp 54–55°; ir (neat) 3230, 1735 cm^{-1}; nmr ($CDCl_3$) δ 4.28 (4 H, complex multiplet), 3.60 (5 H, complex multiplet), 2.52 (1 H, J = 6.5 Hz), 2.0 (2 H, t, J = 6 Hz), 1.12 (m, 21 H); *m/e* 331 (molecular ion).

Anal. Calcd for $C_{17}H_{33}NO_5$: C, 61.60; H, 10.04; N, 4.23. Found: C, 61.51; H, 10.02; N, 4.29.

N,3-Disubstituted Pyrrole 8. The tetrahydrooxazine **7a** (0.55 g, 2.30 mmol) in 10 ml of toluene, along with a catalytic amount of trifluoroacetic acid, were refluxed for 2 hr under an atmosphere of nitrogen. The cooled solution was washed with 10 ml of saturated sodium bicarbonate solution, dried over anhydrous potassium carbonate, and concentrated *in vacuo* to an oil, 0.413 g. The total product was chromatographed on silica gel (tlc, 20 × 40 cm plate, eluted with acetone) and distilled (135–145°, 0.02 mm) to give 0.33 g (83% yield) of oily product: ir (film) 3350, 1705, 1695, and 1540 cm^{-1}; nmr ($CDCl_3$) δ 7.50 (m, 1 H), 6.82 (m, 1 H), 4.28 (q, 2 H, J = 7 Hz), 3.66 (m, 1 H), 1.92 (s, 1 H), 1.91 (s, 1 H), 1.66 (s, 3 H), 1.59 (s, 3 H), 1.33 (t, 3 H, J = 7 Hz), 1.10 (d, 3 H, J = 6 Hz); *m/e* 239 (molecular ion).

Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.41; H, 9.06; N, 5.96.

Pyrrolooxazine 12. The oxazine ester **4** (0.32 g, 1.5 mmol) and the lactone **10** (0.192, 1.5 mmol)[3] in 1 ml of dry ethanol were heated in a sealed Pyrex tube for 24 hr at 130–140°. The tube was cooled in a Dry Ice–acetone bath and opened, and the solvent was removed under vacuum. The deep scarlet residue partially crystallized. Trituration with ether–petroleum ether gave 0.097 g of light yellow crystalline solid, mp 107–108°. Evaporation of the filtrate gave a red oil which was chromatographed on silica gel (8.5 × 1 cm column) and eluted with ether. The first fractions afforded an additional 0.09 g of pyrrole (total yield 50%). The product was purified by sublimation (100–110°, 0.02 mm): mp 111–112.5°; ir (KBr) 1675, 1535 cm^{-1}; nmr ($CDCl_3$) δ 6.06 (q, 1 H, J = 1.5 Hz), 4.27 (q, superimposed on a multiplet, 2 H, J = 7 Hz, m, 1 H), 2.2 (d, 3 H, J = 1.5 Hz), 1.95 (s, 1 H), 1.83 (s, 1 H), 1.50 (d, 3 H, J = 6 Hz), 1.50 (s, 6 H), 1.30 (t, 3 H, J = 7 Hz); *m/e* 251 (molecular ion).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.13; H, 8.40; N, 5.64.

When the oxazine ester **4** (0.93 g, 4.39 mmol) and the lactone **10** (0.56 g, 4.38 mmol) were heated at 140–150° for 4 hr in a sealed Pyrex tube in acetonitrile solvent and worked up as above, 1.0 g (91% yield) of **12** was obtained, mp 108–110°. The ir and nmr spectra were superimposable with those of the product obtained above.

Oxazine Diester 14. To the oxazine ester **4** (0.400 g, 1.88 mmol) and the unsaturated ester **13** (0.442 g, 2.18 mmol)[3] in 1.5 ml of dry ethanol (distilled from calcium hydride) in a Pyrex tube was added a catalytic amount of sodium ethoxide (prepared by dissolving ~15 mg of sodium metal in 0.3 ml of dry ethanol and then using 3 drops of this solution). The tube was sealed and heated at 145° for 42 hr. Concentration of the reaction mixture gave a viscous oil. The product **14** distilled at 120–145° (0.06 mm) (0.485 g, 62% yield): ir (film) 1740, 1670 cm^{-1}; *m/e* 415 (molecular ion).

Anal. Calcd for $C_{21}H_{37}NO_7$: C, 60.70; H, 8.98; N, 3.37. Found: C, 60.84; H, 9.01; N, 3.52.

Pyrrolooxazine 15. To the acetal **14** (0.357 g, 0.861 mmol) in 10 ml of toluene was added trifluoroacetic acid (3 drops), the flask was fitted with a Dean-Stark trap, and the contents were refluxed under a nitrogen atmosphere for 2 hr. The cooled solution was washed with 10 ml of saturated sodium bicarbonate solution and dried over sodium sulfate. The solvent was evaporated *in vacuo* to give 0.304 g of crude product which crystallized in a freezer overnight, 0.215 g (78% yield). The product crystallized from petroleum ether (bp 30–60°) (ether was used to dissolve product and then boiled off). Recrystallization from the same solvent system afforded the analytical sample: mp 94–95.5°; ir (film) 1740, 1675, 1550 cm^{-1}; nmr ($CDCl_3$) δ 6.24 (t, 1 H, J = 1.5 Hz), 4.21 (q, 2 H, J = 7 Hz), 4.28 (q, 2 H, J = 7 Hz), ~4.3 (m, 1 H), 3.68 (d, 2 H, J = 1.5 Hz), 1.92 (s, 1 H), 1.82 (s, 1 H), 1.48 (d, 3 H, J = 6 Hz), 1.48 (s, 6 H), 1.30 (t, 3 H, J = 7 Hz), 1.27 (t, 3 H, J = 7 Hz); *m/e* 323 (molecular ion).

Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 62.97; H, 7.98; N, 4.48.

Michael Addition of 4 to β-Nitrostyrene. Formation of 17 and 18. The oxazine ester **4** (2.88 g, 0.0135 mol) and β-nitrostyrene (**16**, 2.01 g, 0.0135 mol) were refluxed for 20 hr in dry *tert*-butyl alcohol. The solvent was evaporated *in vacuo* to give a light amber colored oil. The total product was chromatographed on alumina (Fisher, 80–200 mesh, 20 × 4 cm column). Elution was begun with benzene (650 ml), followed by increasing proportions of dichloromethane in benzene (5, 15, 25, 30, and 50%). These fractions afforded 1.3 g (28% yield) of pyrrole **18**: mp 136–137°; ir (mineral oil) 1700, 1545 cm^{-1}; nmr ($CDCl_3$) δ 7.41 (m, 5 H), 6.27 (s, 1 H), 4.13 (q, 2 H, J = 7 Hz), 4.43 (m, 1 H), 1.90 (d, 2 H), 1.5 (d, 2 H, J = 6 Hz), 1.5 (s, 6 H), 1.12 (t, 3 H, J = 7 Hz); *m/e* 313 (molecular ion).

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.89; H, 7.74; N, 5.08.

Continued elution with dichloromethane and finally 95% ethanol afforded 3.0 g (63% yield) of viscous oil. The spectral data are consistent with **17**: ir (film) 1740, 1600, 1555 cm^{-1}; nmr ($CDCl_3$) δ 7.3 (m, 5 H), 5.15–4.80 (m, 2 H), 4.64–3.40 (m, 4 H), 1.80–0.7 (m, 14 H); *m/e* 362 (molecular ion).

Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found: C, 62.68; H, 7.23; N, 7.77.

Iodoacetaldehyde Diethyl Acetal. To bromoacetaldehyde diethyl acetal (Aldrich, 19.7 g, 0.10 mol) in 250 ml of acetone was added sodium iodide (75.0 g, 0.2 mol) and the reaction mixture was refluxed for 6 days. The precipitated salts were removed by filtration and the solvent was evaporated *in vacuo*. The resulting mass was triturated with ether and the precipitate was filtered. Evaporation of the ether *in vacuo* gave a red oil. Distillation (32–34°, 0.075 mm) afforded 17.5 g (71% yield) of light yellow oil. The product was decolorized by filtration through finely ground sodium bisulfite: nmr (CCl_4) δ 4.60 (t, 1 H, J = 5.5 Hz), 3.56 (two quartets, 4 H, J = 7 Hz), 3.20 (d, 2 H, J = 5.5 Hz), 1.20 (t, 6 H, J = 7 Hz).

Anal. Calcd for $C_6H_{13}O_2I$: C, 29.5; H, 5.32; I, 52.1. Found: C, 29.43; H, 5.33; I, 52.09.

Acknowledgment. This study was supported by the National Institutes of Health.

Registry No.—**4**, 36867-19-3; **5**, 34579-33-4; **6**, 34579-31-2; **7a**, 34579-27-6; **8**, 34579-26-5; **10**, 2833-30-9; **12**, 51806-19-0; *cis*-**13**, 10602-40-1; *trans*-**13**, 2960-65-8; **14**, 34579-32-3; **15**, 34579-30-1; **16**, 102-96-5; **17**, 34579-29-8; **18**, 34579-28-7; iodoacetaldehyde diethyl acetal, 51806-20-3; bromoacetaldehyde diethyl acetal, 2032-35-1.

References and Notes

(1) Part 24 of a study on the chemistry of dihydro-1,3-oxazines. For previous papers in this series see G. R. Malone and A. I. Meyers, *J. Org. Chem.*, **39**, 623 (1974). A preliminary report of this study has appeared: A. I. Meyers, T. A. Narwid, and E. W. Collington, *J. Heterocycl. Chem.*, **8**, 875 (1971).
(2) Address all correspondence to this author at Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521.
(3) A. I. Meyers, R. L. Nolen, E. W. Collington, T. A. Narwid, and R. C. Strickland, *J. Org. Chem.*, **38**, 1974 (1973).
(4) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).
(5) G. Wittig, R. Roderer, and S. Fischer, *Tetrahedron Lett.*, 3517 (1973).
(6) We thank Dr. Harvey Taylor for performing these experiments.
(7) All melting points are uncorrected. Microanalyses were performed by Midwest Microlabs, Indianapolis, Ind.

Variations of the Fischer and Piloty Syntheses

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The methyl iodide induced conversion of *N*-methylphenylhydrazones to indoles has been studied and an enehydrazine intermediate **3c** has been isolated. N'-Protonation of the enehydrazine leads to a facile electrocyclic ring closure. Ketazinium methiodides have been converted to pyrroles by heating. Action of acetic anhydride on cyclopentylketazine intercepted an intermediate in the pyrrole synthesis as the acetyl derivative of a tautomer **15**. Some modifications of the known reaction of carbonyl compounds with *N'*-methylhydrazines and phenylhydrazines are described.

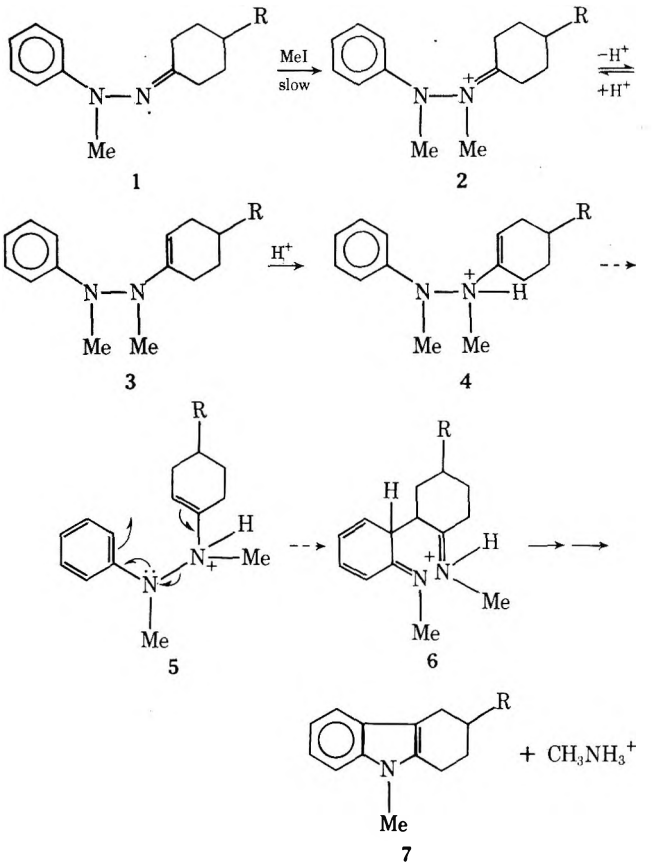
During the course of another research program, 4-cyclohexylcyclohexanone α-methylphenylhydrazone (**1b**) was treated with methyl iodide with the expectation that a hydrazonium salt would result from methylation at the α-nitrogen atom; instead cyclization to the indole **7b** occurred. The unusually mild conditions involved, especially the absence of deliberately added acid, suggested that further study of this system might lead to better understanding of some of the steps of the Fischer indole synthesis.[2] The ideas developed during this phase of the work led to investigation of other indolization procedures, and of the similar Piloty[3] synthesis of pyrroles.

Results and Discussion

Reaction of Phenylhydrazones with Methyl Iodide. A solution of hydrazone **1b** in excess methyl iodide began to deposit a solid within 30 min and precipitation continued slowly at room temperature. After 12 hr the precipitate comprised a nearly quantitative yield of methylammonium iodide, and from the filtrate a good yield of indole **7b** was isolated. Attack of methyl iodide on the hydrazone appears to occur exclusively at the β-nitrogen atom, rather than at the α-nitrogen atom as is true with dimethylhydrazones.[4] No intermediates were observed when the reaction was carried out in the sample cell of an infrared spectrometer, with repeated scanning over several hours; therefore the first step in the reaction sequence, presumably formation of the hydrazinium salt **2** (Scheme I), is rate determining. Hence all subsequent steps are quite rapid at room temperature, including the key conversion of **4** into **6**. This conclusion is supported by the fact that no products are found that result from further methylation of intermediates; these react faster along the path leading to indole than they react with methyl iodide.

To explore the question of acid catalysis in steps following the initial methylation, the reactions of hydrazones **1a**, **1b** and **1c** with methyl iodide were carried out under a variety of proton-scavenging conditions. A limitation on the choice of bases which might be employed is that they must not react with methyl iodide. In the presence of an excess of the hindered amines 2,6-diisopropylpyridine and *N,N*,2,6-tetramethylaniline,[5] **1b** again furnished the indole and methylammonium iodide, although the isolated yield of **7b** from the second solvent was only 28% owing to separation problems. Although these media are formally basic, proton transfer from various ammonium ions which might be present is not precluded. It was found that in methanol solution at room temperature, *N,N*,2,6-tetramethylanilinium iodide slowly catalyzes indole formation from the hydrazone, but methylammonium iodide does not. In the methyl iodide promoted reactions, since methylammonium iodide is produced, direct acid catalysis of indolization by the anilinium ion is eliminated, but acid catalysis of subsequent steps by the methylammonium ion remains a possibility.

Scheme I

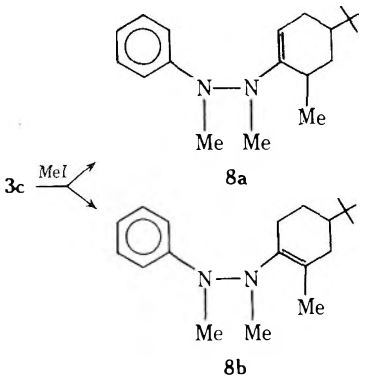


a, R = H
b, R = cyclohexyl
c, R = *tert*-butyl

Treatment of hydrazone **1b** with methyl iodide in a vigorously stirred suspension of anhydrous potassium carbonate in 2-butanone still produced the indole in substantial yield. When the ketone was replaced by the more basic dimethylformamide (DMF), no indole was found. High-vacuum distillation of the product of this reaction gave a viscous oil which could not be purified further nor completely characterized. Spectral and chemical evidence suggested that it was a mixture of enehydrazines containing some C-methylated components. To resolve the problem, two other hydrazones were subjected to similar reaction conditions. Cyclohexanone α-methylphenylhydrazone (**1a**) still gave the indole **7a**. This indicates that the 4-cyclohexyl group of **1b** decreases its rate of indolization, probably by conformational effects in the transition state for cyclization; there-

fore the even bulkier *tert*-butyl group was employed in the next experiments.

4-*tert*-Butylcyclohexanone α-methylphenylhydrazone (**1c**) was treated with 1.2 equiv of methyl iodide in a stirred K_2CO_3–DMF suspension at room temperature, furnishing a 90% yield of the enehydrazine **3c** after appropriate work-up. When only 1 equiv of methyl iodide was used, some unreacted hydrazone remained; when a large excess of methyl iodide was used, the product was a mixture of the C-methylated enehydrazines **8a** and **8b**. Apparently C-methylation of the enehydrazine is somewhat slower than N-methylation of the hydrazone.



It was curiously difficult to find efficient conditions for the cyclization of **3c**, considering that **1c** in methyl iodide alone gave the indole in high yield at room temperature. With catalytic or equivalent amounts of strong acids at room temperature, no indole was formed during several hours. After **3c** was allowed to stand overnight at room temperature with 0.5 equiv of trifluoroacetic acid in methanol, aqueous work-up gave approximately 0.5 equiv each of recovered **3c** and 4-*tert*-butylcyclohexanone.The latter probably arises by hydrolysis of the iminium salt **2c** produced by C-protonation of **3c**. The best yield of indole (45%) when using fairly strong acid catalysts was obtained by refluxing **3c** with 0.05 equiv of trifluoroacetic acid in DMF for 3 hr.

Acetic acid alone does not promote indolization, but when **3c** was refluxed in acetic acid for 10 min in the presence of excess solid ammonium chloride, a 25% yield of **7c** was isolated. This was encouraging, but it was felt that the low solubility of ammonium chloride was deleterious. *tert*-Butylammonium chloride, which is quite soluble in acetic acid, proved to be an effective catalyst. When a cold solution of this salt in acetic acid was added to **3c**, the solution warmed spontaneously, and ir monitoring indicated that the reaction was complete within 15 min. Addition of water afforded a 95% yield of crystalline **7c**.

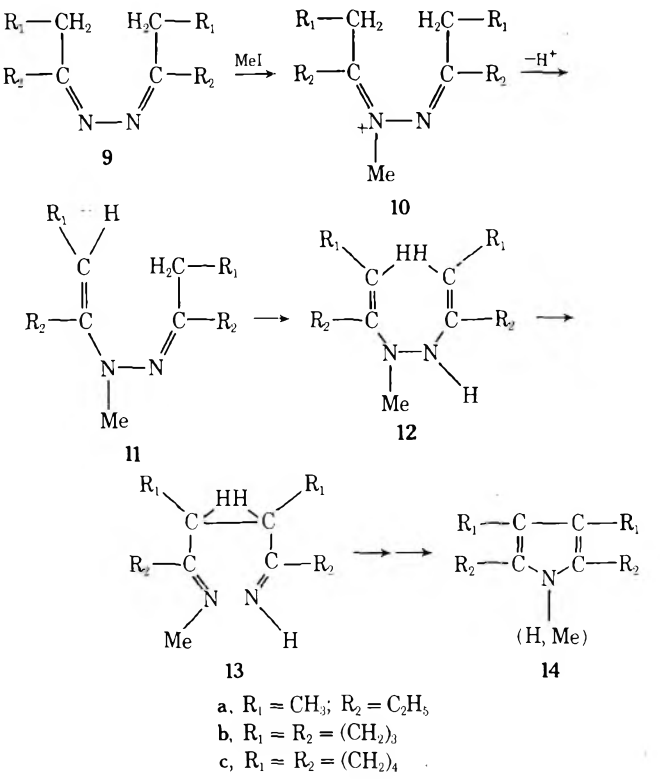
The foregoing results suggest that the carbon–carbon bond-forming step in a typical Fischer indole synthesis is a rapid electrocyclic reaction of the N′-protonated enehydrazine, structure **4**.[2c] N-Protonation may be effected by moderately strong acids, ammonium ions being especially effective. Strong acids, however, result in C-protonation to the iminium salt **2**, which is kinetically immobile under these conditions and does not lead directly to the indole.

Thermal, *i.e.*, non-acid-catalyzed, cyclizations of phenylhydrazones have been reported, but the intervention of trace amounts of acid is difficult to preclude.[6] When **3c** was refluxed with rapid stirring for 7 hr in a K_2CO_3–DMF suspension, a 15% yield of **7c** was produced. This may represent the non-acid-catalyzed cyclization of the enehydrazine, but if so, it is about 10^6 times slower than the acid-catalyzed process described in the preceding paragraphs.

Reaction of Ketazines with Methyl Iodide. Previous workers[3,7] have converted a number of ketazines into pyrroles, usually under rather vigorous conditions similar to those ordinarily employed in the Fischer synthesis. In a number of instances pyrazolines were formed in part or exclusively, especially with methyl ketones.

In an extension of the work described in the first section, three ketazines, diethylketazine, cyclohexylketazine, and cyclopentylketazine, were treated with methyl iodide and monomethiodides were obtained.[8] Heating the ketazinium iodides under various conditions afforded pyrroles in moderate yields. That heat is required for cyclization, in contrast with indole formation from **2**, is not too surprising, since loss of a proton from the ketazinium ion **10** (Scheme II) would produce an enehydrazine function in only one half of the molecule **11**. Presumably conversion of **11** into the dienehydrazine **12** is relatively slow, as in the usual Piloty reactions.

Scheme II



a, $R_1 = CH_3$; $R_2 = C_2H_5$
b, $R_1 = R_2 = (CH_2)_3$
c, $R_1 = R_2 = (CH_2)_4$

The yields in the conversion of the ketazinium salts to pyrroles were fairly good for the salts derived from diethyl ketone and cyclohexanone, but that from cyclopentanone gave only 16%. This would seem to be due to the strain in the 5–5–5 ring system produced in the later stages of the reaction. Another difficulty which detracts from the utility of this pyrrole synthesis arises from the fact that at the stage of the heterocyclic ring closure and the subsequent elimination, either the substituted or the unsubstituted nitrogen atom may be retained. This problem is not encountered in indole syntheses, where it is invariably the anilino nitrogen that is retained.[9] In the cyclohexanone series, *N*-methyloctahydrocarbazolewas the only isolated product, although the presence of some of the nor compound was indicated by the rapid oxidation of the crude material with the production of a deep green color.[7,10] Starting with diethyl ketone, *N*-methyl and N-unsubstituted pyrroles were obtained in 1:2 ratio. With cyclopentanone, only the N-unsubstituted product was detected. If it is possible to generalize from such a small number of observations, it would

Table I
Indoles from 2-Substituted Phenylhydrazines

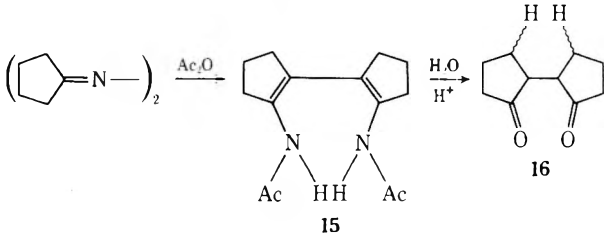
Phenylhydrazine	Registry no.	Carbonyl compd	Registry no.	Catalyst	Time, hr	Yield, %	Mp, °C	Bp, °C (1 mm)	Registry no.
2-Phenyl-	122-66-7	Cyclohexanone	108-94-1	Resin[a]	20	33	117–118		942-01-8
2-Methyl-	622-36-6	Cyclohexanone		Acetic acid	20	20	117		
2-Methyl-		Cyclohexanone		Resin	20	85	118		
2-Methyl-		Cyclopentanone	120-92-3	Resin	20	54	108[b]		2047-91-8
2-Methyl-		2-Heptanone	110-43-0	Resin	45	49[c]		120–122	51801-51-5
2-Methyl-		Heptanal	111-71-7	Resin	42	77		125–130	51801-52-6
2-Methyl-		Acetophenone	98-86-2	*p*-TsOH	20	64	189[d]		948-65-2
2-Methyl-		Propiophenone	93-55-0	Resin	45	25[e]	90–92[f]	155–160	10257-92-8
1,2-Dimethyl-[g]	29195-01-5	Cyclohexanone		Resin	20	29	48[h]	150	6303-88-4
1,2-Dimethyl-		4-Cyclohexylcyclohexanone	92-68-2	Resin	20	6	82		6623-15-0
1,2-Dimethyl-		2-Heptanone		Resin	20	10[i,j]		116–120	51801-53-7

[a] Amberlite IR-20. [b] Lit. mp 108°: W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, **123**, 3242 (1923). [c] 2-Methyl-3-butylindole by nmr. [d] Lit. mp 188–189°: R. L. Shriner, W. C. Ashley, and E. Welch, *Org. Syn.*, **22**, 98 (1942). [e] Minimum, reaction not complete. [f] Lit. mp 90–92°: E. Leete, *J. Amer. Chem. Soc.*, **81**, 6023 (1959). [g] Products are *N*-methylindoles. [h] Lit. mp 50°: W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, **119**, 1825 (1921). [i] Minimum, mechanical loss. [j] 1,2-Dimethyl-3-butylindole by nmr.

seem that cyclization of intermediate **13** is governed by electronic effects in the more facile reactions, as of the cyclohexyl compound, with the more nucleophilic methylated nitrogen attacking the more electrophilic unsubstituted imine function. When adverse steric factors due to the carbon skeleton are already present, the additional steric effect of the *N*-methyl substituent reverses the direction of addition, and becomes product determining.

Reaction of Ketazines with Acetic Anhydride. Suvorov[11] reported obtaining the diacetyl derivative of a vinyl phenylhydrazine by treatment of 2-butanone phenylhydrazone with acetic anhydride. In hope of similarly trapping an intermediate, the three ketazines mentioned in the previous section were treated with acetic anhydride under reflux. Cyclohexylketazine and diethylketazine gave the *N*-acetyl derivatives of the corresponding pyrroles in good yield.[7b] Cyclopentylketazine gave up to 37% yield of a solid, mp 187–189°, which was characterized as 2,2′-bis(acetamido)-1,1′-bicyclopentenyl (**15**) (Scheme III). Hydrolysis of **15** with dilute sulfuric acid gave the previously reported[12] bis-2,2′-cyclopentanone **16a** mp 70–71°, and its diastereoisomer **16b**, mp 37–40°.

Scheme III



15 16

Though conversion of **15** into a pyrrole was not achieved, its formation can nevertheless be considered as the trapping of a tautomeric form of an intermediate which in the methyl iodide promoted reaction did lead to pyrrole, albeit in low yield. That this trapping occurs in the cyclopentyl case, but not the other two, supports the contention made in the previous section that bond strain in the developing 5–5–5 ring system slows the conversion of **12b** to **14b**. A similar result was noted in the cyclization of α-keto-γ-butyrolactone phenylhydrazone,[13] though in that instance the intermediate was isolated as a salt of the imine tautomer. On the other hand, formation of **15** in reasonable yield demonstrates that the strain is less severe in the 5–6–5 ring transition state of the carbon–carbon bond-forming electrocyclic reaction.

Reaction of Carbonyl Compounds with *N*′-Methylphenylhydrazines. Initially it was found that hydrazobenzene reacted with cyclohexanone under appropriate conditions to give 1,2,3,4-tetrahydrocarbazole. The course of this reaction is highly dependent on the experimental conditions, since it is necessary to prevent benzidine rearrangement of the hydrazobenzene, which is the only process observed with strong acids in polar media. The best yields were obtained by prolonged refluxing in toluene with continuous water removal in the presence of a sulfonated cation exchange resin in the acid form. It was felt that the diprotonation which seems to be necessary for the benzidine rearrangement[14] would be less likely under these conditions. Reexamination of the literature showed that a similar transformation had been reported previously,[15] although under more vigorous conditions and in a different research area.

Since the best yield employing hydrazobenzene was only 33%, *N*′-methylphenylhydrazines were used in the subsequent experiments. Five ketones and one aldehyde were treated with 2-methyl-1-phenylhydrazineand furnished indoles in yields of 25–85% (Table I). Because of the experience with hydrazobenzene, the resin catalyst in refluxing toluene was used in most of these runs. Under these conditions methylamine was slowly evolved, as well as water, and was used to monitor the progress of the reactions (odor or pH paper). When hydrazobenzene was employed, the aniline expected as a by-product reacted with cyclohexanone to form *N*-cyclohexylideneaniline; therefore an excess of the ketone was required. This would seem to be unnecessary with the methylphenylhydrazines. It is probably also not necessary to use equivalent amounts of resin, though this was not investigated.

Acetophenone failed to react when the resin was used; substituting *p*-toluenesulfonic acid as the catalyst gave the indole in 63% yield. Propiophenone reacted quite slowly in the presence of the resin; this reaction was not carried to completion and the 25% yield is only a minimum value.

Three ketones were refluxed with 1,2-dimethyl-1-phenylhydrazine and the resin catalyst in toluene. Methylamine was evolved very slowly and the yields of indoles were poor, only 29% from cyclohexanone, although the reactions may not have been completed. This is in distinct contrast with the results of the standard Fischer method employing phenylhydrazones; alkylation of the anilino nitrogen great-

ly facilitates such reactions. Since the presumed iminium intermediate in the reaction of 4-cyclohexylcyclohexanone with 1,2-dimethyl-1-phenylhydrazine would be exactly the same, **2b**, as encountered in the methyl iodide promoted process described in the first section of this discussion, and which afforded a 96% yield of indole, the 6% yield under the more vigorous conditions currently being discussed indicates that the deleterious effect of the 1-methyl substituent operates in the steps leading to **2b**, probably during the nucleophilic attack by the 2-nitrogen atom upon the carbonyl group.

To assess the role of the anilino nitrogen atom in the electrocyclic process, **4** → **6**, an analogous carbon compound was subjected to the reaction conditions of this section. A solution of *N*-methylbenzylamine and cyclohexanone in toluene was refluxed with some *p*-toluenesulfonic acid. Water separation was complete in 6 hr, but no methylamine was evolved. Vacuum distillation gave a single product in good yield; the nmr spectrum indicated that it was the enamine, *N*-methyl-*N*-benzylcyclohexenylamine. Although the greater strength of the C–N bond may be partly responsible, this failure to cyclize suggests that with the enehydrazines, the nonbonding electrons of the 1-nitrogen atom play a part in the electrocyclic reaction. However, *N*-allyl vinylammonium ions have been reported to rearrange by a cyclic mechanism.[16]

Reaction of Ketones with Methylhydrazine and with 1,2-Dimethylhydrazine. Pyrroles were formed rapidly and conveniently when 2 equiv of the ketone was refluxed for a few minutes with 1 equiv of methylhydrazine in glacial acetic acid, followed by addition of an amine salt catalyst. Isolation of the ketone methylhydrazone was unnecessary.[17] In this type of reaction, as in the reaction of ketazines with methyl iodide, either methylamine or ammonia may be eliminated in the latter stages of the process. In numerous preliminary runs with cyclohexanone, besides *N*-methyl-1,2,3,4,5,6,7,8-octahydrocarbazole, a considerable amount of another, very easily oxidizable, material was obtained. This is probably the unmethylated compound, which is reported[7a,10] to be unstable and difficult to purify. The use of methylammonium chloride as the catalyst was found to suppress formation of by-product, and this technique was employed with the other ketones. Even under these conditions, diethyl ketone and cyclopentanone gave complex mixtures. Treatment of cyclohexanone with 1,2-dimethyl hydrazine[6] gave *N*-methyloctahydrocarbazole as a pure white product without unstable impurities. However, this reaction was slower than that with methylhydrazine under comparable conditions, and 1,2-dimethylhydrazine is quite expensive.

Experimental Section

Melting points were determined on a Fisher-Johns block calibrated to give corrected melting points. Infrared spectra were obtained with a Perkin-Elmer Model 21 spectrometer and are reported in microns. Nmr spectra were obtained with a Varian Model A-60 spectrometer, and are reported in parts per million downfield from tetramethylsilane internal standard. Mass spectra were determined on a Bendix Model 12-107 time-of-flight instrument. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill., and by Mrs. G. Libovitz, Cornell University.

4-Cyclohexylcyclohexanone α-Methylphenylhydrazone (1b). 4-Cyclohexylcyclohexanone was prepared by CrO_3–acetic acid oxidation of technical 4-cyclohexylcyclohexanol (cis–trans mixture, Dow Chemical Co.) and was purified through the bisulfite adduct. The hydrazone was prepared by refluxing the ketone with α-methylphenylhydrazine in methanol, without acid catalyst, and was recrystallized from methanol: yield 73%; mp 88–89°; ir (Nujol mull) 6.09, 6.24, 6.67, 7.76, 9.17, 13.32, 14.43 μ.

Anal. Calcd for $C_{19}H_{28}N_2$: C, 80.21; H, 9.86; N, 9.86. Found: C, 80.38, H, 9.55; N, 9.99.

Addition of a small amount of hydrochloric acid to a warm methanolic solution of **1b** resulted in rapid crystallization of a nearly quantitative yield of **9-methyl-3-cyclohexyl-1,2,3,4-tetrahydrocarbazole (7b)**: mp 90°; ir (Nujol mull) 6.16, 7.03, 7.60, 8.19, 8.45, 8.70, 9.86, 11.22, 13.57 μ.

Anal. Calcd for $C_{19}H_{25}N$: C, 85.32; H, 9.43; N, 5.24. Found: C, 85.26; H, 9.40; N, 5.42.

In an attempt to prepare an *N*-benzylphenylhydrazone, 4-cyclohexylcyclohexanone (9.5 g, 0.05 mol) was refluxed for 6 hr with a solution of α-benzylphenylhydrazine hydrochloride (11 g, 0.05 mol) and 10 ml of pyridine in 100 ml of methanol. The oily product was triturated with ether–petroleum ether and crystallized from isopropyl alcohol, yield 9.6 g (56%), mp 115–115.5°. The analysis indicates that cyclization to the indole, **9-benzyl-3-cyclohexyl-1,2,3,4-tetrahydrocarbazole**, had occurred.

Anal. Calcd for $C_{25}H_{29}N$: C, 87.40; H, 8.52; N, 4.08. Found: C, 87.40; H, 8.59; N, 4.32.

Reactions of 1b with Methyl Iodide. A solution of 10 g (0.035 mol) of **1b** in 25 g of methyl iodide was allowed to stand overnight at room temperature. The precipitated solid was filtered, extracted twice with hot chloroform and then with ether, and dried. It was identified as methylammonium iodide, yield 5.0 g (90%), by ir comparison with an authentic sample and by reaction with NaOH solution and phenyl isothiocyanate to produce *N*-methyl-*N'*-phenylthiourea,mp 113° (no depression with an authentic sample). The purity was confirmed by analysis.

Anal. Calcd for CH_6NI: C, 7.55; H, 3.80; I, 79.81. Found: C, 7.44; H, 3.90; I, 80.01 (gravimetric).

The filtrate from the above reaction was evaporated and the residue was crystallized from methanol, yield 7.0 g (75%) of **7b**, mp 90°, no depression with the sample prepared above, ir identical.

In a similar reaction with commercial DMF as diluent, a comparable yield of **7b** was obtained. When the experiment was repeated with DMF dried over calcium hydride, a 96% yield of **7b** was realized.

Reactions in the Presence of Bases. A solution of 1 g of **1b** in 5 ml of methyl iodide and 2 ml of *N,N,*2,6-tetramethylaniline[5] was allowed to stand at room temperature for 4 days. By this time 0.127 g (23%) of methylammonium iodide, identified by ir and iodide determination, had precipitated. Work-up of the filtrate was more difficult than before, because of the necessity of avoiding acidic conditions, but 0.26 g (28%) of **7b** was isolated. A similar reaction in the presence of 2,6-diisopropylpyridine[5] as base gave 64% of **7b** and 26% of methylammonium iodide.

Hydrazone **1b** (1 g, 3.5 mmol) was stirred for 2 days with a suspension of anhydrous potassium carbonate (0.5 g, 3.5 mmol) in 5 ml of 2-butanone and 1 ml (17 mmol) of methyl iodide, yielding 0.55 g (58%) of **7b**. When the reaction time was cut to 12 hr, ir indicated a large amount of unreacted hydrazone.

When **1b** was treated with excess methyl iodide and potassium carbonate in dry DMF, no indole was formed if stirring was efficient enough. The ir of the product after molecular distillation at 0.01 mm (200–230°) showed over 90% conversion of the hydrazone into incompletely identified compounds (see discussion).

4-*tert*-Butylcyclohexanone α-Methylphenylhydrazone (1c). The ketone and the hydrazine were refluxed in methanol for 10 min. Slow addition of water gave a 75% yield of crude product, mp 63°, which was recrystallized from methanol–water, mp 63.5–64°.

Anal. Calcd for $C_{17}H_{26}N_2$: C, 79.07; H, 10.08; N, 10.85. Found: C, 79.05; H, 10.27; N, 10.82.

9-Methyl-3-*tert*-butyl-1,2,3,4-tetrahydrocarbazole (7c). An authentic sample was prepared by briefly refluxing a methanol solution of **1c** containing a small amount of hydrochloric acid: mp 65.5–66° (lit.[18] mp 66.5–67.5°); ir (melt) 6.3 (w), 6.92, 7.45, 8.53, 9.98, 13.8 μ (s).

A solution of 0.85 g of **1c** in 1 ml of methyl iodide was allowed to stand overnight. Water was added, the product was taken up in ether, and after drying the solvent was evaporated, giving 0.80 g (quantitative) of **7c**, mp after crystallization from ethanol 66.5–67.5°.

1,2-Dimethyl-1-phenyl-2-(4-*tert*-butylcyclohexenyl)hydrazine (3c). A suspension of 5 g (35 mmol) of powdered anhydrous K_2CO_3 in 15 ml of dry DMF was stirred for several minutes to scavenge traces of acid; then 2.58 g (10 mmol) of **1c** and 0.75 ml (12 mmol) of methyl iodide were added. Rapid stirring under nitrogen was continued overnight at room temperature. Pentane (50 ml) was added and the mixture was stirred vigorously for 15 min. After settling, the pentane layer was decanted and the extraction was repeated twice. The combined pentane extracts were stirred with

solid NaI for 15 min, then transferred to a fresh portion of NaI and stirred again. This treatment removed practically all of the dissolved DMF. The solvent was stripped and the residue (2.6 g, 95%) slowly crystallized when stored at −50° under nitrogen, mp 40–43°. An analytical sample was prepared by recrystallization from pentane at −50° under nitrogen: mp 44.5–45.5°; ir (melt) 6.11 (m), 6.31 (s), 6.74 (s), 6.89, 9.07, 13.45 (s), 14.52 μ (s); nmr ($CDCl_3$) δ 6.8–7.4 (5 H), 4.8 (br, 1 H, vinyl), 2.81 (s, 3 H) and 2.72 (s, 3 H)(NCH_3's), 2.1 (br, 4 H), 1.25 (br, 2 H), 0.88 (s, 9 H). The methine ring proton signal is buried under the ring methylenes and cannot be located.

Anal. Calcd for $C_{18}H_{28}N_2$: C, 79.41; H, 10.30; N, 10.30. Found: C, 79.26; H, 10.50; N, 10.21.

When only an equivalent amount of methyl iodide was used in the above preparation, the nmr indicated that the crude product contained about 20% of unreacted hydrazone.

Using a similar procedure, 1.6 g (6.5 mmol) of **1c** and 3 ml (6.7 g, 48 mmol) of methyl iodide gave 1.5 g (77%) of a solid, mp 57–60°. In subsequent runs the yield of crude product was quantitative. Upon crystallization from pentane at −50°, various fractions of differing melting points were obtained, 65–70, 65–73, and 70–74° The combustion analyses of these fractions (below) were nearly the same, and the mass spectra all showed a strong parent peak at *m/e* 286, corresponding to a monomethyl derivative of **3c**. The nmr spectra indicated that all fractions are probably mixtures of the double-bond isomers **8a** and **8b**. The lowest melting fraction had a higher integrated value (80% of theory) of the vinyl hydrogen signal at δ 4.6–4.9 and of the saturated-CH_3 doublet at δ 1.05. It evidently consists largely of **1,2-dimethyl-1-phenyl-2-(6-methyl-4-*tert*-butylcyclohexenyl)hydrazine (8a).** In the nmr spectra of the higher melting fractions, these signals were weaker, and the vinyl methyl singlet at δ 2.50 was stronger. These fractions apparently are richer in **1,2-dimethyl-1-phenyl-2-(2-methyl-4-*tert*-butylcyclohexenyl)hydrazine (8b).**

Anal. Calcd for $C_{19}H_{30}N_2$: C, 79.79; H, 10.45; N, 9.79; mol wt, 286. Found: C, 79.66; H, 10.60; N, 9.65; mol wt, 286.

Cyclization of the Enehydrazine 3c. A solution of 1.2 g (10 mmol) of *tert*-butylammonium chloride in 15 ml of glacial acetic acid was cooled to 20° and 2.7 g (10 mmol) of **3c** was added. Within a few minutes the solution warmed spontaneously to 30–35°. After 15 min a little ethanol was added to assist crystallization, and then water was added slowly. The product was filtered and dried, yield 2.3 g (95%), mp 63–64°. After recrystallization from ethanol, the melting point was 66–66.5°, not depressed by authentic **7c**, ir and nmr identical.

Reaction of Ketazines with Methyl Iodide. A. A solution of 168 g (1 mol) of diethylketazine in 284 g (2 mol) of methyl iodide was allowed to stand at room temperature for 5 days (or alternatively, refluxed for several hours) under nitrogen. Crystallization of the oil which separated was induced by trituration with dry ether, and the product was dried under vacuum, yield 279 g (98%), mp 57–60°. The salt was too hygroscopic for satisfactory analysis, but the spectral data indicate that it is ***N*-methyldiethylketazinium iodide (10a):** ir (KBr) 5.68 μ; nmr ($CDCl_3$) δ 4.00 (s, 3 H, NCH_3), 3.13 (q, 2 H), 2.62 (m, 6 H), 1.60–0.90 (m, 12 H).

A solution of 55 g of **10a** in 100 ml of 1-propanol was refluxed under nitrogen for 4 hr. The solvent was stripped, and ether was added to the residue. The crystalline material was collected, washed with ether, and dried. Ir comparison with authentic samples indicated that the solid was a mixture of methylammonium iodide and ammonium iodide, the estimated yields being 30 and 18%, respectively. The ethereal filtrate was distilled, and the higher boiling fractions were separated by preparative glc (Carbowax 20M, 5 ft). In addition to a 6% recovery of diethylketazine, the major products were **3,4-dimethyl-2,5-diethylpyrrole,** yield 37%, bp 210–215° (lit.[3] bp 215°)(750 mm), ir 2.9 μ (NH), nmr (CCl_4) δ 7.02 (br, 1 H, exchanged by D_2O, NH), 2.42 (q, 4 H), 1.83 (s, 6 H), 1.10 (t, 6 H), and **1,3,4-trimethyl-2,5-diethylpyrrole,** yield 18%, ir no HN, nmr (CCl_4) δ 3.32 (s, 3 H, NCH_3), 2.48 (q, 4 H), 1.83 (s, 6 H), 1.03 (t, 6 H).

B. When cyclopentylketazine (164 g, 1 mol) was added to methyl iodide (284 g, 2 mol), a mildly exothermic reaction occurred. After standing for 2 hr, the crystalline mass was extracted with tetrahydrofuran (THF) and dried, yield 295 g (89%), mp 101–103°. A portion was recrystallized from $CHCl_3$–THF (1:10), ***N*-methylcyclopentylketazinium iodide (10b):** mp 107–108°; ir (KBr) 5.68, 5.88 μ; nmr ($CDCl_3$) δ 3.98 (s, 3 H, NCH_3), 3.40 (m, br, 2 H), 2.83 (m, br, 6 H), 2.10 (m, br, 8 H).

Anal. Calcd for $C_{11}H_{19}N_2I$: C, 43.14; H, 6.24; N, 9.14. Found: C, 42.80; H, 6.28; N, 9.08.

Mild hydrolysis of **10b** gave cyclopentanone and methylhydrazinium iodide in a ratio of 2:1.

When a solution of 27.8 g (0.09 mol) of **10b** in 100 ml of 1-butanol was warmed to 75°, an exothermic reaction began. The temperature was then held at 120° for 5 hr. After concentration under vacuum and dilution with chloroform, 3.1 g (21%) of methylammonium iodide separated, identified by ir comparison. The filtrate was distilled, and the fraction boiling at 78–116° (0.4 mm) was further separated by preparative glc (Carbowax 20M, 10 ft). The major component of the complex mixture was collected, yield 2.08 g (16%), mp 84–87°. Because of ease of oxidation, a characteristic of pyrroles with an N–H bond, a completely satisfactory analysis was not obtained, but the nitrogen content excludes a pyrazoline structure. The spectral data indicate that the structure is **bis(cyclopenteno)[*b,d*]pyrrole 14b:** ir 2.9 (w, NH), 6.19, 7.06 μ; nmr ($CDCl_3$) δ 7.31 (s, 1 H, exchanged by D_2O, NH), 3 (m, 8 H) shown by spin decoupling to be two triplets at 2.97 (4 H) and 2.85 (4 H), 2.09 (pentet, 4 H).

Anal. Calcd for $C_{10}H_{13}N$: C, 81.58; H, 8.85; N, 9.51. Found: C, 82.84; H, 8.18; N, 8.83.

C. A solution of 192 g (1 mol) of cyclohexylketazine in 284 g (2 mol) of methyl iodide was allowed to stand at room temperature under nitrogen for 1 day. The crystalline product was filtered, washed with ether and THF, and dried under vacuum, yield 330 g (98%) of ***N*-methylcyclohexylketazinium iodide (10c):** mp 124–126°; ir (KBr) 5.68 μ (cyclohexylketazine 6.18 μ); nmr ($CDCl_3$) δ 3.96 (s, 3 H, NCH_3), 3.30 (m, 2 H), 2.63 (6 H), 1.86 (s, 12 H).

Anal. Calcd for $C_{13}H_{23}N_2I$: C, 46.71; H, 6.93; N, 8.38. Found: C, 46.65; H, 6.95; N, 8.37.

Mild hydrolysis of **10c** produced cyclohexanone and methylhydrazinium iodide in a 2:1 ratio, both identified by ir and nmr comparison with authentic samples. A possible alternative formulation for **10c,** the pyrazoline hydriodide, is reported not to hydrolyze readily.[19]

A suspension of **10c** (8.8 g, 25 mmol) in 30 ml of 1,2-dimethoxyethane was refluxed under nitrogen. After about 10 min, a mildly exothermic reaction ensued and the solid dissolved completely. Refluxing was continued for 2 hr, when the mixture was diluted with some water and cooled. The product soon solidified and was recrystallized from ethanol–water, yield 3.6 g (73%) of **9-methyl-1,2,3,4,5,6,7,8-octahydrocarbazole (14c):** mp 93–95° (lit.[7a] mp 94°); nmr (CCl_4) δ 3.25 (s, 3 H, NCH_3), 2.7–2.1 (m, 8 H), 1.8–1.5 (m, 8 H). The aqueous solution remaining after removal of **14c** was evaporated and the residue was crystallized from chloroform–ethanol (5:1), giving 3.1 g (82%) of white crystals identified by ir comparison as ammonium iodide. Heating **10c** dry or in other solvents on the steam bath also gave **14c,** but in lower yield and purity.

In the nmr spectra of the ketazinium salts, one of the methylene signals is shifted downfield by about 0.6 ppm. Comparison with spectra in the literature suggests that these signals are probably due to the methylene groups on the neutral carbon–nitrogen double bond anti to the positively charged nitrogen atom. In the nmr spectrum of diethylketazine, the methylene region consists of two equal overlapping quartets separated by 0.07 ppm, and the methyl region of two equal overlapping triplets separated by 0.15 ppm, each measured from the respective centers. This must be due to the relative syn and anti positions of the four ethyl groups. With the cyclic ketazines, the α-methylene regions are broadened, but not resolved.

Reaction of Ketazines with Acetic Anhydride. A. A solution of 4.8 g (25 mmol) of cyclohexylketazine and 0.5 g of *p*-toluenesulfonic acid in 25 ml of acetic anhydride was refluxed for 1 hr. The solution was concentrated under vacuum and the residue was crystallized from methanol–water, yield 3.7 g (64%) of ***N*-acetyl-1,2,3,4,5,6,7,8-octahydrocarbazole:** mp 72–74° (lit.[7a] mp 73°); ir 5.9 μ; nmr ($CDCl_3$) δ 2.80 (m, 4 H), 2.44 (s, 3 H, acetyl), 2.34 (m, 4 H), 1.74 (m, 8 H).

B. A solution of 8.4 g (50 mmol) of diethylketazine and 0.2 g of *p*-toluenesulfonic acid in 50 ml of acetic anhydride was refluxed for 3 hr, then fractionally distilled, yield 7.8 g (68%) of ***N*-acetyl-3,4-dimethyl-2,5-diethylpyrrole:** bp 76–78° (0.03 mm) or 242° (750 mm) [lit.[3] bp 180° (88 mm)]; $n^{20}D$ 1.5079; ir 5.9 μ; nmr ($CDCl_3$) δ 2.70 (q, 4 H), 2.44 (s, 3 H, acetyl), 1.83 (s, 6 H), 1.07 (t, 6 H).

C. 2,2′-Bis(acetamido)-1,1′-bicyclopentenyl (15). A solution of 66 g (0.4 mol) of cyclopentylketazine in 200 ml of acetic anhydride was heated at 85° for 4 hr, then 200 ml of methanol was added cautiously to the warm solution. Three crops of crystals were taken by alternately cooling and concentrating the solution, and the combined products were recrystallized from methanol,

yield 37 g (37%) of **15**: mp 187–189°; ir (KBr) 3.0, 6.0 μ; nmr (deuteriopyridine at 80°) δ 8.66 (br, 2 H, NH), 2.99 (m, 4 H), 2.22 (m, 4 H), 2.08 (s, 6 H, acetyl), 1.75 (m, 4 H).

Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.75; H, 8.12; N, 11.28. Found: C, 68.20; H, 8.14; N, 11.20.

2,2'-Diketo-1,1'-bicyclopentyl (16a, 16b). Fifteen grams (60 mmol) of **15** was warmed on the steam bath with 150 ml of 50% sulfuric acid for 3 hr. The oily product was taken up in ether, dried, and distilled, yield 9.5 g (95%), bp 88–89° (0.2 mm). The semisolid product was apparently a mixture of diastereoisomers (meso and racemic) and was separated by repeated fractional crystallization from heptane. At a preliminary stage this afforded 2.5 g of material of mp 65–69° and 2 g of mp 33–37°. Further crystallization gave 1.8 g of **16a**, mp 70–71° (lit.[12] mp 67–69°), and 1.5 g of **16b**, mp 37–40°. The nmr spectra are complex multiplets and are useless for distinguishing the isomers, although consistent with the assigned structures. The ir spectra show some variations in the weaker bands: ir (melt) of **16a**, 5.80 (s), 8.58, 8.71, 8.97, 10.62, 11.07, 12.00, 12.24 μ; ir (melt) of **16b**, 5.80 (s), 8.72 μ. The simpler spectrum of **16b** suggests that it is the meso isomer, which would be centrosymmetric in the anti conformation. The mass spectra of the two isomers are nearly identical, and only that of **16a** is given: mass spectrum (70 eV) *m/e* (rel intensity) 166 (15), 148 (7), 138 (15), 111 (30), 98 (30), 84 (100), 83 (90), 68 (40), 67 (40), 55 (60), 44 (30), 41 (30), 40 (30), 39 (30).

The dinitrophenylhydrazones and semicarbazones melt with extensive decomposition and cannot be trusted for distinguishing **16a** and **16b**. The dioximes, prepared in pyridine–methanol and recrystallized from ethanol–water, are more satisfactory: **16a** dioxime, mp 182–186° with slight decomposition; **16b** dioxime, mp 200–201.5°.

Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.18; H, 8.16; N, 14.27. Found for **16a**: C, 61.14; H, 7.97; N, 14.27. Found for **16b**: C, 61.25; H, 8.16; N, 14.27.

Reaction of Cyclohexanone with Hydrazobenzene. A mixture of 5.75 g (30 mmol) of hydrazobenzene, 6 g (60 mmol) of cyclohexanone, and 20 ml (wet volume) of Amberlite IR-20 resin (30 mequiv) in 90 ml of toluene was refluxed with mechanical stirring to minimize bumping. Water was separated continuously by a Barrett trap. After water evolution ceased (20 hr), the resin was removed by filtration and the solvent was stripped. Repeated crystallization of the residue from ethanol gave 1.75 g (33%) of **1,2,3,4-tetrahydrocarbazole,** mp 117–118° (lit.[20] mp 117–118°), not depressed by an authentic sample.

Vacuum distillation of the mother liquors gave a fraction, bp 80–85° (0.4 mm), whose ir and nmr spectra matched those of an authentic sample of *N*-cyclohexylideneaniline prepared by refluxing cyclohexanone with aniline in the presence of the resin as in the foregoing preparation, bp 83–85° (0.4 mm) [lit.[21] bp 138–142° (19 mm)].

2-Methyl-1-phenylhydrazinewas prepared by a variation of a reported method,[22] but employing sodium hydride in the methylation of formyl phenylhydrazine rather than metallic sodium. It was found advisable to recrystallize the 2-formyl-2-methyl-1-phenylhydrazine three times from ethanol, mp 78–79° (lit.[22] mp 79–80°), before hydrolyzing with base to avoid contamination of the product with 1,2-dimethylphenylhydrazine, whose presence in earlier samples was indicated by a small nmr peak at δ 2.8. **1,2-Dimethyl-1-phenylhydrazine** was prepared similarly, using sodium hydride in toluene for the methylation of 2-formyl-1-methyl-1-phenylhydrazine. In this case basic hydrolysis was unsatisfactory, and Harries' method of acidic alcoholysis[23] was employed.

The syntheses of indoles summarized in Table I were carried out by refluxing the carbonyl compounds with 1 equiv of the appropriate hydrazine and the acid catalyst in toluene with water removal by a trap. In some runs evolved methylamine was trapped in a methanol solution of phenyl isothiocyanate. Chromatography of the crude crystalline product on alumina, eluting with hexane–ethyl acetate, gave two fractions: A, mp 113°, not depressed by authentic *N*-methyl-*N'*-phenylthiourea,and B, mp 91°, whose nmr spectrum suggested that it was methyl *N*-phenylthiocarbamate (lit. mp 93°), derived from the methanol.

Pyrroles from Methylhydrazines.9-Methyl-1,2,3,4,5,6,7,8-octahydrocarbazole. A. A solution of 2.2 g (0.05 mol) of methylhydrazine and 10 g (0.1 mol) of cyclohexanone in 15 ml of glacial acetic acid was warmed on a steam bath for 5 min; hydrazone formation was indicated by the development of a golden yellow color. Upon addition of 1.5 g of methylammonium chloride to the warm solution, the solution immediately became cloudy, and soon an oily layer of product rose to the surface. After an additional 30 min of heating, the mixture was cooled, whereupon the oil solidified. The product was removed, washed with water, and crystallized from methanol, yield 7.5 g (80%), mp 93–94°, not depressed by the sample prepared above.

B. A mixture of 1.3 g (10 mmol) of 1,2-dimethylhydrazine dihydrochloride, 2 g (20 mmol) of cyclohexanone, and 2 g of methylammonium acetate in 10 ml of toluene was refluxed for 1 day with continuous water removal. After a preliminary wash with water, the product was extracted into 10% HCl, liberated by base, and crystallized from ethanol, yield 1.1 g (57%), mp 93°, not depressed by the previous sample.

1-Methyl-2,5-diphenyl-3,4-dibenzylpyrrole was made from dibenzyl ketone by procedure A (above): yield 24%; mp 161.5–162.5°; nmr (CCl_4) δ 7.1 (m, 20 H), 4.05 (s, 4 H), 3.05 (s, 3 H). A solution of this compound in dry chloroform oxidizes rapidly and turns dark blue when exposed to air, especially in the nmr probe.

Anal. Calcd for $C_{31}H_{27}N$: C, 90.00; H, 6.54; N, 3.55. Found: C, 90.03; H, 6.65; N, 3.35.

1,3,4-Trimethyl-2,5-diphenylpyrrole was made similarly in only 10% yield from phenylacetone, accompanied by large amounts of oily by-products: mp 142.5–143°; nmr (CCl_4) δ 7.1 (10 H), 3.50 (s, 3 H), 2.23 (s, 6 H).

Anal. Calcd for $C_{19}H_{19}N$: C, 87.45; H, 7.28; N, 5.36. Found: C, 87.51; H, 7.42; N, 5.47.

Registry No.—**1b,** 6623-14-9; **1c,** 51801-54-8; **3c,** 51801-55-9; **7c,** 22410-72-5; **8a,** 51801-56-0; **8b,** 51801-57-1; **9a,** 1530-17-2; **9b,** 20615-04-7; **9c,** 4278-87-9; **10a,** 51838-68-7; **10b,** 51801-58-2; **10c,** 51801-59-3; **14a** (H), 27301-66-2; **14a** (Me), 51801-60-6; **14b** (H), 51801-61-7; **14c** (Me), 23518-22-1; **15,** 51801-62-8; **16a,** 51820-21-4; **16a** dioxime, 51801-63-9; **16b,** 51820-22-5; **16b** dioxime, 51820-23-6; α-benzylphenyhydrazine hydrochloride, 51801-64-0; 9-benzyl-3-cyclohexyl-1,2,3,4-tetrahydrocarbazole, 51801-65-1; methylammonium iodide, 14965-49-2; *N*-acetyl-1,2,3,4,5,6,7,8-octahydrocarbazole, 51801-66-2; *N*-acetyl-3,4-dimethyl-2,5-diethylpyrrole, 51801-67-3; 1-methyl-2,5-diphenyl-3,4-dibenzylpyrrole, 51801-68-4; dibenzyl ketone, 102-04-5; 1,3,4-trimethyl-2,5-diphenylpyrrole, 24956-46-5; phenylacetone, 103-79-7;4-*tert*-butylcyclohexanone, 98-53-3.

References and Notes

(1) (a) M.S. Thesis, 1969; (b) M.S. Thesis, 1967; (c) M.S. Thesis, 1957, presented in part before the Organic Division, 19th National Meeting of the American Chemical Society, St. Louis, Mo., March 1961.
(2) (a) E. Fischer and F. Jourdan, *Ber.*, **16,** 2241 (1883); (b) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **113,** 639 (1918); B. Robinson, *Chem. Rev.*, **69,** 227 (1969).
(3) O. Piloty, *Ber.*, **43,** 489 (1910).
(4) R. F. Smith and L. E. Walker, *J. Org. Chem.*, **27,** 4372 (1962).
(5) H. C. Brown and M. Grayson, *J. Amer. Chem. Soc.*, **75,** 20 (1953).
(6) W. Sucrow and G. Chondromatidis, *Chem. Ber.*, **103,** 1759 (1970).
(7) (a) W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, **125,** 1503 (1924); (b) F. King and G. Paterson, *ibid.*, **137,** 44 (1936); (c) A. N. Kost and I. I. Grandberg, *J. Gen. Chem. USSR*, **26,** 607 (1956).
(8) (a) H. H. Hatt, *Org. Syn.*, **16,** 51 (1936); (b) M. Lamchen, W. Pugh, and A. M. Stephen, *J. Chem. Soc.*, **155,** 2429 (1954).
(9) C. F. H. Allen and C. V. Wilson, *J. Amer. Chem. Soc.*, **65,** 611 (1943).
(10) A. N. Kost and I. I. Grandberg, *Zh. Obshch. Khim.*, **26,** 565 (1956).
(11) N. N. Suvorov, N. P. Sorokina, and Y. N. Sheinker, *J. Gen. Chem. USSR*, **28,** 1058 (1958).
(12) B. J. F. Hudson and R. Robinson, *J. Chem. Soc.*, **143,** 691 (1942); H. Paul, *Chem. Ber.*, **93,** 2395 (1960).
(13) H. Plieninger, *Chem. Ber.*, **83,** 273 (1950); H. Plieninger and I. Nogradi, *ibid.*, **88,** 1964 (1955).
(14) G. S. Hammond and H. J. Shine, *J. Amer. Chem. Soc.*, **72,** 220 (1950).
(15) A. N. Nesmeyanov and R. V. Golovnya, *Dokl. Akad. Nauk SSSR*, **136,** 836 (1961).
(16) K. C. Brannock and R. D. Burpitt, *J. Org. Chem.*, **26,** 3576 (1961).
(17) P. Schiess and A. Grieder, *Tetrahedron Lett.*, 2097 (1969).
(18) K. D. Berlin, P. E. Cook, and J. T. Schroeder, *Proc. Okla. Acad. Sci.*, **47,** 215 (1968).
(19) A. N. Kost, G. A. Golubeva, and I. I. Grandberg, *J. Gen. Chem. USSR*, **26,** 2201 (1956).
(20) C. U. Rodgers and B. B. Corson, *J. Amer. Chem. Soc.*, **69,** 2910 (1947).
(21) G. Reddelien and O. Meyn, *Ber.*, **53,** 345 (1920).
(22) Beilstein, Vol. XV, p 118, citing DRP 57944.
(23) C. D. Harries, *Ber.*, **27,** 696 (1894).

Quinazolines. II.[1] Oxidation of 2-Aminoindoles and Related Compounds

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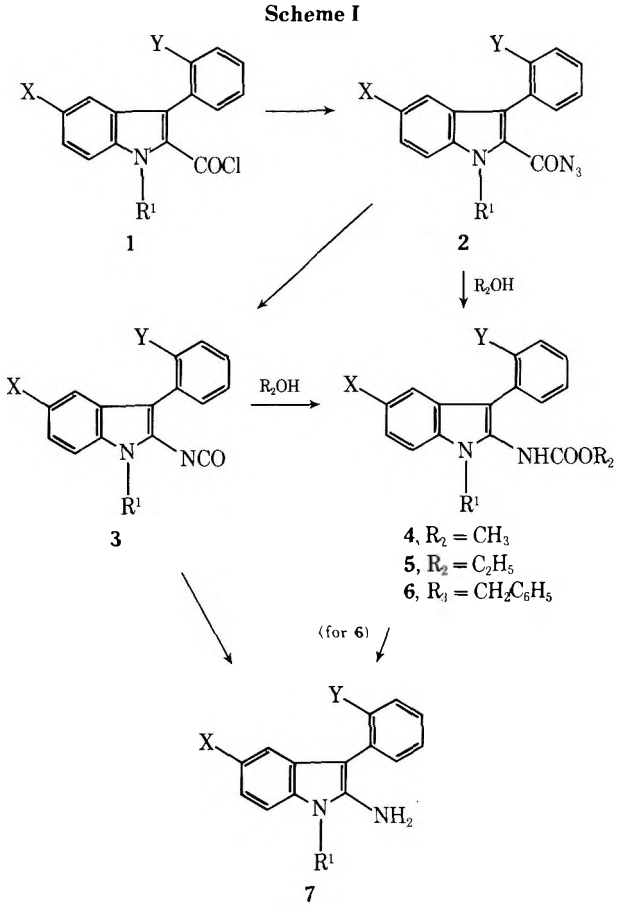
On ozonolysis in acetic acid, 2-amino-5-chloro-1-methyl-3-phenylindole (**7a**) was oxidized to a mixture of 2-imino-3-indolinol (**12a**, 85%) and quinazolinone **11a** (1%), and N-unsubstituted derivative **7c** only to 2-amino-3*H*-indol-3-ol (**14**). Ozonolysis of **7a** in carbon tetrachloride gave only **11a**. Chromic acid oxidation of urethanes **4**, **5**, and **6** gave the corresponding allophanates, which were hydrolyzed with base or acid to give quinazolinones **11**. Indole-2-carboxylic acid azides **2a,b**, precursors of **7a,b**, gave **11a,b** (44, 41%) and small amounts of **12a,b** by chromic acid oxidation, while their rearranged isocyanates **3a,b** yielded mainly **12a,b** (47, 64%) together with **11a,b** (4, 6%). Chromic acid oxidation of N-unsubstituted derivative **2c** led to the isolation of the postulated intermediary oxaniloyl azide **27c**. To a crystalline peroxidic product isolated from ozonolysis of **3a**, the 1,2,4-dioxazol-3-one structure **24** is assigned instead of the expected ozonide structure **23**. The Hofmann reaction of 5-chloro-1-methyl-3-phenylindole-2-carboxamide (**28**) with aqueous sodium hypobromite in tetrahydrofuran gave **11**, while similar reaction with aqueous sodium hypochlorite led to a mixture of oxindoles **29** and **30**. By using methanolic sodium hypobromite the expected urethane **4a** was, in addition to the further oxidized product **31**, obtained, although in poor yield. The possible mechanisms involved in these oxidative transformations are discussed.

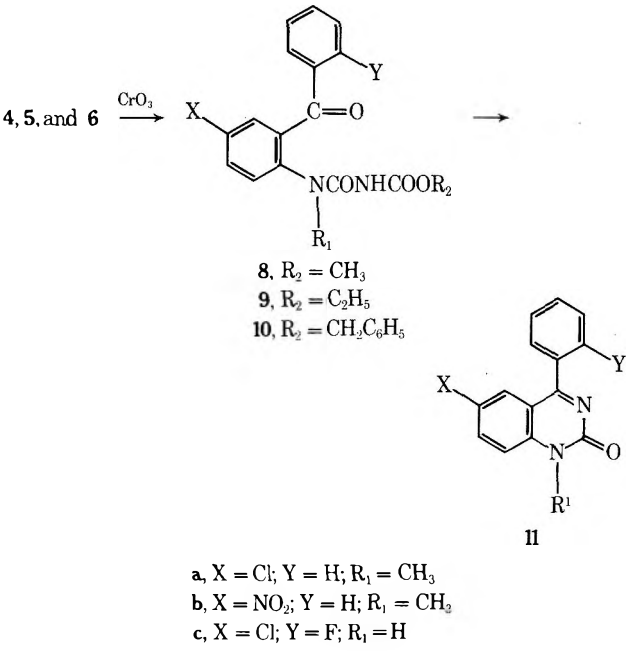
In our previous study,[1] the synthesis of quinazolinones was accomplished *via* oxidation of indole-1,2-dicarboximides, followed by hydrolysis of their oxidation products. As an extension of this work, we have now investigated the oxidation of 2-aminoindoles and their precursors, *i.e.*, indole-2-carboxylic acid azides and their rearranged isocyanates.

3-Phenylindole-2-carboxylic acid azides **2** were prepared from the corresponding acid chlorides **1**[2] by treatment with sodium azide. Azides **2** slowly rearranged to isocyanates **3** at room temperature over a period of 20–40 days. Urethanes **4**, **5**, and **6** were prepared by heating azides **2** or isocyanates **3** in the corresponding alcohols. Hydrogenolysis of benzylurethanes **6a** and **6c** with a palladium on charcoal catalyst[3] afforded 2-aminoindoles **7a** and **7c**, respectively. Compound **7a** was also prepared by hydrolysis of 3a with aqueous potassium hydroxide (Scheme I).

Scheme I



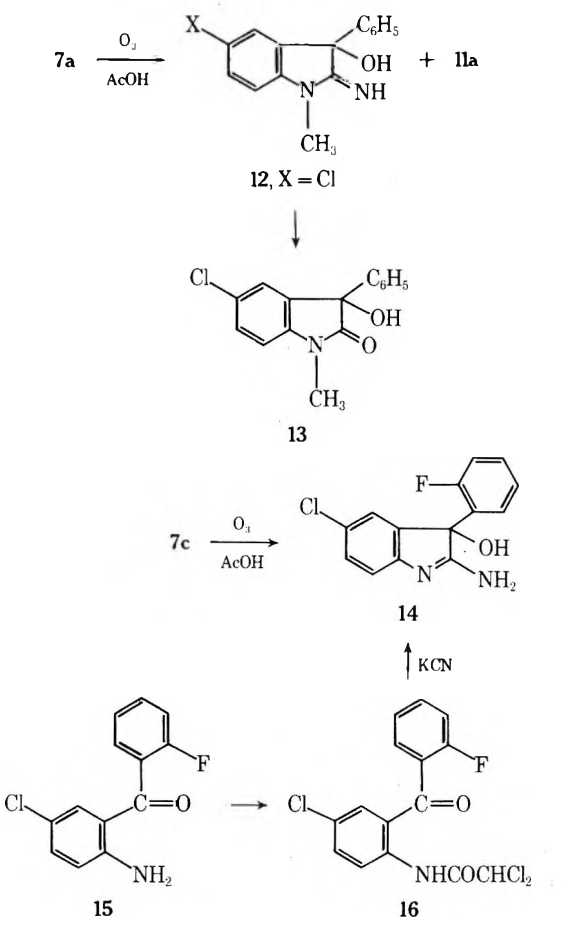
Oxidation of 2-Aminoindoles 7 and Urethanes 4, 5, and 6.[4] Chromic acid oxidation of urethanes **4**, **5**, and **6** gave the expected allophanic acid esters **8**, **9**, and **10**, respectively. Although **8a**, **9a**, and **10a** could not be isolated in crystalline form, they were hydrolyzed with base or acid to give quinazolinone **11a**[5a,c] in 21–43% yields. In the case of **5c**, the crystalline ethyl allophanate **9c** was isolated, although in poor yield, and shown to be identical with the authentic sample.[1]



Chromic acid oxidation of 2-aminoindole **7a** led to a complex mixture with no observable formation of **11a**. On the other hand, ozonolysis of **7a** in acetic acid using ozone–oxygen afforded, in addition to a small amount (1%) of the desired product **11a**, 5-chloro-2-imino-1-methyl-3-phenyl-3-indolinol (**12a**) in 85% yield. Compound **12a** was hydrolyzed with 40% aqueous sodium hydroxide in dimethyl sulfoxide to yield 5-chloro-1-methyl-3-phenyldioxindole (**13**).

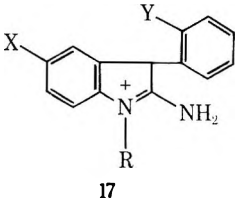
On ozonolysis under the same conditions, **7c** afforded 2-amino-5-chloro-3-(o-fluorophenyl)-3*H*-indol-3-ol (**14**), exclusively. The structure of **14** was confirmed by an alternative preparation[6] from the corresponding 2-aminobenzophenone (**15**) as shown in Scheme II.

Scheme II



Ozone rather than oxygen[7] was shown to be the oxidizing agent in the oxidation of **7a** by the fact that no reaction occurred when oxygen was passed into the reaction mixture.

Although no simple explanation for the results observed can be offered at the present time, the formation of **12** and **14** is probably facilitated by the fact that **7** is present in the conjugate acid form **17**[8] in acetic acid. In fact, ozonolysis of

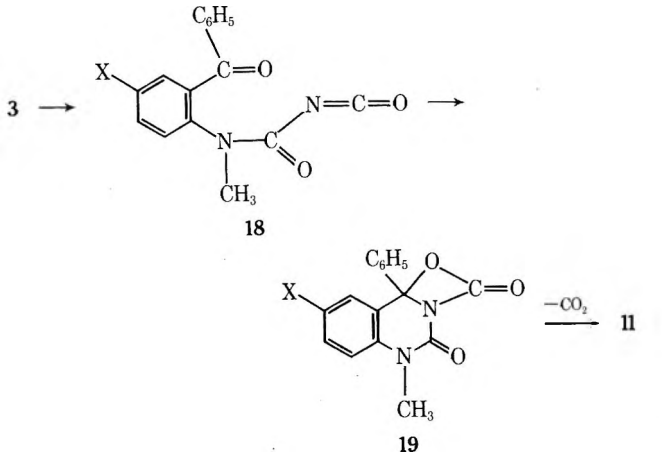


17

7a in the nonpolar solvent carbon tetrachloride[9] gave only **11a** in 7% yield.

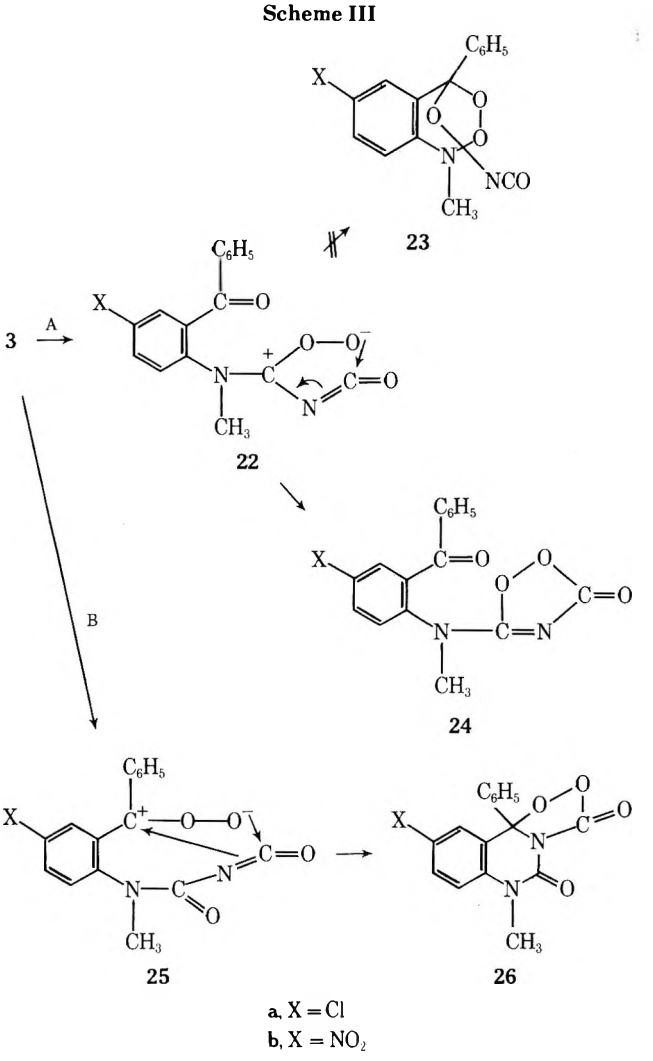
Oxidation of 2-Isocyanatoindoles 3. Chromic acid oxidation of 2-isocyanato-1-methylindoles **3a** and **3b** gave, as the major product, 2-imino-3-indolinols **12a** and **12b**,[10] respectively, together with small amounts of the corresponding **11a** and **11b**, whereas under identical conditions 1-unsubstituted derivative **3c** afforded a complex mixture with no **11c** and **14c** detected.

The formation of **11** as minor products may be explained by initial oxidative cleavage of the indole 2,3 double bond in **3** to give an intermediate **18**. Cyclization of the benzophenone carbonyl group in **18** to the isocyanate group would give an intermediate **19** which eliminates carbon dioxide and yields **11**.[11]



Ozonolysis of **3a** in acetic acid gave, in addition to a small amount of **11a**, a colorless, crystalline peroxidic product of the same molecular formula as that of the expected ozonide **23**. However, this new product did not retain the isocyanate group, as evidenced by the ir spectrum, thus eliminating **23** as a possible structure. On the assumption that this ozonolysis proceeds *via* the formation of either possible zwitterion **22** or **25**,[12] there are possible two other structures, **24** and **26**, which could be formed by the preferential cyclization of **22** and **25** on the isocyanate group rather than on the carbonyl group formed (Scheme III). This

Scheme III



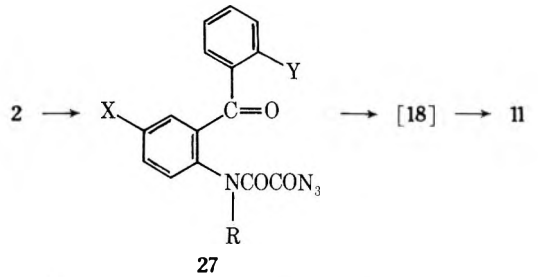
a, X = Cl
b, X = NO_2

might be expected to occur because the isocyanate group should be more reactive as an electrophile. The mass spectrum, which showed major fragment ions characteristic of 2-aminobenzophenones,[13] provided support for structure **24.** Furthermore, the ir absorptions at 1670 (benzophenone C=O), 1638 (C=N), and 1802 cm^{-1} (OCON) seemed more consistent with **24** than with **26.** Thus, we believe structure **24** to be the most likely one for the ozonolysis product of **3.**

Under the same conditions **3b** afforded **24b** as an oil whereas **3c** gave a complicated reaction mixture. Dioxazolones **24a** and **24b** were reduced with sodium iodide to give quinazolinones **11a** and **11b,** respectively.

Oxidation of Indole-2-carboxylic Acid Azides 2. In contrast to isocyanates **3,** chromic acid oxidation of azides **2a** and **2b** gave, as the major product, quinazolinones **11a** and **11b,** respectively, together with small amounts of the corresponding 2-imino-3-indolinols **12a** and **12b.** The latter compounds were probably formed either from isocyanates **3** present as a contaminant in the sample of **2**[14] or those formed by rearrangement prior to oxidation.

The formation of **11** from **2** can be visualized as proceeding *via* a sequence of reactions involving oxaniloyl azides **27** and their rearranged isocyanate intermediates **18.** The



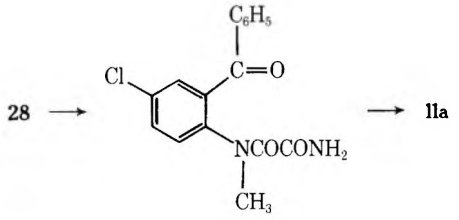
27

a, X = Cl; Y = H; R = CH_3
b, X = NO_2; Y = H; R = CH_3
c, X = Cl; Y = F; R = H

chromic acid oxidation of **2c** led to the isolation of the postulated intermediary oxaniloyl azide **27c.** Compound **27c** is unexpectedly stable and can be kept at room temperature for several weeks without significant change as indicated by the ir spectroscopy. Conversion of **27c** to **11c** was achieved by refluxing in toluene for 6 hr.

Hofmann Reaction of Indole-2-carboxamide 28. Finally, we examined the applicability of the Hofmann reaction[15] to the preparation of 2-aminoindoles **2.** Although 2-aminoindoles have been prepared by other several methods[7] in addition to the Curtius reaction of indole-2-carboxylic acid azides, no reports have appeared on a Hofmann reaction of indole-2-carboxamide.

When a solution of indole-2-carboxamide **28** in tetrahydrofuran[16] was treated with aqueous sodium hypobromite, the unexpected quinazolinone **11a** was obtained in 16% yield together with an unknown dimeric product.[17] The



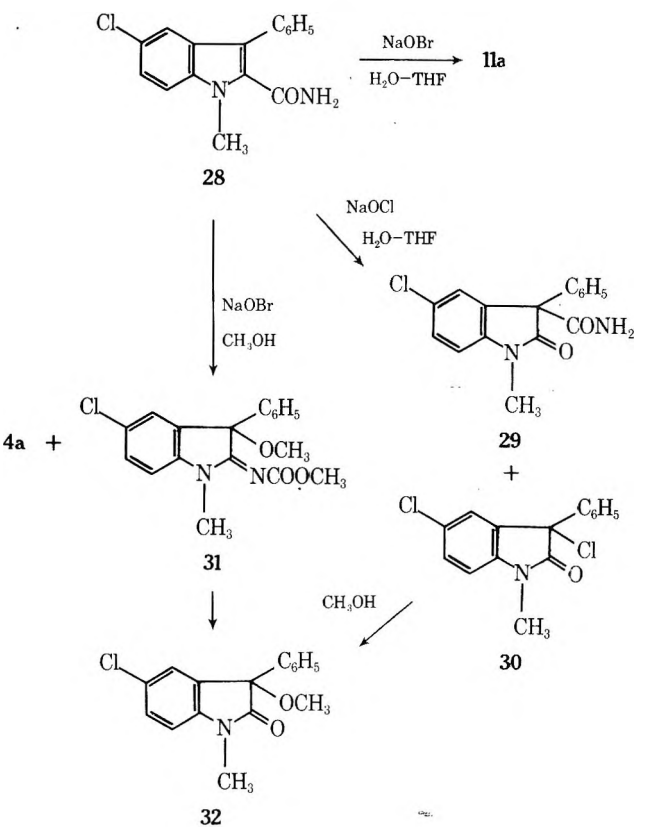
33

reaction probably proceeds *via* initial rearrangement to 2-isocyanato- or 2-aminoindoles **3a** or **7a,** followed by oxidation of the indole 2,3 double bond by the hypobromite present to give **11a.** In fact, both **3a** and **7a** on treatment with aqueous potassium hypobromite gave **11a** in yields of 15 and 17%, respectively.

An alternative route to **11a** involves initial oxidation to an oxamide such as **33,** followed by rearrangement and subsequent cyclization to give **11a.** The inertness of a solution of methyl 5-chloro-1-methyl-3-phenylindole-2-carboxylate (**34**) in tetrahydrofuran toward sodium hypobromite, however, seems to exclude this possibility, although oxamide **33** has been successfully converted to **11a** by performing the Hofmann reaction, as reported in a subsequent paper.[18]

The use of 2.5 molar equiv of aqueous sodium hypochlorite with the addition of tetrahydrofuran led to the formation of oxindoles **29**[19] (34%) and **30** (16%) (Scheme IV) as

Scheme IV



the major products. The structures of these compounds were assigned on the basis of their spectroscopic data. Compound **29** was shown to be identical with the sample obtained as a by-product from chromic acid oxidation of **28** and hydrolyzed to 5-chloro-1-methyl-3-phenyloxindole.[20]

The expected urethane **4a** was obtained, although in poor yield (2%), by employing the Jeffreys modification[15] of the Hofmann reaction. The major product was the further oxidized product **31** (27%), which was easily hydrolyzed to 3-methoxy-3-phenyloxindole(**32**) with acid. The structure of **32** was confirmed by an alternate preparation from **30** by heating with methanol.[21]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (Nujol mulls) were measured on a Hitachi Model EPI-G3 spectrophotometer and nmr spectra on a Varian T-60 instrument using tetramethylsilane as an internal standard. Mass spectra were taken on a Shimadzu LKB instrument with the direct sample inlet system and ionizing potential at 70 eV. Ozone was generated from oxygen using a Nippon ozone 0-10-2 ozonator. All solutions were

Table I

Compd[a]	Method	Recrystn solvent	Mp, °C	Yield, %
2b	A		174–175 dec	95.3
2c[b]	A		113–116 dec	96.7
3b	A		>300	Quantitative
3c	A		77–82	Quantitative
5c	C	EtOH	130.5–132	92.4
6a	B	EtOH	163.5–164.5	39.6
6c	B	*i*-PrOH	115.5–116.5	80.6
7c HCl	D	EtOH	239–241.5	79.8
12b	H	EtOH	227.5–229	46.8[c]

[a] Satisfactory analytical data (±0.4% for C, H, Cl, and N) were reported for all new compounds except **2c** listed in the table: Ed. [b] A satisfactory carbon analysis could not be obtained. [c] Quinazolinone **11b** was obtained in 3.7% yield as the minor product.

dried over anhydrous sodium sulfate and solvents were evaporated under water-aspirator pressure.

The following experiments are typical and illustrate the preparation of the remaining compounds listed in Table I.

5-Chloro-1-methyl-3-phenylindole-2-carboxylic Acid Azide (2a) and Its Conversion into 5-Chloro-2-isocyanato-1-methyl-3-phenylindole (3a). Method A. A mixture of 28.6 g of 5-chloro-1-methyl-3-phenylindole-2-carboxylic acid and 100 g of thionyl chloride was heated under reflux for 1 hr. Excess thionyl chloride was evaporated under reduced pressure and the residual acid chloride was dissolved in 250 ml of acetone. To the cooled solution was added in one portion a solution of 10 g of sodium azide in 30 ml of water. The temperature rose from 5 to 25°. The reaction mixture was cooled to 10° and stirred for 30 min, and 250 ml of water was added. The precipitate that formed was collected by filtration, washed with water followed by 50% aqueous acetone, and dried in a vacuum desiccator at 10° to give 30 g (96.4%) of **2a**: mp 91–94° dec; ir 2130 (N_3), 1666 cm^{-1} (CO). The azide **2a** was too unstable for analysis.

On standing at room temperature, the azide **2a** slowly rearranged to isocyanate **3a**. The course of the reaction was monitored by infrared spectroscopy. After 2 weeks, one-half of **2a** remained. Conversion to **3a** was complete in 40 days: mp 153° dec; ir 2260 cm^{-1} (NCO).

Anal. Calcd for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; Cl, 12.54; N, 9.91. Found: C, 68.09; H, 3.92; Cl, 12.70; N, 10.00.

Methyl 5-Chloro-1-methyl-3-phenylindole-2-carbamate (4a). Method B. A mixture of 1.5 g of **3a** and 50 ml of methanol was heated under reflux for 1 hr. An insoluble material was filtered off and the filtrate was concentrated to about 20 ml and cooled. The precipitate was collected by filtration to give 1.0 g (59.9%) of **4a** as colorless needles: mp 143–145°; ir 3175 (NH), 1722, 1698 cm^{-1}; nmr ($CDCl_3$) δ 3.56 (s, 3, CH_3), 3.71 (s, 3, CH_3), 6.54 (s, 1, D_2O exchangeable, NH), 7.16–7.70 (*m*, 8, aromatic H).

Anal. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; Cl, 11.26; N, 8.90. Found: C, 65.03; H, 4.74; Cl, 11.22; N, 8.88.

Ethyl 5-Chloro-1-methyl-3-phenylindole-2-carbamate (5a). Method C. A mixture of 5.8 g of **2a** and 300 ml of ethanol was refluxed for 2 hr. After evaporation of ethanol, the residue was recrystallized from isopropyl alcohol to give 5.3 g (86.4%) of **5a**, mp 122–123.5°. Further recrystallization from isopropyl alcohol afforded colorless prisms: mp 123–124°; ir 3220, 3130, 1712 cm^{-1}.

Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; Cl, 10.78; N, 8.52. Found: C, 66.03; H, 5.03; Cl, 10.96; N, 8.50.

2-Amino-5-chloro-1-methyl-3-phenylindole (7a). Method D. From 6a. The procedure was essentially that used for the preparation of 2-aminoindole by Rinderknecht, *et al.*[3] A solution of 2.8 g of **6a** in 70 ml of ethanol containing 1 ml of concentrated hydrochloric acid was hydrogenated over 1.0 g of 5% palladium on charcoal until hydrogen uptake had ceased. The catalyst was removed and the filtrate was evaporated. The residue was recrystallized from a mixture of ethanol and ether to give 1.53 g of the hydrochloride of **7a**, mp 254–259° dec. The filtrate was evaporated to dryness and the residue was recrystallized from a mixture of ethanol and acetone to yield an additional 0.43 g of product, mp 257–260° dec, for a combined yield of 1.96 g (93.3%): ir 1700 (C=N), 1610 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}Cl_2N_2$: c, 61.45; H, 4.81; Cl, 24.18; N, 9.55. Found: C, 61.83; H, 4.77; Cl, 24.13; N, 9.46.

The hydrochloride (0.41 g) was suspended in ether and neutralized with aqueous ammonia. The ether layer was separated, washed with water, dried, and evaporated to give 0.31 g (86.3%) of the free base of **7a**, mp 128–131.5°. Two recrystallizations from a mixture of ether and pentane afforded colorless prisms: mp 133–136°; ir 3477, 3377 cm^{-1}; nmr (CCl_4)[9] δ 2.90 (s, NCH_3 in the imino tautomer), 3.35 (s, NCH_3 in the amino tautomer), 3.86 (broad s, 2, D_2O exchangeable, NH_2), 6.87–7.35 (m, 7, aromatic H).

Method E. From 3a. A mixture of 5.0 g of **3a**, 30 ml of benzene, and 20 ml of 50% potassium hydroxide solution was stirred and heated under reflux for 5 min. After cooling, the benzene layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, washed with water, dried, and evaporated. The residue was triturated with ether to give 3.5 g (77.1%) of **7a**, mp 131–135°.[22]

Ethyl 4-[4-Chloro-2-(*o*-fluorobenzoyl)phenyl]allophanate (9c). Method F. To a suspension of 1.0 g of **5c** in 10 ml of acetic acid was added a solution of 1.0 g of chromic anhydride in 1 ml of water. After stirring at room temperature for 15 hr, the reaction mixture was made basic with aqueous ammonia and extracted with chloroform. The chloroform extracts were combined, washed with water, dried, and evaporated. The oily residue was crystallized from ethanol with activated carbon to give 0.28 g of crude **9c**, mp 162–180°. Three recrystallizations from ethanol afforded slightly yellow needles, mp 207–207.5°.[1,22]

Base Hydrolysis of Ethyl 4-(4-Chloro-2-benzoylphenyl)-4-methylallophanate (9a). Following the procedure described in method F, there was obtained 1.92 g of crude **9a** as an oil from 2.0 g of **5a**. The crude **9a** was dissolved in 20 ml of ethanol, mixed with 5 ml of 20% sodium hydroxide solution, and heated under reflux for 30 min. After evaporation of ethanol, the precipitate was collected by filtration, washed with water, and recrystallized from isopropyl alcohol to give 0.60 g (36.4% from **5a**) of **11a**, mp 218–221°.[5c,22]

Acid Hydrolysis of Benzyl 4-(4-Chloro-2-benzoylphenyl)-4-methylallophanate (10a). The crude **10a** (0.94 g from 1.0 g of **6a**) was dissolved in 9 ml of ethanol, mixed with 3 ml of concentrated hydrochloric acid, and heated under reflux for 1 hr. After evaporation of ethanol, the residue was made basic with aqueous ammonia and the precipitate was collected by filtration and washed with water. Recrystallization from ethanol afforded 0.30 g (43.3% from **6a**) of **11a**, mp 218–221°.[22]

The crude **8a** (1.0 g from 1.0 g of **4a**) was hydrolyzed in the same way to yield 0.18 g (21.2% from **4a**) of **11a**, mp 215–218°.[22]

5-Chloro-2-imino-1-methyl-3-phenyl-3-indolinol (12a). Method G. From 7a. An ozone–oxygen stream was passed through a stirred solution of 0.50 g of **7a** in 10 ml of acetic acid at 10–15° for 10 min. The ozonized solution was diluted with 50 ml of water and extracted with chloroform. The chloroform extracts were combined, washed with water, dried, and evaporated. Trituration of the residue with ether followed by recrystallization from isopropyl alcohol furnished 7 mg (1.3%) of **11a**, mp 220.5–224°.[22]

The aqueous layer that separated from the chloroform layer was made basic with aqueous ammonia and extracted with chloroform. The organic extracts were combined, washed with water, dried, and evaporated. Recrystallization of the residue from isopropyl alcohol afforded 0.45 g (84.7%) of **12a** as off-white prisms: mp 200–200.5°; ir 3275 (NH), 3110 (OH), 1648 (C=N), 1610, 1600 cm^{-1}; mass spectrum *m/e* 272 (M^+, base peak).

Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.06; H, 4.80; Cl, 13.00; N, 10.27. Found: C, 66.10; H, 4.61; Cl, 13.28; N, 10,03.

Method H. From 3a. To a suspension of 1.0 g of **3a** in 10 ml of acetic acid was added a solution of 1.0 g of chromic anhydride in 1 ml of water at 15–20°, and the mixture was stirred at room temperature for 3 hr. It was then diluted with water and extracted with chloroform. The insoluble material that formed in the course of extraction was collected by filtration to give 0.94 g of crystals, the infrared spectrum of which [3350–2700, 1700 (C=N), 1615, 935 cm^{-1} (CrO_4^{2-})] indicated that it was probably a chromic acid salt of **12a**. The free base was liberated with aqueous ammonia and recrystallized from isopropyl alcohol to give 0.62 g (64.3%) of **12a** as off-white prisms, mp 199.5–200°.[22]

The chloroform extracts were combined, washed with water, dried, and evaporated. The residue was triturated with ether and recrystallized from isopropyl alcohol to give 0.06 g (6.3%) of **11a**, mp 222–223°.[22]

5-Chloro-1-methyl-3-phenyldioxindole (13). To a solution of 50 mg of **12a** in 4 ml of dimethyl sulfoxide was added 2 ml of 40% sodium hydroxide solution, and the mixture was stirred and heat-

ed to 140° for 1 hr. After cooling, the reaction mixture was diluted with water, acidified with hdyrochloric acid, and extracted with ether. The ether extracts were combined, washed with water, dried, and evaporated. The residue was triturated with isopropyl ether and filtered to give 5 mg (10%) of **13**,[20,22] mp 169–171°. Recrystallization from ether afforded colorless prisms: mp 172–173°; ir 3305, 1717 cm^{-1}.

2-Amino-5-chloro-3-(*o*-fluorophenyl)-3*H*-indol-3-ol (14). Method I. From 7c. A suspension of 1.0 g of **7c** HCl in 10 ml of ether was made basic with aqueous ammonia. The ether layer was separated, washed with water, dried, and evaporated to give 0.88 g of the free base of **7c** as a colorless oil. The base **7c** (0.50 g) was dissolved in 14 ml of acetic acid and subjected to a stream of ozone–oxygen at 14° for 1 hr. The ozonized solution was diluted with water, made basic with 10% sodium hydroxide solution, and extracted with ether. The ether extracts were combined, washed with water, dried, and evaporated. The residue was crystallized from a mixture of ether and isopropyl ether to give 0.12 g (22.6%) of **14**, mp 205.5–207.0°. Recrystallization from isopropyl alcohol furnished colorless needles: mp 205.5–206.5°; ir 3475, 3315, 1650 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}ClFN_2O$: C, 60.77; H, 3.64; Cl, 12.81; N, 10.12. Found: C, 60.53; H, 3.50; Cl, 12.60; N, 10.00.

Method J. From 2-Amino-5′-chloro-2′-fluorobenzophenone (15).[23] To a solution of 2.3 g of **15** in 10 ml of chloroform was added a solution of 1.8 g of dichloroacetyl chloride in 5 ml of chloroform at 5–10°, and the mixture was stirred at room temperature for 3.5 hr. After evaporation of the solvent, the residue was crystallized and recrystallized from ethanol to give 2.05 g (61.7%) of **2′-(*o*-fluorobenzoyl)-2,2,4′-trichloroacetanilide (16)** as yellow needles, mp 90–99.5°.

Anal. Calcd for $C_{15}H_9Cl_3FNO_2$: C, 49.96; H, 2.52; Cl, 29.49; N, 3.88. Found: C, 50.03; H, 2.53; Cl, 29.28; N, 3.87.

To a solution of 1.5 g of **16** in 22 ml of ethanol was added a solution of 0.89 g of potassium cyanide in 7 ml of water. The reaction mixture was stirred at room temperature for 4 hr and diluted with water. The precipitate was collected by filtration and recrystallized from isopropyl alcohol to give 0.45 g (39.1%) of **14**, mp 205.5–206.5°.[22]

Ozonolysis of 7a in Carbon Tetrachloride. An ozone–oxygen stream was passed through a stirred suspension of 1.0 g of **7a** in 30 ml of carbon tetrachloride at −5° for 30 min. During the reaction, an orange-red solution formed from the colorless suspension and then a new suspension appeared. The precipitate was collected by filtration, dissolved in chloroform, and mixed with 5 g of silica gel. After evaporation of the solvent, the residue was placed on a column of 30 g of silica gel. Elution with ethyl acetate and recrystallization from isopropyl alcohol gave 0.07 g (6.6%) of **11a**, mp 221–223°.[22]

5-(2-Benzoyl-4-chloro-*N*-methylanilino)-1,2,4-dioxazol-3-one (24a). An ozone–oxygen stream was passed through a stirred suspension of 2.0 g of **3a** in 30 ml of acetic acid at 15° for 1 hr. The resulting solution was diluted with water and extracted with ether. The extracts were combined, washed with dilute sodium hydroxide solution and then with water, dried, and evaporated. The residue was triturated with ether and filtered to give 1.1 g (47.0%) of crude **24a**, mp 102–103° dec. The crude product was dissolved in tetrahydrofuran and ether was added. The precipitate that immediately formed was filtered off, the filtrate was evaporated to dryness, and the residue was again dissolved in tetrahydrofuran. This process was repeated three times to remove a small amount of contaminating **11a**. Recrystallization of the residue from a mixture of tetrahydrofuran and ether afforded 0.47 g of colorless needles. The product was shown to be pure **24a** by tlc: mp 103.5–105.5 dec; ir 1802 (OCON), 1670 (benzophenone C=O), 1638 (strong, C=N), 1596 cm^{-1}; nmr ($CDCl_3$) δ 3.43 (s, 3, NCH_3), 7.30–7.90 (m, 8, aromatic H); mass spectrum *m/e* (rel intensity) 286 (1), 269 (3), 242 (34), 228 (3), 214 (3), 105 (7), 77 (12), 44 (100).

Anal. Calcd for $C_{16}H_{11}ClN_2O_4$: C, 58.11; H, 3.35; Cl, 10.72; N, 8.47. Found: C, 58.29; H, 3.25; Cl, 10.82; N, 8.57.

The above pure sample (60 mg), when kept at room temperature for 1 month, decomposed to give a brown solid, which after recrystallization from isopropyl alcohol yielded 12 mg (24.4%) of **11a**, mp 218–221.5°.[22]

There was obtained a total of 0.10 g (5.2%) of **11a** from both the original ether filtrate and the insoluble compounds at purification.

The crude oil dioxazolone **24b** was obtained from similar ozonolysis of **3b** in 53.3% yield together with a 5.2% yield of **11b**.

Reduction of 24a with Sodium Iodide. To a cold suspension of 0.20 g of **24a** in 6 ml of acetic acid was added in one portion a solution of 0.18 g of sodium iodide in 4.5 ml of acetic acid. Immediate iodine formation occurred. After stirring for 5 min, the precipitate formed was collected by filtration, washed successively with water, aqueous ammonia and ether, and recrystallized from ethanol to give 45 mg of **11a**, mp 223–224°.[22] The acetic acid filtrate was diluted with water. Filtration of the resulting precipitate and recrystallization from ethanol gave an additional 45 mg of **11a** for a combined yield of 90 mg (57.5%).

A similar reduction of the crude dioxazolone **24b** gave **11b**[5b,22] in 65.7% yield.

Chromic Acid Oxidation of 2a. Compound **2a**, prepared from 2.0 g of the corresponding indole-2-carboxylic acid in the same way as in method A immediately before use, was suspended in 20 ml of acetic acid and treated with a solution of 2.0 g of chromic anhydride in 2 ml of water. The mixture was stirred at room temperature for 3 hr and diluted with water. The precipitate was collected by filtration, washed with water and aqueous ammonia, and dried to give 1.2 g of crude **11a**, mp 200–202° dec. The filtrate was made basic with aqueous ammonia. The precipitate was collected by filtration, washed with dilute hydrochloric acid, and dried to give an additional 0.09 g of **11a**. The two crops were combined and chromatographed over 30 g of silica gel with ethyl acetate. Evaporation of the combined pure fractions and recrystallization from isopropyl alcohol afforded 0.84 g (44.2% from the indole-2-carboxylic acid) of **11a**, mp 223.5–224.5°.[22] A small amount of **12a** was present in the hydrochloric acid washings as determined by thin layer chromatography.

In another run, the compound **12a**[22] was isolated in 4.5% yield together with a 32.9% yield of **11a**.

A similar oxidation of **2b** gave **11b** and **12b**[22] in 40.8 and 16.5% overall yields from the indole-2-carboxylic acid.

4′-Chloro-2′-(*o*-fluorobenzoyl)oxaniloyl Azide (27c). To a suspension of 1.0 g of **2c** in 10 ml of acetic acid was added a solution of 1.0 g of chromic anhydride in 1 ml of water, and the mixture was stirred at room temperature for 3 hr. The precipitate that formed was collected by filtration, washed with water, and dried to give 0.14 g (12.7%) of **27c**: mp 105–106° dec; ir 3230 (NH), 2230, 2165 (N_3), 1720, 1700 (COCO), 1640 (benzophenone CO), 1615 cm^{-1}.

Anal. Calcd for $C_{15}H_8ClFN_4O_3$: C, 51.97; H, 2.33; Cl, 10.23; N, 16.16. Found: C, 52.07; H, 2.29; Cl, 10.38; N, 15.91.

Conversion of 27c to 11c. A suspension of 0.10 g of **27c** in 3 ml of toluene was stirred and heated under reflux for 6 hr. After cooling, the precipitate was collected by filtration and washed with ether to give 55 mg (69.6%) of **11c**, mp >300°.[1,22]

Reaction of 5-Chloro-1-methyl-3-phenylindole-2-carboxamide (28)[2c] with Sodium Hypobromite. Method K. In Water–Tetrahydrofuran. Bromine (1.92 g, 12 mmol) was added dropwise to a solution of 2.4 g (60 mmol) of sodium hydroxide in 20 ml of water cooled to 0°. To the clear yellow solution was added immediately a solution of 1.0 g (3.5 mmol) of **28** in 20 ml of tetrahydrofuran, and the mixture was stirred and heated under reflux for 5 hr. After cooling, the organic layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, washed with saturated brine, dried, and evaporated. The residue was chromatographed over 100 g of silica gel with ethyl acetate, followed by ethyl acetate–ethanol (9:1, v/v). Evaporation of the pure fractions eluted with ethyl acetate yielded 0.15 g (15.8%) of **11a**, mp 223–223.5°.[22]

The fractions eluted with ethyl acetate–ethanol (9:1) left 0.27 g of unidentified dimeric product as an amorphous solid: ir 1665 cm^{-1} (amide CO?); nmr (CCl_4) δ 3.20 (s, 3, NCH_3), 3.88 (s, 3, NCH_3), 6.47–7.55 (m, 18, aromatic H); mass spectrum *m/e* (M^+), 494 (M − $CONH_2$?), 284, 270, 256, 221.

Anal. Calcd for $C_{31}H_{24}Cl_2N_4O$: C, 69.02; H, 4.48; Cl, 13.14; N, 10.38. Found: C, 67.64; H, 4.53; Cl, 13.00; N, 11.94.

The dimer was recovered unchanged both from base hydrolysis in aqueous ethanol and dimethyl sulfoxide, and from chromic acid oxidation in acetic acid.

Method L. In Methanol. Compound **28** (1.43 g, 5 mmol) was added to a solution of 0.92 g (40 mmol) of sodium in 55 ml of methanol. To the suspension was added with stirring 3.2 g (20 mmol) of bromine, and the mixture was stirred and refluxed for 35 min. After evaporation of the solvent, the residue was washed with water, dissolved in chloroform, and chromatographed over 100 g of silica gel with chloroform. The first eluted product, 30 mg (1.9%), mp 139–141°, was found to be urethane **4a**.[22] The second product which was eluted was recrystallized from methanol to give 0.46 g (26.7%) of **5-chloro-3-methoxy-2-methoxycarbonylimino-1-methyl-3-phenylindoline (31)**, mp 173–174.5°. Further recrystal-

lization afforded colorless pillars: mp 174–175°; ir 1722, 1693, 1612 cm^{-1}; nmr ($COCl_3$) δ 3.25 (s, 3, CH_3), 3.33 (s, 3, CH_3), 3.45 (s, 3, CH_3), 6.80–7.43 (m, 8, aromatic H); mass spectrum *m/e* 344 (M^+).

Anal. Calcd for $C_{18}H_{17}ClN_2O_3$: C, 62.70; H, 4.97; Cl, 10.28; N, 8.12. Found: C, 62.71; H, 4.93; Cl, 10.24; N, 8.19.

Repetition of the same reaction using 0.23 g of sodium and 0.8 g of bromine led to a 33% recovery of unreacted **28** in addition to a small amount of **4a** and a 13% yield of **31**.

5-Chloro-1-methyl-3-phenyloxindole-3-carboxamide (29) and 3,5-Dichloro-3-phenyloxindole (30). A 1.8 *N* solution of sodium hypochlorite was prepared by the procedure described by Mallory.[24] To 5 ml (9 mmol) of the sodium hypochlorite solution which had been cooled to −10° was added in one portion a cold solution of 1.0 g (3.5 mmol) of **28** in 20 ml of tetrahydrofuran. The mixture was stirred at −10 to −7° for 1 hr and at room temperature for 1 hr. The tetrahydrofuran layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, washed with saturated brine, and evaporated. The residue was crystallized from chloroform to yield 0.22 g of **29**, mp 209.5–212°. Two recrystallizations from ethanol afforded colorless prisms:[20,22] mp 210–214°; ir 3390, 3235, 1705 (CO), 1676 (amide CO), 1610 cm^{-1}; nmr (DMSO-d_6) δ 3.24 (s, 3, CH_3), 7.10–7.72 (m, 10, aromatic H and NH_2).

Anal. Calcd for $C_{16}H_{13}ClN_2O_2$; c, 63.90; H, 4.36; Cl, 11.79; N, 9.31. Found: C, 64.24; H, 4.39; Cl, 12.00; N, 9.11.

The chloroform filtrate was chromatographed over 50 g of silica gel with chloroform, followed by chloroform–ethanol (9:1, v/v). The oil eluted first with chloroform was crystallized and recrystallized from isopropyl alcohol to give 0.16 g (15.6%) of **30** as colorless prisms: mp 103–105°; ir 1737, 1612 cm^{-1}; mass spectrum *m/e* 291 (M^+), containing two chlorine atoms.

Anal. Calcd for $C_{15}H_{11}Cl_2NO$: C, 61.67; H, 3.80; Cl, 24.27; N, 4.79. Found: C, 61.53; H, 3.88; Cl, 23.91; N, 4.71.

Continued elution with chloroform separated a second fraction which on trituration with ether gave a trace amount of **11a**.[22] The third fraction eluted with chloroform–ethanol (9:1) left 0.18 g of an oil which was crystallized from isopropyl alcohol to yield an additional 0.14 g of **29**, mp 210.5–212°, for a combined yield of 0.36 g (34.1%).

When the same reaction was repeated using 10 ml (18 mmol) of the sodium hypochlorite solution, there were obtained only **30** (46.3%) and **11!** (2.9%) with no **29** detected.

5-Chloro-3-methoxy-3-phenyloxindole (32). Method M. From 31. A mixture of 100 mg of **31**, 3 ml of ethanol, and 1 ml of 20% hydrochloric acid was stirred and heated under reflux for 30 min. The reaction mixture was concentrated and the residue was partitioned between water and ether. The aqueous layer was washed with ether. The combined ether extracts were washed with water, dried, and evaporated. The residue was triturated with ether to give 70 mg (76.6%) of **32**, mp 120–125°. Recrystallization from ether afforded colorless prisms: mp 128–132°; ir 1735, 1615 cm^{-1}; nmr (CCl_4) δ 3.10 (s, 3, CH_3), 3.16 (s, 3, CH_3), 6.68–7.55 (m, 8, aromatic H).

Anal. Calcd for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; Cl, 12.32; N, 4.87. Found: C, 66.43; H, 4.73; Cl, 12.33; N, 5.02.

Method N. From 30. A solution of 0.20 g of **30** in 5 ml of methanol was heated under reflux for 2 hr. The solvent was evaporated and the residue was crystallized from isopropyl ether to yield 0.17 g (86.3%) of **32**, mp 127–130°.[22]

Reaction of 3a with Potassium Hypobromite. Method O. Bromine (1.0 g) was added to a solution of 1.7 g of potassium hydroxide in 10 ml of water cooled to 0°. To the clear yellow solution was added 1.42 g of **3a**. The mixture was stirred at 0° for 30 min and at room temperature for 1 hr, and then heated to 70–80° for 1 hr. After cooling the gummy solid that formed was separated by decantation, washed with water, and dissolved in ethanol by heating. The insoluble material was filtered off and discarded. The filtrate was concentrated to dryness, dissolved in chloroform, and chromatographed over 50 g of silica gel. Elution with ethyl acetate separated an oily solid which on trituration with ether gave 0.24 g (17.3%) of **11a**, mp 218–221°.[22] The ether filtrate was concentrated and the residue was rechromatographed on silica gel layer plates, using ethyl acetate as eluent, to give 85 mg (6.2%) of **13**, mp 172–173°[22] after recrystallization from ether.

When the reaction was carried out with sodium hypochlorite with the addition of tetrahydrofuran in a similar manner as described in method K, there was obtained a 8.4% yield of **11a**.

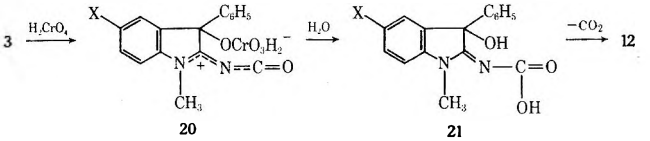
Reaction of 7a with Potassium Hypobromite. The procedure described in method O was followed except that the heating time was extended to 2 hr. The gummy material was crystallized from ether to give 0.10 g (14.8% from 0.64 g of **7a**) of **11a**, mp 222–223°.[22] Considerable amounts of **7a** and **12a** were present in the ether filtrate as determined by thin layer chromatography.

Acknowledgment. We are grateful to Mr. M. Yamamoto for his valuable comments and to Mr. Y. Kameno and Miss R. Kido for skillful technical assistance.

Registry No.—**1a**, 51820-32-7; **1b**, 30008-48-1; **1c**, 32502-22-0; **2a**, 51559-71-8; **2b**, 51820-33-8; **2c**, 51820-34-9; **3a**, 51559-72-9; **3b**, 51820-35-0; **3c**, 51820-36-1; **4a**, 51820-37-2; **5a**, 51820-38-3; **5c**, 51820-39-4; **6a**, 51820-40-7; **6c**, 51820-41-8; **7a**, 51820-42-9; **7a** hydrochloride, 51820-43-0; **7b**, 51820-44-1; **7c**, 51820-45-2; **7c** hydrochloride, 51820-46-3; **9a**, 51820-47-4; **9c**, 40387-16-4; **10a**, 51820-48-5; **11a**, 20927-53-1; **11c**, 40069-75-8; **12a**, 51820-49-6; **12b**, 51820-50-9; **13**, 51820-51-0; **14**, 51820-52-1; **15**, 784-38-3; **16**, 51820-53-2; **24a**, 51820-54-3; **27c**, 51806-10-1; **28**, 21139-24-2; **29**, 51820-55-4; **30**, 20423-55-6; **31**, 51820-56-5; **32**, 51820-57-6.

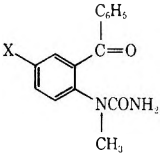
References and Notes

(1) Part I: K. Ishizumi, S. Inaba, and H. Yamamoto, *J. Org. Chem.*, **38**, 2617 (1973).
(2) (a) S. Inaba, K. Ishizumi, and H. Yamamoto, *Chem. Pharm. Bull.*, **19**, 263 (1971); (b) S. Inaba, K. Ishizumi, K. Mori, and H. Yamamoto, *ibid.*, **19**, 722 (1971); (c) H. Yamamoto, S. Inaba, T. Hirohashi, and K. Ishizumi, *Chem. Ber.*, **101**, 4245 (1968).
(3) H. Rinderknecht, H. Koechlin, and C. Niemann, *J. Org. Chem.*, **18**, 971 (1953).
(4) To our knowledge, the only 2-aminoindole reported to have cleaved by oxidation with the retention of the 2-amino nitrogen is 7-phenylindole[1,2-*a*]-6*H*-5-quinazolinone, where the 2-amino group of the indole ring is protected by benzoyl group in the molecule; see J. A. Moore, G. J. Sutherland, R. Sowerby, E. G. Kelly, S. Palermo, and W. Webster, *J. Org. Chem.*, **34**, 887 (1969).
(5) (a) A. M. Felix, J. V. Earley, R. I. Fryer, and L. H. Sternbach, *J. Heterocycl. Chem.*, **5**, 731 (1968); (b) S. Inaba, M. Yamamoto, K. Ishizumi, K. Takahashi, K. Mori, and H. Yamamoto, Japanese Patent 29,858 (1971); *Chem. Abstr.*, **75**, 140877q (1971); (c) K. Ishizumi, S. Inaba, and H. Yamamoto, *J. Org. Chem.*, **37**, 4111 (1972).
(6) S. C. Bell and P. H. L. Wei, *J. Heterocycl. Chem.*, **6**, 599 (1969).
(7) For the autoxidation of 2-aminoindoles, see T. Hino, M. Nakagawa, T. Hashizume, N. Yamaji, Y. Miwa, K. Tsuneoka, and S. Akaboshi, *Tetrahedron*, **27**, 775 (1971), and references cited therein.
(8) The ir spectrum of the hydrochloride of **7a** showed a prominent C=N absorption at 1700 cm^{-1}, which is absent from the spectrum of the free base of **7a**, in good agreement with the observations made in the case of 2-amino-1-methylindole: J. Kebrle and K. Hoffmann, *Helv. Chim. Acta*, **39**, 116 (1956).
(9) In carbon tetrachloride solution the free base **7a** was shown to be present as a 85:15 mixture of the amino and the imino tautomers by nmr spectroscopy.[7]
(10) Although it is impossible to formulate a detailed mechanism for the oxidation of **3** to **12** on the basis of experimental evidence now available, we would like to propose a working hypothesis as shown by the following sequence. Obviously, this hypothesis represents only one of several possible mechanistic pathways. For general reviews of the chromic acid oxidation of C=C bonds, see (a) K. B. Wiberg, "Oxidation in Organic Chemistry," Part A, Academic Press, New York, N. Y., 1968, p 69; (b) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, p 275.



20 21

(11) In the oxidation of **3a**, similar results were realized either in aqueous acetic acid or in acetic acid containing acetic anhydride to maintain anhydrous conditions. In either case, however, water was added in order to isolate products. Therefore, as suggested by a referee, the intermediacy of urea A[18] in the sequence of reactions leading to **11** cannot be rigorously excluded.



A

(12) For a review of ozonolysis, see P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).
(13) M. E. Derieg, R. I. Fryer, S. S. Hillery, W. Metlesics, and G. Silverman, *J. Org. Chem.*, **36**, 782 (1971).
(14) Although azides **2** were prepared immediately before they were to be

used, small amounts of **3** were present as a contaminant in the sample of **2**, as indicated by the ir spectroscopy.
(15) For a review, see E. S. Wallis and J. F. Lane, *Org. React.*, **3**, 267 (1946).
(16) The use of dioxane as a cosolvent in Hofmann reactions was reported: E. Magnien and R. Baltzly, *J. Org. Chem.*, **23**, 2029 (1958).
(17) Originally, Mr. M. Yamamoto of these laboratories found that treatment of **28** with aqueous potassium hypobromite without the addition of tetrahydrofuran gave a trace amount of **11a** with recovery of most of unreacted **28**.
(18) K. Ishizumi, S. Inaba, and H. Yamamoto, *J. Org. Chem.*, **39**, 2587 (1974).
(19) After the completion of this work, the conversion of 5-chloro-3-(o-fluorophenyl)indole-2-carboxamide to the corresponding oxindole-3-carboxamide by reaction with *tert*-butyl hypochlorite was reported: A. Walser, J. F. Blount, and R. I. Fryer, *J. Org. Chem.*, **38**, 3077 (1973).
(20) Unpublished studies of Mr. M. Yamamoto and Mr. M. Koshiba.
(21) J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, 4789 (1957).
(22) The product was identified with an authentic sample by comparison of the infrared spectra.
(23) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962).
(24) F. B. Mallory, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 74.

Quinazolines. III.[1] Curtius and Hofmann Reactions of 2′-Benzoyloxanilic Acids. Novel Syntheses of Quinazolinones

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N-Substituted 2′-benzoyloxaniloyl chlorides **2**, prepared from the reaction of the corresponding 2-aminobenzophenones **1** and oxalyl chloride, were converted through their azides **3** to quinazolinones **6** in good yields by treatment with aqueous sodium azide. N-Unsubstituted derivative **2e** gave the azide intermediate **3e**, which was shown to be identical with the product of chromic acid oxidation of the corresponding indole-2-carboxylic acid azide. For the Hofmann reaction, *N*-(2-benzoylphenyl)oxamides **7a,b,f** were prepared from the corresponding chlorides **2** by treatment with ammonia. Similar reaction of nitro compound **2c** with ammonia led to a mixture of quinazolinone **6c** and 2-hydroxyquinazoline **8**. The desired oxamide **7c**, however, was obtained by chromic acid oxidation of indole-2-carboxamide **10**. *N*-Alkyl-substituted oxamides **7a–c** were converted to the corresponding quinazolinones **6** in satisfactory yields either by treatment with aqueous sodium hypobromite in tetrahydrofuran, or with methanolic sodium hypobromite in methanol.

In an accompanying paper,[1] it was shown that 2′-benzoyloxaniloyl azides and their rearranged isocyanates were intermediates in the oxidative ring enlargement of indole-2-carboxylic acid azides and 2-isocyanatoindoles to quinazolinones. We wish to report now on the Curtius (sodium azide method)[2a] and Hofmann reactions[2b] of 2′-benzoyloxanilic acids. Although oxaniloyl azides have been reported to undergo the Curtius rearrangement in the presence of amines to give biurets,[2d] the Hofmann reaction of oxamides, which is expected to give ureas, has not been investigated.

Curtius Reaction of 2′-Benzoyloxaniloyl Chlorides 2. The required oxaniloyl chlorides **2** (Scheme I) were readily prepared from the corresponding 2-aminobenzophenones **1** by treatment with oxalyl chloride, and utilized in the next step without further purification. When a solution of N-substituted derivatives **2** in acetone was treated with aqueous sodium azide (wet method), the expected quinazolinones **6** were precipitated[3] in high yields, as shown in Table I. This was, however, preceded by the formation of another compound as could be established by thin layer chromatography. In the case of **2a**, this intermediate, urea **5a** could be isolated by carrying out the reaction at low temperature and quenching with water. However, the urea **5a** could not be purified owing to its great tendency to cyclize, although analysis of the crude product agreed with that of the assigned structure. The crude product was cyclized completely to **6a** by refluxing in toluene. The isolation of **5a** indicates that hydrolysis of the isocyanate intermediate **4** occurs prior to cyclization to **6**.

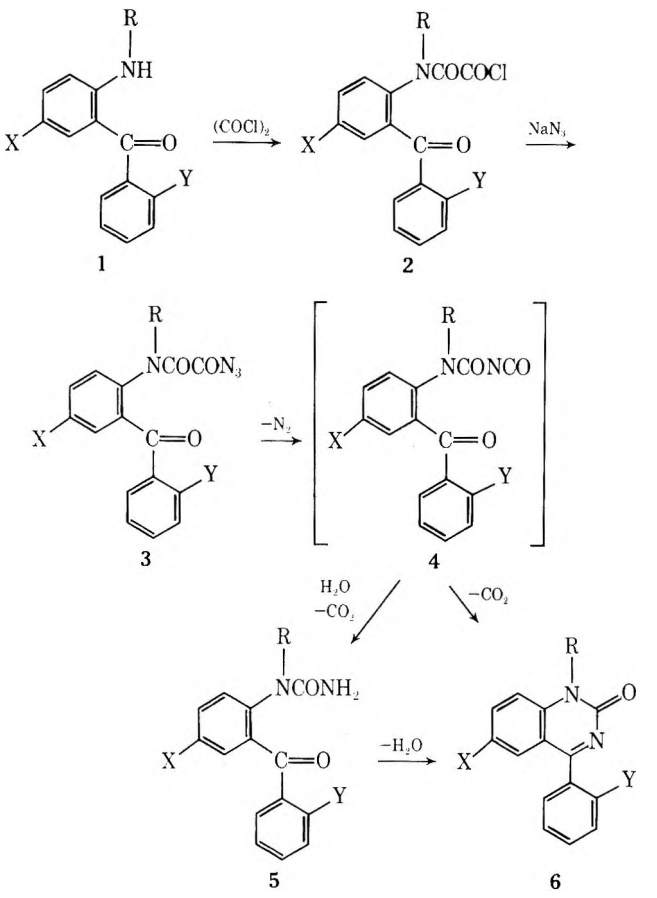
The conversion of **2a** to **6a** was also achieved, although in lower yield, by heating a solution of **2a** in toluene with powdered sodium azide[4] (dry method), a method practicable only for reactive chlorides.[2a] Under these anhydrous conditions, the formation of **6** must involve direct cyclization of **4** with elimination of carbon dioxide to give **6**.

Table I
Reactions of 2′-Benzoyloxaniloyl Chlorides with Sodium Azide

No.	Compd	R	X	Y	Method	Temp, °C	Time, hr	Product	Yield,[a] %	Mp,[b] °C	Lit. mp, °C
1	**2a**	CH_3	Cl	H	Wet	*c*	4.5	**6a**	90	224–224.5	222–223[d]
2	**2a**	CH_3	Cl	H	Dry	100	4	**6a**	36	223–224	222–223[d]
3	**2b**	CH_2-c-C_3H_5	Cl	H	Wet	*c*	4	**6b**	86	173–174	175–176[e]
4	**2c**	CH_3	NO_2	H	Wet	60[f]	3	**6c**	77	269–270	261–262[g]
5	**2d**	$(CH_2)_2OCOCH_3$	NO_2	H	Wet	60[f]	1	**6d**	73[h]	154.5–155.5[h]	155–156[i]
6	**2e**	H	Cl	F	Wet	*c*	0.5	**3e**	*j*		
7	**2e**	H	Cl	F	Dry	112	1.5	**3e** **6e**	19 4	104–106 >300	105–106[k] >300[l]

[a] Overall yield from the corresponding 2-aminobenzophenone and based on product precipitated from the reaction mixture unless otherwise stated. [b] The melting points were taken without recrystallization unless otherwise stated. [c] Room temperature. [d] Reference 5c. [e] Reference 5b. [f] Before heating, the reaction temperature was maintained at room temperature with a reaction time of 1–2 hr. [g] Reference 6. [h] Yield and melting point of the sample recrystallized once from ethanol. [i] Reference 7. [j] The ir spectrum of the reaction product indicated the presence of **3e**. [k] Reference 1. [l] K. Ishizumi, S. Inaba, and H. Yamamoto, *J. Org. Chem.*, **38**, 2617 (1973).

Scheme I



a, X = Cl; Y = H; R = CH_3
b, X = Cl; Y = H; R = CH_2-c-C_3H_5
c, X = NO_2; Y = H; R = CH_3
d, X = NO_2; Y = H; R = $(CH_2)_2OCOCH_3$
e, X = Cl; Y = F; R = H

Reaction of N-unsubstituted oxaniloyl chloride **2e** with aqueous sodium azide gave an intractable mixture containing the azide intermediate **3e**. Under anhydrous conditions, **3e** was actually isolated together with **6c** (Table I). This compound was in every respect identical with the product of chromic acid oxidation of 5-chloro-3-(*o*-fluorophenyl)indole-2-carboxylic acid azide.[1]

The use of the sequence **1** → **2** → **6** to prepare 1-substituted quinazolinones in good yield is particularly interesting, since alkylation of 1-unsubstituted quinazolinones, especially with bulky alkyl halides, results in a mixture of N- and O-alkylated products.[5] The same conversion (**1** → **6**) has previously been achieved in one operation by cyclization with derivatives of carbamic acid, such as urea, urethane, and potassium cyanate–acetic acid. However, these condensation reactions require severe reaction conditions and give relatively low yields of **6**.[5,6] Furthermore, we were unsuccessful in converting **1d** to **6d**[7] by the urethane condensation method, probably the only method applicable for the ring closure of nitro compounds.[5c,6] Consequently, the present method appears to offer major advantages for the preparation of 1-substituted quinazolinones from the corresponding 2-aminobenzophenones.

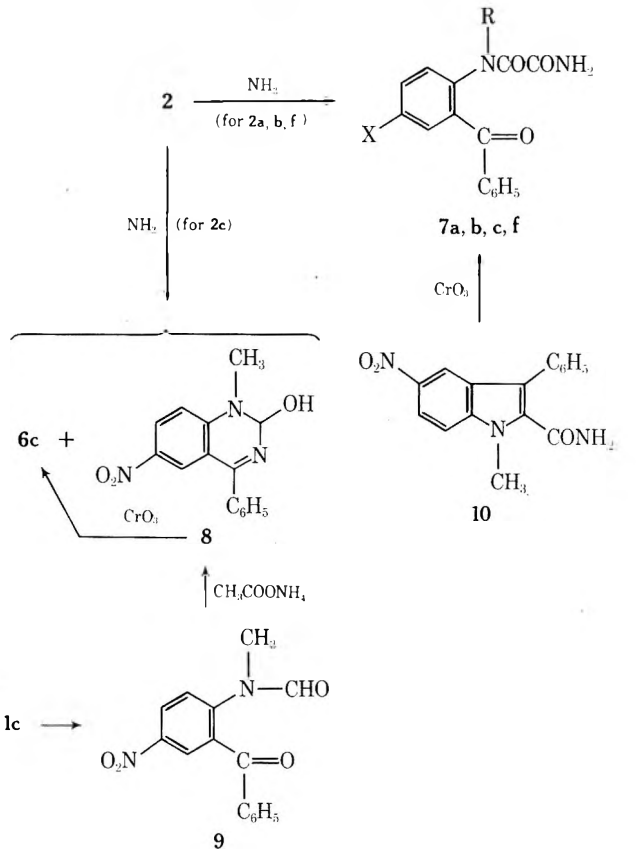
Hofmann Reaction of *N*-(2-Benzoylphenyl)oxamides (7). The chloro oxamides **7a,b,f** (Scheme II) were prepared by treatment of the corresponding oxaniloyl chlorides **2** with ammonia in 79–92% overall yields from **1**. The same treatment of the nitro compound **2c**, however, led to a mixture of quinazolinone **6c** and 2-hydroxyquinazoline **8** instead of the expected oxamide **7c**. The structure of **8** was confirmed both by oxidation to **6c** with chromic acid and by an independent preparation from 2′-benzoyl-*N*-methyl-4′-nitroformanilide (**9**) and ammonium acetate.[8] Compound **9** did not react with ammonia in tetrahydrofuran, conditions under which **2c** gave **8**, thus indicating that **9** is not an intermediate in the conversion of **2c** to **8**. The required oxamide **7c** was, however, obtained in 60% yield by oxidation of 1-methyl-5-nitro-3-phenylindole-2-carboxamide[9] (**10**) with chromic acid.

As expected, the Hofmann reaction of oxamides **7** gave the corresponding quinazolinones **6** with the results summarized in Table II. Although **6a** was obtained by heating **7a** with aqueous sodium hypobromite, a standard procedure for the Hofmann reaction, the yield was improved considerably when **7a** was added as a solution in tetrahydrofuran[1] to the same reagent, presumably because the increase of solubility of **7a** permits a lower reaction temperature. Comparison of runs 2 and 3 indicates the advantage of using hypobromite, contrary to the fact that better results are generally achieved with hypochlorite rather than hypobromite.[2b]

In analogy with the Curtius reaction of **2** using aqueous sodium azide, the Hofmann reaction of **7** to give **6** under aqueous conditions probably involves hydrolysis of the rearranged isocyanate intermediate **4** to **5**, followed by cyclization of **5** to **6**, although **5** could not be isolated.

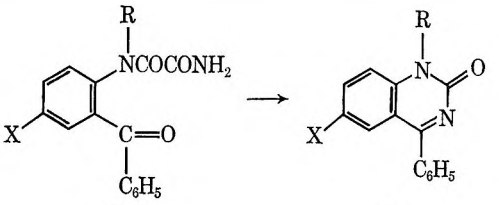
The Jeffreys modification of the Hofmann reaction was also applicable to conversion of **7** to **6**. Thus, heating of **7** with sodium methoxide and bromine in methanol directly precipitated **6** with no observable formation of the expected methyl allophanate (**11**).[10] The conversion of **7** to **6** in methanol seems to be explained simply by direct cycliza-

Scheme II



a, X = Cl; R = CH_3
b, X = Cl; R = CH_2-c-C_3H_5
c, X = NO_2; R = CH_3
f, X = Cl; R = H

Table II
Hofmann Reactions of *N*-(2-Benzoylphenyl)oxamides



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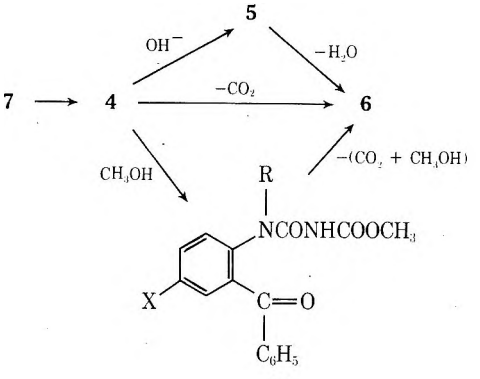
No.	Compd	R	X	Reagent	Temp, °C	Time, hr	Yield, %
1	**7a**	CH_3	Cl	NaOBr	60	1.3	39
2	**7a**	CH_3	Cl	NaOBr (THF)	−5 to −3	2	74
3	**7a**	CH_3	Cl	NaOCl (THF)	−5 to 0	2	35
4	**7a**	CH_3	Cl	NaOBr (CH_3OH)	Reflux	2	67
5	**7b**	CH_2-c-C_3H_5	Cl	NaOBr (THF)	−5 to −4	0.8	82
6	**7c**	CH_3	NO_2	NaOBr (THF)	−5 to 0	4	8
7	**7c**	CH_3	NO_2	NaOBr (CH_3OH)	Reflux	2	50
8	**7f**	H	Cl	NaOBr (THF)	Reflux	1	
9	**7f**	H	Cl	NaOBr (CH_3OH)	Reflux	2	7

tion of the isocyanate intermediate **4** to **6** with elimination of carbon dioxide. However, the formation of methyl allophanate (**11**) as a precursor of **6** cannot be rigorously excluded since **11a**, on heating with sodium methoxide in methanol, gave **6a** (Scheme III).

Scheme III



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The Hofmann reaction of oxamides **7** to give **6** appears to be quite general, although it requires a substituent at the anilino nitrogen to obtain a satisfactory yield of **6**.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (Nujol mulls) were measured on a Hitachi Model EPI-G3 spectrophotometer and nmr spectra on a Varian T-60 instrument using tetramethylsilane as an internal standard. Mass spectra were taken on a Shimadzu LKB instrument with the direct sample inlet system and ionizing potential at 70 eV. All solutions were dried over anhydrous sodium sulfate and solvents were evaporated under water-aspirator pressure. The identity of compounds was established by a comparison of spectral properties.

Preparation of 2-Aminobenzophenones (1). All 2-aminobenzophenones except **1d** have been characterized previously. Compounds **1a**,[11a] **1b**,[5b] and **1c**[11b] were prepared by acid hydrolysis of the corresponding 1,3-dihydro-5-phenyl-2*H*- 1,4-benzodiazepin-2-ones[12according] to the procedure described by Sternbach, *et al.*[11b] Compounds **1e** and **1f** were prepared by the Friedel–Crafts reaction following the procedure described by Sternbach, *et al.*[11a]

2-(2-Acetoxyethyl)amino-5-nitrobenzophenone (1d) was prepared by heating 4.0 g of 2-(2-hydroxyethyl)amino-5-nitrobenzophenone[13] in 40 ml of acetic anhydride containing 4.0 g of sodium acetate at 50–55° for 1 hr. The cooled solution was made basic with aqueous ammonia. The resulting precipitate was collected by filtration, washed with water and ether, and dried. Recrystallization from ethanol gave 3.79 g (82.9%) of **1d**, mp 102.5–103.5°.

Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.42; H, 4.75; N, 8.55.

Reaction of 2′-Benzoyloxaniloyl Chlorides (2) with Aqueous Sodium Azide. Wet Method. The wet procedure may be exemplified by preparation of quinazolinone **6a** (run 1). To 2.5 g of oxalyl chloride was added 1.0 g (4.1 mmol) of **1a** with stirring and cooling in an ice bath, and stirring was continued for 1 hr at room temperature. Excess oxalyl chloride was evaporated and the residual oil, oxaniloyl chloride **2a** was dissolved in 10 ml of acetone. The cold solution was added in one portion to a stirred solution of 0.60 g (9.2 mmol) of sodium azide in 2 ml of water cooled to −5°. An exothermic reaction occurred (the temperature rose to 10°). The mixture was stirred at room temperature for 4.5 hr and then cooled in an ice bath. The precipitate was collected by filtration, washed with water, and dried to give 0.96 g of **6a**, mp 224–224.5°. From the filtrates, an additional 35 mg of product, mp 220–221.5°, was obtained for a combined yield of 995 mg (90.3%).

Similar procedures were used for the preparation of **6b**, **6c**, and **6d** (runs 3, 4, and 5). The acetone-soluble quinazolinone **6d** was isolated by concentrating the reaction mixture, extracting with chloroform, and removing the solvent. The residue was crystallized from ether and recrystallized from ethanol to yield pure product. The results are summarized in Table I.

In the alternative procedure, the addition of aqueous sodium azide solution to the oxaniloyl chloride **2** in acetone solution, the yields of **6** were decreased by 10–25%, probably owing to the increase of hydrolysis reaction which occurs prior to reaction with sodium azide.

Reaction of 2a with Aqueous Sodium Azide at Low Temperature. Isolation of *N*-(2-Benzoyl-4-chlorophenyl)-*N*-methylurea (5a). The urea intermediate **5a** was obtained in the crystalline state only one time. Oxaniloyl chloride **2a**, from reaction of 2.0 g (8.1 mmol) of **1a** and oxalyl chloride, was dissolved in 30 ml of acetone and cooled in an ice bath. To the stirred solution was added in one portion a cold solution of 1.2 g (18.4 mmol) of sodium azide in 4 ml of water. The mixture was stirred under cooling for 2 hr and then 50 ml of ice water was slowly added. On further stirring crystallization occurred. The crystals were collected by filtration and washed with water and 50% aqueous acetone to give 1.81 g (77.0%) of **5a**, which decomposed at 125–128° without melting and melted at 216–220°. Thin layer chromatography indicated that the sample was contaminated with a small amount of **6a** and, after melting at 220°, converted completely to **6a**: ir 3270, 3170 (shoulder), 1643 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}ClN_2O_2$: C, 62.40; H, 4.54; Cl, 12.28; N, 9.70. Found: C, 62.67; H, 4.27; Cl, 12.07; N, 9.39.

From the filtrates 0.14 g (6.4%) of **6a**, mp 223–224.5°, was obtained.

The urea **5a** (0.50 g) was cyclized completely by heating in 5 ml of refluxing toluene for 2.5 hr. The mixture was cooled and the precipitate was collected by filtration to give 0.42 g (89.6%) of **6a**, mp 221–223°.

Attempts to repeat the crystallization of the urea intermediate failed. The reactions behaved the same: apparently the urea formed (tlc), but failed to crystallize from the gummy material after dilution of the reaction mixture with water. The gummy material was converted directly to **6a** during the work-up procedure.

Reaction of 2a with Dry Sodium Azide. Dry Method (Run 2). To a solution of **2a** [from 0.50 g (2.0 mmol) of **1a**] in 10 ml of toluene was added 0.30 g (4.6 mmol) of powdered sodium azide,[4] and the mixture was stirred and heated at 100° for 4 hr. After cooling, the precipitate was collected by filtration, washed with water, and dried to yield 0.16 g of **6a**, mp 223–224°. From the filtrates an additional 0.04 g of product, mp 220.5–221.5°, was obtained for a combined yield of 0.20 g (36.3%).

4′-Chloro-2′-(*o*-fluorobenzoyl)oxaniloyl Chloride (2e). To 4.0 g of oxalyl chloride was added 1.0 g of **1e** with stirring and cooling. The solid mass formed immediately. Toluene (5 ml) was added and stirring was continued at room temperature for 30 min. The solvent and excess oxalyl chloride was evaporated to dryness to yield 1.34 g (98.4%) of **2e**: mp 127.5–130°; ir 3200, 1770, 1728, 1630, 1612 cm^{-1}.

Anal. Calcd for $C_{15}H_8Cl_2FNO_3$: C, 52.96; H, 2.37; N, 4.12. Found: C, 54.82; H, 2.71; N, 4.59.

The analysis indicates that it is perhaps contaminated with a small amount of **2′,2″-bis(*o*-fluorobenzoyl)-4′,4″-dichlorooxanilide (12e).**[14]

When the reaction was carried out by adding oxalyl chloride to **1e**, the oxanilide **12e** was obtained as the major product. After recrystallization from dimethylformamide, colorless needles were obtained: mp > 300°; ir 3170, 1710, 1655, 1620 cm^{-1}.

Anal. Calcd for $C_{28}H_{16}Cl_2F_2N_2O_4$: C, 60.78; H, 2.91; cl, 12.81; N, 5.06. Found: C, 60.76; H, 2.98; Cl, 12.43; N, 5.05.

4′-Chloro-2′-(*o*-fluorobenzoyl)oxaniloyl Azide (3e). Run 7. To a suspension of 0.67 g (2.0 mmol) of **2e** in 10 ml of toluene was added 0.30 g (4.6 mmol) of powdered sodium azide. The mixture was stirred and refluxed for 1.5 hr. Filtration of the cooled mixture and washing with water gave 0.10 g of a solid, which was shown by infrared spectrum to be a mixture of **12e** and **3e**. From the combined filtrations, 0.13 g (18.7%) of **3e**, mp 104–106°, was obtained after removal of the initially precipitated, impure product **3e** (0.19 g) by filtration. The infrared spectrum indicated that the sample was essentially pure and identical with an authentic sample.[1]

The filtrates obtained after removal of **3e** were separated and extracted with ether. The organic layers were combined, washed with water, dried, and evaporated to give 23 mg (4.2%) of **6e**, mp >300°.

When the reaction was carried out with aqueous sodium azide according to the general procedure, the azide **3e** contaminated with unknown compounds was mainly obtained with a small amount of **12e** (run 6).

Attempted Condensation of 1d with Urethane. A mixture of 100 mg of **1d**, 30 mg of zinc chloride, and 150 mg of urethane was stirred and heated at 180–190° for 4 hr. The cooled reaction mixture was dissolved in chloroform and filtered to remove the insoluble material. The filtrate was washed with 5% sodium hydroxide solution and water, dried, and evaporated. An examination of the oily residue (40 mg) by thin layer chromatography indicated the presence of four products, but none of these corresponded to authentic samples of **1d** and **6d**.

***N*-(2-Benzoyl-4-chlorophenyl)-*N*-methyloxamide (7a).** Oxaniloyl chloride **2a** (from 10.0 g of **1a**) was dissolved in 100 ml of tetrahydrofuran and stirred in an ice bath. Ammonia was bubbled in slowly for 30 min and the reaction mixtre was filtered. The insoluble material was washed thoroughly with tetrahydrofuran and the combined filtrates were evaporated. The oily residue was crystallized from ether to give 11.9 g (92.3% overall yield) of **7a**, mp 144–146°. Recrystallization from a mixture of tetrahydrofuran and ether afforded yellow prisms: mp 144–146.5°; ir 3430, 3200, 3055, 1715, 1672, 1662 cm^{-1}; nmr ($CDCl_3$) δ 3.22 and 3.55 (9:2, s, 3, CH_3), 5.90 and 7.10 (1:1, broad s, 2, D_2O exchangeable, NH_2), 7.20–7.93 (m, 8, aromatic H); mass spectrum *m/e* 316 (M^+), 272 (M − $CONH_2$), 258, 230.

Anal. Calcd for $C_{16}H_{13}ClN_2O_3$: C, 60.67; H, 4.14; Cl, 11.19; N, 8.84. Found: C, 60.84; H, 4.14; Cl, 11.19; N, 8.92.

***N*-(2-Benzoyl-4-chlorophenyl)-*N*-cyclopropylmethyloxamide (7b)** was prepared similarly from **1b** in 86.8% yield. Recrystallization from tetrahydrofuran gave pale yellow prisms, mp 143.5–144.5°.

Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80; Cl, 9.94; N, 7.85. Found: C, 63.66; H, 4.95; Cl, 9.84; N, 7.79.

(2-Benzoyl-4-chlorophenyl)oxamide (7f) was prepared similarly in 79.1% overall yield. Recrystallization from tetrahydrofuran afforded colorless prisms, mp 209–210° (lit.[15] mp 209–211°).

Anal. Calcd for $C_{15}H_{11}ClN_2O_3$: C, 59.59; H, 3.36; Cl, 11.71; N, 9.25. Found: C, 59.53; H, 3.70; Cl, 11.38; N, 9.22.

1,2-Dihydro-1-methyl-6-nitro-4-phenylquinazolin-2-ol (8). A. From 2c. Ammonia was bubbled through a stirred solution of **2c** (from 5.0 g of **1c**) in 100 ml of tetrahydrofuran in an ice bath for 20 min. The reaction mixture was filtered. The insoluble material was dissolved in tetrahydrofuran by warming and filtered. The residue, left on concentration of the combined filtrates, was washed with ether and recrystallized from 550 ml of tetrahydrofuran to give 0.86 g (15.6%) of **8**, mp 188–192°. Further recrystallization from tetrahydrofuran afforded yellow needles: mp 195–200°; ir 3070 (broad), 1630, 1615 cm^{-1} (shoulder).

Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.59; H, 4.63; N, 14.83. Found: C, 63.35; H, 4.53; N, 14.42.

The original mother liquor was concentrated and the residue was recrystallized from tetrahydrofuran to give 0.88 g (16.0%) of **6c**, mp 254–260°.

B. From 2′-Benzoyl-*N*-methyl-4′-nitroformanilide (9). A mixture of 5.0 g of **1c**, 4.0 g of sodium formate, and 40 ml of formic acid was heated at 135–140° for 26.5 hr, during which time solution occurred. The formic acid was evaporated and the residue was dissolved in methylene chloride. The solution was washed with dilute sodium hydroxide solution and water, dried, and concentrated to dryness. The residue was chromatographed over 200 g of silica gel with chloroform to give 2.67 g of starting material (53.4% recovered **1c**) and 2.14 g of a brown oil as a second fraction. The oil was crystallized from hexane to yield 2.07 g (37.3%) of **9**, mp 80–84°. Recrystallization from ether afforded slightly yellow plates, mp 85–88°.

Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.26; N, 9.86. Found: C, 63.41; H, 4.54; N, 9.80.

A mixture of 1.0 g of **9**, 2.4 g of ammonium acetate, and 2.7 g of pyridine in 25 ml of dimethyl sulfoxide was stirred and heated at 75–85° for 1.5 hr. The reaction mixture was then poured into ice water. The precipitate that obtained by filtration was chromatographed over 30 g of silica gel. Elution with ethyl acetate yielded 0.33 g (36.6%) of **1c** as a first fraction and 5 mg (0.5%) of **6c**, mp 258–262°, as a second fraction. Continued elution with ethyl acetate gave 0.61 g of a yellow oil, which was crystallized from ether to yield 0.15 g (15.1%) of **8**, mp 194–198°.

When the reaction was carried out by treating a solution of 0.50 g of **9** in 30 ml of tetrahydrofuran with a stream of ammonia and then refluxing the reaction mixture, 0.48 g (96%) of starting material was recovered unchanged.

Chromic Acid Oxidation of 8 to 6c. To a stirred solution of 0.30 g of **8** in 3.5 ml of acetic acid was added a solution of 0.43 g of chromic anhydride in 0.35 ml of water, and the mixture was stirred at room temperature for 3.5 hr. The reaction mixture was then diluted with ice water. The resulting precipitate was collected by filtration, washed with water, and dried to give 0.28 g (94.0%) of **6c**, mp 265–269°.

***N*-(2-Benzoyl-4-nitrophenyl)-*N*-methyloxamide (7c).** To a stirred suspension of 10.0 g of indole-2-carboxamide **10**[9] in 68 ml of acetic acid was added a solution of 10.2 g of chromic anhydride in 10 ml of water below 20°. After stirring at room temperature for 1.5 hr, the mixture was diluted with 500 ml of water and filtered. The solid so obtained was washed with water and dissolved in methylene chloride. The solution was washed with water, dried, and evaporated. The residue was crystallized from methylene chloride and ether to give 6.44 g of **7c**, mp 152–157°. Concentration of the filtrate and crystallization from ether gave an additional 0.23 g of product for a combined yield of 6.67 g (60.2%). After recrystallization from ethanol, yellow needles were obtained: mp 156–158°; ir 3430, 3345, 3190, 3052, 1720, 1702, 1670, 1652 cm^{-1} (shoulder); mass spectrum *m/e* 327 (M^+), 283 (M − $CONH_2$).

Anal. Calcd for $C_{16}H_{13}N_3O_5$: C, 58.71; H, 4.00; N, 12.84. Found: C, 58.65; H, 3.96; N, 12.81.

Reaction of 7a with Sodium Hypobromite. A. In Water (Run 1). Bromine (1.0 g, 12.5 mmol) was added dropwise to a solution of 1.2 g (30 mmol) of sodium hydroxide in 10 ml of water cooled to 0°. To the clear yellow solution was added immediately 0.50 g (1.6 mmol) of **7a**. The mixture was stirred at room temperature for 1 hr and at 60° for 1.3 hr. After cooling, the precipitate was collected by filtration, washed with water, and dried to give 0.23 g of crude **6a**, mp 205–213°. Recrystallization from isopropyl alcohol afforded 165 mg (38.6%) of pure **6a**, mp 223.5–224.5°.

B. In Water–Tetrahydrofuran (Run 2). Bromine (1.92 g, 24 mmol) was added dropwise to a cooled solution of 2.4 g (60 mmol)

of sodium hydroxide in 20 ml of water. To the hypobromite solution was added immediately a cold solution of 1.0 g (3.2 mmol) of **7a** in 20 ml of tetrahydrofuran, and the mixture was stirred at −5 to −3° for 2 hr. The insoluble material was filtered and washed with water to give 0.23 g of **6a**, mp 222.5–224°. The filtrates were separated and the aqueous layer was washed with ether. The combined organic layers were dried and evaporated. Trituration of the residue with ether gave an additional 0.40 g of **6a**, mp 220–224°, for a combined yield of 0.63 g (73.7%).

Similar procedures were used for the preparation of **6b** and **6c** (runs 5 and 6). Compound **7f** was unreactive to the reagent even under reflux, as indicated by thin layer chromatography (run 8).

In another experiment (run 3) 5 ml of 1.8 *N* sodium hypochlorite solution[1] was used in rearrangement of 0.50 g of **7a** in 8 ml of tetrahydrofuran. A similar work-up as above gave 0.15 g (35.1%) of crude **6a**. The results are summarized in Table II.

C. In Methanol (Run 4). Compound **7a** (1.0 g, 3.2 mmol) was added to a solution of 0.23 g (10 mmol) of sodium in 20 ml of methanol cooled to −7. To the solution was added 0.8 g (10 mmol) of bromine. The mixture was stirred at room temperature for 1 hr and then heated under reflux for 2 hr. The solid that separated on cooling was collected by filtration to yield 0.45 g of **6a**, mp 221.5–222.5°. The filtrates were concentrated to about one-third volume and diluted with water. Filtration of the resulting precipitate and washing with ether afforded an additional 0.12 g of **6a**, mp 219–222°, for a combined yield of 0.57 g (66.7%).

Compound **6c**, prepared from similar rearrangement of **7c**, was recrystallized from tetrahydrofuran to give a 49.7% yield of pure product, mp 267–267.5° (run 7).

Compound **6f**[16] was obtained in 6.8% yield by first treating 1.0 g of **7f** and 0.3 g of sodium in 20 ml of methanol with 0.8 g of bromine at −8° for 30 min and at room temperature for 1 hr, and then refluxing the mixture for 2 hr. The insoluble material was removed by filtration, and the filtrate was concentrated to about one-third of the original volume and diluted with water. The red oil that separated, on standing, gradually crystallized. The yellow crystals were collected by filtration, heated in refluxing toluene, cooled, and filtered to yield 55 mg of product, mp >300° (run 9).

Cyclization of Methyl 4-(4-Chloro-2-benzoylphenyl)-4-methylallophanate (11a) to 6a. A solution of 100 mg of crude **11a**[1] in 2 ml of methanol was refluxed for 2 hr, during which time no reaction occurred as indicated by thin layer chromatography. To the solution was added a small piece of sodium, and refluxing was continued for 30 min. After cooling, the precipitate was collected by filtration and washed with water to give 13 mg of **6a**, mp 222–224°. From the filtrates, an additional 10 mg of product was obtained for a combined yield of 23 mg (29.5%).

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Registry No.—**1c**, 51806-03-2; **1d**, 51806-04-3; **1e**, 784-38-3; **2a**, 51806-05-4; **2b**, 51806-06-5; **2c**, 51806-07-6; **2d**, 51806-08-7; **2e**, 51806-09-8; **3e**, 51806-10-1; **5a**, 51806-11-2; **6a**, 20927-53-1; **6b**, 33453-19-9; **6c**, 26953-46-8; **6d**, 49830-84-4; **6e**, 40069-75-8; **6f**, 4797-43-7; **7a**, 51806-12-3; **7b**, 51806-13-4; **7c**, 51806-14-5; **7f**, 19144-18-4; **8**, 51806-15-6; **9**, 51806-16-7; **10**, 30008-50-5; **11a**, 51806-17-8; **12e**, 51806-18-9; 2-(2-hydroxyethyl)amino-5-nitrobenzophenone, 37554-73-7; sodium azide, 12136-89-9.

References and Notes

(1) Part II: K. Ishizumi, S. Inaba, and H. Yamamoto, *J. Org. Chem.*, **39**, 2581 (1974).
(2) (a) P. A. S. Smith, *Org. React.*, **3**, 337 (1946); (b) E. S. Wallis and J. F. Lane, *ibid.*, **3**, 267 (1946); (c) P. A. S. Smith, "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 528–568; (d) P. P. T. Sah, C.-W. Yii, H.-M. Chia, T.-L. Chen, and C. Chao, *J. Chin. Chem. Soc. (Taipei)*, **14**, 52 (1946); *Chem. Abstr.*, **43**, 7446*d* (1949).
(3) Compound **2d** yielded soluble quinazolinone **6d**, which could be isolated by extraction procedures.
(4) Commercial sodium azide was used without activation.[2a]
(5) (a) H. Ott and M. Denzer, *J. Org. Chem.*, **33**, 4263 (1968); (b) H. Yamamoto, *et al.*, *Arzneim, Forsch.*, **23**, 1266 (1973); (c) R. V. Coombs, *et al.*, *J. Med. Chem.*, **16**, 1237 (1973); (d) A. Yoshitake, Y. Makari, K. Kawahara, and M. Endo, *J. Label. Compounds*, **9**, 537 (1973).
(6) S. Inaba, M. Yamamoto, K. Ishizumi, K. Takahashi, K. Mori, and H. Yamamoto, Japanese Patent 40,067 (1972); *Chem. Abstr.*, **78**, 4278e (1973).
(7) Compound **6d** was previously prepared, accompanied by the corresponding O-alkylated product, by alkylation of 1-unsubstituted quinazolinone with chloroethyl acetate and sodium hydride: unpublishec studies of Mr. M. Yamamoto.
(8) This synthetic method was first used by Mr. M. Yamamoto in the conversion of 2′-benzoyl-4′-chloro-*N*-cyclopropylmethylformanilide to the corresponding 2-hydroxyquinazolinone.
(9) S. Inaba, K. Ishizumi, K. Mori, and H. Yamamoto, *Chem. Pharm. Bull.*, **19**, 722 (1971).
(10) When the same reaction was carried out at −5°, followed by evaporation of solvent and subsequent addition of water, a red, oily product (**4a**?) was obtained which was gradually converted to yellow, crystalline quinazolinone **6a**.
(11) (a) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962); (b) L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963).
(12) S. Inaba, K. Ishizumi, K. Mori, and H. Yamamoto, *Chem. Pharm. Bull.* **19**, 722 (1971), and preceding papers.
(13) Mr. M. Yamamoto kindly supplied us with the sample.
(14) It has been reported that oxalyl chloride reaction with N-substituted anilines gives the desired oxaniloyl chloride, whereas reaction with primary aromatic amines leads only to the formation of oxamides; see R. Stolle, *Ber.*, **46**, 3915 (1913); R. Stolle, R. Bergdoll, M. Luther, A. Auerhahw, and W. Wacker, *J. Prakt. Chem.*, **128**, 1 (1930).
(15) H. Zenno, T. Kamiya, and H. Yazawa, Japanese Patent 19,587 (1967); *Chem. Abstr.*, **69**, 188851n (1968).
(16) S. Inaba, M. Yamamoto, K. Ishizumi, K. Takahashi, K. Mori, and H. Yamamoto, German Patent 1,935,404 (1970); *Chem. Abstr.*, **72**, 90494c (1970).

Substituent Constants for the 4,6-Dimethyl-*s*-triazinyl Group from Ionization and Fluorine Nuclear Magnetic Resonance Data[1]

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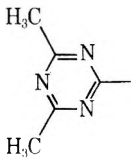
The *m*- and *p*-(4,6-dimethyl-*s*-triazin-2-yl)benzoic acids (**6a** and **6b**) have been synthesized and their pK_a's in 50% aqueous ethanol (v/v) have been determined as 5.15 and 4.94, respectively. The substituent constants calculated from the pK_a data for the 4,6-dimethyl-*s*-triazinyl substituent (**1**) are σ_m +0.25, σ_p +0.39, and σ_I +0.15. The corresponding dimethyl-*s*-triazinyl substituted fluorobenzenes (**3c** and **3d**) have also been synthesized and their ^{19}F chemical shifts have been determined relative to fluorobenzene in carbon tetrachloride, methanol, and dimethyl sulfoxide. The substituent constants for **1** based upon the chemical shifts in methanol are σ_I +0.18 and $\bar{\sigma}_R^p$ +0.19. The substituent constants are discussed.

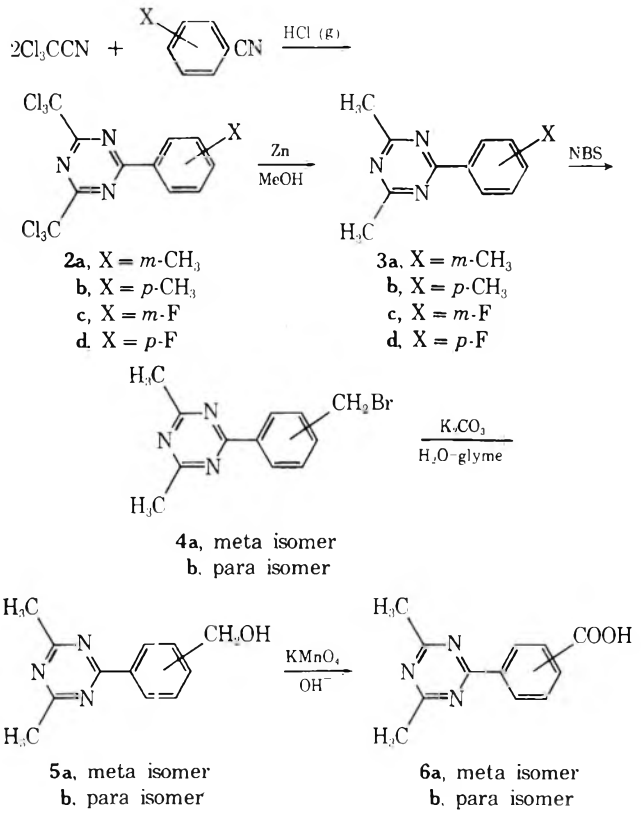
In view of the rather limited number of heterocyclic substituents for which substituent constants have been evaluated,[2] and also the potential insights which such constants might afford, the determination of the substituent constants for the 4,6-dimethyl-*s*-triazin-2-yl substituent (**1**) was undertaken. This substituent was chosen be-



1

cause of the synthetic feasibility of incorporating it into molecules from which the necessary data could be obtained and also because the substituent possesses the electronegative nitrogen atoms as well as a high resonance energy of 41.2 kcal/mol.[3] Presumably, the latter would have to be lost in part when the substituent participated in direct conjugation or through resonance with the reaction centers. With respect to desirability, the unsubstituted *s*-triazine ring or parent substituent would have been preferred over **1**, but the available evidence indicated that compounds containing the former may be more difficult to synthesize[4] and also that the unsubstituted triazinyl substituent may be more susceptible to hydrolysis[5] than **1**.[6] Consequently, substituent **1** was chosen for the studies.

Scheme I



To determine the Hammett substituent constants for **1**, the *m*- and *p*-(4,6-dimethyl-*s*-triazin-2-yl)benzoic acids (**6a** and **6b**) were synthesized according to Scheme I. Among the unsuccessful attempts to synthesize significant amounts of **6a** and **6b**, or their precursors, were the cocyclization of (1) cyanoacetophenone with trichloroacetonitrile in the presence of hydrogen chloride,[7] (2) cyanobenzoic acid with trichloroacetonitrile in the presence of hydrogen chloride,[7] (3) ethyl acetylbenzimidate with ethyl acetimidate in the presence of acetic acid,[8] and (4) cyanobenzoyl chloride with trichloroacetonitrile in the presence of aluminum chloride.[9] Selective oxidation by potassium permanganate of the benzylic methyl group of **3a,b** to yield **6a,b** did not realize success nor did the oxidation of all three methyl groups followed by decarboxylation of the carboxyl groups on the triazine ring[5] to give the parent compounds, *m*- and *p*-triazinylbenzoic acid.

Table I
pK_a's of Substituted Benzoic Acids[a]

Compd	pK_a[b]
m-Toluic acid	5.62
Benzoic acid	5.49
m-Methoxybenzoic acid	5.39
m-Bromobenzoic acid	5.00
m-Nitrobenzoic acid	4.46
6a	5.15
6b	4.94

[a] 0.05 *M* in LiCl. [b] Reference 18a.

Taft[10] has successfully separated the Hammett substituent constants for a large number of meta substituents into two parameters, one which represents the inductive or field effect, σ_I, and the other which represents a resonance effect, σ_R^m. In the case of para substituents the Hammett substituent constant is separated into the inductive parameter and a resonance parameter, σ_R^p, or an effective resonance parameter, σ_R. The latter includes both the resonance polar effect[10b] as well as the direct conjugative or through resonance effect between the substituent and the reaction center.

Another and independent approach to the determination of the inductive effect, σ_I, has also been developed by Gutowsky[11] and Taft[12] through the utilization of the chemical shifts of the ^{19}F nmr signals of substituted fluorobenzenes relative to the unsubstituted fluorobenzene. In the case of meta-substituted fluorobenzenes, the resonance parameter, σ_R^m, apparently makes no significant contribution to the ^{19}F chemical shift, as evidenced by the wide applicability of eq 1 in a given solvent.[13] For

$$\int_H^{m\text{-X}} = -7.10\sigma_I + 0.60 \qquad (1)$$

many para substituents which are electron donating *via* a resonance effect (−R), the ^{19}F chemical shift relative to fluorobenzene was found to correlate well with the inductive parameter and a resonance parameter, σ_R^0, as expressed by the equation[14]

$$\int_H^{p\text{-X}} = -29.5\sigma_R^0 + \int_H^{m\text{-X}} =$$

$$-29.5\sigma_R^0 - 7.10\sigma_I + 0.60 \qquad (2)$$

where σ_R^0 represents a resonance contribution which is free of any direct conjugative or through resonance.[15] However, for para substituents having an electron-withdrawing effect (+R) where through resonance is possible, linearity with respect to a resonance parameter is not realized. However, assuming identical inductive effects within the meta and para isomers,[16] an effective resonance parameter may be solved for from eq 2 by replacing σ_R^0 by $\bar{\sigma}_R$ to give eq 3.[14]

$$\bar{\sigma}_R^p = -0.0339\left(\int_H^{p\text{-X}} - \int_H^{m\text{-X}}\right) \qquad (3)$$

Results and Discussion

The procedure used for the determination of the Hammett σ values for the *m*- and *p*-4,6-dimethyl-s-triazin-2-yl (**1**) substituent was that recommended by Taft.[17] The pK_a's for the acids listed in Table I were determined in 50% (v/v) ethanol–water having a constant ionic strength

of 0.05 *M*.[18] A Hammett plot of the log K_a's of the five reference acids against the recommended corresponding σ values[17] gave, by the method of least squares, a ρ value of +1.47 (reported value 1.464[18a]) and a log K_0 of −5.52.[19] The σ values for the known substituents obtained from the calculated values of ρ and log K_0 did not differ from the recommended σ values by more than ±0.03 and gave a standard deviation of ±0.02. These values fall well within the limits established by Taft of ±0.07 and ±0.03, respectively.[17] Using the experimental values of log K_a obtained for **6a** and **6b**, the Hammett σ values for *m*-**1** and *p*-**1** are calculated as +0.25 and +0.39, respectively. These σ values may then be further separated into the inductive parameter and a resonance parameter.[10,16,20] This separation is achieved by assuming (1) that the inductive effect and field effect of the substituent are identical for the meta and para isomers,[16a] (2) that within a given reaction series the resonance effect of the substituent in the meta position is a constant proportion (α) of its resonance effect in the para position,[16a,17] and (3) that $\rho_I = \rho^m$.[17] These assumptions enable the inductive parameter, σ_I, to be solved for by eq 4.[17] Taft and Lewis have determined the

$$\sigma_I = \left(\frac{1}{\rho(1 - \alpha)}\right)(\log K^m/K_0 - \alpha \log K^p/K_0) \quad (4)$$

value of α for the ionization of benzoic acids in 50% aqueous ethanol at 25° as 0.42.[17] Based upon this value of α, the calculated values for the inductive parameter and the resonance parameter for the substituent **1** are given in Table II.

Table II
σ Values for 1 from Ionization Data

σ_I	+0.15
σ_R^p	+0.24

In an attempt to confirm the above value for the inductive parameter, σ_I, for **1** by another independent method, the ^{19}F chemical shifts of fluorobenzene, **3c**, and **3d** were measured relative to external *p*-difluorobenzene (20% solution in CCl_4),[13] and then the chemical shifts of **3c** and **3d** were calculated relative to fluorobenzene. The use of *p*-difluorobenzene, rather than fluorobenzene, as an experimental reference was necessitated because the signal from the meta isomer, **3c**, was close to or superimposed upon that of fluorobenzene. The chemical shifts were measured in carbon tetrachloride, methanol, and dimethyl sulfoxide, and are given in Table III together with the values for σ_I calculated with eq 1, and $\bar{\sigma}_R^p$ calculated with eq 3. The use of the dual substituent parameter (DSP) equation[21] instead of eq 3 for carbon tetrachloride and dimethyl sulfoxide gave somewhat lower values for $\bar{\sigma}_R^p$, namely, 0.15 and 0.13, respectively. As indicated in Table III, and in accord with Taft's findings in aprotic solvents,[21] the σ_I values are larger in the more polar solvents, but the $\bar{\sigma}_R^p$ values remain essentially unchanged. The σ_I value in methanol (0.18) agrees quite well with the value obtained from the pK_a data in 50% aqueous ethanol (0.15). Likewise, the $\bar{\sigma}_R^p$ values calculated from the ^{19}F chemical shift data (0.18–0.19) agree within acceptable limits[17] with that obtained from the pK_a data (0.24). It might have been anticipated that the $\bar{\sigma}_R^p$ value from the chemical shift data would be larger than that from the pK_a data in view of the possibility that, for an electron-withdrawing group, such as **1**, direct conjugation or through resonance might be realized more fully in the *p*-triazinylfluorobenzene, **3d**, than between the ground states of the corresponding para-substituted benzoic acid, **6b**, and its anion in comparably polar solvents. Indeed, a comparison of the values for $\bar{\sigma}_R^p$ from ^{19}F chemical shift data and pK_a data for six other +R substituents[13,14,19b] does show that the values for $\bar{\sigma}_R^p$ from the chemical shift data do in general exceed or equal those from the pK_a data (+0.12 to −0.03; average +0.03). However, the enhancements are small, and rightly so, in view of the relatively small difference of −0.13 between σ^+ and σ (Hammett) for fluorine. Infrared intensities of para-substituted fluorobenzenes also support the existence of direct conjugation between fluorine and strong electron-withdrawing substituents, but the resulting increase in the σ value is estimated as only 0.03 unit.[22] Thus, the above values for $\bar{\sigma}_R^p$ for **1** from the ^{19}F chemical shift data might be adjusted downward to 0.15–0.16. It would seem somewhat untenable to postulate that the σ_R^p value for **1** from the pK_a data is abnormally high relative to that from the ^{19}F chemical shift data because of the existence of the conjugate acid of **6b**, namely **7**. Two factors would speak against any significant amount of **7**. First, the basicity of the triazine ring is low, approximately of the order

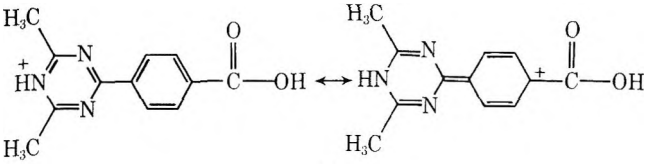


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Table III
^{19}F Chemical Shifts and Calculated Substituent Constants

Solvent	$-\int_{p\text{-F}}^{H^a}$	$-\int_{p\text{-F}}^{m\text{-}1^a}$	$-\int_{p\text{-F}}^{p\text{-}1^a}$	$-\int_{H}^{m\text{-}1^b}$	$-\int_{H}^{p\text{-}1^b}$	σ_I	$\bar{\sigma}_R^p$
CCl_4	7.11	7.10	12.34	−0.01	5.23	0.08	0.18
CH_3OH	3.39	4.07	9.69	0.68	6.30	0.18	0.19
DMSO	6.08	6.63	11.78	0.55	5.70	0.16	0.18

[a] Approximately 3–5% solution (wt/vol) of unsubstituted or substituted fluorobenzene relative to external *p*-difluorobenzene (20%, CCl_4). Negative sign indicates downfield shift. Values not corrected for bulk susceptibility. [b] $\int_{p\text{-F}}^{-x} - \int_{p\text{-F}}^{H}$.

Table IV
Comparison of Substituent Constants for +R Substituents

Substituent	σ_p^a	σ_I^b	σ_R^p
p-NO_2	+0.78	+0.64	+0.14
p-SO_2CH_3	+0.72	+0.55	+0.17
p-CN	+0.66	+0.56	+0.10
p-CF_3	+0.54	+0.41	+0.13
p-CH_3CO	+0.50	+0.28	+0.22
p-CO_2Et	+0.45	+0.31	+0.14
p-**1**	+0.39	+0.15	+0.24

[a] Reference 19b. [b] From reactivities, ref 13.

10^{-11},[23] and second, if **7** were to exist in any significant amount, a much larger σ_I would be anticipated. Thus, the value of 0.24 for σ_R^p from the pK_a data for the substituent **1** is probably the more reliable value, although an average value of 0.20 might be appropriate.

It is worth noting that a comparison of the substituent constants for **1** with those of other +R groups as illustrated in Table IV shows **1** to have the lowest σ_I value, but the largest σ_R^p value.

Experimental Section

Instrumentation. All melting points are corrected and were taken in a stirred silicone oil bath using calibrated Anchuetz thermometers with the sample in an open capillary tube unless noted otherwise. All ir spectra were obtained on a Beckman IR-8 infrared spectrophotometer. All proton nmr spectra were obtained on a Hitachi Perkin-Elmer R-20 spectrometer. The ^{19}F nmr spectra were also taken on a Hitachi Perkin-Elmer R-20 spectrometer having an internal lock-on and equipped with a ^{19}F RF unit, Model R-203F operating at 56.456 MHz. The chemical shifts were counted with a Takeda Riken frequency counter, Model TR-3824X. The ^{19}F spectra were run at 34° with an external reference of *p*-difluorobenzene [20% (v/v) in CCl_4]. The solutions of the fluorine compounds in carbon tetrachloride were approximately 5% (wt/vol), whereas those in methanol and dimethyl sulfoxide were approximately 3%.[21] The spectra for the 4,6-dimethyl-2-(*m*-fluorophenyl)-s-triazine (**3c**) and fluorobenzene were recorded with a sweep width of 10 ppm and a sweep time of 500 sec in all solvents. The spectra for the 4,6-dimethyl-2-(*p*-fluorophenyl)-*s*-triazine (**3d**) were recorded with a sweep width of 10 ppm in methanol and 20 ppm in carbon tetrachloride and dimethyl sulfoxide, and a sweep time of 500 sec. Each spectrum was swept three times in each direction, and the chemical shifts were recorded from the centers of the signals with a precision of ±2 Hz (±0.035 ppm).

pK_a determinations were obtained at 25 ± 0.2° by potentiometric titrations using an IL Deltamatic Model 245 pH meter and an IL 14063 combination pH electrode system. The electrode system was balanced at its isoelectric point with a 6.86 ± 0.01 buffer, and then the pH slope control was adjusted with a 4.01 ± 0.01 buffer.

Solution Preparations. The sodium hydroxide solution was prepared by diluting Hellige concentrate with freshly boiled water and then storing under nitrogen.

The aqueous 1 *M* lithium chloride solution was prepared by quickly weighing the AR grade lithium chloride (vacuum dried several weeks) and dissolving it in freshly boiled water in a volumetric flask. This solution contained no detectable hydroxide as determined by a blank titration. The 0.1 *M* solutions were obtained by dilution of the 1.0 *M* solution with freshly boiled water.

The ethanolic lithium chloride solution was prepared in a manner similar to the preparation of aqueous solution.

The reference benzoic acids were obtained commercially and were recrystallized at least twice to obtain compounds whose melting points were within 2° of literature values.

pK_a Determination.[18] Approximately 0.25 mmol of the substituted benzoic acid was dissolved in 50 ml of distilled, carbonate-free, absolute ethanol. To this solution was added 50 ml of carbonate-free 0.1 *M* aqueous lithium chloride and the resulting solution was titrated under nitrogen, with stirring at 25 ± 0.2°, with equal volumes of 0.02 *N* carbonate-free sodium hydroxide and carbonate-free 0.08 *M* ethanolic lithium chloride. The pK_a of the acid was determined from the pH of the solution at the half-neutralization point. The neutralization point or end point was determined to be the point where the ΔpH was the greatest for the addition of a 0.1-ml aliquot of base.

4,6-Bis(trichloromethyl)-2-(*p*-tolyl)-*s*-triazine (2b). *p*-Tolunitrile (56.3 g, 0.48 mol) and trichloroacetonitrile (138.4 g, 0.96 mol) were combined in a cylindrical reaction flask, and dry hydrogen chloride was bubbled through the mixture *via* a sintered glass bubbler for 7 hr (25°) after which the contents were permitted to stand for 5 days (25°). The resulting solid was removed with difficulty, dissolved in ether, and washed with 2% sodium hydroxide and then with water to pH 6. The ether was dried ($MgSO_4$) and evaporated to yield yellow crystals which were recrystallized from absolute ethanol to yield 101 g (52%) of white crystals: mp 123.7–124.4°; ir (Nujol) 1550 cm^{-1} (triazine).

Anal. Calcd for $C_{12}H_7N_3Cl_6$: C, 35.48; H, 1.74; N, 10.34; Cl, 52.44. Found: C, 35.72; H, 1.70; N, 10.37; Cl, 52.73.

4,6-Dimethyl-2-(*p*-tolyl)-*s*-triazine (3b). To a stirred solution of **2b** (60 g, 0.15 mol) in 2.1 l. of methanol was added approximately 0.5 g of cupric acetate followed by the slow addition of 10 mesh zinc (300 g, 4.6 g-atoms, activated with dilute nitric acid) over a period of 30 min. The stirred solution was refluxed from the beginning of the addition of the zinc, and the color of the solution changed from green to dark gray during the addition and remained dark gray during the course of the reaction. The mixture was stirred and refluxed for 6 days, after which the reaction mixture was cooled and decanted into 2.5 l. of ice water to give a gray precipitate. The mixture was acidified to Congo Red with dilute nitric acid and the precipitate was filtered. The filtrate was extracted with ether and the latter was used to dissolve the precipitate. The ether solution was washed with 5% sodium carbonate and with water to neutrality, dried ($MgSO_4$), and evaporated to yield 21 g (74%) of a yellow-brown solid. This solid was recrystallized from absolute ethanol to yield white crystals: mp 78.5–79.5°; ir (Nujol) 1530 cm^{-1} (triazine); nmr (CCl_4) τ 1.68 (d, 2 H, aromatic H ortho to triazine), 2.85 (d, 2 H, aromatic H meta to triazine), 7.42 (s, 6 H, $-CH_3$ on triazine), and 7.61 (s, 3 H, benzylic $-CH_3$).

Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.34; H, 6.58; N, 21.08. Found: C, 72.40; H, 6.59; N, 20.90.

4,6-Dimethyl-2-(4-bromomethylphenyl)-*s*-triazine (4b). To a stirred solution of **3b** (13.8 g, 0.069 mol) in 75 ml of carbon tetrachloride was added slowly (1 hr) a pulverized mixture of *N*-bromosuccinimide (15.2 g, 0.085 mol) and benzoyl peroxide (2.6 g, 0.011 mol). The solution was refluxed for 5 hr, after which time all the solid was floating. The hot solution was filtered, the solid was discarded, and the filtrate was cooled and filtered again to yield a yellow solid. Second and third crops were also obtained from the filtrate by the same method. The combined crops were triturated with hot water to dissolve any succinimide and filtered to yield 10.6 g (55%) of light colored crystals. A portion of this solid was recrystallized from carbon tetrachloride and sublimed to yield a white powder: mp 145.0–146.0°; ir (CH_2Cl_2) 1530 cm^{-1} (triazine); nmr (CCl_4) τ 1.60 (d, 2 H, aromatic H ortho to triazine), 2.62 (d, 2 H, aromatic H meta to triazine), 5.56 (s, 2 H, benzylic $-CH_2-$), and 7.41 (s, 6 H, $-CH_3$ on triazine).

Anal. Calcd for $C_{12}H_{12}N_3Br$: C, 51.82; H, 4.35; N, 15.10; Br, 28.73. Found: C, 52.13; H, 4.62; N, 14.97; Br, 28.75.

***p*-(4,6-Dimethyl-*s*-triazin-2-yl)benzyl Alcohol (5b).** To a stirred solution of **4b** (10.1 g, 0.036 mol) in 235 ml of glyme was added 235 ml of 5% aqueous potassium carbonate. The resulting cloudy solution was refluxed for 3 hr (the solution was clear after 0.5 hr), after which time the glyme was distilled. The brown oil which had separated from solution was physically removed and discarded. The remaining solution was cooled (0°) overnight to yield 4.88 g (63%) of yellow crystals. The yellow crystals were recrystallized from benzene and then sublimed to yield 2.34 g of white powder: mp 152.5–153.3°; ir (Nujol) 3230 (OH), 1520 (triazine), and 1065 cm^{-1} (CO); nmr ($CDCl_3$) τ 1.63 (d, 2 H, aromatic H ortho to triazine), 2.64 (d, 2 H, aromatic H meta to triazine), 5.32 (s, 2 H, benzylic $-CH_2-$), 6.88 (s, 1 H, alcoholic H), and 7.36 (s, 6 H, $-CH_3$ on triazine); nmr after shaking with D_2O, τ 5.32 (s, sharper) and 6.88 (negligible).

Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 67.14; H, 6.73; N, 19.23.

***p*-(4,6-Dimethyl-*s*-triazin-2-yl)benzoic Acid (6b).** To a stirred solution (0°) of potassium permanganate (2.25 g, 0.014 mol, in 225 ml of freshly boiled water) was added slowly **5b** (2.02 g, 0.0093 mol), followed by 11.2 ml of 5% sodium hydroxide. The solution was stirred at 0° for 3 hr, after which time the solution was filtered and acidified to Congo Red with 6 *N* nitric acid. The resulting precipitate was filtered to yield a white solid which was recrystallized from diethylene glycol and then sublimed to yield 0.75 g (35%) of a white powder: mp 297.2–299.3° (sealed capillary); ir (Nujol) 1700 (C=O), 1525 (triazine), and 1240 cm^{-1} (CO); nmr (DMSO-d_6) τ 0.69 (s, broad, 1 H, carboxyl H), 1.48 (d, 2 H, aromatic H ortho to triazine), 1.90 (d, 2 H, aromatic H meta to triazine), and 7.39 (s, 6 H, $-CH_3$ on triazine).

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.32. Found: C, 62.88; H, 4.88; N, 17.92.

4,6-Bis(trichloromethyl)-2-(*m*-tolyl)-*s*-triazine (2a). *m*-Tolunitrile (44.0 g, 0.38 mol) and trichloroacetonitrile (106.0 g, 0.74 mol) were combined in a cylindrical reaction flask and dry hydrogen chloride was bubbled through the mixture *via* a sintered bubbler for 5 hr (25°), after which the contents were permitted to stand for 7 days (25°) with no apparent results. Dry hydrogen chloride was again bubbled through the solution for 5 hr (25°) and for 0.5 hr (40°) after which the contents were cooled (0°) for 9 days. The unreacted liquid nitriles were decanted from the result-

ing solid product and the latter was dissolved in ether and washed with 5% sodium hydroxide and with water to pH 6. The ether was dried ($MgSO_4$) and evaporated to yield a whitish solid which was recrystallized from absolute ethanol to yield 41.6 g (28%). Additional dry hydrogen chloride (10 hr, 25°) was added to the decanted nitriles and the resulting solution was permitted to stand for 24 hr (0°). The resulting solid was treated as above to yield 35.7 g (24%): mp 87.4–88.6°; ir (Nujol) 1550 cm^{-1} (triazine); nmr (CCl_4) τ 1.62 (m, 2 H, aromatic H ortho to triazine), 2.64 (m, 2 H, aromatic H meta to triazine), and 7.50 (s, 3 H, benzylic $-CH_3$).

Anal. Calcd for $C_{12}H_7N_3Cl_6$: C, 35.48; H, 1.74; N, 10.34; Cl, 52.44. Found C, 35.75; H, 1.81; N, 10.28; Cl, 52.06.

4,6-Dimethyl-2-(*m*-tolyl)-*s*-triazine (3a). Compound **3a** was prepared in 86% yield from **2a** by the same method as described above for the preparation of **3b**. A portion of the product was recrystallized from absolute ethanol and sublimed to yield a white powder: mp 76.0–77.2°; ir (Nujol) 1528 cm^{-1} (triazine); nmr (CCl_4) τ 1.78 (s, 2 H, aromatic H ortho to triazine), 2.80 (d, 2 H, aromatic H meta to triazine), 7.43 (s, 6 H, $-CH_3$ on triazine), and 7.60 (s, 3 H, benzylic $-CH_3$).

Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.34; H, 6.58; N, 21.08. Found: C, 72.24; H, 6.41; N, 21.01.

4,6-Dimethyl-2-(3-bromomethylphenyl)-*s*-triazine (4a). Compound **4a** was prepared in 56% yield from **3a** by the same method described above for the preparation of **4b**. A portion of the product was recrystallized from 95% ethanol and sublimed to yield a white powder: mp 76.7–78.0°; ir (CH_2Cl_2) 1525 cm^{-1} (triazine); nmr (CCl_4) τ 1.48 (m, 2 H, aromatic H ortho to triazine), 2.48 (m, 2 H, aromatic H meta to triazine), 5.47 (s, 2 H, benzylic $-CH_2-$), and 7.36 (s, 6 H, $-CH_3$ on triazine).

Anal. Calcd for $C_{12}H_{12}N_3Br$: C, 51.82; H, 4.35; N, 15.10; Br, 28.73. Found: C, 51.68; H, 4.73; N, 15.01; Br, 28.67.

***m*-(4,6-Dimethyl-*s*-triazin-2-yl)benzyl Alcohol (5a).** Compound **5a** was prepared in 35% yield from **4a** by the same method described above for the preparation of **5b**. A portion of the light yellow product was recrystallized from benzene and sublimed to yield a white powder: mp 100.0–100.7°; ir (CH_2Cl_2) 3450 (OH), 1538 (triazine), and 1062 cm^{-1} (CO); nmr ($CDCl_3$) τ 1.55 (m, 2 H, aromatic H ortho to triazine), 2.48 (m, 2 H, aromatic H meta to triazine), 5.24 (s, 2 H, benzylic $-CH_2-$), 6.50 (s, 1 H, alcoholic H), and 7.36 (s, 6 H, $-CH_3$ on triazine).

Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.89; H, 5.90; N, 19.10.

***m*-(4,6-Dimethyl-*s*-trianzin-2-yl)benzoic Acid (6a).** Compound **6a** was prepared in 73% yield from **5a** by the same method described above for the preparation of **6b**. The off-white product was recrystallized from diethylene glycol and sublimed to a white powder: mp 263.8–264.9° (with darkening); ir (Nujol) 2200–3500 (broad, OH), 1523 (triazine), 1695 (C=O), and 1240 cm^{-1} (CO); nmr (DMSO-d_6) τ 0.92–2.40 (m, 4 H, aromatic H), 4.0 (s, 1 H, very broad, carboxyl H), and 7.32 (s, 6 H, $-CH_3$ on triazine).

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.32. Found: C, 63.11; H, 4.93; N, 17.96.

4,6-Bis(trichloromethyl)-2-(*p*-fluorophenyl)-*s*-triazine (2d). *p*-Fluorobenzonitrile (9.6 g, 0.079 mol) and trichloroacetonitrile (22.9 g, 0.16 mol) were combined in a cylindrical reaction flask and dry hydrogen chloride was added *via* a sintered glass bubbler for 5 hr (25°) per day for 4 consecutive days, after which the reaction was permitted to stand for 2 days at 25° and 8 days at 0° to yield a solid which was filtered, dissolved in ether, and washed with 5% sodium hydroxide and with water to pH 6. The ether was dried ($MgSO_4$) and evaporated to yield 5.84 g (18%) of a white solid. A portion of this solid was recrystallized from absolute ethanol and sublimed to yield a white powder: mp 129.0–130.6°; ir (Nujol) 1548 cm^{-1} (triazine).

Anal. Calcd for $C_{11}H_4N_3Cl_6F$: C, 32.24; H, 0.98; N, 10.25; Cl, 51.90. Found: C, 32.46; H, 1.11; N, 10.22; Cl, 52.34.

4,6-Dimethyl-2-(*p*-fluorophenyl)-*s*-triazine (3d). Compound **3d** was prepared from **2d** by the same method described above for the preparation of **3b**. The yellow-brown product was thrice sublimed to give 123 mg (4.7%) of a white powder: mp 98.4–100.2°; ir (CH_2Cl_2) 1530 cm^{-1} (triazine); nmr (CCl_4) τ 1.40 (m, 2 H, aromatic H ortho to triazine), 2.83 (m, 2 H, aromatic H meta to triazine), and 7.39 (s, 6 H, $-CH_3$ on triazine).

Anal. Calcd for $C_{11}H_{10}N_3F$: C, 65.01; H, 4.97; N, 20.67. Found: C, 65.57; H, 5.14; N, 20.60.

4,6-Bis(trichloromethyl)-2-(*m*-fluorophenyl)-*s*-triazine (2c). *m*-Fluorobenzonitrile (10.0 g, 0.083 mol) and trichloroacetonitrile (23.9 g, 0.17 mol) were combined in a cylindrical reaction flask and dry hydrogen chloride was added *via* a sintered glass bubbler for 10 hr (25°) per day for 5 consecutive days with no visible results. A portion (1.7 g) of the reaction mixture was then chromatographed on silica gel to yield 430 mg of product which was recrystallized from absolute ethanol and sublimed to yield a white powder: mp 75.1–76.2°; ir (CH_2Cl_2) 1550 cm^{-1} (triazine).

Anal. Calcd for $C_{11}H_4N_3Cl_6F$: C, 32.24; H, 0.98; N, 10.25; Cl, 51.90. Found: C, 32.30; H, 1.05; N, 10.53; Cl, 51.62.

4,6-Dimethyl-2-(*m*-fluorophenyl)-*s*-triazine (3c). Compound **3c** was prepared from crude **2c** by the same method described above for the preparation of **3b**. The off-white solid was recrystallized from absolute ethanol and sublimed to yield 250 mg of a white powder: mp 120.5–121.3°; ir (CH_2Cl_2) 1538 cm^{-1} (triazine); nmr ($CDCl_3$) τ 1.75 (m, 2 H, aromatic H ortho to triazine), 2.65 (m, 2 H, aromatic H meta to triazine), and 7.35 (s, 6 H, $-CH_3$ on triazine).

Anal. Calcd for $C_{11}H_{10}N_3F$: C, 65.01; H, 4.97; N, 20.67. Found: C, 65.57; H, 5.04; N, 20.71.

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Registry No.—**2a**, 51751-20-3; **2b**, 3584-22-3; **2c**, 51751-21-4; **2d**, 51751-22-5; **3a**, 51751-23-6; **3b**, 50996-05-9; **3c**, 51751-24-7; **3d**, 51751-25-8; **4a**, 51751-26-9; **4b**, 51751-27-0; **5a**, 51751-28-1; **5b**, 51751-29-2; **6a**, 51751-30-5; **6b**, 51751-31-6; *p*-tolunitrile, 104-85-8; trichloroacetonitrile, 545-06-2; *m*-tolunitrile, 620-22-4; *p*-fluorobenzonitrile, 1194-02-1; *m*-fluorobenzonitrile, 403-54-3.

References and Notes

(1) Taken in part from the M.S. Thesis of B. W., California State University, Northridge, 1973.
(2) H. H. Jaffe and H. L. Jones, *Advan. Heterocycl. Chem.*, **3**, 220 (1964).
(3) E. M. Smolin and L. Rapoport, "s-Triazines and Derivatives," Interscience, New York, N. Y., 1959, p 7.
(4) F. C. Schaefer and G. A. Peters, *J. Amer. Chem. Soc.*, **81**, 1470 (1959).
(5) C. Grundmann, H. Ulrich, and A. Kreutzberger, *Ber.*, **86**, 181 (1953).
(6) C. Grundmann and G. Weisse, *Ber.*, **84**, 684 (1951).
(7) C. Grundmann, G. Weisse, and S. Seide, *Justus Liebigs Ann. Chem.*, **577**, 77 (1952).
(8) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2778 (1961).
(9) A. H. Cook and D. G. Jones, *J. Chem. Soc.*, 278 (1941).
(10) (a) R. W. Taft, Jr., and I. C. Lewis, *J. Amer. Chem. Soc.*, **80**, 2436 (1958); (b) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.
(11) H. S. Gutowsky, D. W. McCall, B. R. McGarvey, and L. H. Meyer, *J. Amer. Chem. Soc.*, **74**, 4809 (1952).
(12) R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **79**, 1045 (1957).
(13) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Amer. Chem. Soc.*, **85**, 709 (1963).
(14) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, G. T. Davis, *J. Amer. Chem. Soc.*, **85**, 3146 (1963).
(15) R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, and R. E. Glick, *J. Amer. Chem. Soc.*, **81**, 5352 (1959).
(16) (a) J. D. Roberts and W. T. Moreland, Jr., *J. Amer. Chem. Soc.*, **75**, 2167 (1953); (b) R. W. Taft and I. C. Lewis, *Tetrahedron*, **5**, 210 (1959).
(17) R. W. Taft, Jr., and I. C. Lewis, *J. Amer. Chem. Soc.*, **81**, 5343 (1959).
(18) (a) J. D. Roberts, E. A. McElhill, and R. Armstrong, *J. Amer. Chem. Soc.*, **71**, 2923 (1949); (b) L. A. Wooten and L. P. Hammett, *ibid.*, **57**, 2289 (1935); (c) E. Berliner and E. A. Blommers, *ibid.*, **73**, 2479 (1951).
(19) (a) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953); (b) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
(20) J. L. Roberts and H. H. Jaffe, *J. Amer. Chem. Soc.*, **81**, 1635 (1959).
(21) R. T. C. Brownlee, S. K. Dayal, J. L. Lyle, and R. W. Taft, *J. Amer. Chem. Soc.*, **94**, 7208 (1972).
(22) P. J. Q. English, A. R. Katritzky, T. T. Tidwell, and R. D. Topsom, *J. Amer. Chem. Soc.*, **90**, 1767 (1968).
(23) The conjugate acid of 3,5,6-trimethyl-as-triazine has a K_a of 1.4×10^{-3}: D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965, p 233.

The "Anomalous" Steric Course of Ring Opening Reactions of Indene Oxide. A Reexamination

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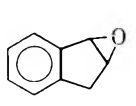
A reexamination of several reports on the apparently anomalous behavior of indene oxide in ring opening reactions has revealed some experimental deficiencies and dubious interpretations and shown that this epoxide behaves in the normal way expected for an aryloxirane, giving both cis and trans adduct in ratios which are dependent on the reagent and the solvent.

Back in 1928 Böeseken[1] reported on a rather awkward dependence of the steric course of the hydrolysis of indene oxide (1) on such factors as reaction time and temperature, type and concentration of the acid catalyst, etc. Some much more recent reports[2,3] confirmed several anomalies and implied that ring opening reactions of 1 may deviate considerably from the normal and by now thoroughly investigated behavior of aryl-substituted epoxides. A recent paper by Gagis, Fusco, and Benedict,[3] stating that 1 reacts with benzoic acid in chloroform to give exclusively anti opening products, induced us to reexamine this reaction, because of our long-standing interest in the reactions of aryloxiranes and because the authors took issue with some of the conclusions reached by our group in one of our early papers on this topic,[4] which were repeatedly confirmed by several later papers[5,6] that apparently escaped their attention; they conclude their paper by stating that on the basis of the exclusive formation of trans adducts in the ring opening of indene oxide in aprotic nonacidic solvents "the reaction mechanism is of an SN2 order, which is considered the normal course for ring openings of epoxides," a statement that may be true for purely aliphatic epoxides, but certainly not for aryloxiranes.[6]

The reaction of 1 with benzoic acid in chloroform was carried out as much as possible according to the described method (the amount of benzoic acid was not indicated in the experimental part of the paper). The crude reaction product was reduced with $LiAlH_4$, basic hydrolysis being avoided in order to prevent any change in configuration through displacement of the benzoyloxy group, or hydrolysis of any epoxide which could still be present. Glpc analysis showed that both the trans and cis diols 2 and 3 were present, in a ratio of 64:36. We think that in the previous work[3] the formation of 3 was overlooked because glpc was apparently not used, and the absence of 3 was deduced from the exclusive isolation of 2, but in an overall yield of only about 66%.



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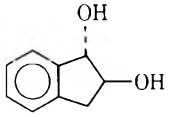

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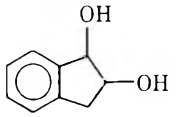


3

We also investigated the reaction of 1 with trichloroacetic acid in several different solvents, since this acid usually gives higher amounts of cis adducts with aryloxiranes than weaker acids.[5a,7] The data in Table I show that the trans/cis ratio is really lower, ranging from 56:44 in carbon tetrachloride to 38.5:61.5 in methylene chloride. Such a solvent dependence has been observed before by us in other epoxide ring opening reactions, and was interpreted in terms of different solvation of the cationic intermediate.[5d,f,g]

It can therefore be concluded that the statement quoted above is not correct, and that indene oxide behaves in its ring opening reactions with carboxylic acids in aprotic solvents quite normally as an aryloxirane. These results can be compared, at least qualitatively, if not quantitatively, because of the different geometries and rigidities, to those obtained with styrene oxide.[5a] These reactions cannot be considered "of an SN2 order," but rather as ones that proceed, at least in part, through ion pairs (4) collapsing to cis adducts, with the amount of benzylic bond breaking in the transition state depending on the strength of the acid and on the type of solvent. It may also be mentioned that 1 has been found to give with hydrogen chloride in dioxane a 75:25 ratio of *trans*- to *cis*-1-chloro-2-indanol.[8]

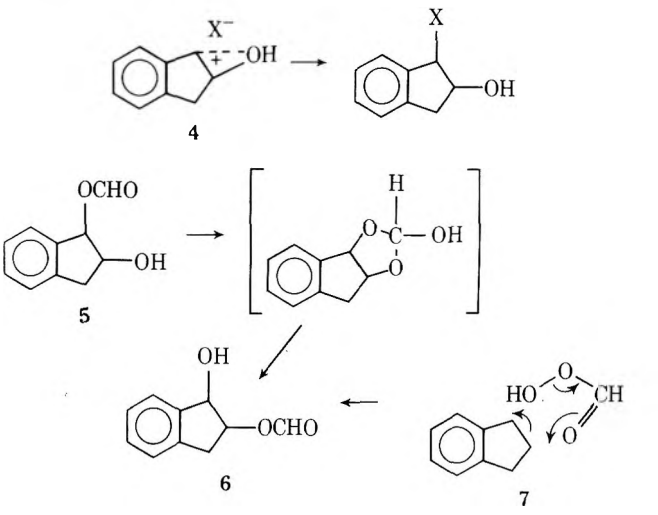
Table I
Ratios of Trans to Cis Adducts in the Ring Openings of Indene Oxide

Acid	Solvent	Trans/cis ratio
C_6H_5COOH	$CHCl_3$	64:36
CCl_3COOH	Cyclohexane	55:45
	CCl_4	56:44
	C_6H_6	48.5:51.5
	$CHCl_3$	47:53
	CH_2Cl_2	38.5:61.5
0.1 *N* H_2SO_4	H_2O	31:69
1 *N* H_2SO_4	H_2O	31:69
HCOOH	HCOOH	25:75

We also decided to check the literature reports on the very irregular behavior of indene oxide in its hydrolysis reactions. According to Böeseken[1] the diols 2 and 3 are obtained in amounts ranging all the way from the exclusive formation of the trans diol 2 (11 months in neutral water) to that of the cis diol 3 (45 min in *N*/60 acetic acid), intermediate ratios being obtained at different reaction times, temperatures, and acid concentrations. Partial support to these results was recently given through glc analysis,[2] when it was shown, for instance, that the ratio of 2 to 3 formed in the sulfuric acid catalyzed hydrolysis of 1 changed from 61.5:38.5 to 45:55 simply on passing from 1 to 0.1 *N* acid. Since such a relevant effect of the acid concentration had never been observed by us in other epoxide ring opening reactions, we repeated the hydrolysis of 1 in 0.1 and 1 *N* sulfuric acid at room temperature, and not at reflux as reported.[2] Under these conditions we found no dependence on acid normality, 2 and 3 being observed in a 31:69 ratio in both cases. The previously reported differences are therefore clearly not due to an influence of the pH of the medium on the primary hydrolysis reaction, but rather to secondary transformations of the glycols at the higher temperatures and reaction times. It has been known for a long time[9] that 2 and 3 equilibrate under acidic catalysis, and that the cis diol 3 is slowly converted into 2-indanone. We actually found that a 1-hr reflux of 2 and 3 in 1 *N* sulfuric acid in dioxane–water gave mixtures of 2 and 3 in ratios of

about 7:3 together with 2-indanone, the amount of which was higher when starting from **3** than from **2**, in accordance with the fact that only the cis diol is directly converted into the ketone, as would be expected for a concerted trans elimination, or, more likely, for a concerted 1,2 hydride shift. The latter results are also in contrast with the statement by Rosen, Dorfman, and Linfield[10] that 2-indanone is formed at the same rate from **2**, **3**, and from the corresponding 2-formyl esters. This was apparently deduced on the basis of very rough data that showed similar yields of ketone from all four substrates after 30-min reflux in 25% or more concentrated sulfuric acid, and taken as a proof that in all four cases the reaction proceeds through open carbonium ions. Beside the fact that under these conditions the formate esters were certainly hydrolyzed to the glycols much faster than they were rearranged, so that the substrates were actually two, and not four, the reaction conditions were so drastic that equilibration of **2** and **3** certainly took place before rearrangement. The more accurate older kinetic measurements,[9b] as well as our observations, clearly demonstrate that the rearrangement of **2** requires prior conversion into **3**, and that a free carbonium ion, which would be common to **2** and **3**, is not involved.

The same paper[10] also reported that the reaction of indene with peroxyformic acid gave almost exclusively cis adducts (**3** and the corresponding 2-formyl ester **6**) with less than 5% trans adducts. On the basis of this result it was proposed that the reaction takes place through a concerted attack by the peroxy acid, such as that shown in **7**, with formation of the 2-formate as a primary product, rather than by the primary formation of the epoxide **1**, followed by ring opening through attack by formate at the benzylic carbon to give **5** and by a 1,2-acyl shift, which should be very rapid in the acidic medium.[5,7b,11] The former hypothesis was preferred on the basis of the fact that the product composition of the indene–peroxyformic reaction was reported to be very different from that of the indene oxide–formic acid reaction. Since the latter composition was not specified, we also checked this point and found that the reaction of indene with peroxyformic acid, under the reported conditions,[10] gave after hydrolysis of the crude reaction mixture the diols **2** and **3** in a ratio of 15:85 (that is, much more of the trans isomer than reported), whereas the reaction of indene oxide with formic acid under conditions reproducing as much as possible those of the peroxyformic acid oxidation yielded the same two diols in a ratio of 25:75. Examination of the crude reaction mixtures from the two reactions by glc before hydrolysis revealed in both of them the presence of seven peaks, three of which were identified as due to the cis diol **3**, its 2-formate ester **6** (main product) and the trans diol **2**; the other four peaks were probably due to the other three possible monoformates and to the diformate, since only the two diols, traces of 2-indanone, and no other products were obtained after hydrolysis. The relative intensities of some of the peaks were a little different in the crudes from the two types of reactions, but the ratios of the cis 2-formate (**6**, the main product) to the cis diol were the same. Since a primary attack of formic acid at the nonbenzylic 2 position of the epoxide is extremely unlikely, the latter results indicate that the large amount of **6** in the reaction product from indene and peroxyformic acid can in no way be taken as a proof of the concerted mechanism **7**. The distribution of the diols and mono- and diformates rather appears to be due to a secondary equilibration in the formic acid–water medium, involving esterifications, hydrolyses, and acyl shifts, but not changes in relative configurations. The difference in the ratios of trans to cis adducts we have observed in the two types of reaction could imply for the peroxyformic acid oxidation a mechanism not involving the free epoxide as an intermediate, but we are rather inclined to assume, in view of the small size of this difference, that it stems from the difficulty in reproducing the exact experimental conditions in the two different types of reactions.



Experimental Section

Melting points were taken on a Kofler block. Gas–liquid chromatographic analyses were carried out on a Carlo Erba Fractovap Model G. V. equipped with a flame ionization detector and with 2-m glass columns. The mixtures of the diols **2** and **3**, 2-indanol, and 2-indanone were analyzed on a column of 5% DC-550 silicone oil on 80–100 mesh silanized Chromosorb W: injector block temperature 160°, column temperature 100°, nitrogen flow 35 ml/min; relative retention times of 2-indanone, 2-indanol, **3**, and **2**, 1:1.1:3.4:4.1. Petroleum ether refers to the fraction of bp 30–50°. $MgSO_4$ was always used as the drying agent in work-up procedures. Solvents used in the ring opening reactions were distilled from P_2O_5.

Starting and Reference Compounds. 1,2-Epoxyindan (**1**), mp 29–30° (from petroleum ether) (lit.[3] mp 30°), was obtained by cyclization of *trans*-2-bromo-1-indanol with base.[3] The latter compound was prepared by the following modification of the method of Suter and Milne.[9b] A solution of indene (20 g, 0.18 mol in 8:2 dioxane–water, v/v, 480 ml) was treated with *N*-bromoacetamide (26.2 g, 0.19 mol) in 1:1 dioxane–water (300 ml), heated for 10 min on a steam bath, and then poured onto ice to give the solid crude bromohydrin (32 g), after crystallization from ethanol, mp 127–128degr (lit.[9b] mp 126–127°).

trans-1,2-Indandiol (**2**) was prepared by 5-hr reflux of the epoxide **1** (2.0 g) in 2 *N* aqueous KOH (200 ml), followed by saturation with NaCl, extraction with ether, and crystallization from toluene, mp 158–160° (lit.[3,10] mp 157–159°).

cis-2-Formyloxy-1-indanol (**6**), mp 125–127° (lit.[10] mp 132–134°), was prepared according to Rosen, Dorfman, and Linfield[10] and converted into *cis*-1,2-indandiol (**3**), mp 98–100° (lit.[10] mp 99–101°).

2-Indanone, mp 50–52° (lit.[12] mp 57–58°), was obtained from **1** (0.50 g) in dry benzene (25 ml) through treatment with boron trifluoride–ethyl ether complex (0.58 ml) for 5 min, washing with aqueous $NaHCO_3$, evaporation, and crystallization from petroleum ether.

2-Indanol, mp 67–68° (lit.[13] mp 69°), was obtained by lithium aluminum hydride reduction of a solution of 2-indanone in ether, followed by decomposition of the excess of hydride with the minimum amount of water and 2 *N* NaOH.

Reaction of 1 with Benzoic Acid. A solution of **1** (0.250 g, 1.9 mmol) and benzoic acid (0.250 g, 2.0 mmol) in neutral, dry $CHCl_3$ (3 ml) was allowed to stand for 3 days at room temperature and then diluted with more $CHCl_3$ (10 ml) and washed with saturated aqueous $NaHCO_3$ (3 ml). The washing was extracted with three 10-ml portions of $CHCl_3$ and the combined organic layers were dried and evaporated to give a residue of benzoic esters (0.41 g). $LiAlH_4$ (0.4 g) was added in small portions to a solution of this residue in dry tetrahydrofuran (15 ml). After a 30-min reflux the excess of hydride was decomposed with the minimum amount of water and 2 *N* NaOH, the slurry was filtered, and the solid residue

was washed four times with portions of 25 ml of warm tetrahydrofuran. The combined organic solutions were dried and evaporated under reduced pressure. The residue was analyzed by glc and shown to contain the glycols **2** and **3** in a ratio of 64:36. This ratio did not change when a similar reaction mixture was left at room temperature for 80 days and then worked up as above. When the reaction was conducted in a more dilute solution (1.13 mmol of **1** and 1.24 mmol of benzoic acid in 15 ml of $CHCl_3$ for 20 days at room temperature) the ratio of **2** to **3** was 71:29. In all cases glc revealed the presence of some 2-indanol (5–10%), which could derive either from some unreacted epoxide or from some 2-indanone in the primary reaction products.

Reactions of 1 with Trichloroacetic Acid. These reactions were carried out in carefully dried vessels and solvents in the following way. A solution of **1** (0.53 mmol) in the appropriate solvent (7 ml) was treated with trichloroacetic acid (0.58 mmol) as a *ca.* 1 *M* solution in the same solvent, left at room temperature for 24 hr, and then evaporated *in vacuo*.[14] The residue was taken up in dry tetrahydrofuran (15 ml), treated with lithium aluminum hydride (0.300 g), and refluxed for 30 min. Work-up was carried out as in the case of the benzoic acid reaction. The ratios of **2** to **3** obtained by glc are shown in Table I. Amounts of 2-indanone (revealed as 2-indanol), ranging from 13 to 20%, were also found.

Hydrolysis of 1. A suspension of **1** (0.100 g) in 0.1 or 1 *N* aqueous H_2SO_4 (10 ml) was stirred for 24 hr at room temperature and then made alkaline with $NaHCO_3$, saturated with NaCl, and extracted with five 25-ml portions of ether. The residue obtained after evaporation of the dried extract was analyzed by glc; see Table I. The diols **2** and **3** were found to be stable under the reaction conditions. Small amounts of 2-indanone (1 and 4% in the reactions carried out in 0.1 and 1 *N* H_2SO_4, respectively) were found.

Equilibration and Rearrangement of 2 and 3. Solutions of each of the diols (50 mg) in 1 *N* H_2SO_4 in 75:25 dioxane–water (v/v, 5 ml) were refluxed for 1 hr and then worked up as above. Glc analysis gave the following results: from the trans diol **2**, 7% 2-indanone, 93% **2** + **3** (ratio 67:33); from the cis diol **3**, 18% 2-indanone, 82% **2** + **3** (ratio 69:31).

Comparison between the Reactions of Indene with Peroxyformic Acid and of 1 with Formic Acid. A. A mixture of 90% formic acid (7 ml), water (0.36 ml), and 35% hydrogen peroxide (1.2 ml) was heated at 35° for 15 min. Indene (1.16 g, 10 mmol) was then slowly added under stirring, while the temperature was kept at 35–40°. Stirring was continued for 1 hr at 35°, then at room temperature for 1 night. NaOH (6 *N*, 25 ml) was added; the mixture was heated at 90° for 3 hr, cooled, saturated with NaCl, and extracted with six 30-ml portions of ether. The dried extract was evaporated; glc analysis of the residue revealed the presence of **2** and **3** in a ratio of 15:85.

In a second run, with the same amounts of reagents and reaction conditions, the reaction product was not treated with base, but instead diluted with water (10 ml), saturated with NaCl, and extracted with five 30-ml portions of ether. The ether extracts were washed with water (2 × 25 ml), saturated $NaHCO_3$ (6 × 10 ml), and water (5 ml). The combined washings were extracted again with three 20-ml portions of ether, all the ether solutions were combined and evaporated, and the residue was examined by glc. The results are discussed in the introductory part.

B. The reactions were repeated under exactly the same conditions as in A, except for the reagents, that were 90% formic acid (7 ml), water (1.33 ml), 35% hydrogen peroxide (0.22 ml), and 1,2-epoxyindane (1.32 g, 10 mmol). In the hydrolyzed crude product **2** and **3** were present in a ratio of 25:75.

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Registry No.—**1**, 768-22-9; **2**, 4647-43-2; **3**, 4647-42-1; **6**, 19597-99-0; *trans*-2-bromo-1-indanol, 10368-44-2; 2-indanone, 615-13-4; 2-indanol, 4254-29-9.

References and Notes

(1) J. Boeseken, *Recl. Trav. Chim. Pays-Bas*, **47**, 683 (1928).
(2) J. G. Buchanan and K. Z. Sable in "Selective Organic Transformations," Vol. 2, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1972, p 85.
(3) A. Gagis, A. Fusco, and J. T. Benedict, *J. Org. Chem.*, **37**, 3181 (1972).
(4) G. Berti and F. Bottari, *J. Org. Chem.*, **25**, 1286 (1960).
(5) For example, (a) G. Berti, F. Bottari, P. L. Ferrarini, and B. Macchia, *J. Org. Chem.*, **30**, 4091 (1965); (b) G. Berti, F. Bottari, B. Macchia, and F. Macchia, *Tetrahedron*, **21**, 3277 (1965); (c) G. Berti, B. Macchia, and F. Macchia, *ibid.*, **24**, 1755 (1968); (d) G. Bellucci, B. Macchia, and F. Macchia, *Ann. Chim. (Rome)*, **59**, 1176 (1969); (e) G. Berti, B. Macchia, and F. Macchia, *Gazz. Chim. Ital.*, **100**, 334 (1970); (f) G. Bellucci, G. Berti, B. Macchia, and F. Macchia, *ibid.*, **103**, 345 (1973); (g) A. Balsamo, P. Crotti, B. Macchia, and F. Macchia, *Tetrahedron*, **29**, 199 (1973); (h) A. Balsamo, P. Crotti, B. Macchia, and F. Macchia, *ibid.*, **29**, 2183 (1973).
(6) Reference 2, pp 8–17.
(7) (a) G. Berti, F. Bottari, and B. Macchia, *Gazz. Chim. Ital.*, **90**, 1783 (1960); (b) *Ann. Chim. (Rome)*, **52**, 1101 (1962).
(8) H. Bodot, J. Jullien, and E. Leblanc, *Bull. Soc. Chim. Fr.*, 41 (1962).
(9) (a) P. H. Hermans, *Ber.*, **57**, 824 (1924); (b) C. M. Suter and H. Bayard Milne, *J. Amer. Chem. Soc.*, **62**, 3473 (1940).
(10) W. E. Rosen, L. Dorfman, and M. P. Linfield, *J. Org. Chem.*, **29**, 1723 (1964).
(11) G. Berti, F. Bottari, and B. Macchia, *Tetrahedron*, **20**, 545 (1964).
(12) J. E. Horan and R. W. Schiessler, *Org. Syn.*, **41**, 53 (1961).
(13) W. F. Whitmore and A. I. Gebhart, *J. Amer. Chem. Soc.*, **64**, 912 (1942).
(14) Quenching with aqueous base was avoided in order to minimize loss of water-soluble products, after it was established that direct evaporation of the reaction solutions did not produce any appreciable changes in product compositions.

Ring Closure Reactions. III.[1] Synthesis of Some Medium-Sized Cyclic Aromatic Ethers from *o*-(ω-Bromoalkyl)phenols

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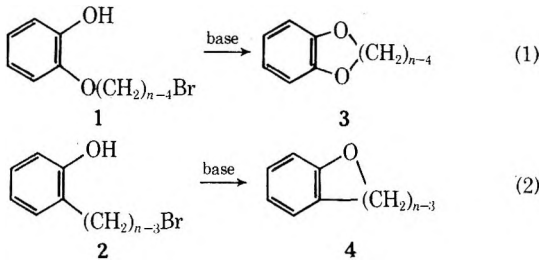
A synthesis of cyclic ethers of ring size n = 8, 9, and 10 as an alternative, convenient route to Ziegler's high-dilution technique is described. It is based on the highly favorable cyclization of *o*-(ω-bromoalkyl)phenate ions (**2**) in DMSO solution to yield 3,4,5,6-tetrahydro-2*H*-1-benzoxocin (**4**, n = 8), 2,3,4,5,6,7-hexahydro-2*H*-1-benzoxonin (**4**, n = 9), and 3,4,5,6,7,8-hexahydro-2*H*-1-benzoxecin (**4**, n = 10). The formation of varying amounts of isomeric alkenylphenols as by-products is recorded and discussed. Two alternative routes to the open-chain precursors from ω-X-alkyl *o*-anisyl ketones (**6** and **12**) are compared. In one of them the interesting competitive cyclization of 5-bromopentyl *o*-hydroxyphenyl ketone to cyclopentyl *o*-hydroxyphenyl ketone (**9**) is observed.

In the course of our investigation on the kinetics of ring closure of the anions derived from ω-bromoalkoxy- and ω-bromoalkylphenols, **1** and **2**, to the cyclic diethers[1] and monoethers,[2] **3** and **4**, respectively, cyclization on a preparative scale of compounds **2**, n = 8, 9, and 10, to the corresponding new macrocyclic monoethers[3] **4** was re-



quired. This could be accomplished by the high-dilution method given by Ziegler, Lüttringhaus, and Wohlgemuth[4] for the cyclization of **1**, n = 7–14, in boiling amyl alcohol in the presence of an excess solid K_2CO_3. However, the high-dilution technique suffers from long reaction times, large volumes of solvent, and an awkward set-up for the slow addition of the reagent to the reaction medium,[5] so that a more expeditious, less cumbersome procedure was highly desirable. Preliminary kinetic data showed that intramolecular alkylation of phenoxides occurred in DMSO some 10^4 times as fast as in aqueous ethanol, the $t_{1/2}$ for the cyclization of compounds **2**, n = 8, 9, and 10, being about 0.3, 3, and 2 min at 30°, respectively. This finding led us to an alternative method for the preparation of the three cyclic ethers **4**, n = 8, 9, and 10, involving the cyclization of the corresponding ω-bromoalkylphenols in DMSO by conventional procedures and apparatus and under mild conditions. Thus, since the reactants could be mixed in a relatively concentrated state and the addition times were as short as 1 hr, the high-dilution technique was avoided.

The results are reported in Table I. The yields are satisfactory in two out of the three reactions. With n = 8 and 9 the cyclic ether is accompanied by an open-chain isomer, the alkenylphenol **14**, to a different extent. Since the eight-membered ring is formed significantly faster than the nine- and ten-membered homologs and identical experimental conditions were adopted in all cases, a second-order β-elimination reaction of the E2 type with OH^- as a base may be ruled out, because it should compete the more favorably the slower the cyclization reaction, yielding the greatest amount of **14** for n = 9. The fact that just the opposite is observed indicates that an intramolecular β-elimination reaction is likely to be responsible for olefin formation, the phenoxide oxygen acting as a base. It should be noted that olefins were also found to accompany eight- and nine-membered ring formation in the closely related reaction 1.[1] The high intramolecular elimination/intramolecular substitution ratio observed is probably due to a steric congestion in the transition states leading to the eight- and nine-membered rings of both series, as strongly supported by our kinetic data.[1,2]

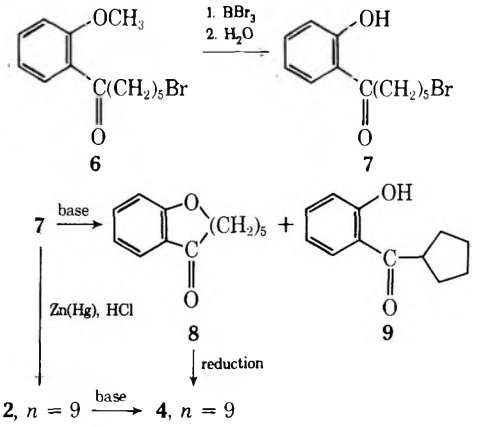
For the syntheses of the bifunctional precursors the alternative routes reported in Scheme I were first attempted in the case of n = 9. Compound **6** was readily prepared by standard methods. However, Clemmensen reduction of **7**

Table I
Products Obtained from Reaction of o-(ω-Bromoalkyl)phenols 2 with Sodium Hydroxide in DMSO at 55°

o-(ω-Bromoalkyl)phenol	n[b]	Products, %[a] Cyclic ether 4	Alkenylphenol 14
o-(5-Bromopentyl)phenol	8	30	56.5
o-(6-Bromohexyl)phenol	9	62	11.5
o-(7-Bromoheptyl)phenol	10	82	None

[a] Per cent of actually isolated products as based on the starting phenol. [b] Size of ring formed.

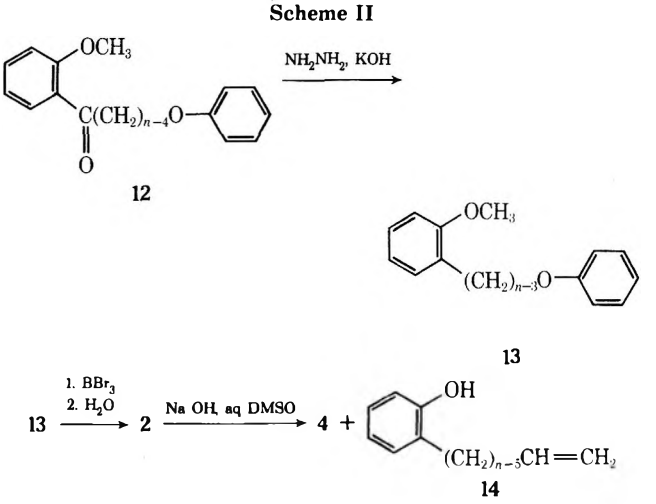
Scheme I



to **2**, n = 9, was unsuccessful, as the reduced phenolic material did not contain any bromine. Moreover, treatment of **7** with base under varying experimental conditions gave only low yields of the expected macrocyclic keto ether, 3,4,5,6-tetrahydro-2*H*-1-benzoxonin-7-one (**8**), the major product being cyclopentyl o-hydroxyphenyl ketone (**9**), presumably formed *via* a carbanion intermediate. Thus, it appears that the lower acidity of the α-methylene group as compared to that of the phenolic hydroxyl is more than offset by the extremely greater ease of cyclization to a five-membered ring rather than to a nine-membered one. An analogous phenomenon was recently reported by Greco and Warchol,[6] in connection with the unexpected formation of a five-membered ring instead of a larger one.

Protection of the $-CH_2Br$ function by phenoxylation together with the proper modifications of Scheme I resulted in a substantial improvement, the above complications being thus avoided (Scheme II, n = 8, 9, and 10). Huang-Minlon reduction of ketones **12** gave the diethers **13** in fairly good yields. A simultaneous cleavage of both ethereal functions of the latter compounds was achieved by treatment with 2 equiv of BBr_3 and afforded the desired o-(ω-bromoalkyl)phenols.

Scheme II



Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 257 spectrophotometer, from 2% solutions in CCl_4. Proton magnetic resonance spectra were obtained in CCl_4 solutions either on a Varian A-60 or Jeol JNM-C60HL spectrometer, using TMS as the internal standard. Mass spectra were performed on a AEI MS 12 spectrometer. The preliminary rate experiments for the cyclization of compounds **2** were performed by monitoring the disappearance of

the phenoxide ions absorption at either 263 or 312 nm on a Beckman DB GT spectrophotometer.

1,4-Dibromobutane (Fluka), 1,5-dibromopentane (Fluka), 1,6-dibromohexane (Merck), *o*-bromoanisole (Fluka), boron tribromide (Merck), and phenol (Erba RP) were all commercial samples and used as such.

The purity of synthesized compounds was thoroughly checked by tlc using several eluents.

***o*-Hydroxyphenyl 5-Bromopentyl Ketone (7).** Treatment of 1,5-dibromopentane with KCN in water–ethanol[7] gave 6-bromohexanenitrile (**5**) in 31% yield, bp 80° (2 mm), n^{19}D 1.4777. Interaction of **5** with the Grignard reagent derived from *o*-bromoanisole, followed by acid hydrolysis,[8] afforded 5-bromopentyl *o*-anisyl ketone (**6**) in 52% yield, ir 1675 cm^{-1} (C=O). Demethylation of **6** to **7** was effected in 73% yield by treatment with slightly more than the equimolecular amount of BBr_3 in dry CH_2Cl_2 at −20°.[9] Compound **7** was crystallized from methanol: mp 44.5–45°; ir 1640 (C=O), 3000–3500 cm^{-1} (OH, very broad); pmr δ 12.2 (s, 1 H, OH), 6.6–7.8 (m, 4 H, nuclear protons), 3.35 (t, 2 H, $COCH_2$ protons), 2.95 (t, 2 H, CH_2Br protons), 1.4–2.1 (m, 6 H, "central" methylene protons).

Cyclization Experiments with 7. These were effected by treatment with base under various experimental conditions, *i.e.*, (i) anhydrous K_2CO_3 in boiling dry amyl alcohol under high-dilution conditions;[4] (ii) NaOH in refluxing 1-butanol, 20 hr; (iii) NaOH in boiling 75% ethanol, 7 hr; (iv) NaOH in 95% aqueous DMSO at 70°, 5 hr. The crude reaction products showed in all cases in the ir spectra a very broad hydroxyl absorption at 3000–3500 cm^{-1} together with two carbonyl absorptions at 1640 and 1675 cm^{-1}. The lower frequency band was the more intense one. Chromatography on silica gel (eluent $CHCl_3$) of the crude product coming from the reaction carried out in 75% ethanol allowed the elution of the following components as separate, pure (tlc) fractions in the given order. Cyclopentyl *o*-hydroxyphenyl ketone (**9**), 47.5% yield, and 3,4,5,6-tetrahydro-2*H*-1-benzoxonin-7-one (**8**), 23% yield. Structure assignments were effected on the basis of spectral data. Compound **9**: ir 3000–3500 (OH), 1640 cm^{-1} (C=O); pmr δ 12.4 (s, 1 H, OH), 6.6–7.8 (m, 4 H, nuclear protons), 3.2–4.0 (m, 1 H, α carbonyl proton), 1.3–2.3 (m, 8 H, cyclopentyl methylene protons). Compound **8**: ir 1675 cm^{-1} (C=O); pmr δ 6.7–7.7 (m, 4 H, nuclear protons), 4.1 (m, 2 H, CH_2O protons), 3.0 (m, 2 H, $COCH_2$ protons), 1.7 (m, 6 H, "central" methylene protons). In the mass spectrum both isomers showed a molecular peak at *m/e* 190 (calcd, 190), together with a base peak at *m/e* 121, probably due to the fragment *o*-$HOC_6H_4CO^+$.

***o*-(ω-Bromoalkyl)phenols (2, *n* = 8, 9, and 10).** ω-Phenoxy bromides **10** were obtained by the reaction of sodium phenoxide with the appropriate α,ω-dibromoalkane with a procedure derived from that of Marvel and Tanenbaum,[10] the major difference being that longer reaction times were used, namely 5, 7.5, and 20 hr for *n* = 8, 9, and 10, respectively. The compounds were purified by fractional distillation: compound **10**, *n* = 8, 65% yield, bp 110–123° (2.5 mm), mp 37.5–39.5°; compound **10**, *n* = 9, 52% yield, bp 126–130° (2 mm), n^{27}D 1.5446; compound **10**, *n* = 10, 73% yield, bp 107–112° (0.2 mm), n^{27}D 1.5291. Treatment of such compounds with KCN gave nearly quantitative yields of the phenoxy nitriles **11**, ir 2250 cm^{-1} (C≡N). The crude nitriles **11** were converted as above (see formation of **6** from **5**) to the corresponding ketones **12** in 90% yield, ir 1680 cm^{-1} (C=O). The crude ketones were reduced to the diethers **13** in about 55% yield by the Huang-Minlon modification of the Wolff–Kischner reduction. The diethers were purified by chromatography on silica gel using $CHCl_3$–light petroleum (2:1) as eluent: *n* = 8, n^{28}D 1.5497; *n* = 9, n^{28}D 1.5470; *n* = 10, n^{28}D 1.5384. Treatment with 2 equiv of BBr_3[9] gave **2**, *n* = 8, 9, and 10, in 53, 60, and 75% yield (16, 16, and 28% overall yield), respectively. After work-up of the reaction mixtures the crude reaction products were dissolved in light petroleum and repeatedly washed with water in order to remove phenol, until a negative test with $FeCl_3$ was obtained in the aqueous washings. After drying over anhydrous sodium sulfate and removal of the solvent, the product was purified by fractional distillation: compound **2**, *n* = 8, bp 127–133° (1 mm), $n^{24.5}$D 1.5549; compound **2**, *n* = 9, bp 153–157° (1 mm), $n^{24.5}$D 1.5471; compound **2**, *n* = 10, bp 137–140° (0.2 mm), $n^{24.5}$D 1.5420. All three compounds showed the expected ir and pmr spectra: ir 3605 cm^{-1} (OH); pmr δ 6.5–7.2 (m, 4 H, nuclear protons), 4.9 (s, 1 H, OH), 3.35 (t, 2 H, $-CH_2Br$), 2.4–2.8 (distorted t, 2 H, benzylic CH_2), 1.2–2.1 (m, "central" methylene protons).

Anal. Calcd for $C_{11}H_{15}BrO$, *n* = 8: C, 54.34; H, 6.22; Br, 32.86. Found: C, 54.49; H, 6.41; Br, 32.72. Calcd for $C_{12}H_{17}BrO$, *n* = 9: C, 56.04; H, 6.63; Br, 31.07. Found: C, 56.00; H, 6.60; Br, 31.11. Calcd for $C_{13}H_{19}BrO$, *n* = 10: C, 57.58; H, 7.06; Br, 29.46. Found: C, 57.55; H, 7.16; Br, 29.41.

Cyclization of Compounds 2, *n* = 8, 9, and 10. To 100 ml of DMSO 2.5 ml of 40% (w/w sodium hydroxide was added with stirring. To the vigorously stirred suspension heated to 55° about 8 mmol of **2** in DMSO (50 ml) was added dropwise over 1 hr. Heating and stirring was continued for additional 30 min. When cold, the yellow-brown mixture was diluted with water, made strongly alkaline with sodium hydroxide, then repeatedly extracted with hexane; the combined extracts were washed with water and dried over anhydrous sodium sulfate and the solvent was removed by distillation. Chromatography of the residue on silica gel, eluent $CHCl_3$–light petroleum (1:1), afforded the cyclic ethers **4**, *n* = 8, 9, and 10. The yields are reported in Table I. Analytical samples were obtained after one distillation: 3,4,5,6-tetrahydro-2*H*-1-benzoxocin (**4**, *n* = 8), bp 82° (1.8 mm), n^{19}D 1.5353; 2,3,4,5,6,7-hexahydro-1-benzoxonin (**4**, *n* = 9), bp 101° (1.8 mm), mp 29–31°, n^{19}D 1.5394 (supercooled liquid); 3,4,5,6,7,8-hexahydro-2*H*-1-benzoxecin (**4**, *n* = 10), bp 111° (1.6 mm), n^{19}D 1.5410.

Any phenolic material present in the above alkaline solution was recovered by acidification with concentrated hydrochloric acid, followed by ether extraction. After the usual work-up, elution with chloroform on silica gel yielded the pure alkenylphenols **14**, *n* = 8 and 9. No definite product was isolated for *n* = 10. Yields are reported in Table I. For analytical purposes, the compounds were further purified by distillation: o-(4-pentenyl)phenol (**14**, *n* = 8), bp 104° (1.8 mm); *o*-(5-hexenyl)phenol (**14**, *n* = 9), bp 115° (1.5 mm).

Structure assignments for both the cyclic ethers and alkenylphenols were made on the basis of spectral data and elemental analyses: cyclic ethers **4**, *n* = 8, 9, and 10, pmr δ 6.6–7.2 (m, 4 H, nuclear protons), 4.15 for *n* = 9 and 10, 3.95 for *n* = 8 (m, 2 H, $-CH_2O$), 2.7 (m, 2 H, benzylic protons), 1.2–2.0 for *n* = 8 and 9 and 0.8–2.0 for *n* = 10 (m, "central" protons); alkenylphenols **14**, *n* = 8 and 9, ir 3605 (OH), 1640, 990, 915 cm^{-1} ($-CH=CH_2$); pmr δ 6.4–7.1 (m, 4 H, nuclear protons), 5.2–6.1 (m, 1 H, vinylic proton), 4.6–5.1 (m, 2 H, terminal vinylic protons), 5.0 for *n* = 8 and 4.7 for *n* = 9 (1 H, OH, superimposed to terminal olefinic protons), 2.25 (distorted t, 2 H, benzylic protons), 1.2–2.3 (m, allylic and "central" protons).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found for **4**, *n* = 8: C, 81.31; H, 8.63. Found for **14**, *n* = 8: C, 81.28; H, 8.71. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found for **4**, *n* = 9: C, 81.71; H, 9.14. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found for **4**, *n* = 10: C, 81.87; H, 9.67.

Registry No.—**2** (*n* = 8), 51795-89-2; **2** (*n* = 9), 51795-90-5; **2** (*n* = 10), 51795-91-6; **4** (*n* = 8), 51060-43-6; **4** (*n* = 9), 51795-92-7; **4** (*n* = 10), 51795-93-8; **5**, 6621-59-6; **6**, 51795-94-9; **7**, 51821-14-8; **8**, 51795-95-0; **9**, 51795-96-1; **10** (*n* = 8), 22921-72-8; **10** (*n* = 9), 51795-97-2; **10** (*n* = 10), 51795-98-3; **13** (*n* = 8), 51795-99-4; **13** (*n* = 9), 51796-00-0; **13** (*n* = 10), 51796-01-1; **14** (*n* = 8), 51796-02-2; **14** (*n* = 9), 51796-03-3.

References and Notes

(1) Part II: G. Illuminati, L. Mandolini, and B. Masci, *J. Amer. Chem. Soc.*, **96**, 1422 (1974).
(2) Work in progress in this laboratory.
(3) Actually, K. Ziegler in Houben-Weyl, "Methoden der Organischen Chemie," Vol. 9, Georg Thieme Verlag, Stuttgart, 1955, Part 4/2, p 772, claimed that some of the *p*-methyl derivatives of the cyclic ethers (**4**) have been prepared by Ziegler and Rohrurst in 1955, but the pertinent data do not appear to have ever been published.
(4) K. Ziegler, A. Luttringhaus, and K. Wohlgemuth, *Justus Liebigs Ann. Chem.*, **528**, 162 (1937).
(5) K. Ziegler, H. Eberle, and H. Ohlinger, *Justus Liebigs Ann. Chem.*, **504**, 94 (1933).
(6) C. V. Greco and J. F. Warchol, *J. Org. Chem.*, **36**, 604 (1971).
(7) B. Cloke and O. Ayers, *J. Amer. Chem. Soc.*, **56**, 2144 (1934).
(8) C. R. Hauser, W. J. Humphlett, and M. J. Weiss, *J. Amer. Chem. Soc.*, **70**, 426 (1948).
(9) J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968).
(10) C. S. Marvel and A. L. Tanenbaum, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 435.

Chemistry of α-Halo Aldehydes. IV. Reaction of 2-Halo-2-methylpropanal with Acylacetates in the Presence of Base[1]

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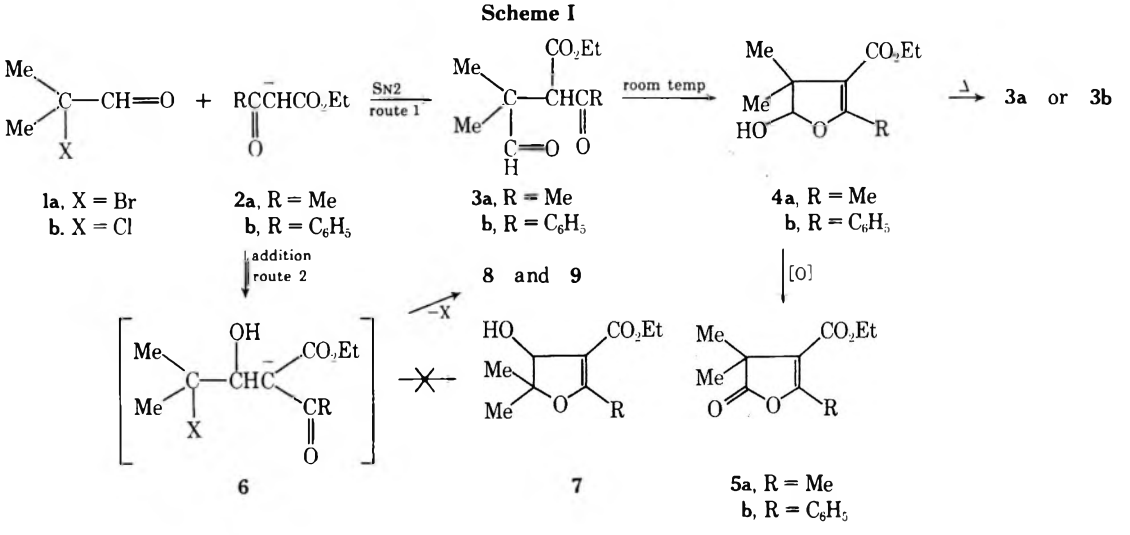
The reaction of 2-halo-2-methylpropanal (1) with acylacetate (2) in basic media has been investigated. In nonaqueous media, tautomeric mixtures of 4-substituted 2,2-dimethyl-3-ethoxycarbonyl-4-oxobutanal (3) and 5-substituted ethyl 2-hydroxy-3,3-dimethyl-2,3-dihydrofuran-4-carboxylate (4) were obtained. When kept for 2 weeks at room temperature, this mixture equilibrated to give mainly 4. The cyclic hemiacetal 4 can be reconverted partly to 3 by heating. The chromic acid oxidation of 4 gave γ-substituted α,α-dimethyl-β-ethoxycarbonyl-$\Delta^{\beta,\gamma}$-butenolide (5). In aqueous media, the enolate anion of 2 attacked the carbonyl carbon of 1 to give α-acyl-β-acylethoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (9). Compound 9 was decomposed to 2 and α-acyl-γ,γ-dimethyl-$\Delta^{\alpha,\beta}$-butenolide (8) when heated at 160–170° under reduced pressure. The butenolide 8 readily reacted with 1 mol of acylacetate in aqueous K_2CO_3 to regenerate the saturated butyrolactone 9. While the alkaline hydrolysis of α-acetyl-β-acetylethoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (9a) underwent both deacylation in the side chain and deacylation at the α position of the lactone ring to give terpenylic acid (11), that of α-benzoyl-β-benzoylethoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (9b) afforded β-phenacyl-γ,γ-dimethyl-γ-butyrolactone (10) as a result of decaylation only at the α position of the lactone ring.

We have been studying the reactions of α-halo aldehyde with active hydrogen compounds.[2-4] In the previous paper,[4] we reported the reaction of 2-halo-2-methylpropanal (1) with malonic ester, which gave γ-butyrolactones of versatile utility such as terpenylic acid. Franke, *et al.*,[5] in 1922 reported that the base-catalyzed condensation of 2-bromo-2-methylpropanal (**1a**) with ethyl acetoacetate (**2a**) afforded a product with the formula of $C_{10}H_{16}O_4$ and undetermined structure. It was anticipated that 3-hydroxydihydrofuran (7) might be produced which would be promising as the precursor to make 3-furanones such as bullatenone;[6] hence we became interested in investigating the reaction of 1 with benzoylacetoacetate (**2b**) as well as with **2a**. Because of the bifunctionality of the substrate 1, two pathways can be postulated for the reaction as is shown in Scheme I. One involves SN2 substitution leading to 1,4-dioxo compound **3**, which may be cyclized to 2-hydroxydihydrofuran 4 (route 1). Another possibility is nucleophilic attack of the enolate anion of 2 on the carbonyl carbon of the substrate 1 (route 2). As the nature of the solvent appreciably influences the pathway,[4] we conducted the reaction under various conditions in order to study the solvent effect: (a) using sodium ethoxide as base and absolute ethanol as solvent (same condition as Franke's);[5] (b) using sodium ethoxide in dry ether; (c) using potassium carbonate in tetrahydrofuran (THF); (d) using potassium carbonate in water. The present paper describes and discusses the results of these reactions.

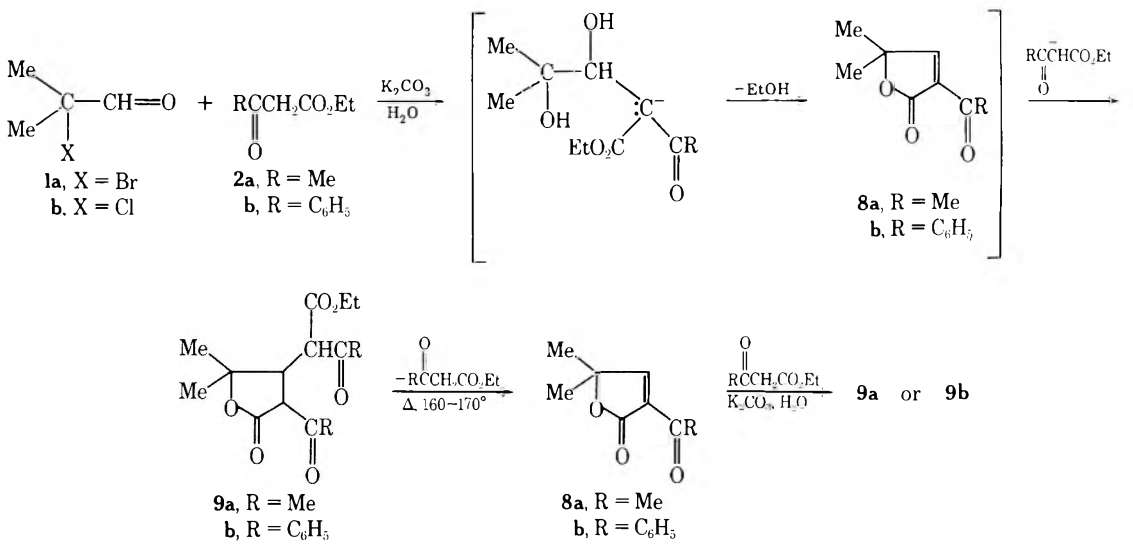
Results and Discussion

In all cases except d, tautomeric mixtures of **3** and **4** were obtained. Structural assignments of the products were made principally on the basis of ir and nmr spectra. Compound **3** seems to predominate in the mixture during the distillation; however, these compounds gradually equilibrate *via* an intramolecular conversion. For instance, from the reaction of 2-bromo-2-methylpropanal (**1a**) with **2a** under the condition b, a tautomeric mixture[7] of 2,2-dimethyl-3-ethoxycarbonyl-4-oxopentanal (**3a**) and ethyl 2-hydroxy-3,3,5-trimethyl-2,3-dihydrofuran-4-carboxylate (**4a**) was obtained as an oily product in a 67% yield.[8] The elemental analysis and mass spectrum of this oil were compatible with the formula $C_{10}H_{16}O_4$ reported by Franke, *et al.*[5] The nmr spectrum of freshly distilled product exhibited proton signals of **3a** at δ 2.24 (s, $COCH_3$), 3.83 (s, $CHCO_2C_2H_5$), and 9.62 ppm (s, CHO), while **4a** showed three singlets at 2.19 (=CCH_3), 2.98 (OH), and 5.29 ppm (methine proton), respectively. When kept for 2 weeks at room temperature, this mixture equili-

Scheme I



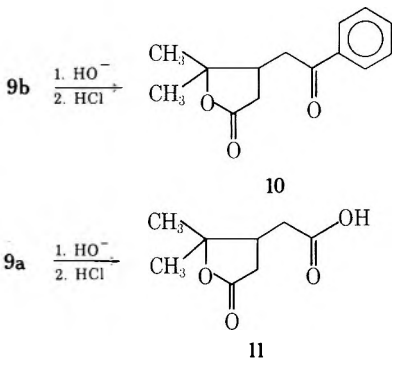
Scheme II



brated to give a ratio of **4a** to **3a** of *ca.* 40:1. The ir bands at 1670 and 1635 cm^{-1} appear in the spectrum as the absorption at 1720 cm^{-1} disappears, indicating that transformation of the system to an α,β-unsaturated ester has occurred. The cyclic hemiacetal **4a** can be reconverted partly to **3a** by heating. Ethyl benzoylacetate (**2b**) reacted with **1b** similarly, affording ethyl 2,2-dimethyl-3-ethoxycarbonyl-4-phenyl-4-oxobutanal (**3b**) which, when kept at room temperature for several days, tautomerized to ethyl 2-hydroxy-3,3-dimethyl-5-phenyl-2,3-dihydrofuran-4-carboxylate (**4b**).

The oxidation of **4a** with CrO_3 gave α,α,γ-trimethyl-β-ethoxycarbonyl-$\Delta^{\beta,\gamma}$-butenolide (**5a**) in a 64% yield. The ir spectrum of **5a** showed a strong band at 1800 cm^{-1} due to $\Delta^{\beta,\gamma}$-butenolide carbonyl.[9] Chromic acid oxidation of **4b** also gave $\Delta^{\beta,\gamma}$-butenolide (**5b**) in a 40% yield.

In contrast with reactions under nonaqueous conditions, the enolate anion of acylacetate (**2**) attacked the carbonyl group of **1** in aqueous media to give α-acyl-β-acylethoxycarbonylmethyl-γ-butyrolactone (**9**). The reaction of **1b** with acetoacetate in aqueous K_2CO_3 afforded α-acetyl-β-acetylethoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (**9a**) in a 91% yield. From the reaction of **1b** with **2b** in aqueous K_2CO_3, α-benzoyl-β-benzoylethoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (**9b**) was obtained as a crystalline product in a 94% yield. The butyrolactone **9** eliminated 1 mol of ethyl acylacetate to give α-acyl-γ,γ-dimethyl-$\Delta^{\alpha,\beta}$-butenolide (**8**) when heated at 160–170° under reduced pressure. Mass spectra of both **8b** and **9b** showed a clean molecular ion peak of **8b** at *m/e* 216.[10] Furthermore, the butenolide **8** readily reacted with 1 mol of acylacetate in aqueous K_2CO_3 solution to regenerate the saturated butyrolactone **9** in good yields. Based on this fact, it is reasonable to consider that the butenolide **8** is produced first in the reaction of **1** and **2**, and then undergoes Michael addition of **2** as is shown in Scheme II. In aqueous alkaline solution, 2-halo-2-methylpropanal promptly undergoes displacement of halogen to give 2-hydroxy-2-methylpropanal (**1c**).[11] Therefore, it is possible that the hydroxy aldehyde **1c** produced in the reaction medium is the real substrate in this reaction.[12] Compound **9b** can be prepared also by the condensation of **1c** with enolate anion of **2b** even in nonaqueous media. The alkaline hydrolysis of the lactonic ester **9b** is complicated by the deacylation at the α position affording β-phenacyl-γ,γ-dimethyl-γ-butyrolactone (**10**). The lactonic ester **9a** underwent both deacylation in the side chain and deacylation at the α position of the lactone ring under the same condition as above, giving *dl*-terpenylic acid (**11**) in a 52



% yield. The reaction described in the present article will be helpful for synthesizing ketone carrying γ-butyrolactone or $\Delta^{\alpha,\beta}$-butenolide rings.

Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were carried out by Mr. Eiichiro Amano. We are indebted to Mr. Heizan Kawamoto and Miss Hiromi Ootani for nmr measurements. Analytical determinations by glpc were performed on a Hitachi Model K-53 gas chromatograph filled with the following materials (3 mm o.d. × 1 m): A, 10% Apiezone Grease L on Chromosorb W; B, 10% polyneopentyl glycol succinate on Chromosorb W. The preparative isolations by glpc were performed on a Yanagimoto Model GCG-550T gas chromatograph (3 mm o.d. × 2.25 m, 10% Apiezone Grease L on Chromosorb W). The nuclear magnetic resonance spectra (60 MHz) were recorded with Hitachi Model R-24 and R-20 spectrometers. Mass spectra were obtained with a Hitachi Model RMS-4 mass spectrometer. Thin layer chromatography (tlc) was done on silica gel GF_{254} (E. Merck AG, Darmstadt) with layers of 0.25-mm thickness. Preparative tlc was performed on silica gel PF_{254} (E. Merck AG, Darmstadt) with 1.0-mm layers.

Starting materials such as 2-bromo-2-methylpropanal (**1a**),[13] 2-chloro-2-methylpropanal (**1b**),[14] 2-hydroxy-2-methylpropanal (**1c**),[15] and ethyl benzoylacetate (**2b**)[16] were prepared by procedures described in the literature.

Tautomeric Mixture of 2,2-Dimethyl-3-ethoxycarbonyl-4-oxopentanal (3a) and Ethyl 2-Hydroxy-3,3,5-trimethyl-2,3-dihydrofuran-4-carboxylate (4a). Procedure A (Condition a). An ethanolic solution of ethyl sodioacetoacetate was prepared by dissolving 1.9 g (0.082 mol) of sodium in the mixture of 10.7 g (0.082 mol) of ethyl acetoacetate (**2a**) and 50 ml of ethanol. To the stirred solution, 12.3 g (0.082 mol) of **1a** was added dropwise at 0°. The mixture was stirred for 30 min at 0° and then for 1 hr at room temperature. After being refluxed for an additional 1 hr,

the mixture was poured into a large excess of water. The organic layer was extracted with ether and dried over $MgSO_4$. After removal of the solvent, the residual oil was distilled to give 4.3 g (26%) of a tautomeric mixture[17] of **3a** and **4a** (1:4):[7] bp 102–103° (3 mm); ir (neat)[18] 3400 (OH), 1720 (C=O), 1690 (C=O), 1635 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.24 (s, 7.5, CH_3), 1.28 (t, 3.75, J = 7 Hz, $CO_2CH_2CH_3$), 2.19 (s, 3, $=CCH_3$), 2.24 (s, 0.75, $COCH_3$), 2.98 (broad s, 1, OH), 3.83 (s, 0.25, $CHCO_2Et$), 4.19 (q, 2, J = 7 Hz, ester $-CH_2-$ of **4a**), 4.24 (q, 0.55, J = 7 Hz, ester $-CH_2-$ of **3a**), 5.29 [s, 1, $-OCH(OH)-$], 9.62 (s, 0.25, CHO); mass spectrum (70 eV) m/e (rel intensity) 200 (37, M^+), 185 (25, $M^+ - CH_3$), 171 (49, $M^+ - C_2H_5$), 157 (30, $M^+ - COCH_3$), 155 (38), 139 (49, $M^+ - COCH_3 - H_2O$), 129 (96, $CH_3COCHCO_2Et^+$), 125 (100), 113 (75), 111 (63).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.21; H, 7.78.

The ir and nmr spectra of this product changed slowly until the spectral shift data ceased to be observable 2 weeks after distillation: ir[19] (neat) 3400 (OH), 1690, 1670 (C=O), 1635 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.24 (s, 6, 2 CH_3), 2.16 (s, 3, $=CCH_3$), 4.10 (broad s, 1, OH), 4.18 (q, 2, J = 7 Hz, ester $-CH_2-$ of **4a**), 5.29 [s, 1, $-OCH(OH)$], and 9.62 (s, trace, CHO).

Procedure B (Condition b). Sodium (2.3 g, 0.1 mol) was dissolved in 15 ml of absolute ethanol with cooling. After complete evaporation of excess ethanol, 13.0 g (0.1 mol) of **2a** dissolved in 30 ml of dry ether was added. To the resulting mixture, 15.1 g (0.1 mol) of **1a** was added dropwise at 0° in the course of 1 hr. The stirring was continued for 2 hr at 0°, and then for an additional 2-hr period at room temperature. After being allowed to stand overnight, the mixture was worked up in the same way as in procedure A to give 13.3 g (67%) of the tautomeric mixture of **3a** and **4a** (7:13),[7] bp 116–119° (6 mm). Glpc analysis[20] showed one peak with a retention time of 13 min. Both ir and nmr spectra showed patterns similar to those of the product described in the preceding section. In 2 weeks after distillation, the ratio of **4a** to **3a** in the mixture changed to 40:1.[7]

Procedure C (Condition c). To a dry THF solution (50 ml) of potassium carbonate (16.8 g, 0.12 mol) and **2a** (15.6 g, 0.12 mol), 12.8 g (0.12 mol) of **1b** was added dropwise at 0° with stirring. The mixture was stirred for 40 hr at room temperature and for an additional 10-hr period at 50°. It was worked up as described above to give 10.5 g (44%) of a mixture of **3a** and **4a**, bp 130–134° (15 mm). Its ir and nmr spectra were almost identical with those of the product in procedure B, finally exhibiting only the characteristic pattern of **4a**.[19]

Ethyl 2,2-Dimethyl-3-ethoxycarbonyl-4-phenyl-4-oxobutanal (3b) and Ethyl 2-Hydroxy-3,3-dimethyl-5-phenyl-2,3-dihydrofuran-4-carboxylate (4b). Procedure A. To a suspension of 17.4 g (0.125 mol) of potassium carbonate in 50 ml of dry THF was added 24 g (0.125 mol) of **2b** at room temperature. After the mixture was stirred for 20 min, 13.3 g (0.125 mol) of **1b** was added dropwise at 0°. The stirring was continued for 4 hr at room temperature, and then for an additional 11 hr at 65°. The reaction mixture was filtered to remove solid material, which, after being dissolved in water, was extracted with ether. The filtrate combined with the ethereal extract was washed with water and then dried over $MgSO_4$. It was subjected to vacuum distillation to give 20.8 g of **3b**, clean oil, yield 63%: bp 156–157° (0.06 mm); ir (neat)[18] 2720 (CHO), 1725 (C=O), 1683 (C=O), 1595 and 1577 cm^{-1} (benzene C=C); nmr ($CDCl_3$) δ 1.13 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.22 (s, 3, CH_3), 1.24 (s, 3, CH_3), 4.11 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 4.65 (s, 1, $-CHCO_2Et$), 7.22–8.1 (m, 5, C_6H_5), 9.79 (s, 1, -CHO); mass spectrum (70 eV) m/e (rel intensity) 262 (3, M^+), 234 (31, $M^+ - CH_2{=}CH_2$), 192 (19, $PhCOCH_2CO_2Et$), 187 (30, $M^+ - CO_2Et$), 173 (22), 161 (79), 129 (93), 105 (100, PhCO), 101 (74).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.66; H, 7.12.

The patterns of ir and nmr spectra of **3b** shifted completely to those of **4b** in 2 weeks after distillation. **3b** was quantitatively transformed to white crystals of **4b**: mp 78–79° after recrystallization from benzene–petroleum ether; ir (KBr) 3430 (OH), 1678 (conjugated C=O), 1620 (C=C), 1600 and 1573 cm^{-1} (benzene C=C); nmr ($CDCl_3$) δ 1.13 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.32 (s, 6, 2 CH_3), 4.0 (broad s, 1, OH), 4.08 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 5.36 (d,[21] 1, J = 6 Hz, $-OCHOH-$), 7.2–7.7 (m, 5, C_6H_5); mass spectrum (70 eV) m/e (rel intensity) 262 (9, M^+), 247 (2, $M^+ - CH_3$), 234 (28, $M^+ - CH_2{=}CH_2$), 192 (21, $PhCOCH_2CO_2Et$), 187 (49, $M^+ - CO_2Et$), 173 (25), 161 (88), 129 (99), 105 (100, PhCO), 101 (75).

Distillation of 4b under diminished pressure regenerated **3b** quantitatively, bp 130° (0.1 mm).

Procedure B. To the mixed solution of ethyl sodiobenzoylacetate (0.05 mol) in 140 ml of ether was added dropwise 5.4 g (0.05 mol) of **1b** at 5–10° with stirring. The mixture was stirred for 5 hr at 30°, and then was made acidic with dilute HCl. From the ethereal extract, which was worked up in the usual way, 3.5 g of **3b** was collected by distillation, yield 27%, bp 140–143° (0.06 mm). This product also tautomerized quantitatively to the crystalline product of **4b**.

Procedure C. To a solution of **2b** (1.92 g, 0.01 mol) and **1b** (1.07 g, 0.01 mol) in 10 ml of dry hexamethylphosphoramide was added 1.38 g (0.01 mol) of potassium carbonate with moderate coolling. The mixture, stirred for 23 hr at room temperature, was poured into a large excess of water and then acidified with 10% HCl. The ethereal extract of the organic layer was washed with water and dried over $MgSO_4$. After removal of the solvent, the residual oil was distilled to give 1.15 g (44%) of **3b**, bp 141–143° (0.05 mm).[22]

α,α,γ-Trimethyl-β-ethoxycarbonyl-$\Delta^{\beta,\gamma}$-butenolide (5a). To a mixed solution of 8 g (0.08 mol) of chromium trioxide in 20 ml of 70% acetic acid was added 8.0 g (0.04 mol) of the tautomeric mixture of **3a** and **4a** (7:13)[7] in several portions with cooling. The mixture was stirred for 2 hr at room temperature and then for 2 hr at 60°. After 80 ml of water was added to the mixture, it was extracted with ether. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent left 6.8 g of a clean oil[23] which showed two peaks on glpc analysis.[24] The components, retention times (minutes), and integrated percentages are as follows: 1, 0.8, 15%; 2, 5.2, 74%. The retention time of component 1 was identical with that of acetic acid. Component 2 was collected by preparative glpc and identified as **5a**: yield 64%; nmr ($CDCl_3$) δ 1.30 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.41 (s, 6, 2 CH_3), 2.40 (s, 3, $=CCH_3$), 4.22 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$); mass spectrum (70 eV) m/e (rel intensity) 198 (38, M^+), 183 (20, $M^+ - CH_3$), 170 (7, $M^+ - CH_2{=}CH_2$), 159 (14), 155 (28, $M^+ - CH_3CO$), 153 (18), 125 (69, $M^+ - CO_2Et$), 124 (39), 109 (38), 96 (100).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.39; H, 7.12. Found: C, 60.68; H, 7.00.

α,α-Dimethyl-β-ethoxycarbonyl-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (5b). Compound **4b** (1.7 g, 0.0065 mol) was oxidized with chromium trioxide (5 g, 0.05 mol) in 77% acetic acid (13 ml) in the same way as **4a**. From the reaction mixture, 0.8 g of a clean oil was obtained. Glpc analysis[25] of this oil showed two peaks. The components, retention times, and integrated percentages are as follows: 1, 24.8, 85%; 2, 40, 15%. The retention time of component 2 was identical with that of **4b**. Component 1 was collected by preparative glpc and identified as **5b**: yield 40%; ir (neat) 1806 (lactone C=O), 1723 and 1700 (ester C=O), 1632 (C=C), 1596 and 1578 cm^{-1} (benzene C=C); nmr ($CDCl_3$) δ 1.22 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.56 (s, 6, 2 CH_3), 4.20 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 7.3–8.1 (m, 5, C_6H_5); mass spectrum (70 eV) m/e (rel intensity) 260 (29, M^+), 245 (44, $M^+ - CH_3$), 231 (3), 199 (25), 187 (18, $M^+ - CO_2Et$), 171 (6), 158 (45), 105 (100, PhCO), 77 (75, C_6H_5).

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.25; H, 6.15.

α-Acetyl-β-acetylethoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (9a). To a solution of **1b** (6.4 g, 0.06 mol) in 50 ml of water was added 8.4 g (0.06 mol) of potassium carbonate in several portions. After the mixture was stirred for 2 hr at room temperature, 7.8 g (0.06 mol) of **2a** was added. After being stirred for 14 hr at room temperature, it was neutralized with dilute HCl. The organic layer was extracted with ether and the extract was dried over $MgSO_4$. After removal of the solvent, 7.7 g of crude **9a** was obtained: yield 91%;[26] mp 168–169° dec after one recrystallization from the mixed solvent of acetone–*n*-hexane (1:1, v/v); ir (Nujol) 3400 (enolic OH), 1740 and 1710 cm^{-1} (C=O); nmr[27] (CD_3SOCD_3) δ 1.20 (t, 3, J = 7.5 Hz, $CO_2CH_2CH_3$), 1.30 (s, 6, 2 CH_3), 1.49 (s, 2.9), 2.13 (s, 0.2), 2.48 (d, J = 12 Hz), 2.90 (d, 0.8, J = 9 Hz), 3.18 (s, 1.4), 3.31 (s, 1.6), 3.62 (d, 0.6, J = 2 Hz), 3.80 (d, 0.4, J = 2 Hz), 4.15 (q, 2, J = 7.5 Hz, $CO_2CH_2CH_3$), 5.29 (s, 0.8); mass spectrum (70 eV) m/e (rel intensity) 284 (0.5, M^+), 266 (9, $M^+ - H_2O$), 194 (27), 180 (44), 136 (94), 134 (100), 108 (91), 107 (95), 80 (72), 79 (75).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.63; H, 6.70.

α-Acetyl-γ,γ-dimethyl-$\Delta^{\alpha,\beta}$-butenolide (8a). Procedure A. To a solution of **2a** (6.5 g, 0.05 mol) and potassium carbonate (3.5 g, 0.025 mol) in water (50 ml) was added 7.6 g (0.05 mol) of **1a** at

room temperature with stirring. The mixture was stirred at room temperature for 24 hr, and finally at 50° for 20 hr. After being neutralized with dilute HCl, it was extracted with ether. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent left 7.1 g of yellow oil which, on distillation, gave 4.8 g (62%) of **8a**: bp 93–102° (5 mm); mp 64–65° (benzene); ir (Nujol) 1750 (conjugated lactone C=O), 1670 (acetyl C=O), 1620 cm^{-1} (conjugated C=C); nmr ($CDCl_3$) δ 1.58 (s, 6, 2 CH_3), 2.55 (s, 3, $COCH_3$), 8.10 (s, 1, =CH); mass spectrum (70 eV) *m/e* (rel intensity) 154 (48, M^+), 139 (100, $M^+ - CH_3$), 136 (85), 111 (88, $M^+ - COCH_3$), 97 (91), 69 (71), 67 (65).

Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.04; H, 6.25.

Procedure B. Distillation of **9a** (7.2 g, 0.025 mol) under reduced pressure afforded 3.3 g of **8a**, yield 86%, bp 99–121° (5 mm).

Addition of 2a to 8a in the Presence of K_2CO_3. The mixed solution of **2a** (0.37 g, 0.0029 mol), **8a** (0.44 g, 0.0029 mol), and potassium carbonate (0.40 g, 0.0029 mol) in 5 ml of water was stirred for 2 hr at 30°. White crystals (0.085 g) precipitated; they were collected, washed with dilute HCl and then with water, and identified as **9a** by comparison of ir spectrum with that of an authentic sample, yield 10%. From the filtrate, 0.59 g of oil was recovered. Alkaline hydrolysis of this oil with 10% NaOH gave 0.14 g of crude terpenylic acid (**11**), yield 27%.

α-Benzoyl-β-benzoylethoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (9b). To the mixed solution of **2b** (11.5 g, 0.06 mol) and potassium carbonate (8.4 g, 0.06 mol) in 30 ml of water was added 5.3 g (0.05 mol) of **1b** with moderate cooling. After the mixture was stirred for 40 hr at room temperature, for a further 6 hr at 50°, and finally for 1 hr at 60–70°, it was poured into a large amount of water. The product separated as a white solid. It was collected and washed with ether to remove excess of **2b**. One recrystallization of crude product from benzene yielded 11.5 g (94%)[28] of **9b**: mp 133–134°; ir (Nujol) 1754 (lactone C=O), 1727 (ester C=O), 1663 (benzoyl C=O), 1588 and 1572 cm^{-1} (benzene C=C); nmr ($CDCl_3$) δ 0.92 (t, 3, J = 8 Hz, $CO_2CH_2CH_3$), 1.33 (s, 3, CH_3), 1.65 (s, 3, CH_3), 3.83 (q, 2, J = 8 Hz, $CO_2CH_2CH_3$), 4.17 (t, 1, J = 9 Hz, C_β H), 4.65 (d, 1, $>CHCO_2C_2H_5$), 5.23 (d, 1, J = 9 Hz, C_α H), 7.3–8.2 (m, 10, 2 C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 216 (17, $M^+ - PhCOCH_2CO_2Et$), 201 (33), 192 (30, $PhCOCH_2CO_2Et$), 173 (38), 170 (28), 158 (85), 146 (35), 106 (60).

Anal. Calcd for $C_{24}H_{24}O_6$: C, 70.58; H, 5.92. Found: C, 70.50; H, 5.96.

Reaction of 2-Hydroxy-2-methylpropanal (1c) with 2b in THF. A solution of **2b** (19.8 g, 0.1 mol), **1c** (8.8 g, 0.1 mol), and potassium carbonate (15.2 g, 0.11 mol) in 30 ml of THF was stirred for 38 hr at room temperature. After work-up of the resulting mixture in the usual manner, 9.8 g of crude **9b** was obtained, yield 48%.

α-Benzoyl-γ,γ-dimethyl-$\Delta^{\alpha,\beta}$-butenolide (8b). Lactone **9b** was distilled at oil-bath temperature (160–170°) under reduced pressure. As the first fraction [bp 101–120° (1.0 mm)], 3.0 g (88%) of **2b** was recovered. As the second fraction [bp 145–150° (1.0 mm)], 2.7 g (71%) of **8b** was obtained. The analytical sample was collected by preparative tlc:[29] mp 65–66°; ir (Nujol) 1750–1780 (lactone C=O), 1650 (benzoyl C=O), 1630 (C=C), 1598 and 1580 cm^{-1} (benzene C=C); nmr ($CDCl_3$) δ 1.58 (s, 6, 2 CH_3), 7.70 (s, 1, =CH), 7.4–7.9 (m, 5, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 216 (2, M^+), 201 (3, $M^+ - CH_3$), 188 (1), 173 (5), 170 (4), 158 (29), 105 (100, PhCO), 77 (57, C_6H_5).

Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.04; H, 5.79.

Addition of 2b to 8b in the Presence of K_2CO_3. A mixture consisting of water (5 ml), potassium carbonate (0.32 g, 0.0023 mol), **2b** (1.0 g, 0.0052 mol), and **8b** (0.4 g, 0.0019 mol) was stirred at room temperature for 20 min and then at 50° for 2 hr. Work-up of the reaction mixture in the usual manner afforded 0.5 g (67%) of white crystals, which were proved to be **9b** by comparison of its infrared spectrum with that of an authentic sample.

γ,γ-Dimethyl-β-phenacyl-γ-butyrolactone (10). The lactone **9b** (1 g, 0.0024 mol) was suspended in aqueous sodium hydroxide which was prepared by dissolving NaOH (2 g, 0.05 mol) in 5 ml of water. After the mixture was stirred for 15 hr at 60°, it was acidified with dilute HCl. The ethereal extract of the organic layer was washed with water and dried over Na_2SO_4. Removal of the solvent left 0.7 g of yellow solid. Tlc analysis[30] of this solid showed two spots at R_f values of 0.25 (component 1) and 0.38 (component 2). Each component was collected by preparative tlc[30] and analyzed. The weight ratio (component 1 to component 2) was 2:3. Component 1 was identified as the lactone **9b** by comparison of its ir spectrum with that of an authentic sample. Component 2 was identified as **10**: yield 73%; mp 97–98°; ir (Nujol) 1750 (lactone C=O), 1683 (benzoyl C=O), 1603 and 1584 cm^{-1} (benzene C=C); nmr ($CDCl_3$) δ 1.34 (s, 3, CH_3), 1.47 (s, 3, CH_3), 1.9–3.3 (m, 5, lactone ring proton and CH_2COPh), 7.3–8.05 (m, 5, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 232 (8, M^+), 217 (19, $M^+ - CH_3$), 214 (12, $M^+ - H_2O$), 203 (1), 174 (12), 146 (49), 105 (100, PhCO), 86 (59), 84 (70), 77 (72, C_6H_5).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.37; H, 7.16.

***dl*-Terpenylic Acid (β-Carboxymethyl-γ,γ-dimethyl-γ-butyrolactone, 11).** Compound **9a** (0.14 g, 0.0005 mol) was hydrolyzed in the same manner as **9b**, using 2 ml of 20% sodium hydroxide. From the ethereal extract, 0.05 g of semisolid material was obtained. Tlc analysis[31] of this material showed that it had 90% purity. The analytical sample collected by preparative tlc was identified as *dl*-terpenylic acid by comparison of its ir and nmr spectra with those of an authentic sample,[4] yield 52%, mp 87° (lit.[4] mp 88–89°).

Registry No.—**1a**, 13206-46-7; **1b**, 917-93-1; **1c**, 20818-81-9; **2a**, 141-97-9; **2b**, 94-02-0; **3a**, 51716-51-9; **3b**, 51716-52-0; **4a**, 51716-53-1; **4b**, 51716-54-2; **5a**, 51716-55-3; **5b**, 51716-56-4; **8a**, 51716-57-5; **8b**, 51716-58-6; **9a**, 51716-59-7; **9b**, 51716-60-0; **10**, 51716-61-1; **11**, 632-04-2.

References and Notes

(1) Presented in part at the 26th Annual Meeting of the Chemical Society of Japan, Hiratsuka, Japan, April 3, 1972, and in part at the 4th International Congress of Heterocyclic Chemistry, Salt Lake City, Utah, July 13, 1973.
(2) A. Takeda, S. Tsuboi, S. Wada, and H. Kato, *Bull. Chem. Soc. Jap.*, **45**, 1217 (1972).
(3) A. Takeda, S. Tsuboi, and T. Hongo, *Bull. Chem. Soc. Jap.*, **46**, 1844 (1973).
(4) A. Takeda, S. Tsuboi, and Y. Oota, *J. Org. Chem.*, **38**, 4148 (1973).
(5) A. Franke and G. Groeger, *Monatsh. Chem.*, **43**, 55 (1922).
(6) A. Takeda, S. Tsuboi, and T. Sakai, *Chem. Lett.*, 425 (1973).
(7) The ratio of **3a** and **4a** was determined by comparing the intensities of nmr signals at δ 9.62 and 5.29 ppm.
(8) The reaction of **1a** and **2a** in the condition described by Franke, *et al.* (ref 5), brought the analogous result.
(9) This fact provides further evidence to support the 2-hydroxy-2,3-dihydrofuran structure of **4a**.
(10) Lactone **9** is readily decomposed to acylacetate and the butenolide **8** at the oven temperature (180°).
(11) Compound **1a** is transformed to 2-hydroxy-2-methylpropanal: 90% in 15 min, 95% in 30 min, and 97% in 60 min.
(12) α-Halo aldehyde such as 2-chlorononanal, which is hardly converted to 2-hydroxy aldehyde under the same condition, undergoes substitution at the α position followed by cyclization to the corresponding 2-hydroxy-2,3-dihydrofuran derivative (unpublished work).
(13) T. A. Favorskaya and D. A. Shkurgina, *J. Gen. Chem. USSR*, **25**, 713 (1955); *Chem. Abstr.*, **50**, 2427 (1956).
(14) C. L. Stevens and B. T. Gillis, *J. Amer. Chem. Soc.*, **79**, 3448 (1957).
(15) R. Dworzak and J. Pierri, *Monatsh. Chem.*, **52**, 141 (1929).
(16) J. M. Straley and A. C. Adams, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 415.
(17) Inseparable by tlc: developer, *n*-hexane–acetone (4:1, v/v); R_f 0.40.
(18) The original spectral data were taken just after distillation.
(19) The spectral data were taken 2 weeks after distillation.
(20) Column A: 3 mm o.d. × 2.25 m; temperature, 140°; carrier gas, N_2 (42 ml/min); detector, FID.
(21) After deuterium exchange, nmr showed a singlet at δ 5.36 ppm. Nmr ($CDCl_3$) of crude **4b** also showed a singlet at 5.36 ppm.
(22) This product also underwent the transformation to **4b** quantitatively within 2 weeks after distillation.
(23) Distillation of this oil gave 2.5 g (32%) of **5a**, bp 93–102° (5 mm).
(24) Column B: temperature, 150°; carrier gas, N_2 (42 ml/min); detector, FID.
(25) Column A: temperature, 180°; carrier gas, N_2 (53 ml/min; detector, FID.
(26) The yield based on **2a**.
(27) Because of complicated patterns, it was difficult to interpret this spectrum. Compound **9a** appears to consist of keto and enol tautomers.
(28) The yield based on **2b**.
(29) Developed with *n*-hexane–acetone (3:1, v/v); R_f 0.25.
(30) Developer: *n*-hexane–acetone (3:1, v/v).

Hydrogenolysis of Carbon–Carbon Bonds in Cyclohexadienones[1]

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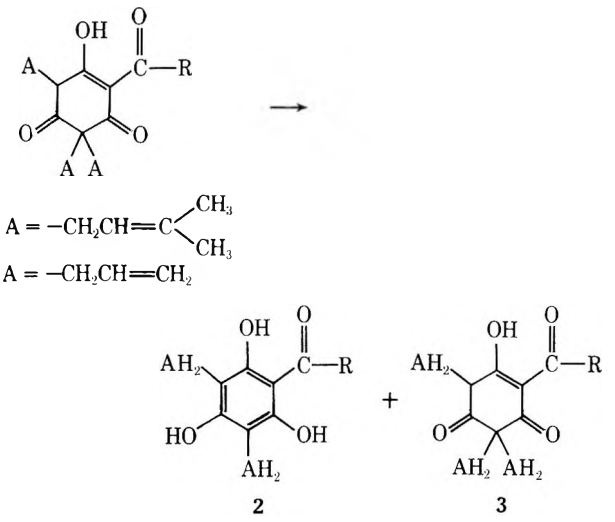
Palladium-catalyzed low-pressure hydrogenation of cross-conjugated and linearly conjugated cyclohexadienones bearing allyl or benzyl groups at the quaternary carbons results in significant hydrogenolysis of the bonds linking the allyl or benzyl groups to the cyclohexadienone rings, as well as reduction of the double bond in the allyl group. The percentage of hydrogenolysis increases with increasing solvent polarity and with increasing hydrogen bonding power of the solvent. No hydrogenolysis occurs with a 2,6-di-*tert*-butylcyclohexadienone. These results are consistent with a hydrogenolysis mechanism involving attack by a hydride ion-like species at the carbon linking the allyl or benzyl group to the ring.

While hydrogenolysis of bonds between carbon and heteroatoms is common, the corresponding cleavage of unstrained carbon–carbon single bonds under mild conditions is quite rare. However, carbon–carbon bond cleavage has been reported to occur during the hydrogenation of cyclic β-diketones bearing highly substituted allyl groups between the two carbonyls.[2-5] For instance, hydrogenation of lupulone[6] and its analogs (**1a**) at room temperature gives appreciable yields of phenol **2**,[3-5] as well as the expected reduction product **3**.[5a] When A is a simple allyl group (**1b**), only reduction to **3** occurs.[4]

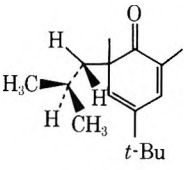


1a, A = $-CH_2CH{=}C(CH_3)_2$
b, A = $-CH_2CH{=}CH_2$

2 **3**

We have now observed that attempted low-pressure reduction of double bonds in allyl groups, even unsubstituted allyl groups, at the quaternary carbons of cyclohexadienones results in appreciable hydrogenolysis of carbon–carbon bonds. The relative rate of hydrogenolysis compared to that of double bond hydrogenation is greatly increased by an increase in the polarity of the solvent employed or by an increase in its hydrogen bonding ability. Our results are summarized in Tables I and II. One run in which the reaction was carried out in the presence of the catalyst (which had previously been hydrogenated) and in polar solvent, but in the absence of hydrogen, gave no reaction. Thus cleavage does not result from a palladium-catalyzed carbenium ion cleavage of the cyclohexadienone, but occurs during the hydrogenation process.

Hydrogenation of the cross-conjugated cyclohexadienone **7** gives, in addition to the hydrogenolysis product 2,4,6-trimethylphenol, a mixture of reduction products which could not be separated. In each solvent, the nmr spectrum of the reduction products suggest that they consist of a mixture of the 4-propylcyclohexadienone and of the corresponding cyclohexenone. Rather surprisingly, no evidence for ring hydrogenation was observed in the hydrogenation of **8** or of the linearly conjugated cyclohexadienones **4** and **5**. The structures of products **10** and **11** were clearly established by their nmr spectra (see Experimental Section). Of interest is the fact that the nmr spectrum of dienone **10** shows two doublets for the methyl groups on the isobutyl side chain at δ 0.76 and 0.88 ppm. This chemical shift difference (0.12 ppm) appears to be the largest such shift recorded for methyl groups in an isopropyl group which is not directly bonded to an asymmetric center.[7] Inspection of molecular models indicates that **11** has a single preferred conformation (**11a**) in which one methyl group (presumably the one



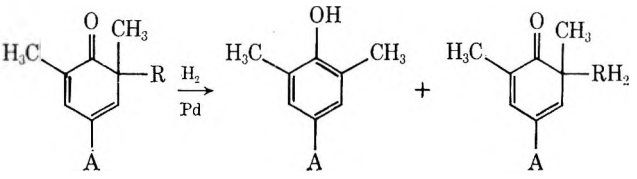
11a

resonating at δ 0.76) is significantly affected by the shielding cone of the C-4–C-5 double bond, while the other methyl group is much less affected by the ring system.

We believe that the results shown in Tables I and II are consistent with a hydrogenolysis mechanism in which a hydride ion-like species displaces a phenoxide ion from an allyl or benzyl group. This mechanism resembles that which Reidl and Nickl have proposed for hydrogenolysis of lupulone.[4] Their mechanism has been supported by Anteunis and Verzele, on the basis of the observation that the ratio of hydrogenolysis to hydrogenation of lupulone increases with increasing hydrogen ion concentration.[5] Reidl and Nickl have proposed, however, that hydride ion attack occurs only following an initial protonation of a carbonyl group of lupulone.[4] The leaving group, according to this mechanism, would be a phenol rather than a phenoxide ion. A similar mechanism seems unlikely for the hydrogenolysis of dienone **5**, at least, since protonation of the carbonyl group would result in a very rapid [3,3] sigmatropic shift of the allyl group to yield **7**.[8] Although protonation therefore does not precede hydrogenolysis, the ability of the solvent to hydrogen bond the developing phenoxide ion is clearly of great importance, as indicated by the sharp increase in the percentage of hydrogenolysis, despite the decrease in dielectric constant, when the solvent is changed from methanol to acetic acid–methanol.

Of particular interest is the absence of any hydrogenolysis in 2,6-di-*tert*-butylcyclohexadienones. In these cases the proposed hydride attack would displace a 2,6-di-*tert*-butylphenoxide anion. These anions are exceptionally strong bases[9] owing to hindrance of solvation at oxygen, and therefore should be very poor leaving groups.

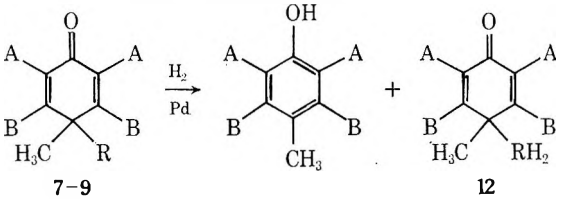
Table I
Hydrogenation of Cyclohexa-2,4-dien-1-ones



4-6 10,11

Dienone	R	A	Solvent	Yield of phenol, %	Other products
4	$-CH_2C(CH_3)=CH_2$	*t*-Bu	Hexane	20	**10**, R = *i*-Bu
5	$-CH_2CH=CH_2$	CH_3	Hexane	13	**11**, R = *n*-Pr; A = Me
5	$-CH_2CH=CH_2$	CH_3	Methanol	49	**11**
5	$-CH_2CH=CH_2$	CH_3	DMF	34	**11**
5	$-CH_2CH=CH_2$	CH_3	Methanol (catalyst only, no hydrogen)	No reaction	
5	$-CH_2CH=CH_2$	CH_3	Acetic acid–methanol (1:3)	85	**11**
6	$-CH_2Ph$	CH_3	Hexane	100	

Table II
Hydrogenation of Cyclohexa-2,5-dien-1-ones



7-9 12

Dienone	R	A	B	Solvent	Yield of phenol, %	Other products
7	$-CH_2CH=CH_2$	CH_3	H	Hexane	0	*a*
7	$-CH_2CH=CH_2$	CH_3	H	Methanol	5	*a*
7	$-CH_2CH=CH_2$	CH_3	H	Acetic acid–methanol (1:3)	63	*a*
8	$-CH_2Ph$	CH_3	CH_3	Hexane	100	
9	$-CH_2CH=CH_2$	*t*-Bu	H	Acetic acid–methanol (1:3)	0	**12**, R = *n*-Pr
9	$-CH_2CH=CH_2$	*t*-Bu	H	Acetic acid	0	**12**, R = *n*-Pr

[a] Apparently a mixture of ketones with zero, one, or two double bonds in the ring (nmr analysis).

Displacement of a phenoxide ion by a hydride-like reagent could conceivably occur at either C-1 or C-3 of the allyl group. A study of the competitive hydrogenations of dienones **4** and **6** in methanol showed that hydrogenolysis of **5** occurred approximately 1.5 times as fast as that of **6**. This rate difference seems too small to require that a mechanism be postulated for the reduction of **4** which is not available to **6**. Thus, a direct SN2-like attack of a hydride ion at the carbon attached to the cyclohexadienone ring seems the best representation of the transition state for hydrogenolysis.

Experimental Section

Preparation of Cyclohexadienones. Cyclohexadienones **5**,[10] **7**,[10] **8**,[11] and **9**[12] were prepared as described in the literature.

6-(2-Methylallyl)-4-*tert*-butyl-2,6-dimethylcyclohexa-2,4-dien-1-one (4) was prepared by Claisen alkylation of sodium 4-*tert*-butyl-2,6-dimethylphenoxide with methallyl bromide in the usual manner.[10] It was obtained in 49% yield as a pale yellow oil after chromatography on Florisil. Its nmr spectrum in CCl_4 showed a multiplet (1 H) at δ 6.99 ppm (hydrogen at C-3), a doublet (1 H, J = 3 Hz) at δ 5.94 (hydrogen at C-5), a broad doublet (2 H) around δ 4.54 (terminal vinyl protons), a doublet (3 H, J = 1.5 Hz) at δ 1.84 (methyl at C-2), a singlet (9 H) at δ 1.13 (*tert*-butyl at C-4), a singlet (3 H) at δ 1.08 (methyl at C-6), a pair of doublets (2 H, J = 14 Hz) at δ 2.11 and 2.76 (methylene at C-6), and a doublet (3 H, J = 1.5 Hz) at δ 1.85.

6-Benzyl-2,4-6-trimethylcyclohexa-2,4-dien-1-one (6) was similarly prepared by Claisen alkylation of sodium 2,4-6-trimethylphenoxide with benzyl bromide, and isolated as a pale yellow oil in 22% yield by chromatography on Florisil. Its nmr spectrum in CCl_4 showed a multiplet (5 H) around δ 6.93 (phenyl group), a quartet (1 H, J = 1.5 Hz) at δ 6.35 (hydrogen at C-3), a singlet (1 H) at δ 5.83 (hydrogen at C-5), a pair of doublets (1 H each, J = 12.5 Hz) at δ 2.60 and 3.04 (methylene at C-6), a doublet (3 H, J = 1.5 Hz) at δ 1.79 (methyl at C-2), a singlet (3 H) at δ 1.71 (methyl at C-4), and a singlet (3 H) at δ 1.16 (methyl at C-6).

Hydrogenation Procedures. All hydrogenations were carried out in a conventional small-scale hydrogenation apparatus, at essentially atmospheric pressure. The cyclohexadienones (10^{-3} mol) were dissolved in 5–10 ml of solvent and *ca.* 5 mg of 5% Pd on charcoal catalyst (obtained from Matheson Coleman and Bell) was added. The mixture was stirred by a magnetic stirrer until uptake of hydrogen essentially ceased and was then filtered to remove the catalyst. Hexane and methanol solutions were evaporated on a steam bath. Acetic acid and acetic acid–methanol solutions were neutralized with sodium bicarbonate solution, and the mixtures were extracted with methylene chloride. The organic layers were washed with water, dried over magnesium sulfate, filtered, and evaporated. Dimethylformamide solutions were diluted with 25 ml of distilled water and extracted with two 10-ml portions of pentane, which were combined and washed with five 20-ml portions of

water. The organic layers were dried over magnesium sulfate, filtered, and evaporated.

Nmr analysis showed the absence of peaks attributable to allyl groups at C-6 of the cyclohexadienones, indicating complete reaction of the starting dienones **4** and **5**. The relative yields of phenols and reduction products from the hydrogenation of compounds **4** and **5** were determined by the relative areas of the aromatic methyl absorptions due to the phenols and the allylic methyl absorptions due to the hydrogenated dienones **10** and **11**. The yield of phenol from hydrogenation of dienone **7** was determined by vpc analysis on a 6 ft × 0.25 in., 3% SE-30 on Chromosorb W column.

Isolation of Products of Hydrogenation. With the exception of the product from reduction of cyclohexadienone **9**, the reaction products from each hydrogenation, after work-up as described above, were dissolved in 10 ml of pentane and extracted with three 10-ml portions of Claisen alkali. The organic fractions were washed with water, dried, and evaporated to give the reduced cyclohexadienones. Pure samples of the previously unreported **10** and **11** were obtained by vpc on a 1 ft × 0.375 in., 30% SE-30 on Chromosorb W column.

The nmr spectrum of **6-isobutyl-4-*tert*-butyl-2,6-dimethylcyclohexa-2,4-dien-1-one (10)** in $CDCl_3$ showed a multiplet (1 H) at δ 7.0 (hydrogen at C-3), a doublet (1 H, J = 2.5 Hz) at δ 5.93 (hydrogen at C-5), a broad singlet (3 H) at δ 1.90 (methyl at C-2), singlets at δ 1.15 (9 H) and 1.08 (3 H) for the *tert*-butyl at C-4 and the methyl at C-6, and doublets (3 H, J = 6 Hz) at δ 0.76 and 0.88 (methyl groups on isobutyl side chain), as well as a multiplet (*ca.* 3 H) at δ 2.30–1.15 (methylene and methine of isobutyl group).

The nmr spectrum of **2,4,6-trimethyl-6-propylcyclohexa-2,4-dien-1-one (11)** in CCl_4 showed a multiplet (1 H) at δ 6.90 (hydrogen at C-3), a broad singlet (1 H) at δ 6.10 (hydrogen at C-5), a doublet (3 H, J = 1.5 Hz) at δ 1.99 (methyl at C-2), singlets (3 H each) at δ 1.93 and 1.11 (methyls at C-4 and C-6), and a multiplet (*ca.* 7 H) at δ 0.73–1.46 (propyl at C-6).

The neutral fraction from hydrogenation of dienone **7** showed a complex spectrum indicating that appreciable hydrogenation of double bonds in the ring had occurred. No pure product could be obtained from this mixture.

The aqueous layers from extraction with Claisen alkalie were acidified with 6 *N* hydrochloric acid and extracted with methylene chloride. The organic layers were washed with water, dried, and evaporated to give essentially pure phenols, which were identified by comparison with samples of known structure.

The hydrogenation product of dienone **9** was shown by vpc to contain a single product, which was identified by its nmr and ir spectrum as the known **2,6-di-*tert*-butyl-4-methyl-4-propylcyclohexa-2,5-dien-1-one.**[13]

Competitive Hydrogenolysis of Benzyl and 2-Methylallyl Groups. A solution of dienones **4** and **6** (3.0×10^{-4} mol of each) in 5 ml of methanol was hydrogenated as usual until *ca.* 20% of the starting materials had reacted. The mixture was filtered free of catalyst, the solvent was evaporated on a steam bath, and the residue was dissolved in 15 ml of pentane and extracted with Claisen alkali. The nmr spectrum of the neutral fraction showed it to consist largely of unreacted starting dienones. The alkaline fraction was acidified and extracted with methylene chloride. The methylene chloride layer was washed with water, dried over magnesium sulfate, and evaporated. The phenols obtained in this manner were analyzed by vpc on a 6 ft × 0.25 in., 5% SE-30 on Chromosorb W column at 170°. Comparison with synthetic mixtures showed the product to be 4-*tert*-butyl-2,6-dimethylphenol and 2,4,6-trimethylphenol in the molar ratio 1.5:1.

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Registry No.—**4**, 51869-07-9; **5**, 4278-92-6; **6**, 41388-92-5; **7**, 4278-95-9; **8**, 31040-77-4; **9**, 2756-79-8; **10**, 51869-08-0; **11**, 51869-09-1.

References and Notes

(1) Reactions of Cyclohexadienones. XXXII. Part XXXI: B. Miller, *J. Amer. Chem. Soc.*, **95**, 8458 (1973).
(2) H. Wieland, *Chem. Ber.*, **58**, 102 (1925).
(3) W. Wöllmer, *Chem. Ber.*, **58**, 675 (1925).
(4) W. Reidl and J. Nickl, *Chem. Ber.*, **89**, 1838 (1956).
(5) (a) M. Anteunis and M. Verzele, *Bull. Soc. Chim. Belg.*, **68**, 476 (1959); (b) J. F. Carson, *J. Amer. Chem. Soc.*, **73**, 1850 (1951).
(6) For the structure of lupulone, see W. Reidl, *Chem. Ber.*, **85**, 692 (1952), and references cited therein.
(7) For other examples of chemical shift differences in methyls distant from an asymmetric center, see G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 2628 (1964).
(8) B. Miller, *J. Amer. Chem. Soc.*, **92**, 6246 (1970).
(9) P. D. Bolton, C. H. Rochester, and B. Rossall, *Trans. Faraday Soc.*, **66**, 1348 (1970).
(10) B. Miller, *J. Amer. Chem. Soc.*, **87**, 5115 (1965).
(11) B. Miller, *J. Amer. Chem. Soc.*, **92**, 6252 (1970).
(12) B. Miller and H. Margulies, *J. Org. Chem.*, **30**, 3895 (1965).
(13) B. Miller and H. Margulies, *J. Amer. Chem. Soc.*, **89**, 1678 (1967).

Cis–Trans Isomerization of Allylic Radicals

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A series of cis and trans allylic halides has been reduced with triphenyltin hydride in a chain reaction which involves allylic radicals. Varying degrees of cis–trans isomerization of the intermediate allylic radicals have been observed and it has been shown that the variation is concentration dependent and also dependent on structure. Attempts to study allylic radicals where there is delocalization of the free electron onto CN, CO_2CH_3, and $CON(CH_3)_2$ by the same technique led to isomerization of starting material or product and thus no conclusion concerning the interconvertibility of the isomeric radicals could be reached. Chlorination of crotonitrile, isocrotonitrile, methyl crotonate, and methyl isocrotonate with *tert*-butyl hypochlorite led to varying amounts of cis–trans isomerization in the intermediate radicals as reflected by the composition of the chloro-substituted products. The factors which control these isomerizations are discussed.

In 1961 Walling and Thaler studied the chlorination of a variety of olefins by *tert*-butyl hypochlorite.[1] They found that in general cis and trans olefins gave cis and trans allylic chlorides, respectively. A notable exception was *cis*-4,4-dimethyl-2-pentene, which at 40° gave *trans*-1-chloro-4,4-dimethyl-2-pentene. It was suggested that the *tert*-butyl group destabilized the intermediate cis allylic radical by introducing steric effects which were not present in the other allylic radicals, and that the rate of conversion of the cis to trans allylic radical was thus enhanced.

Subsequently other workers have investigated the cis–trans isomerization of allylic radicals,[2] and isomerization has been observed under a variety of conditions.[2a-d] In the work being reported here cis and trans allylic radicals have

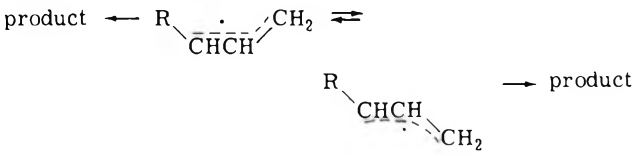
Table I
Composition of Products From Free-Radical Reduction of Allylic Chlorides by Triphenyltin Hydride at 80° in Cyclohexane

RCH=CHCH$_2$Cl	Concn,[a] M	Products, % Trans	Cis	1-Olefin
Trans (R = CH_3)	Neat	65	10	25
Trans (R = CH_3)	0.27	49	23	28
Trans (R = CH_3)	0.027	43	22	35
Trans (R = CH_3)	0.0135	41	23	36
88% cis, 12% trans (R = CH_3)	0.27	35	34	31
88% cis, 12% trans (R = CH_3)	0.027	41	25	34
88% cis, 12% trans (R = CH_3)	0.0135	41	24	35
Trans (R = C_2H_5)	0.027	55	17	28
Trans (R = C_2H_5)	0.0135	53	17	30
Cis (R = C_2H_5)	0.027	50	17	33
Cis (R = C_2H_5)	0.0135	53	18	29
Trans (R = t-C_4H_9)[b]	0.27	~90	0	~10
Cis (R = t-C_4H_9)[b]	0.27	~90	0	~10

[a] Concentrations of allylic chlorides and triphenyltin hydride were equivalent. [b] Purified n-octane was used as solvent for R = t-C_4H_9.

been generated by reduction of the isomeric chlorides with triphenyltin hydride under a variety of conditions[3] and by hydrogen abstraction with *tert*-butoxy radicals generated by decomposition of *tert*-butyl hypochlorite.

Under these conditions allylic radicals are generated and then consumed by attack on either triphenyltin hydride or *tert*-butyl hypochlorite. If the rate of interconversion of the



isomeric radicals can compete with product formation, then isomerization will be found.

Results and Discussion

Reactions of Allylic Chlorides with Triphenyltin Hydride. Several allylic chlorides were allowed to react in a 1:1 mole ratio with triphenyltin hydride. The reactions were carried out in purified cyclohexane at 80° using azobisisobutyronitrile (AIBN) as initiator. For chlorides of the general structure RCH=CHCH$_2$Cl, the product compositions shown in Table I were obtained. In all experiments the purity of the allylic chloride was checked immediately before use by glpc. In the cases of the butenyl and pentenyl chlorides, experiments were performed using an excess of allylic chloride. The purity of the remaining starting material was checked after the reaction was complete. This was done to determine whether isomerization of the starting material occurred under the reaction conditions. In no case where an excess of pure cis or trans allylic chloride was used did isomerized chloride appear in the excess after the reaction was complete. In the case of the 88% cis, 12% trans mixture of butenyl chlorides the composition was observed to change to 76% cis, 24% trans. This change in composition can, on the basis of competition experiments, be attributed to the faster reaction of the cis butenyl chloride. The faster reaction of the cis isomer is probably due to a combination of steric and concentration effects.

For the results to be meaningful in terms of allylic radical isomerization, it is necessary to show that the products as well as the starting materials do not isomerize under the conditions of the reaction. Kuivila and Sommer[4] have shown that triphenyltin hydride will bring about isomerization of *cis*-2-butene on irradiation of neat samples with a 250-W lamp for 24 hr. They suggested that triphenyltin radical adds to the double bond to give a secondary radical. Loss of triphenyltin radical can give either *cis*- or *trans*-2-butene. In principle the secondary radical should be able to react with more triphenyltin hydride to give the addition product. In fact no evidence for addition of triphenyltin hydride to a nonterminal nonactivated double bond has been found. Kuivila and Sommer did find such an addition product from trimethyltin hydride.

The results of Kuivila and Sommer show that isomerization of 2-butenes, etc., by triphenyltin hydride can occur under extreme conditions. The conditions used in this work were much milder than theirs; however, a control experiment was deemed necessary and prudent. Such an experiment was performed by MacGregor at the inception of this work.[2a,5] MacGregor allowed an excess of a mixture of 87% neryl chloride (*cis*-1-chloro-2,7-dimethyl-2,6-octadiene) and 13% geranyl chloride (*trans*-1-chloro-3,7-dimethyl-2,6-octadiene) to react with triphenyltin hydride. After completion of the reaction, the mixture was analyzed for starting material and products. There was no change in the ratio of starting materials and the product ratio showed 87% cis and 13% trans olefin. It was thus concluded that isomerization by addition of triphenyltin radical and subsequent loss of triphenyltin radical does not occur under the conditions of these reactions. Isomerization in solution reactions was found in the neryl and geranyl systems and this was attributed to isomerization of intermediate allylic radicals.[2a] The results of these experiments and those of Kuivila and Sommers have led to the following conclusions: (1) product isomerization is not caused by reaction of product with radicals present in the reaction mixture, and (2) product is not consumed by addition of triphenyltin hydride. In this regard yields of products were not determined in this work; however, indications in the literature indicate that they are extremely high.[6]

The results in Table I show that interconversion and equilibration of allylic radicals is competitive with hydrogen transfer when triphenyltin hydride is the chain transfer agent. By varying the concentration of reactants the rate of the product-forming step, *i.e.*, attack on hydride, and hence the lifetime of the radical is varied. At sufficiently low concentrations the product-forming step slowed to a point where equilibrium between cis and trans radicals was established. As expected, the size of the group R had a profound effect on the position of equilibrium. Thus the amount of cis olefin at equilibrium decreases from R = CH_3 to R = t-C_4H_9.

The results of this study are in agreement with those of others[1,2a-d] and they serve to amplify the observation that cis–trans isomerization can compete with product-forming chain transfer reactions.

The observation of interconverting allylic radicals depends on the successful competition of rotation about a partial double bond with any process that quenches the radical. Providing that the barrier to rotation is not overwhelming, factors which prolong the lifetime of the radical can be manipulated to maximize the observed rotation. Since allylic radicals participating in a radical chain process are destroyed in a bimolecular chain transfer step, it is expected that the amount of unimolecular rotation would increase with dilution. Expressions for the rate constants involved in these processes have been derived by Golden.[2e] These lead to values of $\sim 10^{3.2}$ sec^{-1} for the rate constant for rotation, k_r, and $10^{3.4}$ M^{-1} sec^{-1} for the rate constant for hydrogen abstraction, k_a, at 80°, when the chain trans-

fer agent is triphenyltin hydride. The ratio of the rate of rotation to abstraction (Λ) is therefore

$$\Lambda = \frac{k_r[R\cdot]}{k_a[R\cdot][Ph_3SnH]} = \frac{k_r}{k_a[Ph_3SnH]}$$

$$\Lambda = \frac{10^{3.2}}{10^{3.4}[Ph_3SnH]}$$

Golden's data indicate that rotation should compete with chain transfer at about 1 *M* triphenyltin hydride. Furthermore, each order of magnitude decrease in triphenyltin hydride concentration should lead to a corresponding order of magnitude increase in the amount of rotation over abstraction.

The results of this study qualitatively demonstrate this dilution effect. The amount of isomerization clearly is a function of concentration. Other workers[2c] have shown that butenyl radicals equilibrate readily in the gas phase where optimum conditions prevail.

Reaction of Triphenyltin Hydride with Allylic Chlorides of the Form $ClCH_2CH{=}CHZ$ where Z = CO_2CH_3, $CON(CH_3)_2$, and CN. The reactions of triphenyltin hydride with allylic chlorides in which the carbon–carbon double bond is conjugated with an electron-withdrawing group (Z) were studied in order to investigate the effect that such conjugation would have on the rate of isomerization of the allylic radicals. For each compound studied [Z = CO_2CH_3, $CON(CH_3)_2$, and CN] the same mixture of products was obtained regardless of concentration or geometry of the starting material. Isomerization of products and/or starting material would be expected to yield such results. Further investigation confirmed that isomerization of products occurs for Z = CO_2CH_3 and isomerization of starting material occurs for Z = CN. This was shown by performing the reactions in the presence of excess starting materials and in the presence of isomerically pure product followed by analysis of the reaction mixtures by glpc. Isomerization of starting material or products was not definitely shown for Z = $CON(CH_3)_2$; however, the absence of a concentration effect on product composition and the results from the other compounds strongly suggest that at least one of these isomerization processes is occurring.

The isomerization of starting materials and/or products probably occurs by reversible addition of triphenyltin radical to the carbon–carbon double bond. Such additions have been shown to ocur for conjugated alkenes,[1f] and are expected to be enhanced if the conjugating group is also electron withdrawing.[7]

***tert*-Butyl Hypochlorite Chlorination of Crotononitrile and Isocrotononitrile.** Allylic chlorination of crotononitrile (*trans*-2-butenonitrile) and isocrotonoitrile (*cis*-2-butenonitrile) by *tert*-butyl hypochlorite was performed at 25° employing irradiated AIBN as an initiator. Reactions were performed at varying concentrations in carbon tetrachloride. The data collected in Table II show a definite concentration dependence of the amounts of cis and trans monochlorination products. All reactions were performed in the presence of excess nitrile to prevent polychlorination. The excess nitrile was then analyzed after the reaction to determine whether isomerization had taken place during the reaction. In no case was isomerization observed. The stability of the products was investigated by irradiation of pure samples of the cis and trans chloronitriles in the presence of *tert*-butyl hypochlorite. Again, no isomerization was observed. The absence of the unconjugated isomeric 2-chloro-3-butenonitrile as a product in these reactions was noted and is consistent with the absence of the analogous bromo derivative in the radical bromination of crotononitrile and isocrotononitrile with *N*-bromosuccinimide.[8]

Table II
Allylic Chlorination of $CH_3CH{=}CHZ$ with *tert*-Butyl Hypochlorite at 25° in Carbon Tetrachloride

$CH_3CH{=}CHZ$	Concn of *t*-BuOCl, *M*	Products, % Trans	Products, % Cis
Trans (Z = CN)	Neat	80	20
Trans (Z = CN)	0.3	48	52
Trans (Z = CN)	0.03	46	54
Cis (Z = CN)	Neat	24	76
Cis (Z = CN)	0.3	35	65
Cis (Z = CN)	0.03	42	58
Trans (Z = CO_2CH_3)	Neat	95	5
Trans (Z = CO_2CH_3)	0.03	85	15
Cis (Z = CO_2CH_3)	Neat	37	63
Cis (Z = CO_2CH_3)	0.03	77	23

Miahle and Vessieri[9] have equilibrated the various isomeric chloronitriles under basic conditions in acetonitrile. They find at equilibrium that there are present 26% *cis*-4-chloro-2-butenonitrile, 55% *trans*-4-chloro-2-butenonitrile, 13% *cis*-4-chloro-3-butenonitrile, and 6% *trans*-4-chloro-3-butenonitrile. It is clear that the results obtained in this work are not due to formation of equilibrium mixtures of products by some isomerizing side reaction. It is not clear that the two 4-chloro-3-butenonitriles could be formed by free-radical isomerization of either *cis*- or *trans*-4-chloro-2-butenonitrile; however, free-radical isomerization of either of these would be expected to yield a mixture rich in *trans*-4-chloro-2-butenonitrile (*ca.* 2:1). The results of this work indicate a slight preference for the cis isomer under the most dilute conditions and thus it is safe to conclude that nonequilibrium mixtures of *cis*- and *trans*-4-chloro-2-butenonitrile were obtained.

Walling and Thaler[1] in their pioneering study found that most simple olefinic geometric isomers were chlorinated by *tert*-butyl hypochlorite with preservation of stereochemistry, the notable exception being *cis*-4,4-dimethyl-2-pentene . The conditions used in this work were very nearly the same as employed by Walling and Thaler. They employed neat reaction mixtures and 40° while the results for comparative purposes from this work are neat and 25°. The difference in their results and those obtained here can be attributed to at least two factors.

(1) The ability of the cyano group to accept the unpaired electron, contributor C, leads to less C-2–C-3 double-bond character in the hybrid relative to a nonsubstituted allylic

$$\cdot CH_2CH{=}CHC{\equiv}N \longleftrightarrow CH_2{=}CHCHCN \longleftrightarrow CH_2{=}CHCH{=}C{=}N\cdot$$

A B C

radical. Lowering of the double-bond character lowers the activation energy for rotation and thus increases its rate.

(2) Delocalization of the unpaired electron onto the nitrogen of the cyano group stabilizes the allylic radical relative to a nonsubstituted allylic radical. Such stabilization makes it less reactive toward the chain transfer reaction with *tert*-butyl hypochlorite, and therefore it has a longer lifetime than the unsubstituted allylic radicals. Such an extension of the lifetime allows rotation to compete more effectively with chain transfer.

***tert*-Butyl Hypochlorite Chlorination of Methyl Crotonate and Methyl Isocrotonate.** Allylic chlorination of methyl crotonate (methyl *trans*-2-butenoate) and methyl isocrotonate (methyl *cis*-2-butenoate) gave results (Table II) similar to those obtained in the previous case of

the nitriles. The stabilities of the starting material and products were demonstrated as described for the nitriles.

Miahle and Vessiere[9] have equilibrated the various ethyl 4-chlorobutenoates with the following results: ethyl *cis*-4-chloro-2-butenoate, 4%; ethyl *trans*-4-chloro-2-butenoate, 71%; ethyl *cis*-4-chloro-3-butenoate, 16%; and ethyl *trans*-4-chloro-3-butenoate, 9%. The results obtained in this study indicate a preference for ethyl *trans*-4-chloro-2-butenoate when the reactions were conducted in solution. Whether a near-equilibrium mixture between the two isomers has been achieved cannot be stated definitely. It is quite obvious that such is not the case in the neat reactions. It seems safe to conclude that isomerization occurs in the allylic radicals. The alternative, some kind of adventitious catalysis of isomerization, would have to be more effective in dilute solution than it is in the neat solutions. It should be pointed out that the results with the nitriles and esters do not exclude addition of *tert*-butoxy radicals to the unsaturated system. If the intermediate radicals are captured faster than a *tert*-butoxy radical can be lost, then isomerization would not be observed. Alternatively, although unlikely, addition and loss of the *tert*-butoxy radical before rotation could occur in the intermediate radical would not lead to isomerization. Whether addition occurs in these systems is an interesting question; however, it has not been investigated in this study.

It should be noted that isomerization in the allylic radicals derived from crotononitrile, methyl crotonate, and their geometric isomers has been suggested previously from work on the bromination of the isomeric nitriles with *N*-bromosuccinimide (NBS).[10] In that study it was noted that the same mixture of cis and trans bromonitriles resulted from either cis or trans reactant. An alternate explanation for this observation, however, is that bromine caused isomerization of reactants and/or products by reversible addition of bromine atoms. The geometric integrity of the reactants and products was not reported.

Experimental Section

General. All boiling points and melting points are uncorrected. Unless otherwise indicated all infrared spectra were recorded using a Perkin-Elmer 137 spectrophotometer. Pmr spectra were recorded with a Varian A-60 with tetramethylsilane as internal standard. Unless otherwise indicated all glpc was performed with a Perkin-Elmer 801 instrument equipped with glass injection parts and a flame ionization detector.

Preparation of Allylic Chlorides. All of the allylic chlorides listed in Table I were prepared from their corresponding allylic alcohols by the procedure of Young, Sharman, and Winstein.[11]

A 24.9-g (0.210 mol) quantity of thionyl chloride was added over 2 hr to a stirred, ice–salt water cooled solution of 0.210 mol of the allylic alcohol and 38.5 g (0.210 mol) of tri-*n*-butylamine in 300 ml of absolute anhydrous ether. After the addition was complete, the reaction mixture was stirred at room temperature for 45 min. A low-pressure flash distillation was subsequently performed, and that material which distilled at 0.5 mm without heating above room temperature was collected in a Dry Ice–acetone cooled receiver. After the bulk of the solvent had been removed from the distillate by fractionation through a 25-cm glass helices packed column, a few drops of water and 2 g of anhydrous potassium carbonate were added to the residue. The mixture was then stirred overnight with a magnetic stirring apparatus. After a low-pressure flash distillation from the solid, the product was fractionated. For each chloride the following data were collected: *trans*-1-chloro-2-butene, yield 32%, bp 84–86° (lit.[11] bp 84°), significant ir (neat) bands at 1670 and 975 cm^{-1}, pmr δ 5.3–6.1 (m, 2) 3.94 (d, 2, J = 6.0 Hz), 1.65 (d, 3, J = 4.5 Hz); *cis*-1-chloro-2-butene,[12] yield 53%, bp 84–85° (lit.[11] bp 84°), significant ir bands at 1660 and 750 cm^{-1}, pmr δ 5.2–5.9 (m, 2), 3.98 (d, 2, J = 6.3 Hz), 1.65 (d, 2, J = 5.0 Hz); *trans*-1-chloro-2-pentene, yield 68%, bp 108–110° (lit.[13] bp 103–110°), significant ir bands at 1663 and 969 cm^{-1}, pmr δ 5.3–6.1 (m, 2), 3.97 (d, 2, J = 6.0 Hz), 1.8–2.3 (m, 2), 0.98 (t, 3, J = 7.3 Hz); *cis*-1-chloro-2-pentene, yield 56%, bp 51–51.5° (110 mm), significant ir bands at 1650 and 760 cm^{-1}, pmr δ 5.3–5.9 (m, 2), 4.05 (d, 2, J = 6.5 Hz), 1.8–2.4 (m, 2), 0.98 (t, 3, J = 7.5 Hz); *trans*-1-chloro-4,4-dimethyl-2-pentene, yield 63%, bp 60.0–60.5° (50 mm) [lit.[14] bp 59.0–59.5° (50 mm)], significant ir bands at 1664 and 975 cm^{-1}, pmr δ 5.2–6.0 (m, 2), 3.98 (d, 2, J = 5.0 Hz), 1.02 (s, 9); *cis*-1-chloro-4,4-dimethyl-2-pentene (87% cis), yield 48%, bp 60–61° (52 mm) [lit.[14] bp 58–59° (50 mm)], significant ir bands at 1650 and 775 cm^{-1}, pmr δ 5.1–5.7 (m, 2), 4.18 (d, 2, J = 6.4 Hz), 1.13 (s, 9). The isomeric purity of the allylic chlorides was checked by glpc under the following conditions: *cis*- and *trans*-1-chloro-2-butene, 10 ft × 0.125 in. o.d. 10% β,β'-thiodipropionitrile on 80–100 mesh Chromosorb G at 25°; *cis*- and *trans*-1-chloro-2-pentene, 6 ft × 0.125 in. o.d. Carbowax K20M on 80–100 mesh Chromosorb W at 25°; *cis*- and *trans*-1-chloro-4,4-dimethyl-2-pentene, 10 ft × 0.125 in. o.d. 10% β,β'-thiodipropionitrile on 80–100 mesh Chromosorb G at 50°.

Preparation of *cis*- and *trans*-Crotyl Alcohol. *trans*-Crotyl alcohol was prepared by lithium aluminum hydride reduction of crotonaldehyde using standard techniques. *cis*-Crotyl alcohol was prepared by the semihydrogenation of 2-butyn-1-ol in methanol using Lindlar's catalyst.[15]

Preparation of *trans*-2-Penten-1-ol. *trans*-2-Penten-1-ol was prepared by reduction of 2-pentyn-1-ol with sodium in liquid ammonia using standard techniques, yield 58%, bp 68° (38 mm) [lit.[16] bp 42.2° (7 mm)].

Preparation of *cis*-2-Penten-1-ol. *cis*-2-Penten-1-ol was prepared by semihydrogenation of 2-pentyn-1-ol using Lindlar's catalyst, yield 62%, bp 60–62° (30 mm) [lit.[16] bp 41.2° (7 mm)].

Preparation of *trans*-4,4-Dimethyl-2-penten-1-ol. *trans*-4,4-Dimethyl-2-penten-1-ol was prepared by reduction of 4,4-dimethyl-2-pentyn-1-ol with sodium in liquid ammonia according to the procedure used in preparing trans-2-penten-1-ol, yield 53%, bp 66.5–67.0° (16 mm) [lit.[14] bp 71.2–72.7° (20 mm)].

Preparation of *cis*-4,4-Dimethyl-2-penten-1-ol. *cis*-4,4-Dimethyl-2-penten-1-ol was prepared by the semihydrogenation of 4,4-dimethyl-2-pentyn-1-ol using 5% palladium on barium sulfate as catalyst, yield 57%, bp 73–74° (20 mm) [lit.[14] bp 73.5–74.0° (20 mm)].

Preparation of Triphenyltin Hydride. Lithium aluminum hydride (1.56 g, 0.041 mol) was placed in a 500-ml flask filled with nitrogen. Dry absolute ether (150 ml) was added slowly, with stirring, and the flask was cooled to 0°. Triphenyltin chloride (38.5 g, 0.1 mol) was added to the slurry all at once, and the mixture was stirred at 0° for 15 min. The mixture was then allowed to warm to room temperature and stirring was continued for 4 hr. The mixture was cooled to 0° and 100 ml of water was added slowly with vigorous stirring. The resulting layers were separated. The upper layer was washed twice with water and dried over anhydrous magnesium sulfate. The ether was removed using a rotary evaporator, and the liquid residue was dissolved in 250 ml of methanol at 0°. Some material which did not dissolve was separated in a separatory funnel. The methanol solution was cooled to −78°, and the resulting precipitate of triphenyltin hydride was collected in a Buchner funnel. The recrystallization was repeated and the solid was dried in an evacuated disiccator. This gave approximately 30 g (85%) of triphenyltin hydride, mp 26–27°.

Reaction of *cis*- and *trans*-1-Chloro-2-butene and *cis*- and *trans*-1-Chloro-2-pentene with Triphenyltin Hydride (0.0135 *M*). A 1-l., three-necked flask was fitted with a thermometer that was long enough to reach into the solution, a gas inlet adapter, and a reflux condenser with a narrow spiral path for the vapor. The top of the condenser was fitted with a gas inlet adapter which was connected to two small Dry Ice–acetone cooled traps in series. Approximately 1 ml of ether was placed in the first small trap. (This was omitted in the case of *cis*- and *trans*-1-chloro-2-pentene.)The entire apparatus was then purged with dry, oxygen-free nitrogen for 30 min. Cyclohexane (500 ml), which had been purified by stirring overnight with sulfuric acid and then for several hours with a mixture of sulfuric and nitric acids, washed, dried, and distilled, was then added to the flask. The cyclohexane was deoxygenated by refluxing it in a stream of nitrogen for 30 min and then cooling under a positive pressure of nitrogen. To the solvent was then added, in order, and into an emerging stream of nitrogen, 2.37 g (0.0675 mol) of triphenyltin hydride, 0.0675 mol of the appropriate allylic chloride, and 0.1025 g of azobisisobutyronitrile (AIBN). The flask was quickly closed and heated to a very gentle reflux. The mixture was stirred magnetically for 4 hr with no nitrogen flowing through the apparatus except for short periods of time at irregular intervals. At the end of the 4-hr period the water in the condenser was turned off and drained out. The vapors of cyclohexane were allowed to climb up the condenser until a few drops spilled over into

the trap. At this point heating was stopped and the water in the condenser was turned on to force the vapors to recede. The combined material in the traps was analyzed by glpc as follows: butenes, 15 ft × 0.25 in. o.d. 20% 2,5-hexanedione on 35/80 Chromosorb P at 25°, He flow rate 30 ml/min, analysis was performed using an F and M 500 instrument; pentenes, 12 ft × 0.25 in. o.d. silver nitrate–ethylene glycol on 35/80 Chromosorb P at 25°, He flow rate 30 ml/min, analysis was performed using an F and M 500 instrument.

For experiments at other concentrations the same procedure was followed using an appropriate amount of solvent.

Reaction of *trans*-1-Chloro-2-butene with Triphenyltin Hydride (Neat). Triphenyltin hydride (2.37 g, 0.0067 mol) was placed in a 10-ml flask fitted with a reflux condenser and equipped with a 10/30 gas inlet joint which was connected *via* a stopcock to a nitrogen line. The top of the condenser was connected *via* a stopcock to a Dry Ice–acetone trap containing 1 ml of ether. *trans*-Crotyl chloride (0.608 g, 0.0067 mol) and AIBN (0.05 g) were added under nitrogen and the flask was placed in an oil bath held at 80°. Initiation was evidenced by a moderate evolution of nitrogen after a few minutes. The flask was allowed to remain in the bath for 4 hr, during which nitrogen was allowed to sweep through the apparatus at irregular intervals. After this the contents of the trap were analyzed by glpc as described above.

Reaction of *cis*- and *trans*-1-Chloro-4,4-dimethyl-2-pentene with Triphenyltin Hydride (0.27 *M*). Since the boiling points of the expected products are close to that of cyclohexane (bp 80°), it was found that isolation of the products was very difficult. A higher boiling solvent, *n*-octane (bp 125°), was therefore chosen as the reaction medium. The solvent was purified in a manner similar to that used for cyclohexane.

To a 100-ml, three-necked flask equipped as described above and purged with nitrogen was added 50 ml of purified *n*-octane. The *n*-octane was then deoxygenated by refluxing in a stream of nitrogen for 30 min and then cooling under a positive pressure of nitrogen. To the solvent was added in order, and into an emerging stream of nitrogen, 4.74 g (0.0135 mol) of triphenyltin hydride, 1.782 g of the appropriate chloride, and 0.164 g of AIBN. The mixture was stirred magnetically and heated by means of an oil bath so that the temperature of the contents was 80 ± 3° for 4 hr. At the end of this period the flask was cooled to room temperature, and any material in the condenser was rinsed into the flask with 5–10 ml of *n*-octane. The condenser was replaced by a narrow 30-cm Vigreux column fitted at the top with a short-path condenser leading to two Dry Ice–acetone cooled receivers in series. The flask was heated by means of a mantle to distil out the olefins. Distillation was continued until the temperature of the distillate rose above 120°. Examination of the second trap revealed no condensate and the distillate in the first trap was analyzed by glpc on a 50 ft × 0.125 in. o.d. column of SE-30 on Chromosorb at 25°. Analysis was performed using an F and M 700 instrument.

Preparation of Methyl γ-Chlorocrotonate. In a 250-ml, three-necked flask equipped with thermometer, gas inlet, condenser, and magnetic stirrer were placed 60 g (0.6 mol) of methyl crotonate and 21.6 g (0.2 mol) of *tert*-butyl hypochlorite. Dry oxygen-free nitrogen was bubbled through the methyl crotonate for 20 min before the hypochlorite was added. The flask was then irradiated for approximately 5.5 hr with a G.E. sun lamp. After this time the color of the *tert*-butyl hypochlorite was no longer evident. Fractionation of the mixture at reduced pressure on a spinning band column equipped with a Teflon band yielded the product: bp 65.5° (9 mm) [lit.[18] bp 80–81° (19 mm)]; significant ir bands at 980 and 1660 cm^{-1}; pmr δ 6.7–7.3 (m, 1), 6.15 (d, 1, J = 15.5 Hz), 4.25 (d, 2, J = 6.0 Hz), 3.75 (s, 3).

Preparation of Methyl γ-Chloroisocrotonate. 1,3-Dibromo-2-butanone was prepared according to a previously described method[19] and converted *via* Favorskii rearrangement to isocrotonic acid.[20] The crude isocrotonic acid was then esterified with dimethyl sulfate in the presence of base according to an established procedure.[21]

The methyl isocrotonate was then chlorinated with *tert*-butyl hypochlorite according to the procedure above for methyl crotonate. The product, methyl γ-chloroisocrotonate, was obtained in addition to significant amounts of other products. Fractional distillation on a spinning band column equipped with a Teflon band yielded the pure product: bp 59° (15 mm); significant ir bands at 825 and 1650 cm^{-1}; pmr δ 6.1–6.6 (m, 1), 5.9 (d, 1, J = 11.5 Hz), 4.7 (d, 2, J = 6.6 Hz), 3.7 (s, 3).

Preparation of γ-Chlorocrotononitrile and γ-Chloroisocrotononitrile. A commercial sample of crotononitrile which contained both the cis and trans isomers was fractionated on a spinning band column to give the pure cis isomer (bp 107°) and the pure trans isomer (bp 119°). Each isomer was then chlorinated in the same manner as methyl crotonate.

The resulting product, which contained both the cis and trans chloronitriles,[22] was fractionated to give the pure isomers: γ-chlorocrotononitrile, bp 71–72° (11 mm) [lit.[23] bp 71.0–71.2° (10 mm)], significant ir bands at 968, 1655, and 2250 cm^{-1}, pmr δ 6.6–7.1 (m, 1), 5.8 (d, 1, J = 16.0 Hz), 4.2 (d, 2, J = 5.7 Hz); γ-chloroisocrotononitrile, bp 54–56° (11 mm) [lit.[23] bp 55.1–55.3° (10 mm)], significant ir bands at 782, 1640, and 2250 cm^{-1}, pmr δ 6.4–6.9 (m, 1), 5.6 (d, 1, J = 11.0 Hz), 4.3 (d, 2, J = 7.8 Hz).

Preparation of γ-Chloro-*N*,*N*-dimethylcrotonamide. Methyl γ-bromocrotonate was prepared by allylic bromination of methyl crotonate using *N*-bromosuccinimide and hydrolyzed with aqueous sodium carbonate to give γ-hydroxycrotonic acid. Treatment of this with ethereal thionyl chloride afforded γ-chlorocrotonyl chloride, which was converted to γ-chloro-*N*,*N*-dimethylcroton amide by treatment with ethereal dimethylamine. The product showed the following properties: bp 84° (0.12 mm); significant ir bands at 975, 1610, and 1660 cm^{-1}; pmr δ 6.7 (m, 2), 4.3 (d, 2, J = 4.5 Hz), 3.0 (s, 6).

Reaction of Methyl γ-Chlorocrotonate and Methyl γ-Chloroisocrotonate with Triphenyltin Hydride at 80°. A. 0.027 *M* Solution. Cyclohexane (250 ml) was deoxygenated by refluxing in a stream of nitrogen for 30 min. The appropriate chloroester (0.905 g) was then added followed by 2.37 g of triphenyltin hydride and 0.1025 g of AIBN. The mixture was gently heated under reflux under nitrogen for 4 hr and then cooled to room temperature. Samples were taken from this solution and submitted directly to analysis by glpc on a 10 ft × 0.125 in. o.d. column of 10% β,β′-thiodipropionitrile on 80–100 mesh Chromosorb G at 60°.

B. Neat. Triphenyltin hydride (1.185 g), the appropriate chloro ester (0.453 g), and AIBN were mixed in a 10-ml flask fitted with a reflux condenser. The flask was flushed with nitrogen and then placed in a constant-temperature bath held at 80° for 4 hr. The top of the condenser was open to a nitrogen-filled balloon. After the 4-hr reaction time the flask was allowed to cool to room temperature, whereupon a solid mass formed. Cyclohexane (6–7 ml) was then added and the mixture was stirred magnetically until fine particles of solid were obtained. The supernatant liquid was then analyzed for products by glpc as described above.

Reaction of Methyl γ-Chlorocrotonate with Triphenyltin Hydride at 0°. A. 0.27 *M* Solution. Cyclohexane (12.5 ml), 1.185 g of triphenyltin hydride, 0.905 g of methyl γ-chlorocrotonate, and 0.082 g of AIBN were mixed in a nitrogen atmosphere in a 25-ml flask. A calcium chloride drying tube was attached and the flask was placed in a clear unsilvered Dewar flask which contained ice and water at 0°. The solution was irradiated with a G.E. sun lamp for 3 hr and then analyzed directly by glpc as described above.

B. Neat. Triphenyltin hydride (1.185 g), methyl γ-chlorocrotonate (0.500 g), and 0.042 g of AIBN were mixed under a nitrogen atmosphere in a pressure tube. The tube was closed and placed in a clear unsilvered Dewar flask which contained ice and water at 0°. The mixture was irradiated with a G.E. sun lamp for 3 hr. After this period the tube was opened and 6 ml of cyclohexane was added. A small magnetic stirring bar was added and the mixture was stirred until fine particles of solid were obtained. The supernatant liquid was then analyzed for products by glpc as described above.

Reaction of γ-Chlorocrotononitrile and γ-Chloroisocrotononitrile with Triphenyltin Hydride at 80°. γ-Chlorocrotononitrile and γ-chloroisocrotononitrile were allowed to react with triphenyltin hydride both neat and in solution in a manner analogous to that for methyl γ-chlorocrotonate. Glpc analysis of the products was performed on a 6 ft × 0.125 in. o.d. column of Carbowax K20M on 80–100 mesh Chromosorb W at 40°.

Reaction of γ-Chloro-*N*,*N*-dimethylcrotonamide with Triphenyltin Hydride at 80°. γ-Chloro-*N*,*N*-dimethylcrotonamide was allowed to react with triphenyltin hydride both neat and in solution in a manner analogous to that for methyl γ-chlorocrotonate. Glpc analysis of the products was performed on a 6 ft × 0.125 in. o.d. column of Carbowax K20M on 80–100 mesh Chromosorb W at 120°.

Reaction of *tert*-Butyl Hypochlorite with Crotononitrile and Isocrotononitrile at 25°. A. Solution (0.03 *M* in *tert*-Butyl Hypochlorite). A 250-ml Pyrex photolysis apparatus which was equipped with a water-cooled cold finger was filled with 250 ml of dry carbon tetrachloride. *tert*-Butyl hypochlorite (0.81 g, 0.0075 mol), crotononitrile or isocrotononitrile (1.68 g, 0.025 mol), and a

small amount of AIBN were dissolved in the solvent under a nitrogen atmosphere. The apparatus was closed and irradiated with a G.E. sun lamp for up to 22.5 hr. Samples of the solution were then analyzed by glpc on a 6 × 0.125 in. o.d. column of Carbowax K20M on 80–100 mesh Chromosorb W at 95°.

For experiments at 0.3 *M* the same amounts of reactants were dissolved in 25 ml of solvent in a smaller apparatus.

B. Neat. Crotononitrile or isocrotononitrile (3.35 g, 0.05 mol) was placed in a Pyrex photolysis apparatus of appropriate size so that the cold finger reached into the liquid. To this was added 1.84 g (0.017 mol) of *tert*-butyl hypochlorite and a small amount of AIBN. The mixture was irradiated for up to 21 hr while being stirred magnetically and cooled by the cold finger. Samples of the mixture were then analyzed by glpc as described above.

Reaction of *tert*-Butyl Hypochlorite with Methyl Crotonate and Methyl Isocrotonate at 25°. Methyl crotonate and methyl isocrotonate were allowed to react with *tert*-butyl hypochlorite both neat and in solution in a manner analogous to that used for crotononitrile and isocrotononitrile. Glpc analysis of the products was performed on a 6 ft × 0.125 in. o.d. column of Carbowax K20M on 80–100 mesh Chromosorb W at 110°.

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Registry No.—*trans*-1-Chloro-2-butene, 4894-61-5; *cis*-1-chloro-2-butene, 4628-21-1; *trans*-1-chloro-2-pentene, 6261-25-2; *cis*-1-chloro-2-pentene, 6261-19-4; *trans*-1-chloro-4,4-dimethyl-2-pentene, 19146-05-5; *cis*-1-chloro-4,4-dimethyl-2-pentene, 19146-06-6; triphenyltin hydride, 892-20-6; methyl γ-chlorocrotonate, 999-54-2; methyl crotonate, 623-43-8; *tert*-butyl hypochlorite, 507-40-4; methyl γ-chloroisocrotonate, 999-53-1; methyl isocrotonate, 4358-59-2; γ-chlorocrotononitrile, 7659-46-3; γ-chloroisocrotononitrile, 20592-22-7; *cis*-crotononitrile, 1190-76-7; *trans*-crotononitrile, 627-26-9; γ-chloro-*N,N*-dimethylcrotonamide, 51830-58-1; methyl γ-bromocrotonate, 6000-00-6.

References and Notes

(1) C. Walling and W. A. Thaler, *J. Amer. Chem. Soc.*, **83**, 3877 (1961).
(2) (a) D. B. Denney, R. M. Hoyte, and P. T. MacGregor, *Chem. Commun.*, 1241 (1967); (b) W. A. Thaler, A. A. Oswald, and B. E. Hudson, Jr., *J. Amer. Chem. Soc.*, **87**, 311 (1965); (c) R. J. Crawford, J. Hamelin, and B. Strehlke, *ibid.*, **93**, 3810 (1971); (d) D. C. Montague, *Int. J. Chem. Kinet.*, **5**, 513 (1973); (e) D. M. Golden, *ibid.*, **1**, 127 (1969); (f) W. P. Neumann, H. J. Albert, W. Kaiser, and H. P. Ritter, *Chem. Ber.*, **103**, 1372 (1970); (g) J. K. Kochi and P. J. Krusic, *J. Amer. Chem. Soc.*, **90**, 7157 (1968).
(3) The mechanism of this reaction is well established. See L. W. Menapace and H. G. Kuivila, *J. Amer. Chem. Soc.*, **86**, 3047 (1964).
(4) (a) H. G. Kuivila and R. Sommers, *J. Amer. Chem. Soc.*, **89**, 5616 (1967); (b) R. Sommers and H. G. Kuivila, *J. Org. Chem.*, **33**, 802 (1968).
(5) P. MacGregor, unpublished results.
(6) H. G. Kuivila, *Advan. Organometal. Chem.*, **1**, 47 (1964).
(7) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, p 121.
(8) P. Couvrer and A. Bruylants, *Bull. Soc. Chim. Belg.*, **61**, 253 (1952).
(9) Y. Miahle and R. Vessiere, *Bull. Soc. Chim. Fr.*, 3687 (1969).
(10) (a) C. Walling, A. L. Rieger, and D. D. Tanner, *J. Amer. Chem. Soc.*, **85**, 3129 (1963); (b) G. A. Russell and K. M. Desmond, *ibid.*, **85**, 3139 (1963); (c) R. E. Pearson and J. C. Martin, *ibid.*, **85**, 3142 (1963).
(11) W. G. Young, S. H. Sharman, and S. Winstein, *J. Amer. Chem. Soc.*, **82**, 1376 (1960).
(12) The data for this compound were obtained from the purest sample prepared, which was estimated to 96% cis.
(13) W. M. Lauer and C. S. Benton, *J. Org. Chem.*, **24**, 804 (1959).
(14) L. F. Hatch, H. D. Weiss, and T. P. Li, *J. Org. Chem.*, **26**, 61 (1961).
(15) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).
(16) G. Smets, *Acad. Roy. Belg., Cl. Sci. Mem.*, **21**, 3 (1947).
(17) P. D. Bartlett and L. J. Rosen, *J. Amer. Chem. Soc.*, **64**, 544 (1942).
(18) R. Rembaud and M. Brini-Fritz, *Bull. Soc. Chim. Fr.*, 1426 (1958).
(19) C. Rappe, *Ark. Kemi*, **21**, 503 (1964).
(20) C. Rappe, *Acta Chem. Scand.*, **17**, 2766 (1963).
(21) R. H. Stodola, *J. Org. Chem.*, **29**, 2490 (1964).
(22) The observation of a mixture of *cis*- and *trans*-chloronitrile as product from isomerically pure starting material prompted our further investigation of this reaction.
(23) P. van der Straeten and A. Bruylants, *Bull. Soc. Chim. Belg.*, **66**, 345 (1957).

Three-Electron Oxidations. VII. The Pre-Steady-State Phase of the Chromic Acid Oxidation of Oxalic Acid[1,2]

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The study of the initial rates of formation of chromium(III) in the chromic acid oxidation of oxalic acid shows the absence of an induction period; this result is incompatible with any mechanism following the general scheme Cr(VI) → Cr(V) → Cr(III), according to which all chromium would pass through the chromium(V) state. In agreement with the previously proposed three-electron oxidation mechanism, the initial rate of formation of chromium(III) is never lower than one-half of the rate of reduction of chromium(VI). The initial rates of formation of chromium(III) as well as the maximum concentration of chromium(V) formed depend on both total chromic acid concentration and on the acidity. The results show that the $\cdot CO_2H$ radicals react predominantly with chromium(VI) to yield CO_2 and chromium(V) at high chromic acid concentrations and acidities, but undergo extensive bimolecular dimerization at low chromic acid concentrations and acidities.

In a recent paper from this laboratory[3] it was shown that during the chromic acid oxidation of oxalic acid, a long-lived chromium(V) intermediate is formed in rather large concentrations. The reaction can be described as having two distinct phases. The initial phase is characterized by a decrease in the concentration of chromium(VI) and a rapid buildup of the chromium(V) intermediate. During the second phase of the reaction, after the concentration of chromium(V) has reached its maximum, the concentrations of both chromium(V) and chromium(VI) decrease approximately in parallel, and a quasi-steady-state concentration of chromium(V) with respect to the concentration of chromium(VI) is established and maintained.

The purpose of this study was to obtain answers to two basic questions concerning the mechanism of reaction: (1) does all, or only a fraction, of the total chromium pass through the chromium(V) stage; (2) do all, or only a fraction of the free radicals undergo further oxidation?

The oxidation of oxalic acid takes place by two routes, namely, through a 1:1 and a 2:1 oxalic acid–chromic acid complex.[4] The mechanism for the second route, which (except for very low oxalic acid concentrations) is by far the

Scheme I

$$2(CO_2H)_2 + Cr(VI) \xrightarrow{k_1} 3CO_2 + \cdot CO_2H + Cr(III) \quad (1)$$

$$\cdot CO_2H + Cr(VI) \xrightarrow{k_2} CO_2 + Cr(V) \quad (2)$$

$$(CO_2H)_2 + Cr(V) \xrightarrow{k_3} 2CO_2 + Cr(III) \quad (3)$$

$$2\cdot CO_2H \xrightarrow{k_4} (CO_2H)_2 \quad (4)$$

more important one, is given in Scheme I.[4a] This mechanism requires that at least one-half or a greater fraction (depending on the importance of reaction 4 relative to reaction 2) of chromium(VI) is reduced directly to chromium(III) without passing through a chromium(V) stage.[5]

Mechanisms in which chromium(VI) is either reduced stepwise in a series of one-electron reductions or in which chromium(IV) formed in a two-electron reduction is reoxidized to chromium(V) lead to the same general scheme (Scheme II) according to which all chromium passes *through the chromium(V) stage. If a reaction during which* chromium(V) accumulates in appreciable amounts follows Scheme II, the initial rate of chromium(III) formation should be zero at time $t = 0$; *i.e.*, an induction period for the formation of chromium(III) should be observed.

Scheme II

$$Cr(VI) \longrightarrow Cr(V) \longrightarrow Cr(III)$$

The determination of the initial rate of formation of chromium(III) should thus permit us to distinguish between the mechanisms of Schemes I and II and to assess the importance of the bimolecular free radical process (reaction 4) in the mechanism of Scheme I.

Results and Discussion

The rate of formation of chromium(III) can be followed spectrophotometrically at about 600 nm, where the absorptions of both chromium(VI) and chromium(V) are negligible.[3] *On the other hand, there is no region of the spectrum* in which the concentration of either chromium(VI) or of chromium(V) could be determined without interference from the other species. The concentration of chromium(VI) and its rate of change therefore cannot be determined directly from spectrophotometric measurements.

During the pre-steady-state phase of the reaction the concentration of chromium(V) increases rapidly; consequently, the rates of formation of chromium(III) and of reduction of chromium(VI) may differ considerably. On the other hand, the concentration of chromium(V) changes only slowly during the second phase and the rates of formation of chromium(III) and of the reduction of chromium(VI) are therefore very approximately equal. Thus, if the reaction is carried out under pseudo-first-order conditions, the rate constant of chromium(III) formation in the second phase of the reaction thus provides a satisfactory measure of the rate of reduction of chromium(VI) throughout the reaction. Hence, the ratio of the first-order rate constants for the chromium(III) formation in the initial and in the second phase of the reaction (k_i/k_s) can be used as an adequate measure of the rate of chromium(III) formation relative to chromium(VI) reduction at the beginning of the reaction.

Figure 1 shows typical examples of plots of the absorption at 600 nm *vs.* time used in this study. The results clearly show that the rate of chromium(III) formation indeed changes during the course of the reaction, with the initial rate being considerably slower than the rate in the second phase. In both regions reasonably good straight lines for log (absorbance) *vs.* time plots are obtained, indicating that the rate of chromium(III) formation is first order in the overall concentration of chromium(VI). Table I summarizes the values for k_i (pseudo-first-order rate constants for the initial part of the reaction), k_s (rate constants for the pseudo-steady-state phase), and the ratio k_i/k_s.

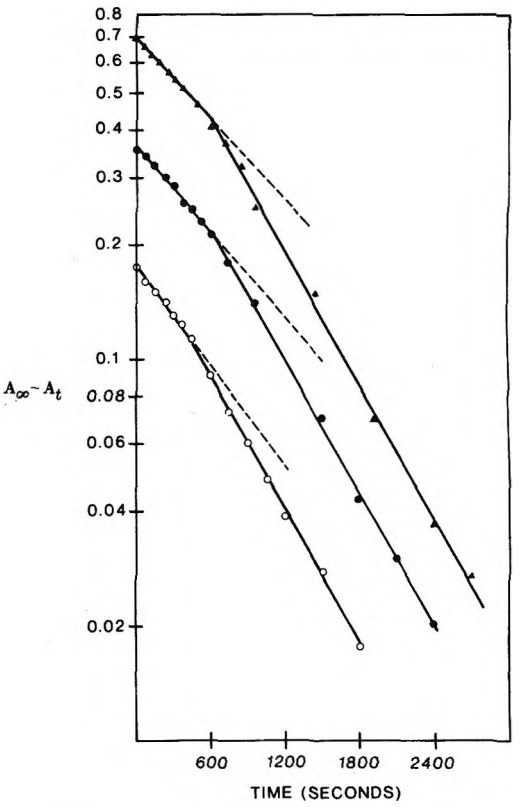

Figure 1. Pseudo-first-order rate plots for the formation of chromium(III) at 25°: oxalic acid 0.115 *M*; perchloric acid 0.388 *M*. Initial concentrations of Cr(VI): ○, 8.12×10^{-4} *M*; □, 2.03×10^{-3} *M*; △, 4.06×10^{-3} *M*.

The results show that the value of k_i/k_s depends both on the concentration of chromic acid and on acidity and varies between 0.50 and 0.85. Under no conditions has a genuine induction period for the formation of chromium(III) been observed. *The results thus are incompatible with any mechanism which would require that all chromium passes through a chromium(V) stage (Scheme II).*

Table I
Rates of Formation of Chromium(III) at 25°

A. Oxalic Acid[a] 0.115 *M*; Perchloric Acid 0.388 *M*

Cr(VI), 10^3 *M*	$10^3 k_i$, sec^{-1}	$10^3 k_s$, sec^{-1}	k_i/k_s
0.812	0.995	1.24	0.80
2.03	0.845	1.24	0.68
4.06	0.782	1.24	0.63
8.12	0.746	1.22	0.61
22.7	0.625	1.22	0.51
40.6	0.621	1.24	0.52

B. Chromium(VI) 4.06×10^{-3} *M*; Oxalic Acid[a] 0.115 *M*

$HClO_4$, 10^2 *M*	$10^4 k_i$, sec^{-1}	$10^4 k_s$, sec^{-1}	k_i/k_s
0.97	0.302	0.354	0.85
2.4	1.23	1.48	0.83
4.8	2.72	3.62	0.75
9.7	4.98	7.02	0.71
24.2	7.27	11.2	0.68
38.8	7.87	12.4	0.63
48.4	7.76	13.0	0.60
96.9	6.56	11.7	0.56

[a] Total (not corrected for dissociation).

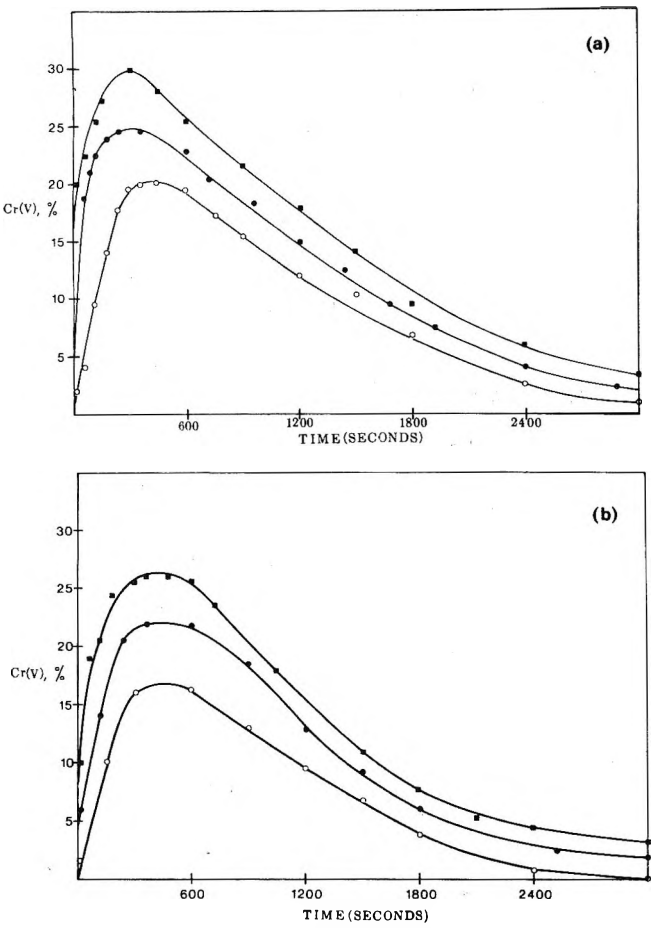

Figure 2. Formation of chromium(V). Initial concentration of Cr(VI): ○, 8.12 × 10^{-4} *M*; ●, 4.06 × 10^{-3} *M*; ■, 8.12 × 10^{-3} *M*. $HClO_4$: a, 0.388 *M*; b, 0.242 *M*.

The observation that the values of k_i/k_s approach the value of 0.50 and depend on reaction conditions is in full agreement with the proposed three-electron mechanism (Scheme I). The results further show that bimolecular[6] *free-radical dimerization does become important at low chromic acid concentrations and low acidities.*

The dependence on acidity is easily understood in terms of the mechanism given in Scheme I, if one assumes that the oxidation of free radicals (reaction 3) is acid catalyzed, as are almost all known chromium(VI) oxidations, and that the dimerization reaction (reaction 4) is not.

The dependence on the concentration of chromic acid is less obvious, but it can be shown at least semiquantitatively that the observed trend is in agreement with the mechanism of Scheme I.

The two competing reactions which will determine the ratio of the initial rate of chromium(III) formation relative to chromium(VI) reduction are the free-radical dimerization (reaction 4) and free-radical oxidation (reaction 2). The relative rates of the two reactions are given in eq 5.

$$\frac{v_4}{v_2} = \frac{k_4[\cdot CO_2H]}{k_2[\mathrm{Cr(VI)}]} \tag{5}$$

Using a steady-state approximation, it can be shown that the concentration of the free-radical intermediate is as shown in eq 6. Dimerization of free radicals (reaction 4)

$$[\cdot CO_2H] = \frac{k_2[\mathrm{Cr(VI)}]}{2k_4}\left(\sqrt{1 + \frac{4k_1k_4}{k_2^2[\mathrm{Cr(VI)}]}} - 1\right) \tag{6}$$

$$\text{Consequently, } \frac{v_4}{v_2} = \frac{1}{2}\left(\sqrt{1 + \frac{4k_1k_4}{k_2^2[\mathrm{Cr(VI)}]}} - 1\right) \tag{7}$$

should become less important relative to their oxidation (reaction 2) as the concentration of chromic acid increases. As more dimerization results in higher values of k_i/k_s, these values should decrease with increasing concentration of chromic acid; this is indeed observed.

According to the mechanism of Scheme I chromium(V) is formed from chromium(VI) and $\cdot CO_2H$. As an increasing fraction of these radicals react by dimerization (reaction 4), the amount of chromium(V) should be reduced. Thus the same factors which increase the values of k_i/k_s should also reduce the amount of chromium(V) formed. The determination of the effect of the concentration of chromic acid and of acidity on the relative amount of chromium(V), formed during the reaction, thus provides an independent check of the above conclusions based on rate studies.

Figure 2 and Table II show that the yield of chromium(V) does indeed depend both on the initial concentration of chromic acid and on the acidity of the solution. The highest concentration of chromium(V) if formed at the highest chromic acid and perchloric acid concentrations, *i.e.*, under conditions which minimize the importance of free-radical dimerization. The lowest concentration of chromium(V) was observed at low chromic acid concentration and low acidity. These results are in full agreement with those of the kinetic study.

Table II
Effect of Reaction Conditions on Maximum Amount of Chromium(V) Formed in the Chromic Acid Oxidation of Oxalic Acid at 25°. Oxalic Acid 0.115 *M*[a]

Cr(VI), 10^3 *M*[b]	$HClO_4$, *M*	$[Cr(V)]_{max}$, 10^3 *M*	$[Cr(V)]_{max}$, %
0.812	0.242	0.132	16.3
	0.388	0.162	19.9
4.06	0.242	0.879	21.7
	0.388	1.00	24.6
8.12	0.242	2.10	25.9
	0.388	2.44	30.0

[a] Total. [b] Initial concentration of chromium(VI).

Experimental Section

Materials. Oxalic acid (Mallinckrodt AR) and sodium dichromate (J. T. Baker, Reagent) were used without further purification. Perchloric acid solutions were prepared from 60% perchloric acid (B & A Reagent).

Kinetic Measurements. The reactions were followed spectrophotometrically using Cary 14 and Cary 15 spectrophotometers equipped with thermostated cell holders. The rates were determined by following the increase in the absorbance of chromium(III) at 600 nm.

Chromium(V). The oxidation of oxalic acid by chromic acid was followed spectrophotometrically at 25° by scanning between 410 and 600 nm at time intervals. For each measurement the concentration of chromium(V) was determined from eq 8, following

$$[\mathrm{Cr(V)}] = \frac{1}{\epsilon_5}(A_{410} - \epsilon_3[\mathrm{Cr(III)}] - \epsilon_6[\mathrm{Cr(VI)}]) \tag{8}$$

essentially Srinivasan's[3] procedure. The concentration of Cr(III) was determined from measurements at 600 nm where Cr(III) is the only absorbing species. The concentration of Cr(VI) was calculated from the expression $[Cr(VI)] = [Cr(VI)]_0e^{-kt}$, where k is the pseudo-first-order rate constant for the reduction of Cr(VI) and was determined separately from measurements at 350 nm. Previously reported values[3] for the extinction coefficients of the chromium species at these wavelengths were used.

Registry No.—Oxalic acid, 144-62-7; chromic acid, 13530-68-2.

References and Notes

(1) Part VI: F. Hasan and J. Roček, *J. Amer. Chem. Soc.*, **96**, 534 (1974).
(2) This investigation was supported by the National Science Foundation.
(3) V. Srinivasan and J. Roček, *J. Amer. Chem. Soc.*, **96**, 127 (1974).
(4) (a) F. Hasan and J. Roček, *J. Amer. Chem. Soc.*, **94**, 9073 (1972); (b) F. Hasan and J. Roček, *Tetrahedron*, **30**, 21 (1974).
(5) In the limiting case, when $k_4[\cdot CO_2H] \gg k_2[CR(VI)]$, all chromium(VI) should be reduced directly to chromium(III) and, consequently, no chromium(V) formation should be observed.
(6) A bimolecular free radical disproportionation reaction $2\cdot CO_2H \rightarrow CO_2 + HCO_2H$ would fit the results of the kinetic study equally well; however, we were unable to detect any formic acid among the reaction products.

Conformational Analysis. CV. The Syn-Diaxial Methyl/Carboethoxy Interaction[1,2]

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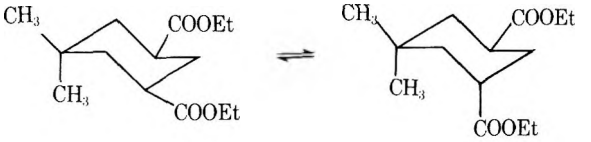
The cis and trans isomers of diethyl 5,5-dimethyl-1,3-cyclohexanedicarboxylate were prepared and equilibrated in alcohol in the presence of ethoxide ion at temperatures ranging from 23 to 102°. For the reaction trans $\rightleftharpoons$ cis, the following thermodynamic parameters were determined: $\Delta G° = -2.44$ kcal/mol, $\Delta H° = -2.98 \pm 0.30$ kcal/mol, and $\Delta S° = -1.84 \pm 0.60$ eu. These numbers permit us to assign the syn-diaxial CH_3/COOEt interaction energy as 3.2 kcal/mol.

Because of their simplicity, cyclohexane rings have been an important foundation in conformational studies.[3] The conformational energies of all of the common substituents, and many less common ones, on a cycohexane ring are now pretty well known.[4] Surprisingly, data on systems which contain two syn-axial groups are very sparse. The systems for which data are available seem to be limited to OH/OH ($\Delta G°$ = 1.9 kcal/mol[5]), OAc/OAc ($\Delta G°$ = 2.0 kcal/mol[6]), CH_3/OH ($\Delta G°$ = 1.9–2.4 kcal/mol[7]), CH_3/CH_3 ($\Delta G°$ = 3.7 kcal/mol[8]), Cl/Cl ($\Delta G°$ = 5.5 kcal/mol[9]), CH_3/Br ($\Delta G°$ = 2.2 kcal/mol[10]), CH_3/F ($\Delta G°$ = 0.37 kcal/mol[11]), and CH_3/X ($\Delta G° > 1.0$ kcal/mol for X = Cl, Br, and I[11]). The present paper is concerned with a determination of the value for the syn-diaxial CH_3/COOEt interaction.

To measure the interaction in question, the equilibrium between the cis and trans isomers of diethyl 5,5-dimethyl-1,3-cyclohexanedicarboxylate (**1**) was studied in alcoholic solution in the presence of base at temperatures ranging from 23 to 102°.



1e **1a**

One might question whether or not this equilibrium would measure simply a steric effect. After all, the carboethoxyl groups are polar groups, and they change their relative distance and orientation in the epimerization. The question is not easy to answer theoretically, because the charge distribution in a carboethoxyl group is complicated, and various conformational isomers are possible, which differ by rotations about the ester groups. However, it is known experimentally that the enthalpy of isomerization of diethyl 1,3-cyclohexanedicarboxylate[12] does not differ significantly from that of ethyl carboxylate or from those of the ethyl 4-alkylcarboxylates.[13]

Results and Discussion

Synthesis. Compound **1** presented some unusual synthetic problems, since the axial methyl group obviated many of the usual condensation routes to this type of compound. The synthetic sequence used is shown. The synthesis of **6** by this method has been previously reported[14] and will not be discussed here. Treatment of **6** with base, followed by acidification, rapidly effects a decarboxylative elimination to yield the unsaturated tricarboxylic acid **7**. An examination of Dreiding models points out the great steric crowding which exists in **6**, and the rapid decarboxylative elimination of the tetraacid of **6** probably reflects the large decrease in steric repulsion in the product. An interesting aspect of the unsaturated triacid **7** is its inability to undergo facile hydrogenation at

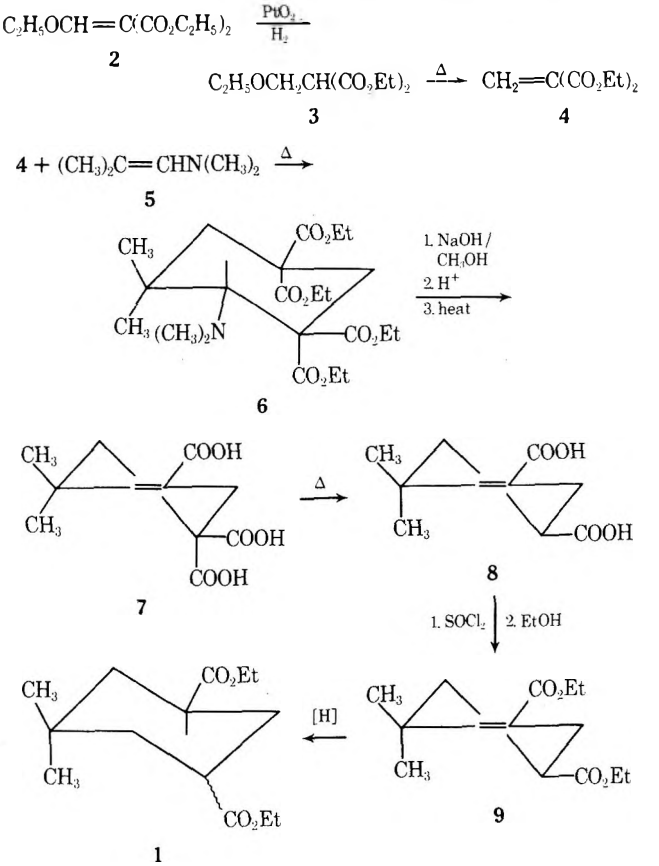


Table I
Equilibration Data for *trans*- ⇌ *cis*-Diethyl 5,5-dimethyl-1,3-cyclohexanedicarboxylate

Temp, °C	% cis[a]	σ[b]	−ΔG°, kcal/mol[c]
23 ± 2	98.59 (7)	0.26	2.50
52	97.64 (3)	0.27	2.40
56	97.15 (7)	0.21	2.31
70	96.49 (3)	0.35	2.27
76	96.57 (4)	0.32	2.32
102	95.29 (4)	0.32	2.24
23.2	98.57 (3)	0.32	2.49
56.5	97.55 (8)	0.29	2.41
78.5	96.68 (7)	0.08	2.36
100	95.74 (7)	0.37	2.31

[a] Number of independent runs in parentheses. [b] Standard deviation of % cis data. [c] Equilibrium approached from the trans side for the first six entries in Table I, and from the cis side for the remaining four.

room temperature (as the triester) despite the fact that the corresponding unsaturated diester **9** was readily reduced to **1** under these conditions. Apparently in the case of the unsaturated triester there is considerable steric inhibition of hydrogenation.

Separation of the isomers (**1a** and **1e**) was accomplished by gas chromatography. Each isomer so isolated was at least 99.4% pure. Assignment of the structures of the isomers was based on nmr analysis of the pure sample collected from gc, or by fractional distillation through a spinning band column.

Conformational Study. The equilibration of *cis* ⇌ *trans*-diethyl 5,5-dimethyl-1,3-cyclohexanedicarboxylate (**1**) was carried out from both sides of the equilibrium point under basic conditions at various temperatures. The results are summarized in Table I. Utilizing the usual linear relationship between ln K, $\Delta H°$, and $\Delta S°$, the thermodynamic parameters reproduced in Table II were generated.[15] The calculated entropy of −2.78 eu for the trans ⇌ cis equilibration which was obtained including the data at 23° suggests that in the trans conformation, the molecule exists to some extent in the flexible or boat form. It seems unreasonable, however, that the syn-diaxial CH_3/CO_2Et interaction is large enough to force the molecule to exist in the boat form, especially since neither the experimental nor the theoretical evidence suggests that any appreciable amount of boat is present in *trans*-1,1,3,5-tetramethylcyclohexane, in which there is an even larger syn-diaxial interaction.[8] Consequently, the values calculated for $\Delta H°$ and $\Delta S°$ using all the data seem too large. If one considers that the room temperature data represent an amount of trans isomer of only 1.4%, an amount not easily measurable by our method, then more accurate thermodynamic parameters can probably be obtained by neglecting the room temperature data as inaccurate. Ignoring this point, a least-squares fitting of the remaining data gives 2.98 kcal/mol and 1.84 eu, respectively, for the enthalpy and entropy of the cis ⇌ trans reaction.

The value of 1.84 eu calculated for the entropy of the cis ⇌ trans equilibrium is slightly higher than (but within the experimental error of) the value of 1.38 eu predicted on the basis of a *dl* pair in the trans isomer. This may be attributable to experimental error or may be characteristic of the equilibrium. A possible explanation for the higher entropy in the trans isomer would be if the number of rotational conformers of the ester group is restricted in the cis isomer with respect to the trans. Normally, the entropy of an equatorial group might be expected to be higher than the entropy of an axial group, since the rotation of the axial group is hindered by the syn-diaxial interaction.

Table II
Calculated Thermodynamic Parameters for the Trans ⇌ Cis Equilibration

ΔG°, kcal/mol	ΔH°, kcal/mol	ΔS°, cal/deg mol
−2.50[a]	−3.31 (±0.3)[a,c]	−2.78 (±0.8)[a,c]
−2.44[b]	−2.98 (±0.3)[b,c]	−1.84 (±0.6)[b,c]

[a] Including room temperature data. [b] Excluding room temperature data. [c] Standard statistical methods were used.[16]

However, in the case of the cis diester, the ester groups will attempt to align themselves so as to minimize dipole–dipole interactions and consequently the rotation of the ester groups in the cis isomer will be to some extent interdependent. If this argument is correct, then the entropy of the cis ⇌ trans equilibrium will be larger than 1.38 eu, the value expected on the basis of a *dl* pair in the trans isomer. To the best of our knowledge, only one other equilibration has been attempted using 1,3-diesters, *i.e.*, the basic equilibration of diethyl 1,3-cyclohexanedicarboxylate.[12] In that case the entropy change was *assumed* to be just the entropy of mixing of the *dl* pair in the trans isomer.

Using the enthalpy calculated for the basic equilibration of 1,3-dicarboethoxy-5,5-dimethylcyclohexane (**1**), the conformational enthalpy of the syn-diaxial methyl/carboethoxy interaction can be readily calculated. The enthalpy calculated for the trans ⇌ cis equilibrium is in reality the sum of the syn-diaxial interactions in the trans isomer less those in the cis isomer. Assuming additivity of interactions, this relationship can be expressed as follows.

$$\Delta H°_{equil} = -H°_{trans} + H°_{cis}$$

$$\Delta H°_{equil} = -(CH_3/CO_2Et + CH_3/H + CO_2Et/H) + (2\,CH_3/H)$$

Using experimentally known values of 0.8 and 0.6 kcal/mol for the syn-diaxial CH_3/H and CO_2Et/H interactions, respectively,[4a] and omitting the room temperature data point, the syn-diaxial CH_3/CO_2Et interaction is calculated to be 3.12 kcal/mol.

Experimental Section

1,1-Dicarboethoxyethylene (4). Ninety-five grams of **3** (prepared by catalytic reduction of **2**) was slowly heated above 150°, until **4** began to distil. The yield was 85% of pure **4**, bp 210–226° [lit. bp 210–216° (730 mm)].[17] This compound will dimerize (or polymerize) very rapidly, but can be stored for extended periods in the refrigerator. The monomer can be regenerated from the dimer (or polymer) by heating with a fused salt bath at 250°. The monomer exhibits olefinic stretching vibrations in the infrared region at *ca.* 1630 cm^{-1}.

2-Methyl(*N,N*-dimethylamino)propene (5).[18] Fifty-six grams of isobutyraldehyde was dissolved in 100 ml of xylene and charged into a high-pressure bomb. To this solution was added 30 g of anhydrous potassium carbonate (granular) and the bomb was stoppered and cooled to Dry Ice–acetone temperature. To the cooled bomb was added 37 g of previously cooled dimethylamine (anhydrous). *Caution:* Cooling ampoules of dimethylamine at low temperatures can be hazardous, and it is recommended that the ampoules be cooled in an ice–water mixture (*not Dry Ice!*) before opening. The bomb was sealed, shaken, and heated to 150° for 20 hr. It was then cooled as before and opened. The mixture was filtered to remove the salts, and the filtrate was distilled to yield **5** (67%), bp 88–90° (lit. bp 88–89°). The infrared spectrum was consistent with the required enamine.

1,1,3,3-Tetracarboethoxy-4-(*N,N*-dimethylamino)-5,5-dimethylcyclohexane (6).[10] To 58.03 g of **4** (distilled immediately before using and stabilized with a pinch of hydroquinone) under nitrogen was added 17.86 g of enamine **5**. On stirring, the temperature of the mixture rose to *ca.* 100° and then began to fall. The

solution was then heated at 180° for 12 hr. Distillation afforded a high-boiling fraction, bp 185–188° (1–2 mm), which proved to be the desired tetraester **6** [lit.[14] bp 165–175° (1 mm)], yield 41.3%. The molecular weight as determined by mass spectral analysis was 443 (calcd 443.5). Additional purification can be accomplished by column chromatography on silica (J. T. Baker 3405) using benzene and ethyl acetate–benzene mixtures as the eluting solvents.

1,5-Dicarboethoxy-3,3-dimethylcyclohexene (9) Five grams of **6** in 10 ml of metanol was added to a previously prepared solution of 10 g of sodium hydroxide in 100 ml of methanol. The mixture was refluxed for 4 hr, with the gradual precipitation of a white solid. The solution was cooled in an ice bath and acidified to pH 1 with dilute sulfuric acid. The methanol was evaporated slowly and the residual salts were dissolved in 20 ml of water. The organic acid was recovered from the aqueous solution by continuous extraction with ether. The ethereal solution was dried over magnesium sulfate and filtered, and the ether was evaporated to yield 2.4 g of **7**. Although **7** could be readily isolated and identified as its triethyl ester if the acidification was carried out at low temperatures, it was more convenient to heat **7** *in situ* to 180–200° at 1 mm for 6 hr with evolution of CO_2 to obtain **8** directly. After heating, the residue was cooled to room temperature, and 20 ml of thionyl chloride was added. The thionyl chloride solution was refluxed gently for 1 hr, or until the residue had dissolved, and any excess thionyl chloride was removed by distillation. The residue was allowed to cool and an excess of ethanol was added. The excess ethanol was evaporated and the diester olefin was distilled, bp 120–125° (5 mm), to yield 47% of the unsaturated diester **9**. The nmr spectrum did not lend itself well to integration, but is consistent with the desired compound. The infrared spectrum exhibited characteristic olefinic vibrations at *ca.* 1670 $cm.^{-1}$

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.22; H, 8.68.

Diethyl 5,5-Dimethylcyclohexane-1,3-dicarboxylate (1). Four grams of **9** was dissolved in 20 ml of absolute ethanol and 1 g of 84% platinum oxide was added. The mixture was hydrogenated on a Parr hydrogenator until an equivalent amount of hydrogen had been absorbed. The catalyst was removed by filtration through Celite, and the solvent was evaporated to yield quantitative amounts of crude **1**.

The crude mixture was separated on a Nester-Faust spinning-band column into two major components. The higher boiling component, bp 130–132° (5 mm), representing 93% of the product, was collected in three fractions. The first fraction was shown by nmr analysis to contain *ca.* 70% trans and 30% cis diester. The third fraction contained *ca.* 77% cis and the remainder trans diester and the second fraction about 50% of each isomeric diester. Fraction 2 was analyzed.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.70; H, 9.38.

Mass Spectral Analysis. The mass spectrum gave the molecular weight as 256 g/mol (calcd 256.3 g/mol).

Nmr Analysis. The first and third fractions from the spinning band separation exhibited the following patterns (Table III).

Separation of Cis and Trans Diesters. Using gas chromatography (12 ft, 10% Carbowax 20M/Chromosorb W at 170° and 150 ml/min helium) it was possible to separate the isomers and obtain each in at least 99.38% purity, as measured using a flame ionizing detector.

Equilibration Conditions. The esters were equilibrated from both sides of the equilibrium point at temperatures ranging from 233 to 102° using a constant-temperature bath. A standard solution of sodium ethoxide was prepared by dissolving 1 g of clean sodium in 50 ml of dry ethanol. Two milliliters of this solution was transferred to a small combustion tube (16 × 1 cm) and 10 ± 1 mg of diester mixture was added. The combustion tube was fitted with a drying tube, cooled, and sealed. The tube was then heated at the desired temperature for a period of time, which was not less than 3 days. At the end of the equilibration period, the tubes were rapidly quenched in an ice–water bath, opened, and poured into 10 ml of a 6 *N* HCl solution. The pH was checked to ensure that the solution was acid and the aqueous solution was extracted with three 10-ml portions of diethyl ether. The ethereal extracts were washed with a saturated solution of sodium carbonate and dried over magnesium sulfate. Filtration of the solution and evaporation of the solvent gave the equilibrated diester mixture, which was analyzed as below.

Table III

Ppm	Moiety	Integration Theor	Integration Actual
1st Fraction (Mostly Trans)			
4.1 (q)	OCH_2CH_3	1.0	1.0
2.7 (m)	$CHCO_2C_2H_5$	0.5	0.47
1.85 (t)	CH_2	0.5	0.47
1.58 (d)	CH_2	1.0	0.9
1.2 (t)	OCH_2CH_3	1.5	1.6
1.0 (s)[a], 0.95 (s)[a], 0.89 (s)[b]	CH_3 (gem)	1.5	1.4
3rd Fraction (Mostly Cis)			
4.1 (q)	OCH_2CH_3	1.0	1.0
2.8–1.4	CH, CH_2	3.5	3.6
1.2 (t)	OCH_2CH_3		
1.0 (s)[a], 0.95 (s)[a], 0.89 (s)[b]	CH_3 (gem)	1.5	1.6

[a] Represents nonequivalent geminal methyls in cis isomer with a separation of 2–3 Hz. [b] Represents the trans isomer.

Analysis of Equilibrated Mixtures. The mixture of diesters obtained above was dissolved in 1–3 drops of diethyl ether or hexane and chromatographed on a Perkin-Elmer F-11 flame ionizing gas chromatograph using a 50-ft capillary column (Carbowax 20M, S.C.O.T.C.) or on a Perkin-Elmer Model 881 Gas Chromatograph using a 12 × 0.125 in. column (3.6% FFAP and 2.4% EGSP-2 on Chromosorb P[19]) at 210°. The relative amount present was determined by the triangulation method.

Registry No.—*cis*-**1**, 51593-44-3; *trans*-**1**, 51592-65-5; **6**, 51592-66-6; **7**, 51592-67-7; **8**, 51592-68-8; **9**, 51592-69-9.

References and Notes

(1) Part CIV: N. L. Allinger, J. T. Sprague, and T. Liljefors, *J. Amer. Chem. Soc.*, **96**, 5100 (1974).
(2) This work was supported by Grant GP-15263 from the National Science Foundation, and is largely abstracted from the Ph.D. Dissertation submitted by J. C. G. to Wayne State University, June 1971.
(3) (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley-Interscience, New York, N. Y., 1965, p 42; (b) M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965.
(4) (a) J. A. Hirsch, *Top. Stereochem.*, **1** 199 (1967); (b) F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Amer. Chem. Soc.*, **91**, 344 (1969).
(5) S. J. Angyal and D. J. McHugh, *Chem. Ind. (London)*, 1147 (1956).
(6) R. U. Lemieux and P. Chu, Abstracts of Papers, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 1958, 31N.
(7) (a) E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, **26**, 3504 (1961); (b) G. Chiurdoglu and W. Masschelein, *Bull. Soc. Chim. Belg.*, **70**, 782 (1961); (c) E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.*, **79**, 5986 (1957).
(8) N. L. Allinger and M. A. Miller, *J. Amer. Chem. Soc.*, **83**, 2145 (1961).
(9) V. K. Schwabe, *Z. Electrochem.*, **60**, 151 (1956).
(10) N. L. Allinger, J. Allinger, L. W. Chow, and G. L. Wang, *J. Org. Chem.*, **32**, 522 (1967).
(11) D. S. Bailey, J. A. Walder, and J. B. Lambert, *J. Amer. Chem. Soc.*, **94**, 177 (1972).
(12) N. L. Allinger and R. J. Curby, Jr., *J. Org. Chem.*, **26**, 933 (196[illegible]).
(13) R. A. Ford and N. L. Allinger, *J. Org. Chem.*, **35**, 3178 (1970).
(14) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **29**, 801 (1964).
(15) Reference 3a, p 141.
(16) B. Ostle, "Statistics in Research," Iowa State University Press, 1960, p 127 ff.
(17) W. Feely and V. Boekelheide, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 298.
(18) K. C. Brannock and R. D. Burpitt, *J. Org. Chem.*, **26**, 3576 (1961).
(19) Available from Applied Science Labs, University Park, Pa.

Terpenes and Related Systems. IX.[1] A Synthesis of (+)-Himachalene Dihydrochloride and (+)-*ar*-Himachalene

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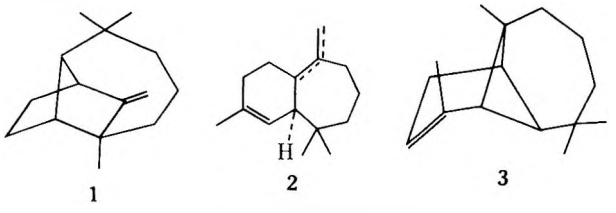
A seven-step synthesis of (+)-himachalene dihydrochloride and (+)-*ar*-himachalene from the tricyclic sesquiterpene longifolene is described. The successful route involved the preparation of a key bifunctional longibornane derivative (**12**) as the initial target. This was obtained from ω-bromolongifolene (**9**) *via* an acid-catalyzed rearrangement involving an intramolecular 1,5-hydride shift. The bicyclic homodecalinenones **22**, **23**, and **24** were obtained from **12** in a novel base-catalyzed fragmentation reaction that removes the carbon-to-carbon span which gives longibornane its tricyclic bridged structure. Elaboration of β,γ-unsaturated ketone **22** to the title compounds **30** and **31** was achieved through Wolff-Kishner reduction followed by either hydrochlorination or aromatization. Attempts to convert enones **22** and **24** to α-longipinene (**3**) are also included.

The diversity of carbocyclic structures replete with a wide variety of functionalities makes sesquiterpenes attractive and formidable targets of chemical synthesis. It is not surprising, therefore, that intense activity[3] has been witnessed in this area during the past few years. In a majority of the reported syntheses, the C_{15} network of sesquiterpenes has been created by a combination or elaboration of small synthons (fragments) employing routine or novel reactions and reagents. An alternate approach utilizing naturally occurring sesquiterpenes as synthons for complex synthesis, on the other hand, has only received limited attention.[4] Such an approach, besides furnishing optically active compounds, is likely to be economical and would essentially require the reorganization of a carbocyclic network through suitable bond-breaking and -making processes. The efficacy of such a synthetic approach is exemplified here by considering the possibility of employing the readily available tricyclic hydrocarbon longifolene (**1**) for the synthesis of α- and β-himachalenes (**2**),[5] chief constituents of the essential oil of *Cedrus deodar* Loud., and α-longipinene (**3**),[6] a component of the essential oils of

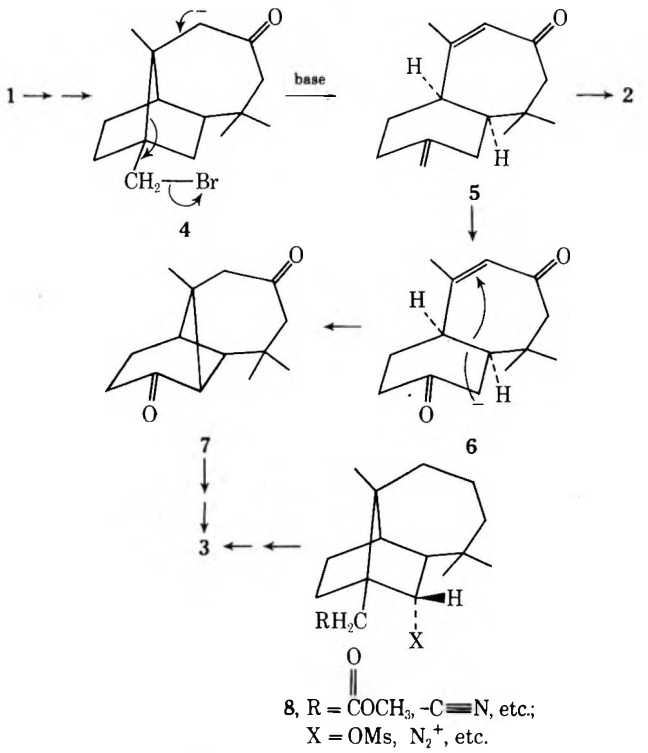


1 2 3

α = exocyclic olefin
β = endocyclic olefin

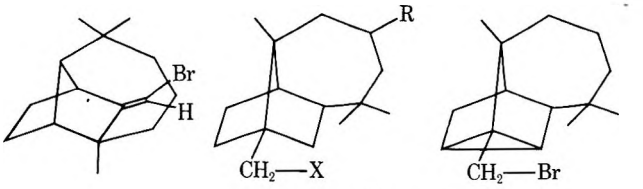
Pinus longifolia Roxb. and *Pinus silvestris* L. The choice of longifolene (**1**) for the contemplated synthesis is dictated by its close biogenetic relationship[7] with **2** and **3**. The synthetic route adopted and executed here constitutes a reversal of the biogenetic pathway in terms of the gross carbocyclic skeletons, *i.e.*, longifolene → longibornane type → himachalene type. The pathways by which **1** can eventuate in **2** and **3** by logical and conceptually plausible steps are shown in Scheme I. The synthetic strategy depicted in Scheme I consists of the preparation of suitably functionalized longibornane precursors **4** and **8** followed by key transformations involving a base-catalyzed fragmentation **4** → **5**,[8,9] an intramolecular Michael addition **6** → **7**,[10] and solvolytic ring contraction **8** → **3**.[11] The other subordinate steps in the scheme are easy to comprehend and can be carried out through well-established reactions. A particularly hopeful feature of the fragmentation of the tricyclic longibornane derivative **4** was the expectation that removal of the carbon bridge would lead to a cis-fused homodecalin corresponding to the stereochemistry of

Scheme I



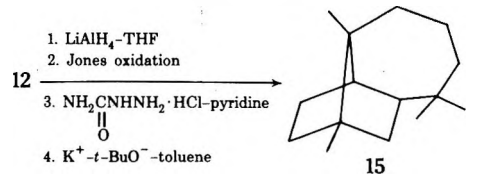
naturally occurring himachalenes. In this paper is described the synthesis of (+)-himachalene dihydrochloride (**30**)[12] and (+)-*ar*-himachalene (**31**)[13] and preparation of synthons related to the synthesis of α-longipinene (**3**) from longifolene through the reaction sequence **1** → **4** → **5** → **30**.

(*E*)-ω-Bromolongifolene (**9**), readily available[1e] from **1**, appeared to be ideally suited as a starting material which has sufficient functionality, properly disposed, for elaboration into bifunctional longibornane derivative **12**. Reac-

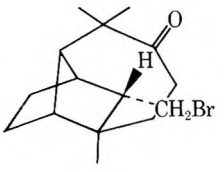


9 10, X = Br; R = OCCF3 14
11, X = Br; R = OH
12, X = Br; R = =O
13, X = H; R = OH

Scheme II



tion of **9** with trifluoroacetic acid (TFA) furnished a complex mixture of hydrocarbons and a trifluoroacetate (**10**). Hydrolysis with alcoholic potassium hydroxide and purification on a silica gel column gave a hydrocarbon fraction followed by the secondary alcohol **11**, mp 65–66°. The hydrocarbon fraction consisted of at least six components and only the major component (~50%) was obtained pure and characterized on the basis of spectral evidence (see Experimental Section) as longicyclenyl bromide (**14**).[15] Oxidation of alcohol **11** with Jones reagent resulted in the isolation of two crystalline ketones, mp 72 and 103°, which could be readily separated by column chromatography. That the low-melting ketone possessed the requisite structure **12** was indicated by its carbonyl absorption in the ir spectrum at 1700 cm^{-1} and signals in the pmr spectrum for three quaternary methyls (δ 0.91, 0.97, and 1.07), a bromomethyl group (δ 3.5, AB quartet, J = 12 Hz), and two deshielded methylene groups flanking the carbonyl (δ 2.4, AB quartet, J = 11 Hz). The structure of this key ketone (**12**) required for the fragmentation reaction was further verified by an unambiguous conversion to the known[16] hydrocarbon longibornane (**15**) through steps outlined in Scheme II. This correlation of **12** with **15** rules out of contention alternate structures **16** and **17** for the



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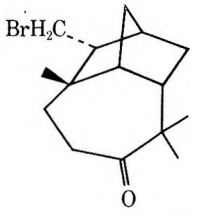

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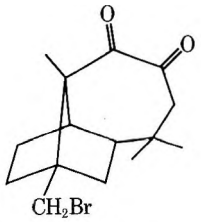
low-melting ketone.[17] The high-melting ketone analyzed for $C_{15}H_{21}O_2Br$ and showed ir absorption due to carbonyl group at 1720 cm^{-1} (broad). Its pmr spectrum exhibited quaternary methyl singlets at δ 1.01, 1.1, and 1.14, a bromomethyl as a doublet of doublets at δ 3.60 (J = 10 Hz), and another doublet of doublets due to methylene flanking the carbonyl at δ 2.51 (J = 12 Hz). This spectral data clearly indicated a diketone structure (**18**) for the high-



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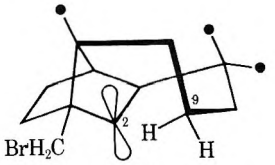
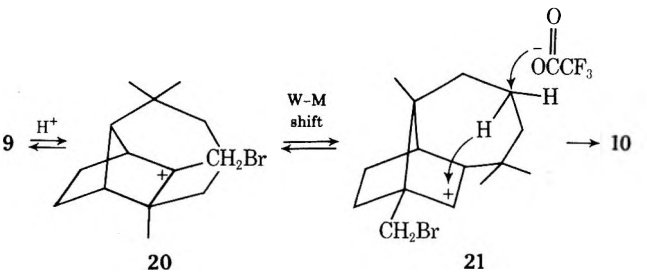


19, —●, CH_3 groups

melting ketone and was fully supported[18] by an independent X-ray crystal structure determination.

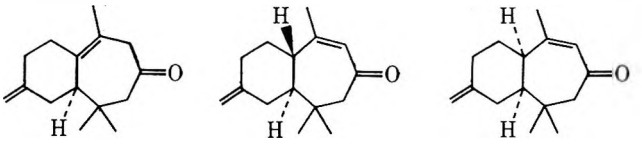
The formation of trifluoroacetate **10** from the rearrangement of ω-bromolongifolene (**9**) in TFA can be rationalized in terms of the protonation of **9** to equilibrating ions **20** and **21** followed by a precedented[1b,19] transannular 1,5-hydride migration and capture by the nucleophile (Scheme III). This intramolecular hydride shift is facilitated by the favorable conformation (**19**) of the eight-membered ring resulting in the proximity of the hydrogen at C_9 with the sp^2 center at C_2. Proton loss from ions **20** and **21** accounts for the formation of the tetracyclic bromide **14**.

Scheme III



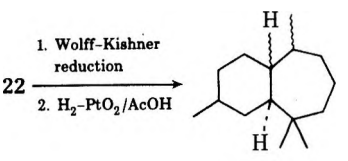
20 21

With the structure of longibornane precursor **12** firmly established and its adequate supply assured, we turned our attention toward the key fragmentation step (Scheme I), which to our expectation proved extremely facile and easy to execute. Indeed, exposure of **12** to methylsulfinyl carbanion[20] at room temperature and quenching with water resulted in the formation of three ketones A, B, and C in a ratio of 15:4:1 in 96% yield. The major ketone A could be conveniently isolated by column chromatography and is formulated as the unconjugated homodecalin ketone (**22**).[21] The structure of this product is indicated by



22 23 24

the lack of uv absorption, the presence of unconjugated carbonyl (1705 cm^{-1}) and terminal methylene (3100, 1600, 890 cm^{-1}) in the ir spectrum, and the pmr absorption (Figure 1, two quaternary methyls, a vinylic methyl, and two olefinic protons). The ketone B was clearly an α,β-unsaturated ketone, as revealed by its uv spectrum [λ_{max} (MeOH) 244 nm] and exhibited complimentary carbonyl absorption (1640 cm^{-1}) in the ir spectrum. The pmr spectrum (Figure 2, two quaternary methyls, a vinylic methyl, two terminal methylene protons, and a vinylic proton) was fully consistent with the gross structure **23**. The trans stereochemistry at the ring junction in **23** was established through equilibration studies (*vide infra*). The minor ketone C which had earlier[1d] eluded isolation but whose presence was vital to our contemplated internal Michael addition (Scheme I) in fact turned out to be the cis-fused α,β-unsaturated ketone **24**. Its structure follows from its uv spectrum [λ_{max} (MeOH) 244 nm], carbonyl (1650 cm^{-1}) and terminal methylene absorption in the ir spectrum, and pmr data (Figure 3, two quaternary methyls, a vinylic methyl, two terminal methylene protons, and a vinylic proton). The gross carbocyclic structure of the ketones **22**, **23**, and **24** was ascertained by the transformation of the major ketone **22** into the saturated hydrocarbon **25** *via* Wolff-Kishner reduction and catalytic hydrogenation. The compound **25** was found to be similar to the parent hydrocarbon himachalane[5] obtained from the reduction of natural β-himachalene.



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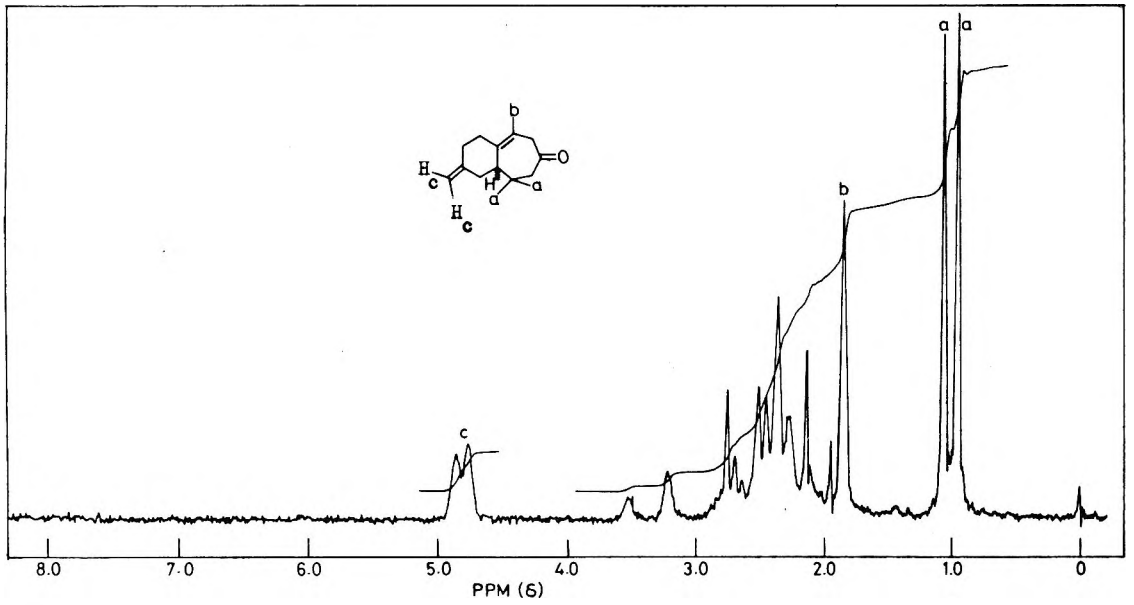


Figure 1. Pmr spectrum (60 MHz) of β,γ-unsaturated ketone **22**.

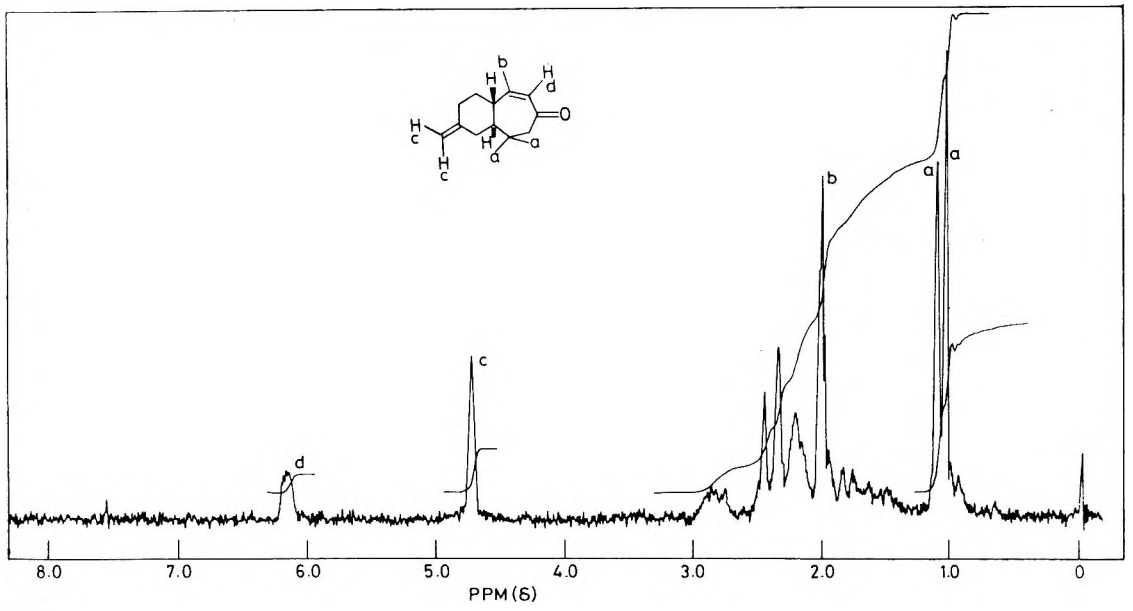


Figure 2. Pmr spectrum (60 MHz) of trans α,β-unsaturated ketone **23**.

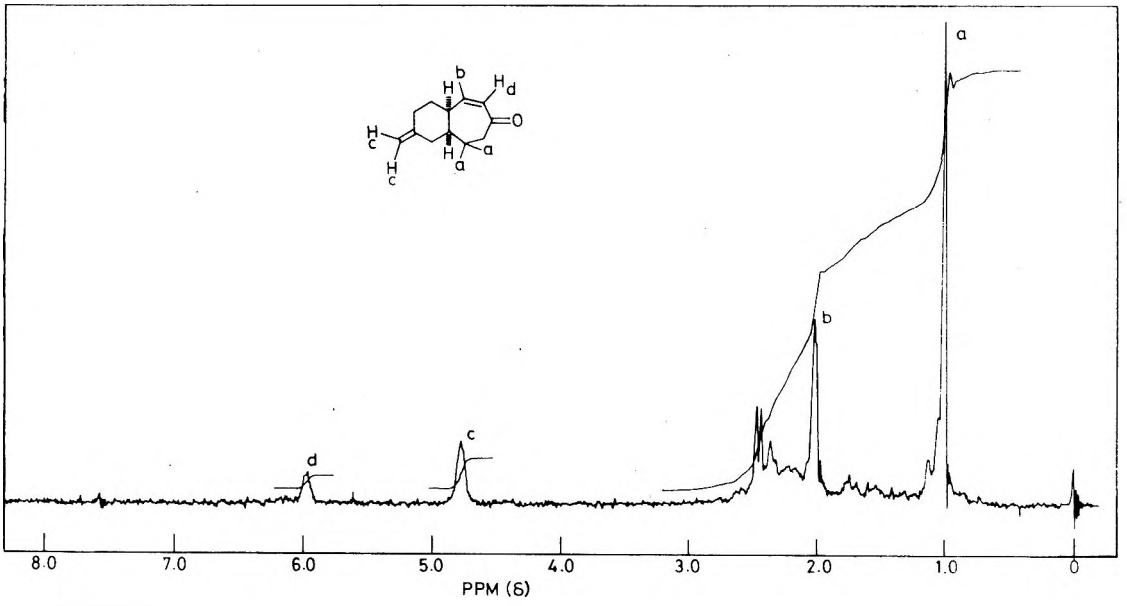
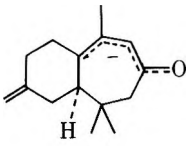


Figure 3. Pmr spectrum (60 MHz) of cis α,β-unsaturated ketone **24**.

The formation of structurally related ketones **22**, **23**, and **24** in the fragmentation reaction suggests that they are derived from **26** through the base-catalyzed equilibra-



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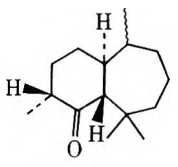
tion under experimental conditions. This contention is substantiated by the fact that when pure ketones **22**, **23**, or **24** or their mixtures were equilibrated with methylsulfinyl carbanion in DMSO, the product consisted of the three ketones in the same ratio in which they were originally isolated from the fragmentation reaction. In the light of these equilibration studies, the α,β-unsaturated ketone **23** predominating under equilibrium conditions is assigned the more stable trans stereochemistry at the ring junction. The greater stability of *trans*-perhydrobenzosuberone over the corresponding cis isomer has been experimentally established.[22] In the himachalene series itself the trans isomers **27** and **28** have been shown[12b,23,24] to



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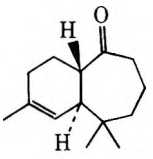

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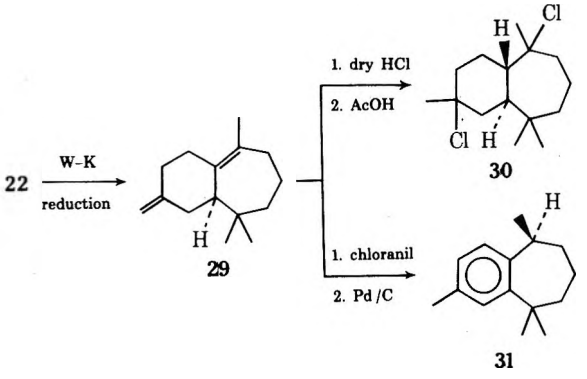
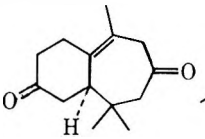
predominate over their cis isomers under equilibrium. The conjugated ketone **24** present in trace amounts only is, therefore, recognized as the less stable cis isomer.

The β,γ-unsaturated ketone **22** was now converted to the target compounds **30** and **31** through the reaction sequence summarized in Scheme IV. Thus, Wolff-Kishner reduction of **22** and purification ($AgNO_3$-silica gel) gave himachalene isomer **29**. A passage of a stream of dry HCl gas through an acetic acid solution of **29** led to the isolation of (−)-himachalene dihydrochloride (**30**), mp 118–119°, indistinguishable (mixture melting point, ir, $[\alpha]D$) from the material prepared from natural α- and β-himachalene. Since himachalene dihydrochloride (**30**) has already been converted[12a] into β-himachalene, this also constitutes a formal synthesis of the latter. Dehydrogenation of **29** with chloranil followed by aromatization over Pd/C gave (+)-*ar*-himachalene (**31**) found identical (ir, nmr) with the naturally occurring material. The *S* configuration (**31**) of (+)-*ar*-himachalene at the asymmetric center is based on its $[\alpha]D$ of +7.7°, which is comparable to the $[\alpha]D$ of +5.90° of (+)-*ar*-himachalene prepared[14] from (+)-*ar*-turmerone, a compound of well-established absolute stereochemistry.

Scheme IV



Finally, it was of obvious interest to attempt the transformation of ketones **22**–**24** to α-longipinene (**3**). Several attempts to selectively ozonize the ketone **22** to the enedione **32** required for the internal Michael addition met with failure and resulted in the formation of highly polar, intractable material. Efforts to ketalize the carbonyl function in **22** prior to ozonolysis led to the isomerization of the exocyclic double bond and formation of undesired ketal mixture **33**. Similarly, attempted preparation of enone **34** for a Lewis acid catalyzed Stork-Grieco type[25] cyclization to a bridged cyclobutane derivative also proved futile.



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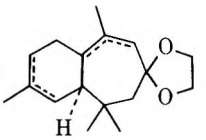

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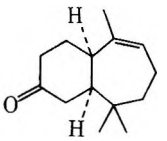

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Experimental Section[26]

(*E*)-ω-Bromolongifolene (9). This was prepared according to the previously reported[1c] procedure. The material used for the present investigation had bp 120–125° (6 mm); mp 40–41°; $n^{35}D$ 1.5315; and $[\alpha]D$ +52.06° (c 1.96).

Rearrangement of (*E*)-ω-Bromolongifolene (9) in Trifluoroacetic Acid. A solution of (*E*)-ω-bromolongifolene (12 g) in 25 ml of methylene chloride was slowly added to a cooled (5–10°) solution of trifluoroacetic acid (50 ml) over a period of 15 min with vigorous stirring. The stirring was continued for 4 hr at room temperature (35°) after which the reddish-brown reaction mixture was quenched by pouring into iced sodium bicarbonate solution. The product was extracted with ether (two 150-ml portions), washed with brine, and dried. Removal of solvent gave 14.8 g of an oily mixture of hydrocarbons and trifluoroacetate **10**, ir 1775 (ester carbonyl) and 1230 cm^{-1}.

Base Hydrolysis of (*E*)-ω-Bromolongifolene Rearrangement Product. The above mixture (14.8 g) was taken up in 40 ml of ethanol and potassium hydroxide (3 g) in 30 ml of water was added. After stirring for 8 hr at ambient temperature the reaction mixture was diluted with water, extracted with ether (three 100-ml portions), washed with brine, and dried and solvent was evaporated to furnish a viscous residue (12 g). This material was adsorbed on a silica gel (200 g) column and readily separated into a hydrocarbon fraction by successive elution with petroleum ether and benzene. Fraction 1 (4 g, 27%), bp 110–115° (2 mm), was revealed to be a mixture of seven components by vpc analysis. The major component (~50%) was isolated by preparative layer chromatography (20 × 20 cm plates, solvent system petroleum ether) and found to be the tetracyclic bromide **14**:[27] $n^{30}D$ 1.5584; ir (neat) (cyclopropane CH) 845 cm^{-1} (tricyclene type nucleus); pmr (CCl_4) δ 0.83 (CCH_3, 3 H, s), 0.88 (CCH_3, 6 H, s), 3.41 (CCH_2Br, 2 H, q, J = 9 Hz), 0.72 (cyclopropane, 1 H, s), 0.95 (cyclopropane, 1 H, s). *Anal.* Calcd for $C_{15}H_{23}Br$; C, 63.60; H, 8.12. Found: C, 63.82; H, 8.54.

Fraction 2 (6 g, 53%) solidified on standing and was twice sublimed at 90° (2 mm) to furnish white, waxy crystals of bromo alcohol **11**: mp 65–66°; $[\alpha]D$ +23.5° (*c* 1.47); ir (KBr) 3300 (hydroxyl), 1250, 1060, 1040 cm^{-1}; pmr (CCl_4) δ 0.95 (CCH_3, 6 H, s), 1.03 (CCH_3, 3 H, s), 3.45 (CCH_2Br, 2 H, q, J = 12 Hz), 4.05 (HCOH, 1 H, m), *Anal.* Calcd for $C_{15}H_{25}OBr$: C, 59.80; H, 8.36. Found: C, 59.53; H, 8.05.

Jones Oxidation[29] of Bromo Alcohol 11. A stirred solution of 5.4 g of **11** in 60 ml of acetone was treated dropwise at room temperature with Jones reagent (50 ml) until the brown color persisted. The mixture was stirred for 5 hr, diluted with water, and extracted with ether (two 100-ml portions). The organic layer was successively washed with aqueous sodium carbonate and brine and dried. Removal of solvent gave a semisolid residue (4.7 g) which was adsorbed on a silica gel (200 g) column. Elution with petroleum ether–benzene (60:40) afforded 1.5 g (27%) of the crystalline diketone **18**. Recrystallization from petroleum ether gave pale-colored, stout crystals: mp 103°; $[\alpha]D$ −47.6° (*c* 2.99); uv λ_{max} (MeOH) 310 nm (ϵ 52); ir (KBr) 1710 (carbonyl), 995, 800 cm^{-1}; pmr (CCl_4) δ 1.01 (CCH_3, 3 H, s), 1.11 (CCH_3, 3 H, s), 1.14 (CCH_3, 3 H, s), 3.60 (CCH_2Br, 2 H, q, J = 10 Hz), 2.51 [$-C(=O)CH_2-$, 2 H, q, J = 12 Hz]. *Anal.* Calcd for $C_{15}H_{21}O_2Br$: C, 57.52; H, 6.76. Found: C, 57.38; H, 6.5.

The semicarbazone of ketone 18 was prepared by the pyridine method and crystallized from ethanol as colorless needles, mp 218–219°. *Anal.* Calcd for $C_{16}H_{24}O_2N_3Br$: C, 51.89; H, 6.48; N, 11.35. Found: C, 51.75; H, 6.70; N, 11.77. Further elution of the column with petroleum ether–benzene (40:60) afforded 3 g (55%) of crystalline ketone **12**. Recrystallization from petroleum ether gave an analytical sample of bromo ketone **12**: mp 72°; $[\alpha]D$ +47.7° (*c* 5.33); uv λ_{max} (MeOH) 290 nm (ϵ 46); ir (KBr) 1700 (carbonyl), 1300, 920 cm^{-1}; pmr (CCl_4) δ 0.91 (CCH_3, 3 H, s), 0.97 (CCH_3, 3 H, s), 1.07 (CCH_3, 3 H, s), 3.5 (CH_2Br, 2 H, q, J = 12 Hz). *Anal.* Calcd for $C_{15}H_{23}OBr$: C, 60.21; H, 7.75. Found: C, 60.60; H, 7.31.

A portion of the ketone **12** was converted to the semicarbazone derivative by the pyridine method and recrystallized from ethanol to give colorless, needle-shaped crystals, mp 222–223°. *Anal.* Calcd for $C_{16}H_{26}ON_3Br$: C, 53.93; H, 7.30; N, 11.79. Found: C, 54.36; H, 6.9; N, 11.94.

Lithium Aluminum Hydride Reduction of Bromo Ketone 12. The bromo ketone (500 mg) in tetrahydrofuran (5 ml) was slowly added to a stirred slurry of lithium aluminum hydride (200 mg) in dry tetrahydrofuran (20 ml). The stirring under reflux was continued for 7 days and the complex was decomposed by careful addition of ice-cold water. The organic product was isolated by extraction with ether (two 50-ml portions), washed with brine, and dried. Removal of solvent gave 350 mg of a viscous oil consisting of an epimeric mixture of longibornan-9-ols.

Longibornane (1,4,4,8-Tetramethyltricyclo[6.3.0.0^{3,9}]undecane 15. To a stirred solution of the above alcohols in 5 ml of acetone was added Jones reagent dropwise till the yellow color persisted. The reaction mixture was further stirred for 0.5 hr and worked up as described above to give a pale yellow oil (350 mg). This material was adsorbed on a silica gel (10 g) column and eluted with petroleum ether–benzene (80:20) to give longibornan-9-one (270 mg, 74%): ir (neat) 1698 cm^{-1} (carbonyl); pmr ($CDCl_3$) δ 0.86 (CCH_3, 3 H, s), 0.88 (CCH_3, 6 H, s), 1.05 (CCH_3, 3 H, s). To a solution of the above ketone (80 mg) in 2 ml of ethanol was added a solution of semicarbazide hydrochloride (50 mg) in 1 ml of water containing a few drops of pyridine. The mixture was left overnight and the solid was filtered. Recrystallization from ethanol gave 60 mg of white needles, mp 213–214°.

The semicarbazone of longibornan-9-one (200 mg) and potassium *tert*-butoxide[30] (250 mg) in dry toluene (10 ml) were refluxed for 24 hr. The reaction mixture was poured into water and the organic layer was separated. Removal of solvent and filteration of a petroleum ether solution through silica gel furnished 70 mg of hydrocarbon longibornane (15). The ir spectrum of this material was found indistinguishable from that of an authentic sample[31] of longibornane.

Fragmentation of Ketone 12 with Methylsulfinyl Carbanion. A solution of methylsulfinyl carbanion in 20 ml of DMSO was prepared under nitrogen atmosphere according to Corey's procedure from 2 g of sodium hydride (50% dispersion in mineral oil). To this reagent was added a solution of 5 g of bromo ketone **12** in 20 ml of DMSO with the aid of a hypodermic syringe and the reaction mixture was stirred at room temperature for 0.5 hr. The reaction mixture was diluted with water and extracted with petroleum ether (two 100-ml portions). The organic phase was washed with brine, dried, and freed of solvent to give 3.6 g (96%) of an oily mixture of ketones. This material was adsorbed on a silica gel (100 g) column and chromatographed. Elution with petroleum ether–benzene (60:40) afforded 2.7 g (75%) of the major ketone **22**: bp 110–120° (0.6 mm); $n^{30}D$ 1.5215; $[\alpha]D$ +12.32° (c 2.75); uv λ_{max} (MeOH) 296 nm (ϵ 160); ir (neat) 1705 (unconjugated carbonyl), 3100, 1600, 890 cm^{-1} (terminal methylene); pmr (CCl_4) δ 0.93 (CCH_3, 3 H, s), 1.05 (CCH_3, 3 H, s), 1.84 ($H_3CC{=}C-$, 3 H, s), 4.81 ($H_2C{=}C<$, 2 H, d), 2.0–3.3 (allylic and α to carbonyl, 11 H, m). *Anal.* Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.85; H, 10.15. A portion of the ketone **22** was converted to the semicarbazone derivative by the pyridine method and recrystallized from ethanol to give colorless crystals, mp 115° dec. *Anal.* Calcd for $C_{16}H_{25}ON_3$: C, 69.78; H, 9.15; N, 15.26. Found: C, 69.59; H, 8.8; N, 14.98.

Elution of the column with petroleum ether–benzene (40:60) gave 0.6 g (20% yield) of the α,β-unsaturated ketone **23**: bp 110–120° (0.6 mm); $n^{30}D$ 1.5305; $[\alpha]D$ −45.8° (c 2.10); uv λ_{max} (MeOH) 244 nm (ϵ 10,700); ir 1640 (conjugated carbonyl), 3090, 1630, and 890 cm^{-1} (terminal methylene); pmr (CCl_4) δ 1.06 (CCH_3, 3 H, s), 1.14 (CCH_3, 3 H, s), 2.01 ($CH_3C{=}C<$, 3 H, broad s), 4.76 ($H_2C{=}C<$, 2 H, s), 6.2 ($HC{=}C<$, 1 H, broad s). *Anal.* Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.74; H, 10.25.

A small quantity of the ketone **23** was transformed (pyridine method) into its semicarbazone derivative and crystallized from ethanol to give colorless microcrystals, mp 197–198° dec. *Anal.* Calcd for $C_{16}H_{25}N_3O$: C, 69.78; H, 9.15; N, 15.26. Found: C, 69.90; H, 9.25; N, 15.56. Further elution of the column with benzene gave a fraction containing 105 mg of ketone **24**: bp 110–115° (2 mm); $[\alpha]D$ −48.3° (c 1.61); uv λ_{max} (MeOH) 244 nm (ϵ 9400); ir 1650 (conjugated carbonyl), 3090, 1630, and 895 cm^{-1} (terminal methylene); pmr (CCl_4) δ 0.99 (CCH_3, 6 H, s), 2.01 ($H_3CC{=}C<$, 3 H, s), 4.78 ($H_2C{=}C<$, 2 H, s), 5.96 ($HC{=}C<$, 1 H, broad s). *Anal.* Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.27; H, 10.2.

Equilibration of Ketone 22 with Methylsulfinyl Carbanion. A solution of methylsulfinyl carbanion in 5 ml of DMSO was prepared from 0.5 g of sodium hydride (50% dispersion in mineral oil) as described in the above experiment. To this reagent was added a solution of 0.1 g of β,γ-unsaturated ketone **22** in 5 ml of DMSO with the aid of a hypodermic syringe and the reaction mixture was stirred at room temperature for 0.5 hr. The reaction mixture was worked up as in the above experiment and gave 0.1 g of product, which consisted of the three ketones in the same ratio as in the above reaction.

Similarly experiments were carried out for ketones **23** and **24** and the same mixtures were obtained in the same ratio.

Wolff–Kishner Reduction of β,γ-Unsaturated Ketone 22. To a solution of enone **22** in 15 ml of ethanediol was added 10 ml of hydrazine (80%) under nitrogen atmosphere and the mixture was stirred for 1 hr at 100°. Potassium hydroxide pellets (2.5 g) were then added and stirring was continued for a further period of 2 hr at 200°. The reaction mixture was poured into an ice-cold solution of dilute HCl. Extraction with ether (two 50-ml portions), washing with saturated sodium bicarbonate and brine, and removal of solvent gave 0.26 g of a mixture of hydrocarbons. This material was adsorbed over 15 g of 20% $AgNO_3$-impregnated silica gel. Elution with petroleum ether–benzene (90:10) gave 0.15 g of pure hydrocarbon **29**: bp 110–115° (4 mm); $[\alpha]D$ +40.76° (*c* 0.85); ir (neat) 3090, 1650, 890 cm^{-1} (terminal methylene); pmr (CCl_4) δ 0.83 (CCH_3, 3 H, s), 0.91 (CCH_3, 3 H, s), 1.76 ($H_3CC{=}C-$, 3 H, s), 4.76 ($H_2C{=}C<$, 2 H, d). *Anal.* Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.06; H, 11.7.

Catalytic Hydrogenation of 29 to Tetrahydrohimachalene (Himachalane 25). A solution of 0.1 g of hydrocarbon **29** in glacial acetic acid (5 ml) was hydrogenated over Adams catalyst (20 mg) at room temperature and 1 atm pressure of hydrogen. The catalyst was removed by filtration and the filtrate was poured into 25 ml of water. Extraction with petroleum ether (two 20-ml portions), washing with sodium bicarbonate and brine, and removal of solvent gave 0.1 g of oily material. This was filtered through a 20% $AgNO_3$-impregnated silica gel column with petroleum ether to give **25** as a colorless oil: bp 110–115° (4 mm); ir 1450, 1390, 1380, 870, 860 cm^{-1}. The ir spectrum was found to be similar to that of the material obtained by the catalytic hydrogenation of naturally occurring α- and β-himachalene mixture obtained as described in the literature.[14]

(+)-Himachalene Dihydrochloride (30). An ice-cooled solution of 80 mg of hydrocarbon **29** in glacial acetic acid (1 ml) was saturated with a slow stream of dry hydrogen chloride gas until the solution turned deep brown. This solution was left overnight at −5° and the colorless crystals were collected by filtration. Recrystallization from petroleum ether–benzene gave long, white needles: mp 118–119°; $[\alpha]D$ +3.4° (*c* 1.62); ir 1440, 1450, 1360, 1100, 840 cm^{-1}. The melting point was undepressed on admixture with an authentic specimen prepared from α- and β-himachalene. The ir spectra of the two were also completely superimposable.

(+)-*ar*-Himachalene (31). A mixture of 0.23 g of hydrocarbon **29** and 0.5 g of chloranil in dry benzene was refluxed for 4 hr under a nitrogen blanket. The reaction mixture was filtered and the precipitate was washed with 10 ml of benzene. The organic phase was concentrated, diluted with petroleum ether, and passed through a silica gel (10 g) column. The petroleum ether eluate on concentration gave 0.23 g of a hydrocarbon mixture.

The above mixture (0.23 g) was refluxed with 200 mg of 10% Pd/C in dry benzene for 12 hr. The reaction mixture was filtered and the precipitate was washed with 10 ml of benzene. Removal of solvent furnished 0.2 g of a pale yellow liquid. This was dissolved in 10 ml of acetone–water (9:1) and stirred with an excess of powdered potassium permanganate to destroy olefinic impurities. The reaction mixture was again filtered and diluted with water. Extraction with petroleum ether (two 25-ml portions), washing with brine, drying, and removal of solvent furnished 120 mg of pure (+)-*ar*-himachalene (**31**): bp 110–115° (2 mm); $n^{35}D$ 1.5249; $[\alpha]D$ +7.7° (c 1.02); ir (neat) 3010, 1620, 1580, 1450, 810

cm^{-1}; pmr (CCl_4) δ 1.26 (CCH_3, 3 H, s), 1.30 (CCH_3, 3 H, s), 1.38 (CCH_3, 3 H, s), 2.26 ($ArCH_3$, 3 H, s), 6.91 (Ar, 1 H, s), 7.03 (ArH, 1 H, s). The literature records[14] $[\alpha]D$ +2.92° (c 1.7) for the naturally occurring material and $[\alpha]D$ +5.9° (c 1.04) for the (+)-*ar*-himachalene obtained from (+)-*ar*-turmerone. *Anal.* Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.12; H, 10.4.

Ozonolysis of β,γ-Unsaturated Ketone 22. A 440-mg solution of ketone **22** in ethyl acetate (15 ml) was treated with 0.097 g of ozone generated in a Welsbach ozonizer at −80°. The solvent was then removed under reduced pressure and the residue was treated with aqueous sodium carbonate and a few drops of hydrogen peroxide (30%). Dilution with water, extraction with benzene, and removal of solvent gave 400 mg of glassy residue. Tlc behavior indicated it to be a complex mixture of highly polar material and the ir spectrum displayed multiple carbonyl and hydroxyl absorptions.

Ketalization of Ketones 22, 23, and 24. To a stirred solution of 800 mg of ketones **22**, **23**, and **24** in dry benzene (50 ml) was added ethylene glycol (7 ml) and *p*-toluenesulfonic acid in catalytic amounts. The reaction mixture was refluxed for 2 hr and poured into water. Extraction with ether (two 30-ml portions), washing with aqueous sodium bicarbonate and brine, and removal of solvent afforded 1.07 g of **33**: bp 150° (1 mm); $n^{30}D$ 1.5172; uv λ_{max} (MeOH) 208 nm (ϵ 4900); ir no absorption at 890 cm^{-1} due to terminal methylene. *Anal.* Calcd for $C_{17}H_{26}O_2$: C, 77.86; H, 9.92. Found: C, 78.00; H, 10.00.

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Registry No.—**9**, 1139-15-7; **11**, 51599-80-5; **12**, 51599-81-6; **12** semicarbazone, 51599-82-7; **14**, 51635-66-6; **15**, 51599-83-8; **18**, 51599-84-9; **18** semicarbazone, 51599-60-1; **22**, 51704-14-4; **22** semicarbazone, 51599-85-0; **23** semicarbazone, 51599-86-1; **24**, 51704-15-5; **25**, 20479-45-2; **29**, 51599-87-2; **30**, 33496-01-4; **31**, 19419-67-1; **33**, 51635-68-8.

References and Notes

(1) For earlier papers in the series, see (a) G. Mehta, *Indian J. Chem.*, **7**, 565 (1969); (b) G. Mehta, Chem. Ind. (London), 1264 (1970); (c) G. Mehta, *J. Org. Chem.*, **36**, 3455 (1971); (d) G. Mehta and S. K. Kapoor, *Tetrahedron Lett.*, 715 (1972); (e) G. Mehta, *Chem. Ind. (London)*, 762 (1972); (f) G. Mehta, N. M. Pattnaik, and S. K. Kapoor *Tetrahedron Lett.*, 4947 (1972); (g) G. Mehta and S. K. Kapoor, *ibid.*, 497 (1973); (h) G. Mehta and S. K. Kapoor, *ibid.*, 2385 (1973).

(2) Junior Research Fellow of CSIR (1970–present).

(3) Recent reviews in sesquiterpene synthesis: (a) J. M. Mellor and S. Munavalli, Quart. Rev., Chem. Soc., **18**, 270 (1964); (b) G. Mehta and A. Bhattacharyya, *J. Sci. Ind. Res.*, **32**, 118 (1973); (c) G. Mehta, A. Bhattacharyya, and S. K. Kapoor, *ibid.*, **32**, 191 (1973).

(4) Some of the recent syntheses achieved through sesquiterpene → sesquiterpene transformations and involving alteration of the carbocyclic framework are (a) α-santonin → dihydrocostunolide, E. J. Corey and A. G. Hortmann, *J. Amer. Chem. Soc.*, **85**, 4033 (1963); (b) longifolene → (+)-sativene, P. de Mayo and R. E. Williams, *ibid.*, **87**, 3275 (1965); (c) α-santonin → 1-epicyclocolorenone, G. Buchi, J. M. Kaufman, and H. J. E. Lowenthal, ibid., **88**, 3403 (1966); (d) α-cyperone → cyperolone, H. Hikino, N. Suzuki, and T. Takemoto, *Chem. Pharm. Bull.*, **15**, 1395 (1967); (e) germacatriene → eudesmane types, E. D. Brown, M. D. Solomon, J. K. Sutherland, and A. Torre, *Chem. Commun.*, 111 (1967); (f) β-himachalene → cuparene, H. N. Subba Rao, N. P. Damodaran, and S. Dev, *Tetrahedron Lett.*, 2213 (1968); (g) α-cyperone → α-bulnesene E. Piers and K. F. Chang, *Can. J. Chem.*, **48**, 2234 (1970); (h) α-santonin → achillin, E. H. White and J. N. Marx, *Tetrahedron*, **25**, 2177 (1969); (i) α-santonin → pseudoguaianolides, J. B. Hendrickson, C. Ganter, D. Dorman, and H. Link, *Tetrahedron Lett.*, 2235 (1968); (j) methyl farnesate → (±)-junenol, M. A. Schwartz, J. D. Crowell, and J. H. Musser, *J. Amer. Chem. Soc.*, **94**, 4361 (1972); (k) thujopsene → cuparene and α-chamigrene, S. Ito, M. Yatagi, and K. Endo, *Tetrahedron Lett.*, 1149 (1971).

(5) J. B-Son Bradenberg and H. Erdtman, *Acta Chem. Scand.*, **15**, 685 (1961); T. C. Joseph and S. Dev, *Tetrahedron*, **24**, 3809 (1968).

(6) H. Erdtman and L. Westfelt, *Acta Chem. Scand.*, **17**, 2351 (1963); L. Westfelt, *ibid.*, **21**, 159 (1967).

(7) J. B. Hendrickson, *Tetrahedron*, **7**, 83 (1959); W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev., Chem. Soc.*, 331 (1967).

(8) This is a typical example of Grob fragmentation with elimination: C. A. Grob and P. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967). For examples of C_1–C_7 bond scission in the bicyclo[2.2.1]heptane system, see P. G. Gassman and J. G. Macmillan, *J. Amer. Chem. Soc.*, **91**, 5527 (1969); D. H. Gustafson and W. F. Erman, *J. Org. Chem.*, **30**, 1665 (1965).

(9) This reaction has been reported in a preliminary communication.[1d]

(10) The examples on which this expectation was based are provided by the work of (a) S. Cannizzaro and F. Sestini, *Gazz. Chim. Ital.*, **2**, 241 (1873); (b) R. B. Woodward, F. I. Brutschy, and H. Baer, *J. Amer. Chem. Soc.*, **70**, 4216 (1948); (c) E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *ibid.*, **86**, 478 (1964).

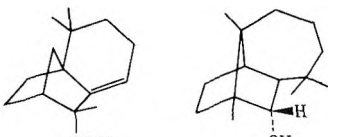
(11) A similar approach for the synthesis of tricyclic sesquiterpene copaene from santonic acid has been considered: A. G. Hortmann and D. S. Daniel, *J. Org. Chem.*, **37**, 4446 (1972). Also see Y. Lin and A. Nickon, *J. Amer. Chem Soc.*, **92**, 3496 (1970); W. Kirmse, G. Arend, and R. Siegfried, *Angew. Chem., Int. Ed. Engl.*, 165 (1970).

(12) For the previously reported synthesis of (±)-himachalene dihydrochloride and (±)-himachalenes, see (a) B. D. Challand, H. Hikino, G. Kornis, G. Lange, and P. de Mayo, *J. Org. Chem.*, **34**, 794 (1969); (b) E. Wenkert and K. Naemura, Syn. Commun., **3**, 45 (1973).

(13) This compound has been found to occur[14] in the essential oil of *Cedrus deodar* Loud. and a synthesis[14] of its racemate along traditional lines has been reported.

(14) R. C. Pandey and S. Dev, *Tetrahedron*, **24**, 3829 (1968).

(15) The complexity of the hydrocarbon mixture and formation of tetracyclic bromide **14** was quite unexpected. The analogous rearrangement[1b] of longifolene (**1**) in trifluoroacetic acid followed by hydrolysis has been shown to give isolongifolene (i, 60%) as the major product, a secondary alcohol (**13**, 35%), and longiborneol (ii, 5%). However, in the rearrangement of **9** no product corresponding



i, X = H ii
iii, X = Br

to iii was encountered. This substituent-induced dichotomy in the rearrangement of **1** and the total suppression of a pathway leading to iii from **9** has certain mechanistic implications on the longifolene-isolongifolene rearrangement. For relevant discussion see G. Ourisson, *Proc. Chem. Soc.*, 274 (1964); R. Ranganathan, U. R. Nayak, T. S. Santhanakrishnan, and S. Dev, *Tetrahedron*, **26**, 621 (1970); J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *J. Amer. Chem. Soc.*, **89**, 2590 (1967); J. E. McMurry, *J. Org. Chem.*, **36**, 2826 (1971).

(16) P. Naffa and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1410 (1954); S. Akiyoshi and H. Erdtman, *Tetrahedron*, **9**, 237 (1960).

(17) Acid-catalyzed rearrangement products from longifolene (**1**) bearing the carbon skeleton of **16** and **17** have been reported: L. Stehelin, J. Lhomme, and G. Ourisson, *J. Amer. Chem. Soc.*, **93**, 1650 (1971); R. Coates and J. P. Chen, *Chem. Commun.*, 1481 (1970).

(18) We wish to thank Dr. K. Venkatesan, Indian Institute of Science, Bangalore, for this information. These results will be published separately.

(19) J. R. Prahlad, U. R. Nayak, and S. Dev, *Tetrahedron*, **26**, 663 (1970); S. G. Patnekar and S. C. Bhattacharyya, *Indian J. Chem.*, **8**, 36 (1970).

(20) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 866 (1962); E. J. Corey, R. B. Mitra, and H. Uda, *ibid.*, **86**, 485 (1964).

(21) The absolute configuration of bicyclo[5.4.0]undecane derivatives **22**–**31** follows from the known absolute configuration of longifolene. The absolute configuration of naturally occurring himachalenes (**2**) has been deduced[23] from their correlation with longifolene (**1**): G. Ourisson, *Bull. Soc. Chim. Fr.*, 895 (1954); S. Munavalli and G. Ourisson, *ibid.*, 2825 (1964).

(22) D. Ginsberg and W. J. Rosenfelder, *Tetrahedron*, **1**, 3 (1957).

(23) T. C. Joseph and S. Dev, *Tetrahedron*, **24**, 3841 (1968).

(24) T. C. Joseph and S. Dev, *Tetrahedron*, **24**, 3853 (1968).

(25) G. Stork and P. A. Grieco, *Tetrahedron Lett.*, 1807 (1971).

(26) Melting points and boiling points are uncorrected. Melting points were taken in capillaries on a Fischer-Jones melting point apparatus. Boiling points refer to bath temperature in those cases where short-path bulb-to-bulb distillations were carried out. The petroleum ether corresponds to the fraction of bp 60–80°. All solvent extracts were dried over anhydrous sodium sulfate. Specific rotations were measured in chloroform on a JASCO DIP automatic polarimeter. The ultraviolet spectra were recorded on a Beckman DU spectrophotometer in methanol. infrared spectra were recorded on a Perkin-Elmer Model 137B spectrophotometer as neat liquids or solids as KBr disks. Pmr spectra were obtained on approximately 10–15% solutions in CCl_4 or $CDCl_3$ on a Varian A-60 spectrometer. The chemical shifts are reported in parts per million downfield from internal tetramethylsilane at δ 0.00 as internal standard. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Microanalyses were performed by Mr. A. H. Siddiqui in the microanalytical laboratory of our department.

(27) The structural assignment of **14** is further supported by the fact that the same tetracyclic bromide is also formed on the addition of Br_2 to longifolene (**1**). There is thus, a close analogy[28] in the formation

of 14 from longifolene and the addition of halogens to camphene, the isoprenolog of 1, leading to tricyclene derivatives.
(28) B. H. Jennings and G. B. Herschbach, *J. Org. Chem.*, **30**, 3902 (1965); H. G. Richey, J. E. Grant, T. J. Garbacik, and D. L. Dull, *ibid.*, **30**, 3909 (1965).
(29) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(30) M. F. Grunden, H. B. Henbest, and M. D. Scott, *J. Chem. Soc.*, 1855 (1963).
(31) P. Naffa and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1410 (1955).

Syntheses Employing Hexamethyl(Dewar benzene). Reactions of Methyl-Substituted Carbonium Ions with Triethylamine[1]

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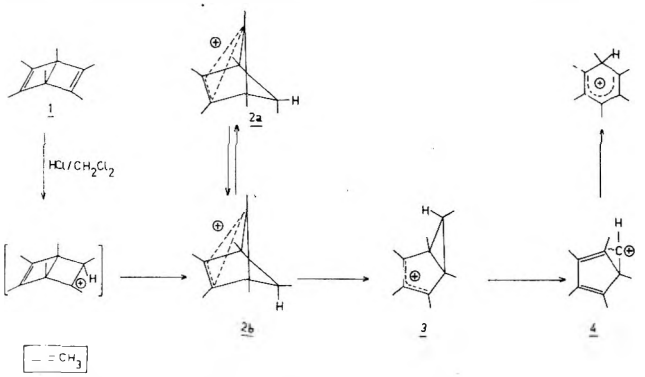
Syntheses of 1,2,3,5,6-pentamethyl-4-methylenebicyclo[3.1.0]hex-2-ene (**5**), 1,2,4,5,6-pentamethyl-3-methylenetricyclo[2.2.0.0^{2,6}]hexane (**8**), 1,2,5,6-tetramethyl-3,4-dimethylenetricyclo[3.1.0.0^{2,6}]hexane (**9**), and 5-α-chloroethyl-1,2,4,5-tetramethyl-3-methylenecyclopentene (**16**) are reported. These involve proton abstraction by triethylamine from the corresponding carbonium ions. The proton abstraction is proposed to be a kinetically controlled process occurring at the methyl group adjacent to the carbon atom bearing the highest positive charge.

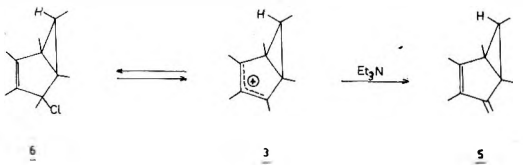
Reactions of hexamethyl(Dewar benzene) (**1**) with acids have been the subject of many investigations in recent years.[2,3] Protonation of **1** followed by rearrangement will give isomers of **1** after subsequent proton abstraction. Triethylamine appeared to be particularly useful for performing these proton abstractions. Some other carbonium ions originating from **1** have been treated in the same way and the low-temperature abstraction of a proton from a methyl-substituted carbonium ion with triethylamine seems to be generally applicable as a good synthetic method for preparing strained compounds with exocyclic methylene groups. The results of this reaction are presented below.

Results and Discussion

It has been shown that the reaction path of **1** with HCl followed by subsequent isomerization is as follows.[2d] The

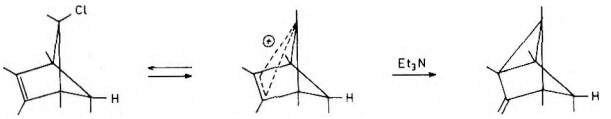


homofulvene **5**, which is an isomer of **1**, was prepared *via* reaction of **1** with HCl at −40° to give **6**. Compound **6** will dissociate to give cation **3**, which then reacts with triethylamine with loss of a proton. The homofulvene **5** was pre-

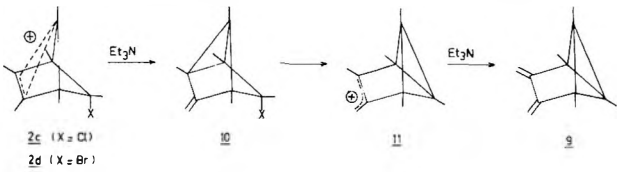


pared previously by a photochemical isomerization of **1**,[4] and also by quenching of a strongly acidic solution of **3** with sodium bicarbonate in methanol.[5] The stereochemistry of **5**, once supposed to be exo-H,[6] is accepted now to be endo-H. The assignment is based on comparison[5,7] of the pmr chemical shifts of **5** and the related ion **3** with those of the homofulvene and the cation with the inverted H and CH_3 configuration.[8]

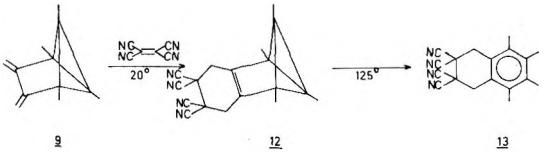
For the preparation of a tricyclic isomer of **1**, compound **8**, the following procedure was developed. The cation mixture **2a,b** (3:1 in equilibrium[3a]), obtained from reaction of **1** with HCl in methylene chloride at −80°,[2d] was poured into triethylamine at −80°. The pmr spectrum of this mixture indicates that **7**[2d] is formed first; subsequently **7** will dissociate to give ion **2a** and triethylamine will then abstract a proton from the methyl group adjacent to the carbon atom bearing the highest positive charge[9] in ion **2a**.



Another application of the reaction of methyl-substituted carbonium ions with triethylamine is found in the synthesis of **9**. The cations **2c** and **2d**, formed from the reaction of **1** with chlorine and bromine, respectively,[9] give **9** upon proton abstraction with triethylamine. This product can be accounted for by assuming that the proton abstraction to give **10** occurs in the same way as with **2a**. The intermediate **10** will presumably dissociate to give cation **11**, which then undergoes another proton abstraction to give **9**. Compound **9** was obtained also by pouring a solution of

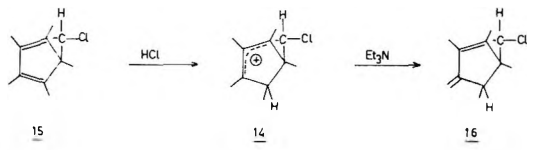


dication $(CCH_3)_6^{2+}$ in a triethylamine solution at low temperature.[10] Structure **9** was assigned on the basis of



the spectra and the Diels–Alder reaction of **9** with tetracyanoethylene to give **12**, which in turn isomerized to **13** on heating.

The role of the positive charge in determining the site of the proton abstraction is shown by the reactivity of ions **2a**, **2c**, and **2d**. It is suggested by the products that the reactions are kinetically controlled; otherwise thermodynamically favored[9] bicyclic products would have formed. The kinetic control of proton abstraction from methyl-substituted carbonium ions is illustrated by the reactivity of cation **14**. Cation **14** is obtained on protonation of **15**, which is itself formed by reaction of **1** with HCl at room temperature. Triethylamine did not give the reverse reaction with **14**, *i.e.*, proton abstraction yielding **15**; instead the amine abstracted a methyl proton to give **16**. Compound **16** was observed previously[11] as a product of the reaction of compound **8** with HCl at low temperature. The isomerization of **16** to **15** occurs almost instantaneously at room temperature on addition of a trace of acid. This behavior of **16** shows **15** to be the thermodynamically more stable isomer. Thus, proton abstraction from **14** has to be a kinetically controlled process. Presumably this is general for low-temperature proton abstraction from methyl-substituted carbonium ions with triethylamine.



15 14 16

Experimental Section

Proton magnetic resonance spectra were recorded at 60 MHz using a Varian A-60D spectrometer. Chemical shifts are calculated relative to internal TMS at δ 0. Natural abundance carbon-13 nuclear magnetic resonance spectra were obtained with a Varian XL-100 spectrometer operating at 25.2 MHz. Spectra were recorded using Fourier transform and were proton-noise decoupled. Chemical shifts were calculated relative to external (capillary) TMS. Mass spectra were determined with an AEI MS 902 mass spectrometer and ir spectra were obtained with use of a Perkin-Elmer 257 spectrometer. Only representative peaks are given. Uv spectra were measured with a Beckman DB-G spectrophotometer.

1,2,3,5,6-Pentamethyl-4-methylenebicyclo[3.1.0]hex-2-ene (5). In a 250-ml three-necked bottle equipped with a mechanical stirrer, 3.20 g (0.02 mol) of hexamethyl(Dewar benzene) was dissolved in 60 ml of methylene chloride. The solution was cooled to −40° and 1.80 g (0.05 mol) of dry hydrogen chloride gas was introduced. A solution of 10.0 g (0.1 mol) of triethylamine in 30 ml of methylene chloride was added rapidly with stirring. The temperature of the reaction mixture was allowed to rise to 20° while stirring was continued for 2 hr, after which the solvent was evaporated and pentane (50 ml) and water (500 ml) were added. The organic layer was separated, washed with water until the smell of triethylamine had disappeared, and dried over sodium sulfate. The pentane was evaporated and the crude product was distilled to give a 2.45-g (0.015 mol, 75%) yield of **5**, bp 74–76° (5 mm); it was characterized by its nmr and ir spectra.[7]

1,2,4,5,6-Pentamethyl-3-methylenetricyclo[2.2.0.0^{2,6}]hexane (8). In a 250-ml three-necked bottle equipped with a mechanical stirrer, 3.20 g (0.02 mol) of hexamethyl(Dewar benzene) was dissolved in 60 ml of methylene chloride. The solution was cooled to −80° and 1.80 g (0.05 mol) of dry hydrogen chloride gas was introduced. A solution of 10.0 g (0.1 mol) of triethylamine in methylene chloride at −80° was added rapidly and with stirring from a cooled dropping funnel. The reaction mixture was stirred at −70° for 3 hr and warmed to room temperature over another 3 hr. The solvent was evaporated and pentane (50 ml) and water (500 ml) were added. The organic layer was separated, washed with water until the smell of triethylamine had disappeared, and dried over sodium sulfate. The pentane was evaporated and the crude product was distilled, bp 47.5–48.5° (3.7 mm), to give a 2.55-g (0.016 mol, 80%) yield of **8** as a colorless liquid. An analytically pure sample was obtained by preparative glc (SE-30 column, all temperatures below 200°). Compound **8** is rapidly oxidized upon exposure to the air at room temperature: mass spectrum parent peak at *m/e* 162; ir spectrum *inter alia* 3070 (=CH_2 stretching), 1655 (C=C stretching), and 860 cm^{-1} (=CH_2 out-of-plane deformation); pmr spectrum (CCl_4) δ 4.57 (d, J = 0.8 Hz, 1 H), 4.54 (d, J = 0.8 Hz, 1 H), 2.01 (q, J = 7 Hz, 1 H), 1.33, 1.28, 1.03, 1.00 (s, each 3 H), and 0.86 (d, J = 7 Hz, 3 H); cmr spectrum[9] (CH_2Cl_2) peaks at 166.2, 97.4, 47.7, 45.0, 45.0, 27.2, 24.2, 18.5, 9.5, 8.7, 4.7 and 4.3 ppm downfield from external (capillary) TMS.

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.5; H, 11.3.

1,2,5,6-Tetramethyl-3,4-dimethylenetricyclo[3.1.0.0^{2,6}]hexane (9). In a 250-ml three-necked bottle equipped with a mechanical stirrer, 3.20 g (0.02 mol) of hexamethyl(Dewar benzene) was dissolved in 60 ml of methylene chloride. The solution was cooled to −80° and about 1 equiv of dry chlorine gas was introduced to give a solution of ion **2c**. Alternatively a solution of 4.0 g (0.025 mol) of bromine in 10 ml of methylene chloride was introduced slowly at −80° to give a solution of ion **2d**. The solutions of ions **2c** or **2d** were treated with 4.0 g (0.04 mol) of triethylamine in 10 ml of methylene chloride, which was introduced from a dropping funnel in 15 min with stirring. The temperature of the reaction mixture was not allowed to exceed −70° during the addition and 2 hr thereafter, during which time triethylammonium salt precipitated. After warming to room temperature (over 2 hr), the solvent was evaporated and 50 ml of pentane and 500 ml of water were added. The organic layer was separated, washed with water until the smell of triethylamine had disappeared, and dried over sodium sulfate. The pentane was evaporated, leaving 3.0 g of a crude product, which consisted according to the nmr spectrum of 85% of **9**. Vacuum distillation provided 1.9 g (0.012 mol, 60% yield) of **9**, bp 69–70° (12 mm). The residue contained hexamethylbenzene (0.3 g, 0.002 mol, 10%). An analytically pure sample was obtained by preparative glc (SE-30 column, all temperatures below 150°). Compound **9** is oxidized rapidly upon exposure to the air at room temperature: mass spectrum parent peak at *m/e* 160; ir spectrum *inter alia* 3080 (=CH_2 stretching), 1640 (C=C stretchig), and 865 cm^{-1} (=CH_2 out-of-plane deformation); uv spectrum λ_{max} (ethanol) 204 nm (log ϵ 3.95) and 250 (3.78); pmr spectrum (CCl_4) δ 5.00 (s, 2 H), 4.53 (s, 2 H), 1.42 (s, 6 H), 1.14 (s, 6 H); cmr spectrum (CH_2Cl_2) peaks at 157.5, 98.7, 47.1, 31.4, 10.0, and 6.0 ppm downfield from external (capillary) TMS.

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.2; H, 10.1.

Reaction of 9 with Tetracyanoethylene. Tetracyanoethylene (128 mg, 1.0 mmol) was added as a solid to a stirred solution of 160 mg (1.0 mmol) of **9** in 3 ml of chloroform at room temperature. After 10 min the solvent was evaporated to leave 285 mg (1.0 mmol, 100%) of the adduct **12**. It was purified by crystallization from CCl_4–$CHCl_3$: mass spectrum parent peak at *m/e* 288; *inter alia* 2260 (weak, C≡N) and 1665 cm^{-1} (weak, C=C); pmr ($CDCl_3$) δ 3.12 (s, 4 H), 1.47 (s, 6 H), 1.16 (s, 6 H).

Anal. Calcd for $C_{18}H_{16}N_4$: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.5; H, 5.6; N, 19.2.

Pyrolysis of 12. On warming a neat sample of **12** at 125° a reaction took place without melting. The product obtained,[12] **13**, showed a melting point of 230–232°: mass spectrum parent peak at *m/e* 288, base peak at *m/e* 160; ir *inter alia* 2260 (weak, C≡N) and 740 cm^{-1} (ortho-disubstituted benzene); pmr ($CDCl_3$) δ 3.72 (broad s, 4 H), 2.30 (s, 6 H), 2.20 (s, 6 H); uv λ_{max} ($CHCl_3$) 274 nm (log ϵ 2.60).

Anal. Calcd for $C_{18}H_{16}N_4$: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.7; H, 5.7; N, 19.3.

5-α-Chloroethyl-1,2,4,5-tetramethyl-3-methylenecyclopentene (16). In a nmr tube, 100 mg (0.5 mmol) of 1-α-chloroethyl-1,2,3,4,5-pentamethylcyclopenta-1,3-diene[2b] (**15**) was dissolved in 0.5 ml of methylene chloride. This solution was cooled to −80° and 180 mg (5 mmol) of dry hydrogen chloride gas was introduced at this temperature to give a solution of cation **14**, which was detected by its pmr spectrum at −80°.[11] The solution of cation **14** was poured with stirring into a mixture of 1.00 g (10 mmol) of triethylamine and 20 ml of methylene chloride at −80°, after which triethylammonium salt precipitated. The reaction mixture was kept at −70° for 1 hr and then warmed up to room temperature. After the solvent was evaporated, 20 ml of pentane and 200 ml of water were added and the organic layer was separated, washed with water until the smell of triethylamine had disappeared, and dried over sodium sulfate. The solvent was evaporated, leaving 95 mg of a yellow liquid, which consisted of 90% **16** (determined by pmr). Upon standing at room temperature **16** rapidly isomerized

to **15**: mass spectrum parent peak at *m/e* 198, 200 (3:1); ir *inter alia* 3100 (=CH_2 stretching), 1625 (C=C stretching), and 880 cm^{-1} (=CH_2 out-of plane deformation); pmr (CCl_4) δ 4.75 (m, 1 H), 4.60 (m, 1 H), 4.10 (q, J = 7 Hz, 1 H), 2.85 (m, 1 H), 1.72 (broad s, 6 H), 1.50 (d, J = 7 Hz, 3 H), 1.09 (s, 3 H), 0.98 (d, J = 7 Hz, 3 H).

Registry No.—**1**, 7641-77-2; **5**, 20379-83-3; **8**, 40265-14-3; **9**, 50590-86-8; **12**, 50590-87-9; **13**, 51751-70-3; **15**, 19835-61-1; **16**, 41694-21-7; triethylamine, 121-44-8; tetracyanoethylene, 670-54-2.

References and Notes

(1) Preliminary publishing in part: (a) H. Hogeveen and P. W. Kwant, *Tetrahedron Lett.*, 5357 (1972); (b) *ibid.*, 3747 (1973).
(2) (a) W. Schafer and H. Hellmann, *Angew. Chem.*, **79**, 566 (1967); (b) L. A. Paquette and G. R. Krow, *Tetrahedron Lett.*, 2139 (1968); (c) M. Kunz and W. Luttke, *Chem. Ber.*, **103**, 315 (1970); (d) H. Hogeveen and P. W. Kwant, *Tetrahedron Lett.*, 3197 (1972).
(3) (a) H. Hogeveen and H. C. Volger, *Recl. Trav. Chim. Pays-Bas*, **87**, 385, 1042 (1968); **88**, 353 (1969); (b) L. A. Paquette, G. R. Krow, J. M. Bollinger, and G. A. Olah, *J. Amer. Chem. Soc.*, **90**, 7147 (1968).
(4) H. Hogeveen and H. C. Volger, *Chem. Commun.*, 1133 (1967).
(5) V. A. Koptyug, L. I. Kuzabova, I. S. Isaev, and V. I. Mamatyuk, *J. Org. Chem. USSR*, **6**, 1854 (1970).
(6) M. Rey, U. A. Huber, and A. S. Dreiding, *Tetrahedron Lett.*, 3583 (1968).
(7) (a) R. Criegee and H. Grüner, *Angew. Chem.*, **80**, 447 (1968); (b) V. A. Koptyug, L. I. Kuzubova, I. S. Isaev, and V. I. Mamatyuk, *Chem. Commun.*, 389 (1969); (c) R. Criegee, H. Grüner, D. Schönleber, and R. Huber, *Chem. Ber.*, **103**, 3696 (1970).
(8) This implies that the assignment of the related structures in ref 2d is endo-H rather than exo-H.
(9) H. Hogeveen and P. W. Kwant, *J. Amer. Chem. Soc.*, 95, 7315 (1973).
(10) Reference 1b; H. Hogeveen and P. W. Kwant, *J. Amer. Chem. Soc.*, **96**, 2208 (1974).
(11) H. Hogeveen and P. W. Kwant, *Tetrahedron Lett.*, 5361 (1972).
(12) In cooperation with Drs. W. F. J. Huurdeman. For another synthetic pathway see H. Hogeveen and W. F. J. Huurdeman, *Tetrahedron Lett.*, 1255 (1974).

Double Bond *vs.* Cyclopropane Ring Reactivity toward Different Acids[1]

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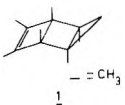
The reactions of compounds **2**, **3**, and **4** with the strong acid $FHSO_3$ and with $HCl-CH_2Cl_2$ have been studied and mechanisms for these reactions are discussed. It is concluded that the reaction with $FHSO_3$ takes place at the methylene groups of the compounds investigated. The reaction with HCl, however, takes place at the cyclopropane rings of compounds **2** and **3** and possibly also of compound **4**. Tentative explanations are given, based on the different nature of the acids and different structural properties of the substrate compounds.

Some aspects of the mechanism of the protonation of cyclopropane, *e.g.*, the relative stability of the face-protonated, edge-protonated, and corner-protonated cyclopropane and the question whether the protonation occurs *via* an inversion or a retention mechanism, have been amply discussed.[2,3] Another aspect of the protonation of cyclopropane, namely the relative reactivity of cyclopropanes and double bonds, has gained less attention. From the few examples known[2d] the general trend seems to be that cyclopropane rings are more reactive toward acids than are carbon–carbon double bonds. We wish to add a new element to this discussion; it appears that in compounds containing a cyclopropane ring as well as a double bond the nature of the acid plays an important role in determining whether the cyclopropane ring or the double bond reacts first. Previously[3a] it was found that compound **1**,



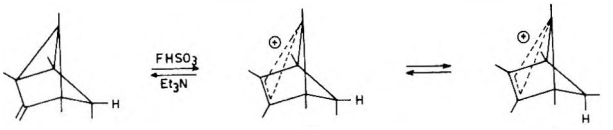
1

containing a double bond and a cyclopropane ring, reacted at the cyclopropane ring with hydrogen chloride in methylene chloride. Superacids such as $FHSO_3-SO_2ClF$, $FHSO_3-SbF_5$, $FHSO_3-SbF_5-SO_2F_2$, and $HF-BF_3$, however, did not give the product expected upon protonation of the cyclopropane ring. Perhaps reaction at the double bond occurred as the first step under the latter conditions.

Results and Discussion

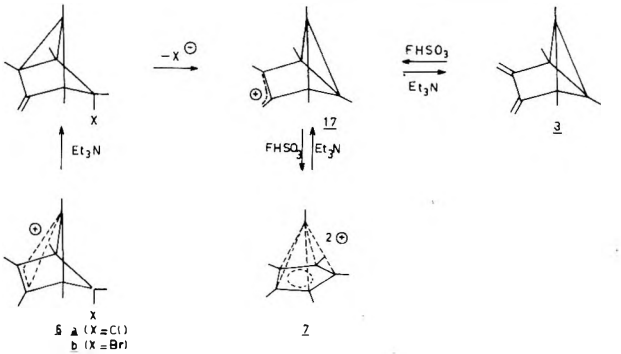
The different behavior of the superacids and $HCl-CH_2Cl_2$ toward compounds containing cyclopropane rings and double bonds was investigated with use of the model compounds **2**, **3**, and **4**, containing different numbers of the reactive structural components mentioned. These model compounds are readily accessible in two-step reactions starting from hexamethyl(Dewar benzene).[1,4] In the first step the carbonium ions **5a**, **6**, **7**, and **8**, respectively, are generated and in the second step triethylamine abstracts a proton from these carbonium ions at the methyl group adjacent to the carbon atom bearing the highest positive charge.[4c]

Reactions with $FHSO_3$. The reactions of **2**, **3**, and **4** with $FHSO_3$ show the exact reverse of the triethylamine-induced deprotonation step in the syntheses of **2**, **3**, and **4**. When **2** was dissolved in $FHSO_3$ at −80°, the pmr spectrum of the solution showed the presence of a 3:1 equilibrium mixture[5] of **5a** and its endo-H isomer **5b**. Extraction



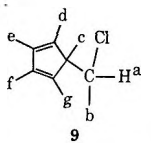
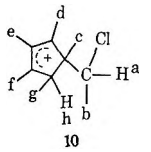
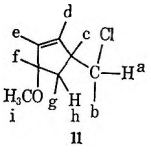
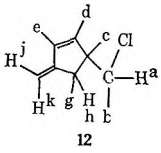
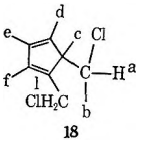
2 **5a** **5b**

of a solution of **3** in methylene chloride with $FHSO_3$ at −90° afforded the dication **7**, which presumably was ob-

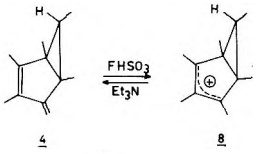


tained by successive protonation of the two methylene groups of **3**.[4b] From the literature[6,7] it is known that **4**

Table I
Pmr Spectral Data[a] of Compounds 9,[b,c] 10,[d] 11,[c] 12,[d] and 18[d]

 9	a, 4.05 (1 H, q, J = 6.5 Hz); b, 1.02 (3 H, d, J = 6.5 Hz); c, 1.08 (3 H, s); d, e, f, and g, 1.68 (3 H, broad s), 1.75 (6 H, broad s), and 1.87 (3 H, broad s)
 10	a, 4.52 (1 H, q, J = 7 Hz); b, 1.77 (3 H, d, J = 7 Hz); c, 1.38 (3 H, s); d and f, 3.00 (6 H, m); e, 2.27 (3 H, m); g,[e] 1.53 (3 H, d, J = 7 Hz); h, 3.52 (1 H, m)
 11	a,[f] 4.05 (1 H, q, J = 7 Hz); b,[f] 1.44 (3 H, d, J = 7 Hz); c, 1.01 (3 H, s); d and e, 1.59 (6 H, d); f, 1.21 (3 H, s); g,[f] 0.96 (3 H, d, J = 7 Hz); h,[f] 2.12 (1 H, q, J = 7 Hz); i, 3.01 (3 H, s)
 12	a,[f] 4.29 (1 H, q, J = 7 Hz); b,[f] 1.54 (3 H, d, J = 7 Hz); c, 1.06 (3 H, s); d and e, 1.72 (6 H, broad s); g,[f] 1.02 (3 H, d, J = 7 Jz); h,[f] 2.77 (1 H, m); j and k, 4.77 (1 H, m) and 4.67 (1 H, m)
 18	a, 4.15 (1 H, q, J = 7 Hz); b, 1.10 (3 H, d, J = 7 Hz); c, 1.13 (3 H, s); d, e, and f, 1.88 (6 H, broad s) and 1.80 (3 H, m); l, 4.27 (2 H, s)

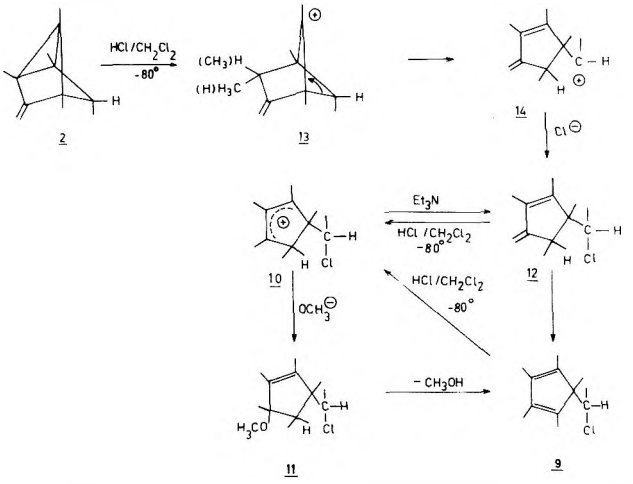
[a] δ in parts per million relative to internal TMS. [b] Reference 8b. [c] Solvent CCl_4. [d] Solvent CH_2Cl_2. [e] The peaks of this doublet show additional structure owing to coupling with methyl groups of the ring when the spectrum is recorded at 100 MHz (XL-100). [f] These assignments were confirmed by double-resonance experiments.


4 8

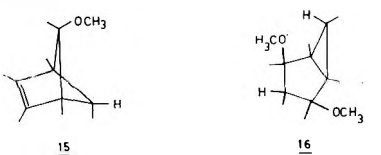
gives **8** on reaction with $FHSO_3$ at −70°. The three model compounds **2**, **3**, and **4** apparently prefer low-temperature reaction with $FHSO_3$ at the methylene groups, rather than reaction at the cyclopropane ring.

Reactions with HCl-CH_2Cl_2. The reaction of these compounds with HCl followed in part another pathway. When compound **2** was dissolved in HCl-CH_2Cl_2 (1:1 molar ratio) at −80°, the yellow solution showed a pmr spectrum which was identical with that of a solution of **9**[8] under the same conditions. This spectrum was assigned to the cyclopentenyl cation **10**, the structure of which is assigned on the basis of the pmr spectrum (see Table I) and product analysis after quenching of a solution of **10** with excess sodium methoxide in methanol at −80°. After work-up of the reaction mixture, pmr indicated compound **11** to have been formed. Assignment of structure **11** is based on the spectral data (see Table I and Experimental Section) and the observation that the product decomposed into **9** and methanol upon standing at 40° for several hours. Mechanistically two possibilities for the reaction of **2** with HCl have to be envisaged. The first possibility is double bond attack, just as in the case of $FHSO_3$. In this way cation **5a** should be formed, which exists in equilibrium with **5b**.[5,9] It is known that a solution of these ions with Cl^- as counterion, as is the case, can give **9**[9] and it is shown above that **9** is protonated under the reaction conditions. However, the reaction of **5a,b** in HCl-CH_2Cl_2 (1:1 molar ratio) was never observed to occur at −80°.[9] The second, more likely, possibility is attack at the cyclopropane ring. Experimental support for this idea was obtained in a reaction of a solution of **2** in methylene chloride with *ca.* 0.7 equiv of dry HCl gas at −80°. In this case the pmr spectrum of the solution indicated the presence of **12** together with starting material **2**. The assignment of structure **12** depends on the pmr spectrum (see Table I), the room-temperature isomerization of **12** to **9** which is enhanced enormously upon addition of a trace of acid, the protonation of **12** in HCl-CH_2Cl_2 at −80° to give cation **10**, and the independent synthesis of **12** from **10** by deprotonation with triethylamine.[4c]

From these experiments the conclusion can be drawn that HCl in CH_2Cl_2 at −80° attacks **2** at the cyclopropane ring. The reaction scheme of **2** with HCl-CH_2Cl_2 at −80° is almost complete now; only the steps from **2** to **12** are missing. Therefore we look at the six different ways in which proton addition and subsequent opening of the cyclopropane ring can occur. A reaction path *via* **13** and **14** involves only two steps and the intermediates are not extremely unstable. The five other ways either lead to different products or involve more steps, so that we propose the intermediates **13** and **14** to complete the reaction scheme.


2 13 14 10 12 11 9

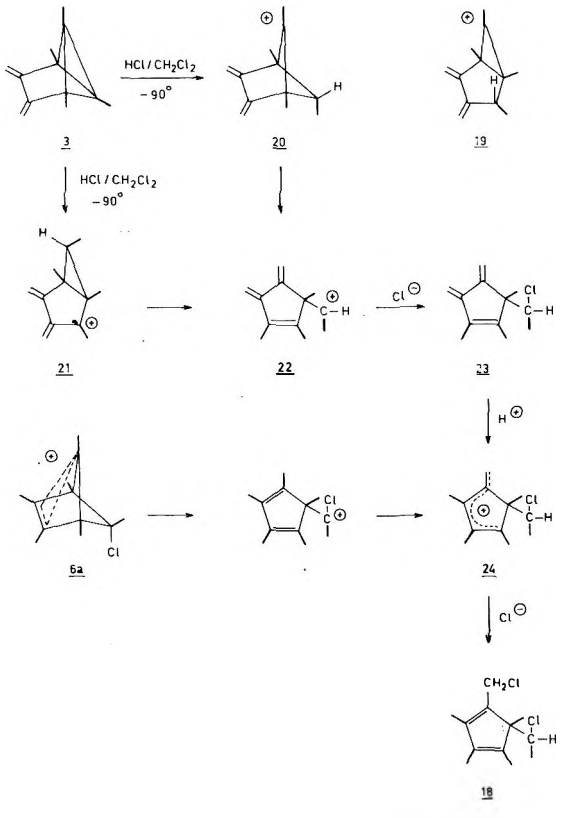
When the reaction of **2** with excess HCl (2- to 100-fold) was carried out at temperatures above −60° followed by quenching with sodium methoxide and methanol at the same temperature, the products were found to be not only **9**, **11**, and hexamethylbenzene, but also **15** (maximum amount found, 5%) and **16** (maximum 25%). The latter


15 16

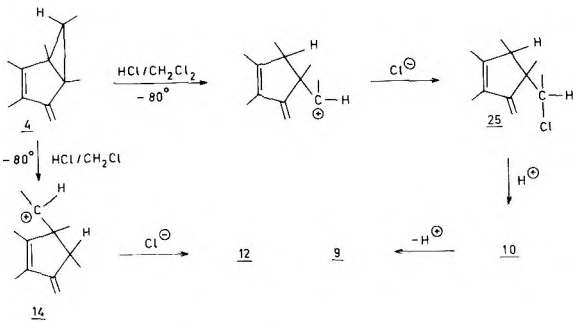
compounds have been obtained before from **5a,b**,[9] so that it is possible that at temperatures above −60° the reaction is less selective and HCl attacks the double bond as well as the cyclopropane ring.

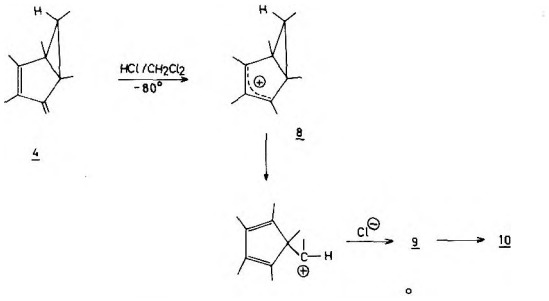
Compound **3** also shows a different behavior in reactions with $FHSO_3$ and HCl. Addition of successive portions of dry HCl to a methylene chloride solution of **3** at −90° did not give rise to observable amounts of **7** or the presumed monoprotonation product **17**.[4b] The pmr spectrum of the reaction mixture at −90° showed compound **18** to be

formed even when an excess of 3 was still present. The pmr spectrum of the reaction mixture remained unchanged upon warming to room temperature and 18 was isolated by evaporating the solvent. The assignment of structure 18 depends on the spectral data (see Table I and Experimental Section) and independent synthesis from 6a by intramolecular rearrangement.[1b,10] It is difficult to rationalize the formation of compound 18 in the reaction of 3 with HCl by assuming protonation of a methylene group of 3 to be the first step. However, assuming initial attack on a cyclopropane ring, a reasonable mechanism can be drawn. According to Wiberg and Szeimies[11] the protonation of the bicyclobutane system is proposed to occur with retention of configuration. Owing to symmetry, only three intermediates are conceivable: 19, 20, and 21. Intermediate 19 is considered to be unlikely because it is energetically unfavorable and would open to a cyclohexyl ion.[12] Both intermediates 20 and 21 are possible, although 21 is expected to be the most stable one. Moreover, owing to symmetry, the formation of 21 is statistically favored by a factor of 2. Intermediates 20 and 21 are supposed to give the five-membered ring compounds 22, 23, and 24 in subsequent steps. Finally intermediate 24, proposed to be an intermediate also in the thermal reaction of 6a, reacts with chloride anion to give product 18.[1b,10]



The mechanism of the reaction of 4 with HCl in methylene chloride could not be established unambiguously. Addition of an excess of dry HCl gas to a methylene chloride solution of 4 at −80° resulted in the formation of ion 10. This can be explained either by a reaction at the cyclopropane ring or by reaction at the double bond. In the former case six intermediates are conceivable, but only the five-membered ring compounds 12 and 25 with an exocyclic methylene group can explain the product 10. When the reaction was carried out, however, with 0.6 equiv of HCl, so that 4 was still present, the methylene signals present in the pmr spectrum of the reaction mixture at −80° were due solely to 4. The only other compound present in this solution was 9. In a similar experiment with 2, the intermediate 12 appeared to be observable under these conditions (see above). Only 25 remains therefore as a possible intermediate in the case of reaction at the cyclopropane ring and one has to assume that 25 is rapidly isomerized under the reaction conditions. The other possibility is attack at the exocyclic double bond, followed by β-fission of the resulting ion 8 and reaction with Cl^- to give 9.[9] However, the isomerization of ion 8,[10]





which escapes detection in these experiments, has to be assumed to occur in this medium much faster than in strongly acidic solutions,[6,7] where ion 8 has been observed at even higher temperatures. This possibility cannot be excluded, so that an unambiguous decision on the direction of the initial attack by HCl cannot be made.

Conclusions

The experiments show a striking difference between the two acids $FHSO_3$ and $HCl-CH_2Cl_2$ in their reactivity toward double bonds and cyclopropane rings in the compounds 2, 3, and, perhaps, 4. Literature data on $FHSO_3$,[13] $HCl-CH_2Cl_2$,[14] and liquid HCl[15] indicate that, whereas in the strong acid solvated protons are available for the reaction, this is not the case with low-temperature $HCl-CH_2Cl_2$ mixtures or liquid HCl, in which the reacting particles are polar HCl molecules. This difference obviously can change the reaction pattern dramatically.[16]

Experimental Section

Spectroscopic Measurements. Proton magnetic resonance spectra were recorded at 60 MHz using a Varian A-60D or a Jeol C60HL spectrometer equipped with a variable-temperature probe, unless otherwise stated. Chemical shifts are calculated relative to internal TMS at δ 0. Mass spectra were determined with an AEI MS9 mass spectrometer and ir spectra were obtained with use of a Perkin-Elmer 257 spectrometer; only representative peaks are given. Uv spectra were measured with a Beckman DB-G spectrophotometer.

Reaction of 2 with $FHSO_3$. Reaction of 2 with $FHSO_3$ was performed by cooling an nmr tube containing 50 mg of 2 in liquid nitrogen and subsequent introduction of 0.4 ml of $FHSO_3$. The nmr tube was warmed in a bath at −80° and stirring was applied as soon as possible.

Preparation of Solutions in $HCl-CH_2Cl_2$. The substrate (50 mg) was dissolved in methylene chloride (0.2–0.4 ml). This solution was cooled to −80° and dry HCl gas was introduced until the indicated ratio was reached as concluded from the pmr spectrum of the products.

Preparation of 11. A solution of 50 mg of 2 in 0.4 ml of $HCl-CH_2Cl_2$ (1:1 molar ratio) at −80° was poured in 800 mg of sodium

methoxide in 10 ml of methanol at −80°. The reaction mixture was warmed to room temperature, water was added, and the mixture was extracted with pentane. Washing with water, drying over anhydrous sodium sulfate, and evaporating the solvent gave 69 mg of a crude product which consisted of 95% of **11**. Standing at 40° for 1 day caused quantitative decomposition of **11** into **9** and methanol. The mass spectrum of **11** showed a parent peak at *m/e* 230 corresponding with $C_{13}H_{23}OCl$; for the pmr spectrum, see Table I.

Preparation of 18. A solution of 48 mg (0.3 mmol) of **3** in 0.4 ml of methylene chloride was cooled to −80° and dry HCl gas (0.5 mmol) was introduced. The solution was warmed to room temperature and the solvent was evaporated. The pmr spectrum of the remaining 63 mg of product indicated 80% of **18** and 15% of starting material to be present. The mass spectrum of **18** showed parent peaks at *m/e* 232, 234, and 236 (intensity ratio 9:6:1), corresponding with $C_{12}H_{18}Cl_2$; pmr spectrum, see Table I; ir *inter alia* absorption at 1620 cm^{-1}; uv λ_{max} (pentane) 275 nm.

Registry No.—**2**, 40265-14-3; **3**, 50590-86-8; **4**, 20379-83-3; **9**, 19835-61-1; **10**, 51751-32-7; **11**, 41694-19-3; **12**, 41694-21-7; **18**, 50590-88-0; HCl, 7647-01-0; $FHSO_3$, 7789-21-1.

References and Notes

(1) For preliminary communications see (a) H. Hogeveen and P. W. Kwant, *Tetrahedron Lett.*, 5361 (1972); (b) *ibid.*, 3747 (1973).
(2) (a) C. J. Collins, *Chem. Rev.*, **69**, 543 (1969); (b) C. C. Lee, *Progr. Phys. Org. Chem.*, **7**, 129 (1970); (c) D. M. Brouwer and H. Hogeveen, *ibid.*, **9**, 229 (1972); (d) C. H. de Puy, *Top. Curr. Chem.*, **40**, 73 (1973).
(3) (a) H. Hogeveen, C. F. Roobeek, and H. C. Volger, *Tetrahedron Lett.*, 221 (1972); (b) K. B. Wiberg, K. C. Bishop, and R. B. Davidson, *ibid.*, 3169 (1973); (c) A. H. Andrist, *J. Amer. Chem. Soc.*, **95**, 5731 (1973); (d) J. M. Lehn and G. Wipff, *J. Chem. Soc., Chem. Commun.*, 747 (1973).
(4) (a) H. Hogeveen and P. W. Kwant, *J. Amer. Chem. Soc.*, **95**, 7315 (1973); (b) *ibid.*, **96**, 2208 (1974); (c) *J. Org. Chem.*, **39**, 2624 (1974).
(5) H. Hogeveen and H. C. Volger, *Recl. Trav. Chim. Pays-Bas*, **87**, 385, 1042 (1968); **88**, 353 (1969).
(6) V. A. Koptyug, L. I. Kuzubova, I. S. Isaev, and V. I. Mamatyug, *J. Org. Chem. USSR*, **6**, 1854 (1970).
(7) V. A. Koptyug, L. I. Kuzubova, I. S. Isaev, and V. I. Mamatyug, *Chem. Commun.*, 389 (1969).
(8) (a) L. A. Paquette and G. R. Krow, *Tetrahedron Lett.*, 2139 (1968); (b) M. Kunz and W. Lüttke, *Chem. Ber.*, **103**, 315 (1970).
(9) H. Hogeveen and P. W. Kwant, *Tetrahedron Lett.*, 3197 (1972).
(10) H. Hogeveen, P. W. Kwant, E. P. Schudde, and P. A. Wade, submitted for publication.
(11) K. B. Wiberg and G. Szeimies, *J. Amer. Chem. Soc.*, **92**, 571 (1970).
(12) P. v. R. Schleyer, T. M. Su, M. Saunders, and J. C. Rosenfeld, *J. Amer. Chem. Soc.*, **91**, 5174 (1969); L. Radom, J. A. Pople, and P. v. R. Schleyer, *ibid.*, **95**, 8194 (1973).
(13) R. J. Gillespie and T. E. Peel, *J. Amer. Chem. Soc.*, **95**, 5173 (1973).
(14) N. G. Dorofeeva and O. K. Kudra, *Ukr. Khim. Zh.*, **27**, 306 (1961); *Chem. Abstr.*, **56**, 5455 (1962).
(15) M. E. Peach and T. C. Waddington, *J. Chem. Soc.*, 600 (1962).
(16) Perturbation theory might help to explain the different behavior. The equation for the perturbation energy contains a Coulombic term and an orbital term. In the case of reactions with cations, in particular protons, the Coulombic term is the most important one and the reaction is called charge controlled. When the charge decreases, as is the case in going from a proton to a polar HCl molecule, the importance of the Coulombic term decreases and the reaction becomes orbital controlled, which means that the direction of the reaction depends on the magnitude of the frontier orbital coefficients.[17] It is obvious that charge control and orbital control will not a *priori* give rise to different reactions, but in these cases where more nucleophilic centers are available, the different reactivity toward protons and HCl might be explained by a charge-controlled reaction in the former case and an orbital-controlled reaction in the latter case. Calculations are planned to test the validity of this hypothesis.
(17) R. F. Hudson, *Angew. Chem., Int. Ed. Engl.*, **12**, 36 (1973).

Bufadienolides. 26. Synthesis of Scillarenin[1,2]

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Bufalin (**1**), previously synthesized from digitoxigenin, was utilized as relay in a new synthetic route to scillarenin (**4**). Important steps in the synthesis of scillarenin included bromination and dehydrohalogenation of bufalone (**2a**) to yield scillarenone (**3**). The overall transformation from digitoxigenin also comprised the first conversion of a plant cardenolide to a plant bufadienolide (**4**).

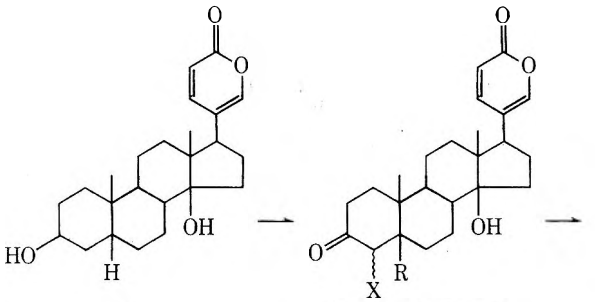
Careful hydrolysis of, *e.g.*, proscillaridin A from the ancient Egyptian medicinal plant *Scilla maritima* yields the aglycone scillarenin (**4**).[3] The parent glycoside, proscillaridin A, is a useful clinical agent for certain cardiac problems. This 3β-rhamnose derivative of scillarenin (**4**) has also been found to be an outstandingly effective cell-growth inhibitor of the National Cancer Institute's human epidermoid carcinoma of the nasopharynx cell culture (9KB).[4]

Recently we completed partial syntheses of marinobufagin and marinobufotoxin starting with telocinobufagin (**5**) isolated from Ch'an Su.[5] The objective of the present study[6] was to extend our earlier total synthesis of bufalin[1,6,7] (**1**) to the plant bufadienolide, scillarenin[8] (**4**). The latter substance could then serve as relay in a formally continuous route[5] to telocinobufagin (**5**).

Selective chromic acid oxidation (Sarett) of bufalin (**1**) to the previously known 3-oxo derivative, bufalone (**2a**), provided a useful precursor of scillarenin (**4**). Controlled bromination of ketone **2a** with *N*-bromosuccinimide gave an epimeric mixture of the C-4 bromo derivatives (**2b**), which were dehydrobrominated in low yield using hot α-collidine or pyridine. An improved procedure involved treatment of ketone **2a** with bromine in dimethylformamide or acetic acid to give the corresponding 4-bromo derivative, which was subjected directly to dehydrobromination with lithium bromide in dimethylformamide or lithium chloride in dimethylacetamide. After preparative thin layer chromatography, scillarenone (**3**) was isolated in 30–40% yields.

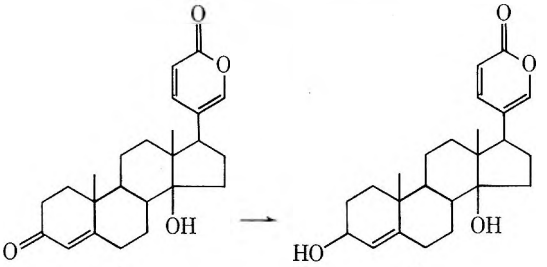
A partial synthesis of scillarenone (**3**) from telocinobufagin (**5**) was also evaluated. As part of the original structural study[9] of telocinobufagin (**5**) the 3β-hydroxyl was selectively oxidized to provide ketone **2c**, which upon treatment with hot acetic acid gave scillarenone (**3**). The Meyer[9] route was conveniently modified as follows. Oxidation of telocinobufagin to ketone **2c** was accomplished in good yield with *N*-bromoacetamide and selective elimination of the tertiary 5-hydroxyl group was readily achieved using an acidic ion-exchange resin. The samples of ketone **3** prepared from bufalin and telocinobufagin were shown to be identical.

Reduction of ketone **3** to scillarenin (**4**) and thereby completion of a new formal total synthesis of this plant

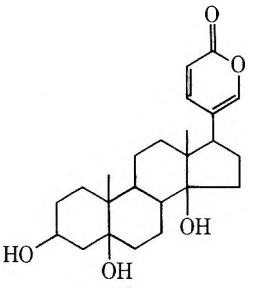


1

2a, X = H; R = H
b, X = Br; R = H
c, X = H; R = OH



3 4



5

bufadienolide was readily achieved as previously described.[8] We readily confirmed that application of lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran at ice-bath temperature for 5 hr affords scillarenin in approximately 75% yields. A further examination of the scillarenone (3) → scillarenin (4) reduction reaction included the original Meerwein-Ponndorf approach as well as a comparison of lithium aluminum hydride, lithium borohydride, sodium borohydride, and potassium borohydride methods. From this comparison study it was ascertained that the lithium tri-*tert*-butoxyaluminum hydride and lithium borohydride techniques gave highest yields of the 3β epimer. In each instance the specimen of scillarenin (4) isolated was identical with an authentic sample kindly provided by Dr. W. Haede.[8]

As digitoxigenin was used as relay for our bufalin synthesis,[1,6] extension of the route to scillarenin also represents the first chemical synthesis of a plant bufadienolide from a plant cardenolide.

Experimental Section

The bufalin used in this investigation was isolated from the Chinese toad venom extract Ch'an Su.[10] All solvent extracts of aqueous solutions were dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure using a rotary evaporator. Commercial (E. Merck, Darmstadt) silica gel HF_{254} preparative layer (1 mm) plates were employed and eluted with 3:3:4 acetone–chloroform–*n*-hexane. Analogous thin layer plates were developed with concentrated sulfuric acid. Each analytical sample was colorless and exhibited one spot on a thin layer chromatogram. The identical composition of specimens was established by mixture melting point determination and by comparing infrared spectra and thin layer chromatograms.

Spectral data was provided by Miss K. Reimer and Messrs. R. Scott and E. Kelley. Melting points were determined using a micro hot stage apparatus (Reichert, Austria) and are uncorrected. Ultraviolet spectra were determined using methanol as solvent. Infrared spectra were recorded using potassium bromide pellets and pmr data were observed using deuteriochloroform solution with tetramethylsilane as standard. A description of the instruments used in this study has been summarized in a preceding part.[10] The elemental microanalyses were determined in the laboratory of Dr. A. Bernhardt, 5251 Elbach uber Engelskirchen, West Germany.

3-Oxo-14β-hydroxy-5β-bufa-20,22-dienolide (Bufalone, 2a). The following experiment corresponds to modification of a previous chromic acid oxidation of bufalin to bufalone.[6] A solution of bufalin (1, 0.24 g) in pyridine (3.8 ml) was added to the freshly prepared complex from chromium trioxide (0.22 g) and pyridine (2.2 ml). After a 22-hr period at room temperature the mixture was poured into ice–water and extracted with chloroform. The combined extract was washed with water, dilute hydrochloric acid, and water. Removal of solvent and recrystallization of the product from acetone–methanol gave 0.21 g (89% yield) of ketone **2a** as needles melting at 242–245° (lit.[6] mp 241–243°); uv λ_{max} 301 nm (log ϵ 3.74); ir ν_{max} 3510 (OH), 1720 (CO), 1700 (conjugated CO), 1634, 1540 (conjugated CO), 947 and 751 cm^{-1} (C=C); pmr δ 0.72 (18-methyl), 1.00 (19-methyl), 6.24 (1 H, d, J = 2.5 Hz, 21-proton), and 7.73 (1 H, q, J = 10.5 and 2.5 Hz, 22-proton); mass spectrum M^+ 384, 366 ($M^+ - H_2O$), 348, 333, 323, 296, 248, 231, and 230.

Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.99; H, 8.38.

3-Oxo-14β-hydroxy-5β-bufa-4,20,22-trienolide (Scillarenone, 3). Method A. A solution prepared from glacial acetic acid (4 ml), bromine (0.035 g), and anhydrous sodium acetate (0.018 g) was added (30 min) dropwise to a solution of ketone **2a** (0.07 g) in 6% hydrogen bromide–acetic acid (0.1 ml). The mixture was stirred and maintained at 10–15°. When the reaction with bromine was complete the mixture was diluted with a solution of sodium acetate (0.18 g) in water (6 ml) and poured into ice–water. The crude bromo derivative (0.08 g, R_f 0.42 and yellowish brown color with sulfuric acid on a thin layer chromatogram) was collected and heated at reflux (7 hr) in dimethylacetamide (2 ml) containing anhydrous lithium chloride (0.08 g). The mixture was poured into ice–water and extracted with chloroform. Before removing solvent from the combined extract it was washed with water, dilute hydrochloric acid, and water. The residue (0.07 g) was subjected to preparative thin layer chromatography and the zone corresponding to R_f 0.35 was eluted with 4:1 chloroform–methanol. Recrystallization of this fraction from acetone gave 0.027 g of scillarenone (3) as needles, mp 246–249°, identical with an authentic specimen.[6]

Method B. Bromine (0.04 g) in dimethylformamide (1 ml) was added during 30 min with stirring to a mixture prepared from ketone **2a** (0.08 g), *p*-toluenesulfonic acid monohydrate (0.002 g), and dimethylformamide (2 ml). Two hours later the reaction mixture was diluted with chloroform and poured into water. The chloroform extract was washed successively with water, dilute sodium bicarbonate solution, dilute hydrochloric acid, and water. The crude bromo derivative (0.08 g) and anhydrous lithium bromide (0.08 g) were heated (at reflux under nitrogen) in dimethylformamide (3.5 ml) for 8 hr. The product (3, 0.022 g, mp 246–248°) was isolated and identified as summarized above in method A.

Method C. From Bufalin (1). A mixture prepared from bufalin (1, 0.155 g), *N*-bromosuccinimide (75 mg), and carbon tetrachloride (15 ml) was heated at reflux for 45 min. The solution was filtered, diluted with chloroform, and poured into water. The solvent layer was washed with water, dilute sodium bicarbonate solution, and water. Removal of solvent gave 0.13 g of bromo ketone **2b**. A solution of the crude bromo derivative (**2b**, 84 mg) in α-collidine (10 ml) was heated at reflux in a nitrogen atmosphere for 6 hr. The brownish residue (77 mg) obtained by removing solvent was separated by preparative thin layer chromatography. The zone corresponding to R_f 0.36 was eluted with 4:1 chloroform–methanol. Recrystallization of this fraction from acetone afforded 8.5 mg of scillarenone (3) as needles melting at 247–249°.

In another experiment[11] bromo ketone **2b** (48 mg) in pyridine (4 ml) was heated in a sealed ampoule at 140° for 90 min. Upon cooling and removal of solvent 50 mg of brown residue was obtained. After purification by preparative thin layer chromatography and recrystallization from acetone (as described above) 4.3 mg of scillarenone (3) melting at 244–248° was isolated.

Method D. From Telocinobufagin (5). A solution of *N*-bromoacetamide (0.11 g) in methanol (2 ml)–water (0.4 ml) was added to a solution of telocinobufagin (**6**, 0.10 g) in methanol (8

ml)–acetone (5 ml). Before pouring the mixture into ice–water and extracting with chloroform, it was allowed to remain at 14–17° for 2 days. The combined chloroform extract was washed with water, dilute sodium sulfite solution, and water. After the solvent was removed the cystalline residue was recrystallized from methanol–acetone to afford 87 mg of **3-oxo-5β,14β-dihydroxy-5β-bufa-20,22-dienolide (2c)** as needles melting at 251–253°: uv λ_{max} 298 nm (log ϵ 3.73); ir ν_{max} 3400–3280 (OH), 1720 (CO), 1710 (conjugated CO), 1630, 1530 (conjugated C=C), 945 and 760 cm^{-1} (C=C); pmr (in pentadeuteriopyridine) δ 0.95 (18-methyl), 1.13 (19-methyl), 6.27 (d, J = 10 Hz, 23-proton), *ca.* 7.48 (21-proton, indistinct peak overlapped with pyridine peak), and 8.14 (q, J = 10 and 3 Hz, 22-proton); mass spectrum M^+ 400, 382 ($M^+ - H_2O$), and 364 ($M^+ - 2H_2O$).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.94; H, 8.06.

A mixture prepared from ketone **2c** (62 mg), 0.60 g of Amberlite CG-120 (H^+ form), and methanol (3 ml) was stirred at room temperature for 6 hr. The solution was filtered and the filtrate was concentrated to dryness. The crude product thereby obtained was purified by preparative thin layer chromatography and ketone **3** was recrystallized as summarized in method A to yield 53 mg of ketone **3** melting at 246–248°.

Each specimen of scillarenone (**3**) was found identical with an authentic sample prepared[12] by chromic acid oxidation of scillarenin (**4**). The authentic specimen recrystallized from acetone as needles melting at 247–249° and exhibited uv λ_{max} 239 nm (log ϵ 4.20) and 300 (3.75); ir ν_{max} 3470 (OH), 1740–1710, 1700 (conjugated CO), 1657, 1635, 1613, 1533 (conjugated C=C and normal C=C), 957 and 748 cm^{-1} (C=C); pmr δ 0.78 (18-methyl), 1.19 (19-methyl), 5.7 (s, 4-proton), 6.21 (d, J = 10.5 Hz, 23-proton), 7.23 (d, J = 2.5 Hz, 21-proton), 7.81 (q, J = 10.5 and 2.5 Hz, 22-proton); mass spectrum M^+ 382, 364 ($M^+ - H_2O$), 349, 339, 322, 242, 228.

Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.22; H, 7.90.

Scillarenin (4). Method A. Lithium Tri-*tert*-Butoxyaluminum Hydride. Reduction of scillarenone (**3**, 20 mg) was conducted employing the lithium tri-*tert*-butoxyaluminum hydride (0.13 g in 3 ml of tetrahydrofuran) method of Stache and colleagues.[8] The crude product was separated by preparative thin layer chromatography and the zone corresponding to R_f 0.27 was eluted with chloroform–methanol (2:1). Recrystallization of the scillarenin from methanol afforded 16 mg of prisms melting at 230–232° (lit.[8,12] mp 234 and 232–235°).

Method B. Lithium Aluminum Hydride. Scillarenone (**3**, 20 mg) in dry tetrahydrofuran (3 ml) was slowly (a drop at a time) added to a mixture of lithium aluminum hydride (80 mg) and dry tetrahydrofuran (2 ml) maintained at ice-bath temperature. Stirring was continued for 5 hr. Excess hydride was carefully removed with dilute acetic acid and the product was extracted with chloroform and separated by preparative thin layer chromatography. Recrystallization of the scillarenin (**4**) from methanol yielded 12 mg melting at 227–230°.

Method C. Lithium Borohydride. The reduction reaction described in method B was modified by substituting lithium borohydride (11 mg) for the lithium aluminum hydride. In this case 20 mg of scillarenone (**3**) led to 15.5 mg of **4** melting at 228–231°.

Method D. Sodium Borohydride. To a solution of scillarenone (**3**, 20 mg) in methanol (1.5 ml)–tetrahydrofuran (1.5 ml) was added sodium borohydride (9 mg) and the mixture was allowed to remain at ice-bath temperature for 6 hr. The product was isolated and recrystallized as summarized in method A to yield 12.2 mg, mp 229–231°, of scillarenin (**4**). A repeat of this reduction reaction with substitution of potassium borohydride for the sodium borohydride gave 13 mg of scillarenin (**4**) melting at 228–230°.

Essentially the same yield (14 mg, mp 229–233°) of scillarenin was attained by modification (preparative layer chromatography as noted in method A) of the earlier[12] Meerwein–Ponndorf reduction of scillarenone (**3**, 20 mg).

The specimens of scillarenin prepared by methods A–D were mutually identical and indistinguishable from an authentic specimen of the natural products.

Registry No.—**1**, 465-21-4; **2a**, 4029-65-6; **2c**, 51567-97-6; **3**, 545-28-8; **4**, 465-22-5; **5**, 472-26-4; lithium tri-*tert*-butoxyaluminum hydride, 17476-04-9; lithium aluminum hydride, 16853-85-3; lithium borohydride, 16949-15-8; sodium borohydride, 16940-66-2.

References and Notes

(1) For Bufadienolides. 25 and Steroids and Related Natural Products. 84, refer to Y. Kamano and G. R. Pettit, *J. Org. Chem.*, **38**, 2202 (1973).

(2) This investigation was supported in part by Public Health Research Grants CA 10612-04 and CA 10612-05 from the National Cancer Institute. We are also grateful to the J. W. Kieckhefer Foundation, Mrs. Virginia L. Bayless, Arizona Public Service Co., The Salt River Project of Arizona, Mr. Elias M. Romley, Mountain Bell Telephone Co., and Western Electric Co. for financial support.

(3) For pertinent references consult G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **35**, 1367 (1970).

(4) J. L. Hartwell and B. J. Abbott, *Advan. Pharmacol. Chemother.*, **7**, 117 (1969).

(5) Y. Kamano and G. R. Pettit, *Experientia*, **28**, 768 (1972). The synthetic route from scillarenin to telocinobufagin has since been completed: G. R. Pettit and Y. Kamano, *J. Org. Chem.*, **39**, 2632 (1974).

(6) A preliminary account has been summarized in a communication: Y. Kamano and G. R. Pettit, *J. Amer. Chem. Soc.*, **94**, 8592 (1972).

(7) N. Höriger, D. Živanov, H. H. A. Linde, and K. Meyer, *Helv. Chim. Acta*, **55**, 2549 (1972); F. Sondheimer and R. L. Wife, *Tetrahedron Lett.*, **10**, 765 (1973); W. Haede, W. Fritsch, K. Radscheit, and U. Stache, *Justus Liebigs Ann. Chem.*, 5 (1973).

(8) An elegant and entirely different total synthetic approach to scillarenin has already been completed by U. Stache, K. Radscheit, W. Fritsch, W. Haede, H. Kohl, and H. Ruschig, *Justus Liebigs Ann. Chem.*, **750**, 149 (1971). For recent chemical and microbiological transformations of scillarenin, refer to B. Görlich and J. Wolter, *ibid.*, **753**, 106 (1971), and B. Görlich, F. H. Dürr, and J. Wolter, *ibid.*, **753**, 116 (1971).

(9) K. Meyer, *Helv. Chim. Acta*, **32**, 1593 (1949).

(10) G. R. Pettit and Y. Kamano, *J. Org. Chem.*, **37**, 4040 (1972).

(11) Compare H. Schroter, R. Rees, and K. Meyer, *Helv. Chim. Acta*, **42**, 1385 (1959).

(12) A. Stoll, J. Renz, and A. Brack, *Helv. Chim. Acta*, **35**, 1934 (1952).

Bufadienolides. 27. Synthesis of Telocinobufagin[1,2]

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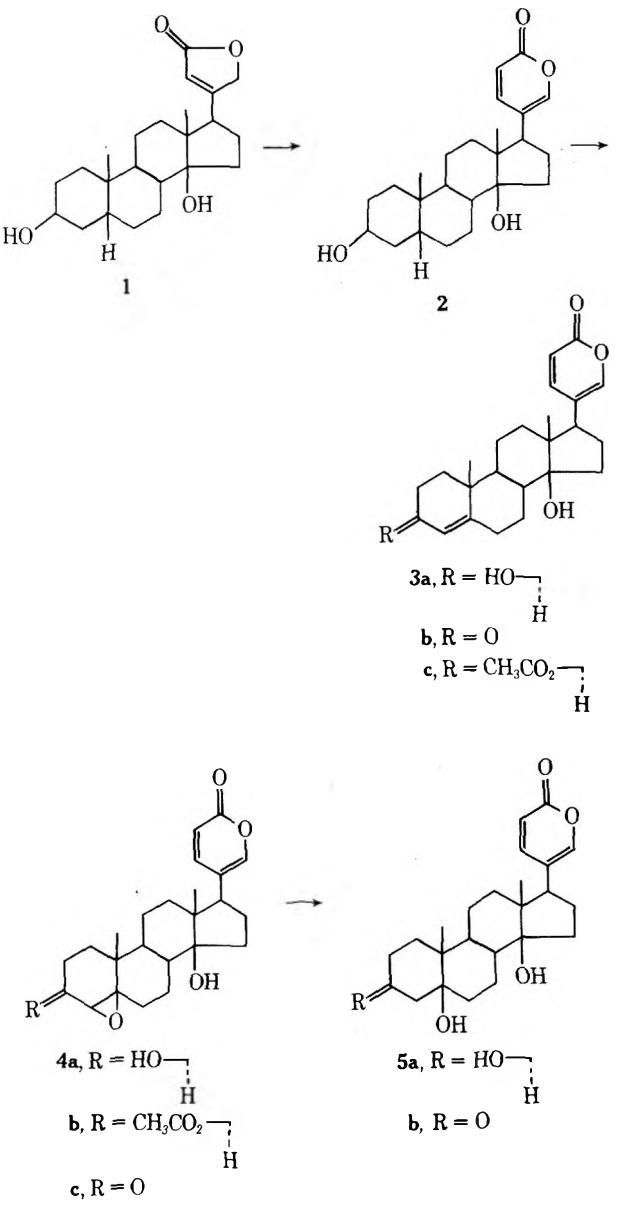
The South American toad, *Bufo marinus*, was originally released in the Caribbean and southeastern United States to assist in controlling the sugar cane beetle and now enjoys a wide range.[3] A constituent common to the venom of this large (up to 12 cm in length) amphibian, the Chinese medicinal preparation, Ch'an Su,[4a] and venom of the European toad, *Bufo vulgaris*,[5] is the cytotoxic (9KB cell line) bufadienolide telocinobufagin (**5a**).[6,7]

For the several purposes of providing unequivocal support for the structure of telocinobufagin, making this substance more readily available for biological studies, and to allow its use as a relay in the formal total syntheses of marinobufagin and marinobufotoxin (summarized in the following paper), we undertook the problem of synthesis. The most direct solution seemed to be by extending our earlier completed transformation of digitoxigenin (**1**) to bufalin[8] (**2**) and scillarenin[2] (**3a**) onward to telocinobufagin (**5a**). This approach proved eminently feasible and has been outlined in the sequel.

With the synthesis of scillarenin (**3a**) in hand,[2,9,10] attention was directed at completing the synthetic link to telocinobufagin (**5a**). Oxidation of olefin **3a** with *m*-chloroperbenzoic acid yielded (60%) β-epoxide **4a**. The β orientation of the 4,5-epoxy group was firmly supported by proton magnetic resonance data. Selective acetylation of epoxy alcohol **4a** easily gave acetate **4b**, which was also obtained by direct peracid oxidation of acetate **3c**. Numerous attempts to selectively reduce epoxy alcohol **4a** or acetate **4b** directly to telocinobufagin (**5a**) proved unproductive. While lithium aluminum hydride in tetrahydrofuran (at low temperatures) did on several occasions lead to detectible amounts of telocinobufagin, attempts to increase the yield and reproducibility were unsuccessful. Similar observations were noted employing lithium tri-*tert*-butyoxyaluminum hydride in tetrahydrofuran. However, a less direct procedure was eventually found far superior.

Oxidation of alcohol **4a** by either chromium trioxide–pyridine or *N*-bromoacetamide procedures provided ketone **4c** in good conversions. The same ketone was obtained more efficiently by peracid epoxidation of scillarenone (**3b**). Reaction of epoxy ketone **4c** with chromium(II) acetate[11] in alcohol afforded telocinobufagone (**5b**, 55–63% yields) and a lesser amount (20%) of scillarenone (**3b**). The synthetic telocinobufagone (**5b**) was identical with an authentic sample prepared from telocinobufagin (**5a**).

While sodium borohydride would be an obvious reagent for reduction of ketone **5b**, the necessary stereoselectivity would be lacking and this was indeed found to be the case. As expected, formation of the equitorial 3α epimer was favored[11] and only 20% conversion to telocinobufagin (**5a**) was realized. However, treating 3-ketone **5b** with either Urushibara nickel A[12] or W-2 Raney nickel[11] in alcohol provided 80–90% yields of telocinobufagin (**5a**). The synthetic and natural specimens of telocinobufagin were identical.



As scillarenin (**3a**) is potentially available in quantity from the naturally occurring glycoside proscillaridine A, the synthesis of telocinobufagin just described now allows more readily access to this interesting bufadienolide and related substances.

Experimental Section

Telocinobufagin was isolated from Ch'an Su.[4a] Careful hydrolysis of proscillaridine A was employed to obtain scillarenin.[10] We are grateful to Dr. W. Haede for providing an authentic specimen of scillarenin.

All solvents were redistilled and ligroin refers to the fraction boiling at 60–80°. Solvent extracts of aqueous solutions were dried over magnesium sulfate. Concentration or evaporation of solvent was conducted under reduced pressure using a rotatory evaporator. Silica gel HF_{254} (E. Merck, Darmstadt) on microscope slides was employed for analytical thin layer chromatography and a 1-mm layer was utilized for preparative layer chromatography. Unless otherwise noted the solvent system for thin layer chromatography consisted of hexane–chloroform–acetone (4:3:3). The plate was developed with sulfuric acid or iodine spray. All analytical samples exhibited a single spot on a thin layer chromatogram and were colorless. By means of comparison, infrared spectra,

thin layer chromatography, and mixture melting point determination, the mutual identity of authentic and synthetic samples was established.

The equipment employed for ultraviolet (methanol solution), infrared (potassium bromide pellets), pmr (deuteriochloroform solution unless otherwise noted), and mass spectral measurements has been noted in the introduction to the Experimental Section of Bufadienolides. 21.[4a] Each of the spectral measurements was recorded by Mr. E. Kelly, Miss K. Reimer, or Mr. R. Scott. Melting points are uncorrected and were determined using a hot-stage apparatus (Reichert, Austria).

3β,14β-Dihydroxy-4β,5β-epoxybufa-20,22-dienolide (4a). A mixture prepared by adding *m*-chloroperbenzoic acid (0.2 g) to scillarenin (**3a**, 0.4 g) in chloroform (20 ml) was allowed to remain at room temperature for 2 hr. The mixture was poured into ice-water and extracted with chloroform and the combined extract was washed with water, dilute sodium thiosulfate solution, and water. Removal of solvent gave a residue (0.41 g) which was chromatographed on a column of silica gel (E. Merck, Darmstadt). The fraction eluted with 49:1 chloroform–methanol led to 0.25 g of β-epoxide **4a** as plates decomposing at 243–250.5°. A pure sample of epoxide **4a** displayed tlc R_f 0.32 using hexane–ethyl acetate (1:9); blue color with sulfuric acid; λ_{max} 299 mμ (log ε 2.38); ν_{max} 3480 (OH), 1720 (conjugated CO), 1632, 1537 (conjugated C=C), 1249 (epoxy CO), 958, 950 (C=C), 828 (epoxy CO), 752 cm^{-1} (C=C); pmr (in pentadeuteropyridine) δ 0.93 (18-methyl), 1.06 (19-methyl), 3.37 (d, J = 3.5 Hz, 4α-proton), 4.33 (broad d, J = 3.5 Hz, 3α-proton), 6.30 (d, J = 10 Hz, 23-proton), 7.42 (d, J = 3 Hz, 21-proton), 8.16 (q, J = 10 and 3 Hz, 22-proton); mass spectrum M^+ 400, 382 ($M^+ - H_2O$), 367, 364 ($M^+ - 2H_2O$), 339, 331, 278.

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.05, H, 8.01.

3β-Acetoxy-14β-hydroxy-4β,5β-epoxybufa-20,22-dienolide (4b). Method A. From Alcohol 4a. Alcohol **4a** (0.051 g) was acetylated employing acetic anhydride (0.8 ml)–pyridine (1.2 ml) at room temperature. Recrystallization of the product from acetone–hexane afforded acetate **4b** (0.048 g) as needles melting at 207–210°: λ_{max} 300 mμ (in methanol); ν_{max} 3490 (OH), 1740, 1720–1710 (conjugated CO and ester CO), 1635, 1540 (conjugated C=C), 1250~1235 (ester CO and epoxy CO), 948, 910 (C=C), 840 (epoxy CO), 752 cm^{-1} (C=C); pmr δ 0.74 (18-methyl), 1.04 (19-methyl), 2.10 (3-acetyl), 3.17 (d, J = 3.5 Hz, 4α-proton), 5.11 (broad d, J = 3.5 Hz, 3α-proton), 6.22 (d, J = 10 Hz, 23-proton), 7.21 (d, J = 2.5 Hz, 21-proton), 7.80 (q, J = 10 and 2.5 Hz, 22-proton); mass spectrum M^+ 442, 424 ($M^+ - H_2O$), 382 (M^+ – AcOH), 357, 339, 330.

Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.73; H, 7.68.

Method B. From Scillarenin Acetate (3c). A solution of scillarenin acetate (**3b**, 0.02 g) in chloroform (10 ml) was oxidized with *m*-chloroperbenzoic acid (0.01 g) as described above for the preparation of epoxide **4a**. Recrystallization of the product from acetone–hexane yielded 0.014 g of epoxide **4b**, mp 206.5–210°, which was identical with the specimen obtained by method A.

3-Oxo-4β,5β-epoxy-14β-hydroxybufa-20-22-dienolide (4c). Method A. Oxidation of alcohol **4a** (0.06 g in 2 ml of pyridine) with chromium trioxide (0.4 g)–pyridine (3.5 ml) complex was conducted (22 hr, room temperature) as summarized for the preparation of bufalone.[2] The crude product (0.056 g) was purified by preparative thin layer chromatography and the zone corresponding to R_f 0.32 was eluted with chloroform–methanol (5:1). Recrystallization of this fraction from methanol yielded 0.038 g of ketone **4c** as needles: mp 230.5–239°; ν_{max} 3490 (OH), 1720 and 1700–1695 (conjugated CO and ketone), 1630 and 1535 (conjugated C=C), 1240, 1125 (epoxy CO), 950, 910 (C=C), 832 (epoxy CO), 750 cm^{-1} (C=C); pmr δ 0.75 (18-methyl), 1.16 (19-methyl), 3.02 (s, 4α-proton), 6.27 (d, J = 10 Hz, 23-proton), 7.31 (d, J = 3 Hz, 21-proton), 7.86 (q, J = 10 and 3 Hz, 22-proton).

Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.33; H, 7.59. Found: C, 72.27; H, 7.56.

Method B. A solution of *N*-bromoacetamide (0.03 g) in methanol (0.5 ml)–water (0.1 ml) was added to alcohol **4a** (0.025 g) in methanol (2 ml)–acetone (2 ml). The mixture was allowed to remain at 15–20° for 40 hr, poured into ice–water, and extracted with chloroform. The combined chloroform extract was washed with water, dilute sodium sulfite solution, and water. The residue (0.03 g) obtained by removal of solvent was purified by preparative thin layer chromatography as described above in method A. Recrystallization from methanol led to 0.014 g of ketone **4b** melting at 230–239°.

Method C. A 0.02-g specimen of scillarenone (**3b**) was oxidized with *m*-chloroperbenzoic acid (0.012 g) in chloroform (1 ml) as described above for preparation of epoxide **4a**. The product was isolated by preparative thin layer chromatography and recrystallized from methanol to yield 4 mg of ketone **4c** melting at 229–238°.

The specimens of ketone **4c** prepared by methods A–C were found mutually identical.

3-Oxo-5β,14β-dihydroxybufa-20,22-dienolide (Telocinobufagone. 5b). Method A. Freshly prepared chromium(II) acetate[11] (0.14 g) was added to epoxide **4c** (0.035 g) in ethanol (3.5 ml). After 30 min at room temperature the mixture was diluted with chloroform and poured into ice–water. The chloroform layer was washed with water and the solvent was removed to provide a 0.04-g residue. The product was separated by preparative thin layer chromatography and the zone with R_f 0.15 was eluted with chloroform–methanol (4:1). Recrystallization of this fraction from methanol–ethyl acetate yielded telocinobufagone (0.022 g, mp 250–253°) as needles. The synthetic specimen was identical with an authentic sample (mp 251–253°) prepared by oxidation of telocinobufagin.

The preparative thin layer zone with R_f 0.35 was eluted with chloroform–methanol. Recrystallization of the product from acetone afforded 0.011 g of scillarenone (**3b**, mp 245–248°) as needles. The sample of scillarenone was identical with an authentic specimen prepared from scillarenin[2] (**3a**).

When methanol was substituted for the ethanol used as solvent in the preceding reaction the yields of telocinobufagone and scillarenone remained unchanged. However, the product ratio changed when 0.015 g of epoxy ketone **4c** was treated with chromium(II) acetate (0.06 g) in acetone (3.5 ml)–acetic acid (0.1 ml)–water (0.4 ml) containing sodium acetate trihydrate (0.14 g). Here, 0.013 g of telocinobufagone (**5b**, mp 248–251°) and 0.009 g of scillarenone (**3b**, mp 243–248°) were obtained.

Telocinobufagin (5a, 3β,5β,14β-trihydroxybufa-20,22-dienolide). Method A. A refluxing (1 hr) solution of ketone **5b** (0.01 g) in ethanol (1 ml) was treated with a large excess of freshly prepared Urushibara nickel A.[12] The solution was filtered and the product was isolated by preparative thin layer chromatography using hexane–ethyl acetate (1:9) as solvent. The zone of R_f 0.33 was eluted by chloroform–methanol (4:1) and this fraction was recrystallized from acetone to afford telocinobufagin (**5a**, 0.009 g) with the characteristic double melting point (163–177 and 210–211°). The synthetic telocinobufagin (as prisms) was identical with the natural product isolated from Ch'an Su.

When the reaction was repeated using freshly prepared Raney nickel (W-2) the yield of telocinobufagin (mp 160–170 and 207–210°) from 0.01 g of ketone **5b** was 0.008 g.

Method B. Sodium borohydride (0.01 g) was added to a solution of ketone **5b** (0.015 g) in dioxane (2.5 ml)–water (0.5 ml) and the mixture was allowed to remain at room temperature for 3 hr. Excess sodium borohydride was removed by adding dilute sulfuric acid at 5–10° and the resulting mixture was poured into water and extracted with chloroform. After washing with water, solvent was removed from the combined extract and the residue (0.017 g) was purified by preparative thin layer chromatography as described in method A. By this means only 3 mg of telocinobufagin (mp 158–170 and 205–209°) was isolated. A second zone corresponding to R_f 0.12 on the preparative thin layer chromatogram was assumed to be the 3α epimer, but was not further identified.

The specimen of telocinobufagin prepared by method B was also found identical with the natural product.

Registry No.—**3a**, 465-22-5; **4a**, 29599-08-4; **4b**, 51567-95-4; **4c**, 51567-96-5; **5a**, 472-26-4; **5b**, 51567-97-6.

References and Notes

(1) This investigation was supported in part by Public Health Research Grant CA10612-05 from the National Cancer Institute. We are also indebted to the J. W. Kieckhefer Foundation, Fannie E. Rippel Foundation, The Salt River Project of Arizona, Mrs. Virginia L. Bayless, The Arizona Public Service Co., and Mountain Bell Telephone Co. for financial assistance.

(2) For Bufadienolides. 26 and Steroids and Related Natural Products. 85 refer to Y. Kamano and G. R. Pettit, *J. Org. Chem.*, **39**, 2629 (1974).

(3) See, for example, M. S. Cannon, *Smithsonian*, **4**, 53 (1973).

(4) (a) G. R. Pettit and Y. Kamano, *J. Org. Chem.*, **37**, 4040 (1972); (b) M. Hóriger, D. Živanov, H. A. Linde, and K. Meyer, *Helv. Chim. Acta*, **55**, 2549 (1972); Y. Kamano, K. Hatayama, M. Shinohara, and M. Komatsu, *Chem. Pharm. Bull.*, **19**, 2478 (1971).

(5) H. R. Urscheler, C. Tamm, and E. Reichstein, *Helv. Chim. Acta*, **38**, 883 (1955).

(6) The delay in uncovering telocinobufagin from Ch'an Su was respon-

sible for its name (Greek *tele*, far): L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., p 793. For a recent review of bufadienolide chemistry, consult R. Ode, Y. Kamano, and G. R. Pettit, *MTP (Med. Tech. Publ. Co.) Int. Rev. Sci.: Org. Chem., Ser. One*, **8**, 151 (1972).
(7) This interesting substance was first described by K. Meyer, *Helv. Chim. Acta*, **34**, 2147 (1951). See also K. Meyer, *Pharm. Acta Helv.*, **24**, 222 (1949). The cytotoxicity of telocinobufagin has been reported: J. L. Hartwell and B. J. Abbott, *Advan. Pharmacol. Chemother.*, **7**, 117 (1969).
(8) G. R. Pettit, L. E. Houghton, J. C. Knight, and F. Bruschweiler, *J. Org. Chem.*, **35**, 2895 (1970); G. R. Pettit, Y. Kamano, F. Bruschweiler, and P. Brown, *ibid.*, **36**, 3736 (1971); and Y. Kamano and G. R. Pettit, *ibid.*, **38**, 2202 (1973).
(9) Y. Kamano and G. R. Pettit, *J. Amer. Chem. Soc.*, **94**, 8592 (1972).
(10) See also U. Stache, J. Radscheit, W. Fritsch, W. Haede, H. Kohl, and H. Ruschig, *Justus Liebigs Ann. Chem.*, **750**, 149 (1971). With 15α-hydrocortexone as starting material, this group has summarized an excellent 17-step synthesis of scillarenin.
(11) An excellent study of analogous reactions with chromium(II) acetate leading to 3β,5β-diols has been summarized by C. H. Robinson and R. Henderson, *J. Org. Chem.*, **37**, 565 (1972). The reagent was prepared essentially as described by J. H. Balthis and J. C. Bailar, *Inorg. Syn.*, **1**, 122 (1939).
(12) K. Hata, "Urushibara Catalysis," University of Tokyo Press, Tokyo, 1971, p 39; K. Hata, I. Motoyama, and S. Sakai, *Org. Prep. Proced. Int.*, **4**, 179 (1972).

Phytadienes from the Pyrolysis of Pheophytin a

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In the course of a study on organic compounds in polluted water,[1] a particularly facile pyrolytic reaction was observed when extracts containing pheophytin a were injected into a gas chromatograph which was operated with an injection port temperature of 250°. Since most thermal decompositions take place at much higher temperatures, a brief study of the pyrolytic behavior of this compound was undertaken.

Pheophytin a was pyrolyzed at 250, 350, and 400° directly onto a high-resolution gas chromatographic (gc) column the effluent of which was monitored with a fast-scanning computerized mass spectrometer. Four major fractions were observed and they were identified as various phytadiene isomers (**1**–**4**) from their mass spectra and gc retention indexes (see below for details). These data and the relative abundances of the various isomers are given in Table I. It can be seen that the relative yield of the pyrolysis products observed at the three temperatures is not significantly different and that at least 94% of these products are phytadienes. The remaining 5–6% were at least 15 different compounds and, judging from their gc retention times, all contained less than ten carbon atoms; they were not investigated further. In addition, any nonvolatile pyrolytic products which were not transmitted by the gas chromatograph were not studied.

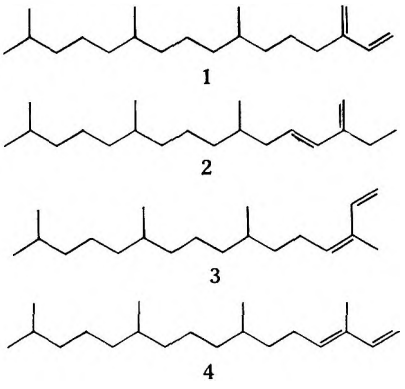
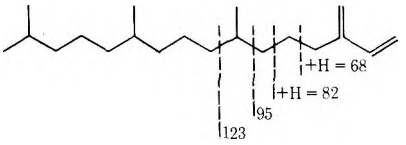


Table I
Compounds Identified in the Pyrolysate of Pheophytin a

Compd	Relative yield,[a] % 250°	350°	400°	Retention index (±1)	Mass spectrum, *m/e* (rel intensity)[b]
1[c]	61	63	64	1841	68 (100), 57 (86) 43 (80), 82 (73)
2[d]	2	2	1	1848	43 (100), 68 (90) 57 (84), 41 (79)
3	12	10	11	1863	43 (100), 82 (96) 68 (90), 57 (89)
4	20	19	18	1882	82 (100), 43 (78) 57 (77), 81 (71)
Others	5	6	6		

[a] Absolute total molar yield, relative to pheophytin a, is 40–60%. [b] See paragraph at end of paper regarding supplementary material. [c] Common name: neophytadiene. [d] Tentative structure.

The information which lead to these identifications is as follows. The mass spectra of the four major components were quite similar to each other. They all exhibited abundant ions at *m/e* 43, 57, 68, 82, 95, and 123 and a molecular ion at *m/e* 278. These ions are consistent with phytadienes and must originate by cleavage of the indicated bonds (using neophytadiene as an example). Ions at *m/e* 68 and



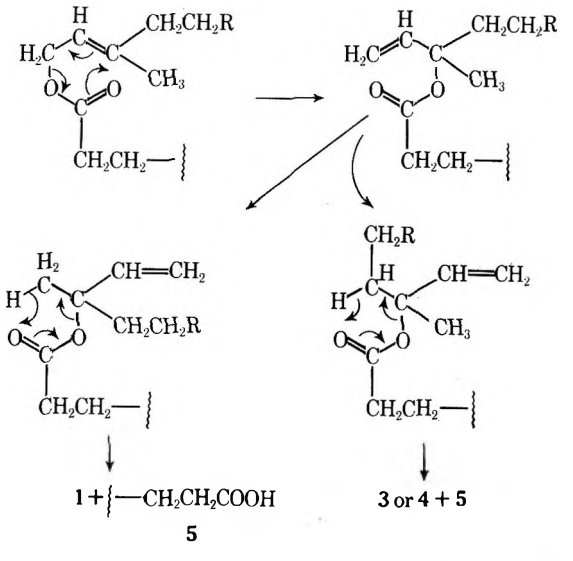
82 require the rearrangement of one hydrogen atom. The ions at *m/e* 95 and 123 indicate that the diene system is located at the formerly esterified terminus of the molecule. In addition, the mass spectrum of the most intense gc peak was identical with that of synthetic neophytadiene (**1**). In this way all four peaks were identified as phytadienes.

The exact positions of the double bonds could not, of course, be completely established by mass spectrometry. Fortunately, however, the gc retention indexes of several phytadienes isolated from zooplankton and identified by ozonolysis and infrared spectrometry have been reported.[2] The retention indexes of compounds **1**, **3** and **4** (see Table I) are identical with this reference data. The tentative structure **2** was assigned on the basis of gc retention characteristics (indicating a terminal methylene group) and a less abundant *m/e* 82 ion relative to the other isomers.

Although the above information is not sufficient to prove a reaction mechanism, the following suggestion (see Scheme I) nicely accounts for the identity and abundance of the products. This suggested mechanism involves two steps, the first step being a Cope-type rearrangement of the phytyl group and the second being the elimination of pheophorbide (**5**) by way of a six-membered cyclic transition state in which the carbonyl oxygen interacts with the various α-hydrogen atoms. The observed product distribution is close to that which would be expected based on the number of protons available. Since there are three primary protons and two secondary protons, the statistical product distribution should be 60% **1**, 20% **3**, and 20% **4**, and in fact these values are very close to those observed (see Table I).

A similar mechanism has been suggested for the pyrolysis of certain allylic acetates.[3] For example, 2-acetoxy-*trans*-3-heptene pyrolyzes at 350° to give a mixture of 1,3- and 2,4-heptadiene. Isomerization of the ester was demon-

Scheme I



R = $(CH_3)_2CHCH_2CH_2CH_2CH(CH_3)CH_2CH_2CH_2CH(CH_3)CH_2$—

strated by isolation of 4-acetoxy-*trans*-2-heptene in the pyrolysate.[3]

It should be noted that tobacco smoke contains several phytadiene isomers, the most abundant of which is neophytadiene.[4] Since all of the phytadienes reported in Table I (except **2**) have been found in tobacco smoke, it seems likely that pyrolysis of the residual phytol esters originally present in tobacco as chlorophyll produces some of the phytadienes observed in smoke.

Besides tobacco, the only other reported occurrence of phytadienes is in zooplankton.[2] Since an injector port temperature of 250° is sufficient to produce phytadienes from pheophytin a, before reporting the presence of phytadienes in an extract it is important to demonstrate the absence of chlorophyll or its degradation products in that extract. In this respect it is possible that the phytadienes reported to be present in zooplankton[2] may have been an artifact.

Experimental Section

The samples were pyrolyzed directly into the gas chromatographic column using a CDS Pyroprobe 190 system. The sample (*ca.* 300 μg) was coated from solution (CH_2Cl_2) on a platinum ribbon (35 × 1.5 × 0.0127 mm); after solvent evaporation, the ribbon assembly was inserted into the injection port of the chromatograph (held at 240 ± 10°). After restabilization of the helium carrier gas flow (1–2 min), the ribbon was heated at 10°/msec to 250, 350, or 400° and held there for 2 sec. Pyrolysis products were immediately vaporized and swept onto the gc column. The estimated maximum residence time of the products at temperature was less than 100 msec; thus isomerization was avoided.

Samples were also pyrolyzed by injecting the solution (CH_2Cl_2) directly into the heated injection port. Injector temperatures of 250–320° were sufficient to pyrolyze the pheophytin a to give a low yield (5–10%) of phytadienes. Although the results of injector port pyrolyses were not as reproducible as those of the platinum ribbon system, the identities and distribution of products were approximately the same as shown in Table I.

Two gc columns were used: (a) 300 ft × 0.01 in. i.d. stainless steel, wall coated with SF-96 containing 5% Igepal 880 operated isothermally at 180° (110,000 theoretical plates), and (b) 150 ft × 0.02 in i.d. stainless steel, wall coated with OV-101; temperature programmed from 130 to 200° at 3°/min. Both columns gave identical retention indexes and the resolution was such as to verify that there were no more than four phytadienes present. The computerized combined gas chromatograph–mass spectrometer system has been described previously;[5] however, since capillary columns with carrier gas flow rates of 0.5–1.5 ml/min were used for this study and since the restrictors in the fritted glass interface between the gas chromatograph and mass spectrometer were adjusted for flow rates of 15–40 ml/min, it was necessary to add carrier gas after the column to bring the total gas flow into the interface up to these higher values. A flame ionization detector chromatogram was recorded in parallel to the gas chromatograph–mass spectrometer and was used for the quantitative values shown in Table I.

Pheophytin a was prepared by acid hydrolysis[6] of chlorophyll a which was, in turn, isolated from a mixed culture of green algae and blue-green algae (cultured in a modified Allen's medium[7] for 3 weeks). The cells were collected by centrifugation, and the chlorophyll a was isolated by chromatographic procedures.[6] The visible spectrum of the isolated pheophytin a (in ether) exhibited peaks at 410, 474, 506, 535, 562, 612, and 671 nm and was in agreement with published spectra.[8] Methyl pheophorbide a was prepared by Fisher's method,[6] and the mass spectrum was obtained by inserting the sample directly into the ion source at 380°; it showed characteristic ions at *m/e* 606, 576, 548, and 461 and agreed with the published mass spectrum of methyl pheophorbide a.[9]

Acknowledgments. Iwan Hirsan provided valuable assistance; the instrumentation was supported (in part) by National Institutes of Health Research Grant RR00317 from the Division of Research Facilities and Resources (K. Biemann, principal investigator).

Registry No.—**1**, 504-96-1; **2**, 51806-25-8; **3**, 21980-71-2; pheophytin a, 603-17-8.

Supplementary Material Available. Complete mass spectra of compounds **1**–**4** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2634.

References and Notes

(1) R. A. Hites, *J. Chromatogr. Sci.*, **11**, 570 (1973); R. A. Hites, *Envrion. Health Perspec.*, **3**, 17 (1973); R. A. Hites and K. Biemann, *Science*, **178**, 158 (1972).
(2) M. Blumer and D. W. Thomas, *Science*, **147**, 1148 (1965).
(3) F. L. Greenwood, *J. Org. Chem.*, **24**, 1735 (1959).
(4) R. L. Stedman, *Chem. Rev.*, **68**, 153 (1968).
(5) R. A. Hites and K. Biemann, *Anal. Chem.*, **42**, 855 (1970); **40**, 1217 (1968); **39**, 965 (1967).
(6) F. C. Pennington, H. H. Strain, W. A. Svec, and J. J. Katz, *J. Amer. Chem. Soc.*, **86**, 1418 (1964).
(7) M. B. Allen, *Arch. Mikrobiol.*, **17**, 34 (1952).
(8) A. S. Holt in "Chemistry and Biochemistry of Plant Pigments," T. W. Goodwin, Ed., Academic Press, New York, N. Y., 1965, p 14.
(9) D. R. Hoffman, *J. Org. Chem.*, **30**, 3512 (1965).

A New, Practical Synthesis of L-2-Hydroxytryptophan and Its Derivatives

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DL-2-Hydroxytryptophan[2] (**3**) has been prepared by three- or four-step syntheses originating with the reaction products from ethyl 2-(*o*-nitrophenyl)acetate and diethyl methylenemalonate,[3] isatin and ethyl pyruvate,[4] or 3-chloromethyleneoxindole and diethyl formamidomalonate.[5] Yields, however, are modest (15–24% overall) and resolution, when the biologically important[3-6,8,9] L isomer is desired, poses difficulties.[4]

A one-step oxidation of L-tryptophan with peracetic acid in acetic anhydride[6,7] or aqueous hydrolysis (130°) of its symmetrical 2,2′-disulfide,[8] obtained by reaction with di-

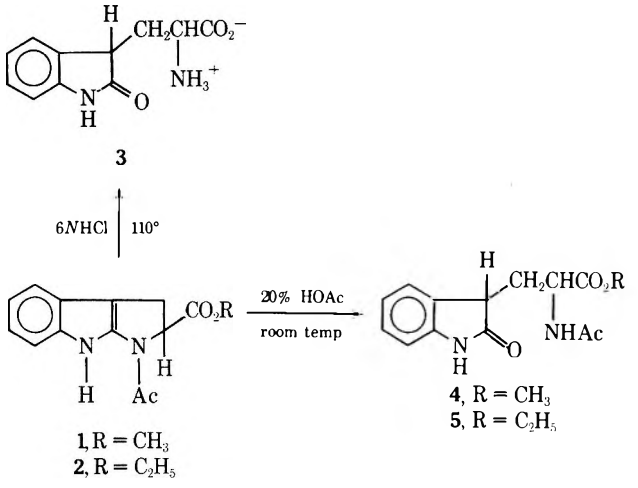
sulfur dichloride, affords the L isomer directly, although yields are still low.

A recent modification of the latter reaction, whereby 2-thio(4-nitrophenyl)-L-tryptophan is hydrolyzed with 20% aqueous acetic acid at 110°, is reported to give **3** in 70% yield.[10] The starting material is easily prepared by reaction of L-tryptophan with 4-nitrophenylsulfenyl chloride in acetic acid. This procedure and most likely the disulfide hydrolysis above suffer a limitation in being applicable only to tryptophan or tryptamine derivatives having a free amino group which apparently participates in the hydrolysis.[10]

We wish to report a convenient, high-yield procedure for the synthesis of L-2-hydroxytryptophan, which is also suitable for the preparation of *N*-acyl, ester derivatives.

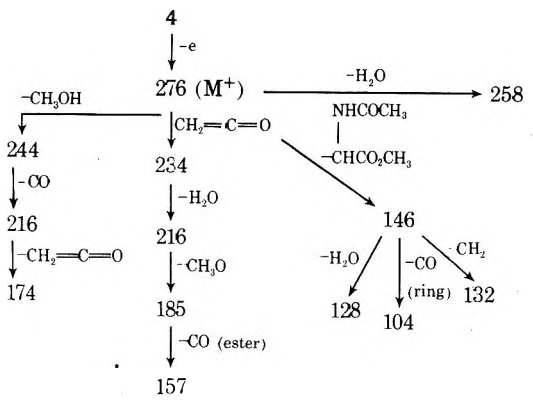
The method consists in the acidic hydrolysis of 2,3-dihydropyrrolo[2,3-*b*]indoles (*e.g.*, **1** and **2**) which are synthesized easily in a one-step oxidation of *N*-acetyl-L-tryptophan methyl or ethyl ester with *N*-bromosuccinimide at pH 8.5–9.0 or preferably with *tert*-butyl hypochlorite in triethylamine-buffered methylene chloride.[11] Sealed-tube hydrolyses (110°) of either **1** or **2** with constant-boiling HCl afforded **3** in 75% yield after conversion to the free amino acid by a Dowex-1 (acetate form) column in order to remove HCl (**3** is unstable toward alkali[5]), while hydrolysis with 20% acetic acid at room temperature provided the *N*-acetyl methyl (**4**) and ethyl (**5**) esters of **3** in 63 and 74% yields, respectively. When the room-temperature hydrolysis was performed with 0.1 *N* HCl, side reactions intervened and the yields of **4** or **5** decreased (Scheme I).

Scheme I



A low-resolution mass spectrum of **4** is consistent with the fragmentation pathways as indicated in Scheme II. The base peak at *m/e* 146 probably corresponds to the 3-methyleneindolin-2-one ion. This ion apparently loses methylene, H_2O, or CO to give ions at *m/e* 132, 128, and 104, respectively. A mass spectrum of **5** indicated fragmentations analogous to those of **4** and exhibited metastable peaks at *m/e* ~255 and ~112 (among others) corresponding to the loss of H_2O from the parent ion (*m/e* 290) and base peak (*m/e* 146), respectively.

Scheme II



A 100-MHz pmr spectrum of **3** in D_2O containing sufficient DCl for dissolution reveals an unexpectedly complex pattern which is interpreted as originating from a 1:1 mixture of 3*S*,α*S* and 3*R*,α*S* diastereoisomers. In addition to a common aromatic multiplet at δ 7.10–7.60 (relative to the internal HOD reference at δ 5.00), the following signals are observed. One isomer gives rise to a one-proton triplet (J = 6.5 Hz) at δ 4.60 coupled to a two-proton AB-type quartet (δ_A 2.66, δ_B 2.53; J_{AB} = 15 Hz; eight lines) with signals assigned to the α proton and β-methylene protons, respectively. The α-proton triplet of the other isomer (no attempt is made to assign stereochemistry) is centered at δ 4.48 (J = 7.0 Hz) and likewise splits the β-methylene AB quartet (δ_A 2.81, δ_B 2.45; J_{AB} = 15 Hz) into eight lines. The two NH protons and the 3-H proton are exchanged under these conditions. The pmr spectrum of **4** (see Experimental Section) reveals a much simpler spectrum in which diastereoisomers cannot be distinguished.

Experimental Section

Melting points are uncorrected. Thin layer chromatography was performed in ethyl acetate–methanol (9:1 v/v) (solvent 1) or 1-butanol–acetic acid–water (4:1:5 v/v, upper layer) (solvent 2). Spots were detected by ninhydrin or 47% HBr followed by heating. Ultraviolet spectra were measured on a Shimazu UV-200 spectrophotometer equipped with a U-125 MU recorder. Infrared spectra were obtained with a Hitachi Perkin-Elmer Model 225. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Pmr spectra were obtained on a Varian Associates HA-100 spectrometer. Chemical shifts are reported as δ values (parts per million) with tetramethylsilane or HOD as an internal reference. Low-resolution mass spectra were measured with a double-focusing Hitachi RMU-6E spectrometer.

L-2-Hydroxytryptophan [L-3-(2-Amino-2-carboxyethyl)indolinone, 3]. The pyrroloindole **2**[11] (1.25 g, 4.5 mmol) was dissolved in constant-boiling hydrochloric acid (40 ml) and heated at 110° for 20 hr in a sealed tube. The dark yellow solution was evaporated nearly to dryness. The residue was dissolved in water, decolorized with charcoal, and dried by evaporation. It exhibited a single band on high-voltage paper electrophoresis (pH 2.08). The hygroscopic syrup was dissolved in water (25 ml) and passed through a 1.8 × 10 cm column of Dowex-1 (acetate form, 100–200 mesh) and the column was washed with water. The eluate was filtered through Toyo filter paper No. 5c and lyophilized to give 0.75 g (75%) of material, mp 233–235°, which proved to be 98.5–99% pure by amino acid analysis in pH 5.82 buffer on a short column where its peak just preceded that of tryptophan. This product (200 mg) was dissolved in oxygen-free water (0.6 ml) and the solution was stirred gently with a spatula. Crystals appeared spontaneously. Crystallization was complete after several hours in the refrigerator. The crystals were separated by centrifugation and dried *in vacuo* over P_2O_5: 130 mg; mp 248–250°; $[\alpha]^{20}D$ +39.8° (*c* 2.13, 1 *N* NaOH) [lit. mp 244–245° dec,[4] 246–247° dec,[8] 248–249° dec,[3] 249–253° dec,[9] 250–252°,[10] 254–256°,[6] 256° dec;[5] +21°,[6] +20.6°,[8] +30.1°,[10] +31.8°,[8] +39.2°[9] (*c* 0.81–2.75, 1 *N* NaOH)]; R_f 0.60 (2); λ_{max} (H_2O) 250 nm (ε 6900), shoulder 280 (1400) [lit. λ_{max} (H_2O) 250 nm[10,12] (ε 7200),[10] 7250)[12]]; λ_{max} (KBr) 3300–2600 (broad), 1625, 1565, 1470, 1390, 1325 cm^{-1}; pmr, see text.

Attempted crystallization from aqueous ethanol produced sizable amounts of ninhydrin-positive impurities and led to a poor recovery.

Anal. Calcd for $C_{11}H_{12}O_3N_2$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.78; H, 5.54; N, 12.85.

L-3-(2-Acetamido-2-methoxycarbonylethyl)indolinone (4). The pyrroloindole **1**[11] (490 mg, 1.90 mmol) was dissolved in 20% acetic acid (45 ml) with stirring. The reddish solution which resulted within 10 min was stirred for 50 min and lyophilized. The pale yellow residue was chromatographed over silica gel (contain-

ing 12% alumina, 325 mesh and finer, product from Nakarai Chemicals Inc., Kyoto) and eluted with ethyl acetate–methanol (9:1 v/v). Homogeneous fractions (checked by tlc) were combined and evaporated below 35° nearly to dryness. Crystallization resulted on standing under petroleum ether in a refrigerator. The crystals were crushed and filtered to give 330 mg (63%) of an almost colorless product: mp 148–150°; $[\alpha]^{20}D$ −16.5° (*c* 2.38, $CHCl_3$); R_f 0.83 (1); λ_{max} (EtOH) 250 nm (ϵ 7000), shoulder 280 (1470); ν_{max} ($CHCl_3$) 3435, 3300–3200 (broad), 3000, 1730, 1720, 1670, 1620, 1470, 1440, 1370, 1330 cm^{-1}; pmr (100 MHz, $CDCl_3$) δ 9.18 (broad, one proton, NH of oxindole, exchanges rapidly with D_2O), 6.86–7.52 (five protons, aromatic multiplet + NHAc, exchanges slowly over several hours with D_2O), 4.98 [one-proton quartet, $J \simeq 7$ Hz, α proton, changes slowly to two overlapping doublets, 4.95 (J = 6 Hz) and 4.87 (J = 7 Hz), on D_2O exchange], 3.70 (three-proton singlet, OCH_3), 3.50 (one-proton triplet, J = 6 Hz, 3-H), 2.38 (two-proton skewed triplet, $J \simeq 7$ Hz, collapses to doublet, J = 7 Hz, on irradiation at center of 4.96 triplet, β-CH_2 groups), 2.02 ppm (three-proton singlet, NAc) The fragmentation on low-resolution mass spectrometry is shown in Scheme II.

Anal. Calcd for $C_{14}H_{16}O_4N_2$: C, 60.86; H, 5.84; N, 10.14. Found: C, 61.12; H, 5.86; N, 10.05.

L-3-(2-Acetamido-2-ethoxycarbonylethyl)indolinone (5). The pyrroloindole 2[11] (400 mg, 1.47 mmol) was dissolved in 20% acetic acid (40 ml) with stirring. The solution was treated in the same manner as the methyl ester analog above. The crude product (150 mg) was chromatographed on silica gel and eluted with ethyl acetate–methanol (9:1 v/v). Homogeneous fractions were pooled and evaporated. The syrupy residue failed to crystallize and was stored under vacuum, then pulverized. The resulting amorphous powder was collected with petroleum ether to afford 112 mg: mp 113–117°; R_f 0.85 (1); λ_{max} (EtOH) 250 nm (ϵ 6800), shoulder 280 (1420); ν_{max} ($CHCl_3$) 3420, 3300–3200, 2950, 1720, 1670, 1620, 1470, 1440, 1370 cm^{-1}; M^+ *m/e* 290. The fragmentation pathways were similar to those of **4**.

Anal. Calcd for $C_{14}H_{18}O_4N_2$: C, 62.05; H, 6.25; N, 9.65. Found: C, 62.27; H, 6.51; N, 9.54.

Registry No.—**1**, 25690-48-6; **2**, 21018-88-2; **3**, 32999-55-6; **4**, 51806-22-5; **5**, 40846-93-3.

References and Notes

(1) Department of Chemistry, Faculty of Science, Kyushu University, Fukuoka, Japan.
(2) The amino acid **3** has been variously referred to as hydroxytryptophan,[4,9] α-hydroxytryptophan,[3,5,6] 2-hydroxytryptophan,[8,10] β-oxindole-3-alanine,[5] and β-3-oxindolylalanine.[4] Current usage would seem to favor 2-hydroxytryptophan, although the oxindolealanine nomenclature would more correctly reflect the structure.
(3) M. Kotake, T. Sakan, and T. Miwa, *J. Amer. Chem. Soc.*, **72**, 5085 (1950).
(4) J. W. Cornforth, R. H. Cornforth, C. E. Dalgliesh, and A. Neuberger, *Biochem. J.*, **48**, 591 (1951).
(5) H. Behringer and H. Weissauer, *Chem. Ber.*, **85**, 743 (1952).
(6) B. Witkop, *Justus Liebigs Ann. Chem.*, **558**, 98 (1947).
(7) Oxidation of tryptophan or certain derivatives with *N*-bromosuccinimide [N. M. Green and B. Witkop, *Trans. N. Y. Acad. Sci., Ser. II*, **26**, 659 (1964)] or *tert*-butyl hypochlorite (M. Ohno and K. Ogata, unpublished results) in acidic aqueous media also affords **3** or its derivatives as the major product. The preparative application of these reactions has yet to be realized.
(8) T. Wieland, O. Weiberg, W. Dilger, and E. Fischer, *Justus Liebigs Ann. Chem.*, **592**, 69 (1955).
(9) H. Wieland and B. Witkop, *Justus Liebigs Ann. Chem.*, **543**, 171 (1940).
(10) F. M. Veronese, A. Fontana, E. Boccù, and C. A. Benassi, *Z. Naturforsch. B*, **23**, 1319 (1968).
(11) M. Ohno, T. F. Spande, and B. Witkop, *J. Amer. Chem. Soc.*, **90**, 6521 (1968); **92**, 343 (1970).
(12) J. W. Cornforth, C. E. Dalgliesh, and A. Neuberger, *Biochem. J.*, **48**, 598 (1951).

New Syntheses in Dihydrojasmone Series

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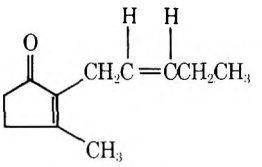
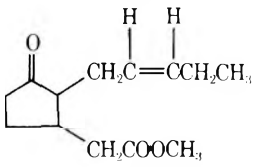
cis-Jasmone and methyl jasmonate are primary odorous principles of the flower oils of several varieties of *Jasminum*. Several syntheses of jasmone[1–5] and methyl jasmonates[6–8] have been published. Dihydrojasmone (**6**) is closely related to jasmone both in structure and in odor, is useful in perfumery, and has been synthesized by several procedures.[5,9–12]



cis-jasmone



methyl jasmonate

We wish now to describe an efficient five-step synthesis of dihydrojasmone (**6**) and tetrahydrojasmone (**7**), and a seven-step synthesis of methyl dihydrojasmonate (**12**). The starting point in the present synthetic scheme was the alkylation of 2-carbethoxycyclopentanone(**1**). This was accomplished by using NaH in DMF with RBr.[13] The key intermediate **3** was prepared by acid hydrolysis of **2**.[14] 2-Pentylcyclopentan-1-one (**3**) was then treated with isopropenyl acetate, yielding **4**, which was converted into **5** by the bromination–dehydrobromination method.[15] Methylation of **5** with methyllithium and oxidation of the resulting carbinol with chromium trioxide[8,16] led to the expected dihydrojasmone (**6**). The cuprous chloride catalyzed addition of a Grignard reagent, CH_3MgI, to **5** formed tetrahydrojasmone (**7**). Michael addition of dimethyl malonate to **5** yielded **8**, which upon hydrolysis and decarboxylation[8,17] was transformed to dihydrojasmonic acid (**9**), which was methylated to yield methyl dihydrojasmonate (**12**). We also explored a different route for synthesis of **12**, *via* intermediates **10** and **11**. Methyl-2-pentylcyclopent-2-en-1-ol acetate (**10**) was prepared either by treating **5** with lithium methyl acetate or with Reformatzky reagent.[18]

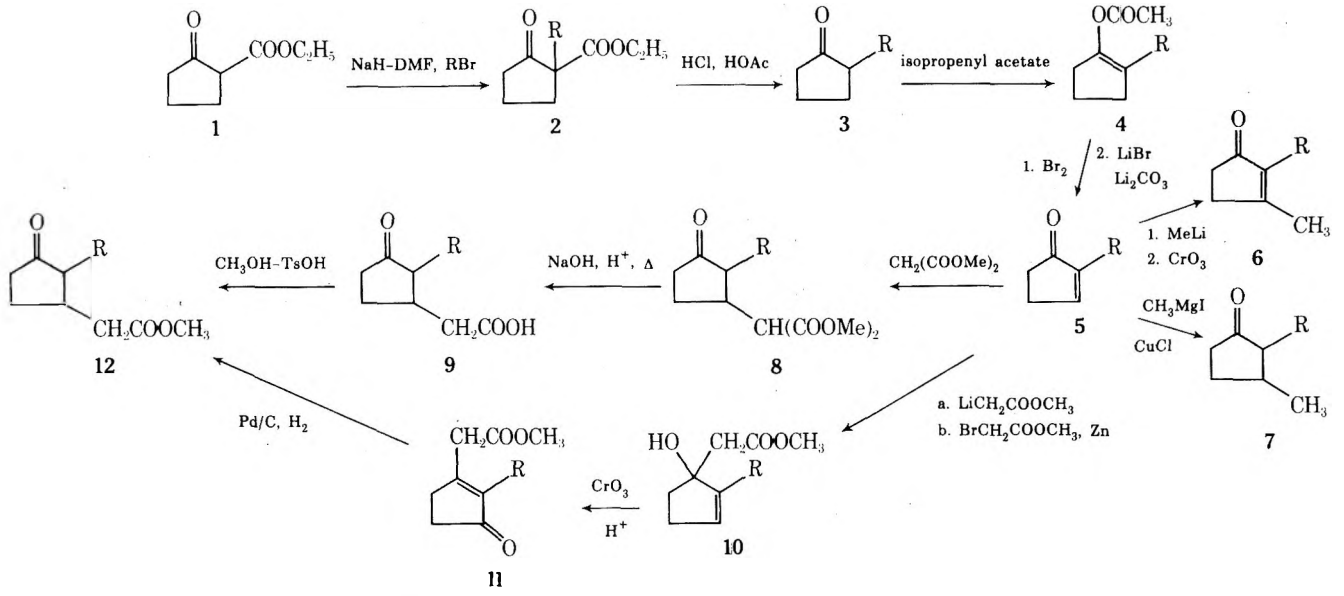
The lithium method seemed more elegant and attractive; it yielded 82% of **10**, as compared to 60% by Reformatzky's method. Oxidation of **10** with chromium trioxide afforded **11**, which was reduced catalytically to **12**.[17] Methyl dihydrojasmonate (**12**) prepared by both methods had identical spectroscopic (ir, nmr), and chromatographic properties.

It is noteworthy that compounds **6**, **11**, and **12** possess the characteristic long-lasting jasmone-like odors. The advantages of the present synthesis is that the starting materials are relatively inexpensive and easily accessible and the overall yields of the products are satisfactory.

Experimental Section

Microanalyses were performed at the Microanalytical Laboratory of the Hebrew University. Melting points were determined on a Thomas-Hoover apparatus. The following spectrometers were used: nuclear magnetic resonance (nmr), Varian T-60; infrared (ir), Perkin-Elmer Model 137; mass spectrometer (mass spectrum), Varian MAT-311; ultraviolet (uv), Unicam SP-800; vapor phase chromatography (vpc) analyses were performed on a Varian Aerograph 90-P instrument using a 3% SE-30 column. Infrared spectra were measured in sandwich cells (sc), uv spectra in ethanol, and nmr spectra in deuteriochloroform, unless otherwise stated.

2-Pentyl-2-carbethoxycyclopentan-1-one (2). 2-Carbethoxycyclopentanone(308 g, 1.97 mol) was added dropwise under a nitrogen atmosphere over a 3-hr period to a suspension of sodium hydride (100 g, 2.5 mol) in dry dimethylformamide (DMF) (1.2 l.) at 20°. After the addition was completed, the reaction mixture was stirred for 15 min at room temperature and then for 15 min at 50°. *n*-Pentyl bromide (300 g, 1.98 mol) was then added during 30 min. The reaction mixture was stirred overnight at room temperature, poured into water, and extracted thrice with ether. The organic layer was washed with a saturated solution of sodium chloride and dried over magnesium sulfate, and the solvents were removed *in vacuo*. Distillation through a small column afforded 2-pentyl-2-carbethoxycyclopentan-1-one: 284 g (64%); bp 100° (0.1 mm); ir



6, dihydrojasmone
7, tetrahydrojasmone
12, methyl dihydrojasmonate

(liquid) 1755, 1730, 1630, 1468, 1230, 1150, 1030, cm^{-1}; nmr ($CDCl_3$) δ 0.85 (3 H, t), 1.10–2.66 (17 H, m), 4.04 (2 H, 9).

Anal. Calcd for $C_{13}H_{22}O$: C, 68.99; H, 9.80. Found: C, 68.90; H, 9.65.

2-Pentylcyclopentan-1-one (3). 2-Pentyl-2-carbethoxycyclopentan-1-one (**2**, 280 g, 1.24 mol) in the presence of glacial acetic acid (350 ml) and hydrochloric acid (20%, 600 ml) was refluxed for 24 hr. The reaction mixture was cooled and water was added. It was then extracted with ether and the organic layer was washed with sodium bicarbonate and sodium chloride solutions and dried over magnesium sulfate. The solvents were removed *in vacuo* and the residue was distilled through a small column, affording 152 g (79.5%) of 2-pentylcyclopentan-1-one: bp 60–62° (0.5 mm); ir (liquid) 1738, 1470, 1455, 1410, 1155, 929 cm^{-1}; nmr ($CDCl_3$) δ 0.82 (3 H, t), 1.03–1.50 (8 H, m), 1.66–2.41 (7 H, m).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.92; H, 11.69. Found: C, 78.08; H, 11.77.

1-Acetoxy-2-pentylcyclopent-1-ene (4). 2-Pentylcyclopentan-1-one (**3**, 145 g, 0.94 mol) and isopropenyl acetate (200 g, 2 mol) in the presence of *p*-toluenesulfonic acid (1 g) was refluxed overnight. The red-colored reaction mixture was poured into a cold solution of potassium bicarbonate (10%), extracted with ether, and dried over magnesium sulfate. The solvents were removed *in vacuo* and the residue was distilled through a small column, affording 155 g (84%) of 1-acetoxy-2-pentylcyclopent-1-ene: bp 65° (0.2 mm); ir (liquid) 1755, 1700, 1470, 1370, 1305, 1210 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (3 H, t), 1.04–1.49 (4 H, m), 1.72–2.55 (10 H, m), 2.01 (3 H, s).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.50; H, 9.86.

2-Pentycyclopent-2-en-1-one (5). Bromine (120 g, 0.75 mol) in carbon tetrachloride (150 ml) was added dropwise during 1 hr to a mixture of 1-acetoxy-2-pentylcyclopent-1-ene (149 g, 0.76 mol), chloroform (450 ml), water (600 ml), and calcium carbonate (55 g). After stirring for 1 hr the organic layer was separated and washed with solutions of sodium thiosulfate and sodium chloride. The organic layer was dried over magnesium sulfate and the solvents were removed *in vacuo*. The residue was dissolved in dry DMF (750 ml) and in the presence of dry lithium bromide (130 g) and dry lithium carbonate (130 g) was refluxed for 45 min. Cold water (1 l.) was added and the red-colored solution was neutralized with hydrochloric acid (20%) and extracted with ether. The organic layer was washed with sodium chloride solution and dried over magnesium sulfate. Distillation afforded 90 g (78%) of 2-pentylcyclopent-2-en-1-one: bp 60° (0.2 mm); ir (liquid) 1700, 1633, 1445, 1253, 1198, 1050, 1000 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (3 H, t), 1.08–1.63 (6 H, m), 1.88–2.72 (6 H, m), 7.05 (1 H, m); uv (EtOH) 230 nm (ϵ 9900).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.76; H, 10.60.

2-Pentyl-2-methylcyclopent-2-en-1-one (6, Dihydrojasmone). Methyllithium (14 ml, 20 mmol, of 1.9 *M* ethereal solution) was added dropwise with stirring at 0° and under a nitrogen atmosphere to 2-pentylcyclopent-2-en-1-one (**5**, 1.41 g, 9.28 mmol) in dry ether (30 ml). After the addition was completed, the reaction mixture was stirred for 15 min at room temperature, poured into cold water, and extracted with petroleum ether. The organic layer was washed with water and dried over magnesium sulfate, and the solvents were removed *in vacuo*. The residue of crude carbinol was dissolved in ether (30 ml), cooled to 0°, and treated with chromium trioxide (1 g) in sulfuric acid (10 ml, 5%). After a period of 15 min, water was added and the product was extracted with petroleum ether. The organic layer was washed with a solution of sodium bicarbonate (10%) and dried over magnesium sulfate, and the solvents were distilled off. The oily residue was distilled through a small column, yielding 0.6 g (39%) of 2-pentyl-2-methylcyclopent-2-en-1-one: bp 79–81° (0.2 mm); ir (liquid) 1700, 1645, 1445, 1388, 1180, 1070, 810 cm^{-1}; nmr ($CDCl_3$) δ 0.84 (3 H, t), 1.05–1.69 (6 H, m), 1.98 (3 H, s), 1.90–2.63 (6 H, m); uv (EtOH) 236 nm (ϵ 12,700).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.44; H, 10.64.

2-Pentyl-3-methylcyclopentan-1-one (7, Tetrahydrojasmone). Cuprous chloride (0.1 g) was added in one portion under a nitrogen atmosphere to methylmagnesium iodide, prepared from magnesium turnings (0.5 g, 0.021 g-atom) and methyl iodide (2.8 g, 0.02 mol) in dry ether. 2-Pentylcyclopent-2-en-1-one (**5**, 2 g, 0.013 mol) was then added dropwise over a period of 20 min. After addition was completed, stirring proceeded for 45 min and the reaction mixture was poured into ice-cold dilute hydrochloric acid. It was then extracted with ether. The organic layer was washed with solution of sodium bicarbonate and water, and dried over magnesium sulfate. Purification by preparative gas–liquid chromatography afforded 1.5 g (68%) of 2-pentyl-3-methylcyclopentan-1-one: ir (liquid) 1735, 1460, 1380, 1155, 790 cm^{-1}; nmr ($CDCl_3$) δ 0.63–0.98 (6 H, m), 1.00–1.70 (8 H, m), 1.82–2.63 (6 H, m).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.55; H, 11.60.

2-Pentyl-3-dimethylmalonylcyclopentan-1-one (8). 2-Pentylcyclopent-2-en-1-one (**5**, 15.2 g, 0.1 mol) in dry methanol (50 ml) was added dropwise (while stirring) during 30 min and under a nitrogen atmosphere to a cold (−5°) solution of sodiodimethyl malonate prepared from dimethyl malonate (16.5 g, 0.12 mol), sodium metal (0.3 g, 0.077 g-atom), and dry methanol (20 ml). After the addition was completed, the stirring was continued for 1 hr. Acetic acid (1.5 g, 0.025 mol) was added and the solvents were distilled off *in vacuo*. The residue was extracted with ether and the organic layer was washed with a solution of sodium chloride and dried over magnesium sulfate. Ether was distilled off and the residue was distilled, affording 13.4 g (63%) of 2-pentyl-3-dimethylmalonylcyclopentan-1-one: bp 126–127° (0.3 mm); ir (liquid) 1755, 1740, 1440, 1220, 1160 cm^{-1}; nmr (CCl_4) δ 0.85 (3 H, t), 1.04–1.55 (8 H, m), 1.78–2.29 (6 H, m), 3.39 (1 H, d), 3.61 (6 H, s).

Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.75; H, 8.47.

2-Pentyl-3-oxocyclopentylacetic Acid (9, Dihydrojasmonic

Acid). Sodium hydroxide (5.2 g) in water (50 ml) was added with vigorous agitation over a period of 1 hr and under a nitrogen atmosphere to 2-pentyl-3-dimethylmalonylcyclopentan-1-one (**8**, 17.5 g, 0.062 mol). The reaction mixture was stirred overnight at room temperature and extracted with ether, and the aqueous layer was acidified with sulfuric acid (7 g in 15 ml of water). The aqueous layer was refluxed until gas evolution ceased. The cold solution was extracted with ether, washed with water, and dried over magnesium sulfate. The solvents were removed *in vacuo* and the residue was distilled, affording 13.3 g (95%) of 2-pentyl-3-oxocyclopentylacetic acid: bp 168–170° (0.3 mm); ir (liquid) 3070–3020, 1740, 1712, 1465, 1410, 1165 cm^{-1}; nmr (CCl_4) δ 0.85 (3 H, t), 1.05–1.65 (8 H, m), 1.84–2.74 (8 H, m), 11.2 (1 H, s).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.08; H, 9.31.

Methyl-2-pentyl-3-oxocyclopentyl Acetate (12, Methyl Dihydrojasmonate). 2-Pentyl-3-oxocyclopentylacetic acid (**9**, 2 g, 0.094 mol), dry methanol (20 ml), and *p*-toluenesulfonic acid (10.05 g) were refluxed overnight. Methanol was distilled and the residue was extracted with ether. The ether solution was washed successively with a solution of sodium chloride, sodium bicarbonate, and again with sodium chloride and dried over magnesium sulfate. Distillation yielded 1.7 g (80%) of methyl-2-pentyl-3-oxocyclopentyl acetate: bp 105–107° (0.2 mm); ir (liquid) 1740, 1440, 1269, 1170 cm^{-1}; nmr (CCl_4) δ 0.85 (3 H, t), 1.01–1.58 (8 H, m), 1.82–2.51 (8 H, m), 3.55 (3 H, s).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.72; H, 9.60.

Methyl-2-pentylcyclopent-2-en-1-ol Acetate (10). Method A. Methyl acetate (1.71 ml, 25 mmol) was added dropwise over a period of 2 min (under a nitrogen atmosphere) into a THF solution of lithium bis(trimethylsilyl)amide (25 ml, 1.0 *M*) at −78°. After the addition was completed, the stirring proceeded for 15 min. 2-Pentylcyclopent-2-en-1-one (**5**, 3.8 g, 25 mmol) was injected through a septum inlet. After a period of 15 min, hydrochloric acid (5 ml, 20%) was injected. After the reaction was completed, the mixture was extracted with hexane. The organic layer was separated, washed with a saturated solution of sodium bicarbonate and water, and dried over sodium sulfate. Hexane was distilled off and the residue was distilled under reduced pressure, yielding 4.63 g (82%) of methyl-2-pentylcyclopent-2-en-1-ol-acetate: bp 97° (0.4 mm); ir (liquid) 3500, 1740, 1440, 1203 cm^{-1}; nmr (CCl_4) δ 0.93 (3 H, t), 1.13–1.50 (8 H, m), 1.71–2.24 (4 H, m), 2.42 (2 H, s), 2.52 (2 H, s), 3.31 (1 H, s), 3.69 (3 H, s), 5.42 (1 H, m).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.03; H, 9.74. Found: C, 69.10; H, 9.47.

Method B. 2-Pentylcyclopent-2-en-1-one (**5**, 1.52 g, 10 mmol) and methyl bromoacetate (1.1 ml, 10 mmol) in dry benzene (8 ml) were added slowly to activated zinc (0.65 g, 0.02 g-atom) in boiling benzene (2 ml). After the exothermic reaction had subsided, the mixture was refluxed for 30 min and cooled and acetic acid (5 ml, 10%) was added. The benzene layer was separated, washed with a solution of sodium bicarbonate and water, and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was distilled under reduced pressure affording 1.36 g (60%) of the product, bp 97° (0.4 mm), ir and nmr identical with those obtained by method A.

Methyl-2-pentyl-3-oxo-1-cyclopentenyl Acetate (11). Chromium trioxide (1 g) in sulfuric acid (10 ml, 5%) was added dropwise at 0° to methyl-2-pentylcyclopent-2-en-1-ol acetate (**10**, 2.03 g, 9 mmol) in ether (30 ml). After the addition was completed, the stirring proceeded for 45 min at 5°. Water was added and the product was extracted with hexane. The organic layer was separated, washed with a solution of sodium bicarbonate (10%) and water, and dried over sodium sulfate. The solvent was evaporated and the oil was distilled, affording 1.75 g (87%) of methyl-2-pentyl-3-oxo-1-cyclopentenyl acetate: bp 118–119° (0.4 mm); ir (liquid) 1740, 1705, 1645, 1435, 1175 cm^{-1}; uv (EtOH) 237 nm (ϵ 9200); nmr (CCl_4) δ 0.88 (3 H, t), 1.15–1.41 (8 H, m), 2.01–2.80 (4 H, m), 3.35 (2 H, s), 3.68 (3 H, s).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.64; H, 8.93. Found: C, 69.73; H, 9.20.

Methyl-2-pentyl-3-oxocyclopentyl Acetate (12, Methyl Dihydrojasmonate). Methyl-2-pentyl-3-oxo-1-cyclopentenyl acetate (**11**, 115 mg, 0.51 mmol), with sodium hydroxide (0.05 g) and methanol (15 ml) in the presence of Pd/C (0.21 g, 5%), was hydrogenated at room temperature. After the hydrogenation was completed, the catalyst was removed by filtration and the methanol was evaporated *in vacuo*. Methyl dihydrojasmonate (50 mg, 43%) was obtained by preparative glc. Its spectroscopic (ir, nmr) and chromatographic (glc) data were identical with those of methyl dihydrojasmonate prepared from compound **9**.

Registry No.—**1**, 611-10-9; **2**, 24852-03-7; **3**, 4819-67-4; **4**, 24851-93-2; **5**, 25564-22-1; **6**, 1128-08-1; **7**, 13074-63-0; **8**, 51806-23-6; **9**, 3572-64-3; **10**, 51806-24-7; **11**, 24863-70-5; **12**, 24851-98-7.

References and Notes

(1) T. Yoshida, A. Yamaguchi, and A. Komatsu, *Agr. Biol. Chem.*, **30**, 370 (1966).
(2) G. Stork, F. Rouessac, and O. Gringore, *J. Amer. Chem. Soc.*, **93**, 3091 (1971).
(3) J. E. McMurry and J. Melton, *J. Amer. Chem. Soc.*, **93**, 5309 (1971).
(4) P. A. Grieco, *J. Org. Chem.*, **37**, 2363 (1972).
(5) H. C. Ho, T. L. Ho, and C. M. Wong, *Can. J. Chem.*, **50**, 2718 (1972).
(6) E. Demole and M. Stoll, *Helv. Chim. Acta*, **45**, 692 (1962).
(7) K. Sisido, S. Kurozumi, and K. Utimoto, *J. Org. Chem.*, **34**, 2661 (1969).
(8) G. Büchi and B. Egger, *J. Org. Chem.*, **36**, 2021 (1971).
(9) J. L. E. Erickson and F. E. Collins, *J. Org. Chem.*, **30**, 1050 (1965).
(10) R. T. Dahill, *J. Org. Chem.*, **31**, 2694 (1966).
(11) J. Ficini, J. D'Angelo, and J. P. Genêt, *Tetrahedron Lett.*, 1569 (1971).
(12) S. M. Supta and S. S. Deshapanda, *J. Indian Chem. Soc.*, **30**, 23 (1963).
(13) J. Bagli and T. Bogri, *Tetrahedron Lett.*, 3815 (1972).
(14) J. Bagli, T. Bogri, R. Deghenghi, and K. Wiesner, *Tetrahedron Lett.*, **No. 5**, 465 (1966).
(15) P. L. Stotter and K. A. Hill, *J. Org. Chem.*, **38**, 2576 (1973).
(16) K. Oshima, H. Yamamoto, and H. Nozaki, *J. Amer. Chem. Soc.*, **95**, 4446 (1973).
(17) E. Demole, E. Lederer, and D. Mercier, *Helv. Chim. Acta*, **45**, 685 (1962).
(18) M. W. Rathke, *J. Amer. Chem. Soc.*, **92**, 3222 (1970).

Synthesis of Some Bridged Triterpene Ethers[1a]

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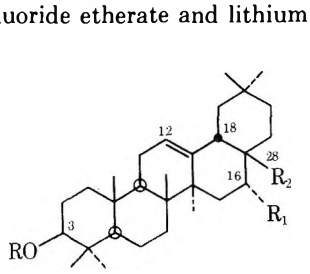
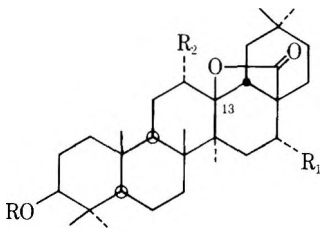
Several 13β,28-epoxyoleananes with additional oxygen functions in the molecule have recently been isolated from plants.[2-10] An unambiguous synthesis of the simplest of these, protoprimulagenin A (**21**), was desired to confirm this structural feature.

Although protoprimulagenin A was isolated from *Primula sieboldi* roots as recently as 1968,[10] Tschesche and coworkers had prepared such a compound from echinocystic acid (**3**) in 1964.[3,5] By heating in acetic and concentrated hydrochloric acids for several hours, **3** was converted to a 13β,28-lactone which was then reduced to a 13β,28-epoxide with boron trifluoride etherate and lithium aluminum hydride.[3]

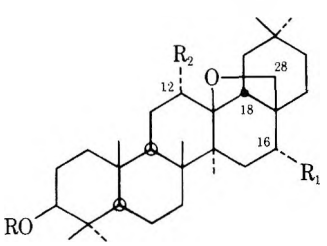


1, R = R_1 = H; R_2 = CO_2H
2, R = R_1 = H; R_2 = CO_2CH_3
3, R = H; R_1 = OH; R_2 = CO_2H
4, R = H; R_1 = OH; R_2 = CO_2CH_3
5, R = Ac; R_1 = OAc; R_2 = CO_2H
6, R = R_1 = H; R_2 = CH_2OH
7, R = Ac; R_1 = H; R_2 = CH_2OH
8, R = R_1 = H; R_2 = CH_2OAc
9, R = Ac; R_1 = H; R_2 = CH_2OAc
10, R = H; R_1 = OH; R_2 = CH_2OH
11, R = H; R_1 = OH; R_2 = CH_2OH
with Br at 12 or OH at 13

However, it is reported that heating an olean-12-en-28-oic acid with acetic and concentrated hydrochloric acids is liable to produce **13** rather than **12**.[11] There is no appreciable difference between the specific rotations of the two and unless both are known and have different melting points it is not easy to distinguish between them. We therefore prepared the epoxide through a route which is certain to retain the 18β-H stereochemistry of **3**.



12, R = R_1 = R_2 = H
13, R = R_1 = R_2 = H($C_{18}\alpha$-H)
14, R = Ac; R_1 = OAc; R_2 = Br
15, R = R_2 = H; R_1 = OH
16, R = H; R_1 = OH; R_2 = Br
17, R = Ac; R_1 = OAc; R_2 = H



18, R = R_1 = R_2 = H
19, R = Ac; R_1 = R_2 = H
20, R = R_1 = H; R_2 = Br
21, R = R_2 = H; R_1 = OH

Olean-12-en-28-oic acids are known to give oleanane-12α-bromo-13β,28-lactones on treatment with bromine in acetic acid.[12] As these bromolactones are readily converted to the parent acid on treatment with zinc and acetic acid,[12] this mode of preparation of an oleanane bromolactone ensures the retention of stereochemistry at position 18. Before starting the synthesis we made sure that no isomerization would take place in any of the subsequent steps as well by effecting the following transformations.

Oleanolic acid **1** was first converted to the known lactone **12** by passing dry HCl gas through a chloroform solution. This procedure has been shown to retain the 18β-H stereochemistry of **1**.[11] Reduction of **12** with lithium aluminum hydride and boron trifluoride etherate[13] gave the epoxy compound **18** as characterized by its spectral properties and elemental analysis. Acetylation of **18** gave the 3-monoacetate **19**. Treatment of **19** with boron trifluoride etherate in benzene gave a quantitative yield of a monoacetate monoalcohol, which from its mode of formation and spectral properties was assigned the structure **7** of erythrodiol-3-monoacetate.[14] This was confirmed by acetylating **7** to the diacetate **9** identical with that obtained by acetylating erythrodiol **6**.[15] As **6** is obtained by reducing **2** with $LiAlH_4$, **6** has its 18-H β oriented. Thus these reaction sequences prove that in the reaction with HCl gas in chloroform at room temperature, or with boron trifluoride etherate and lithium aluminum hydride, or with boron trifluoride etherate in benzene, no epimerization at position 18 takes place.

The conversion of **19** to **7** as indicated above is an unambiguous method of preparing the pure 3-monoacetate **7**.

In an attempt to prepare **18** directly from **6**, the latter was treated with dry HCl gas in acetic acid at room temperature for 15 min. The product isolated, however, was a monoacetate of **6** different from **7**, which therefore must be the 28-acetate **8**. This was confirmed by further acetylating **8** to give **9** identical in all respects with the authentic sample. This procedure could be useful in selectively acetylating a primary alcohol in the presence of secondary alcohols.

Treatment of **6** with bromine in acetic acid gave a product in about 50% yield which was characterized as **20** by its spectral and other properties. Reduction of **20** with lithium aluminum hydride gave **18** identical with that obtained before. As **18** has already been shown to retain the stereochemistry of the 18-H, that is, β, this sequence of reactions gives independent proof that the cyclization from C_{28} to C_{13} by bromination does not isomerize the 18β-H.

Reduction of **4** with lithium aluminum hydride gave **10**.[16,17] An attempt to convert **10** directly to **21** by passing dry HCl gas through a chloroform solution was not successful.

Similarly attempted bromination of **10** with bromine in acetic acid yielded only the starting material. Although the bromolactone **16** was prepared from **3** with bromine in acetic acid, it was barely soluble in the solvents used for the $LiAlH_4$ reduction, and consequently its reduction did not yield the desired product **21**.

Hence **5** was converted to **14**[18] and reduced with boron trifluoride etherate and lithium aluminum hydride to give **21**, which, as discussed previously, should definitely have its 18-H β oriented. This compound was found to be identical with protoprimulagenin A (**21**) by its spectral properties, R_f value in tlc, and melting point and mixture melting point with an authentic sample.[10]

Experimental Section[19]

3β-Hydroxy-13β,28-epoxyoleanane (18). The lactone **12** was prepared by passing HCl gas for 15 min through a $CHCl_3$ solution of **1**.[11] To a stirred suspension of $LiAlH_4$ (150 mg) in dry ether (20 ml) kept at 0° was added during the course of 15 min a solution of **12** (300 mg) in dry ether (30 ml) containing boron trifluoride etherate (3 ml). Stirring was continued for 2 hr at 0–5° and for 8 hr at room temperature. The reaction was then quenched at 0° with a saturated $NaHCO_3$ solution and the excess $LiAlH_4$ was destroyed with ethyl acetate, ice, and sodium potassium tartrate. Extraction with ether (295 mg) and chromatography over basic alumina (20 g) gave in ethyl acetate–benzene (8:92) **18** (98 mg): mp 229°; $[\alpha]_D$ +2°; M^+ *m/e* 442; ir, transparent in the carbonyl region; nmr δ 3.15, 3.45 (AB q, J = 8 Hz, 2 H) and absence of vinyl proton. *Anal.* Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.27; H, 11.48. Further elution with ethyl acetate–benzene (15:85) gave erythrodiol **6** (60 mg), mp 234°, $[\alpha]_D$ +76°, and oleanolic acid **1** (20 mg), mp 310°, $[\alpha]_D$ + 77°. Compounds **6** and **1** were identified by direct comparison (tlc, ir, nmr, mixture melting point) with authentic samples.

The acetate **19** prepared from **18** showed mp 222°; $[\alpha]_D$ +0.3°, M^+ *m/e* 484; ν_{max} 1725 and 1250 cm^{-1}; nmr δ 2.2 (s, 3 H), 3.18 and 3.48 (AB q, J = 8 Hz, 2 H), 4.5 (m, 1 H), and absence of vinyl proton. *Anal.* Calcd for $C_{32}H_{52}O_3$: C, 79.28; H, 10.81. Found: C, 79.21; H, 10.83.

28-Hydroxyolean-12-en-3β-yl Acetate (7). To a solution of **19** (50 mg) in dry benzene (2 ml), boron trifluoride etherate (0.01 ml) was added. After 10 min the reaction was quenched with $NaHCO_3$ solution. Extraction with ether and crystallization from ether–methanol furnished **7** (45 mg):[14] mp 238°; $[\alpha]_D$ +73° (lit.[14] mp 238.5–239°; $[\alpha]_D$ +71°); M^+ *m/e* 484; ν_{max} 1725, 1240, and 3505 cm^{-1}; nmr δ 5.1 (s, br, 1 H), 4.5 (m, 1 H), and 3.35 (q, 2 H). Acetylation in the usual way gave the diacetate: mp 186°; $[\alpha]_D$ +64° (lit.[14] mp 186°; $[\alpha]_D$ +66.7°); M^+ *m/e* 526; ν_{max} 1720 and 1240 cm^{-1}; nmr δ 5.1 (s, br, 1 H), 2.1 (s, 6 H). It was identical with an authentic sample of **9** prepared by reducing **2** with $LiAlH_4$ and subsequent acetylation.

3β-Hydroxyolean-12-en-28-yl Acetate (8). HCl gas was bubbled through a solution of **6** (1 g) in acetic acid (25 ml) for 15 min at room temperature and the solution was poured into water. Extraction with ether and chromatography over basic alumina (40 g) gave **8** (104 mg): mp 196°; $[\alpha]_D$ +36.8°; M^+ *m/e* 484; ν_{max} 1748,

1230, and 3500 cm^{-1}; nmr δ 2.1 (s, 3 H) and 5.1 (s, br, 1 H). *Anal.* Calcd for $C_{32}H_{52}O_3$: C, 79.28; H, 10.81. Found: C, 79.45; H, 10.75. This was converted to the diacetate **9** (pyridine, acetic anhydride), mp 186°, $[\alpha]D$ +64°, M^+ *m/e* 526, identified by direct comparison (tlc, ir, nmr, mixture melting point) with an authentic sample.

3β-Hydroxy-13β,28-epoxy-12α-bromooleanane (20). A solution of bromine in acetic acid (3%, 4.5 ml) was added dropwise to a stirred solution of **6** (500 mg) and NaOAc (2.0 g) in 90% aqueous acetic acid (50 ml). After 3 hr the solution was poured into water containing $Na_2S_2O_3$. Usual work-up furnished **20** (250 mg): mp 180°; $[\alpha]D$ +3.6°; M^+ *m/e* 520; ν_{max} 3400 cm^{-1}; nmr δ 4.3 (m, 1 H), 3.5 (q, 2 H), and no vinyl proton signal. *Anal.* Calcd for $C_{30}H_{49}BrO_2$: C, 69.1; H, 9.5. Found: C, 68.9; H, 9.6.

3β-Hydroxy-13β,28-epoxyoleanane (18) from 20. A solution of **20** (50 mg) in THF (5 ml) was added to a refluxing slurry of $LiAlH_4$ (50 mg) in THF (25 ml). Refluxing and stirring were continued for 8 hr. Usual work-up and crystallization from ether–methanol yielded **18** (15 mg), mp 229°, $[\alpha]D$ +1.9°, M^+ *m/e* 442, identified by tlc, nmr, melting point, and mixture melting point with an authentic sample.

Echinocystic Acid[20] Bromolactone (16). A solution of bromine in acetic acid (3%, 2–3 ml) was added dropwise during the course of 3 hr to a stirred solution of **3** (100 mg) and NaOAc (400 mg) in 90% aqueous acetic acid (10 ml). The reaction mixture was then poured into water containing $Na_2S_2O_3$. The crystalline material was filtered (45 mg) and recrystallized from $CHCl_3$–MeOH to yield **16** (30 mg): mp 246°; $[\alpha]D$ +61°; M^+ *m/e* 550; ν_{max} 1750 cm^{-1}; nmr δ 4.3 (m, 1 H) and absence of vinyl proton signal. *Anal.* Calcd for $C_{30}H_{47}BrO_4$: C, 65.31; H, 8.59. Found: C, 65.62; H, 8.81.

Reduction of 16 (200 mg) with boron trifluoride etherate (2 ml) and $LiAlH_4$ (200 mg) in THF (25 ml) for 8 hr yielded a mixture (185 mg) whose ir spectrum was transparent in the carbonyl region. Its nmr spectrum showed signals at δ 4.3 (m, 1 H) and 3.3 (2 H) and no vinyl proton signal. This was again reduced with $LiAlH_4$ (150 mg) in refluxing THF (30 ml) for 7 hr to yield a mixture (170 mg) which on chromatography on alumina (10 g) did not yield **21** but furnished **10** (38 mg), mp 242°, $[\alpha]D$ +41°, identified by direct comparison (tlc, ir, mixture melting point) with an authentic sample prepared by reducing **4** with $LiAlH_4$. It also gave a compound (34 mg), mp 168–170°, which was not **11** and was not further characterized.

A solution of **10** (200 mg) in $CHCl_3$ (15 ml) was treated with gaseous HCl for 1 hr at room temperature. Usual work-up gave a solid (185 mg) which on chromatography on alumina (10 g) furnished the starting material (98 mg) and another product (48 mg), mp 246°, M^+ *m/e* 486, which was not further characterized.

Echinocystic Acid Lactone (15). A stream of gaseous HCl was passed through a solution of **3** (100 mg) in $CHCl_3$ (50 ml) for 15 min at room temperature. Removal of the unreacted acid with 15% aqueous KOH yielded the neutral **15** (23 mg): mp 280°; $[\alpha]D$ +14°; ν_{max} 1753 cm^{-1}; nmr spectrum showed the absence of vinyl protons. *Anal.* Calcd for $C_{30}H_{48}O_4$: C, 76.22; H, 10.24. Found: C, 76.31; H, 10.41. Reduction of **15** with boron trifluoride etherate and $LiAlH_4$ did not give **21**.

Protoprimulagenin A (21). A solution of **14**[18] (300 mg) in THF (20 ml) containing boron trifluoride etherate (3 ml) was added to a stirred suspension of $LiAlH_4$ (250 mg) in THF (250 ml) at 0°. Stirring was continued for 2 hr at ice-bath temperature. Usual work-up and chromatography on basic alumina gave in benzene–ethyl acetate (1:1) **21** (48 mg): mp 262°; $[\alpha]D$ +22°; ν_{max} 3600–3500 cm^{-1}; nmr δ 3.1–3.5 (m, 3 H) and 3.91 (1 H). This was identified by direct comparison (tlc, ir, nmr, mixture melting point, etc.) with an authentic sample.[10]

Acknowledgments. We are indebted to Professor I. Kitagawa for an authentic sample of protoprimulagenin A and to the CSIR (India) for the award of a junior research fellowship to one of us (A. A. N.).

Registry No.—**3**, 545-88-0; **6**, 545-48-2; **7**, 7089-38-5; **8**, 51820-71-4; **12**, 1721-60-4; **14**, 51830-03-6; **15**, 51829-67-5; **16**, 51829-68-6; **18**, 35738-40-0; **19**, 43059-47-8; **20**, 39701-58-1; **21**, 2611-08-7.

References and Notes

(1) (a) National Chemical Laboratory Communication No. 1818. (b) Institut de Chimie, Université Louis Pasteur, Strasbourg, France.
(2) K. Venkateswara Rao, *Tetrahedron*, **20**, 973 (1964).
(3) R. Tschesche, F. Inchaurrondo, and G. Wulff, *Justus Liebigs Ann. Chem.*, **680**, 107 (1964).
(4) R. Tschesche, H. Striegler, and H. W. Fehlhaber, *Justus Liebigs Ann. Chem.*, **691**, 165 (1966).
(5) R. Tschesche, B. Tjiong Tjoa, and G. Wulff, *Justus Liebigs Ann. Chem.*, **696**, 160 (1966).
(6) N. Aimi and S. Shibata, *Tetrahedron Lett.*, 4721 (1966).
(7) I. Yosioka, T. Nishimura, N. Watani, and I. Kitagawa, *Tetrahedron Lett.*, 5343 (1967).
(8) T. Kubota and H. Hinoh, *Tetrahedron Lett.*, 4725 (1966); *Tetrahedron*, **24**, 675 (1968).
(9) R. O'Dorchai and J. B. Thomson, *Tetrahedron Lett.*, 2223 (1965); *Tetrahedron*, **24**, 1377 (1968).
(10) I. Kitagawa, A. Matsuda, and I. Yosioka, *Tetrahedron Lett.*, 5377 (1968).
(11) D. H. R. Barton and N. J. Holness, *J. Chem. Soc.*, 78 (1952).
(12) See, *e.g.*, F. E. King, T. J. King, and J. M. Ross, *J. Chem. Soc.*, 3995 (1954); 1333 (1955).
(13) G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **26**, 4557 (1961).
(14) V. Prelog, J. Norymberski, and O. Jeger, *Helv. Chim. Acta*, **29**, 360 (1946).
(15) C. Djerassi, R. M. McDonald, and A. J. Lemin, *J. Amer. Chem. Soc.*, **75**, 5940 (1953).
(16) B. Bischof, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **32**, 1911 (1949).
(17) D. H. R. Barton, A. Hameed, and J. F. McGhie, *J. Chem. Soc.*, 5176, 5182 (1962).
(18) W. R. White and C. R. Noller, *J. Amer. Chem. Soc.*, **61**, 984 (1939); C. Sannie, H. Lapin, and I. P. Varshney, *Bull. Soc. Chim. Fr.*, 1440 (1957).
(19) Melting points are uncorrected and were taken in capillary tubes in a Gallenkemp melting point apparatus. Optical rotations were determined in 1% $CHCl_3$ solution on a Perkin-Elmer spectropolarimeter. Ir spectra were recorded on a Perkin-Elmer Model 221 or Infracord spectrophotometer in $CHCl_3$ solution. Nmr spectra were determined on a Varian A-60 or T-60 spectrometer in $CDCl_3$ solution using TMS as an internal standard. Mass spectra were recorded on a CEC Model 21-110 B mass spectrometer at 70 eV, by direct inlet system. Tetrahydrofuran (THF) was distilled over lithium aluminum hydride.
(20) Echinocystic acid (**3**) was isolated from the seeds of *Albizzia lebbek* by the procedure of I. P. Varshney, *Indian J. Chem.*, **7**, 446 (1949).

Nucleophilic Addition of Aliphatic Hydroxylamines to *p*-Tolylsulfonylacetylenes. Competitive Nitrogen and Oxygen Attack

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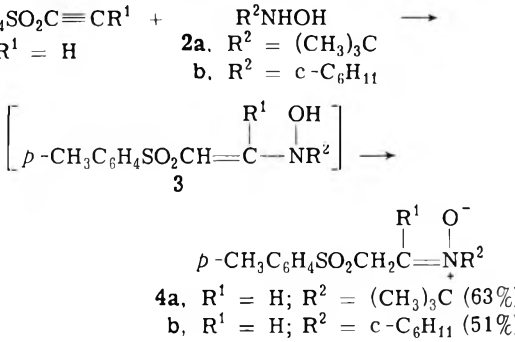
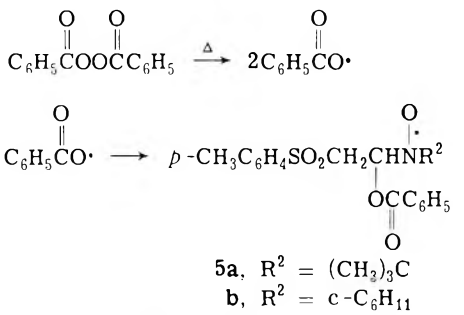
Acetylenes activated by sulfonyl substitution at the triple bond usually undergo facile nucleophilic addition.[1-4] Particularly the addition reactions of primary and secondary amines have been subjected to detailed investigation. However, there seems to be no literature precedent for the reaction of hydroxylamines with acetylenic sulfones. We report here a few examples of such reactions.

When *p*-tolylsulfonylacetylene (**1a**) was allowed to react with *N*-*tert*-butylhydroxylamine (**2a**) or *N*-cyclohexylhydroxylamine (**2b**) in ethanol at room temperature, a smooth reaction occurred. The analytical and spectral properties of the crystalline products obtained were entirely consistent with the nitrone structures[5] **4a,b**. The pres-



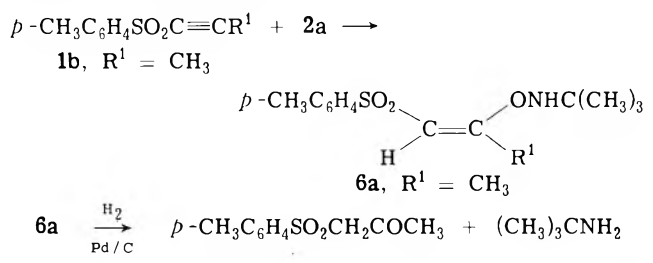
ence of a nitrone functionality in **4a,b** is further supported by the successful utilization of these compounds as spin

traps.[6] Thus, benzoyloxy radicals rapidly add to **4a,b** to give paramagnetic species that exhibit esr spectra in accordance with the nitroxide radical structures **5a,b** (*cf.* Experimental Section).



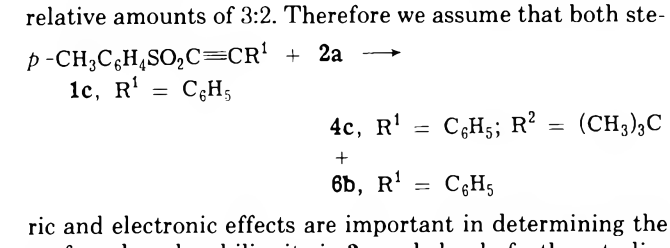
Presumably, the formation of **4a,b** from **1a** proceeds *via* preferential attack of nitrogen[7] on the triple bond, to give initially *N*-hydroxyenamines of type **3,** followed by isomerization through proton shift from oxygen to α-sulfonyl carbon.[8]

Interestingly, the addition of **2a** to the nonterminal sulfonylacetylene **1b** took a completely different course. The 1:1 adduct, isolated in a yield of 86%, possessed spectral properties which were inconsistent with a nitrone product like **4** ($R^1 = CH_3$). We assign the *O*-sulfonylpropenylhydroxylamine structure **6a** to this adduct on the basis of the following observations. First of all, the ir spectrum, taken in carbon tetrachloride, showed a rather sharp absorption at 3248 ± 2 cm^{-1} and no (broad) OH stretch around 3500 cm^{-1} as would be expected for an *N*-hydroxyenamine **3** [$R^1 = CH_3$; $R^2 = (CH_3)_3C$].[9,10] The isolation of *p*-tolylsulfonylacetone (91%) upon mild hydrogenation[11] of **6a** and the failure of **6a** to react with Fehling's reagent[12] lend further support to the proposed structure.[13]



Intramolecular nuclear Overhauser effects (NOE)[14] indicate that **6a** is the *Z* isomer, since saturation of the methyl absorption at δ 2.18 ppm resulted in a 12 ± 2% enhancement of the signal due to the vinyl hydrogen. This provides evidence for trans addition of **2a**,[15] but by analogy with the addition of amines,[2] postisomerization processes may occur. In addition, saturation of the *tert*-butyl signal resulted in a 13 ± 1% increase in the intensity of the vinyl proton absorption. Inspection of molecular models reveals that this result can be reconciled with structure **6a** rather than with **3** [$R^1 = CH_3$; $R^2 = (CH_3)_3C$] since only in **6a** conformations with short vinyl hydrogen–*tert*-butyl hydrogen distances can be attained. There is ample literature precedent for long-range NOE[16] and these effects can also occur if only part of the populated conformations allow for sufficiently short internuclear distances.[14]

The isolation of **6a** indicates that **2a** utilizes oxygen as the nucleophilic site[17] in the addition reaction to **1b.** It is tempting to rationalize this result in terms of the more severe steric demands for addition to **1b,** causing the reaction to occur at the least hindered nucleophilic site in **2a.** The competitive nitrogen *vs.* oxygen attack for addition of **2a** to **1a,b** would then be reminiscent of the behavior of N-monosubstituted hydroxylamines upon acylation. Usually nitrogen is the preferred nucleophilic site but acylation may occur on oxygen when steric hindrance deactivates the nitrogen atom.[18] However, the actual situation is more complicated as demonstrated by the addition of **2a** to the even more hindered **1c.** This reaction afforded in 94% yield a mixture of the nitrone **4c** and the O-substituted hydroxylamine **6b** (structure based on spectral analogy with **6a**) in relative amounts of 3:2. Therefore we assume that both steric and electronic effects are important in determining the preferred nucleophilic site in **2a** and clearly further studies are required in order to obtain further insight into this problem.



Experimental Section

Elemental analyses were carried out in the Analytical Department of this laboratory under the supervision of Mr. W. M. Hazenberg. Melting points were determined using a Mettler FP1 melting point apparatus with a Mettler FP52 microscope attachment. Nmr spectra were recorded on a Varian A-60 spectrometer, using TMS (δ 0) as an internal standard. NOE experiments were performed on a Varian XL-100-15 instrument. Esr spectra were taken on a Varian E-4 apparatus. Ir spectra were measured with a Perkin-Elmer instrument, Model 125 or 257.

The sulfonylacetylenes **1a, 1b,** and **1c** and the hydroxylamines **2a** and **2b** were prepared according to literature procedures.[2-4,7]

Addition of Hydroxylamines to Sulfonylacetylenes. General Procedure. To a solution of the hydroxylamine **2a,b** (1.1 mmol) in 5 ml of ethanol was added dropwise an ethanolic solution of the sulfonylacetylene **1a–c** (1 mmol in 5 ml). After stirring for 2 hr at room temperature the solvent was removed *in vacuo.* Solvents used for crystallization of the obtained solids and yields of analytically pure compounds are given below.

The crude reaction product from the reaction of **1c** with **2a** was dissolved in 100 ml of dichloromethane and washed twice with 100 ml of water. After drying with sodium sulfate and removal of the solvent *in vacuo,* the nmr spectrum of the mixture indicated the presence of 60% of **4c** and 40% of **6b** (total yield 94%). The product composition remained unchanged when the reaction time was doubled. Two crystallizations of the material from petroleum ether (bp 40–60°)–ether (1:1) afforded pure **6b.** Evaporation of the mother liquor gave solid material that was crystallized five times from *n*-pentane–ether (19:1) to give a low yield of **4c.**

C-*p*-**Tolylsulfonylmethyl**-*N*-*tert*-**butylnitrone (4a):** yield 63%; mp 125–126.5° (from CCl_4); nmr ($CDCl_3$) δ 1.35 (s, 9 H, *tert*-butyl), 2.42 (s, 3 H, aryl CH_3), 4.40 (d, J = 6 Hz, 2 H, CH_2), 7.02 (t, J = 6 Hz, 1 H, methine proton), ~7.30–7.91 ppm (AA'BB', 4 H, aryl); ir (KBr) 1582, 1568, 1354, 1310, 1300, 1285, 1148, 1120 cm^{-1}.

Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20; S, 11.91. Found: C, 57.78; H, 7.02; N, 5.06; S, 12.03.

C-*p*-**Tolylsulfonylmethyl**-*N*-**cyclohexylnitrone (4b):** yield 51%; mp 114.5–115.3° (from benzene–*n*-hexane); nmr ($CDCl_3$) δ ~1.0–1.9 (unresolved m, 11 H, cyclohexyl), 2.43 (s, 3 H, aryl CH_3), 4.37 (d, J = 6 Hz, 2 H, CH_2CH=), 6.90 (t, J = 6 Hz, 1 H, methine proton), 7.22–7.88 ppm (AA'BB', 4 H, aryl); ir (Nujol) 1580, 1385, 1310, 1290, 1130 cm^{-1}.

Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74; S, 10.86. Found: C, 61.21; H, 7.43; N, 4.56; S, 10.71.

C-**Phenyl**-*C*-*p*-**tolylsulfonylmethyl**-*N*-*tert*-**butylnitrone (4c):** mp 110–112° (from *n*-pentane–ether); nmr ($CDCl_3$) δ 1.29 (s, 9 H, *tert*-butyl), 2.45 (s, 3 H, aryl CH_3), 4.73 (s, 2 H, CH_2), ~7.20–8.00 ppm (m, 9 H, aryl protons).

Anal. Calcd for $C_{19}H_{23}NO_3S$: C, 66.06; H, 6.71; N, 4.06; S, 9.28. Found: C, 65.86; H, 6.79; N, 4.00; S, 9.23.

N-*tert*-**Butyl**-*O*-**2**-*p*-**tolylsulfonylpropenylhydroxylamine (6a):** yield 86%; mp 122–124° [from petroleum ether (bp 40–60°)–ether (1:1)]; nmr ($CDCl_3$) δ 1.02 (s, 9 H, *tert*-butyl), 2.18 [s, 3 H, C=C(CH_3)], 2.40 (s, 3 H, aryl CH_3), ~5.1 (br s, 1 H, NH), 6.42 (s, 1 H, vinyl H), 7.25–7.85 ppm (AA'BB', 4 H, aryl); mass spectrum *m/e* 283 (M^+); ir (KBr) 3245, 3085, 1640, 1380, 1360, 1275, 1127 cm^{-1}; ir (0.01–0.04 *M* solution in CCl_4) 3248 ± 2 cm^{-1}.

Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.36; H, 7.47; N, 4.94; S, 11.31. Found: C, 59.33; H, 7.41; N, 4.84; S, 11.17.

Acylation of **6a** with acetyl chloride was attempted under a variety of standard conditions but all experiments led to recovery of **6a** in high yield. Under more drastic conditions extensive decomposition of **6a** was observed. Steric approach to nitrogen is apparently strongly hindered because of the neopentyl-like position. NOE: on a degassed 0.2 *M* solution of **6a** in $CDCl_3$.

***N*-*tert*-Butyl-*O*-2-*p*-tolylsulfonyl-1-phenylethenylhydroxylamine (6b):** yield 32%, mp 152–154°, nmr ($CDCl_3$) δ 1.17 (s, 9 H, *tert*-butyl), 2.38 (s, 3 H, aryl CH_3), 5.63 (s, 1 H, NH), 6.83 (s, 1 H, vinyl H), ~7.20–8.00 ppm (m, 9 H, aryl protons); ir (KBr) 3255, 3085, 1620, 1590, 1365, 1295, 1285, 1127 cm^{-1}.

Anal. Calcd for $C_{19}H_{23}NO_3S$: C, 66.06; H, 6.71; N, 4.06; S, 9.28. Found: C, 65.98; H, 6.62; N, 3.79; S, 9.20.

Reduction of 6a. Using a procedure similar to that described by Nicolaus, *et al.*,[11] a 91% yield of pure *p*-tolylsulfonylacetone, mp 50.5–51.5° (lit.[19] mp 52°), was obtained. The spectral data were in accordance with the structure. *tert*-Butylamine was detected in the reaction mixture by glc comparison with an authentic sample.

Esr Experiments. A 0.05 *M* solution of dibenzoyl peroxide in benzene was mixed with an equimolar solution of **4a** or **4b** in benzene, and the mixture was degassed. After 5 min, the esr spectrum of the spin adduct was recorded: **5a,** a_N = 14.7 G, a_H = 2.8 G (1 H); **5b,** a_N = 14.5 G, a_H = 4.0 (1 H), 6.0 G (1 H).

Acknowledgment. We are indebted to Dr. J. H. Wieringa for performing the NOE experiments.

Registry No.—**1a,** 13894-21-8; **1b,** 14027-53-3; **1c,** 24378-05-0; **2a,** 16649-50-6; **2b,** 2211-64-5; **4a,** 51869-11-5; **4b,** 51869-12-6; **4c,** 51869-13-7; **5a,** 51869-14-8; **5b,** 51869-15-9; **6a,** 51869-50-2; **6b,** 51869-16-0.

References and Notes

(1) H. G. Viehe, "Chemistry of Acetylenes," Marcel Dekker, New York, N. Y., 1969.
(2) W. E. Truce and D. G. Brady, *J. Org. Chem.*, **31**, 3543 (1966).
(3) C. J. M. Stirling, *J. Chem. Soc.*, 5863 (1964).
(4) C. H. McMullen and C. J. M. Stirling, *J. Chem. Soc. B*, 1217 (1966).
(5) The sharp melting points and the nmr spectra of **4a,b** point to the presence of only one geometrical isomer. Configurational isomerization is expected to be slow at 37°: T. S. Dobashi, M. H. Goodrow, and E. J. Grubbs, *J. Org. Chem.*, **38**, 4440 (1973).
(6) E. G. Janzen, *Accounts Chem. Res.*, **4**, 31 (1971), and references cited therein.
(7) The usual preference for nitrogen as the nucleophilic site in N-monosubstituted hydroxylamines is well documented: B. Zeeh and H. Metzger in Houben-Weyl, "Methoden der Organischen Chemie," Vol. X-1, Georg Thieme Verlag, Stuttgart, 1971, p 1091.
(8) There is only a very limited amount of literature on the addition of hydroxylamines to any sort of carbon–carbon triple bond: (a) E. Huntress, T. E. Lesslie, and W. M. Hearon, *J. Amer. Chem. Soc.*, **78**, 419 (1956); (b) W. C. Agosta, *J. Org. Chem.*, **26**, 1724 (1961); (c) E. Winterfeldt and W. Krohn, *Chem. Ber.*, **102**, 2336, 2346, (1969); (d) F. de Sarlo, G. Dini, and P. Lacrimini, *J. Chem. Soc. C*, 86 (1971); (e) T. Sheradsky and S. Lewinter, *Tetrahedron Lett.*, 3941 (1972).
(9) It is highly unlikely that the observed peak is due to an OH stretch shifted to lower frequency as a result of hydrogen bonding. To test for intermolecular H bonding, ir spectra were taken at concentrations as low as 10^{-2} mol $l.^{-1}$ but no free OH stretch could be detected. The frequency of the absorption is too low to be the result of intramolecular H bonding of OH in a structure like **3** to a weak H-bond acceptor moiety like the sulfonyi group; see J. W. Dallinga and J. B. F. N. Engberts, *Spectrochim. Acta*, in press.
(10) (a) G. Rawson and J. B. F. N. Engberts, *Tetrahedron*, **26**, 5653 (1970); (b) M. Davies and N. A. Spiers, *J. Chem. Soc.*, 3971 (1959).
(11) O–N bond cleavage upon hydrogenation of *O*-alkylhydroxylamines is a well-known reaction: B. J. R. Nicolaus, P. Pagin, and E. Testa, *Helv. Chim. Acta*, **45**, 358 (1962).
(12) Hydroxylamines containing an unsubstituted OH group give a positive test with Fehling's reagent; see ref 7.
(13) Attempts to isomerize **6a** into the isomeric nitrone by heating in toluene either with or without *p*-toluenesulfonic acid as a possible catalyst were unsuccessful and only led to decomposition.
(14) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect," Academic Press, New York, N. Y., 1971.
(15) One could imagine that the barrier to rotation around the carbon–carbon double bond in **6a** is substantially lowered owing to resonance interaction involving partial electron pair localization at α-sulfonyl carbon. However, nmr spectra of **6a** taken in CS_2 down to −110° did not show any splitting of the appropriate signals.
(16) See, for instance, R. Rowan, III, A. Warshel, B. D. Sykes, and M. Karplus, *Biochemistry*, **13**, 970 (1974), and references cited therein.
(17) N,N-Disubstituted hydroxylamines occasionally add through oxygen attack; see ref 7.
(18) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, New York, N. Y., 1966, p 10.
(19) J. Tröger and O. Beck, *J. Prakt. Chem.*, **87**, 289 (1913).

Thermal Rearrangement of Deltacycline to Indan. A Facile and Deep-Seated Aromatization

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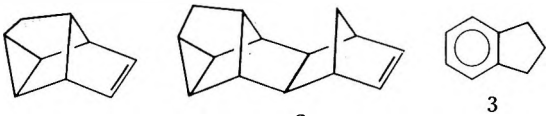
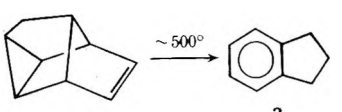
We have been investigating the mass spectral behavior of deltacyclene (tetracyclo[4.3.0.$0^{2,4}$.$0^{3,7}$]non-8-ene, **1**)[1] and a series of related compounds and have observed very strong peaks at *m/e* 118 and 117 in the mass spectra of many of these molecules, especially deltacyclene itself and its thermal precursor, the head-to-side norbornadiene dimer (**2**).[1b,c] This mass spectral pattern is suggestive of the aromatic C_9H_{10} isomer indan (**3**) under similar conditions[2] and indicates that deltacyclene rearranges upon electron impact to indan, which then loses hydrogen in apparent analogy with the mass spectral rearrangement of toluene to the tropylium ion.[3] Since deltacyclene is formed from dimer **2**



1 2 3

via pyrolysis at ~480°,[1] the mass spectrum of **2** first of all indicates that the analogous fragmentation (a retro Diels–Alder reaction) apparently occurs in the mass spectrometer and, secondly, raises the possibility that deltacyclene might undergo pyrolysis to indan.

Accordingly, deltacyclene was pyrolyzed at temperatures between 480 and 510°. This resulted in a strikingly clean aromatization to indan (eq 1).

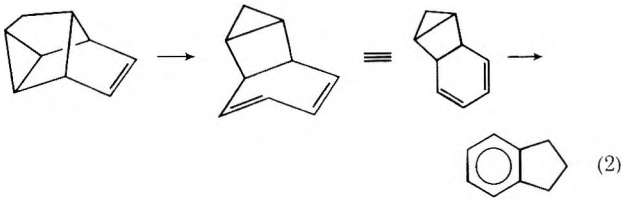


1 3 (1)

A number of side products, most with molecular weights of 118, were also formed, but their total concentration was low. In a typical experiment, deltacyclene vapor, mixed with dry nitrogen, was pyrolyzed in a flow system by passing a stream of nitrogen over a reservoir of starting material, passing the mixture through a heated Pyrex tube, and then trapping the products at Dry Ice or liquid nitrogen temperatures. Product mixtures were initially analyzed on a gas chromatograph–mass spectrometer combination, and indan was confirmed as the major product by comparing the mass spectrum, gas chromatographic retention times, and nmr spectrum of the product with the corresponding data for commercial indan. All were indistinguishable. When the mixture was analyzed on SE-30 or FFAP columns at least eight products could be detected, but unreacted deltacyclene (16%) and indan (70%) were by far the major components, with the next most plentiful product (also *m/e* 118) having a concentration of 8% (percentages are based on total volatile product; see Experimental Section). When the dimer **2** was pyrolyzed at temperatures higher than 480° and, especially, with larger contact times, the product mixture contained increasing amounts of indan presumably formed *via* secondary pyrolysis of deltacyclene; this system (**2** → **3**) actually constitutes a fairly good synthesis of indan.

The deltacyclene → indan transformation is reminiscent of the thermal conversion of norbornadiene to toluene, which has been postulated to occur *via* initial formation of cycloheptatriene.[4] The analogous pathway in this system,

however, appears to require intolerable strain, and the most straightforward rationalization appears to involve a sequence such as that shown in eq 2.



(2)

This process requires the breaking of two carbon–carbon single bonds in addition to two hydrogen migrations, and the high conversions and low production of side products are somewhat surprising in this context. An interesting *a priori* alternative pathway, the thermally allowed[5] retro homo-Diels–Alder reaction to yield acetylene and bicyclo[2.2.1]heptadiene, is at best a minor process in this pyrolysis, even though it is apparently important in the electron impact reactions of some closely related molecules.[2]

The mechanism of the rearrangement of deltacyclene to indan is under investigation in conjunction with our study of mass spectral behavior of this series of compounds; details will be furnished in a later report.

Experimental Section

Materials. The norbornadiene dimer (hexacyclo[9.2.1.$0^{2,10}$.$0^{3,8}$.$0^{4,6}$.$0^{5,9}$]tetradec-12-ene, **2**) and deltacyclene were prepared according to published procedures.[1] Indan was purchased from Aldrich Chemical Co.

Pyrolyses. The pyrolysis of dimer **2** was carried out in an apparatus essentially the same as that described by Katz[1b,c] and by Cannell,[1a] consisting of a vertical Pyrex tube, 2.5 cm × 1 m, packed with sections of Pyrex tubing and wrapped with heating tape. The reactant was dropped into this tube from a pressure-compensated addition funnel, and the product mixture was collected in a cold trap at the bottom of the tube. A steady flow of nitrogen was maintained during the reaction. Temperatures were measured inside the apparatus with calibrated thermocouples.

Gas-phase pyrolyses were conducted in a generally similar apparatus but with a small pyrolysis tube (10 mm × 25 cm) held in a horizontal position. An inlet reservoir was arranged to allow dry nitrogen to pass directly over a small amount of liquid reactant. The concentration of reactant in the vapor mixture was controlled by cooling or warming the reservoir. The outlet was connected directly to a cold trap which was protected by a Nujol bubbler and a drying tube. After reaction, the product mixtures were warmed to room temperature and samples were injected directly into a flame-ionization gas chromatograph. For experiments with very dilute vapor, the small amount of product was generally dissolved in ether prior to gc analysis.

Preparative pyrolyses of deltacyclene were performed in the large-scale vertical apparatus and the major product was isolated by preparative gas chromatography; the product from the high-temperature, longer contact time pyrolysis of dimer **2** was isolated by fractional distillation. In both cases, the product was identical in all respects with commercial indan.

In the preparative pyrolyses, the product mixture was typically a dark brown liquid which was separable into about 80% indan and 20% viscous, high-boiling polymer. Material balances were generally in the range of 80–90%, which corresponded to yields of indan of 65–75%. In the vapor-phase pyrolyses, the total amounts of material involved were very small (of the order of a few milligrams); so material balances were difficult to determine. The product mixtures, however, appeared to contain much less polymeric material than those in the preparative liquid pyrolyses; so material balances in these systems were probably at least as high as in the preparative reactions.

Preparative gas chromatography was done on a Varian Aerograph 90-P thermal conductivity instrument using a 5 ft × 0.25 in. stainless steel column packed with 15% SE-30 on 60/80 Chromosorb W. Analytical gas chromatography was done on a Perkin-Elmer 990 flame-ionization instrument using 10 ft × 0.125 in. aluminum columns packed with 3–5% SE-30 or FFAP on 80/100 Chromosorb W.

Acknowledgment. This research was supported by grants from the Research Corporation and from the Boston University Graduate School. The mass spectrometer was purchased through a grant from the National Science Foundation.

Registry No.—**1**, 7785-10-6; **2**, 7781-74-0; **3**, 496-11-7.

References and Notes

(1) (a) L. G. Cannell, *Tetrahedron Lett.*, 5967 (1966); (b) J. J. Mrowka and T. J. Katz, *J. Amer. Chem. Soc.*, **88**, 4012 (1966); (c) T. J. Katz, J. C. Carnahan, Jr., and R. Boeke, *J. Org. Chem.*, **32**, 1301 (1967).
(2) J. S. Wishnok, unpublished observations.
(3) K. L. Rinehart, A. C. Bucholz, G. E. Van Lear, and H. C. Cantrill, *J. Amer. Chem. Soc.*, **90**, 2983 (1968).
(4) B. C. Roquitte, *Can. J. Chem.*, **42**, 2134 (1964); S. Meyerson, J. C. McCollum, and P. N. Rylander, *J. Amer. Chem. Soc.*, **83**, 1401 (1961).
(5) R. Hoffman and R. B. Woodward, "The Conservation of Orbital Symmetry," Verlag Chemie, Weinheim/Bergstr., Germany, 1970, p 106.

Tetrabutylammonium Fluoride. A New Reagent for the Synthesis of Hydantoins

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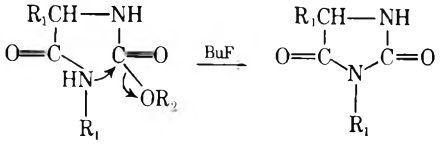
Tetraalkylammonium fluorides have been used more and more for different purposes in preparative organic chemistry in the last couple of years, for example, for the cleavage of *tert*-butyldimethylsilyl ether[1] or for the fluorination of fluoroolefins.[2] Furthermore, it proved to be a useful reagent in a number of elimination reactions.[3–5]

Results

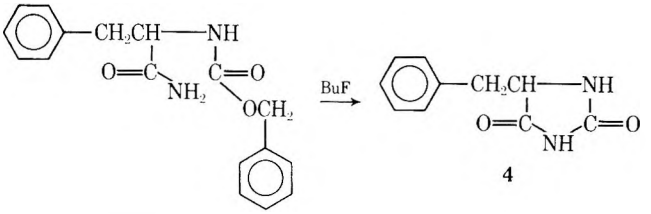
We have now found that tetrabutylammonium fluoride (BuF) has a remarkable capacity to enable intramolecular cyclizations of the following type to proceed.



1 **2**

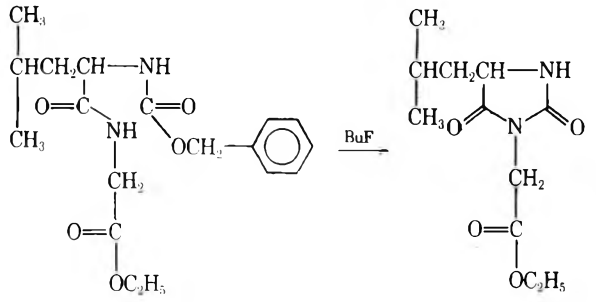
R_1 = H, CH_3, $C_6H_5CH_2$
R_2 = CH_3, $C_6H_5CH_2$

Thus in boiling tetrahydrofuran carbobenzoxyphenylalaninamide gives the corresponding hydantoin in over 90% yield.



3 **4**

The same reaction could be performed with a series of carbamates to produce substituted hydantoins in excellent yields. Extending this reaction to peptides we found that, *e.g.*, carbobenzoxydipeptides like Z-Leu-Gly-OEt, if exposed to BuF in THF, undergo cyclization with similar ease.



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It is both remarkable and advantageous that BuF allows these cyclizations to take place under essentially neutral conditions. Previous methods invariably relied on strongly alkaline media; side reactions could not be avoided and the yield of the cyclized product was often very low (20–40%).

There are many—at first sight—unique features of this ring closure, in particular with regard to the polarity of the solvent and the nature of the quaternary ammonium salt.

(1) In protic solvents like alcohols or solvent mixtures containing water, cyclization does not take place.

(2) Solvents of very low polarity diminish the yield considerably.

(3) Tetrahydrofuran seems to be the solvent of choice.

(4) Cyclization is limited to the fluoride salt; salts of other anions such as tetrabutylammonium chloride or bromide do not yield any noticeable amount of hydantoin.

(5) We have found that the use of 2–3 molar equiv of BuF and refluxing for 12–14 hr represent the optimal reaction conditions.

Discussion

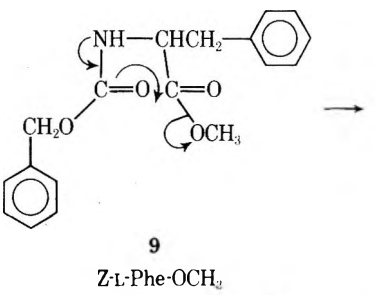
The strong proton acceptor capacity of quaternary ammonium halides is well known,[6] but this alone cannot be a sufficient explanation for this ring formation, since the bromide and chloride salts do not give hydantoins.

Thus the existence of "naked" F^- seems to be essential for cyclization and BuF is an ideal source of it. BuF is completely dissociated[7] unlike the corresponding bromide or chloride salts, even in solvents of medium polarity like tetrahydrofuran. F^- is not solvated in this solvent and represents a weak nucleophile and a strong base at the same time, facilitating certain types of base-catalyzed cyclization reactions. The role of quaternary ammonium salt would be then simply to produce the necessary amount of F^- in organic solvents. Several reactions have been reported as being catalyzed by potassium fluoride, such as the Knoevenagel reaction[8] or the cyclization of adipic acid derivatives[9] to the corresponding cyclopentanones. All of these reactions are typically base catalyzed, similarly to the hydantoin formation described in this paper.

Indirect evidence of another type of cyclization with the participation of neighboring groups has also been observed with BuF. When carbobenzoxy-L-phenylalanine methyl ester was treated with BuF under the conditions already mentioned, the only product isolated in nearly quantitative yield was carbobenzoxy-DL-phenylalanine. A possible explanation of this saponification coupled with racemization would be the formation of the corresponding azlactone intermediate, which is known to be involved in several racemization phenomena.[10]

Azlactone, which is relatively unstable, could not be isolated, since it is immediately hydrolyzed by the small amount of water always present in BuF.

For this racemization reaction the same observations which regard to solvent and type of quaternary salt were valid as for the hydantoin formation.



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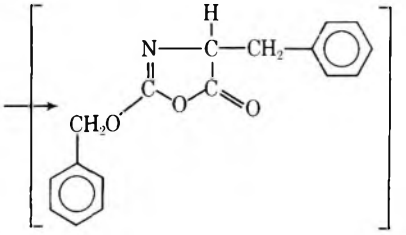
Z-L-Phe-OCH_3



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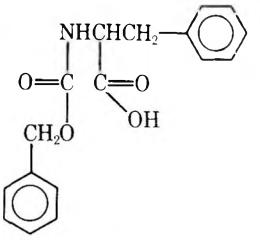

11

Z-DL-Phe-OH

The use of BuF for other base-catalyzed reactions is certainly not limited to the two SNi reaction types described here. Other applications of this reagent extending its use to those reactions which are known to be catalyzed by potassium fluoride are under study.

Experimental Section

Synthesis of BuF. Two methods are described in the literature for the synthesis of BuF,[11] but both of them are relatively complicated and time consuming. In our experience the simplest way to produce BuF is the following. A 100-ml ion exchanger Amberlite IRA 410 is transformed into the OH form on a column with dilute NaOH and washed with water until neutral. Aqueous HF is then passed through the column and finally 10 g of tetrabutylammonium bromide dissolved in 100 ml of water. After the resin is washed with water the combined water fractions are repeatedly evaporated *in vacuo* until no water is present. The resulting BuF, isolated in quantitative yield, is a colorless oil which becomes crystalline in the presence of humidity.[11]

Typical Procedure for Hydantoin Formation. *N*-Carbobenzoxyphenylalanylhomoveratrylamide (6.4 g, 13.5 mmol) and 10.6 g (40 mmol) of BuF are dissolved in 200 ml of tetrahydrofuran and refluxed for 14 hr. After partial evaporation of the solvent the product is precipitated by adding water. It is filtered and washed with water and ether. Without recrystallization 4.6 g (97%) of hydantoin is isolated, mp 157–158°, in analytically pure form.

Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.7; H, 6.3; N, 7.9; O, 18.1. Found: C, 67.3; H, 6.2; N, 7.7; O, 18.6.

Acknowledgment. I wish to thank Professors W. Oppolzer and E. Winterfeldt for valuable discussions and Mr. K. Lintner and Mrs. H. Tanner for their technical assistance.

Registry No.—2 (R = $C_6H_5CH_2$; R′ = homoveratryl), 51849-51-5; *N*-carbobenzoxyphenylalanylhomoveratrylamide, 51849-52-6; tetrabutylammonium fluoride, 429-41-4.

References and Notes

(1) E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, **94**, 6190 (1972).

(2) W. T. Miller, J. H. Fried, and H. Goldwhite, *J. Amer. Chem. Soc.*, **82**, 3091 (1960).
(3) J. Hayami, N. Ono, and A. Kaji, *Tetrahedron Lett.*, 1385 (1968); 2727 (1970).
(4) R. F. Cunico and E. M. Dexheimer, *J. Amer. Chem. Soc.*, **94**, 2868 (1972).
(5) T. H. Chan and W. Mychajlowskij, *Tetrahedron Lett.*, 171 (1974).
(6) A. Allerhand and P. R. Schleyer, *J. Amer. Chem. Soc.*, **85**, 1233 (1963).
(7) See, for example, C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969.
(8) L. Rand, J. Swisher, and C. Cronin, *J. Org. Chem.*, **27**, 3505 (1962).
(9) L. Rand, W. Wagner, P. O. Warner, and L. R. Kovac, *J. Org. Chem.*, **27**, 1034 (1962).
(10) See, for example, J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Wiley, New York, N. Y., 1961.
(11) W. Y. Wen, S. Saito, and C. Lee, *J. Phys. Chem.*, **70**, 1244 (1966).

Fluorination with Xenon Difluoride. Fluorine Addition to 1-Phenylacetylenes

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Electrophilic addition of halogens to olefinic systems has been the subject of considerable study.[1] The analogous additions[1,2] to acetylenic systems have received much less attention. In particular, the addition of molecular fluorine,[3] chlorine monofluoride,[4] bromine monofluoride,[4,5] and iodine monofluoride[4] to acetylenes has been studied. Our recent observations that xenon difluoride adds fluorine to 1-aryl-substituted olefins[6,7] and the phenanthrene system[8] to form vicinal difluorides led us to investigate the fluorine addition to carbon–carbon triple bond with this reagent.

Although there is a structural relationship between carbon–carbon double bonds and triple bonds, the reactivities of the two systems toward electrophilic reagents are quite different. In a very recent work,[9] the rate ratio $k_{olefin}/k_{acetylene}$ of the order of 10^5 in bromination and chlorination of styrene–phenylacetylene and other olefin–acetylene pairs was observed. This difference was explained in terms of different ease of formation of carbonium ions and vinyl cations in electrophilic additions. In view of this consideration it was not certain that XeF_2 would add fluorine to 1-phenylacetylenes at all. Recently, propyne[10] was found to be resistant to fluorine addition with XeF_2 in a gas-phase reaction. After 100 days at room temperature it gave 2,2-difluoropropane in a 33% yield and at least nine other trace products. On the other hand, the addition across the triple bond might undergo accompanying substitution of the phenyl ring if one takes into account the ease of fluorination of benzene derivatives[11] with XeF_2. Therefore a study was undertaken to establish these points.

The fluorine additions to acetylenes (**1**) with xenon difluoride were conducted at 25° in methylene chloride with anhydrous hydrogen fluoride as catalyst. Less than stoichiometric amounts of xenon difluoride did not favor difluoro olefin formation and only tetrafluoride (**2**) and unreacted acetylene were found in the reaction mixture. However, the use of 2.5 equiv of XeF_2 led to the formation of **2** in over 50% yield.

$$\underset{\mathbf{1}}{PhC{\equiv}CR} + 2XeF_2 \xrightarrow[CH_2Cl_2]{HF} \underset{\mathbf{2}}{PhCF_2CF_2R} + 2Xe$$

a, R = Ph
b, R = CH_3
c, R = n-C_3H_7

The structures of previously known **2a**[3] and **2b**[3] were identified and that of unknown **2c** assigned by its ir, ^1H and ^{19}F nmr, and mass spectra.

The acetylenes seem to fluorinate completely to tetrafluoride, which implies that difluoro olefin is more reactive for fluorine addition than is the parent acetylene. The same results were found in molecular fluorine addition[3] to acetylenes at low temperature. We also observed the facile fluorine addition to 9,10-difluorophenanthrene[8] with XeF_2, yielding 9,9,10,10-tetrafluoro-9,10-dihydrophenanthrene as the reaction product.

One anomalous reaction was noted in this series of experiments. Phenylacetylene did not give 1,1,2,2-tetrafluoro-1-phenylethane, the expected product. Instead, some polymeric material was formed in this reaction.

The fluorine addition to acetylenes with XeF_2 appears to be strongly catalyzed by HF, as indicated by observation that in the absence of this catalyst reactions are very slow. We found evidence neither for the formation of fluorine-substituted products which might arise *via* a substitution fluorination of the phenyl ring nor for the presence of HF addition products, observed in the gas-phase fluorinations[10] with XeF_2. Extensive work is in progress on acid-catalyzed liquid—phase fluorination of various acetylenic systems with this reagent, which appears to be useful also for applications on a large scale.

Experimental Section[12]

Materials. The acetylenes were obtained from commercial sources and purified by vpc to conform with published physical and spectral data. Xenon difluoride was prepared by the photosynthetic method[13] and its purity was better than 99.5%. Methylene chloride was purified by the method[14] and stored over molecular sieves. Hydrogen fluoride of Fluka purum quality was used.

1,1,2,2-Tetrafluoro-1,2-diphenylethane (2a). To a solution of **1a** (0.178 g, 1.0 mmol) in methylene chloride (6 ml), xenon difluoride (0.423 g, 2.5 mmol) was added at 25° and under stirring anhydrous HF (0.100 g, 5.0 mmol) was introduced into the reaction mixture. After a few seconds the colorless solution turned dark blue and xenon gas was slowly evolved. After 6 hr gas evolution had ceased and the reaction appeared to be complete. The reaction mixture was diluted with methylene chloride (15 ml), washed (10 ml of 5% aqueous $NaHCO_3$), and dried (Na_2SO_4), and solvent was evaporated *in vacuo*. The crude product was sublimated (50°, 0.1 mm) to give **2a**: mp 121–122° (lit.[3] mp 119.3–120.5°); yield 0.163 g (64%); mass spectrum *m/e* 254 (M^+).

1,1,2,2-Tetrafluoro-1-phenylpropane (2b). To a solution of **1b** (0.116 g, 1.0 mmol) in methylene chloride (5 ml), xenon difluoride (0.338 g, 2 mmol) was added at 25° and under stirring anhydrous HF (0.02 g, 1 mmol) was introduced into the reaction mixture. After a few seconds the colorless solution turned dark blue and xenon gas was evolved slowly. After 6 hr, the reaction mixture was diluted with methylene chloride (15 ml), washed (10 ml of 5% aqueous $NaHCO_3$), and dried (Na_2SO_4), and solvent was evaporated *in vacuo*. The crude oily product was purified by vpc (6 × 0.25 in. SE-30 10% on Chromosorb A, 160°) to give **2b** as a colorless, stable liquid, yield 0.102 g (53%); mass spectrum *m/e* 192 (M^+); nmr (CCl_4) δ 1.75 (tt, 3 H, $-CH_3$, J = 19 Hz, $-CF_2CH_3$, J = 1 Hz, $-CF_2CF_2CH_3$), 7.35 (m, 5 H, Ph).

1,1,2,2-Tetrafluoro-1-phenylpentane (2c). The fluorination, work-up procedure and vpc purification were essentially the same as described for **2b**. **2c** was a colorless stable liquid: yield 0.122 g (55%); high-resolution mass spectrum *m/e* 144.0931 $(M - 4F)^+$ (calcd for $C_{11}H_{12}$, 144,0934); nmr (CCl_4) δ 0.93 (t, 3 H, $-CH_3$), 1.8 (m, 4 H, $-CH_2CH_2-$), 7.26 (m, 5 H, Ph), −125.0 (m, $PhCF_2-$), −127.8 (m, $-CF_2C_3H_7$).

Acknowledgment. We thank Professor J. Slivnik for xenon difluoride, Professor J. Marsel for providing facilities, and Dr. V. Kramer for mass spectral data. The Boris Kidrič Foundation is acknowledged.

Registry No.—**1a**, 501-65-5; **1b**, 673-32-5; **1c**, 4250-81-1; **2a**, 425-32-1; **2b**, 14210-87-8; **2c**, 51821-09-1; XeF_2, 13709-36-9.

References and Notes

(1) R. C. Fahey, *Top. Stereochem.*, **3**, 237 (1968).
(2) G. Modena and V. Tonellato, *Advan. Phys. Org. Chem.*, **9**, 185 (1971).
(3) R. F. Merrit, *J. Org. Chem.*, **32**, 4124 (1967).
(4) G. A. Olah, M. Nojima, and I. Kerekes, *Synthesis*, 780 (1973).
(5) R. E. A. Dear, *J. Org. Chem.*, **35**, 1703 (1970).
(6) M. Zupan and A. Poliak, *J. Chem. Soc., Chem. Commun.*, 845 (1973).
(7) M. Zupan and A. Pollak, *Tetrahedron Lett.*, in press.
(8) M. Zupan, Ph.D. Thesis, University of Ljubljana, 1974.
(9) K. Yates, G. H. Schmid, T. W. Regulski, D. G. Garrat, H.-W. Leung, and R. McDonald, *J. Amer. Chem. Soc.*, **95**, 160 (1973).
(10) T. C. Shieh, E. D. Feit, C. L. Chernick, and N. C. Yang, *J. Org. Chem.*, **35**, 4020 (1970).
(11) M. J. Shaw, H. H. Hyman, and R. Filler: *J. Org. Chem.*, **36**, 2917 (1971).
(12) ^1H and ^{19}F nmr spectra were obtained on Jeol PS 100 spectrometer. Mass spectra were recorded on a CEC 21-110C spectrometer. Melting points were determined on a Kofler melting point apparatus and are uncorrected.
(13) S. M. Williamson, *Inorg. Syn.*, **11**, 147 (1968).
(14) J. H. Mathews, *J. Amer. Chem. Soc.*, **48**, 562 (1926).

Selective Cleavage of β-Keto Esters by 1,4-Diazabicyclo[2.2.2]octane (Dabco)

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As a result of a continuing study utilizing nitrogenous bases,[1-4] we now wish to report that 1,4-diazabicyclo[2.2.2]octane (Dabco) is useful for the cleavage of β-keto esters.

β-Keto ester **1** was treated with 6 equiv of Dabco in 16 equiv of o-xylene at reflux (165°) for 6 hr to give ketone **10** as a white, crystalline solid in 84% yield. Ketone **10** was identical by ir, nmr, mass spectrum, glc retention time, and mixture melting point with an authentic sample prepared from **1** by a known procedure.[5]

The generality of Dabco as a reagent for cleaving β-keto esters is demonstrated by the results illustrated in Scheme I. Typically, a mixture of 1 equiv of the appropriate β-keto ester and 10 equiv of Dabco in 15 equiv of o-xylene was heated to reflux for 4 hr.[11] The resulting ketones (**11–14**) were obtained in greater than 96% yield by glc analyses and were identical by mass spectral and glc retention time comparison with authentic samples.[5,8]

The selectivity of the cleavage reaction is demonstrated by the application of Dabco to the cleavage of substrate **9** to give compound **15.** This result shows that only the β-keto esters with at least one α hydrogen were cleaved. The report[4] that a variety of nonconjugated esters are stable under conditions similar to those which cleaved β-keto esters provides further evidence of selectivity.

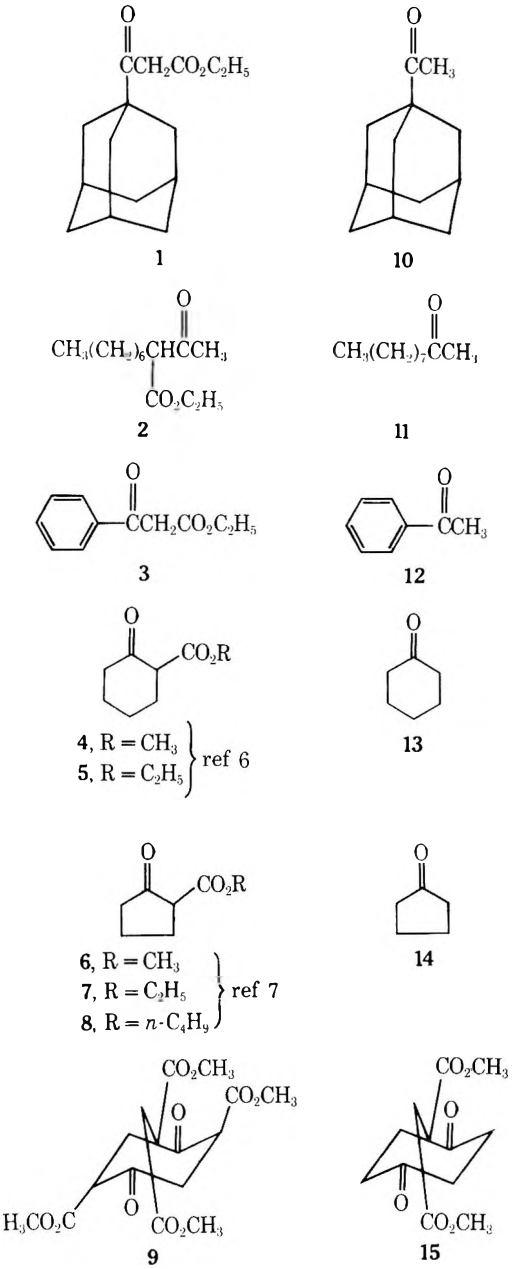
The facile cleavage of methyl, ethyl, and *n*-butyl β-keto esters with a reagent (Dabco) that does not cleave saturated esters by either the *O*-alkyl cleavage or hydrolytic routes suggests that a mechanism similar to that reported by Krapcho and Lovey[5,12] for the cleavage of β-keto esters with sodium chloride and DMSO is probably operative.

A variety of reagents have been reported for achieving the cleavage of β-keto esters.[5,9] However, to our knowledge this is the first report involving the utilization of a nonionic reagent in a relatively nonpolar solvent system.

Experimental Section

Infrared spectra were obtained using a Perkin-Elmer Model 137G spectrophotometer. Nuclear magnetic resonance spectra were obtained using a Jeolco Minimar spectrometer. Tetramethylsilane was used as an internal standard. Mass spectra were obtained using a Perkin-Elmer Model 270 mass spectrometer. Gas–liquid chromatography (glc) was performed using a Hewlett-Packard Model 402 gas chromatograph with a hydrogen flame detector. A glass column (6 ft × 3 mm i.d.) packed with 5% SE-30 on 80/100 mesh Chromosorb W (programed from 70 or 100° to 200° at 5°/min) with a nitrogen flow rate of 11 ml/min was used for the glc analyses of most compounds. A metal column (6 ft × 2 mm i.d.) packed with 4% SE-30 and 6% QF-1 on 80/100 mesh Chromosorb W (programed from 100 to 200° at 5°/min) with a nitrogen flow rate of 10 ml/min was used for the glc analyses of compounds **3** and **12.** A glass column (6 ft × 3 mm i.d.) packed with 5% Apiezon L on 80/100 mesh Chromosorb W (programed from 62 to 200° at 5°/min) with a flow rate of 10 ml/min was used for the glc analyses of compounds **4, 5,** and **13.** Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Scheme I



Decarbethoxylation of β-Keto Ester 1. A mixture of β-keto ester **1** (2.239 g, 9.9 mmol) and Dabco (5.926 g, 52.9 mmol) in o-xylene (14.639 g, 138.1 mmol) was heated to reflux for 6 hr in an oil bath with constant stirring. The ether extract of the acidified (0.6 *M* HCl) reaction mixture was washed with water, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The crude product was purified through a column packed with silica gel alumina and recrystallized from methanol to give 1.289 g (84%) of white, crystalline **10:** mp 55.5–56.5° (lit.[10] mp 53–54°); λ_{max} (KBr) 2780, 1670, 1430, 1330, 1240 cm^{-1}; nmr ($CDCl_3$) δ 1.77 (15 H, multiplet), 2.07 (3 H);

mass spectrum M^+ *m/e* 178. *Anal.* Calcd for $C_{12}H_{18}O$: C, 80.90; H, 10.11. Found: C, 80.97; H, 9,95. Compound **10** was identical by ir, nmr, mass spectrum, glc retention time, and mixture melting point with an authentic sample prepared according to the procedure described by Krapcho and Lovey.[5]

General Procedure for the Decarbalkoxylation of β-Keto Esters 2–8. A mixture of 10 equiv of Dabco, 1 equiv of β-keto esters 2–8, and 15 equiv of o-xylene was heated to reflux for 4 hr with constant stirring. The cooled prodct mixtures were analyzed by glc and mass spectral analysis. The corresponding ketones (11–14) were identical by comparison of mass spectra and glc retention time with those of authentic samples.[8]

Decarbomethoxylation of β-Keto Ester 9. A mixture of 1.158 g (3.0 mmol) of compound **9** and 3.371 g (30.1 mmol) of Dabco in 10.434 g (98.4 mmol) of o-xylene was heated at 85–92° for 1 hr with constant stirring. The chloroform extract of the acidified (0.6 *M* HCl) reaction mixture was washed with water, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give 0.890 g of crude compound **15** in 72% yield by glc analysis. The crude product was purified through a column packed with silica gel and eluted with hexane–chloroform to give 0.541 g (67%) of crystalline compound **15**: mp 189–191°; λ_{max} (KBr) 2820, 1690, 1440, 1240, 1020 cm^{-1}; nmr ($CDCl_3$) δ 3.63 (6 H), 2.43 (10 H, multiplet); mass spectrum M^+ *m/e* 268. *Anal.* Calcd for $C_{13}H_{16}O_6$: C, 58.21; H, 5.97. Found: C, 58.06; H, 5.95.

Acknowledgments. We wish to thank the graduate school and the Biological and Physical Sciences Institute for partial financial support.

Registry No.—**1**, 19386-06-2; **2**, 40778-30-1; **3**, 94-02-0; **4**, 41302-34-5; **5**, 1655-07-8; **6**, 10472-24-9; **7**, 611-10-9; **8**, 6627-69-6; **9**, 6966-22-9; **10**, 1660-04-4; **15**, 51869-06-8; Dabco, 280-57-9.

References and Notes

(1) D. H. Miles and E. J. Parish, *Tetrahedron Lett.*, 2987 (1972).
(2) E. J. Parish and D. H. Miles, *J. Org. Chem.*, **38**, 1223 (1973).
(3) E. J. Parish and D. H. Miles, *J. Org. Chem.*, **38**, 3800 (1973).
(4) E. J. Parish, N. V. Mody, P. A. Hedin, and D. H. Miles, *J. Org. Chem.*, **39**, 1592 (1974).
(5) A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, 957 (1973). Sample R = 40% methyl and 60% ethyl.
(7) Aldrich Chemical Co. Sample R = 50% methyl and 50% ethyl.
(8) The appropriate ketones were from Aldrich Chemical Co., Inc., Milwaukee, Wis. 53233.
(9) J. R. Johnson and F. D. Hager, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1944, p 351; R. Mayer in "Newer Methods of Preparative Organic Chemistry," Vol. 2, W. Forest, Ed., Academic Press, New York, N. Y., 1963, pp 101–131: W. J. Bailey and J. J. Daly, Jr., *J. Org. Chem.*, **22**, 1189 (1957); **29**, 1249 (1964); R. E. Bowman, *J. Chem. Soc.*, 325 (1950); R. E. Bowman and W. D. Fordham, *ibid.*, 2758 (1951).
(10) J. Bernstein (E. R. Squibb and Sons Inc.), U. S. Patent 3,379,754 (April 23, 1968); *Chem Abstr.*, **69**, 51731w (1968).
(11) Compound **2** was heated to reflux for 6 hr.
(12) A. P. Krapcho, E. G. E. Jahngen, Jr., and A. J. Lovey, *Tetrahedron Lett.*, 1091 (1974).

New Synthetic Reactions. A Convenient Approach to Methyl 3-Oxo-4-pentenoate

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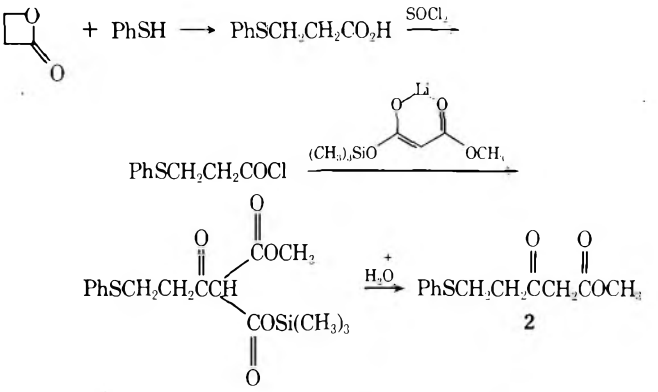
The utility of methyl 3-oxo-4-pentenoate (**1**) as an annelating agent in the synthesis of terpenes and alkaloids has been previously demonstrated.[1-4] Nevertheless, this reagent is not easily synthesized. The original method requires an acid-catalyzed elimination as the last step (eq 1) and proceeded in 7–12% overall yields from readily available starting materials. In our hands, this step never went

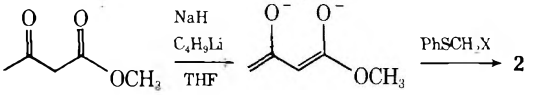
$$C_2H_5OCH_2CH_2COCH_2CO_2CH_3 \xrightarrow{TsOH} H_2C{=}CHCOCH_2CO_2CH_3 \quad (1)$$

to completion without substantial decomposition. An alternative approach based upon a retro Diels–Alder reaction to introduce the unsaturation proceeds in excellent yields (68% overall) but requires the availability of a special high-temperature pyrolysis apparatus.[5] The facility of dehydrosulfenylations as a method to introduce unsaturation conjugated to a carbonyl group suggested this reaction for the introduction of the double bond.[6] We wish to report utilization of this approach as a particularly convenient one for the preparatin of **1**. More generally, this methodology represents a novel approach to the introduction of a methylene group α to a carbonyl group.[7]

The synthesis of the requisite phenylthio derivative **2** initially paralleled a modified route for the formation of the ethoxy precursor.[8] While three steps are required, **2**

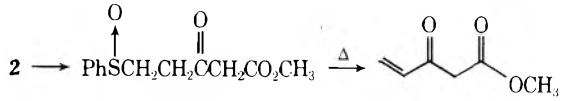


was prepared in 62–76% overall yield. A more convenient one-step synthesis of **2** involved the alkylation of the dianion of methyl acetoacetate[9] with halomethyl phenyl sulfide. Alkylation proceeds in about 40% yield with chloro-



methyl phenyl sulfide, but in 63–80% yield with iodomethyl phenyl sulfide. Equally important to the increased yield with the latter reagent was the formation of fewer side products.

Oxidation to the sulfoxide proceeds nearly quantitatively with sodium metaperiodate at room temperature. Heating the sulfoxide in refluxing chloroform for 12 hr followed by evaporation of the solvent and distillation *in vacuo* produced methyl 3-oxo-4-pentenoate in 97% yield. This three-step synthesis produces methyl acryloylacetate in an overall yield of 60–76% from readily available materials. The alternative five-step route proceeded in an overall yield of 60–72%.



Experimental Section

Infrared spectra were determined on a Beckman IR-8 spectrophotometer. Nmr spectra were determined on a Varian Associates Model A-60A spectrometer. Chemical shifts are given in δ units, parts per million relative to TMS as an internal standard. Mass spectra were taken on a MS-902 mass spectrometer at an ionizing current of 40 mA and ionizing voltage of 70 eV.

All reactions were carried out under nitrogen. Thick layer chromatography was performed in 1.5-mm layers of silica gel PF-254 (E. Merck AG, Darmstadt). Removal of solvents from products normally involved rotary evaporation at water aspirator pressure followed by evacuation of the flask to approximately 1 mm to remove the last traces of the solvent.

3-Phenylthiopropionic Acid. A neat mexture of 19.41 g (269

mmol) of β-propiolactone and 28.5 g (259 mmol) of phenyl mercaptan was stirred at 80° for 24 hr. The flask was then fitted with a distillation column and heated to 60° (4 mm) for 1 hr to remove unreacted starting materials. The remaining 41.8 g (89% yield) of yellow oil was essentially pure (>95%) 3-phenylpropionic acid: ir (CCl_4) 3125–2940 (acid OH), 1712 (acid C=O), 687 cm^{-1} (Ph); nmr (CCl_4) δ 11.45 (s, 1 H, $-CO_2H$), 7.3 (M, 5 H, (Ph), 3.2 (AA′, 2 H, $-SCH_2-$), 2.6 (BB′, 2 H, $-CH_2CO_2-$); mass spectrum *m/e* (rel intensity) 182 (59), 123 (47), 111 (10), 110 (100), 109 (50), 77 (16).

Anal. Calcd for $C_9H_{10}O_2S$: mol wt, 182.040. Found: mol wt, 182.040.

3-Phenylthiopropionyl Chloride. To 119 g (71.8 ml, 1.0 mol) of thionyl chloride was added 122.1 g (0.67 mol) of 3-phenylthiopropionic acid in 1–2-g portions over a 15-min period. The reaction mixture was stirred at 40° for 4 hr. Excess thionyl chloride as removed by vacuum distillation (40–60°, 4 mm). The remaining brown liquid (121.5 g, 90% yield) was essentially pure (>95%) acid chloride which was utilized directly in the next step. The material could be further purified by vacuum distillation to give a yellow oil: bp 120–127° (0.5 mm); ir (CCl_4) 1795 (acid chloride C=O), 690 cm^{-1} (Ph); nmr (CCl_4) δ 7.25 (m, 5 H, Ph), 3.05 (s, 4 H, $-SCH_2CH_2COCl$ coincidental chemical shifts).

Iodomethyl Phenyl Sulfide. A solution of 83.9 g (80.0 ml, 0.675 mol) of thioanisole in 500 ml of methylene chloride was heated to reflux. A solution of 90.0 g (54 ml, 0.667 mol) of sulfuryl chloride (technical grade) in 150 ml of methylene chloride was added dropwise over a 1.25-hr period. Reflux was continued for 2 hr, and then the reaction was allowed to cool to room temperature. The contents of the flask were then transferred to a 2-l. round-bottomed flask and the solvent was removed by rotary evaporation *in vacuo* to give 104 g (98.6% yield) of chloromethyl phenyl sulfide as a yellow liquid. The product was sufficiently pure to be used in the next reaction, but could be further purified by distillation: bp 66° (0.2 mm) [lit.[10] bp 103–104° (12 mm)]; ir (CCl_4) 720, 690 (Ph), 653 cm^{-1} (CCl); nmr (CCl_4) δ 7.3 (m, 5 H, Ph), 4.82 (s, 2 H, $-CH_2Cl$).

A solution of 16.0 g (0.107 mol) of sodium iodide in 85 ml of acetone (reagent grade) was added to 15.88 g (0.100 mol) of chloromethyl phenyl sulfide and the reaction mixture was stirred at room temperature for 11 hr. The reaction mixture was then diluted with 100 ml of water and extracted with 2 × 100 ml of ether. The combined ether layers were washed with 25 ml of 5% aqueous sodium thiosulfate solution and 3 × 50 ml of saturated aqueous sodium chloride solution and dried over magnesium sulfate. The solvent was removed by rotary evaporation *in vacuo* to give 22.8 g (91% yield) of nearly pure (>95%) iodide as a yellow oil which was utilized directly in the next step: ir (CCl_4) 690 cm^{-1} (Ph); nmr (CCl_4) δ 7.3 (br s, 5 H, Ph), 4.48 (s, 2 H, $-CH_2I$). (Note: This material darkens rapidly on standing and should be used immediately after preparation.)

Methyl 3-Oxo-5-phenylthiopentanoate (2). Method A (From 3-Phenylthiopropionyl Chloride). A stirred solution of 19.0 g (100 mmol) of trimethylsilyl 2-methoxycarbonylacetate[8] in 100 ml of anhydrous ether (Mallinckrodt) was cooled to −78° and 69 ml (100 mmol) of *n*-butyllithium (1.45 *M* in hexane) was injected dropwise through a septum. The reaction mixture was stirred at −78° for 20 min, and then 10.0 g (50 mmol) of 3-phenylthiopropionyl chloride in 80 ml of dimethoxyethane (distilled from sodium benzophenone ketyl immediately before use) was added dropwise over a 1-hr period. A white precipitate formed over the course of the addition. Upon completion of the addition the reaction mixture was allowed to warm to room temperature over a 2-hr period and then stirred at room temperature for 12 hr. At the end of this period the reaction mixture was a clear, colorless solution with a thick, white gum on the walls of the flask. The reaction mixture was quenched with 50 ml of water and about 100 ml of solvent was removed by rotary evaporation *in vacuo*. The white suspension was poured into 200 ml of water and extracted with 300 ml of ether. The ether layer was washed with 100 ml of 1 *N* hydrochloric acid and 3 × 100 ml of saturated aqueous sodium chloride solution. The ether layer was dried over magnesium sulfate and solvent was removed by rotary evaporation *in vacuo* to give 11.2 g (93% yield) of sufficiently pure (>85%) sulfide **2** to be utilized directly in the oxidation step. Preparative tlc of a 0.519-g portion of this sample with chloroform (R_f 0.28) gave 0.422 g of methyl 3-oxo-5-phenylthiopentanoate (**2**) (77%, based on 3-phenylthiopropionyl chloride): ir (CCl_4) 1744 (ester C=O), 1724 (ketone C=O), 1235 (CO), 690 cm^{-1} (Ph); nmr (CCl_4) δ 7.1 (m, 5 H, Ph), 3.55 (s, 3 H, $-CO_2CH_3$), 3.32 (s, 2 H, $-COCH_2CO_2-$), 2.9 (m, 4 H, $-SCH_2CH_2CO-$); mass spectrum *m/e* (rel intensity) 238 (12), 225 (20), 218 (33), 196 (16), 185 (14), 164 (29), 159 (44), 144 (35), 143 (75), 136 (55), 127 (13), 123 (22), 110 (40), 109 (46), 108 (24), 101 (28), 69 (85), 65 (20), 58 (32), 57 (30), 55 (100).

Anal. Calcd for $C_{12}H_{14}O_3S$: mol wt, 238.006. Found: mol wt, 238.006.

Method B (From Methyl Acetoacetate). A 57% dispersion of sodium hydride in mineral oil (4.64 g of dispersion, 2.64 g of active hydride, 0.11 mol) was washed free of the mineral oil with ether. Tetrahydrofuran (300 ml) was distilled from sodium benzophenone ketyl directly into the flask containing the hydride. The mixture was cooled to 0° in an ice bath and 11.60 g (0.10 mol) of methyl acetoacetate in 25 ml of dry tetrahydrofuran was added dropwise over a 10-min period. The reaction mixture was stirred 10 min at 0°, and then 75 ml (0.11 mol) of 1.5 *M* *n*-butyllithium in hexane was injected dropwise over a 5-min period and the red suspension was stirred for 15 min at 0°. Then a solution of 22.8 g (0.09 mol) of iodomethyl phenyl sulfide in 50 ml of dry tetrahydrofuran was added dropwise over a 20-min period. The reaction mixture was stirred for 1 hr at 0° and then poured into a mixture of 100 ml of 3 *N* hydrochloric acid and 200 ml of ice water and extracted with 2 × 300 ml of ether. (Note: During alkylation, the temperature of the reaction mixture should not be allowed to rise above 0°). The combined ether layers were washed with 4 × 100 ml of saturated aqueous sodium chloride solution and dried over magnesium sulfate. Solvent was removed by rotary evaporation *in vacuo* to give 22.5 g of brown oil. Preparative tlc of a 0.523-g portion of this sample with chloroform (R_f 0.28) yielded 0.394 g (79%) of sulfide **2**.

Column chromatography allowed easy purification. (This simple filtration through silica gel is required. When it was omitted, oxidation proceeded smoothly, but the thermal elimination of sulfoxide proceeded in poor yield.) A 17.2-g sample of the crude alkylation product was applied directly to the top of a dry-packed silica gel column (29 g in a 2.0 × 34 cm column) and covered with 4 cm of sand. Elution with 270 ml of pentane removed the less polar impurities. Changing to 2% ether in pentane (v/v) eluted the sulfide (*ca.* 2 l.). Chromatography was discontinued when the sulfide showed contamination with more polar impurities. In this way, 10.4 g (63%, based on iodomethyl phenyl sulfide) of pure methyl 5-phenylthio-3-oxopentenoate (**2**) was obtained.

Methyl 3-Oxo-5-phenylsulfinylpentanoate. A solution of 9.80 g (41.1 mmol) of methyl 3-oxo-phenylthiopentanoate(**2**) in 220 ml of methanol (reagent grade) was immersed in an ice bath and stirred with a mechanical stirrer while 100 ml of saturated aqueous sodium metaperiodate solution (*ca.* 15 g, 65.1 mmol) was added in 5-ml portions over a 5-min period. A thick white precipitate formed almost immediately upon completion of the addition. The ice bath was removed after 10 min and stirring was continued at room temperature for 12.5 hr. The reaction mixture was then diluted with 500 ml of water and extracted with 4 × 200 ml of chloroform. The combined chloroform layers were washed once with 200 ml of saturated sodium chloride solution and dried over magnesium sulfate. Solvent was removed by rotary evaporation *in vacuo* at room temperature to give 10.2 g (98%) of sulfoxide of sufficient purity to be used without further purification (Note: Because of the facility of elimination which occurs slowly even at room temperature, the sulfoxide should not be heated above room temperature): ir (CCl_4) 1754 (ester C=O), 1724 (ketone C=O), 1053 (S=O), 690 cm^{-1} (Ph); nmr ($CDCl_3$) δ 7.6 (m, 5 H, Ph), 3.68 (s, 3 H, $-CO_2CH_3$), 3.5 (s, 2 H, $-COCH_2CO_2-$), 3.0 (m, 4 H, $-SCH_2CH_2CO-$).

Methyl 3-Oxo-4-pentenoate (1). A solution of 10.2 g (39.8 mmol) of methyl 3-oxo-5-phenylsulfinylpentanoate in 100 ml of chloroform was refluxed for 12 hr. The solution was concentrated to approximately 20 ml by distillation of chloroform at atmospheric pressure. This solution was then transferred to a 50-ml round-bottom flask equipped with a 6-cm Vigreux distillation head and distillation was continued at 50° (80–120 (80–120 mm) until the chloroform was totally removed. The receiver flask was then immersed in a Dry Ice–isopropyl alcohol bath and the pressure was reduced slowly to 2 mm. A colorless liquid distilled at 35–39° (1–2 mm) [lit.[5] bp 78–81° (18 mm)] to give 4.92 g (97% yield) of methyl 3-oxo-4-pentenoate (**1**): ir (CCl_4) 1736 (C=O ester), 1661 (α,β-unsaturated ketone C=O), 1642 (C=C), 1582 (enol), 1232 (CO ester), 976 cm^{-1} (C=CH_2); nmr (CCl_4) δ 6.1 (m, 2 H, -HC=CH-), 5.5 (dd, 1 H, =CH-), 5.0 (s, 1 H, enol $-CHCO_2-$), 3.65 (s, 3 H, $-CO_2CH_3$), 3.55 (s, 1 H, keto $-CH_2CO_2-$) (*cf.* ref 8).

Acknowledgment. We wish to thank the National Science Foundation and the National Institutes of Health for their generous support of our programs. We thank the

NSF and WARF for their support of the Instrumentation Center of the Department of Chemistry.

Registry No.—1, 37734-05-7; 2, 51849-20-8; 3-phenylthiopropionic acid, 5219-65-8; β-propiolactone, 57-57-8; phenyl mercaptan, 108-98-5; 3-phenylthiopropionyl chloride, 51849-21-9; iodomethyl phenyl sulfone, 51849-22-0; thioanisole, 100-68-5; trimethylsilyl 2-methoxycarbonylacetate, 51849-23-1; methyl acetoacetate, 105-45-3; methyl 3-oxo-5-phenylsulfinylpentanoate, 51849-24-2.

References and Notes

(1) I. N. Nazarov and S. I. Zavyalov, *Zh. Obshch. Khim.*, **23**, 1703 (1953). Also see J. E. Ellis, J. S. Dutcher, and C. H. Heathcock, *Syn. Commun.*, **4**, 71 (1974).
(2) E. Wenkert, A. Adriano, B. Bredenberg, C. Kaneko, and A. Tahara, *J. Amer. Chem. Soc.*, **86**, 2038 (1964).
(3) S. W. Pelletier, R. L. Chappell, and S. Prabhakar, *J. Amer. Chem. Soc.*, **90**, 2889 (1968).
(4) G. Stork and R. N. Guthikonda, *J. Amer. Chem. Soc.*, **94**, 5109 (1972).
(5) G. Stork and R. N. Guthikonda, *Tetrahedron Lett.*, 2755 (1972).
(6) B. M. Trost and T. N. Salzmann, *J. Amer. Chem. Soc.*, **95**, 6840 (1973).
(7) *Cf.* H. J. Reich and J. M. Renga, *Chem. Commun.*, 135 (1974). It should be noted that these workers showed that aryl bromomethyl sulfides do not alkylate simple ketone enolates well in contrast to the observations reported herein.
(8) L. Pichat and J. P. Beaucourt, *Synthesis*, 537 (1973).
(9) S. N. Huckin and L. Weiler, *J. Amer. Chem. Soc.*, **96**, 1082 (1974).
(10) F. G. Bordwell and B. M. Pitt, *J. Amer. Chem. Soc.*, **77**, 572 (1955).

Synthesis of Some Derivatives of 1,2-Diaza-3,5-phospholene 3-Oxides. A New Heterocyclic System[1]

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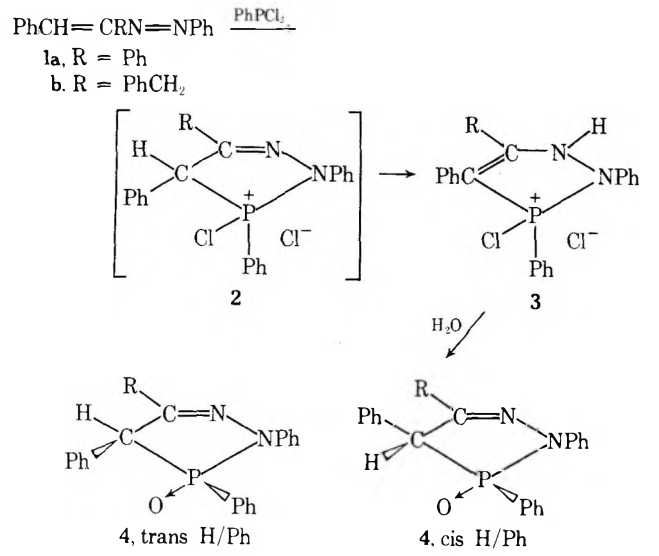
In our study of phosphorus heterocycles from phosphines, we have obtained a new five-membered diazaphospholene by a cycloaddition similar to that reported by McCormack with conjugated dienes and phosphonous dihalides.[2,3] All the isomers of phenylazostilbene[4,5] (**1a**) and of 2-phenylazo-1,5-diphenylpropene[6] (**1b**) easily react with phenyldichlorophosphine at room temperature to form cycloadducts (**2** and **3**). These adducts are quenched with water and give (75% total yield) a mixture of cis and trans[7] phospholene oxides **4** (Scheme I). That an isomer mixture

Scheme I



was obtained was readily apparent from the proton nmr spectrum, which showed two PCH doublets. The two isomers were isolated in pure form by fractional crystallization or by silica gel column chromatography. They formed colorless needles; the infrared spectra showed bands characteristic of P=O and PPh groups. The nmr spectrum ($CDCl_3$) showed for the crude hydrolyzed product mixture **4a** and **4b** an isomer ratio of about 3:2 (cis:trans) and 5:2, respectively. The isomer ratio may sometimes vary, and probably depends on the mode of quenching or on the amount of water present in the reagents. Analogous variations have been observed[8] in the case of phosphetanium salts.

Assignment of Configuration. The steric configurations of the diazaphospholenes have been made on the basis of nmr spectra. The difference between the chemical shifts of the methine proton in the two isomers of **4a** is 0.45 ppm, with the upfield signal at δ 4.55 ppm, while in the two isomers of **4b** it is 0.40 ppm, with the upfield signal at δ 4.29 ppm. The cis configuration was assigned to the isomer showing an upfield methine signal, since only in this isomer is the phenyl ring capable of shielding the methine proton.

Compound *trans*-**4a** has a significantly higher coupling constant (J_{PCH} = 22.5 Hz) than *cis*-**4a** (J_{PCH} = 7.5 Hz). The same large difference was observed for the two isomers **4b** (22.8 and 6 Hz).

This correlation permits the assignment of the trans configuration to the isomers having high J_{PCH} and cis to those having a low value. Examples of analogous assignments are reported in the literature for similar systems.[9] The same effects, less marked, are observed in the benzyl methylene protons of the isomers **4b**. The benzylic protons appeared as the AB portion of an ABX pattern (where X = ^{31}P), with $J_{AX} = J_{BX}$ = 1 Hz, δ_A 3.82 ppm, δ_B 3.36 ppm, J_{AB} = 15 Hz for *cis*-**4b** and J_{AX} = 2 Hz, $J_{BX} < 1$ Hz, δ_A 3.85 ppm, δ_B 14 Hz for *trans*-**4b**.

The ABX signal persisted at 150°, indicating that the magnetic nonequivalence arises from proximity of the benzylic group to an asymmetric center rather than to restricted rotation. Preliminary results showed little tendency for cis–trans interconversion in **4a** or **4b**. This will be subject of further study.

The adducts **3** are highly reactive toward water and are not readily characterized. We have, however, succeeded in obtaining the pmr spectrum in deuteriochloroform when all operations were conducted under a dry nitrogen atmosphere. Although isomeric diazaphospholene oxides are produced on hydrolysis, the nmr spectra of the cycloadducts did not show the presence of an isomeric mixture. The signals of the methine protons were not present but signals of the amine protons were. Rearrangement must therefore occur during subsequent hydrolysis. The nmr spectra are in agreement with the tautomeric structure **3** and the large downfield shifts of protons (see Experimental Section) suggests that in these adducts, at least in solution, phosphorus is ionic rather than covalent.

Experimental Section

All operations involving trivalent phosphorus compounds were performed under a nitrogen atmosphere. Hexane was dried by distillation over sodium. Phenyldichlorophosphine was obtained from Alfa Inorganic Derivatives. **1a** and **1b** were obtained by published procedures.[4-6] The nmr spectra were determined on a Jeol J.M.MC 60-HL spectrometer. Proton nmr chemical shifts are expressed in parts per million from internal TMS. Ir spectra were run as KBr disks on a Perkin-Elmer 337 with NaCl optics. The microanalyses were performed on mixture of the isomers as well as on pure isomers. The results obtained were pratically identical.

Synthesis of 3a and 4a. Phenyldichlorophosphine (3.74 g, 0.02 mol) was added to **1a** (5.68 g, 0.02 mol) in 400 ml of dry hexane. After 1 hr at room temperature the adduct began to separate as a crystalline solid. The reaction was completed in a 24–26-hr period (until the orange color of the solution disappeared). A small por-

tion of the mixture was filtered under reduced pressure in a prepurified nitrogen atmosphere, and the adduct (**3a**) was washed with dry hexane and dried *in vacuo;* its nmr spectrum ($CDCl_3$) showed peaks at δ 6.57–8.15 (m, 20 H, aromatic) and 13.55 (broad s, 1 H, NH).

The remainder of the mixture was filtered and washed with dry hexane and the adduct (**3a**) was added to 30–40 ml of water, cooled with an ice bath, and stirred for 1 hr. While cold, the mixture was neutralized with concentrated sodium hydroxide and extracted three times with $CHCl_3$. The combined organic layers were dried over sodium sulfate and evaporated to give a crude solid which after crystallization from CH_2Cl_2–hexane gave 6.20 g of **4a** (75% based on phenylazostilbene used in preparing **3a**). The nmr spectrum ($CDCl_3$) of the crude product showed two isomers in a 3:2 ratio (cis:trans) (estimated by relative integration of methine peaks). Separation of small amounts of the pure isomers was accomplished by chromatography on a silica gel column and elution was performed by benzene–ether (8:2) mixture. The cis isomer **4a** had mp 202–204°; its nmr spectrum ($CDCl_3$) showed absorption at δ 4.55 (d, 1 H, J_{PCH} = 7.5 Hz) and 6.7–7.8 (m, 20 H, aromatic).

The trans isomer had mp 174–177°; its nmr spectrum ($CDCl_3$) showed peaks at δ 5.0 (d, 1 H, J_{PCH} = 22.5) and 6.6–7.8 (m, 20 H, aromatic). Ir spectra were consistent with the assigned structures. Larger quantities of isomer were obtained by fractional crystallization. The first fractions were richer in cis, the final fractions in trans.

Anal. Calcd for $C_{26}H_{21}N_2OP$: C, 76.45; H, 5.10; N, 6.80; P, 7.59. Found: C, 76.51; H, 5.20; N, 6.75; P, 7.70.

Synthesis of 3b and 4b. The same procedure as above was followed, using 5.86 g (0.02 mol) of **1b** in 400 ml of hexane and 3.74 g (0.02 mol) of phenyldichlorophosphine. The reaction was completed in a 27–30-hr period. A small amount of the mixture was filtered under reduced pressure under a nitrogen atmosphere; the adduct **3b** was dissolved in $CDCl_3$ and its nmr spectrum showed peaks at δ 6.25–8.1 (m, 21 H, aromatic and –NH) and 4.2 (broad s, 2 H, CH_2Ph). The remainder of the mixture was treated as above, yielding 6.30 g (74%) of the isomeric oxides **4b**. The nmr spectrum ($CDCl_3$) of the crude product showed an isomer ratio of about 5:2 (cis:trans).

The isomer mixture was separated by silica gel column chromatography as well as by fractional crystallization.

Nmr spectra revealed the isomer's purity to be about 98%. The cis isomer **4b** had mp 171–173°; its nmr spectrum ($CDCl_3$) showed absorption at δ 3.20–3.98 (AB multiplet of ABX system, 2 H, $-CH_2Ph$), 3.89 (d, 1 H, J_{PCH} = 6 Hz), and 6.7–7.9 (m, 20 H, aromatic).

The trans isomer **4b** had mp 163–165°; its nmr spectrum ($CDCl_3$) showed peaks at δ 3.32–4.0 (AB multiplet of ABX system, 2 H, CH_2Ph), 4.29 (d, 1 H, J_{PCH} = 22.8 Hz), and 6.4–7.5 (m, 20 H, aromatic).

Anal. Calcd for $C_{27}H_{23}N_2OP$: C, 76.74; H, 5.97; N, 6.65; P, 7.34. Found: C, 76.92; H, 5.90; N, 6.50; P, 7.28.

Acknowledgment. We thank Professor G. Rosini for his personal communications and the Italian C. N. R. for financial support.

Registry No.—**1a,** 25769-36-2; **1b,** 51849-76-4; **3a,** 51849-77-5; **3b,** 51898-95-4; *cis*-**4a,** 51849-78-6; *trans*-**4a,** 51849-79-7; *cis*-**4b,** 51849-80-0; *trans*-**4b,** 51849-81-1; phenyldichlorophosphine, 644-97-3.

References and Notes

(1) This research was preliminarily announced in part of the Emilian Section of the Italian Council Society, Dec 1973; *cf.* Abstract in *La Chimica e l'Industria.*
(2) (a) W. B. McCormack, U. S. Patents 2,663,736 and 2,663,737 (Dec 22, 1953; (b) *Chem. Abstr.,* **49,** 7601 (1955).
(3) The literature on this reaction has been reviewed: L. D. Quin, "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, Chapter 3.
(4) S. Brodka and H. Simon, *Chem. Ber.,* **102,** 3647 (1969).
(5) G. Rosini, private communication.
(6) E. Foresti Serantoni, L. Riva di Sanseverino, and G. Rosini, *J. Chem. Soc. B,* 2372 (1971).
(7) The prefixes cis and trans refer to the relationship between the *P*-phenyl and methine proton groups; for a review of phosphorus stereochemistry, see M. J. Callagher and I. D. Jenkins, *Top. Stereochem.,* 1 (1968).
(8) S. E. Cremer, F. L. Weltl, F. R. Farr, P. W. Kremer, G. A. Gray, and H.-O. Hwang, *J. Org. Chem.,* **38,** 3199 (1973), and references cited therein.
(9) D. L. Quin and T. P. Barker, *J. Amer. Chem. Soc.,* **92,** 4303 (1970).

Reaction of 2*H*-Azirines with Nitrones

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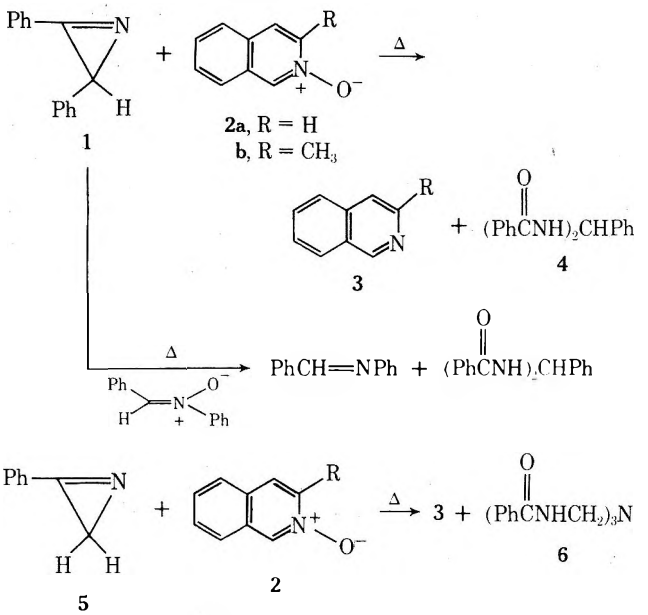
2*H*-Azirines represent versatile substrates which can serve as useful precursors for the synthesis of other heterocyclic rings.[1-6] An unusual feature of this three-membered heterocyclic ring is that it is susceptible to attack by both electrophilic and nucleophilic reagents.[7] In addition, the 2-π electrons present in the ring can participate in thermally allowed [$_\pi 4_s$ + $_\pi 2_s$] cycloadditions as dienophiles[8,9] or as dipolarophiles.[10] Azirines are also known to act as 1,3-dipoles in photochemical reactions.[11,12] Another intriguing aspect of this ring system is that it can participate as a dipolarophile in 1,3-dipolar cycloaddition reactions.[10,13,14] Reaction with diazoalkanes[10,13,14] and nitrile oxides[10] transforms the 2*H*-azirine system into allylic azides and carbodiimides, respectively. The photodimerization of 2*H*-azirines has been recently shown to produce 1,3-diazabicyclo[3.1.0]hex-3-enes as primary photoproducts.[15] The formation of these dimers was explained in terms of 1,3-dipolar addition of an initially generated nitrile ylide onto the azirine ring.[16] As part of our continued interest in the 1,3-dipolar cycloaddition reactions of arylazirines, we have investigated the reaction of the 2*H*-azirine system with several nitrones.

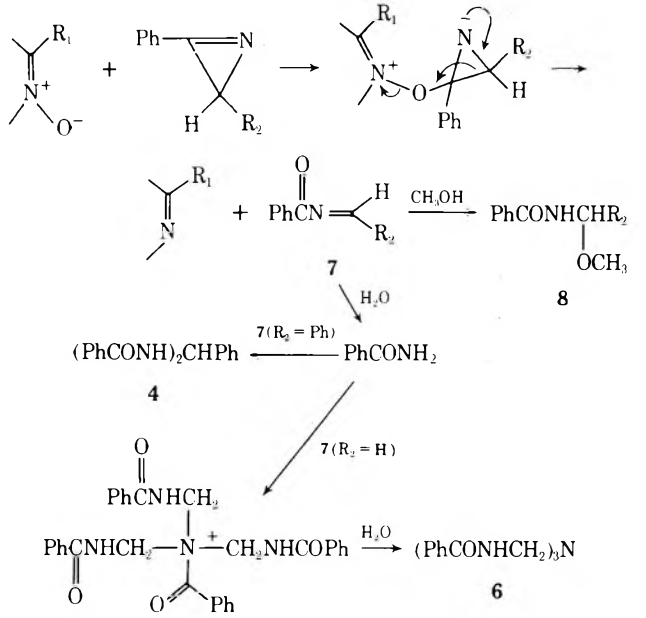
When diphenylazirine (**1**) was heated with isoquinoline *N*-oxide (**2a**) in benzene at reflux temperature for 18 hr, two new compounds were formed in high yield and were identified as isoquinoline (**3a**) and bis(benzamino)phenylmethane (**4**) by comparison with authentic samples.[17] Similar results were observed with **1** and 3-methylisoquinoline *N*-oxide (**2b**). *N*-Benzylideneaniline and bis(benzamino)phenylmethane were the major products obtained upon treatment of **1** with *N,C*-diphenylnitrone. Reaction of phenylazirine (**5**) with isoquinoline *N*-oxide (**2a** or **2b**) gave the corresponding isoquinoline and tris(benzaminomethyl)amine (**6**). The structure of **6** was verified by comparison with an authentic sample.[18]



We suggest that the reaction responsible for the deoxygenation of the isoquinoline *N*-oxide involves initial attack

* Alfred P. Sloan Foundation Fellow, 1968–1972.

of the nitrone oxygen on the reactive C=N double bond of the azirine ring. This step bears close resemblance to the formation of alkoxyaziridines from the reaction of 2*H*-azirines with alkoxide anions.[7] The reaction is completed by bond reorganization, which gives the deoxygenated nitrone and *N*-benzoylimine (**7**) as a transient intermediate. Partial hydrolysis of **7** will produce benzamide, which reacts further with the reactive imine to give **4** or **6**.[19,20]



In agreement with this interpretation, we have found that when the above reactions involving diphenylazirine were carried out in the presence of methanol, a new product was formed and identified as the methanol adduct of *N*-benzoylbenzaldimine (**8b**, R_2 = Ph), mp 102–104°.[21] Similar results were obtained with the corresponding phenylazirine system (*i.e.*, **8a**, R_2 = H): nmr ($CDCl_3$) τ 6.63 (3 H, s), 5.11 (2 H, d, J = 7.0 Hz), 2.4–2.8 (5 H, m), and 2.1–2.4 (1 H, broad s); mass spectrum *m/e* 150, 133, 121, 105 (base), and 77. Careful examination of the residue revealed no detectable amounts of **4** or **6**. The isolation of the methoxyamides (**8**) strongly supports the presence of a transient benzoylimine which reacts with the added methanol to give a product different from that previously observed (*i.e.*, **4** or **6**), but which is totally compatible with the mechanism outlined above.

Experimental Section

Reaction of 2,3-Diphenylazirine with 3-Methylisoquinoline *N*-Oxide. A solution containing 1.26 g (0.065 mol) of diphenylazirine and 0.98 g (0.062 mol) of 3-methyisoquinoline *N*-oxide in 100 ml of benzene was heated at reflux for 5 days. Upon cooling, a white solid (0.6 g, 0.018 mol, 58%) precipitated from the reaction mixture. Recrystallization of this material from ethanol gave white needles: mp 229–230°; ir (KBr) 3.08, 6.05, 6.46, 6.65, 6.75, 7.41, 7.86, 8.76, 9.52, 12.40, 13.90, and 14.36 μ; nmr (DMSO) τ 2.83 (1 H, t, J = 9.0 Hz), 1.9–2.6 (15 H, m), 0.91 (2 H, d, J = 9.0 Hz); mass spectrum *m/e* 209, 180, 121, 105 (base), and 77.

Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.24; H, 5.55; N, 8.42.

This material was identified as bis(benzamino)phenylmethane (**4**) by comparison with an authentic sample.[17] The only other product which could be identified from the filtrate was 3-methylisoquinoline.

When the above reaction was carried out in the presence of methanol (2-mol excess) a reddish-brown residue was obtained. This material was chromatographed on a thick layer plate using an acetone–cyclohexane (1:4) mixture as the eluent. The major product obtained was identified as the methanol adduct of *N*-benzoylbenzaldimine (**8b**),[21] mp 102–104°, ir (KBr) 2.95, 3.42, 5.98, 6.23, 6.32, 6.70, 7.44, 8.00, 8.82, 9.12, 9.28, 9.70, 10.22, and 11.05 μ, nmr ($CDCl_3$) τ 6.46 (3 H, s), 3.60 (1 H, d, J = 9.0 Hz), 2.3–2.8 (10 H, m), and 2.0–2.2 (1 H, br s), mass spectrum *m/e* 209, 197, 180, 121, 105 (base), and 77, by comparison with an authentic sample.

A similar set of results was obtained when diphenylazirine was heated in the presence of isoquinoline *N*-oxide (**2a**).

Reaction of 2,3-Diphenylazirine with *N,C*-Diphenylnitrone. A solution containing 0.96 g (0.048 mol) of *N,C*-diphenylnitrone and 0.94 g (0.018 mol) of diphenylazirine in benzene was heated at reflux for 4 days. Upon cooling, 0.5 g of a white, crystalline solid (64%) precipitated from the reaction mixture. Recrystallization of this material from ethanol gave a white solid, mp 229–230°, whose structure was identified as bis(benzamino)phenylmethane by comparison with an authentic sample. The residue obtained on removal of the solvent was chromatographed on a thick layer plate using chloroform as the eluent. The two solids obtained were identified as benzanilide (15%) and *N*-benzylideneaniline (60%) by comparison with authentic samples.

Reaction of Phenylazirine with 3-Methylisoquinoline *N*-Oxide. A solution containing 1.58 g (0.01 mol) of 3-methylisoquinoline *N*-oxide and 1.18 g (0.01 mol) of 2-phenylazirine in 175 ml of benzene was heated at reflux for 24 hr. Removal of the solvent left a yellow oil which was recrystallized from methanol to afford 0.42 g (42%) of a white solid: mp 193–194°; ir (KBr) 3.00, 6.07, 6.50, 6.70, 7.22, 7.48, 7.64, 7.70, 8.48, 9.27, 9.60, 7.72, 12.32, and 14.35 μ; nmr ($CDCl_3$) τ 5.32 (2 H, d, J = 7.0 Hz), 2.3–2.9 (5 H, m), and 1.8–2.0 (1 H, br s); mass spectrum *m/e* 148, 134, 121, 105 (base) and 77; uv (methanol 230 nm (ϵ 21,500).

Anal. Calcd for $C_{24}H_{24}N_4O_3$: C, 69.21; H, 5.81; N, 13.45. Found: C, 68.86; H, 5.87; N, 13.45.

This material was identified as tris(benzaminomethyl)amine(**6**) by comparison with an authentic sample.[18] The only other product which could be identified from the filtrate was 3-methylisoquinoline. A similar set of results was obtained when phenylazirine was heated in the presence of isoquinoline *N*-oxide.

When the above reaction was carried out in the presence of methanol (2 *M* excess) a reddish brown residue was obtained. This residue was chromatographed on a thick layer plate and the major product obtained was identified as methoxy amide **8a**: ir ($CHCl_3$) 2.95, 3.42, 5.98, 6.23, 6.42, 6.62, 6.73, 7.20, 7.65, 7.78, 8.92, 9.30, and 10.96 μ; nmr ($CDCl_3$) τ 6.63 (3 H, s) 5.11 (2 H, d, J = 7.0 Hz), 2.42–2.80 (5 H, m), and 2.1–2.3 (1 H, br s); mass spectrum *m/e* 150, 133, 121, 105 (base), and 77.

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health (Grant CA-12195-07). The National Science Foundation provided financial assistance in the purchase of the nmr spectrometer used in this research.

Registry No.—**1**, 16483-98-0; **2a**, 1532-72-5; **2b**, 14548-00-6; **4**, 14328-15-5; **5**, 7654-06-0; **6**, 51912-07-3; **8a**, 13156-28-0; **8b**, 10387-93-6.

References and Notes

(1) F. W. Fowler and A. Hassner, *J. Amer. Chem. Soc.*, **90**, 2875 (1968).
(2) A. G. Hortmann and D. A. Robertson, *J. Amer. Chem. Soc.*, **89**, 5974 (1967).
(3) S. Sato, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jap.*, **50**, 2936 (1967).
(4) G. Smolinsky and B. Feuer, *J. Org. Chem.*, **31**, 1423 (1966).
(5) F. P. Woerner, H. Reimlinger, and R. Merenyi, *Chem. Ber.*, **104**, 2786 (1971).
(6) A. Hassner, A. S. Miller, and M. J. Haddadin, *Tetrahedron Lett.*, 1353 (1972).
(7) F. W. Fowler, *Advan. Heterocycl. Chem.*, **13**, 45 (1971).
(8) A Hassner and D. J. Anderson, *J. Amer. Chem. Soc.*, **93**, 4339 (1971); *J. Org. Chem.*, **38**, 2565 (1973).
(9) V. Nair, *J. Org. Chem.*, **37**, 802 (1972).
(10) V. Nair, *J. Org. Chem.*, **33**, 2121 (1968); *Tetrahedron Lett.*, 4831 (1971).
(11) A. Padwa and J. Smolanoff, *J. Amer. Chem. Soc.*, **93**, 548 (1971).
(12) H. Giezendanner, M. Marky, B. Jackson, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **55**, 745 (1972).
(13) A. L. Logothetis, *J. Org. Chem.*, **29**, 3049 (1964).
(14) J. H. Bowie, B. Nussey, and A. D. Ward, *Aust. J. Chem.*, **26**, 2547 (1973).
(15) A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., *J. Amer. Chem. Soc.*, **95**, 1954 (1973).
(16) A. Padwa, J. Smolanoff, and S. I. Wetmore, *J. Org. Chem.*, **38**, 1333 (1973).
(17) H. Hellmann, G. Aichinger, and H. Wiedemann, *Justus Liebigs Ann. Chem.*, **626**, 35 (1959).
(18) M. Descude, *Ann. Chim. Phys.*, **29**, 540 (1903).

(19) It should be pointed out that the stoichiometry of the reaction requires 2 mol of diphenylazirine for every mole of bisamide **4** produced. Benzaldehyde was also detected in small quantities in the reaction mixture. When the solvent was rigorously dried, the yield of bisamide **4** (or trisamine **6**) was significantly diminished.

(20) The reaction of benzamide with benzoylimine, **7** to form bisamide **4** has been reported[21] to require an acid catalyst (BF_3). Our reaction conditions, however, are much more vigorous than that previously reported.[21] This would account for the reaction proceeding in the absence of a catalyst.

(21) S. Breuer, T. Bernath, and D. Ben-Ishai, *Tetrahedron Lett.*, 4569 (1966).

Condensation–Cyclization Reactions of Electron-Deficient Aromatics with Organic Bases. VIII.[1] Ortho Substituent Attack *vs.* Meta Ring Attack in 3,5-Dinitrobenzophenone

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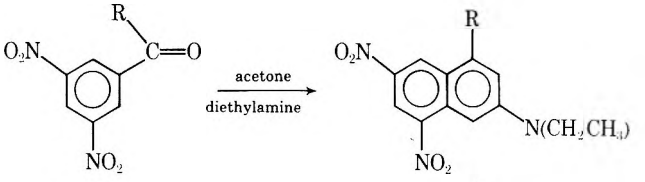
A recent report of the formation of naphthalene derivatives, **2**, from reaction of 3,5-dinitroacetophenone and related aromatics with acetone and diethylamine was of considerable interest to us.[2] The conclusions that only naphthalenoid products result from such reactions conflicted with expectations based on our earlier work[1a] and prompted us to attempt the reaction on related substrates.



1 **2**

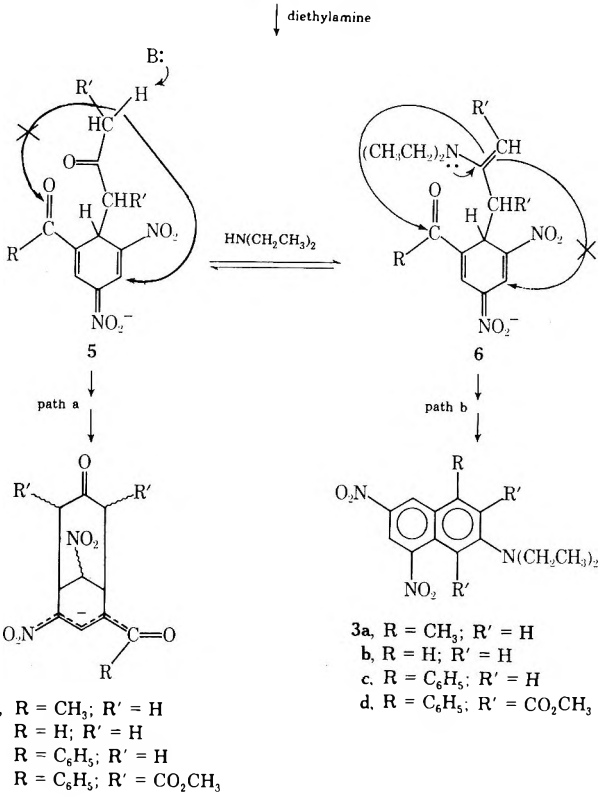
Previous observations of meta-bridged products isolated from other 3,5-dinitro-X-substituted aromatics under similar conditions lead us to believe that internal meta bridging in ketonic σ complexes of **1** could lead to compounds like **4** with appropriate ketones and secondary amines (Scheme I, path a). Although all our previous work with 3,5-dinitro-X-substituted aromatics had been done with substrates in which X = NO_2, CN, and CO_2CH_3,[1a] we suspected that the particular mode of cyclization would depend on the nature of the ketone, not the X substituent, and that either **3** or **4** could be obtained from the same aromatic precursor.

The previously published report[2] considers reaction of acetone with 3,5-dinitroacetophenone or 3,5-dinitrobenzaldehyde. With these reactants only **3a** and **3b** are formed by a postulated mechanism involving enamine intermediates. There was no evidence for products like **4a** or **4b**, analogous to those we have previously isolated with more acidic ketones and 3,5-dinitro-X-substituted aromatics.[1a]

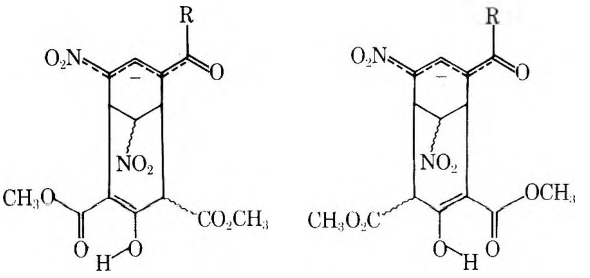
We have found that under conditions reported for the formation of **3a** and **3b** 3,5-dinitrobenzophenone, **1** (R = C_6H_5), reacts rapidly with acetone and diethylamine to yield black needles of the analogous 1-phenyl-3-diethylamino-5,7-dinitronaphthalene (**3c**). The pmr and visible spectra as well as the elemental analysis are completely in accord with this structure[2] (see Experimental Section). There was no evidence for the bicyclic structure **4c**. Such results are in agreement with those reported for the reactions of **1** (R = CH_3 or H) with diethylamine in acetone.[2]

Most interestingly, substituting 1,3-dicarbomethoxyacetone for acetone in this reaction yields bright yellow crystals of the bicyclic anion **4d** as the diethylammonium salt.

Scheme I



The pmr and visible spectra as well as the elemental analysis strongly support this structure. There was no evidence for even trace amounts of the naphthalene **3d**. Formation of **4d** is the first example of a 3-substituted propene nitronate in which the stabilizing group is a carbonyl function. This product likely forms through σ-complex intermediates, analogous to formation of meta-bridged products resulting from the reaction of 1-cyano- and 1-carbomethoxy-3,5-dinitrobenzene studied earlier.[1a,g] The double maxima in the visible spectrum of the reaction solution is characteristic of anionic σ-complex intermediates.[1h] As with other bicyclic adducts prepared from dicarbomethoxyacetone, the anion of **4d** exists in one enolic form in solution. A distinction between the two possible isomers cannot be made on the basis of the spectral data at hand.



The mechanism for ortho substituent attack and the factors favoring this mode of reaction over meta bridging in the case of acetone but not dicarbomethoxyacetone deserve some comment. There has been considerable evidence presented in earlier reports that condensations of ketones with electron-deficient aromatics involve enamine or carbanion intermediates.[1b,g] The latter are important for acidic ketones in the presence of secondary amines. Assuming that initial attack occurs para to NO_2 in **1**[1f] the possibilities for cyclization to **3** and **4** are shown in Scheme I.

It has been shown earlier that internal cyclizations involving dicarbomethoxyacetone, R′ = CO_2CH_3 in Scheme I, do not involve enamine intermediates like **6**.[1a,g] Complex **5** (R′ = CO_2CH_3; R = C_6H_5) is thus most likely the precursor to **4d**. Detailed kinetics of similar cyclizations have been reported earlier.[1g] It appears that **5** (R′ = CO_2CH_3; R = C_6H_5) cyclizes by path a and not b in Scheme I.

It is well known that σ complexes prepared from acetone and *sym*-trinitrobenzene are quite stable in the presence of *tertiary* amines.[3,4] Addition of *secondary* amines causes rapid reaction to a variety of products through enamine intermediates.[4,5] In the case of the σ complex of acetone with *sym*-trinitrobenzene a bridged product analogous to **4** is rapidly formed with the negative charge delocalized on a nitropropene nitronate function.[1b,4,5] Since 3,5-dinitroacetophenone does not react with acetone in the presence of tertiary amines to give isolable products, it is thus quite likely that **6** (R = C_6H_5; R′ = H) is the precursor to **3c** and that attack on the ortho substituent occurs *via* path a as previously proposed[2] (Scheme I). An attempt was made to directly observe **6** in the pmr spectrum of the reaction solution. In the region without reactant or product absorption two overlapping triplets develop at δ ~5 (about 1% of the total absorption) and rapidly disappear as those for **3c** increase. These could result from protons on the tetrahedral ring carbons of **5** and **6** (R′ = H; R = C_6H_5).[6]

The reactivity differences causing **5** (R′ = CO_2CH_3; R = C_6H_5) to cyclize *via* path a and **6** (R′ = H; R = C_6H_5) *via* path b could result from increased flexibility in the side chain of the former relative to the latter. Such flexibility would allow the nucleophilic site in **5** (R′ = CO_2CH_3; R = C_6H_5) to more closely approach the meta ring position. Such ideas are supported by Drieding models of **5** and **6**. Alternately it may be that the initial product of intramolecular ortho substituent attack in **5** does not have a suitable route for aromatization to **3**.

Experimental Section

Melting points are uncorrected. Pmr spectra were obtained on a Jeol MH-100 spectrometer in $CDCl_3$ or DMSO-d_6 using tetramethylsilane as an internal standard. Uv spectra were obtained on a Perkin-Elmer 402 spectrometer in anhydrous methanol. Elemental analyses were performed by George I. Robertson Laboratories, Florham Park, N. J.

1-Phenyl-3-diethylamino-5,7-dinitronaphthalene (3c). To a solution of 0.5 g (0.0018 mol) of 3,5-dinitrobenzophenone[7] in the minimum of distilled dry acetone to effect dissolution was added 0.5 ml of diethylamine. The dark greenish-black solution which developed was kept at 25° for 12 hr and then cooled to about 8° for 2 days. Black needles deposited from the solution. These were filtered, washed with a small portion of cold ether, and dried at 0.5 mm and 50° for 8 hr. The resulting product (~0.25 g) melted at 167–168° and had uv–visible maxima in MeOH at 245, 320, 355, 420, and 468 nm. The pmr spectrum in DMSO-d_6 (saturated) had absorptions at δ 8.95 (d, 1 H, $J \simeq 2$ Hz), 8.75 (d, 1 H, $J \simeq 2$ Hz), 7.75 (d, 1 H, $J \simeq 2$ Hz), and 7.2 (d, 1 H, $J \simeq 2$ Hz) for the aromatic ring protons of **3c**. The phenyl group appeared as a complex multiplet centered at δ 7.5 (5 H) and the $N(CH_2CH_3)_2$ absorptions appeared as a coupled triplet (6 H) and doublet (4 H) at δ 1.25 and 3.6, respectively, J = 7.0 Hz. *Anal.* Calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50.Found: C, 65.71; H, 5.49; N, 11.28.

Preparation of 4d. The procedure for the preparation of **3c** was followed exactly except that dicarbomethoxyacetone (Aldrich) was used instead of acetone. The reaction solution turned brilliant yellow and did not deposit crystals on cooling, however. It was extracted with five 100-ml portions of anhydrous ether, yielding a yellow oil. The oil was covered with 20 ml of ether and enough ethanol was added to effect dissolution with warming. After standing at 8° for 3 days bright yellow crystals were formed. These were filtered and dried at 0.5 mm and 50° for 8 hr. The resulting product (~0.5 g) melted at 110–113° and had uv–visible maxima in MeOH at 245, 252, and 411 nm. The pmr spectrum of a saturated solution in acetone-d_6 had absorptions at δ 7.5 (m, 6 H) for the C_6H_5 and $-CCHC{=}NO_2^-$ protons, δ 5.25 (br, 1 H) and 5.15 (br, 1 H) for the bridgehead protons, and δ 4.30 (br, 1 H) for the $CHNO_2$ bridge in **4d**. The $CHCO_2CH_3$ proton appears at δ 3.9 (s, br, 1 H). The two CO_2CH_3 methyls appear as sharp singlets at δ 3.8 and 3.7 (3 H each). The triplet and quartet of the $H_2N(CH_2CH_3)_2^+$ cation appear at δ 1.2 and 2.8 (6 H and 4 H, respectively). Although this spectrum is not particularly well resolved, comparison with similar spectra of other bicyclic adducts of 3,5-dinitro-X-substituted benzenes and dicarbomethoxyacetone[1a,f] supports the proposed structure. The visible maximum and elemental analysis further substantiate the compound as **4d**. *Anal.* Calcd for $C_{24}H_{29}N_3O_{10}$: C, 55.49; H, 5.63; N, 8.09. Found: C, 55.47; H, 5.87; N, 7.79.

Acknowledgment. The author thanks the U. S. Army Research Office at Durham for support of this work.

Registry No.—**1** (R = Ph), 51911-74-1; **3c**, 51911-76-3; **4d**, 51911-79-6; diethylamine, 109-89-7.

References and Notes

(1) Previous papers: (a) M. J. Strauss, T. C. Jensen, H. Schran, and K. O'Conner, *J. Org. Chem.*, **35**, 383 (1970); (b) H. Schran and M. J. Strauss, *ibid.*, **36**, 856 (1971); (c) M. J. Strauss and S. P. B. Taylor, *ibid.*, **36**, 3059 (1971); (d) *ibid.*, **37**, 3658 (1972); (e) *ibid.*, **38**, 856 (1973); (f) *ibid.*, **38**, 1330 (1973); (g) M. J. Strauss, H. F. Schran, and R. R. Bard, *ibid.*, **38**, 3394 (1973); (h) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).
(2) S. R. Alpha, *J. Org. Chem.*, **38**, 3136 (1973).
(3) R. Foster and C. A. Fyfe, *Tetrahedron*, **21**, 3363 (1965).
(4) M. J. Strauss and H. Schran, *J. Amer. Chem. Soc.*, **91**, 3974 (1969).
(5) R. Foster and C. A. Fyfe, *Tetrahedron*, **22**, 1831 (1966).
(6) The possibility that these result from two isomeric complexes formed by nucleophilic attack para to NO_2 and para to COC_6H_5 cannot be ruled out, however.
(7) W. Waters, *J. Chem. Soc.*, 2110 (1929).

A Convenient Stereospecific Synthesis of (+)-α-Cyperone[1]

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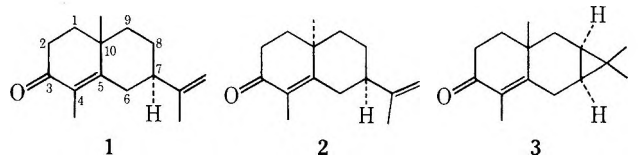
The eudesmane derivative (+)-α-cyperone (**1**)[2] has been rather widely used as a starting material for the synthesis of various other fused-ring sesquiterpenes.[3] However, convenient syntheses of **1** itself are rather limited. The original Howe and McQuillin synthesis of **1** which involves the Robinson annelation of (+)-dihydrocarvone with the methiodide of 1-diethylaminopentan-3-one allows the isolation of **1** in less than 5% yield.[2] This is because **1** is formed only as a minor product of the reaction and its separation from (−)-10-*epi*-α-cyperone (**2**) and the corresponding ketol which are the major reaction products is difficult. Piers and Cheng have found that (−)-α-santonin can be converted into **1** *via* an eight-step sequence.[4] Although lengthy, this synthesis represents a significant improvement over the method of Howe and McQuillin, since **1** was obtained in about 20% yield overall. Fringuelli, Taticchi, and Traverso have recently reported an apparently useful synthesis of α-cyperone.[5] These workers found that the tricyclic enone **3**, prepared by annelation of *cis*-4-caranone with 1-penten-3-one, undergoes preferential cleavage of the 8,11 bond of the cyclopropane ring with hydrogen bromide to form the 2-bromopropane derivative **4a** which could be converted into a mixture of α- and β-cyperone on dehydrohalogenation. An important feature of this synthesis is that annelation of the bicyclic ketone allows the establishment of the cis relationship of the angular methyl group and the dimethyl-substituted cyclopropane ring which ultimately becomes the three-carbon side chain in **1**. We wish to report a



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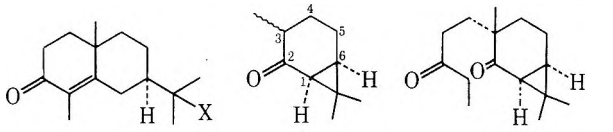

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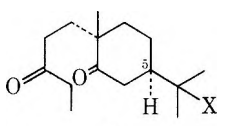

7

a, X = Br
b, X = Cl

convenient stereospecific synthesis of **1** which employs a similar concept and utilizes (−)-2-carone (**5**), which is readily available from (+)-dihydrocarvone,[6] as the starting material.

Michael reaction of **5** with 1-penten-3-one using alcoholic potassium hyroxide as the base gave a single product in 72% yield based upon recovered starting material. The subsequently described transformation demonstrated that this material should be assigned the structure **6** and its spectral properties were in agreement with this assignment.[7] Although carone (**5**) has been shown to be capable of undergoing base-catalyzed exchange of both the α hydrogens,[8] Michael reaction at the 3 position is expected, since the presence of the cyclopropane ring should cause the 1-enolate anion to be much less stable than the 2-enolate.[9,10] In addition, the top side of the 2-enolate is hindered by the endo methyl group on the cyclopropane ring so that nucleophilic attack on the Michael acceptor should take place exclusively from the bottom side of the molecule. No evidence was obtained for the formation of epimaalienone,[11] the possible product of base-catalyzed cyclization of the diketone **6**. Indeed, efforts to prepare this compound by treatment of **6** with a variety of basic catalysts were unsuccessful. This observation is in complete agreement with the previous report of Büchi and coworkers.[7]

By reaction of **6** with an anhydrous saturated ethanolic solution of hydrogen chloride the chloro enone **4b** was obtained in 78% yield. Opening of the three-membered ring of the conjugated cyclopropyl ketone system with acid should take place with exclusive cleavage of the 1,7 bond, leading to a tertiary carbonium ion which could be attacked by halide ion to produce a diketone intermediate, *i.e.*, **7**.[12,13] This species can then undergo rapid acid-catalyzed aldol cyclization to produce **4b**. Acid-catalyzed cyclizations of 1,5-diketones related to **7** often lead to partial or exclusive formation of bicyclo[3.3.1]nonanone derivatives.[14] However, the formation of such products requires the ketonic side chain to adopt a pseudo-axial orientation with respect to the enolized cyclohexanone ring. In the case of **7** this would require the six-membered ring to adopt a half-boat conformation or a half-chair conformation having the bulky 5 substituent axial. Both of these conformations would be of relatively high energy with respect to the species having the side-chain carbonyl group enolized and the cyclohexanone ring in a chair conformation with the 5 substituent equatorial. Cyclization of the latter would lead to **4** *via* the corresponding cis- and/or trans-fused ketols.

The synthesis of **1** was completed by dehydrohalogenation of **4b** with sodium acetate in acetic acid.[10] A crude product which was greater than 85% **1** by glc was obtained. The minor product of the reaction mixture showed identical glc behavior with an authentic sample of β-cyperone. Distillation of the oil obtained from dehydrohalogenation of **4b** afforded a fraction (82% yield) which was greater than 94% **1** by glc. This material showed identical spectral properties and glc behavior with an authentic sample of **1** prepared by the method of Howe and McQuillin.[2]

Experimental Section[15]

Synthesis of the Diketone 6. To a solution of 28.95 g (0.19 mol) of (−)-2-carone (**5**) in 290 ml of anhydrous ether was added a solution of 2.20 g (0.04 mol) of potassium hydroxide in 22.0 ml of anhydrous ethyl alcohol under nitrogen. The mixture was cooled to −5° and a solution of 15.85 g (0.19 mol) of ethyl vinyl ketone in 160 ml of anhydrous ether was added dropwise with stirring. After the addition was complete stirring was continued for 75 min while the mixture was allowed to warm to room temperature and the mixture was poured into 350 ml of an ice-cold solution of 10% hydrochloric acid. The aqueous layer was saturated with sodium chloride and extracted with three 100-ml portions of ether, and the combined organic extracts were washed with two 75-ml portions of a saturated aqueous solution of sodium bicarbonate followed by two 75-ml portions of a saturated sodium chloride solution. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo* to give a pale yellow oil. Distillation yielded 17.0 g of (−)-2-carone, bp 45–55° (0.1 mm), and 14.35 g (72%) of **6**: bp 109–120° (0.1 mm); uv λ_{max} (95% EtOH) 216 nm (ϵ 2790);[16] ir (CCl_4) 1721 and 1692 cm^{-1};[16] nmr δ_{TMS} (CCl_4) 0.83 (s, 3 H), 1.02 (s, 3 H), 1.10 (s, 3 H), 0.98–1.24 (broad absorption, 5 H), 1.33–2.51 (broad absorption, 10 H): *m/e* (70 eV) 236.177 (calcd, 236.177); $[\alpha]^{25}D$ −149° (*c* 0.57, $CHCl_3$).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.17; H, 10.25.

Reaction of 6 with Ethanolic Hydrogen Chloride. The diketone **6** (6.04 g, 0.026 mol) was added dropwise with stirring to 60 ml of an anhydrous saturated solution of ethanolic hydrogen chloride at 5°. After the addition was complete the reaction mixture was allowed to warm to room temperature and stirring was continued for 30 min. The reaction mixture was then poured into 60 ml of ice water and extracted with four 60-ml portions of chloroform. The combined chloroform extracts were then washed with a saturated solution of sodium chloride until the washings were neutral. The organic layer was than dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo* to give a yellow solid (6.0 g). Recrystallization of this material from pentane gave 5.09 g (78%) of **4b**: mp 86–87°; uv λ_{max} (EtOH) 248 nm (ϵ 20,100); ir (CCl_4) 1668 and 1612 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.22 (s, 3 H, 10-CH_3), 1.62 (s, 6 H, 13 and 14-CH_3), 1.75 (s, 3 H, 4-CH_3), 1.80–3.20 ppm (broad absorption, 11 H): $[\alpha]^{25}D$ +165° (*c* 0.40, $CHCl_3$).

Anal. Calcd for $C_{15}H_{23}ClO$: C, 70.71; H, 9.10. Found: C, 70.57; H, 9.13.

(+)-α-Cyperone. A solution of 4.0 g (0.016 mol) of **4b** and 6.57 g (0.08 mol) of sodium acetate in 50 ml of glacial acetic acid was stirred rapidly and heated at 90–100° for 1 hr. The reaction mixture was then allowed to cool to room temperature and poured into 50 ml of water. The resulting mixture was extracted with four 50-ml portions of carbon tetrachloride and the combined organic extracts were washed with two 50-ml portions of 2% aqueous potassium hydroxide, one 50-ml portion of 2 *N* hydrochloric acid, one 50-ml portion of 5% aqueous sodium bicarbonate, and three 50-ml portions of a saturated aqueous solution of sodium chloride. The organic layer was then dried over anhydrous magnesium sulfate and the solvent was removed to give 3.65 g of a yellow oil. Glc analysis (column A) of the crude mixture revealed that it contained α- and β-cyperone in *ca.* 85:15 ratio. Distillation of the crude material gave 2.85 g (82%) of (+)-α-cyperone, bp 109–118° (0.05 mm), which was greater than 94% one component by glc (column A). The product showed identical optical properties (ir, nmr, optical rotation) and glc behavior (columns A and B) with an authentic sample of (+)-α-cyperone prepared by the method of Howe and McQuillin.[2]

Registry No.—**1**, 473-08-5; **4b**, 51911-68-3; **5**, 5561-14-8; **6**, 51911-69-4; ethyl vinyl ketone, 1629-58-9.

References and Notes

(1) (a) This work was supported by Public Health Service Research Grant CA 12193 from the National Cancer Institute. (b) Acknowledgment is made to the National Science Foundation for funds for the purchase of the mass spectrometer used in this research.
(2) R. Howe and F. J. McQuillin, *J. Chem. Soc.*, 2523 (1955).
(3) For examples, see (a) A. R. Pinder and R. A. Williams, *Chem. Ind. (London)*, 1714 (1961); (b) A. R. Pinder and R. A. Williams , *J. Chem. Soc.*, 2773 (1963); (c) D. C. Humber, A. R. Pinder, and R. A. Williams, *J. Org. Chem.*, **32**, 2335 (1967); (d) H. Hikino, N. Suzuki, and T. Takemoto, *Chem. Pharm. Bull.*, **14**, 1441 (1966); (e) E. Piers and K. F. Cheng, *Can. J. Chem.*, **48**, 2234 (1970).
(4) E. Piers and K. F. Cheng, *Can. J. Chem.*, **46**, 377 (1968).
(5) F. Fringuelli, A. Taticchi, and G. Traverso, *Gazz. Chim. Ital.*, **99**, 231 (1969); *Chem. Abstr.*, **71**, 22198p (1969).
(6) See, W. G. Dauben, G. W. Shaffer, and E. J. Deviny, *J. Amer. Chem. Soc.*, **92**, 6273 (1973), and references cited therein.
(7) R. B. Bates, G. Büchi, T. Matsuura, and R. R. Shaffer, *J. Amer. Chem. Soc.*, **82**, 2327 (1960), have previously reported the preparation of this compound. However, no experimental details and only partial physical data were given.
(8) G. Büchi, M. S. Wittenau, and D. M. White, *J. Amer. Chem. Soc.*, **81**, 1968 (1959).
(9) C. Rappe and W. H. Sachs, *Tetrahedron*, **24**, 6287 (1968).
(10) A. van der Gen, L. M. van der Linde, J. G. Witteveen, and H. Boelens, *Recl. Trav. Chim., Pays-Bas*, **90**, 1045 (1971).
(11) A. E. Greene, J. C. Muller, and G. Ourisson, *Tetrahedron Lett.*, 4147 (1971).
(12) A. J. Bellamy and G. H. Whitham, *Tetrahedron*, **24**, 247 (1968).
(13) F. Fringuelli and A. Taticchi, *J. Chem. Soc. C*, 297 (1971).
(14) J. A. Marshall and D. J. Schaeffer, *J. Org. Chem.*, **30**, 3642 (1965).
(15) Melting points and boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 457 infrared spectrophotometer. Ultraviolet spectra were taken on a Beckman DBGT recording spectrophotometer using 1-cm matched quartz cells. Nmr spectra were determined at 60 MHz with a Varian T-60 spectrometer. Signals are reported in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-7L spectrometer. Microanalyses were obtained by Atlantic Microlab, Inc., Atlanta, Ga. Gas–liquid chromatography was carried out using a Perkin-Elmer 881 gas chromatograph. The following columns were used: A (6 ft × 0.125 in., 10% Carbowax K-20M on Chromosorb W); B (6 ft × 0.125 in., 10% SE-30 on Chromosorb W).
(16) The uv and ir spectra of **6** were essentially identical with those reported by Büchi and coworkers (ref 7).

Synthesis of Furano Steroids and Analogs *via* Claisen Rearrangement

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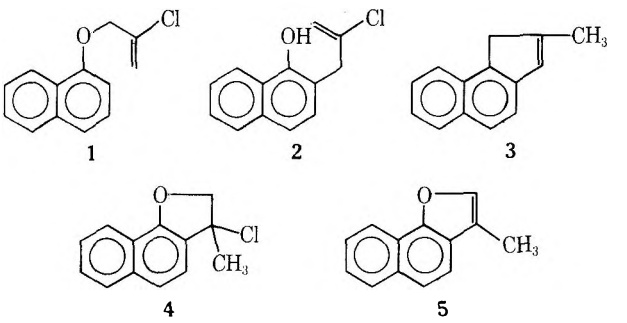
Interest in fused oxa steroids and related systems is evidenced by the variety of synthetic approaches[1] described in the recent literature. We report here the preparation of such compounds through a convenient route based on the work of Hurd and Webb.[2]

Commercially available 2,3-dichropropene-1 was used to alkylate an appropriate phenol and the resulting ether was rearranged by heating in *N,N*-dimethylaniline. Of the two compounds formed the major product was a chlorine-containing phenol derivative which could be cyclized in good yield to the minor product under the influence of a strong acid. The structure of the various compounds could be easily deduced from their pmr spectra.

Thus, the α-naphthol ether **1** produced a phenol **2** and a furanonaphthalene which could be separated on a neutral-alumina column. Two alternative structures **3** and **5** appeared reasonable for the furanonaphthalene, the former arising from the Claisen rearrangement product **2** and the latter *via* a possible intermediate such as **4**.

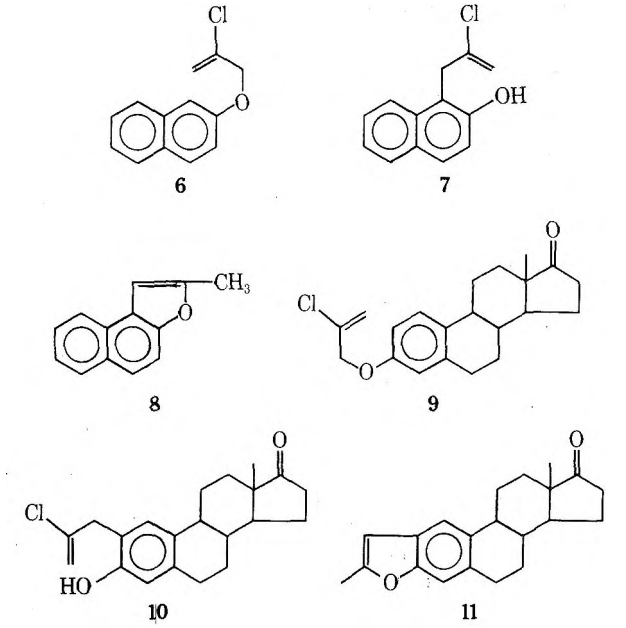


1 2 3 4 5

Extensive studies[3] on the pmr spectra of furan compounds have shown that α protons resonate at about τ 2.5 and β protons at about τ 3.5. A one-proton singlet at τ 3.6 in the pmr spectrum of the minor product from the rearrangement of **1** clearly indicated **3** to be the correct structure. The picrate of this compound had the same melting point as that recorded by Wilds and Johnson[4] for the picrate of **3** prepared by a different method. The intermediacy of a propynyl naphthyl ether in this rearrangement is excluded because such an ether cyclizes to a naphthopyran.[5]

The formation of the minor product **3** in good yield when **2** was treated with polyphosphoric acid is in accord with the assigned structure because the acid hydrolysis of the vinyl chloride would generate an acetyl function. It was observed that heating of the phenolic product **2** (or **7**) for a long period (10–14 hr) at a higher temperature (250°) failed to produce any significant amount of **3** (or **8**).

The allyl ether **6** from β-naphthol gave the rearrangement products **7** and **8**. The structure of the furano compound was again based on pmr spectra and identity of melting point of the picrate with that recorded for the picrate of **8** in the literature.[6]



6 7 8 9 10 11

The β-chloro allyl ether **9** from estrone gave a phenol **10** on rearrangement. The pmr spectrum of this compound showed the presence of two p protons; therefore, the allyl group had migrated to C-2 rather than to C-4. Treatment of the phenol **10** with polyphosphoric acid led to the furano steroid **11** in poor yield; cold sulfuric acid (90%), which proved to be a better cyclizing agent, produced **11** in 15% yield. The single-proton signal at τ 3.6 in the pmr of **11** is in

agreement with the β-unsubstituted furan structure assigned.

Experimental Section[7]

2-Chloro-2-propenyl α-Naphthyl Ether (1). A mixture of α-naphthol (5 g), anhydrous potassium carbonate (20 g), potassium iodide (2 g), and 2,3-dichloropropene (15 ml) in dry acetone (250 ml) was heated under reflux for 24 hr. The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography to give 6.3 g (90%) of **1**: ir 3030 (=CH_2), 660, 650, and 630 cm^{-1} (=CCl); nmr ($CDCl_3$) τ 1.6–2.9 (7 H, m, aromatic H), 4.5 (2 H, d, ClC=CH_2), 5.4 (2 H, s, -OCH_2=CCl-).

Anal. Calcd for $C_{13}H_{11}OCl$: C, 71.40; H, 5.07. Found: C, 71.20; H, 5.00.

Claisen Rearrangement of 1. The allyl ether **1** (2.5 g) was heated with *N,N*-dimethylaniline (4 ml) at 193° under nitrogen for 2 hr. The resulting solution was shaken with ice and dilute hydrochloric acid and extracted with chloroform. Upon evaporation the organic layer gave a mixture of two components (tlc) which were separated on an alumina column using petroleum ether (bp 40–60°) as the eluent. The first fraction was the neutral compound **3**: 0.16 g (6%); mp 21°; picrate (orange needles) mp 113° (lit.[4] mp 113–115°); ir 1620 (aromatic), 820 (trisubstituted double bond), 740 and 680 cm^{-1} (aromatic); nmr ($CDCl_3$) τ 1.6–3.0 (6 H, m, aromatic H), 3.6 (1 H, s, β-H of furan), 7.5 (3 H, s, CH_3).

Anal. Calcd for $C_{13}H_{10}O$: C, 85.69; H, 5.53. Found: C, 85.42; H, 5.50.

The second fraction, which was the major component, was the phenolic product **2**: 2.1 g (84%); mp 53°; ir 3350–3200 (-OH), 3030 (C=CH_2), 885 (C=CH_2), 610, 650, 660 cm^{-1} (-ClC=C-); nmr ($CDCl_3$) τ 1.5–2.8 (6 H, m, aromatic H), 4.7 (2 H, d, H_2C=CH-), 5.5 (1 H, broad, -OH), 5.9 (2 H, s, -CH_2-).

Anal. Calcd for $C_{13}H_{11}OCl$: C, 71.40; H, 5.07. Found: C, 71.52; H, 5.3.

Cyclization of 2. To polyphosphoric acid (prepared by adding 5 g of P_2O_5 to 3 ml of orthophosporic acid) was added **2** (0.5 g) with continuous stirring and heating on a water bath. After about 30 min the reaction mixture was decomposed with cold water and extracted with chloroform. The organic layer was stripped of solvent and the residue was purified by chromatography over alumina; elution with petroleum ether (bp 40–60°) gave a compound (0.3 g, 70%) identical in all respects with the minor fraction (**3**) obtained in the Claisen rearrangement experiment.

2-Chloro-2-propenyl β-Naphthyl Ether (6). Using the same procedure as for the preparation of **1**, there was obtained in 90% yield the title compound: mp 38°; ir 3030 (-C=CH_2), 885–895 (C=CH_2), 625, 690 cm^{-1} (-C=CCl); nmr ($CDCl_3$) τ 0.0–3.0 (7 H, m, aromatic H), 4.5 (2 H, d, -ClCl=CH_2), 5.4 (2 H, broad s, -CH_2O-).

Anal. Calcd for $C_{13}H_{11}OCl$: C, 71.40; H, 5.07. Found: C, 71.25; H, 5.15.

Claisen Rearrangement of 6. The same procedure as before was used. The first compound (minor component) off the neutral alumina column was **8** (yield 7%): mp 52° (lit. mp 56–57°); picrate (orange red crystals) mp 141° (lit. mp 140°); ir 805 cm^{-1} (>C=CH-); nmr ($CDCl_3$) τ 1.5–2.7 (6 H, m, aromatic H), 3.3 (1 H, s, β-H of furan), 7.5 (3 H, s, CH_3).

Anal. Calcd for $C_{13}H_{10}O$: C, 85.69; H, 5.53. Found: C, 85.45; H, 5.45.

The second fraction (major component) corresponded to **7** (yield 87%): ir 3500–3250 (OH), 3030, 1650, and 890 (-CH=CH_2), 690, 660, 610 cm^{-1} (-CCl=C<); nmr ($CDCl_3$) τ 2.0–3.2 (6 H, m, aromatic H), 5.05 (2 H, d, -CCl=CH_2), 5.90 (2 H, s, -CH_2CCl=).

Anal. Calcd for $C_{13}H_{11}OCl$: C, 71.40; H, 5.07. Found: C, 71.15; H, 5.00.

Cyclization of 7. Cyclization with PPA as in the experiment with **2** converted **7** (0.35 g) to **8**, mp 51–52°, picrate (orange red needles) mp 139–140°; the yield was 75%.

2-Chloro-2-propenyl Ether of3-Hydroxy-1,3,5(10)-estratrien-17-one (9). A mixture of estrone (2 g), anhydrous potassium carbonate (20 g), potassium iodide (2 g), 2,3-dichloropropene (4 ml), and dry acetone (200 ml) was heated under reflux for about 25 hr. The reaction mixture was filtered and the filtrate was stripped of solvent to give a residue which after purification by chromatography over alumina amounted to 2.1 g (80%) of **9**: mp 107–108°; ir 1740 (CO), 920, 900, 880 (C=CH_2), 670, 650 cm^{-1} (-CCl=C<); nmr ($CDCl_3$) τ 2.6–3.4 (3 H, m, aromatic H), 4.5 (2 H, d, -ClC=CH_2), 5.4 (2 H, broad s, -CH_2CCl=), 9.1 (3 H, s, 18-CH_3).

Anal. Calcd for $C_{21}H_{25}O_2Cl$: C, 73.13; H, 7.30. Found: C, 72.95; H, 7.13.

Claisen Rearrangement of 9. The allyl ether **9** (1 g) was dissolved in *N,N*-dimethylaniline (3 ml) and heated to 193° in an oil bath under nitrogen for 4 hr. A single product (0.6 g, 60%) was obtained after chromatography which was identified as **10**: mp 203°; ir 3300–3400 (OH), 1740 (CO), 890 (>C=CH_2), 710 cm^{-1} (>C=CCl-); nmr ($CDCl_3$) τ 2.9 (1 H, broad s, aromatic H), 3.5 (1 H, broad s, aromatic H), 4.8 (2 H, d, CH_2=CCl-), 6.35 (2 H, broad s, -CH_2CCl=), 9.10 (3 H, s, 18-CH_3); mass spectrum *m/e* (rel intensity) 346 (1, M^+), 344 (3, M^+).

Anal. Calcd for $C_{21}H_{25}O_2Cl$: C, 73.13; H, 7.30. Found: C, 73.05; H, 7.45.

17-Keto-5′-methylestra-1(10),4-dieno[3,2-*c*]furan (11). Cyclization of **10** (0.5 g) was carried out by stirring with 90% sulfuric acid (4 ml) for 30 min at 0°. The reaction mixture was decomposed with ice water and extracted with chloroform. After the organic layer was stripped of solvent and the residue was purified by preparative tlc (solvent system chloroform–benzene, 70:30), there was obtained 70 mg (15%) of the title compound: mp 155–158°; nmr ($CDCl_3$) τ 2.7 (2 H, 2 broad s, aromatic H), 3.6 (1 H, s, β-H of furan), 7.5 (3 H, s, CH_3 on furan ring), 9.0 (3 H, s, 18-CH_3); mass spectrum *m/e* 308 (M^+).

Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.85; H, 7.53.

Acknowledgment. The authors wish to thank the Department of Atomic Energy, Government of India, for a Junior Research Fellowship (to D. V. L. R.) and Panjab University and Stevens Institute of Technology for support of this research.

Registry No.—**1**, 51911-83-2; **2**, 51911-84-3; **3**, 25826-63-5; **3** picrate, 51911-85-4; **6**, 51911-86-5; **7**, 51911-87-6; **8**, 18747-04-1; **8** picrate, 51911-88-7; **9**, 51933-35-8; **10**, 51933-36-9; **11**, 51933-37-0; α-naphthol, 90-15-3; 2,3-dichloropropene, 78-88-6; β-naphthol, 135-19-3; estrone, 53-16-7.

References and Notes

(1) (a) D. L. Storm and T. A. Spencer, *Tetrahedron Lett.*, 1865 (1967); (b) T. M. Harris, C. M. Harris, and J. C. Cleary, *ibid.*, 1427 (1968); (c) H.-G. Lehman, *ibid.*, 607 (1968); (d) U. K. Pandit, H. R. Reus, and K. DeJonge, *Recl. Trav. Chim. Pays-Bas*, **89**, 956 (1970); (e) M. Derenberg and P. Hodge, *Chem. Commun.*, 233 (1971); (f) P. Crabbe, L. A. Moldonado, and I. Sanchez, *Tetrahedron*, **27**, 711 (1971); (g) M. Stefanović, Lj. Krstić, and S. Mladenović, *Tetrahedron Lett.*, 311 (1971); T. Hosokawa, K. Maeda, K. Koga, and I. Maritani, *ibid.*, 739 (1973); S. R. Ramdas, *J. Sci. Ind. Res.*, 145 (1972); K. Huber and A. von Wartburg, *Experientia*, **25**, 908 (1969).
(2) C. D. Hurd and C. N. Webb, *J. Amer. Chem. Soc.*, **58**, 2190 (1936).
(3) E. J. Corey, G. Slomp, S. Dev, S. Tobinaga, and E. R. Glazier, *J. Amer. Chem. Soc.*, **80**, 1204 (1958).
(4) A. L. Wilds and J. A. Johnson, *J. Amer. Chem. Soc.*, **68**, 86 (1946).
(5) I. Iwai and J. Ide, *Chem. Pharm. Bull.*, **11**, 1042 (1963).
(6) K. Takeda and H. Osaka, *J. Pharm. Soc. Jap.*, **75**, 210 (1955).
(7) Melting points were determined using a sulfuric acid bath and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer 13/B spectrometer using Nujol mulls; nmr and mass spectra were recorded on a Varian A-60 spectrometer and a Hitachi RMU-7 spectrometer, respectively. Neutral alumina was used for column chromatography; tlc separation was carried out on silica gel G plates.

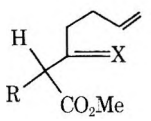
A Route to Furanoid Systems by Intramolecular Homoconjugate Addition

Summary: Intramolecular O-alkylation of β-keto ester enolates by activated cyclopropanes provides a pathway to dihydrofurans and tetrahydrofurylidene derivatives.

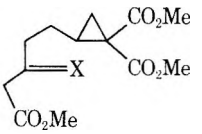
Sir: Recently we reported a new route to the synthesis of carbocyclic[1a] and nitrogen heterocyclic[1b] systems *via* intramolecular homoconjugate addition to activated cyclopropanes. In the cases thus far described,[1] the site of nucleophilic activity was predictable. Reliable rules concerning the sense (spiro *vs.* fused modes[1a]) of opening of the cyclopropanes were developed. It was thus of interest to study the intramolecular opening of such activated systems by enolates of β-keto esters, where ambient nucleophilicity (C- *vs.* O-alkylation) has often been encountered.[2] Below we describe expeditious entries to furanoid derivatives[3] by means of preferential intramolecular O-alkylation of such enolates. We also report an unusually high degree of specificity in the geometry of these enolates as a function of solvent.

Terminal allylation of methyl acetoacetate by the excellent method of Weiler[4] afforded **1**. Attempted cyclopropanation of **1** with dimethyl diazomalonate under the influence of copper bronze gave, as the major product (51%), enone triester **2**, mp 46–48°.[5a,6] While the generality of this potentially useful reaction[7,8] remains to be explored, for our immediate purposes it posed a problem. Accordingly, **1** was converted (91%) to its dioxolane derivative, **3**, and the latter was subjected to cyclopropanation (a solution of 1 equiv of olefin and 1 equiv of diazo compound was added to a mixture of 1 equiv of olefin and 400 mg of copper bronze/0.1 mol of diazo ester, heated at 140°). The ketal triester **4**[5a] so obtained in 70% yield was transformed (1:1 MeOH–concentrated HCl, room temperature) into the desired **5**[5] in 77% yield.

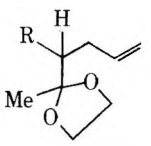
Similarly, cyclopropanation of unsaturated ketal **6**[5a] gave **7** (38%) which afforded **8**[5a] (75%) after deketalization. Finally, cyclopropanation of the dioxolane of allylacetone (**9**)[9] followed by deketalization afforded **10**[5] (49% overall), mp 50–52°.



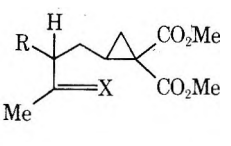
1, X = O; R = H
2, X = O; R = $CH(CO_2Me)_2$
3, X = $-O(CH_2)_2O-$; R = H



4, X = $-O(CH_2)_2O-$
5, X = O



6, R = CO_2Me
9, R = H



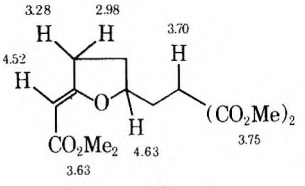
7, X = $-O(CH_2)_2O-$; R = CO_2Me
8, X = O; R = CO_2Me
10, X = O; R = H

Treatment of **5** with 1.6 equiv of sodium hydride in benzene at room temperature for 21 hr gave the tetrahydrofurylidene triester **11**[5] in 71% yield, after chromatography. Starting **5** was recovered (21%). While the possibility of trace amounts of products derived from C-alkylation cannot be excluded, O-alkylation is clearly to dominant pathway.

Reaction of **5** with dimsylsodium[10] (1.1 equiv of triester and 1 equiv of base, room temperature, 3 hr) in DMSO, gave a 49% yield of an isomeric substance, similar to but different from the sodium hydride product. On the basis of data summarized below, this isomer is formulated as **12**.[5] Starting material **5** was recovered to the extent of 5% and there was some indication (tlc) of the formation of **11**. Since the total recovery of neutral fraction was only 78%, O-alkylation is again the predominant pathway.

That the closely related **11**[11] [$\lambda_{max}^{CMCl_3}$ 1725, 1698, 1650 cm^{-1}; λ_{max}^{MeOH} 242 nm (ε 10,300)] and **12** [$\lambda_{max}^{CHCl_3}$ 1745, 1725, 1700, 1640 cm^{-1}; λ_{max}^{MeOH} 242 nm (ε 15,000)] are cis and trans isomers was verified chemically. Each compound, after ozonolysis [(1) O_3–CH_2Cl_2, −78°; (2) Zn–AcOH] gave the lactone diester **13**[5a] (nmr data appear in Chart I[12]). The assignment of configurations to **11** and **12** follows from their nmr spectra (Chart I[12]) in conjunction with known data in 3-alkoxycrotonate systems.[13] Thus, for the trans isomer **12** the resonance for the vinylic proton occurs at higher field than the corresponding resonance for the cis isomer **11**. The reverse order is seen in the allylic resonances.

Chart I[12]



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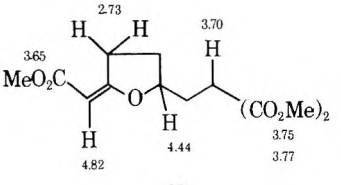

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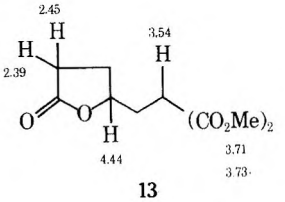

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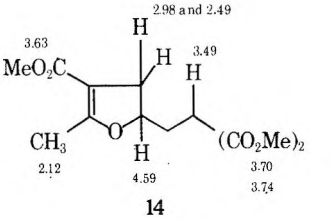

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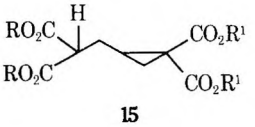

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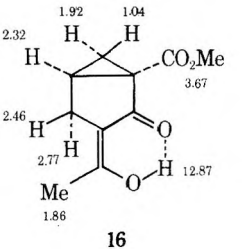

16

Since the counterion for both reactions of **5** is sodium, and since both solvents (benzene and DMSO) are aprotic, the enormous difference in the two cases is likely to be a consequence of solvation. For the case of benzene, the U conformation[2,13] involving chelation of the cation by the β-dicarbonyl enolate ligand might be expected to predominate. This leads to cis product. For a solvent with high cation solvating capabilities, such as DMSO, the W or S conformations[2,13] of the enolates might predominate on dipole

repulsion grounds. Either of these would lead to trans product.[13,14]

Treatment of 8 with sodium hydride–benzene (1 equiv of 8 and 1.6 equiv of base) at room temperature for 96 hr gave a 74% yield of dihydrofuran derivative 14 [$\lambda_{max}^{CHCl_3}$ 1755, 1730, 1690, 1644 cm^{-1}; λ_{max}^{MeOH} 255 nm (ϵ 12,200); *m/e* 286 (P); nmr (Chart I[12]). While we do not rule out the possibility of small amounts of products derived from C-alkylation, O-alkylation is again the predominant pathway. It should be noted that in the case of closely related compound **15**, which differs from **8** only by carboalkoxyl *vs.* acetyl deprotonation induces rapid scrambling of the esters,[1c] undoubtedly *via* homoconjugate attack. Whether such an equilibrium is concurrent with the O-alkylation reaction is not known.

In an attempt to study the consequences of generating a monostabilized enolate in an intramolecular relationship to a cyclopropane ring, compound **10** was treated with sodium hydride–benzene and a trace of methanol. There was thus obtained, in 65% crude yield, the difficultly crystalline Dieckmann product **16**,[5,15] mp 35°. The predominant tautomeric form is tentatively assigned as shown, on the basis of the chemical shifts (Chart I[12]) which seem most compatible with the presence of an allylic type methyl. After Dieckmann cyclization had been undergone, possibility of ring mutation is blunted since an endocyclic type of SN2 displacement would now be required.[16]

Acknowledgments. This research was supported by PHS Grant No. 11207-10. Nmr spectra were measured on the Mellon–Pitt–Carnegie (MPC) 250-MHz facility supported by NIH Grant RR-00292-07.

Supplementary Material Available. The experimental procedures for the reactions described in this investigation will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2658.

References and Notes

(1) (a) S. Danishefsky, J. Dynak, E. Hatch, and M. Yamamoto, *J. Amer. Chem. Soc.*, **95**, 1256 (1974); (b) S. Danishefsky and J. Dynak, *J. Org. Chem.*, **39**, 1979 (1974); (c) S. Danishefsky, J. Dynak, and M. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 81 (1973).
(2) For an excellent review, see H. O. House "Modern Synthetic Reactions," Second ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 520–530.
(3) For a recent synthetic approach to tetrahydrofuryledenes, see T. A. Bryson, *J. Org. Chem.* **38**, 3428 (1973).
(4) S. N. Huckin and L. S. Weiler, *J. Amer. Chem. Soc.*, **96**, 1082 (1974).
(5) (a) The structure of this compound is consistent with its ir, nmr, and low resolution mass spectra; (b) C and H combustion analysis within 0.4% of theory was obtained for this compound.
(6) This experiment was conducted by Dr. M. Yamamoto.
(7) A formal interpretation of this process would involve insertion of the copper carbenoid into the enolic double bond followed by ring opening of the resultant cyclopropanol.
(8) For a novel alkylation scheme based on openings of cyclopropanols, see E. Wenkert, R. A. Mueller, E. J. Reardon, S. S. Sathe, D. J. Scharf, and G. Tosi, *J. Amer. Chem. Soc.*, **92**, 7428 (1970).
(9) Cl. Feugas, *Bull. Soc. Chim. Fr.*, 2579 (1963).
(10) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).
(11) The compounds are easily differentiated by tlc on silica gel plates (Brinkmann Analytical). Thus the R_f values using a 2:1 benzene–ethyl acetate system are 0.26 (**11**) and 0.42 (**12**).
(12) The nmr spectra were measured at 250 MHz. Chemical shifts are reported in δ units from tetramethylsilane as an internal standard. When necessary, decoupling was employed for shift assignments. The spectra of **11** and **12** were measured in deuteriochloroform. Those of **13**, **14**, and **16** were measured in carbon tetrachloride.
(13) A. L. Kurts, M. Macias, I. P. Boletskaya, and O. A. Reutov, *Tetrahedron Lett.*, 3037 (1971).
(14) S. J. Rhoads and R. W. Holder, *Tetrahedron*, **25**, 5443 (1969).
(15) Attempted purification on silica gel was attended by substantial losses of material on the column reducing the yield to 50%.
(16) L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chem. Acta*, **53**, 2050 (1970).

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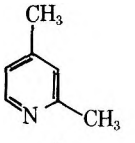
Selective Metalations of Methylated Heterocycles. III. Thermodynamic vs. Kinetic Control

Summary: Ethereal solutions of 2-lithiomethyl-4-methylquinoline (**4a**) can be isomerized to 4-lithiomethyl-2-methylquinoline (**4b**) and vice versa as a function of solvent and time.

Sir: Recently, selective metalations of one or the other of two methyl groups substituted 2 or 4 to the ring nitrogen atoms of 2,4-lutidine (**1**), 2,4,6-collidine (**2**), and 2,4-dimethylquinoline (**3**) as a function of the metalating agent were described.[1] In essence, exclusive metalations of the 2- or 4-methyl groups of such compounds were realized with *n*-butyllithium in ether–hexane and sodium amide in liquid ammonia, respectively.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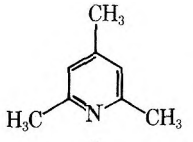
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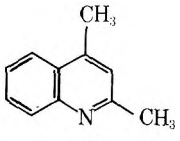
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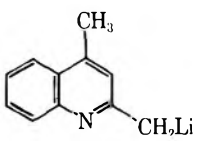
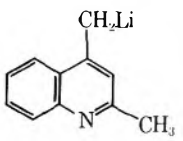
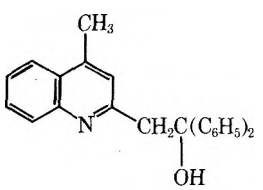
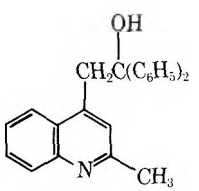
We now wish to report that, though selective metalations of polymethylated pyridines and quinolines continue to be realized, different organolithium derivatives can be cleanly obtained as a function of the ethereal solvent and the reaction periods employed. Thus, metalation of **3** by *n*-butyllithium in THF–hexane gives only **4a** after 1 hr, mixtures of **4a** and **4b** after 24 hr, and only **4b** after 144 hr. That **4a**


4a


4b

and/or **4b** were indeed present was demonstrated by condensation with benzophenone to afford **5a**[1] or **5b**,[1] respec-


5a

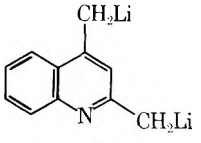

5b

tively. Interestingly, the rate of isomerization of **4a** to **4b** is dramatically increased in the presence of an extra equivalent of **3** since only **4b** is present at the end of 1 hr.

In contrast to the conversion of **4a** to **4b** in THF–hexane, **4a,** prepared from **3** and *n*-butyllithium in ethyl ether–hexane, did *not* isomerize to **4b** even after 96 hr. In fact, the opposite could be realized. Thus, **4b** was prepared from dimethylaminolithium and **3** in THF–hexane and the reaction mixture was divided into two parts. One part was trapped with benzophenone to afford **5b.** The other part was evaporated to dryness and treated with ethyl ether, **3,** and benzophenone to give only **5a.**

It can be concluded from the above that the formation of solvated organometallics **4a** and **4b** is either kinetically or thermodynamically controlled depending on the solvent. Thus, **4a** solvated by THF is the kinetic product while **4a** solvated by ethyl ether is the thermodynamic product. On the other hand, **4b** solvated by THF is the thermodynamic product while **4b** solvated by ethyl ether is the kinetic product. The relative thermodynamic stabilities of solvated **4a** and **4b** can be rationalized on the basis that the less sterically bulky THF interacts less with the peri-hydrogen atom of **4b** than does ethyl ether.

These isomerizations are similar to those obtained with excess alkylbenzenes and alkylsodium and potassium reagents,[2] and to those realized with certain alkali derivatives of benzyldimethylamine,[3] though no solvent effects were reported. The interconversions of **4a** and **4b** probably occur *via* a small amount of unionized **3** but may also involve dianion **4c;** compounds like **4c** have recently been prepared from polymethylpyridines.[4]



4c

In conclusion, synthetically useful side-chain metalations of six-membered polyalkyl nitrogenous aromatic heterocycles can be realized provided that careful attention is directed toward the choice of solvent, metalating agent, metallic cation, and time. Studies on systems other than **3** are currently under investigation in these laboratories.

Supplementary Material Available. Experimental data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2659.

References and Notes

(1) E. M. Kaiser, G. J. Bartling, W. R. Thomas, S. B. Nichols, and D. R. Nash, *J. Org. Chem.*, **38,** 71 (1973).
(2) R. A. Benkeser, J. Hooz, T. V. Liston, and A. E. Trevillyan, *J. Amer. Chem. Soc.*, **85,** 3984 (1963), and references cited therein.
(3) W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **85,** 2467 (1963).
(4) G. B. Trimitsis, S. G. Benzunas, and R. C. Gorski, Abstracts, 7th Great Lakes Regional Meeting of the American Chemical Society, Kalamazoo, Mich., June 1973.

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A Unique Example of Virtual Proton–Proton Coupling in Purine Nucleosides

Summary: A unique long-range virtual coupling between C-1′ H and C-3′ H of 2′-*O*-benzyl derivatives of adenosine and inosine is reported.

Sir: Our interest in developing techniques for the chemical synthesis of oligoribonucleotides of defined chemical structure has led to the synthesis of a number of ribonucleosides having the 2′- or 3′-hydroxyl function selectively protected by a benzyl[1] or *p*-methoxybenzyl[2] group. It was of interest to study the conformation in solution of certain of these benzyl ribonucleosides, since molecular models suggested that overlap (stacking) of the benzene and heterocyclic moieties could occur in the 2′-*O*-benzyl series but not in the 3′-*O*-benzyl nucleosides (Figure 1). As has been previously shown by a number of groups,[3–5] pmr spectroscopy in aqueous (D_2O) solution affords an excellent method of evaluating a stacking interaction between two or more "heteroaromatic" bases in a molecule.

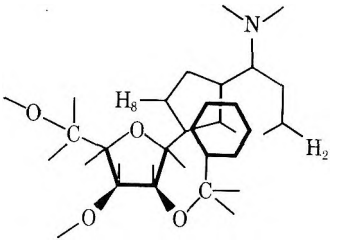

Figure 1

Examination of the pmr spectra of 2′-*O*-benzyladenosine (**1**) and 2′-*O*-benzylinosine (**2**) in D_2O solution (~0.10 *M*) at 60 MHz revealed a striking anomaly in the signal attributable to C-1′ H. β-D-Ribofuranosylpurine spectra normally exhibit $J_{1',2'}$ values of around 6 Hz and the C-1′ H signal appears as a clean doublet. This was indeed the case for **1** and **2** in $(CD_3)_2SO$ solutions. In D_2O, however, the signal due to C-1′ H appeared as a complex multiplet. The spectrum of 2′-*O*-benzyluridine, on the other hand, revealed an entirely normal doublet ($J_{1',2'}$ = 6.0 Hz) attributable to the C-1′ H signal.

As previously observed,[1,2] 2′-*O*-benzyl ribonucleosides in aqueous solution appear to exist in a "folded" conformation (Figure 1) in which the benzene ring is stacked with the heterocyclic moiety. It was, therefore, of interest to determine if an elevated temperature would lead to unstacking and whether this would have an effect on the multiplicity of the C-1′ H signal. Therefore, pmr spectra were recorded of a 0.046 *M* solution of **1** in D_2O at 30° and at 70°. Unstacking at the higher temperatures was confirmed by the downfield shifts of 0.06, 0.13, 0.10, and 0.10 ppm for C-8 H, C-2 H, the phenyl protons, and C-1′ H, respectively. The differential shifts of C-8 H and C-2 H support a conformational model in which the benzene ring is stacked primarily over the pyrimidine ring of the purine. In addition to the deshielding experienced by C-1′ H over this temperature range, the signal collapsed from the multiplet to a clean doublet ($J_{1',2'}$ = 5.5 hz). This observation strongly suggested that the observed multiplicity arose from a conformationally dependent long-range coupling between C-1′ H and another proton in the molecule resulting from stabilization of a specific ribose conformation by an intramolecular stacking interaction. Unstacking at higher temperature presumably permits the establishment of a mobile equilibrium of conformers. Because of the complexity of the spectrum arising from the sugar portion of the molecule

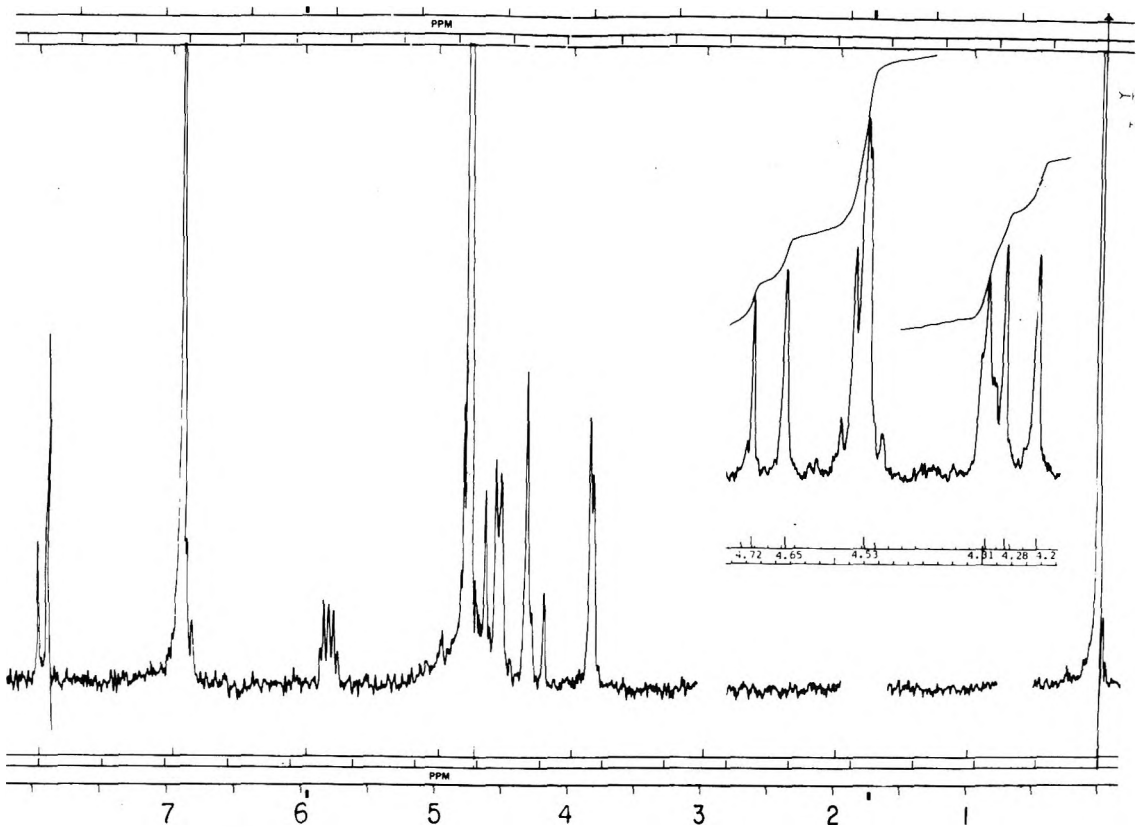

Figure 2. 220 MHz spectrum of 2′-*O*-benzyladenosine (1) in D_2O.

and the benzyl methylene, as well as the presence of a substantial HDO peak in the same region, it initially proved impossible to assign all of the proton signals in spectra obtained at 60 and 100 MHz. The spectrum obtained at 220 MHz (Figure 2) was readily assigned, however, and the possibility of long-range coupling with one of the benzyl methylene protons was eliminated by the identification of the four sharp, well-resolved lines of a typical AB quartet centered at δ 4.47 (J_{HCH} = 12 Hz) for the methylene protons. The anomeric proton signal still appeared as a multiplet; complete assignment of the 220-MHz spectrum revealed that the signals of C-2′ H and C-3′ H were superimposed.

The knowledge obtained from the 220-MHz spectrum enabled the assignment of the superimposed signals arising from C-2′ and C-3′ H at 60 and 100 MHz. Decoupling experiments confirmed that C-1′ H was coupled only to C-2′ H and C-3′ H; irradiation of the signal due to the latter protons caused the collapse of the C-1′ H multiplet to a singlet.

These experiments establish that the unexpected splitting of the anomeric proton signal in **1** and **2** is the result of long-range coupling between C-1′ H and C-3′ H. This could arise either as a result of four-bond coupling or virtual coupling. Four-bond coupling across σ bonds usually requires a planar zigzag conformation of the bonds involved. Examination of molecular models reveal that this criterion is not met in the stacked conformation of **1** and **2**. In order for virtual coupling to occur, three conditions must be met.[6] First, C-2′ H and C-3′ H must be strongly coupled. The dihedral angle between these two protons is small, and according to the Karplus relationship, $J_{2',3'}$ should be large. Only a few such couplings have been determined, but those which have been reported range from 4.5 to 6.5 Hz.[7] The second criterion is that C-1′ H be only weakly coupled to C-3′ H; the usual absence of any measurable coupling in purine nucleosides attests that this condition is met. Finally, the separation between the C-2′ H and C-3′ H signals must be less than $J_{2',3'}$. Careful examination of the 220-MHz spectrum reveals that, even at this high field, only ~1.5 Hz separates the centers of the C-2′ H and C-3′ H signals.

For final confirmation, a partial computer simulation of the 220-MHz spectrum of **1** using the LAOCOON III program was undertaken. The use of $J_{1',2'}$ as 6.5 Hz, $J_{2',3'}$ = 5.0 Hz and the actual chemical shifts of C-1′ H, C-2′ H, C-3′ H, and C-4′ H resulted in a simulated spectrum of the C-1′ H coupling pattern that is in excellent agreement with the measured 220-MHz spectrum.

Based upon these considerations, the unique splitting pattern of the anomeric protons of **1** and **2** have been shown to result from virtual long-range coupling between C-1′ H and C-3′ H. This phenomenon appears from the limited data available to be specific for base type (purine *vs.* pyrimidine) and for aqueous solutions. Solubility limitations in aqueous solutions have prevented similar analysis of 2′-*O*-benzylcytidine and 2′-*O*-benzylguanosine spectra. To our knowledge, this represents the first report of such a phenomenon in a nucleoside.

Studies now in progress are expected to provide more specific information on ribose conformational equilibria in these interesting systems and to reveal the scope of the phenomenon by examination of 2′-*O*-benzyl nucleotides and oligonucleotides.

Acknowledgment. This study was supported by a grant from the National Cancer Institute, Public Health Service, CA 11935. The authors are grateful to Dr. Paul O. P. T'so for making his 220-MHz pmr spectrometer available to us and to Dr. C. Dale Poulter for the use of his LAOCOON III computer program and for helpful discussions.

References and Notes

(1) L. F. Christensen and A. D. Broom, *J. Org. Chem.*, **37**, 3398 (1972).
(2) A. D. Broom, L. F. Christensen and J. T. Uchic, Abstracts of the 164th

National Meeting of the American Chemical Society, New York, N. Y., 1972, ON 137.
(3) P. O. P. Ts'o, M. P. Schweizer, and D. P. Hollis, *Ann. N.Y. Acad. Sci.*, **158**, 252 (1969).
(4) S. J. Chan and G. P. Kreishman, *J. Amer. Chem. Soc.*, **92**, 1102 (1970).
(5) C. D. Barry, J. A. Glasel, A. C. T. North, R. J. P. Williams, and A. V. Xavier, *Biochim. Biophys. Acta*, **161**, 101 (1972).
(6) L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, pp 33–41.
(7) C. Altona and M. Sundaralingam, *J. Amer. Chem. Soc.*, **95**, 2333 (1973).

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Synthesis of the Isomers of 3-Butyl-5-methyloctahydroindolizine, a Trail Pheromone of Pharaoh Ant

Summary: The four stereoisomers of 3-methyl-5-butyloctahydroindolizine, a trail pheromone of the Pharaoh ant, have been synthesized by methods that unambiguously defined their stereochemistry.

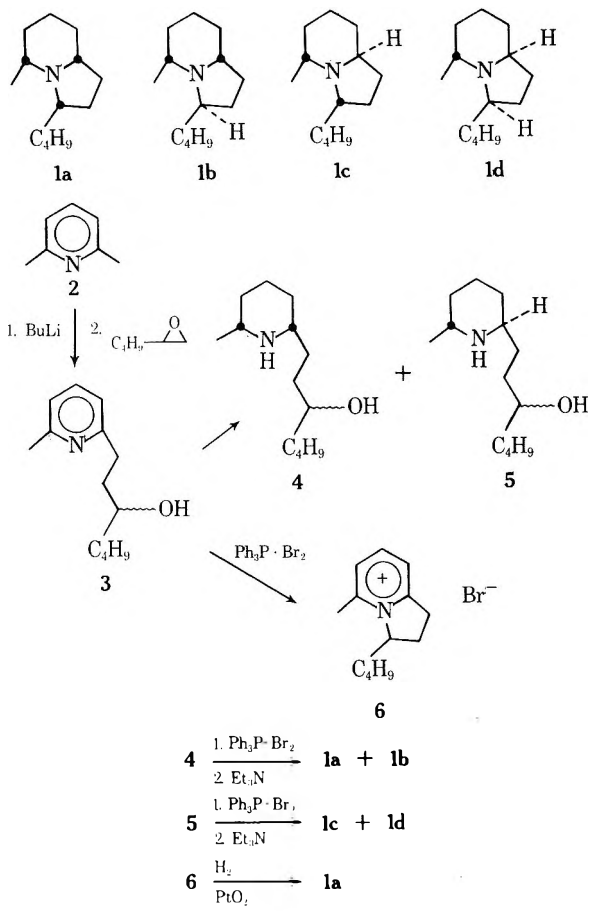
Sir: Ritter, *et al.*,[1] recently described the isolation and identification of a 3-butyl-5-methyloctahydroindolizine as a trail pheromone of the Pharaoh ant, *Monomorium pharaonis* (L.). Which of the four possible geometrical isomers (**1a–d**) of this structure was the active pheromone was not determined. Because of our interest in the synthesis of pheromones of potential utility for pest control,[2] and because the reported[1] synthesis of **1a–d** would not be practical for preparation of the individual isomers, we undertook syntheses of each of the isomers by routes that would define their stereochemistry and allow their isolation. We here report successful preparations of each of the isomers from 2,6-lutidine (**2**) (Scheme I).

Sequential treatment of **2** with *n*-butyllithium and hexene 1-oxide gave the alcohol **3** [bp 92° (0.06 mm), n^{27}D 1.5022].[3] Cyclization of **3** with triphenylphosphine dibromide (Ph_3P-Br_2) provided the dihydroindolizinium bromide **6** (characterized as the iodide, mp 126–127°) which was hydrogenated over PtO_2 to give the *all-cis*[4]-3,5-dialkyloctahydroindolizine **1a** [bp 119° (27 mm), n^{25}D 1.4669].

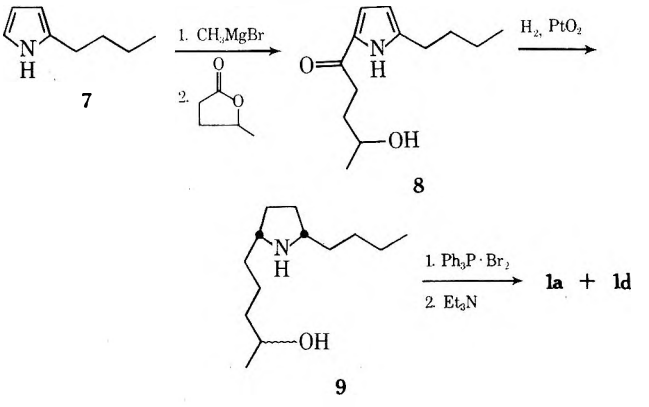
Hydrogenation of **3** gave the *cis*[5]-piperidyl alcohols **4** (mp 55–63°). Cyclization of **4** with Ph_3P-Br_2 followed by triethylamine gave a mixture (separated by spinning-band distillation) of **1a** and **1b** [bp 125° (27 mm), n^{25}D 1.4704].

The final two isomers, **1c** and **1d**, whose substituents on the piperidine ring bear a trans relationship, were prepared analogously. Reduction of **3** with sodium and ethanol gave an 80:20 mixture of **4** and its trans isomer **5**, respectively. Seeding an acetonitrile solution of the crude mixture with **4** initiated crystallization of that isomer; the mother liquor contained approximately equal parts of **4** and **5**. Spinning band distillation achieved final separation of the *trans*-piperidyl alcohol **5** [bp 77° (0.005 mm), n^{25}D 1.4732]. Cyclization of **5** with Ph_3P-Br_2 then gave **1c** [bp 121° (27 mm), n^{25}D 1.4699] and **1d** [bp 125° (27 mm), n^{25}D 1.4695]; these were also separated by spinning-band distillation. A variety of packed glc columns (Carbowax 20M, SE-30, others) served to distinguish the indolizidines and to monitor the distillations. Although **1b** and **1d** could not be separated by gas chromotography, the synthetic routes chosen circumvented the necessity for separation. The production of *cis*-dialkylpiperidines by catalytic hydrogenation of the corresponding pyridines provided the basis for assigning the stereochemistry at positions 6 and 9 of **1a–d**;[6] the stereochemistry at position 3 of **6** (and therefore of **7**) was established by the alternate preparation of **1a** from **6**. To assign the stereochemistry at position 3 of **1c** and **1d**, we again turned to the principle of cis hydrogenation, in this case to produce the cis-2,5-disubstituted pyrrolidine **9** (Scheme II). γ-Valerolactone was added to the Grignard reagent from 2-butylpyrrole (**7**) to give **8** (mp 63–64°). Hydrogenation (PtO_2, 50 psi) of **8** gave the pyrrolidinyl alcohol **9** which was not purified but instead was cyclized directly with Ph_3-Br_2 to a mixture consisting mainly of **1a** and **1d**, thereby establishing **1d** as the isomer with hydrogens at positions 3 and 9 situated cis to each other. Small amounts of

Scheme I



Scheme II



1b and **1c** (total ~15%) were also detected in the reaction mixture, indicating that the hydrogenation of **8** must have provided a small amount of the trans isomer of **9**.[7] However, the fact that **1a** (all-cis) was one of the major products from this cyclization requires that the substituents on the pyrrolidine ring of the other major product must also have been cis.

Experimental details and additional work on this system will be reported at a later date.

References and Notes

(1) F. J. Ritter, I. E. M. Rotgans, E. Talman, P. E. J. Verwiel, and F. Stein, *Experientia*, **29**, 530 (1973).
(2) P. E. Sonnet, *J. Med. Chem.*, **15**, 97 (1972).
(3) Satisfactory elemental analyses and spectral data were obtained for all new compounds.
(4) B. Luning and C. Lundin, *Acta Chem. Scand.*, **21**, 2136 (1967).
(5) For examples of reductions of 2,6-disubstituted pyridines, see (a) R. K. Hill, T. H. Chan, and J. A. Joule, *Tetrahedron*, **21**, 147 (1965); (b) J. Pliml, E. Knobloch, and M. Protiva, *Chem. Listy*, **46**, 758 (1952).
(6) Although no systematic study of the stereochemistry of pyrrole reductions appears to have been published, cis hydrogenations have normally been assumed, and in some cases demonstrated: C. G. Overberger, L. C. Palmer, B. S. Marks, and N. R. Byrd, *J. Amer. Chem. Soc.*, **77**, 4100 (1955).
(7) Attempted analyses of **9** by gas chromatography on a variety of packed columns was unsuccessful, primarily because of excessive tailing.

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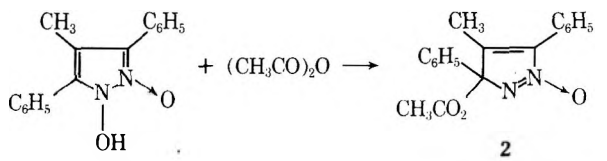
Molecular Rearrangements of *N*-Hydroxypyrazole Derivatives[1]

Summary: The tosylates of *N*-hydroxypyrazoles are hydrolyzed quantitatively to 5-pyrazolones, a reaction involving 1,2 migration in which anti-aromatic diazacyclopentadienyl cations are possible intermediates.

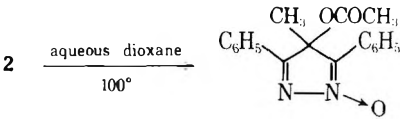
Sir: In an earlier investigation it was observed that acetylation of 1-hydroxy-3,5-diphenyl-4-methylpyrazole 2-oxide (**1**) yielded a *C*-acetoxy compound (**2**) rather than an *N*-



1 **2**

acetoxy compound.[2] Recently others have reported analogous rearrangements in this heterocyclic series.[3] In many respects these reactions resemble some of those reported in the indole[4] and purine[5] series. In each instance the driving force appears to be the exchange of the weak N–O bond for a stronger C–O bond.

Some additional rearrangements have now been observed. Upon heating in aqueous dioxane, acetate **2** further rearranges to acetate **3**. The structure of **3** rests upon its elementary analysis and the similarity of its infrared and nmr spectra to that of the corresponding dioxide.[2,6] Similar sequential 1,2 rearrangements of *N*-methoxypyrazole oxides[3] and *N*-nitropyrazoles[8] have been observed.



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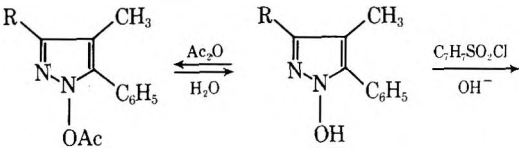
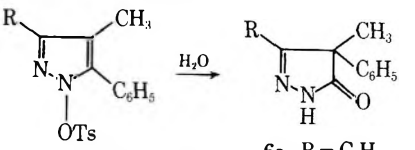
Acetylation of *N*-hydroxy-3,5-diphenyl-4-methylpyrazole (**4a**) produced the *N*-acetoxy derivative which did not rearrange after prolonged heating in boiling xylene. Hydrolysis regenerated the *N*-hydroxypyrazole. However, the corresponding *N*-tosyloxy compound (**5a**) was converted quantitatively, upon heating in aqueous dioxane, to 3,4-diphenyl-4-methyl-5-pyrazolone (**6a**). This transformation



4a, R = C_6H_5
b, R = CH_3



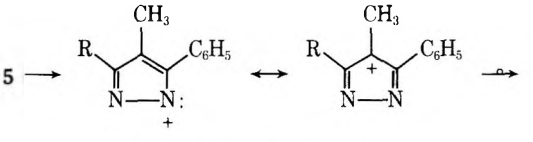
5a, R = C_6H_5
b, R = CH_3

6a, R = C_6H_5
b, R = CH_3

resembles the conversion of indoles into oxindoles by hypochlorite, a sequence which may begin by N-chlorination[4] yielding an intermediate analogous to the *N*-tosylate **5**.[9]

When 3(5)-phenyl-4,5(3)-dimethyl-1-hydroxypyrazole was similarly tosylated and heated in water, the product was again that of phenyl migration, 3,4-dimethyl-4-phenyl-5-pyrazolone (**6b**).

A possible mechanism analogous to those proposed for the indoles[4] involves ionization of **5** to ion **7**, a heterolog of the anti-aromatic cyclopentadiene cation.[10] Isomerization



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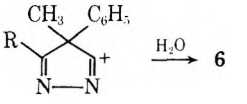

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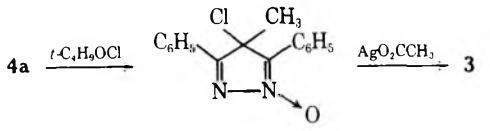
to ion **8** would lead to the product.[11-13] In an effort to determine the chemistry of possible precursors of ions like **7**, the electrophilic substitution reactions of the hydroxypyrazoles are being investigated as sources of such compounds. Treatment of **4a** with *tert*-butyl hypochlorite yields 4-chloro-4-methyl-3,5-diphenylpyrazolenine 1-oxide (**9**). While the *N*-oxide function may strongly influence the reactivity of **9** so that it is a poor model[14] for precursors of ion **7**, it was found that **9** reacts readily with silver acetate to yield acetate **3**. Thus, in this case at least, a reaction which most likely involves a carbonium ion intermediate proceeds

without rearrangement. Of some interest, however, is the comparative ease with which this antiaromatic heteroion is produced. Further studies of such ions are in progress.



9

References and Notes

(1) This research was supported by the National Institute of Health through Grant No. CA 10742, National Cancer Institute.
(2) J. P. Freeman and J. J. Gannon, *J. Org. Chem.*, **34**, 194 (1969).
(3) F. T. Boyle and R. A. Y. Jones, *J. Chem. Soc., Perkin Trans. 1*, 167 (1973).
(4) For leading references, see P. G. Gassman, G. A. Campbell, and G. Mehta, *Tetrahedron*, **28**, 2749 (1972).
(5) For leading references, see T-C. Lee, G. Salemnick, and G. B. Brown, *J. Org. Chem.*, **38**, 3102 (1973).
(6) 4,4-Dialkylpyrazole oxides analogous to **3** isomerize under the influence of light to dialkyl derivatives analogous to **2**.[7] It is not likely that the photochemical and thermal reactions are related mechanistically but the contrasting behavior is interesting.
(7) W. M. Williams and W. R. Dolbier, Jr., *J. Amer. Chem. Soc.*, **94**, 3955 (1972).
(8) J. W. A. M. Janssen, H. J. Koeners, C. G. Kruse, and C. L. Habraken, *J. Org. Chem.*, **38**, 1777 (1973).
(9) Efforts to convert 1-hydroxyindole to its tosylate led to the isolation of only the 3-tosyloxy derivative, a reaction which may involve a 1,3-N→C rearrangement.[4]
(10) R. Breslow, *Accounts Chem. Res.*, **6**, 393 (1973).
(11) The uncertainty in the structure of **5b**[2,12] is unimportant if ion **7** is involved, but it is possible that the structure of the hydroxypyrazole and of the pyrazolone are more intimately related.
(12) F. T. Boyle and R. A. Y. Jones, *J. Chem. Soc., Perkin Trans. 1*, 170 (1973).
(13) Direct attack of water on the ring in an SN2′-type substitution may also be involved, but good nucleophiles such as amines or alkoxide ion attack the sulfonyl group rather than the ring. Concerted mechanisms involving allowed suprafacial 1,5-sigmatropic shifts are among the many other possibilities.
(14) The recently reported silver ion catalyzed reactions of α-chloronitrones indicate extensive back-donation of electron density from oxygen to carbon: U. M. Kempe, T. K. Das Gupta, K. Blatt, P. Gygax, D. Felix, and A. Eschenmoser, *Helv. Chim. Acta*, **55**, 2187 (1972).

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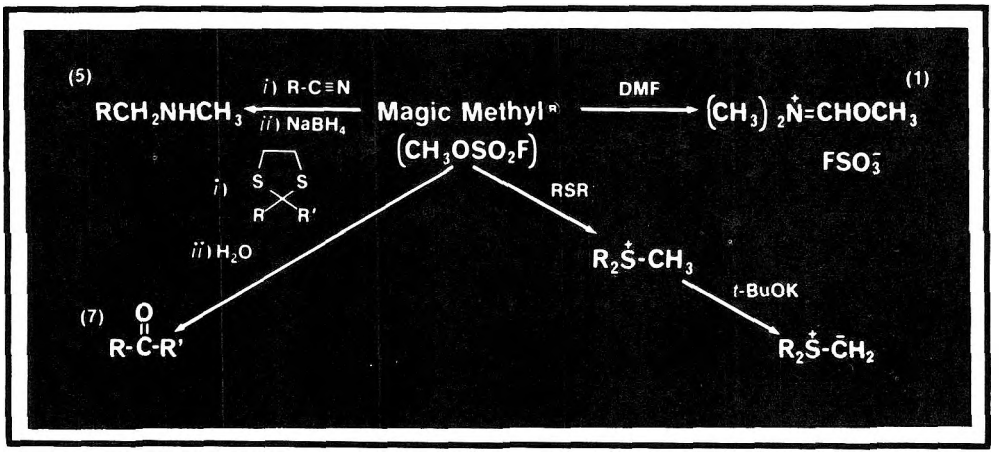

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References

1) M.G. Ahmed, R.W. Alder, G.H. James, M.L. Sinnott, and M.C. Whiting, *Chem. Commun.*, 1533 (1968).
2) R. Grigg, A. Sweeney, G.R. Dearden, A.H. Jackson, and A.W. Johnson, *ibid.*, 1273 (1970).
3) M.G. Ahmed and R.W. Alder, *ibid.*, 1389 (1969).
4) T. Kametani, T. Suzuki, and K. Ogasawara, *Chem. Pharm. Bull.* (Tokyo), **20**, 2057 (1972).
5) R.S. Matthews and T.E. Meteyer, *Chem. Commun.*, 1576 (1971).
6) R.F. Borch, *ibid.*, 442 (1968).
7) R.H. Mitchell and V. Boekelheide, *Tetrahedron Lett.*, 1197 (1970).
8) M. Fetizon and M. Jurion, *Chem. Commun.*, 382 (1972).
9) T. Kametani, K. Takahashi, and K. Ogasawara, *Synthesis*, 473 (1972).

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