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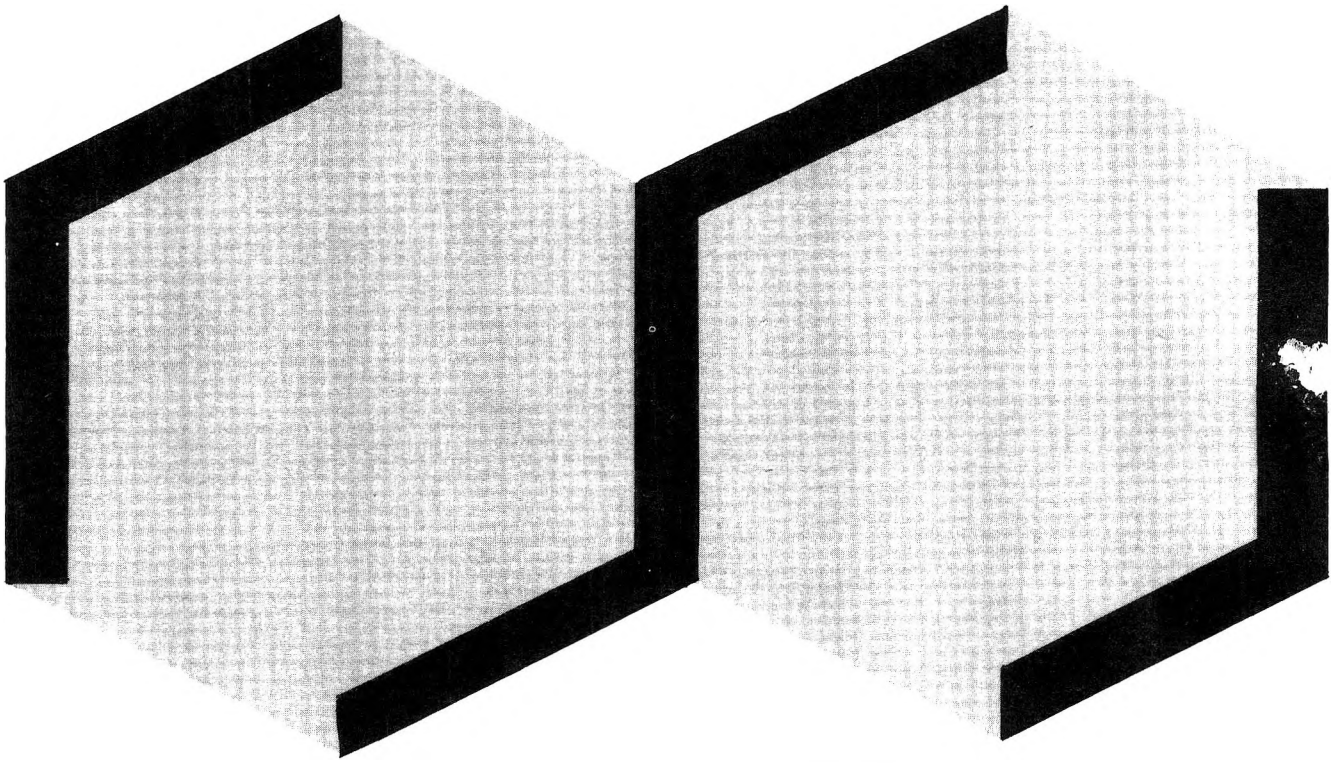

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Stereochemistry and Conformational Preferences of Meso-Alkylated Thioxanthenes by Proton Magnetic Resonance Spectroscopy[1]

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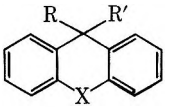
9-Alkylthioxanthenes have been shown to prefer that conformation in which the alkyl group is pseudo-axial (a′), following the pattern established for 9-alkyl-9,10-dihydroanthracenes. The central ring of 9-*tert*-butylthioxanthene is shown to be deformed (flattened). Two other series, 9-methyl-9-alkylthioxanthenes and 1,4-dimethyl-9-alkylthioxanthenes, also have been prepared and studied. Chemical shifts, NOEs, and long-range coupling phenomena have been examined with regard to their utility in conformational assignments in these compounds. Rotameric distributions for ethyl and isopropyl derivatives have been suggested on the basis of pmr parameters.

The derivatives[3] and heterocyclic analogs[4-8] of 9,10-dihydroanthracene (**1**) generally exist as folded structures



1, R = R′ = H; X = CH_2
2, R = R′ = H; X = S
3, R = H; R′ = Me; X = S
4, R = H; R′ = Me; X = CH_2
5, R = H; R′ = Et; X = S
6, R = H; R′ = *i*-Pr; X = S
7, R = H; R′ = *t*-Bu; X = S
12, R = Me; R′ = Et; X = S
13, R = Me; R′ = *i*-Pr; X = S
14, R = Me; R′ = *i*-Pr; X = SO_2
15, R = Me; R′ = H; X = SO

capable of displaying a substituent bound to a meso position in either the pseudo-axial (a′) or the pseudo-equatorial (e′) position. The barrier for conformational interconversion in 9,10-dihydroanthracene and structurally similar heterocycles is quite low, calculated to be on the order of 7 kcal/mol[9a] or less.[9b] Undoubtedly, the major factor responsible for establishing this low barrier is the absence of the need for atoms bonded to the meso position to pass by the peri positions and the atoms bonded to them to achieve conformational exchange. One would imagine, then, that angle deformations of the atoms at the meso positions would account for a large portion of the barrier.[10]

Beckett and Mulley[3a] have discussed the stereochemical consequences of conformational isomerism in meso-substituted 9,10-dihydroanthracenes and suggested that 9-alkyl-9,10-dihydroanthracenes should prefer that conformation in which the substituent at C_9 is a′. Recently, it has been demonstrated[3f,12] that 9-alkyl-9,10-dihydroanthracenes do, indeed, follow the conformational behavior suggested by Beckett and Mulley. Similarly, the preferred conformation of 9-methylthioxanthene (**3**)[13] is one in which the methyl group is predominately a′[14] and this result is qualitatively analogous to that for 9-methyl-9,10-dihydroanthracene (**4**).

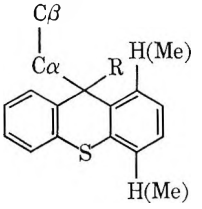
It was of interest to examine the effects of nonbonding interactions between larger alkyl groups and the ring heteroatom (sulfur) and the peri protons since a knowledge of those factors controlling the stereochemistry in these systems should contribute to an elaboration of the mode of action in these drugs.[15] The purpose of this report is to present our findings with respect to the stereochemistry of 9-alkylthioxanthenes as evaluated by pmr spectroscopy (Table I).

Results and Discussion

Preferred Conformational Assignments. First, it seems desirable to comment upon the geometry of the parent compound, thioxanthene (**2**). The presence of molecular dipole moments for both 9,10-dihydroanthracene[16] and thianthrene [17] proves that these two compounds are nonplanar in solution and viewing thioxanthene as a composite of these two systems suggests that it should also be folded in solution.

The pmr spectrum of thioxanthene in carbon disulfide, even at −90°, consists of a complex aryl absorption and a singlet for the methylene protons. Analogous results have been reported for xanthene and acridan although acridan exhibited some broadening at low temperatures.[18] This result cannot be used to distinguish between a rapidly inverting system (hence, a diastereotopomerization[19]) and a static, planar one. More direct evidence for the existence of the shallow boat conformation was obtained from the magnitude of the C_9 geminal coupling constant. It has been previously demonstrated that the angle between the nodal plane of a π system and the H–C–H bond angle of a proximal methylene group should influence J_{gem}.[20] Barfield and Grant[20a] indicate that, when the nodal plane of a double bond bisects an adjacent H–C–H angle, J_{gem} should be maximal representing a presumably negatively signed contribution to a negatively signed J_{gem}. Their argument has been employed,[12] for example, to demonstrate central ring deformation in 9-*tert*-butyl-9,10-dihydroanthracene which is also supported by X-ray studies.[21] The planar molecule, fluorene, where the π system nodal plane bisects the meth-

Table I
Proton Magnetic Resonance Parameters[a] of Substituted Thioxanthenes of Type

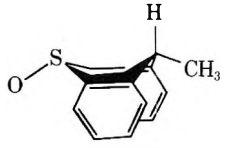


Compd	C9 R (H or CH3)	Cα H	Cβ H
Thioxanthene (**2**)	3.80[b,c]		
9-Methyl-T (**3**)	3.97[b,d] (7.0)	1.44[e] (7.0)	
9-Ethyl-T (**5**)	3.81[b,f] (7.2)	1.73[g,h]	0.80[f] (7.2)
9-Isopropyl-T (**6**)	3.50[b,e] (10.0)	2.22[g]	0.76[e] (6.4)
9-*tert*-Butyl-T (**7**)	3.79[b,c]		0.90[c]
9,9-Dimethyl-T	1.66[c]		
cis-9-Methyl-T 10-oxide (*cis*-**15**)	3.68[b,d] (7.0)	1.90[d]	
trans-9-Methyl-T 10-oxide (*trans*-**15**)	4.26[b,d] (7.0)	1.36[d]	
9-Methyl-9-ethyl-T (**12**)	1.82[c]	1.87[d,h] (7.6)	0.54[f] (7.6)
9-Methyl-9-isopropyl-T (**13**)	1.75[c]	2.85[i] (7.0)	0.41[e] (7.0)
1,4,9-Trimethyl-T (**8**)[j]	4.47[b,d] (7.1)	1.30[e] (7.1)	
1,4-Dimethyl-9-ethyl-T (**9**)[k]	4.16[b,d]	1.43–2.04[l]	0.79[g]
1,4-Dimethyl-9-isopropyl-T (**10**)[m]	3.93[b,e] (10.2)	~2.33[g]	0.74[e,n]
1,4-Dimethyl-9-*tert*-butyl-T (**11**)[o]	4.18[b,c]		0.90[c]

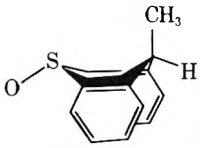
[a] Chemical shifts (δ) are reported in parts per million downfield from internal tetramethylsilane (TMS) and were obtained at 60 or 100 MHz (~30°); solvent is deuteriochloroform. Chemical shifts are followed by coupling constants (*J*) in hertz. [b] R = H. [c] Singlet. [d] Quartet. [e] Doublet. [f] Triplet. [g] Multiplet. [h] Methylene group. [i] Heptet. [j] C_1 CH_3, δ 2.43 ppm; C_4 CH_3, 2.39. [k] C_1 CH_3, δ 2.41 ppm; C_4 CH_3, 2.39. [l] Anisochronous methylene signals (see text for results of spin decoupling experiments). [m] C_1, C_4 CH_3, δ 2.39 ppm. [n] Isochronous methyl groups. [o] C_1 CH_3, δ 2.42 ppm; C_4 CH_3, 2.39.

ylene H–C–H bond angle and maximizes J_{gem}, has J_{gem} = −22.7 Hz.[22,23] We have determined J_{gem} for thioxanthene as −16.3 Hz at 40°. This observation is consistent with an π-orbital–methylene interaction that is less than that observed for fluorene and supports the view that thioxanthene is folded in solution.[24]

The chemical shift of a substituent at C_9 of the thioxanthene system is dependent on the conformational distribution [pseudo-axial (a′)/pseudo-equatorial (e′)] adopted by the molecule. For structurally similar compounds a′ substituents are generally shielded relative to their corresponding e′ counterparts, this effect being attributed, in the main, to the diamagnetic anisotropic influence of the aryl rings.[26] This proposition is supported by the relative chemical shifts of the C_9 methyl groups of the isomeric 9-methylthioxanthene 10-oxides (**15**).[14] For example, the cis diastereoisomer (*cis*-**15**)[27] exhibits its e′ methyl absorption at δ 1.90 and its a′ CH absorption at 3.68 ppm while the trans isomer (*trans*-**15**) displays an a′ methyl at δ 1.36 and



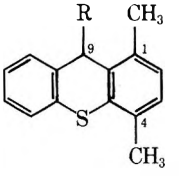
cis-(9e′,10e′)-**15**



trans-(9a′,10e′)-**15**

the corresponding CH methine at 4.26 ppm. The fact that the methyl groups of 9-methyl-T[14] and 9-methyl-9,10-dihydroanthracene[3b] become more shielded as the temperature decreases (*i.e.*, as *K* (= [a′]/[e′]) increases) also substantiates this view.

With this rather large disparity in chemical shift between the a′ and e′ methyl groups of the preferred conformers of the isomeric sulfoxides, it was clear to us that the preferred conformations of 9-methyl-T (**3**), 9-ethyl-T (**5**), 9-isopropyl-T (**6**), and 9-*tert*-butyl-T (**7**) could be convincingly established by comparing the pmr parameters of these compounds with those of appropriate models. It is also clear from an examination of Dreiding and Stuart–Briegleb molecular models that a methyl group at C_1 (peri position) would destabilize the equatorial position for any alkyl group. The model compounds chosen for this study were 1,4,9-trimethyl-T (**8**), 1,4-dimethyl-9-ethyl-T (**9**), 1,4-dimethyl-9-isopropyl-T (**10**), and 1,4-dimethyl-9-*tert*-butyl-T (**11**). The assignment of the a′ conformation to all



R = Me (**8**); Et (**9**); *i*-Pr (**10**); *t*-Bu (**11**)

the monoalkyl thioxanthenes reported herein was confirmed by comparison of the chemical shifts of the alkyl groups. Thus, the methyl group of 9-ethyl-T and its conformationally homogeneous (anancomeric[29]) counterpart[30] **9** absorb at δ 0.80 and 0.76, respectively.[31]

While these peri-substituted thioxanthene derivatives serve as structural models, only the chemical shift of the alkyl group is directly extrapolable between 9-alkyl-T and 1,4-dimethyl-9-alkyl-T. The chemical shift of C_9 H is deshielded in the model compounds presumably because of van der Waals steric compression.[32]

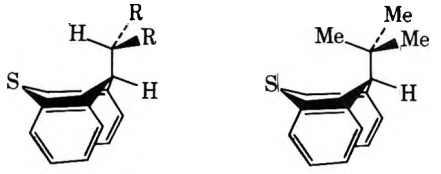
While the chemical shift of the C_9 proton proved to be of dubious value regarding conformational assignments, we chose to exploit the angular dependence documented for allylic couplings[33] hoping to gain further insight into conformational preferences in these systems which might be inaccessible from chemical shift correlations.

A proton bonded to C_9 and occupying the a′ conformation is properly oriented for strong long range coupling with the aryl protons. It has already been demonstrated[34] that the greatest effect results when the benzylic C–H bond lies perpendicular to the aromatic ring, thus allowing for efficient σ–π overlap. The coupling is identified by an increased broadening of the a′ proton absorption relative to the e′ and confirmation of this effect is obtained by multi-

ple irradiation techniques.[34] For example, it has been observed that the a′ proton in thioxanthene 10-oxide (**16**) sharpened by 41% during irradiation of the aryl protons while the e′ proton sharpened only 15%.[35] To a first approximation, it seemed reasonable to assume that an examination of the broadness (and sharpening) of the C_9 proton absorption for a number of 9-substituted thioxanthenes would indicate the position of that proton. The appropriate data for several 9-substituted thioxanthenes are summarized in Table II.[36,37]

It can be seen that the change in the band width at half height of the C_9 proton decreases in going from 9-methyl-T to 9-ethyl-T to 9-isopropyl-T but then increases to a value approximating that of **3** for 9-*tert*-butyl-T.

These data are interpreted in the following fashion. The methyl derivative **3** as already shown,[14] is quite clearly a mixture of a′ and e′ conformers, the half bandwidth of the C_9 proton reflecting this distribution. As the larger alkyl groups increasingly favor the a′ position, the half bandwidth decreases, thus reflecting the anticipated decrease in long range coupling to the aryl proton by the (now) e′ C_9 proton. In the *tert*-butyl derivative **7** transannular repulsion between the alkyl group and the sulfur atom may result in a flattening of the central ring.[38] Only in **7** (as compared to **3, 5,** and **6**) must a methyl group be proximal to the sulfur atom; in **3, 5,** and **6** a hydrogen atom may occupy this position.



3, 5, and **6** **7**

This flattening of the central ring in 9-*tert*-butyl-T causes a displacement of the C_9 H to a position which is more a′ in character with an apparent concommitant increase in its half bandwidth.

Zurcher[39] has suggested that methyl groups may be better conformational probes than single protons because of decreased sensitivity of methyl groups to minor geometric (and solvation) changes. With these points in mind we have prepared and examined the pmr spectra of 9-methyl-9-ethyl-T (**12**) and 9-methyl-9-isopropyl-T (**13**) to evaluate the efficacy of the chemical shift of the C_9 methyl group to serve as a conformational probe. Moreover, determination of the stereochemistry of these compounds will permit a testing of our conclusion that the larger alkyl group occupies the a′ conformation. Estimates of the anticipated chemical shifts of a′ and e′ C_9 methyl groups can be garnered from the pmr spectra of *cis*- and *trans*-9-methyl-T 10-oxides (**15**). These data suggest that a chemical shift of δ ~1.90 ppm may be considered representative of the e′ methyl group.

The chemical shift of the C_9 methyl group in 9-methyl-9-ethyl-T and 9-methyl-9-isopropyl-T correlate satisfactorily with the e′ methyl group of the cis sulfoxide **15** and this was considered a distinctive feature of an e′ conformation. This conclusion supports the view that the larger alkyl group prefers the a′ conformation.

A final, and direct, evaluation of the steric environment of the C_9 methyl group was obtained by establishing the presence of a spin-lattice relaxation mode between the C_9 methyl and the peri protons employing the nuclear Overhauser effect (NOE).[40]

The intensity enhancement measurements of the aryl absorptions while irradiating the C_9 methyl group clearly established the C_9 methyl as being proximal to the $C_{1,8}$ peri protons and therefore e′. Thus, while saturating the C_9 methyl absorption (δ 1.82 ppm) and observing the aromatic absorptions of 9-methyl-9-ethyl-T, a 21% increase in the integrated intensity of the low field aryl protons was observed.[41] In a similar experiment with 9-methyl-9-isopropyl-T, a 19% increase was observed.

Table II
Long Range Spin-Spin Decoupling of 9-Alkyl Thioxanthenes[a]

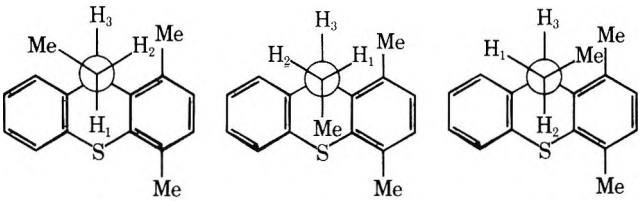
Compd	ω_2[b]	W_H[c]	W_H[d]	% change[e]
9-Methyl-T (**3**)	7.26–7	1.73	1.37	21 (±1.5)
9-Ethyl-T (**5**)	7.21–2	1.54	1.30	16 (±1.5)
9-Isopropyl-T (**6**)	7.16–8	1.62	1.40	14 (±1.5)
9-*tert*-butyl-T (**7**)	7.18–9	1.38	1.08	22 (±1.5)

[a] Decoupling experiments were performed at ambient temperature (~32°) at 100 MHz with deuteriochloroform as solvent. [b] Irradiating frequency, generated from an H.P. Model 200 CD wide range oscillator, in parts per million downfield from internal tetramethylsilane. [c] Band width at half height [hertz before irradiation of aryl region. Values are an average of 8 to 14 traces (sweep width 100 Hz, sweep time 100 sec)]. [d] Band width at half height during irradiation of the aryl region. Values are an average of 10 to 15 traces (sweep width 100 Hz, sweep time 100 sec). [e] Calculated from $\% = |(W_H{}^d - W_H{}^c)/W_H{}^c| \times 100$.

Rotameric Distribution. Although this report has centered upon the disposition of the C_9 meso substituent, the ethyl and isopropyl groups possess additional features which allow for an assessment of a preferred rotamer. Even though eclipsing interactions cannot be safely extrapolated from substituted ethanes to this system, it seems reasonable to assume that gauche conformers are lower in energy than eclipsed forms.

The C_9 proton of 1,4-dimethyl-9-ethyl-T appeared as a quartet reminiscent of unequal coupling from nearby vicinal methylene protons. The quartet pattern was consistent with vicinal coupling constants of 6.2 and 9.0 Hz.[42]

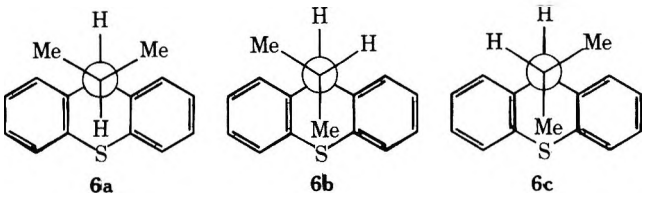
The relative magnitudes of the nonidentical vicinal coupling constants suggest (with the assistance of the Karplus relationship[43]) that a rotamer energetically similar to **9a** is favored. This also makes intuitive sense since in conformer **9b** transannular interactions between sulfur and the "inside" methyl group would be unfavorable and in **9c** methyl–



9a **9b** **9c**

methyl interactions (Dreiding molecular models) would afford considerable steric hindrance to this rotamer. Assuming 9-ethyl-T exists predominantly as rotamer **9a** or **9c** (without the 1,4-methyl groups),[44] conversion to the 9-ethyl-9-methyl derivative **12** should destabilize rotamer **9a** because of the extra methyl–methyl gauche interaction. The net observable effect should be an upfield shift of the methyl group (CH_3CH_2) since its average environment over the diamagnetic region of the aryl rings has increased. Thus, the methyl triplet of **12** occurs 0.25 ppm to higher field than the methyl triplet of 9-ethyl-T. Similarly, the deshielding of the methylene protons may be accounted for by removal of the methylene group from the shielding region of the aryl rings.[45]

Employing similar arguments, the most acceptable rotamer for 9-isopropyl-T appears to be **6a** since the populations of **6b** and its mirror image are presumably diminished by the sulfur–methyl interaction. Indeed, the isopropyl



6a **6b** **6c**

methyl resonance of **13** is 0.35 ppm upfield from the methyl signal of **6**. This is consistent with a rotamer whose average lifetime over the aryl rings has increased.

Additional, although indirect, information about the rotameric distribution of the isopropyl moiety was obtained by examining the pmr spectrum of 9-methyl-9-isopropyl-T 10,10-dioxide (**14**). In deuteriochloroform the pmr spectrum of **14** exhibited a singlet for the single methyl (δ 1.77 ppm), a multiplet for the isopropyl methine (2.84), and a doublet at 0.70 for the isopropyl methyls. The chemical shifts of the C_9 methyl and isopropyl methine are virtually equivalent in sulfide **13** and sulfone **14**; however, the isopropyl methyls are deshielded in the sulfone ($\Delta\delta$ = 0.29 ppm) relative to the disubstituted sulfide **13**. The conclusion is that both **13** and **14** exist in the a′ conformation and populate that rotamer in which the isopropyl methyls are proximal to the heteroatom (S and SO_2, respectively).

The temperature dependence of the pmr spectrum of 9-isopropyl-T has been examined and the results support these views. As the temperature is decreased (carbon disulfide solution) from +35 to −90° the vicinal coupling constant between the proton and the isopropyl methine changes from 9.52 ± 0.02 Hz to 10.24 ± 0.02 Hz, suggesting a small but increasing population of **6a**. As the temperature increases (tetrachloroethylene solution) from +35 to +120°, J_{vic} decreases from 9.33 Hz to 8.86 Hz, suggesting a decrease in the mole fraction of **6a**.

Experimental Section[46]

The preparation of thioxanthene (**2**), 9-methyl-T (**3**), and the *cis*- and *trans*-9-methyl-T 10-oxides (**15**) has been described elsewhere.[14]

9-Methyl-9-ethyl-T (12). A suspension of 9-methyl-T (4.10 g, 19.3 mmol) in 100 ml of anhydrous ether was cooled to 0–5° (ice bath) and then treated with 7.47 ml of a 22.3% solution of *n*-butyllithium in hexane. The resulting red suspension was allowed to warm to room temperature and then treated with a solution of ethyl iodide (3.10 g, 19.9 mmol) in 25 ml of ether: the heat resulting from the dropwise addition of the ethyl iodide solution was used to reflux the reaction mixture. The resulting suspension was stirred for ~12 hr and then diluted with water (100 ml). The ethereal solution was separated, washed with water (two 50-ml portions), dried ($MgSO_4$), and concentrated to 4.50 g of a yellow oil.

This yellow oil was column chromatographed (silica gel, hexane eluent), a procedure which served as a "rough" purification technique, to afford 4.26 g of crude product. Vacuum distillation gave 2.97 g (12.4 mmol, 66.2% yield) of the desired dialkyl sulfide **12**, bp 111–112° (0.33 mm).

Anal. Calcd for $C_{16}H_{16}S$: C, 79.84; H, 6.71; S, 13.34. Found: C, 79.82; H, 6.73; S, 13.23.

9-Methyl-9-isopropyl-T (13). A suspension of 9-methyl derivative **3** (3.50 g, 16.5 mmol) in 100 ml of ether was cooled to 0–5° (ice bath) and then treated with 6.75 ml of a 22.3% solution of *n*-butyllithium in hexane. After stirring for 10 min at room temperature, a solution of isopropyl bromide (2.01 g, 16.4 mmol) in 25 ml of ether was added to the suspension of the carbanion of **3**. The resulting suspension was stirred at room temperature for 10 hr and then diluted with water (100 ml). The ethereal layer was separated, washed with water (two 100-ml portions), dried ($MgSO_4$), and concentrated (stream of nitrogen gas) to afford an orange, viscous oil. Molecular distillation (60° at 0.1 mm) of this material afforded **13** as a clear light yellow liquid (4.10 g, 16.2 mmol, 99% yield). Thin layer chromatography indicated this material to be essentially homogeneous.

Anal. Calcd for $C_{17}H_{18}S$: C, 80.26; H, 7.13; S, 12.60. Found: C, 80.30; H, 7.19; S, 12.42.

9-Ethyl-T (5). A suspension of **2** (10.0 g, 50.0 mmol) in 200 ml of ether was cooled to 0–5° (ice bath) and then treated with 21 ml of a 22.3% solution of *n*-butyllithium in hexane. A solution of ethyl iodide (7.8 g, 50 mmol) in 25 ml of ether was added to the above suspension at 0–5°. The reaction mixture was refluxed for 13 hr and then diluted with water (50 ml). The organic phase was separated, washed with water (three 100-ml portions), and dried ($MgSO_4$) to afford a yellow liquid. This liquid was distilled to afford a light yellow oil which was essentially homogeneous to tlc: bp 133–141° (0.2 mm).[47] The results of several reactions indicate an average yield of ~90%.

Anal. Calcd for $C_{15}H_{14}S$: C, 79.60; H, 6.23; S, 14.16. Found: C, 79.42; H, 6.21; S, 13.92.

9-Isopropyl-T (6). A suspension of **2** (19.8 g, 100 mmol) in 400 ml of ether was cooled to 0–5° (ice bath) and then treated with 65 ml of 15.2% solution of *n*-butyllithium in hexane. This mixture was refluxed for 10 min then quenched with a solution of isopropyl bromide (12.3 g, 100 mmol) in 50 ml of ether. The resulting suspension was refluxed for 28 hr and then diluted with water (100 ml). The organic layer was separated, washed with water (two 100-ml portions), dried ($MgSO_4$), and concentrated (steam of nitrogen gas) to afford a red, viscous oil. This liquid was distilled (molecular distillation at 40–45° and 0.05 mm) to afford 17.3 g (72.2 mmol, 72% yield) of a white, crystalline solid, mp 50–51°.

Anal. Calcd for $C_{16}H_{16}S$: C, 79.94; H, 6.71; S, 13.34. Found: C, 79.75; H, 6.80; S, 13.18.

9-*tert*-Butyl-T (7). A solution of *tert*-butyllithium (10.7 ml of a 1.24 *M* solution) was added to a suspension of thioxanthylium perchlorate[48] (4.00 g, 13.5 mmol) in 150 ml of ether at 0–5°. The reaction mixture was stirred for 2 hr and then at room temperature for 7 hr. Water (20 ml) was added to this suspension and the organic layer separated. The organic layer was dried ($MgSO_4$) and concentrated (rotary evaporator) to afford 2.92 g of an oily solid. Glpc[49] indicated the presence of two components, one of which (35%) was identified as thioxanthene[50] by comparison with an authentic sample. Column chromatography (silica gel, hexane eluent) of this oily material afforded 1.23 g (48.4 mmol, 35.9%) of the desired product, mp 156–157°.

Anal. Calcd for $C_{17}H_{18}S$: C, 80.26; H, 7.13; S, 12.60. Found: C, 80.40; H, 7.27; S, 12.30.

1,4-Dimethylthioxanthone. *o*-Xylene (1.00 kg, 9.43 mol) was added, dropwise and with stirring, to a cold (0–5°) suspension of 300 g (1.98 mol) of thiosalicylic acid in 900 ml of concentrated sulfuric acid. Stirring was continued for ~1 hr at room temperature after which the reaction mixture was refluxed for ~5 hr. The resulting dark red suspension was stirred for ~14 hr at room temperature. The acidic suspension was poured, in 300-ml portions, over ice (~2 kg per portion) and each resulting suspension was further diluted with ~3 l. of water. Filtration of each suspension afforded a yellow solid which was then suspended in a saturated solution of sodium bicarbonate (~150 ml). The resulting suspensions were extracted with chloroform and the combined organic phase dried ($MgSO_4$) and concentrated to afford a yellow solid, mp 103–106°.

Recrystallization of the crude product from 95% ethanol afforded 382 g (1.59 mol, 83.5% yield) of product, mp 112.5–113.0° (lit.[51] mp 112°).

1,4-Dimethyl-T.[52] Diborane, produced by the reaction of 5.10 g (135 mmol) of sodium borohydride with 28.5 g (200 mmol) of boron trifluoride etherate, was passed through a suspension of 1,4-dimethylthioxanthone (48.1 g, 223 mmol) in 350 ml of tetrahydrofuran cooled to 0–5° (ice bath). The resulting solution was poured over ~1.5 kg of ice, mixed, and then allowed to stand overnight. The resulting solid was extracted with chloroform; the chloroform solution was separated, dried, and then concentrated (rotary evaporator) to afford an off-white solid. This material was sublimed (70° at 0.1 mm) to afford 36.6 g (181 mmol, 82%) of 1,4-dimethylthioxanthene, mp 80–81°.

Anal. Calcd for $C_{15}H_{14}S$: C, 79.60; H, 6.23; S, 14.16. Found: C, 79.83; H, 6.43; S, 14.18.

1,4,9-Trimethyl-T (8). A solution of 1,4-dimethyl-T (5.00 g, 24.7 mmol) in ether (200 ml) was cooled to 0–5° (ice bath) and treated with 10.33 ml of a solution containing 25 mmol of *n*-butyllithium in *n*-hexane. To the resulting red suspension there was then added, at 0–5°, a solution of methyl iodide (3.55 g, 25 mmol) in 10 ml of ether. The resulting light orange solution was stirred at

25° for 24 hr and then diluted with 100 ml of water. The organic layer was separated, dried ($MgSO_4$), and then concentrated to 5.25 g of a light yellow oil (rotary evaporator). This oil was chromatographed (silica gel, hexane eluent) to afford 5.17 g (24.2 mmol, 98%) of the desired product.

The pmr spectrum was completely consistent with the assigned structure. The mass spectrum (70 eV) displayed the molecular ion at *m/e* 240 (calcd 240 for $C_{16}H_{16}S$).

1,4-Dimethyl-9-ethyl-T (9). A solution of 1,4-dimethyl-T (5.00 g, 24.7 mmol) in 150 ml of ether was cooled to 0–5° (ice bath) and treated with 10.33 ml of a solution of *n*-butyllithium (25 mmol) in *n*-hexane. To the resulting red suspension there was added (at 0–5°) a solution of 3.87 g (24.8 mmol) of ethyl iodide in ether (15 ml). After ~0.5 hr at 0–5° the reaction mixture was warmed to 25° and then maintained at this temperature for 22 hr. The reaction mixture was then diluted with water (~50 ml) and the organic layer separated. The organic layer was washed with water, dried ($MgSO_4$), and concentrated (rotary evaporator) to afford a 5.57 g of an orange oil. This oil was chromatographed (silica gel, *n*-hexane eluent) to afford the desired product (5.49 g, 24.2 mmol, 98%) as a colorless oil.

Anal. Calcd for $C_{17}H_{18}S$: C, 80.26; H, 7.13; S, 12.60. Found: C, 80.25; H, 7.17; S, 12.30.

1,4-Dimethyl-9-isopropyl-T (10). A solution of 1,4-dimethyl-T (5.00 g, 24.7 mmol) in ether (150 ml) was cooled to 0–5° (ice bath) and treated with 10.33 ml of a solution of 25 mmol of *n*-butyllithium in hexane. To the resulting red suspension there was added, after ~10 min a solution of isopropyl bromide (3.00 g, 24.4 mmol) in ether (25 ml). After stirring for 20 min at 0–5°, the reaction mixture was stirred for 3 days at 25°. The resulting yellow solution was diluted with water (80 ml) and the organic layer separated and dried ($MgSO_4$). Concentration (rotary evaporator) of this solution afforded 5.89 g of an orange oil. "Sublimation" of this oil at 45–50° (0.03 mm) gave 5.80 g (24 mmol, 98% yield) of the desired product as a white, crystalline solid, mp 59–60°.

Anal. Calcd for $C_{18}H_{20}S$: C, 80.55; H, 7.51; S, 11.94. Found: C, 80.75; H, 7.70; S, 12.16.

1,4-Dimethyl-9-*tert*-butyl-T (11). The title compound was prepared in a manner similar to that used to prepare **7**. The product was obtained in low yield (<15%), mp 115–116°. This material was homogeneous on thin layer chromatography and exhibited a pmr spectrum totally consistent with the assigned structure.

Anal. Calcd for $C_{19}H_{22}S$: S, 11.35. Found: S, 11.19.

9-Methyl-9-isopropyl-T 10,10-Dioxide (14). Oxidation of sulfide **13** with an excess of hydrogen peroxide (30%) in refluxing acetic acid gave sulfone **14** in 90% yield, mp 82–83°. This material was homogenous on tlc and possessed a pmr spectrum totally consistent with the assigned structure. The ir spectrum (Nujol) exhibited strong absorptions at 1297 and 1161 cm^{-1} (SO_2) and other strong bands at 779, 760, and 731 cm^{-1}.

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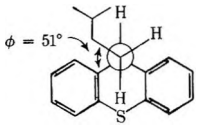
Registry No. 2, 261-31-4; **3,** 16860-11-0; **5,** 28612-38-6; **6,** 28612-39-7; **7,** 28612-40-0; **8,** 51966-06-4; **9,** 51966-07-5; **10,** 51966-08-6; **11,** 51966-09-7; **12,** 51966-10-0; **13,** 51966-11-1; **14,** 51966-12-2; *cis*-**15,** 19018-80-5; *trans*-**15,** 19018-81-6; thioxanthylium perchlorate, 2567-20-6; 1,4-dimethyl-T, 17394-13-7; 1,4-dimethylthioxanthone, 25942-61-4; 9,9-dimethyl-T, 19019-10-4.

References and Notes

(1) A portion of this work was completed at Case Western Reserve University, Cleveland, Ohio 44106, and Dartmouth College, Hanover, N. H. 03755.
(2) (a) The University of Texas at Arlington. (b) Dartmouth College.
(3) (a) A. H. Beckett and B. A. Mulley, *Chem. Ind. (London)*, 146 (1955); *J. Chem. Soc.*, 4159 (1955). (b) M. L. Casper, J. N. L. Casper, J. N. Seiber, and K. Matsumoto, Abstracts, 146th National Meeting of the American Chemical Society, Denver, Colo., 1964, p 30C. (c) W. Carruthers and G. E. Hall, *J. Chem. Soc. B*, 861 (1966). (d) D. Nicholls and M. Szwarc, *J. Amer. Chem. Soc.*, **88,** 5757 (1966); *Proc. Roy. Soc., Ser. A*, **301,** 231 (1967). (e) R. G. Harvey, L. Arzadon, J. Grant, and K. Urberg, *J. Amer. Chem. Soc.*, **91,** 4535 (1969). (f) A. W. Brinkmann, M. Gordon, R. G. Harvey, P. W. Rabideau, J. B. Stothers, and A. L. Ternay, Jr., *ibid.*, **92,** 5812 (1970). (g) H. E. Zieger and L. T. Gelbaum, *J. Org. Chem.*, **37,** 1012 (1972).
(4) J. Chickos and K. Mislow, *J. Amer. Chem. Soc.*, **85,** 594 (1963).
(5) A. L. Ternay, Jr., and D. W. Chasar, *J. Org. Chem.*, **33,** 3814 (1967); A. L. Ternay, Jr., D. W. Chasar, and M. Sax, *ibid.*, **32,** 2465 (1967); O. Schindler, H. Lehner, W. Michaelis, and J. Schmutz, *Helv. Chim. Acta*, **46,** 1097 (1963); W. Michaelis, O. Schindler, and R. Signer, *ibid.*, **49,** 42 (1966); K. K. Andersen, M. Cinquini, and N. E. Papanikolaou, *J. Org. Chem.*, **35,** 706 (1970).
(6) D. W. Allen, J. C. Coppola, O. Kennard, F. G. Mann, W. D. S. Motherwell, and D. G. Watson, *J. Chem. Soc., C*, 810 (1970).
(7) M. Davis and F. G. Mann, *Chem. Ind. (London)*, 1539 (1962); *J. Chem. Soc.*, 3770 (1964). F. G. Mann, *ibid.*, 4266 (1963).
(8) G. A. Taylor and S. A. Procter, *Chem. Commun.*, 1379 (1969); G. A. Taylor and S. A. Procter, *J. Chem. Soc. C*, 2537 (1971).
(9) (a) A. K. Chandra, *Tetrahedron*, **19,** 471 (1963); (b) P. T. Lansbury, *Accounts Chem. Res.*, **2,** 210 (1969); D. M. Wieland and C. G. McCarty, *J. Org. Chem.*, **37,** 4285 (1972); K. Mislow, A. Zimmerman, and J. T. Melillo, *J. Amer. Chem. Soc.*, **85,** 594 (1963).
(10) Assuming that the transition state for interconversion is planar, or nearly so, all of the internal angles of the central ring would approximate 120° in the transition state. The four trigonal carbon atoms of the central ring already possess this requisite geometry in the ground state of the molecule. Introduction of heteroatoms into the meso positions may alter the magnitude of the barrier by delocalization[11] and increased (or decreased) angle strain effects.
(11) Cf. C. Müller, A. Schweig, and W. L. Mock, *J. Amer. Chem. Soc.*, **96,** 280 (1974).
(12) A. L. Ternay, Jr., A. Brinkmann, S. Evans, and J. Herrmann, *Chem. Commun.*, 654 (1969).
(13) Thioxanthene will be abbreviated as T throughout this report.
(14) A. L. Ternay, Jr., L. Ens, S. Evans, and J. Herrmann, *J. Org. Chem.*, **34,** 940 (1969).
(15) See A. Goldstein, L. Aronow, and S. M. Kalman, "Principles of Drug Action," Harper and Row, New York, N. Y., 1969.
(16) I. G. M. Campbell, C. G. LeFevre, J. J. W. LeFevre, and E. E. Turner, *J. Chem. Soc.*, 404 (1938).
(17) E. Bergmann and M. Tschudnowsky, *Chem. Ber.*, **65,** 457 (1932).
(18) Z. Aizenshtat, E. Klein, H. Weiler-Fielchenfeld, and E. D. Bergmann, *Israel J. Chem.*, **10,** 753 (1972).
(19) G. Binsch, E. L. Eliel, and H. Kessler, *Angew. Chem.*, **83,** 618 (1971); *Angew. Chem., Int. Ed. Engl.*, **10,** 570 (1971).
(20) (a) M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, **85,** 1899 (1963); (b) A. A. Bothner-By, *Advan. Magn. Res.*, **1,** 195 (1965).
(21) T. Brennan, E. F. Putkey, and M. Sundaralingam, *Chem. Commun.*, 1490 (1971).
(22) Calculated from $^2J_{HH} = {}^2J_{HD}/0.154$ where $^2J_{HD}$ was found to be 3.50 Hz at ~40°; see also Ch. Brevard, J. P. Kintzinger, and J. M. Lehn, *Chem. Commun.*, 1193 (1969).
(23) A value of −22.3 Hz has been reported for fluorene at 30°: R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron, Suppl.*, **No. 7,** 355 (1966).
(24) This result is in harmony with the report by Aroney, *et al.*,[25a] which reveals a folded conformation (dihedral angle of 135 ± 8°) for thioxanthene in carbon tetrachloride and benzene solution as deduced from molecular polarizability data. Gillean, *et al.*,[25b] also report a folded conformation for **2** (dihedral angle = 135.3°) from X-ray data.
(25) (a) M. J. Aroney, G. M. Hoskins, and R. J. W. LeFevre, *J. Chem. Soc. B*, 980 (1969); (b) J. A. Gillean, III, D. W. Phelps, and A. W. Cordes, *Acta Crystallogr.*, **B29,** 2296 (1973).
(26) (a) C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29,** 1012 (1958); D. Y. Curtin, C. G. Carlson, and C. G. McCarty, *Can. J. Chem.*, **42,** 565 (1964). (b) For other examples, see D. W. Chasar, *Diss. Abstr. Int. B*, **30,** 116 (1969).
(27) It is noteworthy that Jackobs and Sundaralingam have shown that the isomer assigned the cis configuration (9e′,10e′) by pmr spectroscopy possesses an equivalent conformation in the solid state.[28]
(28) J. Jackobs and M. Sundaralingam, *Acta Cryst.*, **B25,** 2487 (1969).
(29) M. Anteunis, D. Tavernier, and F. Borremans, *Bull. Soc. Chim. Belg.*, **75,** 396 (1966).
(30) The C_9 methyl resonance of **8** was practically invariant in carbon disulfide solution from +35 to −90°. This observation is in contradistinction to the temperature dependence exhibited by 9-methyl-T.[14]
(31) It is perhaps noteworthy that under the conditions of the pmr experiment (100 MHz, 30°, $CDCl_3$) the isopropyl methyls of **10** were isochronous while those considered in 2-chloro-9-isopropyl-T (in a different investigation) were anisochronous.
(32) For examples, see W. Nagata, T. Terisawa, and K. Tori, *J. Amer. Chem. Soc.*, **86,** 3746 (1964); S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *ibid.*, **87,** 5247 (1965).
(33) For a recent review of long range coupling phenomena, see S. Sternhell, *Quart. Rev.*, **23,** 236 (1969).
(34) P. T. Lansbury, J. F. Bieron, and A. J. Lacher, *J. Amer. Chem. Soc.*, **88,** 1482 (1966).
(35) L. A. Ens, *Diss. Abstr. Int. B.*, **30,** 4041 (1970).
(36) A. L. Ternay, Jr. and S. Evans, *Chem. Commun.*, 407 (1970).
(37) Decoupling procedures were attempted throughout the entire aromatic region; the values presented in Table II represent the frequency showing the maximal effect.
(38) A related phenomenon has been observed in the 9,10-dihydroanthracene series.[12]

(39) R. F. Zurcher in "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol. II, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Ed., Pergamon Press, New York, N. Y., 1967, Chapter 5, especially p 212.
(40) For excellent reviews, see G. E. Bachers and T. Schaffer, *Chem. Revs.*, **71**, 617 (1971); J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect," Academic Press, New York, N. Y., 1971; R. A. Bell and J. K. Saunders, *Topics Stereochem.*, **7**, 1 (1973).
(41) NOE values represent the average of ~8–10 determinations and are considered reproducible to ±5% of the given value.
(42) Confirmation of these values was obtained by irradiating the methyl resonance (δ 0.79 ppm) of the ethyl group causing the complex methylene region to collapse to an eight-line spectrum. The four-line, low field segment was consistent with a vicinal coupling of 6.2 Hz while the more shielded component gave 9.0 Hz.
(43) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963), and references therein.
(44) The results of an X-ray study on 9-isobutyl-T indicate that in the solid state the isobutyl group is in the pseudo-axial conformation and describes a torsional angle about the thioxanthene frame of 51°. See S. S. C. Chu, *Acta Crystallogr.*, **B29**, 1690 (1973), and S. S. C. Chu and B. Chung, *ibid.*, **B29**, 2253 (1973), and references contained therein.



(45) It is recognized that other factors may also contribute to these changes in relative chemical shifts (*vide supra*).
(46) All melting points were obtained in a Mel-Temp apparatus (open capillary) and are corrected. Pmr spectra were recorded on Varian Models HA-100 and A-60 nmr spectrometers in deuteriochloroform unless otherwise indicated. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Crobaugh Laboratories, Cleveland, Ohio. All compounds were shown to be a homogeneous by thin layer chromatography (silica gel substrate) on glass plates using ethyl acetate or chloroform as eluents and with uv and iodine vapor for visualization. Mass spectra were obtained on a Varian Model M-66 mass spectrometer. Ir spectra were recorded using a Beckman Model IR-8 spectrophotometer. All alkylation reactions were carried out in a nitrogen atmosphere.
(47) On standing this material eventually solidified to produce an off-white solid, mp 42–43°.
(48) C. C. Price, M. Hori, T. Parasaran, and M. Polk, *J. Amer. Chem. Soc.*, **85**, 2278 (1963).
(49) 3 ft × ¼ in. aluminum column, 20% SE-30 on Aeropak.
(50) Thoxanthene is presumed to arise *via* a hydride transfer reaction from *tert*-butyllithium to the thioxanthylium ion. Attempted preparations of **7** by the direct alkylation of the thioxanthyl anion with *tert*-butyl halides have been unsuccessful thus far.
(51) E. G. Marsden and S. Smiles, *J. Chem. Soc.*, 1353 (1911).
(52) The reaction is similar to that already described[14] for the reduction of 1-methyl-4-chlorothioxanthone to 1-methyl-4-chlorothioxanthene.

Syntheses of Cyclic Bisthioacylals. 1,3-Dithiane-4,6-diones and 1,3-Dithiolane-4,5-dione[1]

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Reaction of bisthiomalonic acids **1a,b** with isopropenyl acetate gave thietanediones **3a,b** and thioacetone *via* Grob fragmentation (Scheme I, path a). When bisthio acid **1a** was treated with carbonyl compounds (acetone, acetaldehyde, acetophenone, and benzophenone) and boron trifluoride etherate, **3a** was again obtained (path a) except in the case of *p*-anisaldehyde, where path b was competitive and the 1,3-dithiane-4,6-dione **4c** was also obtained. Treatment of the pyridinium salt of **1a** with methylene iodide or dichlorodiphenylmethane also gave **3a**. The title compounds (**7a, 8c,d,f–i**) were alternately prepared by condensation of oxalyl, malonyl, and certain substituted malonyl halides with *gem*-dithiols. Selective methylation of compounds **8d, 8e,** and **8g** at C-2 and/or C-5 was achieved.

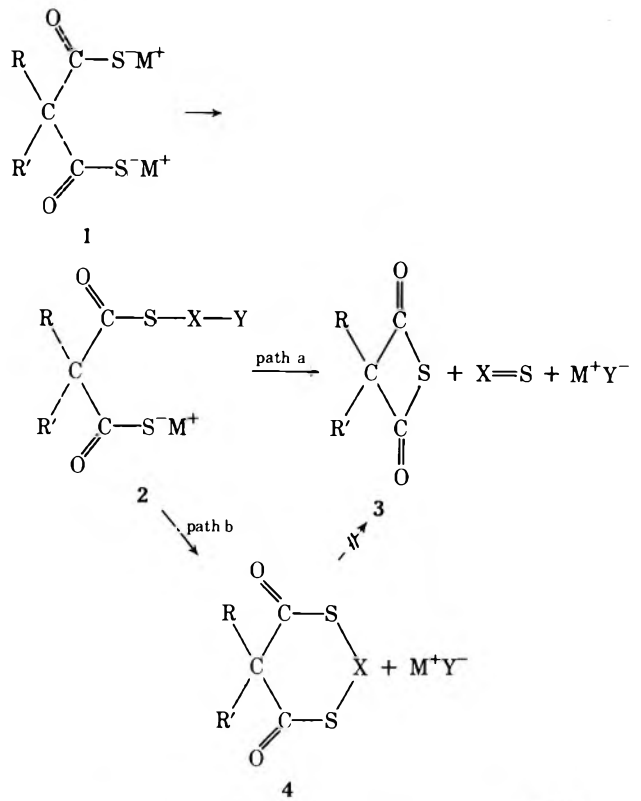
Although 1,3-dioxane-4,6-diones such as Meldrum's acid (**8a**) and a number of its derivatives have received considerable attention,[2] the 1,3-dithio analogs have not been studied. Herein we report the results of investigations into synthetic approaches to these sulfur heterocycles.

Reaction of dimethylmalonic acid with isopropenyl acetate catalyzed by sulfuric acid is known to give 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (**8b**).[2a] In contrast, we have observed that reaction of dimethylbisthiomalonic acid (**1a**) or cyclobutane-1,1-bisthiodicarboxylic acid (**1b**) with isopropenyl acetate under similar conditions afforded the thietanes **3a** and **3b**, respectively, plus thioacetone. This apparently occurs *via* Grob fragmentation[3,4] of the expected intermediates **2a** and **2b** (Scheme I, path a) rather than ring closure to the 1,3-dithiane-4,6-diones (**4a, 4b,** path b). The latter compounds have been synthesized alternately (*vide infra*) and are stable both thermally and toward sulfuric acid, thus excluding them as intermediates to the thietanediones. The possibility that the thietanediones **3a** and **3b** might form directly by acid-catalyzed loss of hydrogen sulfide from the bisthio acids was also ruled out. Thus, the bisthio acids **1a** and **1b** underwent only slow loss of carbonyl sulfide in the presence of sulfuric acid.

Reaction of dimethylbisthiomalonic acid with *p*-anisaldehyde and boron trifluoride etherate in refluxing methylene chloride solution[5] again provided the thietanedione **3a;** however, it was accompanied by 2-(*p*-anisyl)-5,5-dimethyl-1,3-dithiane-4,6-dione (**4c**) in 26% yield. In this case reaction *via* **2c** (Scheme I, path b) apparently competes with Grob fragmentation (path a) and both products are observed. Since **4c** was thermally stable at its melting point (119–124°) it was considered an unlikely precursor to the thietanedione.

Formation of the bisthioacylal **4c** from dimethylbisthiomalonic acid and anisaldehyde–boron trifluoride prompted us to examine such reactions with other carbonyl compounds. Reaction of the bisthio acid with benzophenone or acetone and boron trifluoride gave only thietanedione accompanied by thiobenzophenone or thioacetone, respectively. Similar reactions with acetophenone and with acetaldehyde also netted some thietanedione **3a** (glpc, nmr) but again none of the bisthioacylals (**4f, 4g**). When

Scheme I

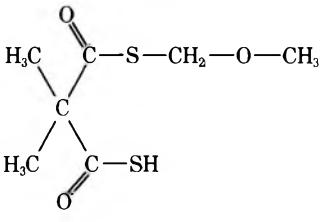


1 2 3 4

$R = R' = CH_3$, except for **1b–4b** for which R, $R' = (CH_2)_3$

	M^+	X	Y
a	H^+	$C(CH_3)_2$	OAc
b	H^+	$C(CH_3)_2$	OAc
c	H^+	$CH(p\text{-}C_6H_4OCH_3)$	OBF_3^-
d	H^+	CPh_2	OBF_3^-
e	H^+	$C(CH_3)_2$	OBF_3^-
f	H^+	CCH_3Ph	OBF_3^-
g	H^+	$CHCH_3$	OBF_3^-
h	H^+	CH_2	$OCH_3BF_3^-$
i	PyH^+	CH_2	I
j	PyH^+	CPh_2	Cl

methylal–boron trifluoride was employed as the electrophilic reagent, **3a** was accompanied by an isolable, unstable compound which was assigned structure **5** on the basis of ir



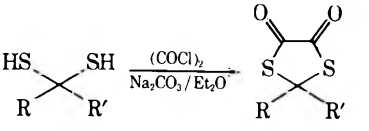
5

and nmr spectral data. This structure, of course, represents the uncomplexed form of intermediate **2h.**

The unique formation of bisthioacylal **4c** from the anisaldehyde–boron trifluoride reaction was quite striking. It appears likely that competitive formation of **4c** may result from a fortuitous combination of enhanced carbonium ion stabilization coupled with a sufficiently low steric factor to permit ring closure *via* path b, Scheme I.

An attempt to prepare 5,5-dimethyl-1,3-dithiane-4,6-dione (**4i**) by reaction of the pyridinium salt of dimethylbisthiomalonic acid with methylene iodide yielded thietanedione **3,** presumably by loss of thioformaldehyde[6] and iodide ion. Likewise, reaction of the pyridinium salt of the bisthio acid with dichlorodiphenylmethane netted thietanedione and thiobenzophenone.[7] These reactions are also explained *via* path a, Scheme I (intermediates **2i, 2j**).

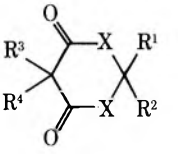
Although 1,3-dithiane-4,6-diones were not generally accessible *via* the bisthiomalonic acids, these compounds have been synthesized alternately. In 1962, Jentzsch, Fabian, and Meyer reported the synthesis of three 1,3-dithiolane-4,5-diones (**7b–d**) by condensation of the *gem*-dithiols



6 7

a, $R = R' = H$
b, $R = R' = CH_3$
c, R, $R' = (CH_2)_4$
d, R, $R' = (CH_2)_5$

6b–d with oxalyl chloride.[8] We have further investigated this reaction with the hope of extending it to the synthesis of other five- to seven-membered ring bisthioacylals. Although it appears to be of rather limited scope, we have utilized it for preparation of the parent, 1,3-dithiolane-4,5-dione (**7a**), and certain 1,3-dithiane-4,6-diones (**8c,d,f–i**).



8

Compd	X	R^1	R^2	R^3	R^4
a	O	CH_3	CH_3	H	H
b	O	CH_3	CH_3	CH_3	CH_3
c	S	H	H	H	H
d	S	H	H	CH_3	H
e	S	CH_3	H	H	H
f	S	CH_3	CH_3	H	H
g	S	CH_3	CH_3	CH_3	H
h	S	H	H	$CH_2CH_2CH_2$	
i	S	$CH_2CH_2CH_2$		$CH_2CH_2CH_2$	
j	S	CH_3	CH_3	=CHPh	
k	S	CH_3	CH_3	$=CH(p\text{-}C_6H_4NO_2)$	

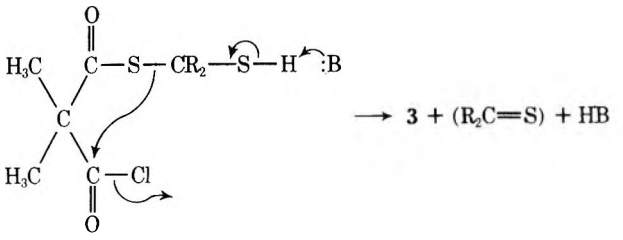
1,3-Dithiolane-4,5-dione (**7a**) was obtained by reaction of oxalyl bromide with methanedithiol and pyridine in ether solution. Use of pyridine rather than anhydrous sodium carbonate resulted in a marked acceleration of the reaction rate and avoided side reactions due to hydrogen bromide (which was not effectively removed by sodium carbonate).

Reaction of malonyl chloride with methanedithiol in chloroform (room temperature) resulted in evolution of hydrogen chloride which continued for ~1.5 hr. Work-up at that time provided 1,3-dithiane-4,6-dione (**8c**) in 53% yield; however, when the reaction was continued for several hours longer, only intractable material could be isolated. Addition of either pyridine or sodium carbonate to the reaction mixture caused a decrease to <5% in yield.

Reaction of methyl- or dimethylmalonyl chloride or cyclobutane-1,1-dicarboxylic acid chloride with methanedithiol in chloroform did not provide the 5-substituted 1,3-dithiane-4,6-diones (**8d, 4h, 8h**); however, **8d** and **8h** were obtained in 19 and 51% yields, respectively, when the reactions were carried out in the presence of 2 equiv of pyridine.

Examination of the crude products from reaction of dimethylmalonyl chloride with methanedithiol in the absence of pyridine revealed the formation of dimethylthie-

tanedione 3 in low yield, presumably *via* Grob fragmentation of intermediate **9a** with loss of thioformaldehyde and hydrogen chloride.



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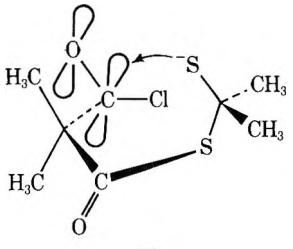
a, R = H; B = Cl^-
b, R = CH_3; B = pyridine

2,2-Dimethyl-1,3-dithiane-4,6-dione (**8f**) and its 5-methyl derivative **8g** have been obtained in 50 and 37% yields by reaction of malonyl chloride or methylmalonyl chloride, respectively, with propane-2,2-dithiol and sodium carbonate in ether solution. These products were accompanied by 2,2,4,4,6,6-hexamethyl-1,3,5-trithiane, which results from hydrogen chloride catalyzed reaction of propane-2,2-dithiol. Attempts to carry out these reactions in the presence of pyridine resulted in intractable products.

2,2,5,5-Tetramethyl-1,3-dithiane-4,6-dione (**4a**) was not accessible by reaction of dimethylmalonyl chloride and propane-2,2-dithiol with sodium carbonate in ether solution. When pyridine was employed as the base, dimethylthietanedione (3) was again identified, apparently *via* Grob fragmentation of intermediate **9b**. It is to be expected that attack of the SH or Ssupn− group of propane-2,2-dithiol on the carbonyl group of dimethylmalonyl chloride would be sterically hindered owing to methyl–methyl and methyl–sulfur interactions, especially during ring closure, depicted in structure **10**. Cyclobutane-1,1-dicarboxylic acid chloride



10

was expected to exhibit a smaller steric effect than dimethylmalonyl chloride; however, reaction of the cyclobutane-1,1-dicarboxylic acid chloride with propane-2,2-dithiol in the absence or presence of pyridine failed to provide the 1,3-dithiane-4,6-dione (**4b**). Interestingly, when the steric requirement of the dithiol moiety was also decreased by use of cyclobutane-1,1-dithiol, the 1,3-dithiane-4,6-dione **8i** was obtained in 39% yield.

By analogy to the unusual acidity exhibited by Meldrum's "acid" (**8a**),[2a] the 1,3-dithiane-4,6-diones **8c,d** and **8e–g** possessing hydrogen at the 5 position are soluble in 5% sodium bicarbonate solution.

The potassium enolate of 2,2-dimethyl-1,3-dithiane-4,6-dione (from **8f** and potassium hydride in DMF) underwent methylation to provide **8g** in very low yield; however, the enolates derived from **8d** and **8g** with sodium hydride in DMF proved to be more reactive, yielding **4h** and **4a** in yields of 63 and 42%, respectively.

It was anticipated that the dianion resulting from deprotonation of the 1,3-dithiane-4,6-dione system at C-2 and C-5 could be utilized to effect selective alkylation at the 2 position. Treatment of **8c** with 2 mol of *tert*-butyllithium or *n*-butyllithium in THF solution, followed by methylation with methyl iodide, did afford the 2-methyl compound **8e**, albeit only in very low yield. Although a large amount of starting material was recovered, 5-methylated products were not observed.

Shuster, *et al.*, condensed Meldrum's acid (**8a**) with various substituted benzaldehydes using Knoevenagel conditions.[9] In a similar manner the 1,3-dithiane-4,6-dione **8f** condensed with benzaldehyde to yield the benzylidene derivative fb8j in 11% yield. *p*-Nitrobenzaldehyde yielded none of the benzylidene derivative **8k**.

Experimental Section

General. Spectral, microanalytical, and yield data and melting points and/or boiling points for new compounds are listed in Table I.

Nmr spectra were recorded with a Varian Associates A-60 spectrometer on $CDCl_3$ and benzene-d_6 solutions. Chemical shifts are reported in δ units (parts per million) downfield from internal tetramethylsilane. Ir spectra were obtained on KBr disks (unless noted otherwise in Table I) with a Perkin-Elmer Model 337 grating spectrophotometer. Glpc was carried out on a Hewlett-Packard F & M Model 700 instrument, employing a 6 ft × 0.25 in. stainless steel column packed with 10% SE-30 on silanized 60–80 mesh Chromosorb W. Tlc was performed on Quantum Industries Q1F plates. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points and boiling points are uncorrected.

Oxalyl bromide and malonyl chloride (Aldrich Chemical Co.), 98% boron trifluoride etherate (Matheson Coleman and Bell), *n*-butyllithium (Foote Mineral Co.), and potassium hydride and sodium hydride (Ventron Corp.) were used as received. Methanedithiol (**6a**),[10,11] propane-2,2-dithiol (**6b**),[8] cyclobutane-1,1-dithiol,[12] methylmalonyl chloride,[13] dimethylmalonyl chloride,[14] cyclobutane-1,1-dicarboxylic acid chloride,[15] dimethylbisthiomalonic acid (**1a**),[16] and cyclobutane-1,1-bisthiodicarboxylic acid (**1b**)[16] were prepared according to literature procedures.

Reaction of Dimethylbisthiomalonic Acid (1a) and Cyclobutane-1,1-bisthiodicarboxylic Acid (1b) with Isopropenyl Acetate. To 10 mmol of **1a** or **1b** in 10 mmol of isopropenyl acetate was added dropwise, with stirring, 0.1 ml of concentrated H_2SO_4. After stirring at room temperature for 24 hr the reaction mixture was distilled. In the case of **1b**, 0.79 g (56%) of 3,3-trimethylenethietanedione (**3b**), bp 40° (0.5 mm), was obtained, accompanied by the characteristic vile odor of thioacetone. When **1a** was employed, 0.65 g (50%) of 3,3-dimethylthietanedione (**3a**), bp 85° (16 mm), was obtained, also accompanied by the stench of thioacetone. The thietanediones **3a** and **3b** were identified by comparison of their ir and nmr spectra and glpc retention times with those for authentic samples.[16]

Stability of 1a to Sulfuric Acid or Boron Trifluoride Etherate. To 0.5 ml of a saturated solution of concentrated H_2SO_4 in benzene-d_6 in an nmr tube was added 50 mg of pure **1a**. No changes were observed in the nmr spectra obtained on this sample over a 15-hr period.

An 82-mg sample of **1a** and an equimolar amount of boron trifluoride etherate in 0.25 ml of CH_2Cl_2 in an nmr tube was heated at 62° for 2 hr. The solvent was removed. Nmr (benzene-d_6) showed only **1a** and a trace of thietane-2,4-dione (**3a**).

2-(*p*-Anisyl)-5,5-dimethyl-1,3-dithiane-4,6-dione (4c). Anisaldehyde (272 mg, 2.0 mmol) and **1a** (352 mg, 2.0 mmol) were combined, under nitrogen, in 10 ml of methylene chloride. The mixture was refluxed for 2 hr, cooled to room temperature, washed with two 30-ml portions of 2% Na_2CO_3 solution, dried ($MgSO_4$), and filtered. The filtrate was evaporated to yield a red oil which crystallized. Sublimation of the crude product at 135° (0.05 mm) gave 148 mg of **4c**. Recrystallization from cyclohexane or resublimation yielded analytically pure **4c**.

Analysis of the crude reaction mixture by glpc and nmr indicated the presence of **3a**.

Reaction of 1a with Acetaldehyde, Acetone, Acetophenone, and Benzophenone in the Presence of Boron Trifluoride Etherate. Five millimoles each of **1a** and the corresponding carbonyl compound were combined, under nitrogen, in 20 ml of methylene chloride. The mixtures were heated under reflux in an oil bath at 60° and 0.4 ml of boron trifluoride etherate was added. After 24 hr the reaction mixtures were analyzed by glpc, tlc, and nmr. In all

Table I
Physical Data

Compd[a]	Mp, °C	Bp, °C (mm)	Yield, %	Ir,[b] cm^{-1}	Nmr, δ
4a	49–56	122–128 (2.8)	42	1658, 1681[c]	1.60 (s, 6, C-5 CH_3's), 1.97 (s, 6, C-2 CH_3's)
4c	119–124		26	1645, 1675	1.48 (s, 3, C-5 CH_3), 1.70 (s, 3, C-5 CH_3), 3.80 (s, 3, OCH_3) 6.25 (s, 1, H), 7.19 (AA'BB' pattern, 4, aromatic)
4h	53–56		63	1653, 1672	1.55 (s, 6), 4.51 (s, 2)
7a	91–93		38	1658	4.64 (s, 2)
8c	101–104		53	1661	4.07 (s, 2, C-5 H's), 4.59 (s, 2, C-2 H's)
8d	101–106	125–140 (0.4–1.0)	19	1667, 1692	1.35 (d, 3, J = 6.5 Hz), 4.29 (q, 1, J = 6.5 Hz), 4.20, 4.98 (AB, d of d, J = 15.0 Hz)[d]
8e	59–62		6	1669	1.80 (d, 3, J = 7.0 Hz), 3.79, 4.07 (AB, d of d, J = 14.5 Hz), 5.35 (q, 1, J = 7.0 Hz)
8f	88–89	144 (0.1)	50	1658	2.02 (s, 6), 4.01 (s, 2)
8g	85–86		37	1664, 1692	1.44 (d, 3, J = 6.5 Hz), 1.88 (s, 3), 2.18 (s, 3), 4.17 (q, 1, J = 6.5 Hz)
8h	87–89	118–138 (0.4–0.35)	51	1653	2.04 ("quintet," 2, J = 8.0 Hz), 2.89 ("t," 4, J = 8.0 Hz), 4.37 (s, 2)
8i	131.5–134.5		39	1667	2.27 (m, 4), 2.80 (m, 8)
8j	135–141		11	1667, 1647	2.00 (s, 6), 7.60 (s, 1),[e] 7.28–7.78 (m, 5)
5		83–89 (0.4–0.35)	23	1672, 1698, 1736	1.55 (s, 6), 3.35 (s, 3), 5.12 (s, 2), 6.15 (s, 1)

[a] Satisfactory analytical data (±0.35% for C, H, S) were obtained for all compounds, except **5**, listed in this table. [b] All of the compounds listed exhibited rather complex bands in the C=O stretch region. This phenomenon has also been observed with Meldrum's acid (**8a**) and is ascribed to vibrational coupling (ref 17). [c] Liquid film. [d] CD_2Cl_2 solution. [e] The chemical shift of the benzylidene proton was verified by use of Ventron's Eu-Resolve-II.

cases **3a** was identified by nmr and by glpc using the retention time and the technique of peak potentiation with an authentic sample.[16] The 1,3-dithiane-4,6-diones could not be detected by nmr. Also, in the case of acetone, tlc comparison of the reaction mixture with authentic **4a** prepared by an alternate route (*vide infra*) failed to indicate this product.

In the case of benzophenone, careful distillation of the reaction mixture yielded 0.38 g (58%) of **3a** and 0.67 g (68%) of the intensely blue thiobenzophenone, bp 111–114° (0.4 mm) [lit.[18] bp 174° (14 mm)]. The other reaction mixtures did not yield isolable products.

Reaction of 1a with Methylal and Boron Trifluoride Etherate. Methylal (380 mg, 5 mmol) and **1a** (821 mg, 5 mmol) were combined, under nitrogen, in 20 ml of methylene chloride. The reaction mixture was heated under reflux in an oil bath at 60° and 0.4 ml of boron trifluoride etherate was added. The mixture was refluxed for 43 hr and then analysed by glpc, tlc, and nmr. **3a** was present in ~40% yield. Distillation of the reaction mixture gave 0.24 g of a liquid, bp 83–89° (0.4–0.35 mm), which gave nmr and ir spectra consistent with structure **5**.

Reaction of Diiodomethane with 1i. To a solution of pyridine (0.79 g, 10 mmol) and **1a** (0.82 g, 5 mmol) in 50 ml of anhydrous ether was added diiodomethane (1, 34 g, 5 mmol) over a period of 20 min. After stirring for 1 hr longer the pyridinium iodide was precipitated by the addition of chloroform and removed by filtration. The filtrate was carefully distilled through a Vigreux column to provide pure **3a** (nmr, glpc).

Reaction of Dichlorodiphenylmethane with 1j. To a solution of **1a** (3.29 g, 0.02 mol) and pyridine (3.16 g, 0.04 mol) in 50 ml of ice-cold chloroform was added dichlorodiphenylmethane (4.76 g, 0.02 mol). The mixture was stirred for 3 hr at 60° under nitrogen. The blue color of thiobenzophenone was apparent after a few minutes. After the chloroform was removed the crude product was distilled at 58° (14 mm) to give **3a** in ~80% yield accompanied by unidentified impurities (nmr). The ir spectrum of a sample of the distillation residue was very similar to that of authentic thiobenzophenone.[18]

1,3-Dithiolane-4,5-dione (7a). Oxalyl bromide (4.32 g, 0.02 mol) was added over a 3–5-min period to a solution of **6a** (1.80 g, 0.02 mol) and dry pyridine (3.16 g, 0.04 mol) in 40 ml of cold (ice bath) anhydrous ether. After stirring overnight at room temperature the mixture was filtered through Celite and the ether was evaporated to yield an off-white solid. Recrystallization from carbontetrachloride–chloroform gave 1.02 g of **7a** as white needles.

1,3-Dithiane-4,6-dione (8c). A solution of 2.82 g of malonyl chloride and 1.80 g of **6a** (0.02 mol of each) in 7 ml of chloroform was stirred at room temperature for 1.5 hr. The reaction mixture was poured into 70 ml of ice-cold 10% Na_2CO_3 solution. The chloroform layer was removed and discarded. The aqueous phase was cooled by addition of ice, acidified with 10% HCl, and extracted three times with 40-ml portions of methylene chloride. The combined extract was dried ($MgSO_4$) and evaporated to yield 1.55 g of crude orange crystals. Recrystallization from benzene–cyclohexane or sublimation at 65° (2.0 mm) yielded white crystals of **8c**.

1,3-Dithiane-4,6-diones (8d,h,i). To a solution of 0.02 mol of the appropriate *gem*-dithiol and 0.04 mol of pyridine in 40 ml of chloroform was added (ice-bath cooling) 0.02 mol of the appropriate acid chloride, over a period of 5 min. The reaction mixtures were stirred for 16 hr at room temperature, 4 hr under reflux, and 12 hr under reflux, respectively, for **8d, 8h,** and **8i**. The chloroform was then removed on a rotary evaporator to obtain a solid residue which was triturated with three portions of boiling ether. The ether solution was filtered through Celite and evaporated to yield the crude product.

The crude **8i** was triturated with boiling petroleum ether (bp 30–60°) and filtered to collect 1.84 g of crude product. Recrystallization from cyclohexane yielded an analytical sample. Crude **8d** and **8h** were purified by short-path distillation *in vacuo*. The distillates, which crystallized upon cooling, were recrystallized: **8d**, 0.62 g, from benzene–cyclohexane; **8h**, 1.92 g, from cyclohexane.

5,5-Dimethyl-1,3-dithiane-4,6-dione (4h). To a cold (ice bath) stirred solution of **8d** (533 mg, 3.29 mmol) in 2 ml of dry dimethylformamide (DMF), under nitrogen, was added 153 mg of a 57% oil dispersion of sodium hydride (3.62 mmol). The mixture was stirred for 15 min, and then methyl iodide (560 mg, 3.95 mmol) was added. After stirring for 16 hr longer at room temperature, the mixture was poured into 50 ml of ice water and extracted four

times with 20-ml portions of methylene chloride. The combined extract was washed twice with 30-ml portions of cold 10% Na_2CO_3 solution, dried ($MgSO_4$), and evaporated to a residue which was extracted once with boiling petroleum ether (30–60°) to remove the mineral oil. After evacuation at 40° (0.1 mm) to remove DMF, the crude **4h** (363 mg) was recrystallized from benzene–cyclohexane.

In an unsuccessful attempt to obtain **4h,** dimethylmalonyl chloride (3.38 g, 0.02 mol) and **6a** (1.80 g, 0.02 mol) were combined in 10 ml of chloroform and stirred for 27 days at room temperature. The solvent was then removed on a rotary evaporator and the crude product was distilled. 3,3-Dimethylthietane-2,4-dione (**3a**) was identified in the first fraction, bp 25–60° (14–15 mm), using the technique of peak potentiation with an authentic sample[16] by both glpc and nmr.

2-Methyl-1,3-dithiane-4,6-dione (8e). A solution of **8c** (1.44 g, 9.72 mmol) in 30 ml of tetrahydrofuran (THF) was prepared under nitrogen with Dry Ice–acetone bath cooling. To this solution was added, dropwise with stirring, 14.9 ml of a 13.01% solution of *n*-butyllithium in hexane (20.0 mmol). The mixture was stirred for 1 hr, and then 1.45 g (10.2 mmol) of methyl iodide was added. After 2 hr, 10 ml of dry THF was added and the mixture was allowed to stand at 5° for 5.5 days. Then 25 ml of 10% HCl was added and the mixture was extracted once with 20 ml of ether and twice with 30-ml portions of methylene chloride. The combined ether–methylene chloride extract was dried ($MgSO_4$) and evaporated to give 1.92 g of material. Column chromatography on silica gel (Woelm) with chloroform as the eluent, followed by tlc on an Analtech silica gel GF Uniplate (chloroform), provided 100 mg of **8e** which was 95% pure by glpc. Analytical samples were collected by glpc.

The use of *tert*-butyllithium under similar conditions also provided **8e;** however, the yield was <5% (nmr).

2,2-Dimethyl-1,3-dithiane-4,6-dione (8f). Anhydrous Na_2CO_3 (6.30 g, 0.06 mol) and **6b** (3.24 g, 0.03 mol) were placed in 100 ml of cold (ice bath) anhydrous ether under nitrogen. A solution of malonyl chloride (4.23 g, 0.03 mol) in 15 ml of ether was added, dropwise with stirring, over a period of 15 min. The mixture was stirred for 2 hr at the ice-bath temperature, then for 16 hr at room temperature. It was then filtered, and the filtrate was evaporated to remove the ether and then distilled *in vacuo.* After a forerun of 0.60 g of 2,2,4,4,6,6-hexamethyl-1,3,5-trithiane, 2.65 g of crude **8f,** bp 144° (0.1 mm), was obtained (crystallized upon cooling). The crude **8f** was recrystallized from cyclohexane.

Hexamethyl-1,3,5-trithiane results *via* acid-catalyzed reaction of the dithiol. Some HCl was present even in the presence of Na_2CO_3; however, when the carbonate was omitted, the yield of **8f** dropped from 50 to 19%. Hexamethyltrithiane of 95% purity [nmr δ 1.78 (s)] was prepared by stirring a solution of **6b** in chloroform saturated with HCl gas for 1 day at room temperature.[19]

2,2,5-Trimethyl-1,3-dithiane-4,6-dione (8g). Preparation of **8g** was carried out by reaction of methylmalonyl chloride and **6b** (0.04 mol each) with Na_2CO_3 in anhydrous ether by a procedure similar to that described for the preparation of **8f,** except that the reaction time was extended to 68 hr at room temperature. After filtration and evaporation of the ether, the crude product was dissolved in 50 ml of boiling cyclohexane, treated with Darco, and filtered. On cooling to room temperature, 2.25 g of white, crystalline **8g** was obtained (second crop 0.58 g). Recrystallization from cyclohexane provided analytically pure **8g.**

2,2,5,5-Tetramethyl-1,3-dithiane-4,6-dione (4a). Powdered sodium hydride (148 mg, 6.0 mmol, prepared from 260 mg of 57% oil dispersion) was added in several portions over a 10-min period to an ice-cold, stirred solution of **8g** (950 mg, 5.0 mmol) in 5 ml of dry DMF under nitrogen. After stirring for 10 min longer, methyl iodide (1.42 g, 10 mmol) was added, and the mixture was stirred for 50 hr at room temperature and then poured into 75 ml of ice water. The mixture was extracted twice with 50-ml portions of ether. The combined extract was then washed three times with 100-ml portions of cold water, followed by two 100-ml portions of cold 2% HCl solution, dried ($MgSO_4$), and evaporated on the steam bath to yield 0.43 g of crude **4a.** The crude product was distilled *in vacuo.* The distillate crystallized very slowly upon standing at room temperature.

2,2-Dimethyl-5-benzylidene-1,3-dithiane-4,6-dione (8j). Benzaldehyde (1.59 g, 15 mmol), **8f** (1.76 g, 10 mmol), glacial acetic acid (0.18 ml), and dry piperidine (0.06 ml) were combined in 30 ml of dry benzene. The mixture was refluxed for 21.5 hr under a Dean-Stark trap and then washed in succession with three 30-ml portions of saturated $NaHSO_3$ solution, one 25-ml portion of 2% HCl, and one 30-ml portion of 10% Na_2CO_3 solution. The solution was dried ($MgSO_4$), filtered, and treated with Norit, and the solvent was evaporated to yield a red oil which partially crystallized on standing. This residue was triturated with anhydrous ether and filtered to collect 285 mg of yellow crystals of **8j.** Repeated sublimation, 150° (0.05 mm), provided analytically pure material.

Registry No.—**1a,** 34803-94-6; **1b,** 34803-96-8; **1i,** 52133-70-7; **3a,** 34804-00-7; **3b,** 34804-02-9; **4a,** 52133-71-8; **4c,** 52133-72-9; **4h,** 52133-73-0; **5,** 52133-74-1; **6a,** 6725-64-0; **6b,** 1687-47-4; **6** [R, R′ = $(CH_2)_3$], 15144-23-7; **7a,** 52133-75-2; **8c,** 52133-76-3; **8d,** 52133-77-4; **8e,** 52133-78-5; **8f,** 52133-79-6; **8g,** 52133-80-9; **8h,** 52133-81-0; **8i,** 52133-82-1; **8j,** 52133-83-2; malonyl chloride, 1663-67-8; methylmalonyl chloride, 39619-07-3; cyclobutane-1,1-dicarboxylic acid chloride, 51816-01-4; isopropenyl acetate, 108-22-5; anisaldehyde, 123-11-5; acetaldehyde, 75-07-0; acetone, 67-64-1; acetophenone, 98-86-2; benzophenone, 119-61-9; methylal, 109-87-5; diiodomethane, 75-11-6; dichlorodiphenylmethane, 2051-90-3; oxalyl bromide, 15219-34-8; dimethylmalonyl chloride, 5659-93-0; benzaldehyde, 100-52-7.

References and Notes.

(1) Presented at the 168th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1974.

(2) See, for example, (a) D. Davidson and S. A. Bernhard, *J. Amer. Chem. Soc.,* **70,** 3426 (1948); (b) E. N. Klimovitskii, L. K. Yuldasheva, and B. A. Arbuzov, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1577 (1973); *Chem. Abstr.,* **79,** 104626f (1973); (c) R. F. C. Brown and K. J. Harrington, *J. Chem. Soc., Chem. Commun.,* 1175 (1972); (d) H. Egger, *Monatsh. Chem.,* **98,** 1245 (1967); (e) P. Margueretha, J. Leitich, and O. E. Polansky, *Tetrahedron Lett.,* 4429 (1969); (f) B. Loev, E. Macko, and I. M. Fried, *J. Med. Chem.,* **12,** 854 (1969); (g) D. Köberl and O. E. Polansky, *Monatsh. Chem.,* **104,** 1421 (1973), and references cited therein.

(3) S. J. Brois, J. F. Pilot, and H. W. Barnum, *J. Amer. Chem. Soc.,* **92,** 7629 (1970).

(4) C. A. Grob, *Angew. Chem., Int. Ed. Engl.,* **8,** 535 (1969), and earlier work.

(5) Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Amer. Chem. Soc.,* **95,** 6490 (1973).

(6) Evidence for the intermediacy of thioformaldehyde in a solution phase reaction has been cited by D. M. Armitage and M. J. Clark, *Chem. Commun.,* **104** (1970).

(7) Formation of thiobenzophenone by reaction of thioacetic acid with dichlorodiphenylmethane probably occurs in a similar fashion, *i.e.,* by Grob fragmentation of $Ph_2CCl(SCOCH_3)$: A. Schönberg, O. Schütz, and S. Nickel, *Chem. Ber.,* **61,** 1375 (1928); E. E. Reid in "Organic Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., New York, N. Y., 1962, p. 17.

(8) J. Jentzsch, J. Fabian, and R. Meyer, *Chem. Ber.,* **95,** 1764 (1962).

(9) P. Schuster, O. E. Polansky, and F. Wessely, *Monatsh. Chem.,* **95,** 53 (1964).

(10) Y. Labat, U. S. Patent 3,655,774 (1972).

(11) M. J. Fielding, U. S. Patent 3,255,075 (1966).

(12) J. Jaz and H. de Suray, *Bull. Soc. Chim. Belg.,* **75,** 843 (1966); *Chem. Abstr.,* **67,** 43452z (1967).

(13) J. D. Williams, Ph.D. Thesis, Vilanova University, 1972.

(14) C. C. Price, E. L. Eliel, and R. J. Convery, *J. Org. Chem.,* **22,** 347 (1957).

(15) W. A. Nevill, D. W. Frank, and R. D. Trepka, *J. Org. Chem.,* **27,** 422 (1962).

(16) J. H. Schauble and J. D. Williams, *J. Org. Chem.,* **37,** 2514 (1972); bisthio acid **1a** was purified by repeated low-temperature recrystallization from pentane.

(17) E. Ernstbrunner, *J. Mol. Struct.,* **16,** 499 (1973).

(18) H. Staudinger and H. Freudenberger, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p. 573.

(19) Hexamethyltrithiane has been similarly prepared by vH. Böhme, J. Roehr, and W. Schlephack, *Justus Liebigs Ann. Chem.,* **648,** 15 (1961).

Syntheses and Reactions of 3,4-Dialkyl-1,3,4-thiadiazolidine-2,5-diones

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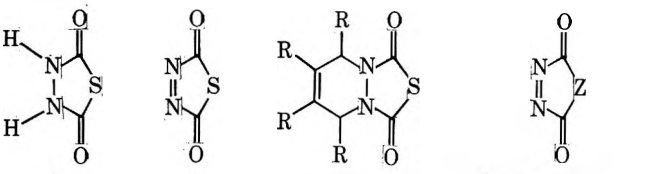
The oxidation of 1,3,4-thiadiazolidine-2,5-dione (**1**) to 1,3,4-thiadiazole-2,5-dione (**2**) is reported. As a dienophile **2** is as reactive as 4-phenyl-1,2,4-triazoline-3,5-dione but decomposes to nitrogen, carbon monoxide, and carbon oxysulfide in acetone at temperatures above −35°. The fragmentation of 3,4-dialkyl-1,3,4-thiadiazolidine-2,5-diones, obtained by $[4_\pi + 2_\pi]$ cycloadditions of **2** followed by reduction or by alkylation of **1**, has been investigated. Reaction to produce a carbon-carbon bond between the alkyl groups is successful only for the conversion of 5,6,7,8-tetrahydro-5,8-methanopyridazino[1,2-*c*]-2-thia-4,9-diazole-1,3-dione (**11a**) to bicyclopentane. An early literature claim of the synthesis of **1** is corrected.

The 1,3,4-thiadiazolidine-2,5-dione ring system appears to have interesting synthetic potential. Oxidation of the parent system **1**[1] should give 1,3,4-thiadiazole-2,5-dione[2,3] (**2**), a species which would be a highly reactive dienophile, and would give adducts, **3**, which should be more amenable to subsequent conversions than those from the related dienophiles **4a–c**.[4–11] Moreover, 3,4-dialkyl-1,3,4-thiadiazolidine-2,5-diones, whether **3**, cycloaddition products of **1**, or **5**, alkylation products of **1**, could undergo a symmetry-allowed fragmentation, giving an azo compound, carbon monoxide, and carbon oxysulfide,[12] or even the latter two products along with nitrogen and carbon–carbon bond formation. Those processes find analogy in a number of reactions, some of which are exceptionally useful.[13] The oxidative conversion of **1** to **2** and the trapping of **2** by $[4_\pi + 2_\pi]$ cycloadditions have been noted.[2,3] We wish to describe our work on this oxidation and trapping, report a comparison of the dienophilic activity of **2** to **4a**, note the syntheses of derivatives of **1** by alkylation procedures, and report one successful case of carbon–carbon bond formation by fragmentation of a derivative of **1**.



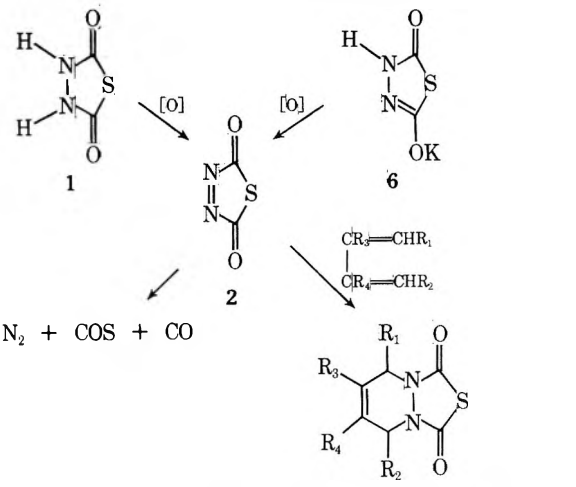
1 **2** **3**

4a, Z = NC_6H_5
b, Z = CR=CR
c, Z = $C(C_2H_5)_2$

Results and Discussion

Diels–Alder Reactions of 1,3,4-Thiadiazole-2,5-dione (2). 1,3,4-Thiadiazole-2,5-dione (**2**) is generated by oxidation of 1,3,4-thiadiazolidine-2,5-dione (**1**) or its monopotassium salt (**6**) with cupric chloride, lead tetraacetate, or *tert*-butyl hypochlorite at 0° in a suitable solvent and may be trapped with reactive dienes to give Diels–Alder adducts. Reaction of dienes with **1** and cupric chloride in dimethylformamide (DMF) gives adducts **3a** from cyclopentadiene (65%), **3b** from 1,3-cyclohexadiene (43%), **3c** from 2,3-dimethylbutadiene (23%), and **3d** from isoprene (4%). Although 1,3-butadiene is unreactive under these conditions, adduct **3e** can be produced in 49% yield by reaction of **1** and *tert*-butyl hypochlorite with the diene in acetone at −78°. The three oxidants give comparable yields of adduct **3a** from **1** and cyclopentadiene in DMF at 0°.

In the absence of a suitable trapping diene, compound **2** decomposes to nitrogen, carbon monoxide, and carbon oxysulfide, as shown by gas chromatographic analysis. An analogous fragmentation has been reported for 1,2,4-triazoline-3,5-dione.[14] Oxidation of **6** with *tert*-butyl hypochlorite in acetone at −78° produces a violet solution, λ_{max} 553 ± 3 nm (ε 170 ± 30). A shoulder on this absorption at 625 nm is consistent with the shift expected for the O,O band of the n, π* transition of **2** relative to analogous transition of closely related compounds.[15] If the acetone solution is allowed to warm to −35°, the color quickly fades.



1 **6** **2**

N_2 + COS + CO

3a, $R_1 + R_2 = CH_2$; $R_3 = R_4 = H$
b, $R_1 + R_2 = CH_2CH_2$; $R_3 = R_4 = H$
c, $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$
d, $R_1 = R_2 = R_3 = H$; $R_4 = CH_3$
e, $R_1 = R_2 = R_3 = R_4 = H$

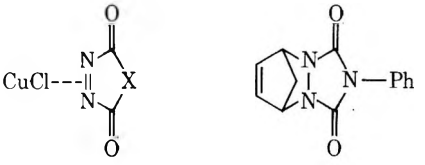
[O] = $CuCl_2$, $Pb(OAc)_4$, +OCl

The potential Diels–Alder dienes hexachlorocyclopentadiene, norbornadiene, 1,3-cyclooctadiene, 1,3-cycloheptadiene, 1,4-diphenyl-1,3-butadiene, 1,3-cycloheptadiene, 1,4-diphenyl-1,3-butadiene, tetraphenylcyclopentadienone, anthracene, furan, and thiophene were found to be unreactive with **2** generated from cupric chloride and **1** in DMF or aqueous acetone. The adduct yields for the dienes reactive with **2** are subject to the same rationales which have been given for the corresponding reactions with maleic anhydrides in terms of conformations of the dienes.[16] The dienophile **2** gives lower yields with the reactive dienes than does 4-phenyl-1,2,4-triazoline-3,5-dione (**4a**) and **4a** is reactive with a number of the above dienes[7] which fail to yield adducts with **2**. Apparently a decreased probability of productive collisions of **2** with unreactive dienes is sufficient to allow competitive decomposition of **2**.

Solvent has a pronounced effect upon the reaction. In general, polar solvents increase the rate of oxidation of **1** and **6** to give **2**, which appears to be stable in such solvents; hexamethylphosphoramide, DMF, and 50% aqueous acetone give equally good yields of adducts. Methylene chloride, which is commonly used for reactions of triazol-

inediones with olefins,[6] is not a suitable solvent for formation and reactions of thiadiazoledione **2** with dienes at 0 or −78°, apparently because the rate of oxidation of **1** and **6** is much slower in this solvent than in more polar solvents. Moreover, **2** itself appears to be less stable in methylene chloride, since an acetone solution of **2** when mixed with methylene chloride at −78° decomposes at −53°, 18° below the temperature at which an acetone solution of **2** decomposes. Methanol, 95% ethanol, and pyridine, when used as solvents with cupric chloride, **1**, and cyclopentadiene, give **3a** in either lower yield or lower purity than when DMF is used as solvent.

The formation of adducts of **2** from different precursors and with different oxidizing agents and the low-temperature ultraviolet spectrum provide evidence for the intermediacy of free **2**. The oxidations can be rationalized through the generally accepted pathways for the oxidants used.[17-19] It seems likely that **2** and **4a**, formed in cupric chloride oxidations of **1** and 4-phenylurazole (**8**), respectively (*vide infra*), are in equilibrium with the copper complexes **7a** and **7b**.[13a-f] The visible–ultraviolet spectra of the solutions resulting from oxidation do not show absorptions due to the dienophiles **2** and **4a**,[15] but do exhibit absorptions at 386 nm (ε 22 and 33, respectively, for **7a** and **7b**), tentatively attributable to the n–π* absorption of the azo function.[20] The expected Diels–Alder products **3a** and **8** are formed in the presence of cyclopentadiene under these conditions.

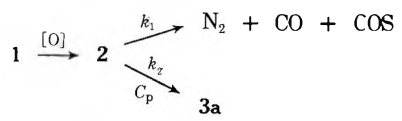


7a, X = S
b, X = NPh

8

Competition of 1,3,4-Thiadiazole-2,5-dione (2) and 4-Phenyl-1,2,4-triazoline-3,5-dione (4a) for Cyclopentadiene. A matter of considerable interest is a comparison of the Diels–Alder reactivity of 1,3,4-thiadiazole-2,5-dione (**2**) with 4-phenyl-1,2,4-triazoline-3,5-dione (**4a**); the latter species is one of the most potent and useful dienophiles.[4-7,13k,q,r,21] Since **2** is less stable than **4a** at ambient temperature, any comparison of **2** and **4a** must be made under conditions such that unimolecular decomposition of **2** does not occur to a significant extent.

A limit on the ratio of decomposition to trapping in oxidation of **1** with cupric chloride in DMF at 0° may be obtained from the data given in Table I, which shows the yield of adduct **3a** as a function of cyclopentadiene concentration. The proportion of **2** undergoing bimolecular trapping to that undergoing unimolecular decomposition is $k_2(Cp)/k_1$ for the scheme below.



If it is assumed that $k_2/k_1 = 100\ M^{-1}$, the values given in the last column of the table are obtained. The discrepancy between those values and the observed yields in the fourth column show that the k_2/k_1 ratio must be greater than 100 M^{-1}, and the correspondence of the theoretical and observed yields over a variation of 1.0 to 0.1 in the cyclopentadiene:**1** ratio suggests that little fragmentation of **2** occurs.

To assess the relative reactivity of **2** and **4a**, a solution of **2** prepared by oxidation of **6** with *tert*-butyl hypochlorite in acetone at −78° was mixed with an equimolar quantity of **4a** and the dienophiles were allowed to react with a limiting quantity of cyclopentadiene. The ratio of adducts **3a**:**8** was observed to be 1.0 to 1.5, depending upon the amount of **6** oxidized. The quantity of **2** present in solution was determined by uv analysis of **6** remaining after oxidation, and it was assumed that the oxidation product was entirely undecomposed **2**. This assumption is justified because greater than 95% trapping occurred at the lowest cyclopentadiene concentration used and the yields of **3a** formed by reaction of cupric chloride or lead tetraacetate with **1** and cyclopentadiene at 0° in DMF were comparable with yields of **3a** obtained by reaction of **2** generated from *tert*-butyl hypochlorite and **1** or **6** with cyclopentadiene at −78° in acetone.

Table I
Yield of Adduct 3a for the Oxidation of 1 by Cupric Chloride in Dimethylformamide at 0° with Varying Ratios of Cyclopentadiene to 1

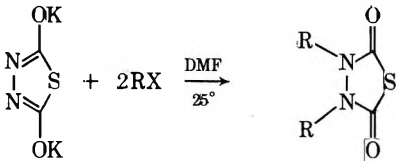
[Cp], mmol	M	$[C_p]/[1]$	[3a], theor, mmol	[3a], found, mmol	[3a] calcd if $k_2/k_1 = 100\ M^{-1}$, mmol
0.06	0.006	0.11	0.06	0.06	0.02
0.12	0.011	0.29	0.12	0.11	0.06
0.24	0.020	0.45	0.24	0.24	0.16
0.6	0.040	1.1	0.52	0.53	0.40
1.2	0.060	2.3	0.52	0.52	0.45

The relative reactivities of **2** and **4a** were also assessed from *in situ* reactions carried out with cupric chloride as oxidizing agent for **1** and 4-phenylurazole (**9**) in the presence of limiting cyclopentadiene or limiting oxidant. These experiments suffer from an additional complication in that the rate constants for oxidation of the precursors now become part of the overall rate expression for the formation of adducts. However, the apparent reactivities of **2** and **4a** in no instance differ by more than an order of magnitude from the ratios obtained in the competition between preformed **2** and **4a**. Thiadiazolidinedione **1** does appear to be oxidized slightly faster than **9**.

It is not surprising that the relative reactivity of **2** should be comparable to that of **4a**, since it is known that *N*-phenylmaleimide, maleic anhydride, and *N*-methylmaleimide have Diels–Alder reactivities which differ by less than an order of magnitude on a scale where tetracyanoethylene exceeds dicyanoethylene in reactivity by nearly six orders of magnitude.[21c] The competition experiments indicate that **2** may be slightly more reactive than **4a** with cyclopentadiene, but for most purposes, the two dienophiles can be considered of comparable reactivity. On the other hand, the competing unimolecular decomposition of **2** which can occur with unreactive dienes (*vide supra*) clearly limits the synthetic utility of this dienophile.

Alkylation of Potassium Salts (6, 10) of 1,3,4-Thiadiazolidine-3,5-dione (1). The monopotassium salt **6** and dipotassium salt **10** can be prepared quantitatively from 1,3,4-thiadiazolidine-2,5-dione (**1**) and potassium hydroxide.

Four alkyl halides were allowed to react with **10** in DMF at room temperature to give dialkylation products: **5a** from benzyl bromide, **5b** from methyl iodide, and **5c** from allyl bromide. Reaction of **10** and *tert*-butyl bromide gave a low yield of **5d**, characterized by ir and nmr spectroscopy. The reaction of monopotassium salt **6** with benzyl bromide and methyl iodide gave dialkylated thiadiazolidinediones **5a** and **5b** and no monosubstituted product.

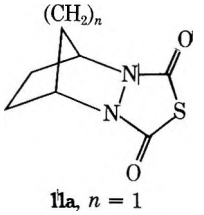


10

5a, R = $PhCH_2$
b, R = CH_3
c, R = CH_2=$CHCH_2$
d, R = $(CH_3)_3C$

The position of alkylation was established for **5a** by treatment with basic peroxide to give benzaldehyde benzylhydrazone in 65% yield. The other alkylated products **5b–d** are presumed to be di-N-alkylated as well, based upon the similarity in location and appearance of their carbonyl bands to the carbonyl bands of **5a** and **3a–e.**

Reduction of Diels–Alder Adducts. Reduction of adduct **3a** with diimide[22] using short reaction times gave the hydrogenated compound **11a.** Attempted catalytic hydro-

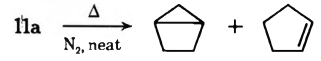


11a, $n = 1$
b, $n = 2$

genation of **3a** over 5% Pd/C gave an unidentified mixture of products having wide melting point ranges. However, catalytic hydrogenation of adduct **3b** over 5% Pd/C gave **11b.**

Decomposition of Thiadiazolidinedione Derivatives. 3,4-Dialkyl-1,3,4-thiadiazolidine-2,5-diones could participate in a symmetry-allowed fragmentation process which would lead to nitrogen, carbon monoxide, carbon dioxide, and carbon–carbon bond formation between the alkyl groups.[12,13a–p] Alternatively, formation of a cis azo compound could intervene but lead to the same result; the well-recognized thermal and photochemical decomposition[13a–p] of a variety of azo compounds provides analogy for the suggested process. Corey and Snider have shown that the thiadiazolidinedione ring can be opened hydrolytically and oxidatively.[3]

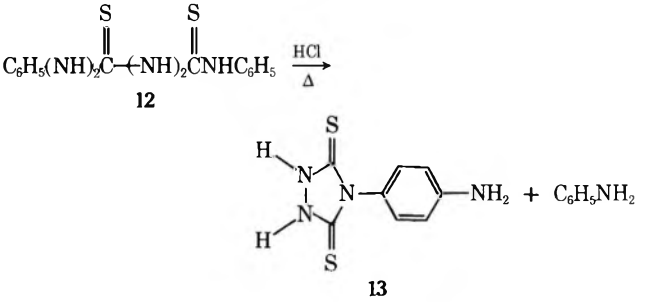
Attempts were made to promote ring fragmentatin in a number of ways, including thermolysis, photolysis, abstraction of sulfur or carbon monoxide, and oxidative attack at the carbonyl group. However, only the thermal decomposition of the reduced cyclopentadiene adduct **11a** gave the desired reaction. When heated to 300–350° for 0.5 hr under a stream of nitrogen, **11a** gives a 4.5:1 mixture of bicyclopentane and cyclopentene in 18% yield. The temperature



required to force the decomposition is substantially higher than the 180–195° required to convert 2,3-diazabicyclo[2.2.1]hept-2-ene to bicyclopentane in 90–93% yield[13b] and the azo compound could well be an intermediate in this process.[13b] Compounds **11b** and **5a** gave only tar when heated under similar conditions.

The photochemical extrusion of sulfur from sulfides with trialkyl phosphites[23] seemed especially promising; however, photochemical and thermal reactions of **5a** with triethyl and triphenyl phosphites did not produce identifiable products, and starting material was recovered in most cases. Several transition metal species were allowed to react with **5a** and **11a** with the expectation that sulfur and/or carbon monoxide would be extruded. Tris(triphenylphosphine)rhodium chloride seemed an especially propitious reagent, since it is known to promote the conversion of a thioanhydride to an olefin.[24] Reaction of tris(triphenylphosphine)rhodium chloride with **11a** in refluxing carbon tetrachloride for 2 hr gave 49% recovery of starting material and no detectable bicyclopentane, cyclopentene, or 2,3-diazabicyclo[2.2.1]hept-2-ene, although isolation of triphenylphosphine sulfide in 39% yield indicated that some reaction had occurred. Treatment of **5a** with 5% Pd/C and hydrogen-free Raney Ni was also unproductive.

Structural Assignment of 4-(*p*-Aminophenyl)-1,2,4-triazolidine-3,5-dithione (13). An early report[25] claims synthesis of the parent system **1.** Repetition of the synthesis by treatment of thioamide **12** with hot hydrochloric acid gave aniline and, after recrystallization from ethanol, a $C_8H_8N_4S_2$ compound having the same melting point as reported. This compound is a para-substituted aromatic



12

13

species, as determined by an AA′BB′ aryl pattern in the nmr spectrum and a strong 825-cm^{-1} band in the ir spectrum. In addition, the nmr spectrum shows four exchangeable hydrogen atoms consisting of two singlets having equal areas. The product, assigned structure **13,** apparently arises from a combination of cyclization and a rearrangement analogous to the benzidine rearrangement.[26,27]

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were taken on Perkin-Elmer 137, 237B, or 521 spectrophotometers and are calibrated against a polystyrene reference band at 1601 cm^{-1}. Nmr spectra were obtained with Varian A-56/60, A-60A, T-60, or HA-100 spectrometers with the assistance of Mr. Robert Thrift and associates. Chemical shifts and chemical shift differences are reported as δ units in parts per million relative to tetramethylsilane as internal standard. Mass spectra were recorded at 70 eV by Mr. J. C. Cook and associates using a Varian MAT CH-5 mass spectrometer. The mass spectral data processing equipment employed was provided by NIH Grants CA 11388 and GM 16864, from the National Cancer Institute and the National Institute of General Medical Sciences, respectively. Elemental analyses were performed by Mr. J. Nemeth and associates. Gas chromatography was performed on a Varian Aerograph A90-P3, with columns and column conditions as indicated. Reactions were carried out at ambient temperature unless otherwise specified. Photolyses were performed with a Rayonet photochemical reactor fitted with 16 low-pressure (2537 Å) or medium-pressure (3000 Å) mercury vapor lamps or with a General Electric 275-W ultraviolet sun lamp.

Materials. Elution chromatography was carried out on Brinkmann 0.05–0.2 mm silica gel. Thin layer chromatography was performed using Eastman silica gel coated strips which were developed with iodine. Commercially available liquid reagents, solid inorganic reagents, and reagent solvents were used without further purification, unless otherwise noted. All organic solid reagents were recrystallized before use to a satisfactory degree of purity. Lead tetraacetate was determined by iodine titration to be 91% pure. *tert*-Butyl hypochlorite was prepared from Clorox and *tert*-butyl alcohol. Potassium azodicarboxylate was synthesized by the method of Thiele.[28] Cyclopentadiene, prepared by thermally cracking dicyclopentadiene, was stored at −20° and its purity was established by nmr analysis to exceed 98%. Dimethyl sulfoxide was distilled from calcium hydride under a nitrogen atmosphere at re-

duced pressure and stored unnnnder argon over Linde 4A molecular sieve.

1,3,4-Thiadiazolidine-2,5-dione (1) was prepared in 47% yield according to the procedure of Rüfenacht by the acidic hydrolysis of 2-methoxy-1,3,4-thiadiazole-5(4*H*)-one.[1] Analytical material, obtained on one recrystallization from 50% aqueous methanol, had mp 250–252° dec (lit.[1] mp 245–248°); ir (KBr and Nujol mull) 3200–2000 (broad cyclic amide NH) and 1690, 1640 cm^{-1} (broad, amide C=O, C=N); nmr (DMSO-d_6) no proton absorption; mass spectrum (70 eV) *m/e* (rel intensity) 118 (6), 116 (10), 62 (21), 60 (100), 58 (25), 44 (36), 43 (21), 32 (100), 30 (22), 28 (34), consistent with the structure of **1**.[1]

5,8-Dihydro-5,8-methanopyridazino[1,2-*c*]2-thia-4,9-diazole-1,3-dione (3a). A From 1 with Cupric Chloride as Oxidant. Anhydrous cupric chloride (1.08 g, 8.02 mmol) in 8 ml of DMF was mixed with cyclopentadiene (2 ml, 24 mmol) at 0° under nitrogen, and **1** (197 mg, 1.66 mmol) in 4 ml of DMF was then added rapidly. After the reaction had been allowed to proceed for 20 min, the solution was poured into 200 ml of anhydrous ether and washed five times with 20-ml portions of water. The ethereal extract was dried ($MgSO_4$) and concentrated to give 196 mg (1.08 mmol, 65%) of **3a**, mp 64–76°, recrystallized from ether–pentene: mp 86.5–87.0° (lit.[3] mp 83.5–84.5°), with bubbling at 105° and pyrolysis at 155°; uv max (methanol) 209 nm (ϵ 7330) and 243 (7410); ir (Nujol) 1670 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.59 (triplet 2, J = 1.5, 1.5 Hz, =CH), 5.21 (multiplet, 2, J = 1.5, 1.5 Hz, =CCH), and 2.37 and 2.07 ppm (two triple doublets, 2, J = 1.5, 9 Hz, CH_2); decoupling of the bridgehead protons causes collapse of the vinylic protons from a triplet to a singlet and collapse of the methano protons from two triple doublets to two doublets; mass spectrum (70 eV) *m/e* (rel intensity) 182 (16), 122 (7), 121 (10), 79 (16), 67 (6), 66 (100), 65 (11), 60 (6), 40 (13), 39 (18), 28 (13).

Anal. Calcd for $C_7H_6N_2O_2S$: C, 46.14; H, 3.32; N, 15.38; S, 17.60. Found: C, 46.30; H, 3.45; N, 15.57; S, 17.53.

B. From 1 with Lead Tetraacetate and *tert*-Butyl Hypochlorite as the Oxidants. When lead tetraacetate was used as oxidant at 0° in DMF, **3a** was obtained in 75% yield; use of the conditions of Corey and Snider[3] at −78° gave **3a** in 82% yield. With *tert*-butyl hypochlorite as oxidant at 0° in DMF, **3a** was produced in 76% yield.

C. From 6 and the Above Oxidants. When cupric chloride was used as oxidant at 0° in DMF with **6**, **3a** was obtained in 38% yield; use of lead tetraacetate under similar conditions gave **3a** in 20% yield. With *tert*-butyl hypochlorite as the oxidant at 0° in DMF, **3a** was obtained in 58% yield; and with acetone solvent at −78°, **3a** was produced in 30–50% yield based upon partial oxidation of the monopotassium salt.

5,8-Dihydro-5,8-ethanopyridazino[1,2-*c*]-2-thia-4,9-diazole-1,3-dione (3b) was prepared in 43% yield from 1,3-cyclohexadiene, **1**, and cupric chloride in DMF: mp 137–11h139°, recrystallization from ether, mp 144.0–145.0° (lit.[3] mp 139.5–140°); ir (Nujol) 1680 cm^{-1} (C=O); nmr (acetone-d_6) δ 6.57 (triplet, 2, J = 2 Hz, =CH), 5.1 (multiplet, 2, =CCH), and 2.4–1.6 ppm (multiplet, 4, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 196 (26), 136 (3), 118 (19), 108 (6), 81 (9), 80 (57), 79 (100), 78 (13), 77 (21), 67 (12), 66 (22), 60 (11), 52 (11), 51 (11), 50 (10), 41 (8), 39 (23), 28 (88), 27 (15), 17 (22).

Anal. Calcd for $C_8H_8N_2O_2S$: C, 48.96; H, 4.11; N, 14.28; S, 16.34. Found: C, 49.04; H, 4.09; N, 14.41; S, 16.54.

5,8-Dihydro-6,7-dimethylpyridazino[1,2-*c*]-2-thia-4,9-diazole-1,3-dione (3c) was prepared in 23% yield from 2,3-dimethylbutadiene, **1**, and cupric chloride in DMF: mp 134–155°, recrystallization from methylene chloride-hexane, mp 160–161° (lit.[3] mp 153.5–154.4°); ir (Nujol) 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.13 (singlet, 4, CH_2) and 1.78 ppm (singlet, 6, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 200 (6), 199 (12), 198 (100), 138 (2), 137 (2), 123 (7), 110 (13), 95 (3), 82 (31), 67 (45), 54 (13), 41 (24), 39 (20), 28 (29).

Anal. Calcd for $C_8H_{10}N_2O_2S$: C, 48.46; H, 5.08; N, 14.13; S, 16.18. Found: C, 48.62; H, 4.92; N, 14.25; S, 16.15.

5,8-Dihydro-6-methylpyridazino[1,2-*c*]-2-thia-4,9-diazole-1,3-dione (3d) was prepared in 4% yield from iosprene, **1**, and cupric chloride in DMF: mp 99–103°, further recrystallization gave mp 103–104° (lit.[3] mp 99–100°); ir (Nujol) 1670 cm^{-1} (C=O); nmr ($CDCl_3$) δ 5.63 (multiplet, 1, =CH), 4.20 (sharp multiplet 4, $=CCH_2$), and 1.87 ppm (sharp multiplet, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 185 (12), 184 (100), 124 (10), 96 (24), 68 (49), 67 (28), 53 (28), 39 (24), 28 (60).

Anal. Calcd for $C_7H_8N_2O_2S$: C, 45.64; H, 4.38; N, 15.21; S, 17.41. Found: C, 45.82; H, 442; N, 15.36; S, 17.28.

5,8-Dihydropyridazino[1,2-*c*]-2-thia-4,9-diazole-1,3-dione (3e). To **1** in 20 ml of acetone at −78° was added *tert*-butyl hypochlorite (0.47 ml, 4.1 mmol), causing the solution to turn black-violet. After 1 hr, butadiene (90 ml, *ca.* 1.1×10^3 mmol) was condensed into the flask and the violet color discharged. A white, crystalline solid resulted on evaporation under nitrogen. Recrystallization from methylene chloride–pentane gave 175.1 mg (1.03 mmol, 49%) of 5,8-dihydropyridazino[1,2-c]-2-thia-4,9-diazole-1,3-dione (**3e**): mp 118.5–120.5°; further recrystallization gave mp 121.0–122.0°; ir (Nujol) 1680 cm^{-1} (C=O); nmr ($CDCl_3$) δ 5.95 (sharp multiplet, 2, =CH) and 4.32 ppm (sharp multiplet, 4, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 170 (100), 110 (42), 82 (50), 54 (83), 39 (69), 28 (84).

Anal. Calcd for $C_6H_6N_2O_2S$: C, 42.34; H, 3.55; N, 16.46; S, 18.84. Found: C, 42.58; H, 3.61; N, 16.72; S, 19.02.

5,8-Dihydro-5,8-methano-2-phenyl-*s*-triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (8) was prepared from 4-phenylurazole, cupric chloride, and cyclopentadiene in DMF under conditions identical with those used for **1** to give **8** in 54% yield, mp 133.5–140.0°; recrystallization from methylene chloride–hexane gave mp 140.5–143.0° (lit.[6] mp 141.5–144°); ir, nmr, and mass spectra and analytical properties consistent with those of the assigned structure **8**.[6]

1,3,4-Thiadiazolidine-2,5-dione Monopotassium Salt (6). Evaporation to dryness of an aqueous solution of **1** (2.46 g, 20.8 mmol) and 85% potassium hydroxide (1.37 g, 20.8 mmol) gave a white solid which, after one recrystallization from methanol–2-propanol, yielded 2.00 g (12.8 mmol, 62%) of monopotassium salt **6**: mp 196–197° dec; ir (Nujol) 3260 (NH), 1650 (C=O), and 1550 cm^{-1} (C=N); nmr (D_2O) no peaks.

Anal. Calcd for $C_2HN_2O_2SK$: C, 15.38; H, 0.65; N, 17.94. Found: C, 15.49; H, 0.74; N, 17.88.

1,3,4-Thiadiazolidine-2,5-dione dipotassium salt (10) was prepared in 44% yield in a manner similar to that for **6** from **1** and 85% potassium hydroxide containing 2.5 molar excess of base. Recrystallization from methanol–2-propanol provided the hygroscopic dipotassium salt **10**: mp 253–260° dec; ir (Nujol) 1650 (C=O) and 1550 cm^{-1} (C=N).

Anal. Calcd for $C_2N_2O_2SK_2$: C, 12.36; N, 14.42. Found: C, 12.51; H, 0.34; N, 13.87.

***N,N'*-Dibenzyl-1,3,4-thiadiazolidine-2,5-dione (5a).** The dipotassium salt **10** (5.00 g, 25.7 mmol) suspended in 180 ml of DMF, was allowed to react with benzyl bromide (7.5 ml, 63 mmol) for 5 days. The reaction mixture was then poured into anhydrous ether and washed five times with water. The ethereal portion was dried ($MgSO_4$) and evaporated to give a mobile, light yellow liquid which crystallized when treated with pentane. One recrystallization from ether–pentane gave 4.90 g (16.4 mmol, 64%) of white crystals of **5a**: mp 113.0–115.0; further recrystallization gave mp 115.0–117.0°; ir (Nujol) 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.31 (multiplet), 10, ArH) and 4.85 ppm (singlet, 4, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 298 (3), 119 (2), 92 (8), 91 (100), 65 (9), 28 (5).

Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39; S, 10.75. Found: C, 64.17; H, 4.77; N, 9.49; S, 10.80.

The dialkylated product **5a** was formed in 73% crude yield when **6** was allowed to react under nitrogen with equimolar benzyl bromide in 5 ml of DMF for 19 days.

***N,N'*-Dimethyl-1,3,4-thiadiazolidine-2,5-dione (5b).** The dipotassium salt **10** (396.7 mg, 2.04 mmol) suspended in 10 ml of DMF was allowed to react with methyl iodide (1.00 ml, 16.1 mmol) under nitrogen for 20 hr. The solution was evaporated to dryness, 1 ml of water was added, and evaporation was repeated. The moist solid was treated with 50 ml of boiling methylene chloride and filtered, and the filtrate was dried ($MgSO_4$) and evaporated to give a light orange oil which crystallized after being scratched with a glass rod to give 153.4 mg (1.05 mmol, 52%) of **5b**, mp 62–68°. Column chromatography with ether eluent and recrystallization from carbon tetrachloride–hexane gave mp 75.0–75.5°; ir (Nujol) 1660 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.40 ppm (sharp singlet, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 146 (60), 86 (21), 58 (48), 43 (100), 28 (19).

Anal. Calcd for $C_4H_6N_2O_2S$: C, 32.86; H, 4.14; N, 19.17; S, 21.94. Found: C, 33.09; H, 4.03; N, 19.22; S, 21.88.

The product **5b** was produced in 37% crude yield when the monopotassium salt **6** was allowed to react under nitrogen with an eightfold excess of methyl iodide in 20 ml of DMF for 46 hr. Compound **1** does not react under these conditions.

***N,N'*-Diallyl-1,3,4-thiadiazolidine-2,5-dione (5c)** was prepared in 77% yield from reaction of the dipotassium salt **10** suspended in DMF with a fivefold excess of allyl bromide for 22 hr. Extractive work-up with ether produced **5c**: mp 40–45°; recrystal-

lization from ether–pentane gave mp 49.0–50.0°; ir (Nujol) 1690 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.2–5.0 (multiplet, 3, =CH) and 4.22 ppm (doublet with fine structure, 2, J = 6 Hz, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 199 (2), 198 (16), 157 (2), 69 (10), 41 (100), 39 (19), 28 (6).

Anal. Calcd for $C_8H_{10}N_2O_2S$: C, 48.46; H, 5.08; N, 14.13; S, 16.18. Found: C, 48.53; H, 5.11; N, 14.36; S, 16.23.

N,N'-Di-*tert*-butyl-1,3,4-thiadiazolidine-2,5-dione (5d) was prepared in 6% yield from reaction of the dipotassium salt **10** suspended in DMF with a fivefold excess of *tert*-butyl bromide for 7 days. Extractive work-up with ether gave 27.6 mg (0.12 mmol, 6%) of a solid: mp 101–109°; ir (Nujol) 3100 (medium, NH attributed to 1,3,4-thiadiazolidine-2,5-dione as an impurity) and 1650 cm^{-1} (strong, C=O); nmr ($CDCl_3$) δ 1.68 ppm (singlet, CH_3).

5,6,7,8-Tetrahydro-5,8-methanopyridazino[1,2-*c*]-2-thia-4,9-diazole-1,3-dione (11a) was prepared in 49% yield by reduction of **3a** in methanol for 5 min with diimide generated from 4.5 equiv of potassium azodicarboxylate and excess acetic acid. Material obtained by extractive work-up with ether was recrystallized twice from ether-pentane to give **11a**: mp 79.5–80.0°; uv max (methanol) 222 nm (ε 9110); ir (Nujol) 1650 cm^{-1} (C=O); nmr (CCl_4) δ 4.94 (multiplet, 2, CH) and 2.16 ppm (multiplet, 6, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 184 (100), 124 (45), 96 (15), 68 (70), 67 (78), 28 (41).

Anal. Calcd for $C_7H_8N_2O_2S$: C, 45.64; H, 4.38; N, 15.21; S, 17.41. Found: C, 45.86; H, 4.27; N, 15.49; S, 17.34.

5,6,7,8-Tetrahydro-5,8-ethanopyridazino[1,2-*c*]-2-thia-4,9-diazole-1,3-dione (11b) was prepared in 47% yield by catalytic reduction of **3b** in ethyl acetate at atmospheric pressure with 5% palladium on carbon. Recrystallizations from methylene chloride–ether–pentane and ether–pentane gave **11b** in 47% yield, mp 99–110°. Additional recrystallization provided a solid: mp 137.0–137.5° (lit.[3] mp 129–131°); ir (Nujol) 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.67 (multiplet, 2, CH) and 2.00 ppm (multiplet, 8, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 198 (59), 110 (38), 82 (28), 67 (100).

Anal. Calcd for $C_8H_{10}N_2O_2S$: C, 48.46; H, 5.08; N, 14.13; S, 16.18. Found: C, 48.80; H, 4.94; N, 14.34; S, 16.18.

4-(*p*-Aminophenyl)-1,2,4-triazolidine-3,5-dithione (13). Phenylthiocarbohydrazide–thiocarbophenylamide (**12**), prepared from phenylthiocarbonylhydrazide[29] and phenyl isothiocyanate, was mixed with 25 ml of concentrated hydrochloric acid and the solution was stirred under reflux for 1.5 hr. Steam distillation after neutralization with sodium carbonate gave a brown solid. Recrystallization of this solid from ethanol gave 0.31 g (1.38 mmol, 22%) of 4-(*p*-aminophenyl)-1,2,4-triazolidine-3,5-dithione (**13**) as a light tan powder: mp 219–220°; further recrystallization gave mp 225.0–225.5° (lit.[25] mp 222°); ir (KBr) 3480, 3380, 3280, 3100 (NH), 1575 (C=N), and 825 cm^{-1} (para-substituted aryl hydrogen bend); nmr DMSO-d_6) δ 7.27 (doublet of triplets, 2, J_o = 8, $J_{m,p}$ = 1.5 Hz, ArH), 7.09 (singlet, 2, NH_2, exchangeable with D_2O), 6.62 (doublet of triplets, 2, J_o = 8, $J_{m,p}$ = 1.5 Hz, ArH), and 5.52 ppm (singlet, 2, thioamide H, exchangeable with D_2O); mass spectrum (70 eV) *m/e* (rel intensity) 224 (90), 150 (11), 136 (16), 124 (61), 106 (100), 80 (35), 79 (37), 74 (14), 65 (25), 52 (28), 39 (17), 28 (14).

Anal. Calcd for $C_8H_8N_4S_2$: C, 42.84; H, 3.60; N, 24.98; S, 28.59. Found: C, 43.03; H, 3.53; N, 24.99; S, 28.64.

1,3,4-Thiadiazole-2,5-dione (2). The monopotassium salt **6** (312 mg, 2.00 mmol) was allowed to react with *tert*-butyl hypochlorite (0.24 ml, 2.0 mmol) in acetone at −78° under nitrogen for 3⅓ hr, after which time unreacted monopotassium salt was removed by filtration and a violet solution of **2** was obtained. If the solution was allowed to warm to −35°, the color changed to yellow within 20 sec. 1,3,4-Thiadiazole-2,5-dione (**2**) in acetone at −78° gave λ_{max} 550–555 nm ($139 \leq \epsilon \leq 203$). The unreacted monopotassium salt was analyzed by uv analysis in water and the reaction was determined to be 66–96% complete after 3⅓ hr.

Rate of Unimolecular Decomposition of 2 Relative to Trapping by Cyclopentadiene. To determine whether gaseous decomposition of **2** is competitive with its trapping by cyclopentadiene, a series of reactions was run at ambient temperature with cupric chloride oxidant in DMF with a cyclopentadiene/thiadiazolidinedione ratio which varied from 2.0 to 0.1. Analysis of the reaction mixtures was performed by nmr after the usual extractive work-up with biphenyl as an internal standard. The results show (*vide supra*) that competitive unimolecular decomposition of **2** is not a serious problem under these conditions.

Relative Reactivities of 1,3,4-Thiadiazole-2,5-dione (2) and 4-Phenyl-1,2,4-triazoline-3,5-dione (4a). The relative reactivities of **2** and **4a** were evaluated under conditions of competitive reaction of known amounts of the two reagents for a limited quantity of cyclopentadiene; the products were analyzed by nmr.

A. From the Azo Diones. The monopotassium salt **6** of 1,3,4-thiadiazolidine-2,5-dione (89 mg, 0.570 mmol) suspended in 6 ml of acetone was mixed with *tert*-butyl hypochlorite at −78° under nitrogen. This reaction was previously determined (*vide supra*) to give thiadiazoledione **4** in 66–96% yield under similar conditions. After the reaction had been allowed to proceed for 3.5 hr, **4a**[30] (68 mg, 0.380 mmol) in 3 ml of acetone at −78° under argon was rapidly added. After 1 min, cyclopentadiene (21 μl, 0.25 mmol) in 1 ml of acetone at −78° was added. Extractive work-up provided a mixture of 61% **3a** and 39% **8**.

B. From the Hydrazo Diones. 1,3,4-Thiadiazolidine-2,5-dione (**1**, 59.2 mg, 0.500 mmol) and 4-phenylurazole (88.2 mg, 0.497 mmol) were dissolved in 5 ml of DMF and rapidly mixed with a solution of excess cupric chloride (339.2 mg, 2.52 mmol) and limiting cyclopentadiene (21 μl, 0.25 mmol) in 11 ml of DMF at 0°. Extractive product isolation showed 57% of thiadiazoledione adduct **3a** and 43% of phenyltriazolinedione adduct **8**. An experiment in which cupric chloride was limiting and cyclopentadiene was in excess gave an oil which showed 91% **3a** and 9% **8**.

Nmr analysis of product mixtures was carried out by integration of the vinylic proton signals for **3a** and **8** at 396 (δ 6.60 ppm) and 388 Hz (δ 6.47 ppm), respectively, on an expanded 50-Hz sweep width. Standard solutions of the two adducts indicated correct integration within experimental error, and control experiments using excess cyclopentadiene and oxidizing reagent gave the expected proportions of adducts. The identity of the assigned vinylic absorptions was confirmed by addition of authentic samples of **3a** and **8**. Neither adduct was selectively fractionated by the ether–water extractive work-up.

Thermal Decomposition of 5,6,7,8-Tetrahydro-5,8-methanopyridazino[1,2-*c*]-2-thia-4,9-diazole-1,3-dione (11a). Thermolysis of 325 mg (1.76 mmol) of **11a** under a slow nitrogen stream at 300–350° for 30 min in a Woods metal bath gave vapors which were passed through two traps held at 0 and −78°, respectively. After this period of time, the −78° trap was found to contain a 21-mg mixture of bicyclo[2.1.0]pentane and cyclopentene (0.31 mmol, 18%): ir (neat and in CCl_4) 3020, 2900, 2810, 2260 (COS),[31] 1700 (C=O contaminant), 1460, 1440, 1360, 1270, 1240, 1220, 1100, 1050, 1020, 970, 920, 890, 785, 755, 700, cm^{-1}, in agreement with published spectrum[32] of bicyclo[2.1.0]pentane contaminated with cyclopentene, except for impurities at 2260 and 1700 cm^{-1}; nmr (CCl_4) 77% bicyclo[2.1.0]pentane at δ 2.3–1.8, 1.7–1.1, and 0.8–0.3 ppm (multiplets) (lit.[13b] δ 2.4–1.9, 1.7–1.1, and 0.8–0.3 ppm), 17% cyclopentene δ 6.4 and 5.6 ppm, and 6% unidentified absorption at δ 2.9 ppm; mass spectrum (70 eV) *m/e* (rel intensity) 68 (32), 67 (100), 66 (30), 53 (31), 41 (37), 39 (52) [in addition, a small *m/e* 184 (0.7) peak is seen owing to contamination by starting material **11a**].

The isolated yield was confirmed by means of gas chromatographic analysis with a 5 ft × 0.25 in. stainless steel 3% SE-30 on 100/120 Varaport 30. Use of three traps containing *n*-octane at 0° with *n*-heptane as an internal standard gave an 18.5% yield of the isomeric pentane products and it was assumed that the thermal conductivities of the products are the same as that of *n*-pentane.

Reaction of N,N'-Dibenzyl-1,3,4-thiadiazolidine-2,5-dione (5a) with Basic Hydrogen Peroxide. To 297 mg (0.995 mmol) of **5a** in 10 ml of acetone was added quickly a solution of 30% hydrogen peroxide (1.00 ml, 9.82 mmol) and sodium hydroxide (180 mg, 4.49 mmol) in 5 ml of water. Four sodium hydroxide pellets (*ca.* 360 mg) were added after 45 min; after 70 min, 10 ml of water was added, and the solution was evaporated at reduced pressure at 40° until a moist white solid remained. This solid was dissolved in a mixture of 120 ml of ether and 40 ml of water and the aqueous portion was extracted twice with 50-ml portions of ether. The combined ethereal extracts were washed three times with 10-ml portions of water, dried ($MgSO_4$), and evaporated at reduced pressure at 25° to give 138 mg (0.647 mmol, 65%) of a moist, white solid, mp 60–69°. Recrystallization from ether–pentane gave 35 mg (0.166 mmol, 17%) of odorless plates of benzaldehyde benzylhydrazone: mp 64–70°, mmp 64–71.5° (authentic sample mp[33] 62–70°); ir (Nujol) identical with that of independently prepared material;[33] nmr ($CDCl_3$) δ 7.6–7.2 (multiplet, area 11 ± 1, ArH, CH=N), 5.7 (broad singlet, NH), 4.4 (singlet, 2, CH_2), and 4.1 ppm (broad singlet, area <1, impurity), very similar to that of authentic material.

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Registry No.—**1,** 19692-10-5; **2,** 41316-14-7; **3a,** 4136-15-8; **3b,** 41316-16-9; **3c,** 41316-19-2; **3d,** 41316-17-0; **3e,** 52147-54-3; **4a,** 4233-33-4; **5a,** 52147-55-4; **5b,** 52147-56-5; **5c,** 52147-57-6; **5d,** 52147-58-7; **6,** 52147-59-8; **8,** 15971-63-8; **10,** 52147-60-1; **11a,** 52147-61-2; **11b,** 41316-20-5; **12,** 52147-62-3; **13,** 52147-63-4; cyclopentadiene, 542-92-7; 1,3-cyclohexadiene, 592-57-4; 2,3-dimethylbutadiene, 513-81-5; isoprene, 78-79-5; butadiene, 106-99-0; 4-phenylurazole, 4233-33-4; benzyl bromide, 100-39-0; methyl iodide, 74-88-4; allyl bromide, 106-95-6; *tert*-butyl bromide, 507-19-7; bicyclo[2.1.0]pentane, 185-94-4; cyclopentene, 142-29-0.

References and Notes

(1) K. Rüfenacht, *Helv. Chim. Acta*, **51,** 518 (1968).
(2) S. W. Moje and P. Beak, Program and Abstracts, 7th Great Lakes Regional Meeting of the American Chemical Society, June 7–8, 1973, p 8.
(3) E. J. Corey and B. B. Snider, *J. Org. Chem.*, **38,** 3632 (1973).
(4) B. T. Gillis in "1,4-Cycloaddition Reactions—The Diels-Alder Reaction in Heterocyclic Syntheses," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, pp 143–177.
(5) R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *Tetrahedron Lett.*, 615 (1962).
(6) B. T. Gillis and J. D. Hagarty, *J. Org. Chem.*, **32,** 330 (1967).
(7) J. C. Stickler and W. H. Pirkle, *J. Org. Chem.*, **31,** 3444 (1966); J. C. Stickler, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1971.
(8) T. J. Kealy, *J. Amer. Chem. Soc.*, **84,** 966 (1962).
(9) R. A. Clement, *J. Org. Chem.*, **25,** 1724 (1960).
(10) O. L. Chapman and S. J. Dominianni, *J. Org. Chem.*, **31,** 3862 (1966).
(11) B. T. Gillis and R. A. Izydore, *J. Org. Chem.*, **34,** 3181 (1969).
(12) For such a reaction of 3,4-diphenyl-1,3,4-oxydiazolidine-2,5-dione, see W. A. Henderson, Jr., and A. Zweig, *J. Chem. Soc., Chem. Commun.*, 169 (1972); for a similar reaction of 3,4-diphenyldiazolidin-5-one, see B. T. Gillis and R. Weinkam, *J. Org. Chem.*, **32,** 3321 (1967).
(13) (a) E. L. Allred and R. L. Smith, *J. Amer. Chem. Soc.*, **91,** 6766 (1969); (b) P. G. Gassman and K. T. Mansfield, *Org. Syn.*, **49,** 1 (1969); (c) E. L. Allred and A. L. Johnson, *J. Amer. Chem. Soc.*, **93,** 1300 (1971); (d) K. Shen, *ibid.*, **93,** 3064 (1971); (e) R. M. Moriarty, C.-L. Yeh, and N. Ishibi, *ibid.*, **93,** 3085 (1971); (f) J. C. Hinshaw, "Organic Synthesis Using Cyclic Azo Compounds as Intermediates," Eastman Organic Chemical Bulletin, 44, No. 2, 1 (1972); (g) S. G. Cohen and R. Zand, *J. Amer. Chem. Soc.*, **84,** 586 (1962); (h) J. A. Berson, E. W. Petrillo, Jr., and P. Bickart, *ibid.*, **96,** 636 (1974); (i) H. Schmidt, A. Schweig, B. M. Trost, H. B. Neubold, and P. H. Scudder, *ibid.*, **96,** 622 (1974); (j) P. S. Engel, *ibid.*, **89,** 5731 (1967); (k) T. J. Katz and N. Acton, *ibid.*, **95,** 2738 (1973); (l) N. Rieber, J. Alberts, J. A. Lipsky, and D. M. Lemal, *ibid.*, **91,** 5668 (1969); (m) D. H. R. Barton and B. J. Willis, *J. Chem. Soc., Perkin Trans. 1,* 305 (1972); (n) A. P. Schaap and G. R. Faler, *J. Org. Chem.*, **38,** 3061 (1973); (o) L. A. Carpino, *Accounts Chem. Res.*, **6,** 195 (1973); (p) K. A. Jensen, A. Holm, and J. Wolff-Jensen, *Acta Chem. Scand.*, **23,** 1567 (1969); (q) W. R. Dolbier, W. D. Loehle, and W. M. Williams, *J. Chem. Soc., Chem. Commun.*, 867 (1972); (r) A. B. Evnin, D. R. Arnold, L. A. Karnischky, and E. Strom, *J. Amer. Chem. Soc.*, **92,** 6218 (1970).
(14) J. E. Herweh and R. M. Fantazier, *Tetrahedron Lett.*, 2101 (1973).
(15) (a) Professor J. T. Yardley, private communication, Dec 1972; (b) A. V. Pocius and J. T. Yardley, *J. Amer. Chem. Soc.*, **95,** 721 (1973).
(16) D. Craig, J. J. Shipman, and R. B. Fowler, *J. Amer. Chem. Soc.*, **83,** 2885 (1961); R. L. Lipnick and E. W. Garbisch, Jr., *ibid.*, **95,** 6370 (1973); A. Wasserman, "Diels-Alder Reactions, "American Elsevier, New York, N. Y., 1965, pp 52–53, 83.
(17) For cupric halides: E. M. Kosower and G.-S. Wu, *J. Org. Chem.*, **28,** 633 (1963); C. E. Castro, E. J. Gaughan, and D. C. Owsley, *ibid.*, **30,** 587 (1965).
(18) For lead tetraacetate: J. B. Aylward, *Quart. Rev., Chem. Soc.*, **25,** 407 (1971).
(19) For *tert*-butyl hypochlorite: M. Anbar and D. Ginsburg, *Chem. Rev.*, **54,** 925 (1954).
(20) E. C. Allred, J. C. Hinshaw, and A. L. Johnson, *J. Amer. Chem. Soc.*, **91,** 3382 (1969).
(21) (a) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6,** 25 (1967); (b) J. Sauer and B. Schroder, *Chem. Ber.*, **100,** 678 (1967); (c) J. Sauer, H. Wiest, and A. Mielert, *ibid.*, **97,** 3183 (1964).
(22) C. E. Miller, *J. Chem. Educ.*, **42,** 254 (1965), and references cited therein.
(23) V. Boekelheide, I. D. Reingold, and M. Tuttle, *J. Chem. Soc., Chem. Commun.*, 406 (1973); E. J. Corey and E. Block, *J. Org. Chem.*, **34,** 1233 (1969), and references cited therein.
(24) B. M. Trost and F. Chen, *Tetrahedron Lett.*, 2603 (1971).
(25) P. C. Guha and S. K. Roy-Choudhury, *J. Indian Chem. Soc.*, **5,** 163 (1928).
(26) J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y., 1968, pp 828–830.
(27) For preparation of the dimethyl derivative of **13,** mass spectral analyses, and a complete discussion of the structural assignment in terms of eight alternative structures which can formally be considered, see S. W. Moje, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1974, available from University Microfilms, Ann Arbor, Mich. 48106.
(28) J. Thiele, *Justus Liebigs Ann. Chem.*, **271,** 130 (1892).
(29) P. C. Guha and S. K. Roy-Choudhury, *J. Indian Chem. Soc.*, **5,** 149 (1928).
(30) R. C. Cookson, S. S. Gupte, I. D. R. Stevens, and C. T. Watts, *Org. Syn.*, **51,** 121 (1971).
(31) R. J. Ferm, *Chex. Rev.* **57,** 625 (1957).
(32) R. Criegee and A. Rimmelin, *Chem. Ber.*, **90,** 414 (1957).
(33) T. Curtius, *J. Prakt. Chem.*, **62,** 90 (1900).

Furazans and Furazan Oxides. V.[1] Tropono[4,5-*c*]-, Thieno[2,3-*c*]-, and Biphenyleno[2,3-*c*]furazan Oxides

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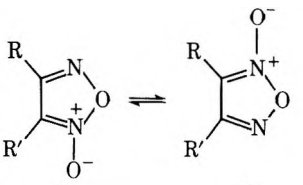
The three title furazan oxides were prepared, and the free energies of activation for their rearrangement were investigated. The relevance of these results to the question of the aromaticity of tropone, thiophene, and biphenylene is discussed. An important factor affecting the ease of the reaction appears to be the size of the ring to which the furazan oxide is fused.

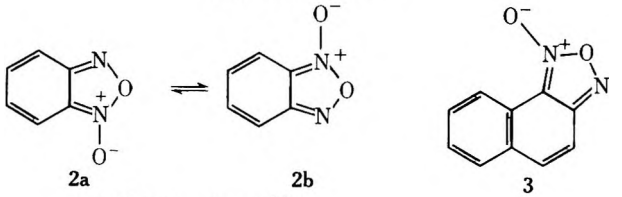
The striking difference (~19 kcal mol^{-1}) between the free energies of activation for the isomerization of a furazan oxide (furoxan[2]) (**1a** ⇌ **1b**) and a benzofurazan oxide (**2a** ⇌ **2b**) has led us to suppose that the reaction may provide a sensitive probe of, and an at least semiquantitative means of determining, the "aromaticity" associated with the ring to which the heterocyclic nucleus is fused. In earlier work,[3] the effect of naphtho[1,2] fusion (**3**) was found to be intermediate (ΔG^* ~19.5 kcal mol^{-1}) between that of benzo fusion (**2**) and "olefin fusion" (*i.e.*, the unfused system, **1**). However, interpretation of the results from polycyclic fused systems was not straightforward: allowance had to be made for changes in the aromaticity of the further fused ring as the one carrying the furoxan becomes more "benzenoid" upon opening of the heterocyclic ring. Nevertheless, we hoped that it might be possible to obtain a comparison between the aromaticities of naphthalene and biphenylene in this way. The problem does not arise when the furoxan is

anellated to a monocyclic ring, and therefore we decided also to examine the effect of fusion to tropone and thiophene.



1a 1b

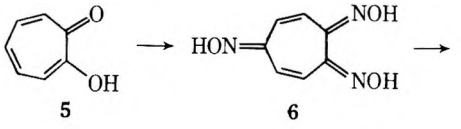
ΔG^* 33 kcal mol^{-1} [1,4]



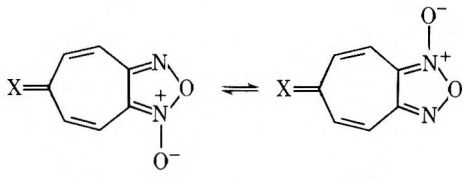
2a 2b 3

ΔG^* 14 kcal mol^{-1} [5]

6-Keto-6*H*-cyclohepta[*c*]furazan 1-Oxide (Tropono-[4,5-*c*]furoxan) (4). In the hope that light could be shed on the much-discussed[6] question of the aromaticity of tropone, we prepared tropono[4,5-*c*]furoxan (4). α-Tropolone (5) was converted into the known trioxime **6**, which was oxidized to the furazan oxide **7**. Removal of the remaining oxime group was difficult, but this was finally achieved using copper carbonate and formic acid.[7]

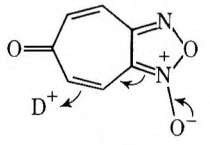


5 6



a b

4, X = O
7, X = NOH



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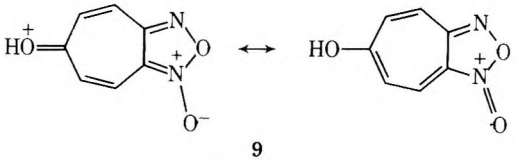


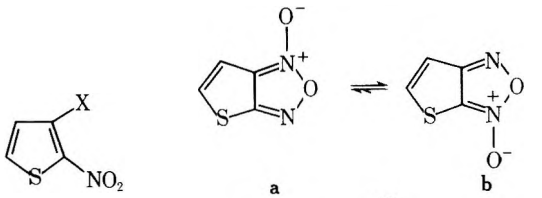
9

The mass spectrum of troponofuroxan (4) showed prominent peaks at P − 16 (–O) and P − 60 ($-N_2O_2$), as is frequently observed in furazan oxides,[8] and also at P − 28 (–CO) and P − 88 ($-CON_2O_2$).

The pmr spectrum of 4 showed two AB patterns (τ_a 2.32, τ_b 3.17, τ_c 2.665, τ_d 3.32; J_{ab}, J_{cd} = 12 Hz), with further long-range coupling (J_{bc} = 2 Hz).[9] No change in the spectrum was observed on heating: up to 150° the peaks were not noticeably broader than at room temperature. Assuming that the coalescence temperature is at least 40° above this, a lower limit of 24 kcal mol^{-1} can be placed on the free energy of activation for the reaction **4a** ⇌ **4b.**

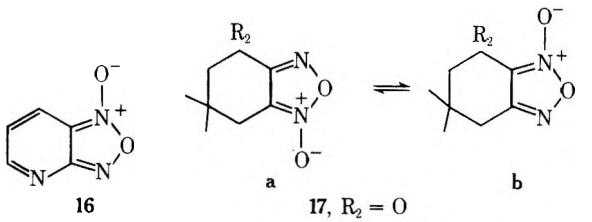
We attempted to exchange one of the protons in 4 for deuterium (*cf.* 8), in order to follow the isomerization by conventional kinetic measurements. However, no exchange was observed on standing the furoxan with CF_3COOD/D_2SO_4 for several hours, or on heating it to 100° for 30 min. The immediate color change seen on adding D_2SO_4 suggested that the tropone oxygen atom was protonated (9); this probably served to prevent further reaction. No coalescence or exchange broadening effects were found in the nmr spectrum of **9,** up to 100°.

Thieno[2,3-*c*]furazan Oxide (10). A few furoxans fused to five-membered rings have been prepared; they are all to some extent unstable.[10] However, no compound containing an aromatic five-membered ring fused to a furoxan has yet been reported. We aimed to prepare the thieno-fused derivative (**10**), because the ease of its isomerization (**10a** ⇌ **10b**) might provide information on the "aromaticity" of thiophene, relative to benzene, from a source independent of other criteria which have been applied in the past (*e.g.*, from ring current,[11] bond localization from coupling constants[12] or from bond lengths,[13] etc.[14]).



a b 10

11, X = Br
12, X = SPh
13, X = SO_2Ph
14, X = N_3
15, X = NH_2



16 a b

17, R_2 = O
18, R_2 = H,OAc

The replacement of the bromine by azide in 3-bromo-2-nitrothiophene (**11**) was effected by the sequence **11** → **12** → **13** → **14,** after attempts at direct replacement by azide ion in **11** had proved fruitless.[15] The azide **14** (the mass spectrum of which[9] showed significant differences from that of the furoxan: *cf.* ref 8b) was decomposed thermally, to give the furoxan **10,** in low yield. Other possible routes to **10,** *via* hypochlorite or phenyliodoso diacetate oxidation of the amine **15,** were still less successful, although the latter reagent did provide some furoxan. The amine was prepared by borohydride reduction of the azide **14,** after attempts directly to aminate the bromide **11** and the sulfone **13** had failed.

The furoxan **10,** characterized by its mass spectrum[9] and analytical data, showed in its pmr spectrum an AB pattern at room temperature, but the two isomers (**a** and **b**) gave separate signals at −45° (Figure 1). By comparison with benzofuroxans,[16,17] the shielding effect of the *N*-oxide group on an adjacent proton identifies the major isomer as **10a;** the equilibrium constant is 8 ± 1 at −45° ($\Delta G°$ 0.95 ± 0.07 kcal mol^{-1}). From the coalescence temperature for the fusion of signals H_a and $H_{a'}$ (−28 ± 10°), the free energy of activation ΔG^* for the isomerization **10b** → **10a** was determined[17] to be 12.3 ± 1 kcal mol^{-1}, the reverse reaction surmounting a barrier ~1 kcal higher.

The results therefore suggest, rather unexpectedly, that the tendency to form the transition state for the furoxan

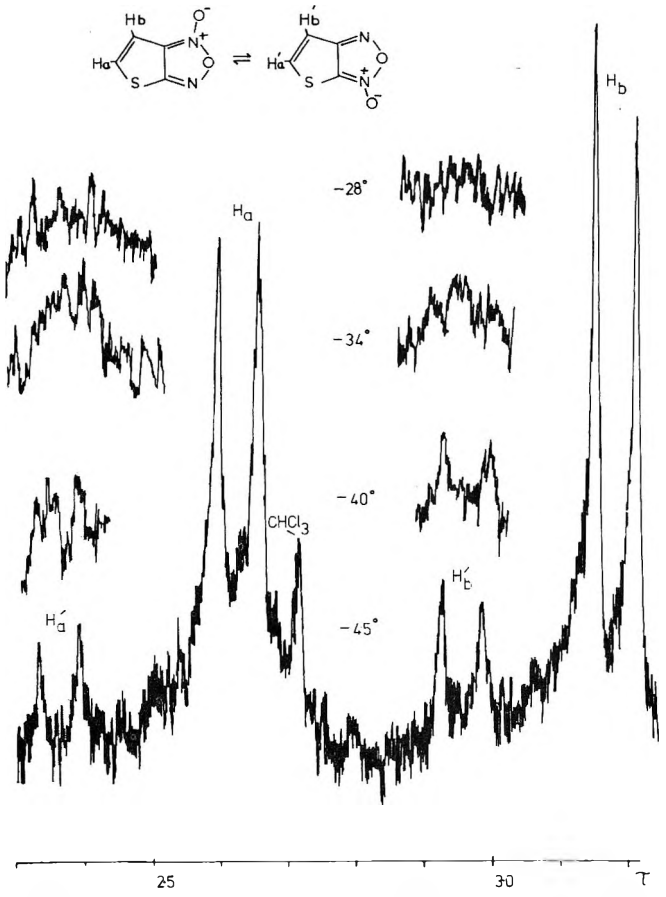


Figure 1. The pmr spectrum of thieno[2,3-*c*]furazan oxide (**10**) at various temperatures.

isomerization is greater in thieno[2,3-*c*]furoxan (**10**) than in benzofuroxan (**2**). It would, however, be unjustified to argue, on the strength of this, and in the face of a considerable body of evidence to the contrary, that the aromaticity of thiophene is greater than that of benzene. Two factors which might tend to lower the activation energy of **10**, by stabilizing 2,3-dinitrosothiophene, are electronic and ring-strain effects. The nitroso group is strongly electron withdrawing,[18] and the dinitrosothiophene would be expected to be stabilized as a result of the conjugation of these groups with the ring, which is generally accepted to be a better electron donor[19] than benzene. However, no evidence for the acceleration of benzofuroxan tautomerism by electron-donor substituents has been found in the past,[17] and furthermore pyrido[2,3-*c*]furoxan (**16**) and its derivatives isomerize at about the same rate as benzofuroxan,[20] despite the electron-withdrawing effect of the pyridine ring.

Ring strain provides a reasonable explanation for the observed results. We have already noted[10] that furoxans fused to five-membered rings show unusual properties, and even when fused to six-membered rings, as in the cases of compounds 17 and 18,[21] the energy of activation for their isomerization (**a** ⇌ **b**) is slightly but significantly lower than that for unfused, provided that they are not amino conjugated, examples (1), by ~1 kcal mol^{-1}.

A number of furoxans have been studied by X-ray crystallography,[22-25] and the "natural" bond angles in unfused compounds may be used to give an indication of whether or not fusion to another ring introduces strain, *tending* to widen the angle between the C=N bonds, and thus lengthen and weaken the O—N-2 bond. The published data on unfused furoxans give a mean value of 37° (± 2°) for this angle (α; see Figure 2b), which is close to

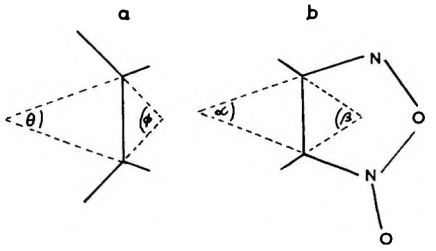


Figure 2. Bond angles in fused rings: $\theta = 360/n$; $\phi = 180(1 - 4/n)$; n = number of sides of a regular polygon.

that expected (36°) for the angle between nonadjacent sides of a regular pentagon. It is considerably smaller than the angle (θ; see Figure 2a) between radii of a regular hexagon (60°); indeed, for a regular n-gon θ falls to 37° only when n approaches 10.

The angle between the bonds to the 3 and 4 substituents of a furoxan (β in Figure 2b) is expected to be very susceptible to steric effects. For four substituted furoxans (the isomeric pairs of methyl *p*-bromophenyl[24] and methyl carbohydrazide[25] compounds) it is 80 ± 4°. This may be greater than that in the (unknown) unsubstituted compound, because of steric repulsion between substituents, but, accepting it as normal, it is comfortably satisfied by seven-membered ring fusion (ϕ = 77.1° when n = 7 in Figure 2a). These considerations suggest, therefore, that there is no appreciable extra strain involved in fusing a regular seven-membered ring to a furoxan, over that which the (substituted) five-membered ring itself contains. The angle ϕ in tropone (positions 4 and 5) is 76°, from X-ray diffraction data;[26] θ is 57° (nematic phase nmr measurements[27]).

For fusion to bond b of thiophene, the relevant angles θ and ϕ, derived from the microwave determination of the geometrical parameters by Bak, *et al.*,[28] are 72 and 44°. The former is considerably greater than α (37°) for furoxan: in drawing together the substituents on the thiophene ring to close the furoxan, ~35° of angle deformation has to be accommodated by the two bond angles interior to the furoxan ring at the fusion bond. This compares with 23° (60 − 37°) for benzo fusion. (X-ray diffraction data on benzofuroxans[23] indicate that these angles are the same, within a fairly wide margin of error, as in the unfused compounds.[22,24,25]) We consider that the extra bond angle strain in thieno[2,3-*c*]furoxan satisfactorily explains the anomalously low activation energy of isomerization of this compound.

Arising out of the above argument is the notion that benzofuroxan (**2**) may also be strained somewhat, and therefore the activation energy for the degenerate tautomerism of **4** would not have provided a reliable measure of the aromatic resonance stabilization energy of tropone, unless the effects of strain in **2** could be taken into account. Not wishing to become involved in the making of corrections of this kind, we therefore concentrated our attention upon the tautomerism of furoxans fused only to six-membered rings.

Biphenyleno[2,3-*c*]furazan Oxide (19). Introduction and Synthesis. Comparisons of the properties of biphenylene and naphthalene have been made on numerous occasions, since the early observations that, in contrast to naphthalene, bond orders, as revealed by chemical reactivity and bond lengths, indicated a greater degree of double-bond character between the 2 and 3 positions of biphenylene than between the 1 and 2—the "bond fixation" effect (see discussion in ref 29). This was satisfactorily explained using the Hückel MO theory.[30] For a quantitative comparison between the two systems, a distinction must be made between total delocalization energies, for the molecules as a whole, and the "local aromatic properties," in which the

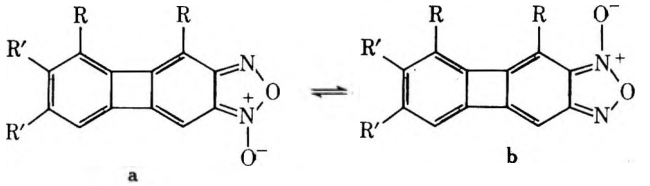
Table I
Bond Alternation and "Local Aromaticity" Comparisons

Compd	π-bond order,[a] larger/smaller	Aromaticity index[b]	Ortho coupling constants (Hz), larger/smaller[a,c]	Bond lengths (Å), longer/shorter[a,d]
Benzene	0.667/0.667 = 1.00	0.00	7.5/7.5 = 1.00	1.39/1.39 = 1.00
Naphthalene	0.725/0.603 = 1.20	1.803	8.2/6.9 = 1.19	1.415/1.364 = 1.037
Biphenylene	0.691/0.621 = 1.11	0.506	8.1/7.1 = 1.14	1.423/1.385 = 1.027

[a] Data relate only to the 1,2 and 2,3 bonds. [b] Defined in, and taken from, ref 31. [c] From ref 37, and G. Englert, P. Diehl, and W. Niederberger, *Z. Naturforsch. A*, **26,** 1829 (1971). [d] From ref 35, and E. G. Cox, D. W. J. Cruickshank, and J. A. S. Smith, *Nature*, **173,** 75 (1954).

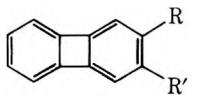
aromaticity associated with the individual rings of a molecule is assessed. The concept of local aromatic properties in polycyclic systems has been developed by Kruszewski,[31] who used the results of HMO theory, rather than any experimentally derived index of bond alternation, and classified biphenylene, together with naphthalene, as containing "moderately aromatic rings." Julg and François[13] have proposed an index of aromaticity based upon measurements of bond alternation, and for this the use of H–H coupling constants instead of bond orders (between which a linear relationship approximately obtains[32]) has been applied.[12] Bond alternation in fused benzene rings has recently been investigated in this way.[33] MO theory,[30,34] X-ray diffraction data,[35] and nmr coupling constant measurements[36,37] all agree in assigning to naphthalene a greater degree of bond alternation than to biphenylene, which according to these criteria has a higher aromaticity in its six-membered rings than has naphthalene (see Table I for relevant details).

For both naphthalene and biphenylene there are two possible ways of fusion of a furoxan ring—across the 1,2 and 2,3 bonds. While naphtho[1,2-c]furoxan (**3**) has been investigated,[3] naphtho[2,3-c]furoxan is unknown, and attempts to prepare it have failed.[3,38] For comparison with the known isomer, we set out to prepare biphenyleno[2,3-c]furoxan, and to determine the energy of activation for its (degenerate) isomerization (**19a** ⇌ **19b**). One substituted derivative, **20,** has been reported previously,[39] but it was not suitable for the present study.

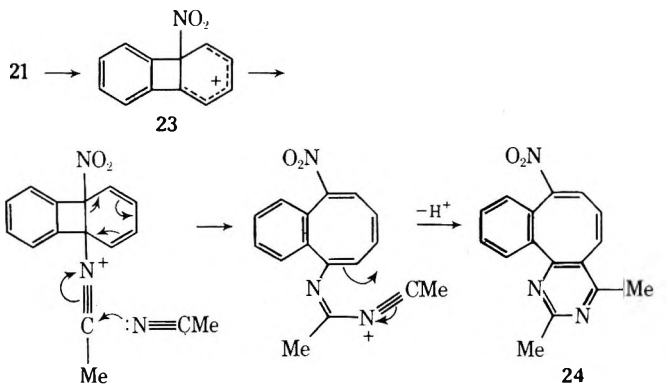


a b

19, R = R′ = H
20, R = Me; R′ = OMe



21, R = R′ = H
22, R = NH_2; R′ = NO_2



23 24

Biphenylene (**21**) was nitrated,[40] and the 2-nitrobiphenylene was aminated[41] to give 2-amino-3-nitrobiphenylene (**22**). The nitro amine (**22**) was oxidized [$PhI(OAc)_2$][42] to the furoxan **19** in good yield.

The first two stages of the synthesis, however, both proceed in low yield. We therefore tried (unsuccessfully) to find an alternative route to 2-nitrobiphenylene. Attempted nitration ($C_5H_{11}ONO_2$) of 2-lithiobiphenylene (prepared from **21** by bromination[43] and metal–halogen exchange) gave biphenylene as the only identified product. The major product of nitration of biphenylene in acetic anhydride is 5-acetoxy-10-nitrobenzocyclooctene;[44] this presumably arises by addition of acetate ion to the biphenylene–nitronium ion adduct **23,** followed by ring opening. We hoped to reduce the importance of this reaction by reducing the nucleophilic power of the solvent, and therefore tried nitration with nitric acid in trifluoroacetic acid (TFA) and its anhydride, and TFA/dichloromethane (1:5). In no case was any nitrobiphenylene isolated from the reaction. With nitronium tetrafluoroborate in acetonitrile a yellow product was obtained, to which, on analytical and spectral evidence and a logical mechanism for its formation, we assign the fused pyrimidine structure **24.** Particularly revealing in the nmr was the ABX pattern from the protons on the eight-membered ring (τ_A 3.67, τ_B 3.38, τ_X 2.33; J_{AB} = 11.7 Hz, J_{AX} = 3 Hz, J_{BX} = 0.7 Hz).

Results and Discussion. The nmr spectrum of **19,** in CCl_4 at 34°, showed a 4 H singlet at τ 2.63 and two 1 H doublets (J = 1 Hz) at 3.195 and 2.925, for H-5–8, and H-4 and H-9, respectively. Heating (DMSO; sealed tube) resulted in (reversible) coalescence of the latter signals, with T_c 129 ± 4°. Application of the Gutowski–Holm approximation and Eyring's equation to the rate of inversion **19a** ⇌ **19b** so obtained[17] gives a value of 20.6 ± 1 kcal mol^{-1} for the free energy of activation ΔG^* at T_c. This is slightly *higher* than that obtained[3] for naphtho[1,2-c]furoxan (**3**). Since the evidence summarized in the introduction suggested that the individual rings of biphenylene displayed *less* bond alternation than those in naphthalene, this result is unexpected. There is not necessarily a linear correlation between the activation energy for tautomerism of a fused furoxan and either any measure of the "local aromaticity" of the ring to which it is fused, or (more simply) the order of the bond between the atoms carrying the nitroso groups in the intermediate (or transition state). However, the reversal in the order suggested by naive prediction is not easy to explain.

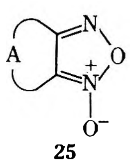
An alternative approach is to treat the delocalization energies of the heterocycle (**25**) and the dinitroso compound (**26**), in the following way. Consider the fused furoxan (**25**) to be built up from an alternant π-electron system A and the heterocyclic ring H. The delocalization energy of the fused system (**25**), DE_F, is $DE_A + DE_H + X$, where X is the increment resulting from the overlap of the two systems A and H. Similarly, the dinitroso compound (**26**) has

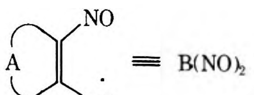
Table II
HMO π-Delocalization Energies[a]

Compd	DE_A	DE_B	$DE_B - DE_A$
2	0.47	2.00	1.53
3	2.42	3.68	1.26
19	3.15	4.51	1.35

[a] All figures, in units of β, are rounded off to second decimal place.[30,47,48]

delocalization energy $DE_D = DE_B + 2DE_{NO} + Y$, Y being the increase in delocalization energy produced by the addition of the two nitroso groups to the system B. If the transition state is approximately represented by **26**, then the dif-


25


26

ference in activation energies between two fused furoxan systems P and Q should be given by the difference between the delocalization energy differences ($DE_F - DE_D$) for the two systems, changes in σ-bonding energies, those due to strain,[45] etc., cancelling in the subtraction process. Furthermore, if we can set the contributions DE_H, DE_{NO}, X, and Y as equal between the systems,[46] then the difference in activation energies is given by $(DE_B - DE_A)_P - (DE_B - DE_A)_Q$. These quantities are readily accessible from simple Hückel MO calculations.[34,47,48]

The results from this approach were at first sight promising (Table II): the difference in activation energies between naphtho[1,2-*c*]furoxan (**3**) and benzofuroxan (**2**) is calculated to be 0.27β, equivalent[49] to ~5 kcal mol^{-1}, which is, within experimental error, just what is observed. Unfortunately, in the case of biphenyleno[2,3-c]furoxan (**19**), the calculated value is 1.6 kcal mol^{-1} (0.09β) *below* that of **3**; the value found is ~1 kcal *above*. Clearly, a more sophisticated approach[46,50] is necessary before the rationalization of the activation energies for isomerization of fused furoxans can be achieved. Until then, it does not seem likely that the reaction can be used to provide any useful quantitative information about aromaticity, "local" or otherwise.

Experimental Section

Melting points are uncorrected. Nmr spectra were of $CDCl_3$ solutions, taken on a Varian HA-100 instrument, with V4343 variable temperature probe attachment, unless otherwise specified. Ir spectra were of samples mulled with bromoform, unless otherwise stated. Mass spectra (70 eV ionizing potential) were measured on a Hitachi Perkin-Elmer RMU 21 instrument.

6-Hydroxyimino-6*H*-cyclohepta[*c*]furazan 1-Oxide (7). α-Tropolone[51] was converted by sodium nitrite in acetic acid into 5-nitrosotropolone[52] (cyclohepta-3,6-diene-1,2,5-trione 5-oxime). This (0.5 g) was heated under reflux 2 hr in ethanol (50 ml) with hydroxyammonium chloride (0.75 g). Removal of solvent left a dark red oil, which was dissolved in the minimum quantity of hot water and decanted from a small amount of undissolved tar. On cooling, the solution deposited buff prisms of the trioxime **6** (0.45 g, 82%), mp 206–207° (lit.[53] mp 204°). The trioxime (1.2 g) in aqueous NaOH (1 *N*, 50 ml) was stirred for 10 min with potassium ferricyanide (3 g in 20 ml of H_2O). The brown precipitate which formed was filtered off, dissolved in ether, dried ($MgSO_4$), and purified by chromatography on silica (eluant hexane–ethyl acetate, 2:1), giving the hydroxyiminofuroxan **7** as pale yellow prisms (0.4 g, 34%), mp 185–186° (sublimes), which, despite the sharp melting point, was probably a mixture of isomers: ir 3180–2740 (br), 1595, 1520, 1480, 1440, 1020 cm^{-1}; mass spectrum *m/e* (rel intensity) 179 (73), 163 (20), 149 (31), 119 (100).

Anal. Calcd for $C_9H_7N_3O_4$: C, 48.9; H, 3.2; N, 19.0. Found: C, 47.4; H, 3.1; N, 23.2.

In acetic anhydride the oxime **7** formed an acetate: mp 143–165° (from ethyl acetate–hexane); ir 1786, 1598, 1530, 1363 cm^{-1}. Both this compound and the oxime **7** gave complex nmr spectra in the region of τ 2.5–3.5, not analyzable as simple ABCD systems and suggesting the presence of geometrical isomers. The spectra were unchanged up to 130°.

Anal. Calcd for $C_9H_7N_3O_4$: C, 48.9; H, 3.2; N, 19.0. Found: C, 48.4; H, 3.5; N, 18.7.

6-Keto-6*H*-cyclohepta[*c*]furazan 1-Oxide (8). The oxime **7** (0.4 g) in formic acid (20 ml, 98%) was heated for 48 hr under reflux with cupric carbonate (1 g). Water (50 ml) was added, and the acid was neutralized with sodium hydrogen carbonate. The organic material was extracted into ethyl acetate, and the extract was washed with 1 *N* NaOH to remove unchanged oxime. The organic layer was dried ($MgSO_4$), concentrated, and filtered through a short column of alumina, eluting with ethyl acetate. The solvent was removed and the residue was recrystallized from hexane, giving the troponofuroxan **8** as pale yellow needles (0.12 g, 33%): mp 95–96°; ir (CCl_4) 1600 (vs), 1628, 1640 cm^{-1}; nmr (see text).

Anal. Calcd for $C_7H_4N_2O_3$: C, 51.2; H, 2.5; N, 17.0. Found: C, 51.0; H, 2.6; N, 16.9.

The following unsuccessful attempts were made to prepare **8** from its oxime **7**. (a) (*Cf.* ref 54). The oxime (50 mg) was heated in formalin (1 ml) and concentrated hydrochloric acid (1 ml) under reflux for 4 hr. (b) (*Cf.* ref 55). The oxime (50 mg) was heated under reflux for 3 days in ethanol (1 ml) and aqueous sodium hydrogen sulfite (1 ml, 40%). (c) (*Cf.* ref 56). The oxime (75 mg) in methanol (5 ml) was stirred for 10 min with thallium(III) nitrate (185 mg) in methanol (5 ml). Aqueous sulfuric acid (3 *N*, 20 ml) was added, and the solution was extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and filtered through an alumina column. The oxime was recovered unchanged from processes a–c. (d) The oxime (88 mg) was converted into its tosylate (mp 202–204°) using *p*-toluenesulfonyl chloride in pyridine. The tosylate was heated in dioxane for 5 min at 65° with a large excess (~5 mol) of sodium borohydride. Tlc examination showed the tosylate to remain. A catalytic amount (~0.1 mol) of aluminum chloride was added, and heating was continued for 5 min. Addition of water and ether extraction gave unchanged tosylate.

3-Azido-2-nitrothiophene (14). 3-Bromo-2-nitrothiophene (**11**)[57] was converted by alkaline ethanolic benzenethiol into the 3-phenylthio compound **12**,[58] which was oxidized to the sulfone **13**,[59] forming cream-colored prisms, mp 140–141° (from $CHCl_3$–hexane (lit.[59] mp 143°). The sulfone (2 g) was stirred at 20° in dimethyl sulfoxide (50 ml) for 2.5 hr with sodium azide (0.6 g). Water (150 ml) was added, and the mixture was extracted with ether (3 × 50 ml). After drying ($MgSO_4$), the extracts were passed down a short (3 cm) alumina column. The eluate was concentrated and warmed, and hexane was added. The mixture was cooled to provide the azide as prisms (1.1 g, 87%): mp 79–81° dec; ir 2160, 2105, 1540, 1330 cm^{-1}; for mass spectrum see footnote 9. A satisfactory elemental analysis could not be obtained for this compound, owing to its ready decomposition.

3-Amino-2-nitrothiophene (15). Sodium borohydride (0.5 g) in methanol (20 ml) was added to the azide **14** (0.68 g) in methanol (30 ml), cooling in an ice bath to maintain the temperature below 20°. After the initially vigorous reaction had ceased (20 min) the methanol was removed *in vacuo*, water (10 ml) was added, and the acidity was adjusted to pH 7 with dilute HCl. Ether extraction (3 × 20 ml), drying ($MgSO_4$), and removal of solvent from the extract gave the amine as yellow prisms (0.52 g, 90%) (from ethyl acetate–hexane), mp 59–60° (lit.[60] mp 58.5–60°).

Thieno[2,3-*c*]furazan Oxide (10). A. From the Azide 14. The azide (0.22 g) was heated to reflux for 30 min in acetic acid (25 ml). Saturated aqueous NaCl (150 ml) was added to the cooled solution, and the mixture was extracted with ether (3 × 25 ml). The combined extracts were washed once with brine and twice with aqueous sodium hydrogen carbonate, then dried ($MgSO_4$), and filtered through alumina. The ether was removed, and the yellow residue of furoxan **10** was recrystallized from hexane, giving pale yellow needles (0.08 g, 45%): mp 101–102° (sublimes); ir 3100, 1635, 1500, 1470, 1410 cm^{-1}; nmr τ_A 2.6, τ_B 3.15 (J_{AB} = 6 Hz) at 30°; for low temperature spectrum see Figure 1; for mass spectrum see footnote 9.

Anal. Calcd for $C_4H_2N_2O_2S$: C, 33.8; H, 1.4; N, 19.7. Found: C, 33.9; H, 1.5; N, 19.8.

More concentrated azide solutions, treated as above, resulted in lower yields, while no furoxan was isolated from thermolysis in toluene.

B. From the Amine 15. The amine (0.09 g) was allowed to stand

for 24 hr in chloroform (50 ml) with phenyliodoso diacetate (1.0 g), followed by heating to 40° for 1 hr. The solvent was removed, ethyl acetate (10 ml) was added, and the solution was passed through a short alumina column. Removal of solvent gave the crude furoxan **10** (19 mg, 26%), mp 96–99°.

The furoxan **10** was reduced to a complex mixture of products by trimethyl phosphite in ether at 0°, but we were not able to isolate any of the expected furazan from this.

2-Nitrobiphenylene. Biphenylene[61] (3.0 g) was nitrated according to the method of Baker, *et al.*[40] The product was purified by chromatography on silica, giving yellow needles: mp 105–6° (lit.[40] mp 105–106.5°); 0.45 g, 12%.

In an attempt to improve the yield, samples of biphenylene were stirred for 1 hr at 0° with nitric acid (*d* 1.42, 1.2 equiv.) in (a) trifluoroacetic acid, (b) trifluoroacetic anhydride, and (c) dichloromethane–trifluoroacetic acid (5:1). In each case water was next added and the mixture was extracted with ethyl acetate. A tlc examination showed the presence of several components less mobile than biphenylene, but none of the 2-nitro compound was detected.

Biphenylene was converted into 2-bromobiphenylene, using bromine and thallic acetate.[43] 2-Bromobiphenylene (0.53 g) in ether (100 ml) was treated at −50° with *n*-butyllithium in hexane (4 ml, 15%). The solution was allowed to reach room temperature, and, after again cooling to −50°, dry isoamyl nitrate was added and the solution was stirred for 1 hr, the temperature warming to 10°. The mixture was allowed to stand overnight and was then washed with water. Much tarry material was deposited. Examination of the solution and tars by tlc revealed the presence of biphenylene and at least three other components, but no 2-nitrobiphenylene.

2-Amino-3-nitrobiphenylene(22). 2-Nitrobiphenylene (0.45 g) was aminated, using hydroxylamine hydrochloride and potassium hydroxide in methanol.[41] The product **22** (0.19 g, 38%) and unchanged nitrobiphenylene were separated by chromatography on alumina (benzene–chloroform).

Biphenyleno[2,3-*c*]furazan Oxide (19). Iodosobenzenediacetate (0.5 g) in benzene (20 ml) was added to a suspension of 2-amino-3-nitrobiphenylene(0.19 g) in benzene (50 ml), and the mixture was stirred for 15 hr. Removal of solvent *in vacuo* and chromatography on silica (hexane–ethyl acetate, 6:1) gave the furazan oxide **19** as light brown prisms (0.13 g, 70%): mp 198–200°; ir (CCl_4 solution) 1613, 1495, 1456 cm^{-1}; for nmr see text; mass spectrum *m/e* (rel intensity) 210 (P^+, 41%), 194 (40), 178 (18), 164 (18), 152 (22), 151(25), 150 (100).

Anal. Calcd for $C_{12}H_6N_2O_2$: C, 68.6; H, 2.9; N, 13.1. Found: C, 68.6; H, 3.0; N, 13.1.

2,4-Dimethyl-8-nitrobenzocycloocteno[5,6-*d*]pyrimidine (24). Nitronium tetrafluoroborate[62] (1.22 g) in acetonitrile (80 ml, from P_2O_5) was added over 1 hr to a stirred solution of biphenylene (1.2 g) in dry acetonitrile (150 ml) at 0° under N_2. After 1 hr at room temperature the solvent was removed, leaving a green solid which was shaken with saturated aqueous Na_2CO_3 (50 ml) and then with ethyl acetate (50 ml). The bright red organic layer was dried ($MgSO_4$) and filtered through alumina. Concentration and cooling gave the pyrimidine **24** as yellow prisms (0.94 g, 43%): mp 211°; ir 2960, 1550–1530 (br), 1525, 1430, 1380, 1330 cm^{-1}; nmr ($CDCl_3$) τ 7.55 (3 H) and 7.27 (3 H, 2 CH_3), 3.85–3.25 (m, 2 H, H_A, H_B), 2.9–2.5 (4 H, H-9–12), 2.4–2.3 (m, 1 H, H_X) (see text); mass spectrum *m/e* (rel intensity) 279 (P^+, 5%), 233 (58), 192 (100), 151 (82), 150 (23).

Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.8; H, 4.7; N, 15.0. Found: C, 68.9; H, 4.7; N, 14.7.

The pyrimidine **24** gave a crystalline hydrochloride [mp 211° dec; ir (Nujol mull) 2500–2200, 1950, 1630, 1525, 1340 cm^{-1}] by extraction of **24** from ethyl acetate into 10% aqueous hydrochloric acid and precipitation of the salt with acetone.

Attempts to contract the cyclooctene ring with base (*cf.* Barton and Whitaker[44]) led to recovery of starting material. The pyrimidine **24** (0.1 g) in methanol (15 ml) was stirred with potassium carbonate (0.5 g) for 4 days. Removal of methanol and addition of water gave a clear yellow solution from which nothing was extracted by ethyl acetate. Neutralization of the alkali led to recovery of the pyrimidine, which therefore appears to function as an acid by reversible addition of hydroxide (or methoxide) to the nitroalkene part of the molecule. More forcing conditions (reflux with alcoholic KOH) led to decomposition, but to no identified products.

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Supplementary Material Available. Diagrams of the nmr spectra of compound **4** and the mass spectra of compounds **10** and **14**, and HMO data (including polarizabilities) of 1,2-dimethylenebenzocyclobutene, 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-74-2956.

Registry No.—**4**, 52003-13-1; **6**, 52003-14-2; **7**, 52003-15-3; **7** acetate, 52003-16-4; **10**, 52003-17-5; **11**, 24430-27-1; **12**, 52003-18-6; **13**, 33786-80-0; **14**, 52003-19-7; **15**, 52003-20-0; **19**, 52003-21-1; **22**, 18798-45-3; **24**, 52003-22-2; **24** HCl, 52003-23-3; 5-nitrosotropolone, 52003-24-4; 2-nitrobiphenylene, 18931-53-8; biphenylene, 259-79-0; iodosobenzenediacetate, 3240-34-4; 1,2-dimethylenebenzocyclobutene, 20265-84-3.

References and Notes

(1) Part IV: A. Gasco and A. J. Boulton, *J. Chem. Soc., Perkin Trans. 2*, 1613 (1973).
(2) We use the well-established trivial name "furoxan" in this paper, as synonymous with "furazan oxide," to avoid the otiose repetition required by the consistent use of the latter, IUPAC-recommended, name.
(3) M. Altaf-ur-Rahman, A. J. Boulton, D. P. Clifford, and G. J. T. Tiddy, *J. Chem. Soc. B*, 1516 (1968).
(4) F. B. Mallory and A. Cammarata, *J. Amer. Chem. Soc.*, **88**, 61 (1966).
(5) K. I. Dahlqvist and S. Forsen, *J. Mag. Res.*, **2**, 61 (1970).
(6) D. J. Bertelli and T. G. Andrews, *J. Amer. Chem. Soc.*, **91**, 5280 (1969); D. J. Bertelli, T. G. Andrews, and P. O. Crews, *J. Amer. Chem. Soc.*, **91**, 5286 (1969).
(7) T. Nozoe, S. Ito, S. Suzuki, and K. Hiraga, *Proc. Japan. Acad.*, **32**, 344 (1956); *Chem. Abstr.*, **51**, 2806 (1957).
(8) (a) A. J. Boulton, P. Hadjimihalakis, A. R. Katritzky, and A. Majid Hamid, *J. Chem. Soc. C*, 1901 (1969); (b) R. A. Abramovitch, E. P. Kyba, and E. F. V. Scriven, *J. Org. Chem.*, **36**, 3796 (1971).
(9) See paragraph on supplementary material at the end of this paper.
(10) J. Ackrell, M. Altaf-ur-Rahman, A. J. Boulton, and R. C. Brown, *J. Chem. Soc., Perkin Trans. I*, 1590 (1972).
(11) J. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961).
(12) (a) H. Günther, *Tetrahedron Lett.*, 2967 (1967); (b) D. Cremer and H. Günther, *Justus Liebigs Ann. Chem.*, **763**, 87 (1972).
(13) A. Julg and P. Francois, *Theoret. Chim. Acta*, **8**, 249 (1967).
(14) For a recent account of aromaticity in heterocyclic systems, see M. J. Cook, A. R. Katritzky, and P. Linda, *Advan. Heterocycl. Chem.*, **17**, 255 (1974).
(15) R. C. Brown, Ph.D. Thesis, University of East Anglia, 1970. We have since learnt that Professor S. Gronowitz and coworkers (Lund) were able to effect this reaction.
(16) R. K. Harris, A. R. Katritzky, S. Øksne, A. S. Bailey, and W. G. Paterson, *J. Chem. Soc.*, 197 (1963).
(17) A. J. Boulton, A. R. Katritzky, M. J. Sewell, and B. Wallis, *J. Chem. Soc. B*, 914 (1967).
(18) (a) There is some disagreement over the value of σ_R^0 (NO); a recent estimate,[18b] derived from energy barriers to substituent rotation in *p*-nitrosodimethylaniline, is +0.25; *cf.* +0.17 for the NO_2 group.[18c] (b) T. B. Grindley, A. R. Katritzky, and R. D. Topsom, *J. Chem. Soc. Perkin Trans. 2*, in press. (c) R. T. C. Brownlee, R. E. J. Hutchinson, A. R. Katritzky, T. T. Tidwell, and R. D. Topsom, *J. Amer. Chem. Soc.*, **90**, 1757 (1969).
(19) A variety of substituent σ constants are quoted for the 2- and 3-thienyl substituents, ranging from slightly positive (electron withdrawing) to *ca.* −0.4, in strongly electron-demanding situations (σ_p^+ values): see F. Fringuelli, G. Marino, and A. Taticchi, *J. Chem. Soc. (B)*, 1595 (1970); *ibid.*, 2302 (1971); *J. Chem. Soc. Perkin Trans. II*, 158 (1972).
(20) A. J. Boulton, P. J. Halls, and A. R. Katritzky, *J. Chem. Soc. B*, 636 (1970).
(21) (a) J. Ackrell and A. J. Boulton, *J. Chem. Soc. Perkin Trans. 1*, 351 (1973). (b) J. Ackrell, Ph.D. Thesis, University of East Anglia, 1973.
(22) M. Calleri, G. Chiari, and D. Viterbo, *Cryst. Struct. Commun.*, **2**, 335 (1973).
(23) D. Britton and W. E. Noland, *J. Org. Chem.*, **27**, 3218 (1962), and *Acta Crystallogr. B*, **28**, 1116 (1972); D. Britton, G. L. Hardgrove, R. Hegstrom, and G. V. Nelson, *ibid.*, 1121 (1972); D. Britton, J. Konnert, J. Hamer, and L. M. Trefonas, *ibid.*, 1123 (1972); R. C. Gehrz and D. Britton, *ibid.*, 1126 (1972).
(24) M. Calleri, G. Ferraris, and D. Viterbo, *Acta Crystallogr. B*, **25**, 1126, 1133 (1969).
(25) M. Calleri, G. Chiari, and D. Viterbo, *Cryst. Struct. Commun.*, **1**, 407 (1972); C. Germain and D. Viterbo, *ibid.*, 411 (1972).
(26) M. J. Barrow, O. S. Mills, and G. Filippini, *J. Chem. Soc., Chem. Commun.*, 66 (1973).
(27) J. W. Emsley and J. C. Lindon, *Mol. Phys.*, **25**, 641 (1973).
(28) B. Bak, D. Christensen, L. Hansen-Nygaard, and J. Rastrup-Andersen, *J. Mol. Spectrosc.*, **7**, 58 (1961).
(29) M. P. Cava and M. J. Mitchell, "Cyclobutadiene and Related Compounds," Academic Press, New York and London, 1967.
(30) J. D. Roberts, A. Streitwieser, and C. M. Regan, *J. Amer. Chem. Soc.*,

74, 4579 (1952). For review, see H. E. Simmons and A. G. Anastassiou, in ref 29, p 400.
(31) J. Kruszewski, *Soc. Sci. Lodziensis, Acta Chim.*, **16,** 77 (1971). The "aromaticity index" is rather an expression of bond alternation; benzene appears at the origin (zero), and larger values are associated with diminished aromaticity.
(32) N. Jonathan, S. Gordon, and B. P. Dailey, *J. Chem. Phys.*, **36,** 2443 (1962).
(33) H. Günther, A. Shyoukh, D. Cremer, and K. H. Frisch, *Tetrahedron Lett.*, 781 (1974).
(34) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1962, p 268.
(35) J. K. Fawcett and J. Trotter, *Acta Crystallogr.*, **20,** 87 (1966); D. W. J. Cruickshank, *Tetrahedron*, **17,** 155 (1962).
(36) B. Dischler and G. Englert, *Z. Naturforsch.*, **16a,** 1180 (1961).
(37) G. Fraenkel, Y. Asahi, M. J. Mitchell, and M. P. Cava, *Tetrahedron*, **20,** 1179 (1964); A. R. Katritzky and R. E. Reavill, *Recl. Trav. Chim. Pays-Bas*, **83,** 1230 (1964).
(38) R. Selvarajan and J. H. Boyer, *J. Org. Chem.*, **36,** 3464 (1971).
(39) J. F. W. McOmie and D. E. West, *J. Chem. Soc. C*, 1084 (1970).
(40) W. Baker, J. W. Barton, and J. F. W. McOmie, *J. Chem. Soc.*, 2666 (1958).
(41) J. W. Barton, A. R. Grinham, and K. E. Whitaker, *J. Chem. Soc. C*, 1384 (1971).
(42) L. K. Dyall and K. H. Pausacker, *Aust. J. Chem.*, **11,** 491 (1958); K. H. Pausacker and J. G. Scroggie, *ibid.*, 485 (1958), and references therein.
(43) A. McKillop, D. Bromley, and E. C. Taylor, *J. Org. Chem.*, **37,** 88 (1972).
(44) J. W. Barton and K. E. Whitaker, *J. Chem. Soc. C*, 1663 (1968).
(45) We are here dealing only with furoxans fused to six-membered rings.
(46) (a) A referee, quite rightly, points out that this requires justification. DE_H and DE_{NO} are equal by definition. *X* and *Y* we had at first supposed would be equal because the fragments A and B are both alternant hydrocarbon systems, with, therefore, overall charge density of zero on each atom. For a rather more rigorous argument we extend the method of Brown[46b] to the two connections between A and H, and B and the NO groups. This leads to the expression

$$X = -[0.811(\sqrt{\lambda_a\lambda_h} + \sqrt{\lambda_{a'}\lambda_{h'}}) + 0.124]\beta$$

for the furoxan **25,** where λ's are the "self-atom polarisabilities" (also denoted by P, and π_r) of the atoms A and H connected by the fusion. For **26**

$$Y = -[0.811\sqrt{\lambda_{NO}}(\sqrt{\lambda_b} + \sqrt{\lambda_{b'}}) + 0.124]\beta$$

taking λ's as positive. *Y* for o-dinitrosobenzene, 1,2-dinitrosonaphthalene, and 2,3-dinitrosobiphenylene is

$$-(k\sqrt{\lambda_{NO}} + 0.124)\beta$$

where *k* is 1.024, 1.056, and 1.056, respectively. For any reasonable value of λ_{NO}, the difference between these *Y* terms is very small—less than 0.5 kcal. *X* can be simplified, if we adopt a mean value $\lambda_{\bar{h}}$ for the polarisability at the heterocyclic ring, to

$$-[0.811\sqrt{\lambda_{\bar{h}}}(\sqrt{\lambda_a} + \sqrt{\lambda_{a'}}) + 0.124]\beta$$

The polarizabilities relevant to the biphenylenofuroxan case (A is 7,8-dimethylenebicyclo[4.2.0]octa-1,3,5-triene or 1,2-dimethylenebenzocyclobutene) are not available in ref 47 and are published as material supplementary to this paper.[9] *X* for furoxans **2, 3,** and **19** is

$$-(k\sqrt{\lambda_{\bar{h}}} + 0.124)\beta$$

where *k* is 1.283, 1.159, and 1.300, respectively. The differences between *X*'s are not insignificant here: a correction (of *ca.* −2 kcal.) reducing $DE_B - DE_A$ for compound **3,** compared with **2** and **19,** should be made. This brings the calculated result for **3** more into line with the observed comparison between **3** and **19,** but now the comparison between **2** and **3** is upset. (b) R. D. Brown, *Aust. J. Sci. Res.*, **5A, 339** (1952).
(47) A. Streitwieser, J. I. Brauman, and C. A. Coulson, "Supplemental Tables of Molecular Orbital Calculations," Pergamon Press, Oxford, 1965.
(48) S. L. Manatt and J. D. Roberts, *J. Org. Chem.*, **24,** 1336 (1959).
(49) Taking $\beta = -18$ kcal mol^{-1}: J. D. Roberts, "Notes on Molecular Orbital Calculations," W. A. Benjamin, New York, N. Y., 1961. See also ref 34, p 241 ff.
(50) A further step (*cf.* also footnote 46) in this direction was suggested by the referee, who points out that it is incorrect, in biphenylene, to take all the resonance integrals across bonds as equal, the bonds joining the six-membered rings being so much longer than the rest. A small adjustment (to 0.8β) alters the total π energy by 0.187β (3.4 kcal) in the desired direction. However, it seems unreasonable not to introduce a similar correction to the fragment A (1,2-dimethylenebenzocyclobutene), and we find that the total π energy of this system is more sensitive to adjustment of the integrals of the corresponding bonds (π energy raised by 0.247β on reducing integral to 0.8β). This more than cancels out the adjustment made to the intermediate (**26**). We observe that, for both biphenylene and dimethylenebenzocyclobutene, as the resonance integral assigned to the long bonds is increased from 0 (separated systems) through $n\beta$ to 1β, the graph of π energy *vs.* *n* describes a parabolic curve between energies E_0 and E_1 (for 0β and 1β) of form

$$(E_n - E_0) = \sqrt{n}(E_1 - E_0)$$

(51) H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain, and E. J. Gaughan, *J. Amer. Chem. Soc.*, **87,** 5257 (1965).
(52) T. Nozoe and S. Seto, *Proc. Japan. Acad.*, **27,** 188 (1951); *Chem. Abstr.*, **46,** 4522 (1952).
(53) T. Nozoe, Japanese Patent 3724 (1957); *Chem. Abstr.*, **52,** 8204 (1958).
(54) M. P. Cava, R. L. Little, and D. R. Napier, *J. Amer. Chem. Soc.*, **80,** 2260 (1958).
(55) S. H. Pines, J. M. Chemerda, and M. A. Kozlowski, *J. Org. Chem.*, **31,** 3446 (1966).
(56) A. McKillop, J. D. Hunt, R. D. Naylor, and E. C. Taylor, *J. Amer. Chem. Soc.*, **93,** 4918 (1971).
(57) W. Steinkopf, H. Jacob, and H. Penz, *Justus Liebigs Ann. Chem.*, **512,** 136 (1934).
(58) D. Spinelli, G. Guanti, and C. Dell'Erba, *Ric. Sci.*, **38,** 1051 (1968); *Chem. Abstr.*, **71,** 29788 (1969).
(59) G. Guanti, C. Dell'Erba, and P. Macera, *J. Heterocycl. Chem.*, **8,** 537 (1971).
(60) S. Nishimura, T. Kawasaka, and E. Imoto, *Nippon Kagaku Zasshi*, **82,** 1636 (1961); *Chem. Abstr.*, **58,** 13887 (1963).
(61) F. M. Logullo, A. H. Seitz, and L. Friedman, *Org. Syn.*, **48,** 12 (1968).
(62) G. A. Olah and S. J. Kuhn, *Org. Syn.*, **47,** 56 (1967).

Purine N-Oxides. LVIII. N-Hydroxypurine Analogs. N-Hydroxypyrrolo[2,3-d]pyrimidines[1]

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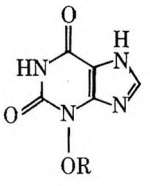
The syntheses of 1-hydroxy-1,2,3,4-tetrahydro-2,4-dioxopyrrolopyrimidine and its 6-methyl derivative are described, and their chemical properties are compared with those of the analogous purines. The N-hydroxy esters of these compounds, prepared in *in situ*, undergo a ready elimination–substitution reaction at room temperature. The ester of the first gave, with water, the 5-oxo derivative. With methionine it gave both 5- and 6-methylmercapto derivatives, and the intermediate 5-methionium derivative was isolable. The esters of the 6-methyl derivative lead to the corresponding 5-substituted products. Tosyl esters, prepared in pyridine, lead to similar pyridinium derivatives. Plausible mechanisms for these reactions are discussed and from the analogies to the reactions of 3-acetoxyxanthine their possible oncogenicity is proposed.

An interest in certain related pyrrolo[2,3-*d*]pyrimidines as antibiotics[3] and our interest in structural analogs of the oncogenic 3-hydroxyxanthine[4,5] prompted us to study *N*-hydroxypyrrolo[2,3-*d*]pyrimidine derivatives. Chemical[6–10] and biochemical[11,12] studies have shown that the oncogenicity of 3-hydroxyxanthine and some of its derivatives are paralleled by unique chemical reactivities of esters of these *N*-hydroxypurines.

In water at room temperature 3-acetoxyxanthine (**1**, R = Ac) undergoes an SN1′ reaction with nucleophiles to yield 8-substituted xanthines.[6–9] In our previous studies of analogs of 3-hydroxyxanthine (**1**, R = H) to determine the features required for this type of reactivity, it was shown that esters of 1-*N*-hydroxypteridines[13] failed to undergo any similar substitution reaction, and esters of 1-*N*-hydroxyquinazoline[14] underwent a similar reaction only under relatively drastic conditions. The differences in reactivity could be attributed to the distribution of π-electron density[15] in each of these compounds.



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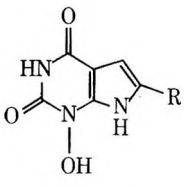

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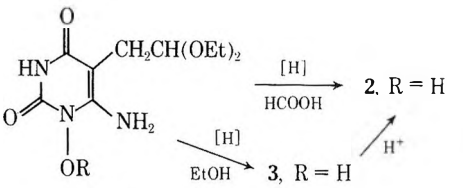
In this paper the reactions of 1-hydroxy-1,2,3,4-tetrahydro-2,4-dioxopyrrolo[2,3-*d*]pyrimidine, which can also be trivially named "3-hydroxy-7-deazaxanthine" (**2**, R = H), and 1-hydroxy-1,2,3,4-tetrahydro-6-methyl-2,4-dioxopyrrolo[2,3-*d*]pyrimidine (**2**, R = Me) are described. Because of the relatively richer π-electron character of the pyrrole ring than that of the imidazole ring, **2**, R = H, and **2**, R = Me, can be expected to be more reactive than 3-hydroxyxanthine and 3-hydroxy-8-methylxanthine, respectively.

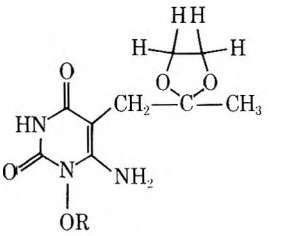
1-Hydroxy-1,2,3,4-tetrahydro-2,4-dioxopyrrolo[2,3-*d*]-pyrimidine was prepared according to a similar procedure for the preparation of 2,4-dihydroxypyrrolo[2,3-*d*]pyrimidine.[16] Condensation of benzyloxyurea with ethyl 2,2-diethoxyethylcyanoacetate in the presence of sodium ethoxide in ethanol gave 6-amino-1-benzyloxy-5-(2,2-diethoxyethyl)uracil (**3**, R = CH_2Ph). Although the condensation could give 6-amino-3-benzyloxy-5-(2,2-diethoxyethyl)uracil as an isomer, the paper and column chromatographies of the product (72%) showed a single component. Comparison of the uv spectrum of the product with that of 6-amino-1-benzyloxyuracil[17] indicated **3**, R = CH_2Ph, to be the product. The uv absorption of thymine at pH 7 shows a bathochromic shift of about 5 nm from that of uracil.[18] Since a 6-nm red shift is observed in the difference of absorptions between **3**, R = CH_2Ph, and 6-amino-1-benzyloxyuracil, the structure of **3** was confirmed. Hydrogenation in ethanol gave the *N*-hydroxyuracil (**3**, R = H), followed by an acid catalyzed ring closure ($t_{1/2}$ = 25 min, at pH 1.0) to give the desired compound (**2**, R = H) in almost quantitative yield or, in one step but in poorer yield, by hydrogenation of **3**, R = CH_2Ph, in formic acid (Scheme I).

Scheme I



3

1-Hydroxy-1,2,3,4-tetrahydro-2,4-dioxo-6-methylpyrrolo[2,3-*d*]pyrimidine (**2**, R = Me) was prepared by a similar condensation of the appropriate ketal with benzyloxyurea, and the identity of **4**, R = CH_2Ph, was established as was the foregoing. Hydrogenation of **4**, R = CH_2Ph, in formic acid gave a mixture from which pure **2**, R = Me, could not be readily isolated. However, hydrogenation of **4**, R = CH_2Ph, in ethanol followed by acid-catalyzed ring closure ($t_{1/2}$ = 70 min, at pH 1.0) gave an excellent yield of **2**, R = Me.



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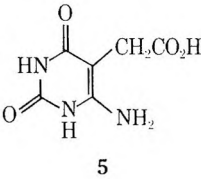

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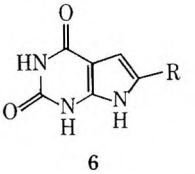


6

Comparison of the nmr spectra of **2**, R = H and R = Me, with those of the known analogs[13,14] of 3-hydroxyxanthine determined that **2**, R = H and R = Me, existed primarily in the tautomeric form shown. Uv spectrum of the neutral

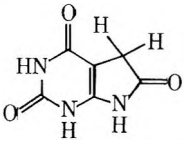
Table I
Uv Spectra and pK_a's

Compd	pH	λ_{max} ($\epsilon \times 10^{-3}$)	pK_a
2, R = H	3.0	279 (7.4), 244 (7.6), 216 (9.5)	6.37 ± 0.002
	10	300 (7.0), 258 (7.2)	~12
2, R = Me	3.6	285 (7.7), 249 (9.2), 216 (12.5)	6.41 ± 0.02
	9	304 (8.8), 262 (14.0)	12.42 ± 0.05
	14	294 (6.6), 266 (7.7)	
6, R = H	2	274 (6.1), 238 (6.7), 214 (14.9)	7.77 ± 0.05
	10	285 (7.1), 248 (9.9), 214 (23.3)	

species of **2**, R = H or CH_3, showed a characteristic, about 5 nm, bathochromic shift[13] relative to the corresponding pyrrolopyrimidine **6**, R = H or Me, thus confirming the N–OH form.

The first ionizations, that of the N–OH, of **2**, R = H or CH_3, occur with pK_a's of 6.37 and 6.41 (Table I). These are more comparable to the pK_a of 6.28[19] of 3-hydroxy-9-methylxanthine rather than to the pK_a of 6.93[19] of the 3-hydroxy-7-methylxanthine or 6.71 of 3-hydroxyxanthine. The spectrum of 3-hydroxyxanthine suggests[19] that the 7-H tautomer predominates, while these pyrrolopyrimidines are comparable to the 9-H tautomer.

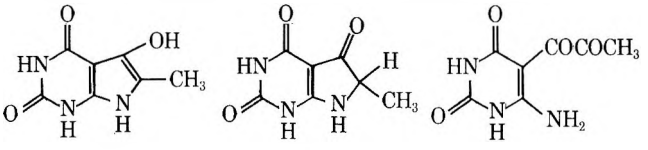
As expected the pyrrolopyrimidine **2** was found to be very reactive. In acetic anhydride alone or with added acetic acid, an instantaneous vigorous reaction takes place that yields a dark, insoluble material, even at 0°. However, the presumed polymerization could be diminished by carrying out the reaction in methanol, ethanol, or water. After separation of the insoluble material, the filtrate was absorbed on a Dowex-50 [H^+] column. Elution with water gave an unidentified fraction, followed by 6-amino-5-carboxymethyluracil (**5**),[20] 1,2,3,4,5,6-hexahydro-2,4,6-trioxopyrrolo[2,3-*d*]pyrimidine (**7**),[21] unchanged starting material (**2**, R = H), and a small amount of the deoxygenated compound **6**, R = H.[16] No intermediate 1-acetoxypyrrolopyrimidine corresponding to 3-acetoxyxanthine from 3-hydroxyxanthine[6-9] could be isolated, even at low temperature. The structure of **7** was confirmed by nmr spectrum, which showed signals for $-CH_2-$ and three NH protons. The uv spectrum of the neutral species showed absorptions at 235, a shoulder, and 287 nm which resembled the spectrum of the known 1,3-dimethyl derivative of **7**, showing absorptions at 234 and 290 nm.[22] The unambiguous proof of the substitution at position 6 was obtained by the hydrolysis of **7** to the known **5**.[20]



7

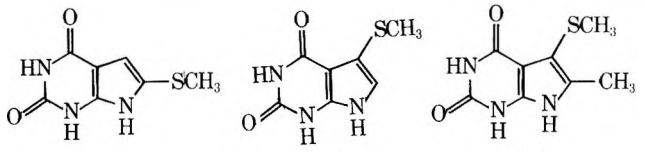
In acid **7** was found to be unstable and underwent hydrolysis to **5** even at room temperature. The readily hydrolysis of **7** prevented the separation of **7** from **5** by recrystallization. It could be achieved by low-temperature chromatography from Dowex-50 [H^+] column, but at high temperature all **7** is hydrolyzed to **5**. The ring opening of **7** takes place at room temperature in 1 *N* HCl solution with a $t_{1/2}$ of *ca.* 1 day.

The reaction of **2**, R = Me, with acetic anhydride alone or in acetic acid yielded only polymerized material, and no soluble component was isolated. Reaction of **2**, R = Me, with acetic anhydride in methanol or water gave the 5-oxopyrrolopyrimidine (**8**), some 6-amino-5-pyruvyluracil ester (**9**), some polymerized material, and a small amount of an unidentified compound. The 6-methyl-2,4,5-trioxopyrrolo[2,3-*d*]pyrimidine (**8**) was found to be relatively stable in Dowex-50 [H^+] at room temperature and could be isolated pure. Prolonged standing of **8** in water resulted in some **9**. Although **8** could exist in either the keto (**8**) or the enol (**8a**) form, the predominance of the keto form was shown by the nmr, with a doublet for methyl protons at δ 1.22 and a quartet for 6-H at 3.81 ppm.



8a 8 9

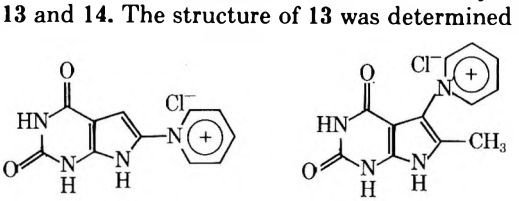
No 6-hydroxymethyl derivative was detected. This contrasts with the reaction of 3-hydroxy-8-methylxanthine,[10] picoline *N*-oxides, and other methyl-substituted aromatic *N*-oxides,[23] from which hydroxymethyl derivatives have been isolated. From the acetyl ester of **2**, R = H or CH_3, prepared *in situ*[24] by addition of acetic anhydride to an aqueous solution of **2** with methionine present, both the 5- and the 6-methylmercapto derivatives were formed. Thus treatment of **2**, R = H, with acetic anhydride in the presence of *dl*-methionine yielded **10** (74%) and two diastereoisomers of the 5-methionium derivative of **6**, R = H (14 and 3%). Each of the isomers was converted to **11** by NaOH. Similar treatment of **2**, R = Me, gave 5-methionium **6**, R = Me, which was also converted to **12** (65%) with NaOH. With buffering to near pH 7 the yield was greatly decreased.



10 11 12

The uv spectra of **11** and **12** were similar, and different from that of **10**, thus confirming structures of **10** and **11**.

Both *N*-hydroxypyrrolopyrimidines reacted in pyridine with tosyl chloride at low temperature to form the corresponding pyridinium betaines, isolable as the hydrochlorides **13** and **14**. The structure of **13** was determined by its nmr spectrum, which showed the signals for 5-H, pyridinium protons, and two NH protons. Hydrolysis of the betaine

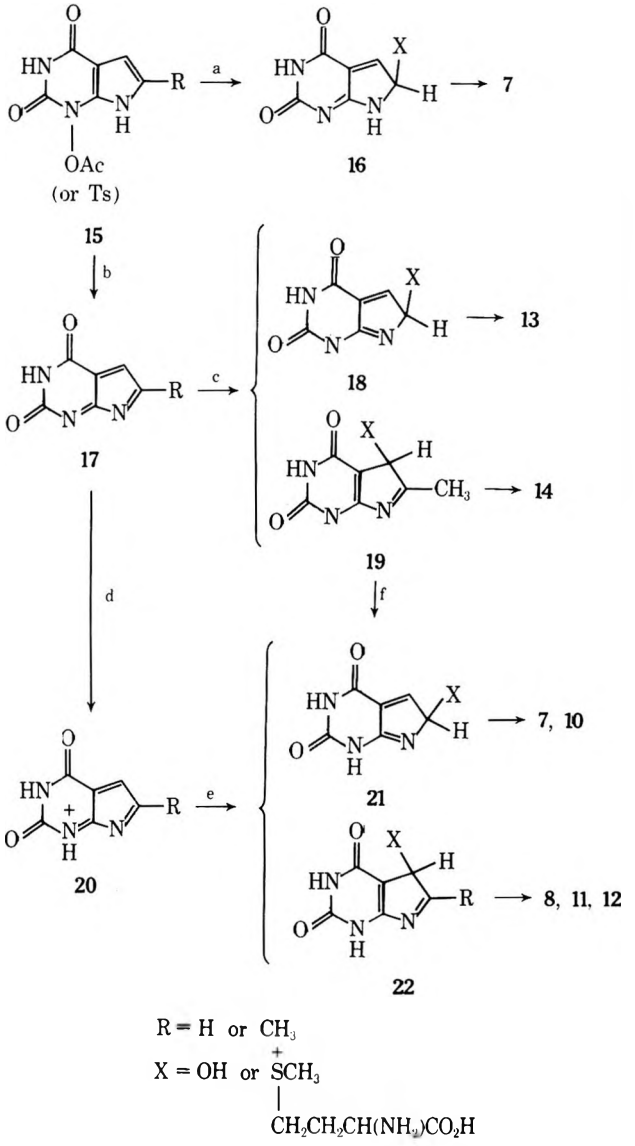


13 14

hydrochloride with 2 *N* NaOH yielded 6-amino-5-carboxylmethyluracil (**5**). The structure of 6-methylpyridinium betaine was determined through its nmr spectrum, which showed no signals for a 5 proton.

Since the acetyl esters of **2**, R = H and R = Me, are so reactive, no direct comparison can be made with the reaction of 3-acetoxyxanthine (**1**, R = Ac). The probable mechanisms of the formation of the substitution products (Scheme II) are similar to those of the reactions of 3-acetoxyxanthine.[9,10] An SN1′ reaction pathway, path a, can explain the formation of **7** from **2** R = H, but not the formations of **13** and **14** nor **8**. More probable is an elimination from **15**, path b, to form **17**, an analog of the dehydroxanthine previously postulated.[9] This can be followed by direct attack of a nucleophile and protonation, paths c and f, or by protonation of **17** to **20** followed by attack of a nucleophile, paths d and e. The latter is preferred, since higher yields were obtained when the reactions were carried out in acidic media.

Scheme II



This work suggests that the relatively π-electron-rich pyrrole ring in place of the imidazole ring increases the reactivity of elimination–substitution reaction in this heterocyclic system. This is in agreement with predictions made from relative π-electron characters of imidazole and pyrrole rings in the fused ring systems. Because of this high reactivity and the chemical similarities of **2** and **1**, it is probable that the pyrrolopyrimidine will also be activated *in vivo* in a manner similar to that of 3-hydroxyxanthine, and may therefore prove to be oncogenic.

Experimental Section

The uv spectra were determined with a Cary 15 spectrometer. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Nmr spectra were determined with a Varian A-60 spectrometer in Me_2SO-d_6 with tetramethylsilane as an internal reference. The melting points are uncorrected. Paper chromatography, ascending, on Whatman No. 1 paper was used to check the purity of each of the compounds prepared. For Dowex-50 chromatography BioRad AG-50, 8X, 200–400 mesh [H^+] resin was used. With a 9 × 150 mm column and 0.05 *N* HCl at 60 ml/hr, the elution values observed follow: **5**, 22; **7**, 33; **2**, R = H, 47; **6**, R = H, 74; **10**, 345.

6-Amino-1-benzyloxy-5-(2,2-diethoxyethyl)uracil (3, R = CH_2Ph). Sodium shot (600 mg, 0.026 mol) was added slowly to a solution of ethyl 2,2-diethoxyethylcyanoacetate[16] (2.22 g, 0.01 mol) in ethanol (60 ml). After the sodium had dissolved, benzyloxyurea (1.66 g, 0.01 mol) was added in small portions. The mixture was then heated under reflux for 16 hr with protection by a drying tube. The clear solution was evaporated nearly to dryness *in vacuo*. Water (30 ml) was added and the brown solution was neutralized with acetic acid to precipitate **3**, R = CH_2Ph. Recrystallization from 20 ml of 50% ethanol yielded needles (2.52 g, 72%): mp 152°; nmr δ 1.10 (t, Me protons), 2.48 (d, 2 H, CH_2, J = 7 Hz), 3.55 (q, CH_2Me, J = 5 Hz), 4.47 (t, –CH–, J = 7 Hz[1]), 5.10 (s, $-CH_2Ph$), 6.60 (s, NH_2), 7.50 (m, Ph), 10.65 (s, NH); uv max (ethanol) 275 nm ($\epsilon \times 10^{-3}$ 18.3). Compare 6-amino-1-benzyloxyuracil, 269 nm ($\epsilon \times 10^{-3}$ 19.7).

Anal. Calcd for $C_{17}H_{23}N_3O_5$: C, 58.44; H, 6.64; N, 12.03. Found: C, 58.55; H, 6.67; N. 11.93.

1-Hydroxy-1,2,3,4-tetrahydro-2,4-dioxopyrrolo[2,3-*d*]pyrimidine (2, R = H). A. 3, R = CH_2Ph (6.98 g, 20 mmol), in methanol (500 ml) was hydrogenated with 5% palladium on charcoal (1.0 g) at room temperature for 15 min, when the required amount of hydrogen had been absorbed. The catalyst was washed with ethanol (3 × 50 ml). Evaporation of the filtrates to dryness yielded **6-amino-1-hydroxy-5-(2,2-diethoxyethyl)uracil (3, R = H)** in almost quantitative yield, as hydroscopic, colorless needles, blue, ferric chloride test: mp 118° dec; nmr δ 1.10 (t, CH_3, J = 7 Hz), 2.49 (d, CH_2, J = 5.5 Hz), 3.51 (q, CH_2Me, J = 7.0 Hz), 4.49 (t, CH, J = 5.5 Hz), 6.53 (s, NH_2), 10.77 (broad, NH + OH). The **3**, R = H (2.00 g), was dissolved in 0.1 *N* HCl (100 ml) and stirred for 5 hr. The pyrrolopyrimidine (**2**, R = H) precipitated slowly as colorless, fine crystals (1.72 g, 99%), mp >120° dec. The crystals became a violet-blue upon exposure to light or heat: nmr δ 6.33 (d, J = 3 Hz), 6.71 (d, J = 3 Hz), 10.77 (s, N^7 H), 11.33 (s, OH), 11.81 (s, N^3 H).

Anal. Calcd for $C_6H_5N_3O_3 \cdot \frac{1}{2}H_2O$: C, 40.91; H, 3.43; N, 23.89. Found: C, 41.25; H, 3.32; N, 24.06.

B. Compound **3**, R = CH_2Ph (6.90 g, 20 mmol), in formic acid (250 ml) was hydrogenated with palladium on charcoal (1.0 g) under hydrogen atmosphere until the theoretical amount of hydrogen was absorbed. Removal of the catalyst and evaporation of formic acid *in vacuo* yielded **2**, R = H, 2.30 g, 70%, identical with that prepared by method A.

6-Amino-1-benzyloxy-5-(2-methyl-1,3-dioxolan-2-ylmethyl)uracil (4, R = CH_2Ph). Ethyl cyano-α-(2-methyl-1,3-dioxolan-2-ylmethyl)acetate[16] (9.37 g, 0.004 mol) was added to the sodium ethoxide solution from 1.012 g of Na in 250 ml of absolute ethanol and refluxed for 0.5 hr. Benzyloxyurea (6.64 g, 0.04 mol) was then added and the mixture was refluxed for 3 days. The ethanol was removed under vacuum and the residue was treated with dilute acetic acid to yield **4**, R = CH_2Ph, 8.8 g, 60%: nmr ($CDCl_3$) δ 1.28 (s, CH_3), 2.75 (s, CH_2), 3.88 (s, CH_2CH_2), 5.21 (s, CH_2Ph), 5.83 (s, NH_2), 7.45 (s, Ph); uv max (ethanol) 275 nm ($\epsilon \times 10^{-3}$ 16.7).

Anal. Calcd for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.74; N, 12.60. Found: C, 57.48; H, 5.82; N, 12.51.

6-Amino-1-hydroxy-5-(2-methyl-1,3-dioxolan-2-ylmethyl)uracil (4, R = H). Hydrogenation of **4**, R = CH_2Ph, in methanol, as was done with the 5-diethoxyethyl isomer, gave colorless crystals in 85% yield: mp 200° dec; nmr δ 1.18 (s, CH_3), 2.58 (s, CH_2), 3.90 (s, CH_2CH_2), 6.55 (s, NH_2), 9.00 (broad, NH); pink ferric chloride test.

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.45; H, 5.39; N, 17.28. Found: C, 44.63; H, 5.34; N, 17.20.

1-Hydroxy-1,2,3,4-tetrahydro-6-methyl-2,4-dioxopyrrolo-

[2,3-*d*]pyrimidine (2, R = Me). Compound **4**, R = H (1.46 g, 0.006 mol), was suspended in dilute HCl (0.0086 *N*, 105 ml) and stirred for 20 hr. The precipitates were collected and washed with ethanol and then with ether to yield colorless **2**, R = Me (0.90 g, 82%), blue ferric chloride test (in ethanol): nmr δ 2.17 (s, CH_3), 5.99 (s, 5-H), 10.70, 11.40, 11.66 (s, N^3 H + N^6 H + OH).

Anal. Calcd for $C_7H_7N_3O_3$: C, 46.41; H, 3.89; N, 23.19. Found: C, 46.29; H, 3.82; N, 23.11.

Reaction of 2, R = H, with Acetic Anhydride. A. To compound **2**, R = H (~30 mg), in methanol (25 ml) was added acetic anhydride (20 mg) with stirring at 0°. The solution became dark gray almost instantaneously. The temperature was allowed to rise to room temperature and the stirring was continued for 2 hr. Several crops of dark blue precipitates were collected (~60%). The filtrate was absorbed in a Dowex-50 [H^+] column and eluted with water to give one unidentified fraction, followed by **5** (7%) and 1,2,3,4,5,6-hexahydro-2,4,6-trioxopyrrolo[2,3-*d*]pyrimidine[20,21] (**7**, 23%), nmr (DMSO) δ 3.33 (s, $-CH_2-$), 10.98, 11.51, and 12.61 (N^1 H + N^3 H + N^7 H), **2**, R = H (10%), and then a trace of **6**, R = H, uv max 235 nm ($\epsilon \times 10^{-3}$ sh, 9.3), 287 (6.3).

Anal. Calcd for $C_6H_5N_3O_3 \cdot \frac{1}{2}H_2O$ (**7**): C, 40.91; H, 3.43; N, 23.85. Found: C, 40.90; H, 3.43; N, 23.62.

B. Acetic anhydride (0.1 ml) was added to compound **2**, R = H (39 mg), in water (15 ml) with stirring at room temperature. After stirring for 24 hr the reaction mixture was chromatographed with a Dowex-50 [H^+] column. Elution with water afforded **5** (0.2%), **7** (28%), and a trace of **6**, R = H.

Reaction of 2, R = Me with Acetic Anhydride. A. 2, R = Me, was treated as described for **2**, R = H. Column chromatography with water from a Dowex-50 [H^+] column gave first a fraction of 6-amino-5-pyruvyluracil (**9**, 15.1%), uv max (pH 5.0) 283 nm ($\epsilon \times 10^{-3}$ 8.4), 244 (10.4), 215 (14.1), uv max (pH 12.0) 290 (9.4), 255 sh (8.4), 231 (17.4), followed by 1,2,3,4,5,6-hexahydro-6-methyl-2,4,5-trioxopyrrolo[2,3-*d*]pyrimidine (**8**, 30%) as the second fraction: uv max (pH 1.0) 277 nm ($\epsilon \times 10^{-3}$ 9.2), 246 (9.6); uv max (pH 5.0) 281 (9.4), 252 (8.6), 232 (14.8); uv max (pH 11.0) 284 (9.7), 255 (9.4), 231 (19.3); nmr (DMSO-d_6) δ 1.22 (d, J = 7 Hz), 3.81 (q, J = 7 Hz), 8.53 (s, N^1 H or N^3 H), 10.41 (s, N^1 H or N^3 H), 11.68 ppm (broad, N^7 H). Further elution with water gave some unchanged **2**, R = Me (15%), and some small unknown fractions.

Anal. Calcd for $C_7H_7N_3O_3$: C, 46.41; H, 3.90; N, 23.20. Found: C, 46.61; H, 3.91; N, 22.96.

B. Acetic anhydride (0.1 ml) was added to compound **2**, R = Me (29 mg), in water (15 ml) and after stirring for 1 day gave **9** (22%) and **8** (16%). The same reaction for 2 days gave a lower yield of **8** (3%).

1,2,3,4-Tetrahydro-2,4-dioxopyrrolo[2,3-*d*]pyrimidine 6-Pyridinium Chloride (13). Tosyl chloride (0.20 g, 1.1 mmol) was added to a stirred and cooled (3°) solution of **2**, R = H (0.167 g, 1 mmol), in pyridine. After 2 days at the same temperature, 50 ml of ether was added. The red precipitate was collected, washed with water, ether, and ethanol, and recrystallized from 1 *N* HCl to yield **13**, (0.146 g, 55%) as a yellow solid: mp >300°; nmr (TFA) δ 7.36 (s, H-5), 8.15–9.30 (m, pyridinium protons).

Anal. Calcd for $C_{11}H_9N_4O_2Cl$: C, 49.91; H, 3.43; N, 21.17; Cl, 13.39. Found: C, 49.70; H, 3.68; N, 20.86; Cl, 13.57.

1,2,3,4-Tetrahydro-2,4-dioxo-6-methyl[2,3-*d*]pyrrolopyrimidine 5-Pyridinium Chloride (14). A. To a stirred solution of **2**, R = Me (0.181 g, 1.0 mmol), in dry pyridine (20 ml), tosyl chloride was added in small amounts under a nitrogen atmosphere. After stirring for 6 days at room temperature paper chromatography showed that most of the starting material had reacted. It was then evaporated *in vacuo* nearly to dryness. Water (20 ml) was then added to the residue and some insoluble material was separated. The filtrate was absorbed in a Dowex-50 [H^+] column (2.5 × 26 cm). Elution with 1 *N* HCl gave some unchanged **2**, with 2 *N* HCl gave pyridine, and with 3 *N* HCl gave **14** (0.120 g, 43%) as a yellow solid after concentration: mp >300°; nmr (TFA) δ 2.48 (s, CH_3), 8.06–9.15 (m, pyridinium protons). An analytical sample was obtained by repeated precipitation of **14** from an aqueous solution with ethanol.

Anal. Calcd for $C_{12}H_{11}N_4O_2Cl$: C, 51.71; H, 3.97; N, 20.10; Cl, 12.72. Found: C, 51.42; H, 3.87; N, 19.95; Cl, 13.00.

B. To a stirred solution of **2**, R = Me (0.181 g, 1.0 mmol), under nitrogen pressure in dry pyridine (15 ml), tosyl chloride (0.228 g, 1.2 mmol) was added in small portions. The solution was refluxed under nitrogen for 22 hr. Paper chromatography showed no **2**, R = Me, remaining. The pyridine was evaporated *in vacuo*, and the residue was triturated with ether and washed with ethanol–ether to give **14** as yellow solid (0.255 g, 91%), mp >300°.

Hydrolysis of 1,2,3,4-Tetrahydro-2,4-dioxo[2,3-*d*]pyrrolopyrimidine 6-Pyridinium Chloride (13). A solution of **13** (390 mg) in 2 *N* NaOH (1.0 ml) was refluxed under nitrogen for 3.5 hr and cooled. After separation of a brown precipitate the filtrate was absorbed on a Dowex-50 [H^+] column (4.3 × 35.5 cm) which was eluted with H_2O to yield 6-amino-5-carboxymethyluracil[20] (30 mg, 11%): mp >300° (from water); nmr (DMSO-d_6) δ 3.11 (s, CH_2), 6.10 (broad, NH_2), 10.01 (s, NH), 10.26 (s, NH); uv max (pH 2.0) 268 nm ($\epsilon \times 10^{-3}$, 15.1), 225 (3.4); uv max (pH 5.0) 274 (12.8); uv max (pH 11) 275 (12.1).

Anal. Calcd for $C_6H_7N_3O_4$: C, 38.96; H, 3.81; N, 22.70. Found: C, 38.78; H, 3.83; N, 22.54.

6- (or 5-) Methylmercapto-1,2,3,4-tetrahydro-2,4-dioxopyrrolo[2,3-*d*]pyrimidine (10 or 11). Compound **2**, R = H (839 mg), and methionine (1490 mg) were suspended in water (50 ml). After stirring for ~1 min, acetic anhydride (2.5 ml) was added to the mixture. The mixture became a clear solution in ~2 min. After 30 min of stirring at room temperature, the precipitate started to form. After 24 hr of stirring at room temperature, the precipitate of **10** (738 mg, 74%) was collected: nmr δ 2.37 (s, SMe), 6.35 (s, 5-4), 8.72 (N^1 H), and 9.77 (broad, N^3 H + N^7 H); uv max (pH 1–2) 276, 255, 216 nm; uv max (pH ~12) 289, 263.

Anal. Calcd for $C_7H_7N_3O_2S$: C, 42.63; H, 3.58; N, 21.31; S, 16.26. Found: C, 42.43; H, 3.97; N, 21.29; S, 16.13.

The portion of water solution from the reaction was absorbed in a Dowex-50 [H^+] column. Eluting with 4 *N* HCl gave two fractions that showed identical uv max: (pH ~5.0) 272, 233 nm sh; (pH ~13), 297, 250, 221. After each fraction was boiled in 0.1 *N* NaOH (25 ml) for 3.5 hr, both gave **11** (135 mg, 14%, from the first fraction, 28 mg, ~3%, from the second fraction). This compound was very insoluble in water: nmr δ 2.32 (s, SMe), 6.42 (s, 6 H), 8.75 (N^1 H), 9.42 and 9.77 (N^3 H + N^7 H); uv max (pH 1) 275 nm sh, 230, 220; uv max (pH 8) 285, 234, 218; uv max (pH 13) 290, 236.

Anal. Calcd for $C_7H_7N_3O_2S$: C, 42.63; H, 3.58; N, 21.31; S, 16.26. Found: C, 42.57; H, 3.68; N, 21.20; S, 16.00.

6-Methyl-5-methylmercapto-1,2,3,4-tetrahydro-2,4-dioxopyrrolo[2,3-*d*]pyrimidine (12). The acetic anhydride (0.5 ml) was added to a suspension of **2**, R = Me (100 mg), and methionine (280 mg) in water (15 ml). The mixture became a clear solution in 10 min and remained so for more than 5 hr. After stirring at room temperature for 20 hr, the reaction mixture was absorbed in a Dowex-50 [H^+] column. Elution with water gave a small amount of **8** and with 4 *N* HCl gave the 5-methionium derivative of **6**: R = Me, uv max (pH 0–5) 272, 230 nm sh; uv max (pH 12–13) 297, 250, 222. This fraction was concentrated to dryness and the acidic residue was neutralized with a few drops of 50% NaOH. The mixture was then added with 0.1 *N* NaOH (15 ml) and heated on a steam bath for 1 hr. **12** precipitated as a pinkish-white solid (76 mg, 65%): nmr δ 2.18 (s, Me), 2.28 (s, SMe), 8.77 (N^1 H), 9.55 and 9.63 (N^3 H + N^7 H); uv max (pH 2.0) 284, 238 sh, and 222 nm; uv max (pH 13.0) 295 and 241.

Anal. Calcd for $C_8H_9N_3O_2S$: C, 45.49; H, 4.29; N, 19.89; S, 15.19. Found: C, 45.29; H, 4.21; N, 19.69; S, 15.11.

Hydrolysis of 10. A small amount of **10** (10 mg) was suspended in 1 *N* HCl and heated on a steam bath for 12 hr. The insoluble **10** was collected and the clear solution was absorbed in a Dowex-50 [H^+] column. Elution with water gave some **5** as one of its degradation products.

Hydrolysis of 1,2,3,4,5,6-Hexahydro-2,4,6-trioxopyrrolo[2,3-*d*]pyrimidine (7). A 10^{-4} *M* solution of **7** in 1 *N* HCl was kept at room temperature and the hydrolysis was followed by recording the uv spectra at various time intervals. **6** was hydrolyzed completely to **5** in 4 days, with a $t_{1/2}$ of about 1 day.

Air Oxidation of 8 in Water. Acetic anhydride (0.1 ml) was added to a suspension of **8** (50 ml) in water (25 ml). After stirring at room temperature for 4 days, insoluble **8** was collected and the filtrate was chromatographed through a Dowex-50 [H^+] column. The chromatograph showed ~30% of **9** formed in the filtrate.

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Registry No.—**2** (R = H), 52133-54-7; **2** (R = Me), 52133-55-8; **3** (R = H), 52133-56-9; **3** (R = CH_2Ph), 52217-41-1; **4** (R = H), 52133-57-0; **4** (R = CH_2Ph), 52133-58-1; **6** (R = H), 39929-79-8; **6**

(R = Me) 5-methionium derivative, 52133-53-6; **7**, 52133-59-2; **8**, 52133-60-5; **9**, 52133-61-6; **10**, 52133-62-7; **11**, 52133-63-8; **12**, 52133-64-9; **13**, 52133-65-0; **14**, 52133-66-1; ethyl 2,2-diethoxyethylcyanoacetate, 52133-67-2; benzyloxyurea, 2048-50-2; ethyl cyano-α-(2-methyl-1,3-dioxolan-2-ylmethyl)acetate, 52133-68-3; 6-amino-5-carboxymethyluracil, 52133-69-4; *dl*-methionine, 59-51-8.

References and Notes

(1) This investigation was supported in part by funds from the National Center Institute (Grants CA 08748 and CA 15274).
(2) G. Salemnick held a David A. Gimbel Memorial Fellowship.
(3) R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970, p 298.
(4) K. Sugiura, M. N. Teller, J. C. Parham, and G. B. Brown, *Cancer Res.*, **30**, 184 (1970).
(5) G. B. Brown, M. N. Teller, I. Smullyan, N. J. M. Birdsall, T.-C. Lee, J. C. Parham, and G. Stöhrer, *Cancer Res.*, **33**, 1113 (1973).
(6) U. Wölcke, N. J. M. Birdsall, and G. B. Brown, *Tetrahedron Lett.*, 785 (1969).
(7) N. J. M. Birdsall, T.-C. Lee, and U. Wölcke, *Tetrahedron*, **27**, 5961 (1971).
(8) N. J. M. Birdsall, U. Wölcke, T.-C. Lee, and G. B. Brown, *Tetrahedron*, **27**, 5969 (1971).
(9) N. J. M. Birdsall, J. C. Parham, U. Wölcke, and G. B. Brown, *Tetrahedron*, **28**, 3 (1973).
(10) D. R. Sutherland and G. B. Brown, *J. Org. Chem.*, **38**, 1291 (1973).
(11) G. Stöhrer and G. B. Brown, *Science*, **167**, 1622 (1970).
(12) G. Stöhrer, E. Corbin, and G. B. Brown, *Cancer Res.*, **32**, 637 (1972).
(13) T.-C. Lee, *J. Org. Chem.*, **38**, 703 (1973).
(14) T.-C. Lee, G. Salemnick, and G. B. Brown, *ibid.*, **38**, 3102 (1973).
(15) A. Albert, "Heterocyclic Chemistry, An Introduction," Athlone Press, University of London, London, 1959.
(16) J. Davoll, *J. Chem. Soc.*, 131 (1960).
(17) W. Klotzer, *Monatsh. Chem.*, **95**, 265 (1964).
(18) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 119 (1952).
(19) J. C. Parham, T. G. Winn, and G. B. Brown, *J. Org. Chem.*, **36**, 2639 (1971).
(20) T. B. Johnson and E. F. Kohmann, *Amer. Chem. J.*, **49**, 184 (1913).
(21) Compound **6** has been detected (ref 20), but the structure was not clearly confirmed.
(22) H. Ogura, M. Sakaguchi, and K. Takeda, *Chem. Pharm. Bull.*, **20**, 404 (1972).
(23) V. J. Traynelis in "Mechanisms of Molecular Migrations," Vol. 2, R. S. Thyagrarajan, Ed., Wiley-Interscience, New York, N. Y., 1969, p 1.
(24) G. Stöhrer, unpublished results.

A Novel, Directed Synthesis of Unsymmetrical Azoxyalkanes and Azoxyaralkanes from *N,N*-Dihaloamine and Nitroso Precursors[1]

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A novel, directed synthesis of unsymmetrical azoxyalkanes and azoxyaralkanes from nitroso compounds (RNO) and *N,N*-dichloroamines ($R'NCl_2$) in the presence of methanolic caustic is described. An investigation of the scope of the reaction revealed that the highest yields of azoxy compounds were produced when R is *tert*-alkyl or aryl and R′ is *tert*-alkyl. This method possesses advantages not offered by prior techniques. Possible mechanistic pathways are also discussed.

Aliphatic azoxy compounds are of interest partly because of the powerful physiological activity of some naturally occurring members.[4,5] To date there are only two useful methods for the production of unsymmetrical[6] alkyl or aralkyl azoxy compounds, which give rise to a single, structurally predictable product.[7] The aralkyl types can be generated by reaction of an azoxy tosylate,[8] eq 1, or azoxy

$$ArN(O)=NTs \xrightarrow{RMgCl} ArN(O)=NR \quad (1)$$

fluoride[9] with a Grignard reagent. The other approach involves reaction of alkyl diazotates with alkyl iodides,[10] eq 2.

$$RN=NO^-K^+ \xrightarrow{R'I} RN=N(O)R' \quad (2)$$

Other techniques, including condensation of nitroso compounds with *N*-alkylhydroxylamines,[10-12] eq 3, and oxidation of azo compounds with peracid,[10,11] suffer from lack of specificity, since mixtures of the two possible isomers often result (see below).

$$RNO + R'NHOH \longrightarrow RN(O)=NR' + RN=N(O)R' \quad (3)$$

We herein describe a new route[33] to azoxyalkanes and azoxyaralkanes entailing reaction of an *N,N*-dichloroamine with a nitroso compound in the presence of base. The scope of the reaction and mechanistic aspects are treated, and a comparison of this new method with those of eq 1 and 2 is given.

Results and Discussion

The general procedure used in most cases for the azoxy products involved reaction of a nitroso compound with an *N,N*-dichloroamine in the presence of caustic, eq 4. Equi-

$$RNCl_2 + R'NO \xrightarrow{OH^-} RN=N(O)R' \quad (4)$$

R = alkyl; R′ = alkyl or aryl

molar quantities of the nitroso compound and *N,N*-dichloroamine, prepared[13] from the amine and calcium hypochlorite, were dissolved in methanol. After potassium hydroxide was added at about 30°, the reaction mixture was stirred until the color disappeared. In the latter stages of the investigation, we discovered that the procedure could be simplified appreciably by adding sodium hypochlorite to a methanolic solution of the amine and nitroso compound, eq 5. Apparently the hypochlorite serves a dual function—

$$RNH_2 + R'NO \xrightarrow{NaOCl} RN=N(O)R' \quad (5)$$

as a chlorinating agent to form the haloamine and as a source of caustic.

Yields of azoxyaralkanes and azoxyalkanes are set forth in Tables I and II, respectively. It is evident that the reaction is sensitive to the nature of the *N,N*-dihaloamine. Tertiary alkyl substituents gave the best results, the primary type provided moderate yields, and secondary groups produced the lowest amount of desired material. Presumably, dehydrohalogenation[14] of the haloamine comprises a competing process, eq 6. Since formation of the *N*-chloroimine

$$\begin{matrix} | \\ HCNCl_2 \\ | \end{matrix} \xrightarrow{OH^-} \begin{matrix} | \\ C=NCl \\ | \end{matrix} \quad (6)$$

should take place more readily with the secondary and primary alkyl groups, the observed yield order, tertiary > primary, secondary, is in accord with this concept. In the case of aliphatic nitroso precursors, only tertiary alkyls were

Table I
Yields of Azoxyaralkanes from C_6H_5NO and $RNCl_2$[a]

Compd	R	Yield, %
1	$CH_3(CH_2)_3$	36[b]
2	$(CH_3)_2CH$	4
3	C_6H_{11}	7[c,d]
4	$(CH_3)_3C$	80[c,e]
5	$(CH_3)_2C(CN)$	72
6	1-Adamantyl	78

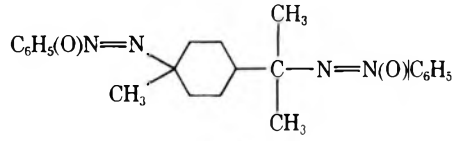
[a] General procedure A. [b] 2:1 molar ratio of $RNCl_2$:C_6H_5NO. [c] Identified by comparison with an authentic sample. [d] 2:1 molar ratio of $RNCl_2$:C_6H_5NO produced a 12% yield. [e] 83% yield from general procedure B.

Table II
Yields of Azoxyalkanes from RNO and R′NCl_2

Compd	R	R′	Yield, %
7	1-Adamantyl	$(CH_3)_3C$	54[a]
8	$(CH_3)_3C$	1-Adamantyl	49[a]
9	$(CH_3)_2C(CN)$	$(CH_3)_2C(CN)$	48[a]
10	1-Chloro-1-cyclohexyl	$(CH_3)_2C(CN)$	68
11	1-Cyano-1-cyclohexyl	$(CH_3)_2C(CN)$	65[a]
12	$(CH_3)_2C(CN)$	1-Cyano-1-cyclohexyl	72[a]
13	$(CH_3)_3C$	$(CH_3)_3C$	42

[a] Identified by comparison with an authentic sample.

used, since base-catalyzed isomerization[15a] to oximes occurs readily with the primary and secondary groups. In an investigation of scope, the reaction was applied to formation of a diazoxy type, **14**, from 1,8-diamino-*p*-menthane



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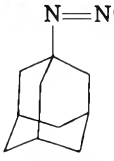
and nitrosobenzene. This appears to be the first disclosure of a diazoxy compound in the aralkyl class. Unsuccessful attempts were made to extend the method to azoxy compounds completely substituted with aromatic nuclei. Treatment of a mixture of nitrosobenzene and aniline with sodium hypochlorite at low temperatures (Dry Ice) resulted in a complex mixture containing none of the desired azoxybenzene. Similarly, no azoxy product was obtained from *o*- or *p*-nitroaniline and nitrosobenzene.

Satisfactory elemental analyses were obtained for all compounds, except **11** and **12**, which appeared to undergo a change which is not understood. The infrared spectra in all cases exhibited strong absorption, characteristic[5] of the azoxy functionality, in the 1300- and 1500-cm^{-1} regions. In addition, nmr was particularly valuable in ascertaining the position of oxygen in the unsymmetrical products. Prior investigations[11,16,17] revealed that protons in the vicinity of the oxidized nitrogen are shifted downfield relative to those near the other nitrogen. Application of this principle to the present studies is summarized in Table III.

Use of chemical evidence was also made for identification. For example, compound **4** yielded phenylazo-*tert*-butane on reduction.

Table III
Nmr Chemical Shifts (δ) of Azoxy Compounds[a]

Compd	Protons: CH_3CN=	Protons: $CH_3CN(O)$=
$C_6H_5N(O)$=$NC(CH_3)_3$	1.20	
C_6H_5N=$N(O)C(CH_3)_3$		1.37
 N(O)=$NC(CH_3)_3$	1.10	
 N=$N(O)C(CH_3)_3$		1.40
$(CH_3)_3CN(O)$=$NC(CH_3)_3$	1.27	1.47

[a] In CCl_4.

In general, for both new and known products, authentic materials were prepared by previously reported routes. Although the condensation of nitroso compounds with hydroxylamines, eq 3, was commonly utilized, isomeric mixtures were obtained in all cases (**7** and **8**, **4** and **18**, **11** and **12**). These results further emphasize the lack of specificity characteristic of this technique. Cyclohexylmagnesium chloride and phenylnitrosohydroxylamine tosylate served as precursors for compound **3**, eq 1. Another approach entailed oxidation of the azo precursor. Freeman[11] noted that reaction of perbenzoic acid with **15** provided **16**,

$$\underset{\mathbf{15}}{C_6H_5N{=}NCH_3} \xrightarrow{C_6H_5CO_3H} \underset{\mathbf{16}}{C_6H_5N(O){=}NCH_3} \qquad (7)$$

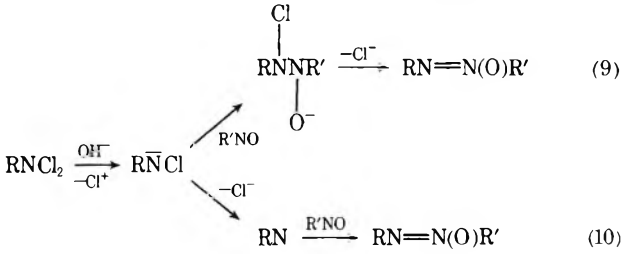
eq 7. An attempt on our part to apply this reaction to the synthesis of **4** from **17** gave isomer **18** instead, eq 8. Factors

$$\underset{\mathbf{17}}{C_6H_5N{=}NC(CH_3)_3} \xrightarrow{C_6H_5CO_3H} \underset{\mathbf{18}}{C_6H_5N{=}N(O)C(CH_3)_3} \qquad (8)$$

favoring the observed site of attack may be the increased inductive effect of *tert*-butyl *vs.* methyl, and steric hindrance[18] by the *tert*-butyl group to reaction on the nitrogen affixed to phenyl.

The geometry of the azoxy compounds is believed to be trans. The nmr spectra of the aralkyl types were quite indicative of the stereochemistry. The ortho protons appeared downfield approximately 0.7 δ from the meta and para ones. If the cis arrangement were present, the ortho protons would be expected to appear upfield with respect to the other aromatic protons.[17a] Also, under the conditions (glpc, 165–200°) generally used for isolation of the azoxyalkyl products, the cis isomer, if present, would be expected to isomerize to the more stable trans form.[16,17]

In relation to the reaction mechanism, several pathways deserve attention. The initial step might consist of nucleophilic attack[14] on the haloamine by hydroxide ion to form



an anion. Subsequent nucleophilic attack on the nitroso entity, which has literature analogy,[15b] could then lead eventually to end product, eq 9. Alternatively, α-elimination would provide a nitrene intermediate[19a] which yields azoxy compound on interaction with nitroso substrate, eq 10. Previous investigators have postulated this type of interaction leading to azoxy formation.[19c] Attempts to trap a nitrene with cyclohexene[20a] or benzene[20b] proved fruitless. In addition, nitrenes can abstract hydrogen to form amines,[19b] or rearrange,[19b] but compounds expected from such reactions were not observed as by-products in our case. A radical pathway should also be considered, eq 11. This ap-

$$RNCl_2 + OH^- \xrightarrow[-Cl^-]{-OH\cdot} RN\dot{C}l \xrightarrow{R'NO} RN(Cl)-N(O\cdot)R' \xrightarrow{-Cl\cdot} RN{=}N(O)R' \quad (11)$$

proach resembles radical formation in the reaction of alkyl and aryl halides with organometallic reagents,[21a] eq 12. Ni-

$$R'X + R^- \longrightarrow R'\cdot + R\cdot + X^- \quad (12)$$

troso compounds can interact with amino radicals to form stable free radicals. In our case, subsequent loss of a chlorine atom gives rise to azoxy product.

As mentioned earlier, the two principal literature methods for directed synthesis of unsymmetrical azoxy compounds are represented by eq 1 and 2. The former is useful only for aralkyl types containing primary and secondary alkyl groups. Equation 2 appears to work satisfactorily when R'I is primary or secondary but poorly when R'I is tertiary. The present method is characterized by simplicity, and is useful for aralkyl and alkyl types. It works best with *tert*-alkyl groups, and thus nicely complements eq 1 and 2. In addition, versatility is displayed in the preparation of unsymmetrical azoxy derivatives containing α-cyano and α-chloro groups. The halogen-containing type appears promising as a source, *via* dehydrohalogenation, of analogs of naturally occurring materials. A number of naturally occurring azoxy compounds contain α,β unsaturation,[5,17] *e.g.*, **19**. Only a few methods[22] are currently available for synthesis of the conjugated types.

$$CH_3(CH_2)_5CH{=}CHN(O){=}NCHCH_2OCH_3$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad CH(OH)CH_3$$

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Experimental Section

Materials. In general, high-purity commercial chemicals were used directly.

Analytical Procedures. Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer with neat samples or potassium bromide pellets with the 1601.8-cm^{-1} band of polystyrene for calibration. Nmr spectra were taken with a Varian Model T-60 (parts per million with tetramethylsilane as internal standard). Gas chromatography was conducted with a Varian Aerograph Hy-Fi 1700, 10 ft × 0.25 in. column, 15% UCON 50HB2000 and 5% NaOH on Chromosorb W.

Quantitative glpc was accomplished by comparison of peak areas of solutions of crude products with those of solutions of authentic materials. Positive chlorine content was determined by standard iodometric titration.[23] Melting and boiling points are uncorrected. The elemental analyses were performed by Baron Consulting Co., Orange, Conn., and Dr. Ronald E. White.

***N,N*-Dichloroamines.** A literature procedure[13] was followed, providing yields in excess of 90%. Removal of methylene chloride provided the crude product, which was used without further purification. Iodometric titration was employed for analysis of the solid or liquid material.

General Procedures for Azoxy Compounds. A. To a solution of the nitroso compound (0.01 mol) in 35 ml of methanol (*tert*-butyl alcohol was used for **7**) was added the crude *N,N*-dichloroamine (0.01 mol). The solution was stirred at ambient temperatures (with compounds **5, 9, 10, 11,** and **12,** the reaction temperature was maintained at 0°) while 2.3 ml of 50% potassium hydroxide solution was added dropwise over a 15-min period. An exotherm was noted, and the reaction mixture was allowed to stir for an additional 30 min, or until the blue color of the nitroso compound disappeared. The reaction mixture was then poured into water and extracted with ether. The ethereal solution was washed with water and dried over $CaCl_2$. After solvent was removed, the compound was purified by distillation, glpc, or column chromatography (alumina with chloroform as eluent).

B. 1. Commercial sodium hypochlorite (28.6 ml, 0.7 *N*) was added dropwise to a solution of nitrosobenzene (1.07 g, 10 mmol) and *tert*-butylamine (0.73 g, 10 mmol) in 110 ml of methanol. The reaction mixture was stirred for 2 hr, and then poured into water. The mixture was extracted with ether, and the organic layer was washed with water and then dried over $CaCl_2$. After the ether was removed, product **4** was isolated in 83% yield.

2. To a solution of 1,8-diamino-*p*-methane (0.85 g, 5 mmol) and nitrosobenzene (1.07 g, 10 mmol) in 110 ml of methanol was added dropwise 28.6 ml of sodium hypochlorite solution (0.7 *N*). After completion of the addition, the reaction mixture was stirred for 2 hr and then poured into water. The mixture was extracted with ether, and the ethereal solution was washed with water and then dried over $CaCl_2$. After the ether was removed, the brown residue was chromatographed on an alumina column with chloroform as eluent, yield 1.4 g (75%) of a yellow oil: ir (neat) 1496 (N=N), 1285 (NO), 768, and 685 cm^{-1}; nmr (CCl_4) δ 8.10 (m, 4 H), 7.40 (m, 6 H), 1.00–2.10 (m, 18 H).

Anal. Calcd for $C_{22}H_{28}N_4O_2$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.72; H, 7.70; N, 14.48.

Characterization of Azoxy Products. *N*-*n*-Butyl-*N'*-phenyldiazine *N'*-oxide (**1**): nmr (CCl_4) δ 8.08 (m, 2 H), 7.40 (m, 3 H), 3.54 (m, 2 H), 0.8–1.60 (m, 7 H); ir (neat) 1485 (N=N), 1295 (NO), 773 and 685 cm^{-1} (aromatic).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.04; H, 7.84; N, 15.42.

N-2-Propyl-*N'*-phenyldiazine *N'*-oxide (**2**): nmr (CCl_4) δ 8.04 (m, 2 H), 7.37 (m, 3 H), 4.30 (m, 1 H), 1.23 (d, 6 H); ir (CCl_4) 1470 (N=N), 1310 (NO), 780 cm^{-1} (aromatic).

N-Cyclohexyl-*N'*-phenyldiazine *N'*-oxide (**3**): nmr (CCl_4) δ 8.08 (m, 2 H), 7.40 (m, 3 H), 4.18 (m, 1 H), 2.20–1.30 (m, 10 H); ir (neat) 1470 (N=N), 1295 (NO), 780 and 690 cm^{-1} (aromatic).

Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.41; H, 8.08; N, 13.53.

N-*tert*-Butyl-*N'*-phenyldiazine *N'*-oxide (**4**): nmr (CCl_4) δ 7.90 (m, 2 H), 7.14 (m, 3 H), 1.20 (s, 9 H); ir (neat) 1475 (N=N), 1290 (NO), 782 and 696 cm^{-1} (aromatic).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.61; H, 8.15; N, 15.38.

N-2-(2-Cyanopropyl)-*N'*-phenyldiazine *N'*-oxide (**5**): nmr (CCl_4) δ 8.00 (m, 2 H), 7.40 (m, 3 H), 1.60 (s, 6 H); ir (neat) 2225 (C≡N), 1470 (N=N), 1310 (NO), 782 and 698 cm^{-1} (aromatic).

Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.73; H, 5.97; N, 22.44.

N-1-Adamantyl-*N'*-phenyldiazine *N'*-oxide (**6**), white powder: mp 96–97.5°; nmr (CCl_4) δ 8.01 (m, 2 H), 7.33 (m, 3 H), 2.10 (s, 9 H), 1.64 (s, 6 H); ir (KBr) 1478 (N=N), 1285 (NO), 780 and 690 cm^{-1} (aromatic).

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 74.62; H, 7.89; N, 11.08.

N-*tert*-Butyl-*N'*-1-adamantyldiazine *N'*-oxide (**7**): nmr (CCl_4) δ 1.96 (s, 9 H), 1.52 (s, 6 H), 1.10 (s, 9 H); ir (neat) 1480 (N=N), 1280 cm^{-1} (NO).

Anal. Calcd for $C_{14}H_{24}N_2O$: C, 71.14; H, 10.24; N, 11.85. Found: C, 71.40; H, 9.96; N, 12.04.

N-1-Adamantyl-*N'*-*tert*-butyldiazine *N'*-oxide (**8**): nmr (CCl_4) δ 1.95 (s, 9 H), 1.65 (s, 6 H), 1.40 (s, 9 H); ir (neat) 1500 (N=N), 1298 cm^{-1} (NO). *Anal.* Calcd for $C_{14}H_{24}N_2O$: C, 71.14; H, 10.24; N, 11.85. Found: C, 71.38; H, 10.34; N, 11.78.

Azoxyisobutyronitrile (**9**), white crystals: mp 35–37° [lit.[24] mp 37°]; ir (KBr) 2222 (C≡N), 1496 (N=N), 1298 cm^{-1} (NO).

N-2-(2-Cyanopropyl)-*N'*-1-(1-chlorocyclohexyl)diazine *N'*-oxide (**10**): nmr (CCl_4) δ 2.32 (m, 4 H), 1.62 (s, 12 H); ir (neat) 2220 (C≡N), 1498 (N=N), 1293 (NO), 768 cm^{-1} (CCl).

Anal. Calcd for $C_{10}H_{16}ClN_3O$: C, 52.28; H, 6.97; N, 18.29. Found: C, 52.13; H, 7.07; N, 18.24.

N-2-(2-Cyanopropyl)-*N'*-1-(1-cyanocyclohexyl)diazine *N'*-oxide (**11**): nmr (CCl_4) δ 1.90–2.32 (m, 10 H), 1.70 (s, 6 H); ir (neat) 2223 (C≡N), 1500 (N=N), 1292 cm^{-1} (NO).

Anal. Calcd for $C_{11}H_{16}N_4O$: C, 59.98; H, 7.32; N, 25.44. Found: C, 60.00; H, 7.75; N, 24.90.

On standing for several weeks, there was a change in the ir spectrum.

N-1-(1-Cyanocyclohexyl)-*N'*-2-(2-cyanopropyl)diazine *N'*-oxide (**12**): nmr (CCl_4) δ 1.90–2.34 (m, 10 H), 2.10 (s, 6 H); ir (neat) 2222 (C≡N), 1496 (N=N), 1295 cm^{-1} (NO).

Anal. Calcd for $C_{11}H_{16}N_4O$: C, 59.98; H, 7.32; N, 25.44. Found: C, 59.30; H, 7.75; N, 24.46.

On standing for several weeks, there was a change in the ir spectrum.

Azoxyisobutane (**13**): bp 46–50° (20–25 mm) [lit.[11] bp 50° (20 mm)]; nmr (CCl_4) δ 1.47 (s, 9 H), 1.27 (s, 9 H).

1-Cyano-*N*-cyclohexylhydroxylamine. A previous method[25] was employed: 65% yield, mp 134–136° after recrystallization (lit.[25] mp 136–137°).

2-Cyano-*N*-(2-propyl)hydroxylamine. A literature procedure[25] was used: 48% yield, mp 102.5–104° after recrystallization (lit.[25] mp 98–99°).

1-Cyano-1-nitrosocyclohexane. A previous method[26] was employed to obtain the nitroso compound as a blue solid, 60% yield, mp 36–37° (lit.[26] mp 37–37.5°).

2-Cyano-2-nitrosopropane. A literature procedure[26] was used to obtain the nitroso compound as a white powder, 34% yield, mp 48–50° (lit.[27] mp 53°).

1-Chloro-1-nitrosocyclohexane. A previous method[28] was employed to obtain the product, blue liquid, 90% yield, which was used without further purification. In another run, attempted distillation resulted in a minor explosion and fire.

1-Nitrosoadamantane. A literature procedure[29] was used with the corresponding hydroxylamine as precursor, 84% yield, mp 172–175° (lit.[29] mp 179.5°).

2-Methyl-2-nitrosopropane. A previous method[30] was employed with the corresponding hydroxylamine (prepared by the method of Stetter and Smulders[29]) as precursor, 72% yield, mp 81–82° [lit.[30] mp 83–84°].

Condensation of Nitroso Compounds with Hydroxylamines.[11,29] Equimolar quantities of the nitroso compound (0.01 mol) and hydroxylamine derivative (0.01 mol) were refluxed in absolute ethanol with catalytic amounts (0.01 g) of potassium hydroxide. After 3 hr, the color had changed from blue to light yellow. The reaction mixture was poured into water and extracted with ether. The organic layer was washed and then dried over $CaCl_2$. After the solvent was removed, the products were collected (glpc). Mixtures synthesized included **7** and **8** (64% yield, 1:1 molar ratio), **4** and **18** (30% yield, 1:2 molar ratio), and **11** and **12** (72% yield, 1:1 molar ratio), In addition, the symmetrical compound **9** was obtained in 41% yield. Since attempts to separate certain pairs of isomers by glpc proved unsuccessful, **7** and **8** and **11** and **12** were analyzed as mixtures. Compounds **4** and **18** were readily separated by glpc and were analyzed individually.

Reduction of *N*-*tert*-Butyl-*N'*-phenyldiazine *N'*-Oxide.[31] To a solution of *N*-*tert*-butyl-*N'*-phenyldiazine *N'*-oxide (**4**, 0.2 g, 1.1 mmol) in 10 ml of ether was added $LiAlH_4$ (0.1 g, 2.6 mmol). After the mixture was refluxed overnight, it was poured into methanol. Water was added and the mixture was extracted with ether. The ethereal solution was washed, dried with $MgSO_4$, and freed of ether. Essentially a quantitative yield of phenylazo-*tert*-butane was obtained. Identification was accomplished by comparison with an authentic sample prepared by the method of Fowler:[32] nmr (CCl_4) δ 7.40–7.81 (m, 5 H), 1.19 (s, 9 H); ir (neat) 1590, 770, and 690 cm^{-1}.

Oxidation of Phenylazo-*tert*-butane with Perbenzoic Acid.[11] To a solution of phenylazo-*tert*-butane (0.3 g, 1.8 mmol) in 10 ml of methylene chloride chilled to 0° was added 10 ml of methylene chloride containing perbenzoic acid (0.4 *N*). The mixture was allowed to stand overnight in a refrigerator. Then a 10% solution of KI was added, followed by sodium thiosulfate until the purple color of iodine disappeared. The organic layer was separated, washed first with $NaHCO_3$ solution and then with water, and dried over $CaCl_2$. The solvent was removed, leaving 0.22 g of a light yellow liquid. The major product was isolated by glpc and identified as *N'*-*tert*-butyl-*N*-phenyldiazine *N'*-oxide (**18**): 40% yield; ir (neat) 1495 (N=N), 1300 (NO), 770 and 690 cm^{-1}; nmr (CCl_4) δ 7.80 (m, 2 H), 7.04 (m, 3 H), 1.37 (s, 9 H).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.57; H, 7.83; N, 15.55.

Phenylazo-2-cyano-2-propane and Perbenzoic Acid. Attempted oxidation of phenylazo-(2-cyano-2-propane with perbenzoic acid (conditions identical with those for oxidation of phenylazo-*tert*-butane to **18**) failed to produce the desired conversion to **5**. Starting material was recovered.

***N*-Cyclohexyl-*N'*-phenyldiazine *N'*-Oxide (3).** A previous method[8] was employed to produce the desired azoxy compound in 36% yield: ir (neat) 1470 (N=N), 1295 (NO), 780 and 690 cm^{-1}; nmr (CCl_4) δ 8.08 (m, 2 H), 7.40 (m, 3 H), 4.18 (m, 1 H), 2.20–1.30 (m, 10 H).

Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.41; H, 8.08; N, 13.53.

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Registry No.—**1**, 52123-78-1; **2**, 52123-65-6; **3**, 52123-66-7; **4**, 52123-67-8; **5**, 52123-68-9; **6**, 52123-69-0; **7**, 52123-70-3; **8**, 52123-71-4; **9**, 52123-72-5; **10**, 52123-73-6; **11**, 52123-74-7; **12**, 52123-75-8; **13**, 16649-52-8; **14**, 52123-76-9; **18**, 52123-77-0.

References and Notes

(1) Paper XXI, Chemistry of *N*-Haloamines; preliminary communication, F. R. Sullivan, E. Luck, and P. Kovacic, *J. Chem. Soc., Chem. Commun.*, 217 (1974).
(2) Postdoctoral Fellow, 1973–1974.
(3) National Science Foundation Undergraduate Research Participant, Summer 1973.
(4) R. Preussmann, H. Druckrey, S. Ivankovic, and A. v. Hodenberg, *Ann. N. Y. Acad. Sci.*, **163**, 697 (1969).
(5) W. J. McGahren and M. P. Kunstmann, *J. Amer. Chem. Soc.*, **91**, 2808 (1969); **92**, 1587 (1970).
(6) The designation as unsymmetrical refers to the nature of the groups attached to the nitrogens.
(7) For a recent review, see S. R. Sandler and W. Karo, "Organic Functional Group Preparations," Vol. II, Academic Press, New York, N. Y., 1971, Chapter 15; J. W. Timberlake and J. C. Stowell "The Chemistry of Functional Groups. The Chemistry of the Hydrazo, Azo, and Azoxy Groups," S. Patai Ed., Wiley, New York, N. Y., in press, Chapter 5.
(8) T. E. Stevens, *J. Org. Chem.*, **32**, 1641 (1967); **29**, 311 (1964).
(9) T. E. Stevens and J. P. Freeman, *J. Org. Chem.*, **29**, 2279 (1964).
(10) R. A. Moss, M. J. Landon, K. M. Luchter, and A. Mamantov, *J. Amer. Chem. Soc.*, **94**, 4392 (1972); R. A. Moss and G. M. Love, *ibid.*, **95**, 3070 (1973); R. A. Moss and T. B. K. Lee, *J. Chem. Soc., Perkin Trans. 1*, 2778 (1973).
(11) J. P. Freeman, *J. Org. Chem.*, **28**, 2508 (1963).
(12) J. G. Aston and D. M. Jenkins, *Nature (London)*, **167**, 863 (1951).
(13) T. A. Kling, R. E. White, and P. Kovacic, *J. Amer. Chem. Soc.*, **94**, 7416 (1972).
(14) P. Kovacic, M. K. Lowery, and K. W. Field, *Chem. Rev.*, **70**, 639 (1970).
(15) J. H. Boyer, "The Chemistry of the Nitro and Nitroso Groups," H. Feuer, Ed., Interscience, New York, N. Y., 1969, Part 1: (a) p 255; (b) pp 276, 277.
(16) J. Swigert and K. G. Taylor, *J. Amer. Chem. Soc.*, **93**, 7337 (1971).
(17) (a) K. G. Taylor and T. Riehl, *J. Amer. Chem. Soc.*, **94**, 250 (1972); (b) C. L. Stevens, B. T. Gillis, and T. H. Haskell, *ibid.*, **81**, 1435 (1959).
(18) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 322.
(19) F. D. Lewis and W. H. Saunders, Jr., in "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y., 1970: (a) p 86; (b) p 58; (c) J. H. Boyer, *ibid.*, p 166.
(20) (a) R. A. Abramovitch and S. R. Challand, *J. Chem. Soc., Chem. Commun.*, 1160 (1972); (b) D. H. R. Barton and L. R. Morgan, Jr., *J. Chem. Soc.*, 622 (1962).
(21) (a) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Amer. Chem. Soc.*, **86**, 1807 (1964); (b) O. E. Edwards, D. H. Paskovich, and A. H. Reddoch, *Can. J. Chem.*, **51**, 978 (1973).
(22) B. T. Gillis and J. D. Hagarty, *J. Org. Chem.*, **32**, 95 (1967); R. A. Moss and G. M. Love, *Tetrahedron Lett.*, 4701 (1973); J. P. Freeman, *J. Org. Chem.*, **27**, 1309 (1962); R. B. Woodward and C. Wintner, *Tetrahedron Lett.*, 2689 (1969).
(23) P. Kovacic and S. S. Chaudhary, *Org. Syn.*, **48**, 4 (1968).
(24) J. G. Aston and G. T. Parker, *J. Amer. Chem. Soc.*, **56**, 1387 (1934).
(25) L. Neelakantan and W. H. Hartung, *J. Org. Chem.*, **23**, 964 (1958).
(26) O. Wichterle, V. Gregor, A. Dubansky, and V. Seidl, *Chem. Listy*, **51**, 605 (1957); *Chem. Abstr.*, **51**, 11354 (1957).
(27) O. Piloty, *Chem. Ber.*, **31**, 1878 (1898).
(28) E. Müller, H. Metzger, and D. Fries, *Chem. Ber.*, **87**, 1449 (1954).
(29) H. Stetter and E. Smulders, *Chem. Ber.*, **104**, 917 (1971).
(30) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 6522 (1957).
(31) R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3738 (1948).
(32) J. S. Fowler, *J. Org. Chem.*, **37**, 510 (1972).
(33) Note Added in Proof. A closely related method involves conversion of nitrosobenzene and dichloroamine to $C_6H_5N(O)$=NCl in the presence of pyridine: W. G. le Noble and W. S. Chang, *Synthesis*, 106 (1073). A similar approach was used for $C_6H_5N(O)$=NTos from nitrosobenzene and chloroamine T: W. V. Farrar and J. M. Gulland, *J. Chem. Soc.*, 368 (1944).

Structure and Stereochemistry of Ristosamine

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Ristosamine, an amino sugar derived from the antibiotic ristomycin A, is shown to be the previously unreported 3-amino-2,3,6-trideoxy-L-*ribo*-hexopyranose.

Ristomycin, an antibiotic produced by *Proactinomyces fructiferi var. ristomycin*,[1] exhibits a wide antibacterial spectrum[2] and can be classified among the vancomycin-type antibiotics.[3] Ristomycin is composed of the variants A and B, each of which gives rise to the same, previously unreported, ninhydrin-positive, reducing deoxy amino sugar under conditions of acidic or alkaline hydrolysis.[4]

In a previous report[5] we have described the neutral carbohydrates attached to ristomycin A aglycone, and the partial structure of the latter. The present study focuses on the investigation of the structure of the trideoxyaminohexose ristosamine (1), isolated after hydrolysis of ristomycin A with 0.5 *N* hydrochloric acid at 100° (Scheme I).

Ristosamine hydrochloride, $C_6H_{13}O_3N$·HCl, gives positive Fehlings, Tollens, Keller–Kiliani, and iodoform reactions, as well as the xanthydrol color test. Oxidation with periodic acid[6] leads to the consumption of approximately 2 mol of the reagent. The formation of formaldehyde could not be detected; however, acetaldehyde is distilled from the reaction mixture and identified as its 2,4-dinitrophenylhydrazone. This observation and the positive iodoform test point to a 6-deoxy sugar.

Although direct conversion of ristosamine to its methyl glycoside could not be achieved, the acidic methanolysis of ristomycin A produced methyl ristosaminide, most conveniently isolated as its crystalline hydrochloride salt (2). The consumption of 0.7 mol of sodium periodate by this compound indicates a pyranoside ring and is consistent with a 2,6 or a 4,6 dideoxy sugar. The formation of acetaldehyde upon periodate cleavage of 1 requires the former, *i.e.*, C-4 must bear either the hydroxyl or amino group. A 2-deoxy sugar is in accord with the positive Keller–Kiliani and xanthydrol tests and the double-resonance nmr studies, which demonstrate spin coupling between the anomeric and methylene hydrogens.

Methyl ristosaminide hydrochloride could be directly converted to methyl *N,O*-diacetylristosaminide (3) and methyl *N*-benzoylristosaminide (4). Acid hydrolysis of the latter yields crystalline *N*-benzoylristosamine (5). Treatment of compound 5 with sodium periodate followed by further oxidation with aqueous bromine leads to the isolation of crystalline *N*-benzoyl-D(−)-aspartic acid (6). The amino group of ristosamine must therefore reside at C-3. These chemical data permit the assignment of the 2,3,6-trideoxy-3-aminohexopyranose structure 1 to ristosamine.

This assignment finds support in the electron-impact studies of compounds 2 and 3 at 70 eV (Table I). The mass spectrum of the hydrochloride salt 2 displays a negligible relative abundance (0.1%) of the molecular ion of the free base at *m/e* 161 and the expected weak peaks at *m/e* 143, 130, 129, and 111 corresponding to M − H_2O, M − OCH_3, M − CH_3OH, and M − (H_2O + CH_3OH), respectively.

Barring deep-seated skeletal rearrangement, which is not considered likely,[7] the remaining prominent peaks in the mass spectrum of compound 2 provide structural information at two levels: that required by the data and that consistent with the data. In the former category, ion *m/e* 117, $C_5H_{11}NO_2$ by high resolution, is M − CH_3CHO, a finding consistent only with a 6-deoxy sugar. Likewise, ion *m/e* 59a, C_2H_5NO, requires hydroxyl and amino groups on adjacent carbon atoms.

The appearance of these two ions narrows the plausible

Scheme I

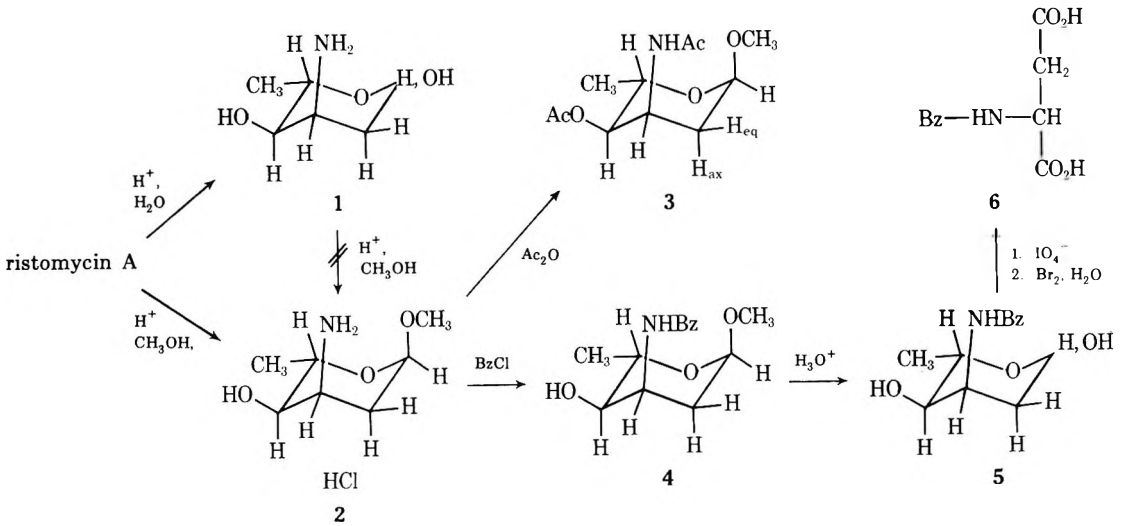


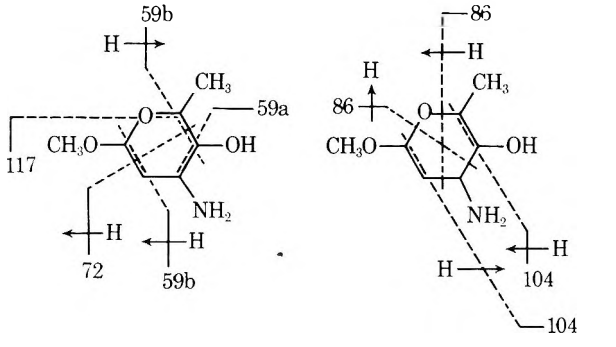
Table I
The 70-eV Mass Spectra of Compounds 2 and 3

Compound 2				Compound 3		
m/e	%[a]		Ion composition[b]	*m/e*	%[a]	Ion composition[b]
161 ($M \cdot^+$)	0.1			214	2	$C_{10}H_{16}NO_4$
143	11		$C_7H_{13}NO_2$	213	1	
130	20		$C_6H_{12}NO_2$	185	4	$C_9H_{15}NO_3$
129	3			153	22	$C_8H_{11}NO_2$
117	7		$C_5H_{11}NO_2$	143	10	$C_6H_9NO_3$
111	3			142	19	$C_7H_{12}NO_2$
104	27		$C_4H_{10}NO_2$	128	14	$C_6H_{10}NO_2$
100	11		$C_5H_8O_2$	117	6	$C_5H_{11}NO_2$
86	55		C_4H_8NO	115	6	$C_5H_9NO_2$
72	77		C_3H_6NO	101	25	$C_4H_7NO_2$
59	100	a 60	C_2H_5NO	86	25	
		b 40	C_3H_7O	72	14	
58	85		C_3H_6O	59	15	
44	84			58	14	
43	53			43	100	
38	25		HCl			
36	74		HCl			

[a] Peak intensity relative to base peak. [b] Derived from high-resolution studies.

molecular structures of methyl ristosaminide to four: 2,3,6-trideoxy-3-amino-, 2,4,6-trideoxy-4-amino-, 3,4,6-trideoxy-3-amino-, and 2,4,6-trideoxy-2-aminohexopyranosides. Ion *m/e* 86 (C_4H_8NO) is inexplicable in terms of the last-named structure, but each of the other three is compatible with the major ions in the mass spectra of compounds **2** and **3**. Only the first-named compound, however, fits the nmr and chemical evidence as well. Scheme II suggests the origin of the structurally significant ions expected from this compound.

Scheme II



The isolation of *N*-benzoyl-D(−)-aspartic acid (**6**) from the oxidative cleavage of compound **5** suggests the *R* configuration at C-3 of ristosamine. Comparing the molecular optical rotation value of **1** (M_D −62.97°) to those of the α and β equilibrium mixtures of the eight possible 2,6-dideoxyhexoses, only the L-ribo compound, L-digitoxose, shows a comparable sign and magnitude of rotation, M_D −68°.[8,9]

The nmr spectrum of crystalline methyl *N,O*-diacetylristosaminide (**3**) at 220 MHz provides strong confirmation of the structure and configuration proposed.

The low-field doublet at δ 4.79 is assigned to the anomeric hydrogen H-1. The low values for both $J_{1,2ax}$ (4 Hz) and $J_{1,2eq}$ (<1 Hz) require an equatorial position for H-1, *i.e.*, crystalline **3** is the α anomer. Irradiation of signal H-1 results in the collapse of two higher field signals: the broadened doublet of doublets at δ 1.89 (H-2eq) to a sharp doublet of doublets (J = 14, 2.5 Hz), and the doublet of triplets at δ 2.09 (H-2ax) to a doublet of doublets (J = 14, 3.5 Hz). The observed coupling of H-1 to two other hydrogens establishes ristosamine as a 2-deoxy sugar. In addition, the low $J_{2ax,3}$ value (3.5 Hz) excludes a H-2ax–H-3ax arrangement; therefore, the acetamido group at C-3 must occupy an axial position.

The assignment of the higher field signal (δ 1.89) of the geminal hydrogens at C-2 to the equatorially rather than the axially disposed hydrogen is in contrast to the general view.[10] While not secure, this assignment is believed likely, and has as its basis the observation that the higher field signal at δ 1.89 displays a smaller coupling (J = <1 Hz) with the anomeric hydrogen H-1 than the lower field methylene hydrogen signal at δ 2.09 (J = 4.0 Hz).

In those α-2-deoxyhexopyranoses that have been thoroughly studied by nmr, $J_{1eq,2eq}$ is always less than or equal to $J_{1eq,2ax}$. In the nmr spectrum of methyl α-*N,O*-dibenzoylvancosaminide, the H-2ax signal is assigned a higher field position than H-2eq, and $J_{1eq,2ax}$ = 4.5 Hz while $J_{1eq,2eq}$ = 0 Hz.[11] Similarly, in the spectrum of methyl α-D-chromoside C, the H-2ax signal is reported upfield of H-2eq, and $J_{1eq,2ax}$ = 3.5 and $J_{1eq,2eq}$ = 1.5 Hz.[12] The axial hydrogen at C-2 of methyl 2-deoxy-D-*arabino*-hexopyranose appears at higher field and $J_{1eq,2ax}$ (3.8 Hz) > $J_{1eq,2eq}$ (1.4 Hz).[13] Values of $J_{1eq,2ax}$ = 3.5 and $J_{1eq,2eq}$ = 1.5 Hz are recorded for methyl α-L-oleandroside.[14] In contrast to this trend, but with incomplete nmr information recorded in each case, Brimacombe and Portsmouth,[15] Hofheinz, Grisebach, and Friebolin,[16] and Arcamone, *et al.*,[9] report $J_{1eq,2ax} = J_{1eq,2eq}$ = 3, $J_{1eq,2ax} = J_{1eq,2eq}$ = 2.4, and $J_{1eq,2ax} = J_{1eq,2eq}$ = 2.0 Hz, respectively, for methyl α-3-*O*-acetylchromoside D, methyl α-L-mycaroside, and methyl *N,O*-diacetyldaunosaminide. Thus, in *no* reported case is $J_{1eq,2ax} < J_{1eq,2eq}$. Consistency with these data, then, requires the assignment of the H-2e signal of compound **3** to the higher field position. It must be emphasized, however, that the proper assignment of the geminal hydrogen signals is not a prerequisite for the correct interpretation of the remaining nmr signals, or the assignment of preferred conformation at each chiral center.

Of the low-field group of signals, H-1, H-3, H-4, and H-5, the last named appears at highest field, as expected. Irradiation of the H-5 signal at δ 3.98 leads to the collapse of the doublet of doublets centered at δ 4.57. The multiplet at slightly lower field, δ 4.66, is unaffected. Thus, the signals centered at δ 4.57 and 4.66 are assigned to H-4 and H-3, respectively. The doublet of doublets assigned to H-4 displays one large coupling constant, 9.5 Hz, characteristic of *vicinal* axial–axial splitting, and one smaller coupling constant, 3.5 Hz, consistent with *vicinal* axial–equatorial interaction. Since the axial nature of the C-3 acetamido group has already been established, these data require an equatorial acetoxy group at C-4 and an equatorial methyl group at C-5. Thus, compound **3** is methyl α-3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-L-*ribo*-hexopyranose. It may be noted that the nature of the H-4 signal clearly distinguishes the L-ribo from the L-xylo configuration.

The nmr spectrum of **3** indicates a high degree of conformational homogeneity (conformation IC) in chloroform solution as expected of α anomer. This suggests the application of reported[9] chemical shift values for the acetyl methyl group (equatorial $OCOCH_3$, δ 2.00–2.09; axial $NHCOCH_3$, δ 2.00–2.09) in the assignment of conformation to the C-3 acetamido and C-4 acetoxy groups. Although there is a good correlation in the case of compound **3**, numerous papers[17] warn of the unreliability of conformational assignments made on this basis; therefore, the correlation is noted, but no strong significance is attached to it. The chemical shift values of the *O*-methyl and C-5 methyl signals also fall into reported[18] ranges (axial OCH_3, δ 3.36–3.46; equatorial C-5 CH_3, δ 1.16–1.24).

A final comment on the proposed higher field position of H-2eq signal relative to H-2ax is in order, as there appears to be no recorded example of such an occurrence[19,20] in a 2-deoxyhexopyranose. The proposal is at least qualitatively explicable in terms of current knowledge. The work of Lemieux and Stevens[21] suggests that the neighboring axial *N*-acetyl group at C-3 would act to deshield the axial hydrogen at C-2 and shield the equatorial hydrogen. There are likely other forces at work, but this factor could indeed influence the relative field positions of the C-2 hydrogens in the direction observed.

In conclusion, ristosamine, as derived from ristomycin A, is a new deoxy amino sugar of natural origin. The assignment of structure reveals that ristosamine differs from both vancosamine[11] (isolated from vancomycin) and daunosamine[9] (derived from daunomycin).

Experimental Section

Ristosamine (1). Ristomycin A (50 g) was hydrolyzed by refluxing for 4 hr in 500 ml of 0.5 *N* HCl. A precipitate which separated on cooling was removed by filtration, and the filtrate was neutralized to pH 6 by means of Dowex 2 (OH^-) ion-exchange resin. The aglycone which precipitated after neutralization was collected and dried (21.10 g).

The neutral solution was slowly passed through a column of *ca.* 150 ml of Dowex 50 (NH_4^+) ion-exchange resin. The column was washed with water until neutral, and ristosamine was then eluted with a 25% aqueous acetone solution containing 0.25 *N* ammonium hydroxide. Elution was continued until a positive reaction with ninhydrin was no longer detectable in the eluate. The combined fractions were concentrated to 8–10 ml under vacuum at 30–40° and then poured into 600 ml of absolute ethanol, whereupon ristosamine precipitated. The mixture was allowed to stand for a few hours in a refrigerator. The precipitate was collected by filtration and dried over concentrated sulfuric acid to yield 2.15 g of light-yellow, amorphous powder.

Ristosamine Picrate. Crude ristosamine (250 mg) was dissolved in 2.5 ml of absolute ethanol with gentle warming, and 7.0 ml of a saturated solution of alcoholic picric acid was added.

The resulting precipitate was collected by filtration and washed with small amounts of absolute ethanol and ether. The dried product amounted to 241 mg (38%). It was purified by dissolution in acetone and precipitation with petroleum ether, mp 118–119° dec.

Anal. Calcd for $C_6H_{13}O_3N{\cdot}HOC_6H_2(NO_2)_3$: C, 38.30; H, 4.28; N, 14.89. Found: 38.67; H, 4.28; N, 14.98.

Ristosamine Hydrochloride. Ristosamine picrate (250 mg) was dissolved in 10 ml of nitrobenzene and the solution was extracted with 15 ml of 1 *N* HCl in a separatory funnel. The aqueous phase was separated, extracted with ether (2 × 10 ml), clarified with decolorizing carbon, and evaporated at a temperature not exceeding 30–40°. On adding acetone to the resulting light yellow syrup, crystalline ristosamine hydrochloride separated, 83.6 mg (68%), $[\alpha]^{21}D$ 34.3° (*c* 0.57, H_2O).

Anal. Calcd for $C_6H_{13}O_3N{\cdot}HCl$: C, 39.25; H, 7.68; N, 7.62; Cl, 19.31. Found: C, 38.81; H, 7.77; N, 7.59; Cl, 19.36.

Qualitative Reactions of Ristosamine. Keller–Kiliani Reaction. With the modified procedure of Euw and Reichstein[22] ristosamine hydrochloride and daunosamine[9] exhibited an intense brownish-red color. Under similar conditions a blue color was obtained with digitoxose, and a greenish-blue color with 2-deoxy-D-ribose.

Xanthydrol Test. As with 2-deoxy-D-ribose and digitoxose, the xanthydrol test produced a reddish-violet color in the case of ristosamine hydrochloride. With glucosamine, galactosamine, and L-rhamnose, which were used as controls, no coloration was observed.

Iodoform Test. From 50 mg of ristosamine hydrochloride, 6 mg of iodoform was obtained, mp 119–120°, mmp 120–121°.

Oxidation of Ristosamine with Periodic Acid. Detection of Formaldehyde. After the oxidation of ristosamine with periodic acid, no formaldehyde was detected by the spectrophotometric method of Speck and Forist.[23] With glucosamine and galactosamine, the determination was reproducible.

Detection of Acetaldehyde. Ristosamine hydrochloride (150 mg) was dissolved in 61.00 ml of 0.05 *N* periodic acid and the mixture was allowed to stand at room temperature for 3 hr in the dark. Then the reaction mixture was distilled *in vacuo* (in a nitrogen atmosphere) into 20 ml of 3% 2,4-dinitrophenylhydrazine. The precipitate was filtered, washed with distilled water, dried *in vacuo* at 56° over phosphorus pentoxide, and recrystallized from *sec*-butyl alcohol to yield 52 mg of acetaldehyde 2,4-dinitrophenylhydrazone, mp 154–157°, mmp 152–156°. The 2,4-dinitrophenylhydrazone displayed a tlc R_f value identical with that of authentic acetaldehyde 2,4-dinitrophenylhydrazone on Kieselguhr G (nitrobenzene–cyclohexane, 1:2). The ir spectra (KBr) of both products were completely identical.

Methyl Ristosaminide Hydrochloride. Ristomycin A sulfate (21.0 g), dried to constant weight at room temperature over P_2O_5, was dissolved in 210 ml of 3 *N* methanolic hydrochloric acid and methanolyzed in a sealed ampoule at 105° for 5 hr. After cooling in an ice bath the ampoule was opened and its contents were evaporated at reduced pressure at 30° to the thickness of a syrup. The residue obtained after evaporation was dissolved in 50 ml of methanol and poured, at a slow rate, onto 170 ml of Dowex 1 (HCO_3^-) ion-exchange resin suspended in 300 ml of distilled water. The precipitated aglycone was then removed from the solution by filtration followed by centrifugation. The pH of the solution was adjusted to 8.0 with 0.5 *N* ammonium hydroxide. The resulting precipitate was removed by filtration.

The filtrate containing the methyl ristosaminide was poured onto a Dowex 50 (NH_4^+) ion-exchange column (30 × 4.5 cm). After washing with distilled water the column was eluted with 0.5 *N* ammonium hydroxide, collection being made in 200-ml fractions. The second fraction was acidified to pH 6.0 with a small amount of 3 *N* methanolic hydrochloric acid and evaporated *in vacuo* at 30° until methyl ristosaminide hydrochloride separated in crystalline form. Recrystallization from ethanol–acetone gave 350 mg (19%) of white, rodlike crystals, mp 168–170°, $[\alpha]^{20}D$ −123.8° (*c* 1, H_2O).

Anal. Calcd for $C_7H_{15}O_3{\cdot}HCl$: C, 42.54; H, 8.15; N, 7.08; Cl, 17.93; OCH_3, 15.70. Found: C, 43.05; H, 8.05; N, 6.73; Cl, 17.43; OCH_3, 15.50.

One mole of **2** prepared as above consumed 0.70 mol of sodium periodate, measured with the procedure of Dixon and Lipkin.[6]

Methyl *N,O*-Diacetylristosaminide. Methyl ristosaminide hydrochloride (200 mg) was dissolved in the mixture of 2 ml of absolute pyridine and 2.0 ml of acetic anhydride and allowed to stand for 24 hr at room temperature. Then the reaction mixture was poured into 100 ml of ice water and extracted in three portions, each with 10 ml of chloroform. The combined organic phase was washed to neutrality with distilled water, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was dried at room temperature in a vacuum desiccator over phosphorus pentoxide to constant weight, 179.6 mg of colorless oil.

Crude methyl *N,O*-diacetylristosaminide was dissolved in the mixture of 1.50 ml of absolute methanol–benzene (15:85), applied onto a silica gel G column (1.5 × 21 cm), and eluted with a solvent mixture of similar composition. Fractions were collected by 2-ml portions. The pure and homogeneous **3** obtained in the eighth fraction was recrystallized, after solvent removal *in vacuo*, from petroleum ether: 109.6 mg (40.1%) of white prisms; mp 51–52°; $[\alpha]^{21}D$ −134° (*c* 0.5, $CHCl_3$); thin layer chromatography R_f 0.31 [silica gel G, absolute methanol–benzene (15:85), sprayed with 50% sulfuric acid and developed at 120°]; nmr (220 MHz, $CDCl_3$) δ 1.22 (3 H, d, J = 7 Hz, C-6), 1.89 (1 H, broadened d of d, $J_{2eq,2ax}$ = 14, $J_{2eq,1}$ < 1, $J_{2eq,3}$ = 2.5 Hz, H-2eq), 2.00 (3 H, s, $NHCOCH_3$), 2.02 (3 H, s, $OCOCH_3$), 2.09 (1 H, d of t, $J_{2ax,2eq}$ = 14, $J_{2ax,1}$ = 4, $J_{2ax,3}$ = 3.5 Hz, H-2ax), 3.43 (3 H, s, OCH_3), 3.98 (1 H, m, H-5), 4.57 (1 H, d of d, $J_{4,3}$ = 4.0, $J_{4,5}$ = 9.5 Hz, H-4), 4.66 (1 H, m, H-3), and 4.79 (1 H, d, $J_{1,2ax}$ = 4, $J_{1,2eq}$ < 1 Hz, H-1).

Anal. Calcd for $C_{11}H_{19}O_5N$: C, 53.87; H, 7.81; H, 5.71; OCH_3, 12.65; $COCH_3$, 35.10. Found: C, 54.27; H, 7.15; N, 5.75; OCH_3, 11.88; $COCH_3$, 35.85.

Methyl *N*-Benzoylristosaminide. Methyl ristosaminide hydrochloride (126 mg) and 143 mg of sodium carbonate were dissolved in 3.7 ml of distilled water and into this solution was dipped, under constant stirring, the solution of 0.083 ml of benzoyl chloride in 1.6 ml of absolute tetrahydrofuran. Stirring was continued for an additional 30 min. Checking with indicator paper showed that during this period of pH of the solution remained weakly alkaline. The reaction mixture was then diluted with 20 ml of distilled water and deionized with 5.0 ml of Dowex 2 (OH^-) and 10 ml of Dowex 50 (H^+) ion exchange resins. The resin was filtered and thoroughly washed with distilled water and the filtrate (pH 6.0) was extracted three times with 10 ml of ether. The combined ethereal phase was dried over magnesium sulfate and filtered and the solvent was evaporated *in vacuo*. The residual colorless oil was dried to constant weight in a vacuum desiccator: 126.0 mg (76.3%);

$[\alpha]^{20}D$ −104.3° (c 0.79, benzene); tlc R_f 0.55 [silica gel G, absolute methanol–benzene (15:85), sprayed with 50% sulfuric acid and developed at 120°].

Anal. Calcd for $C_{14}H_{19}O_4N$: C, 63.29; H, 7.22; N, 5.28. Found: C, 62.95; H, 7.20; N, 5.60.

***N*-Benzoylristosamine.** Methyl *N*-benzoylristosaminide (111 mg) was hydrolyzed in 6.0 ml of 0.1 *N* hydrochloric acid for 1 hr on a steam bath. The cooled solution was neutralized to pH 7.0 with about 1.0 ml of Dowex 2 (OH^-) resin, filtered, and evaporated to dryness. On standing in the refrigerator, the compound **5** crystallized as fleecy needles. Recrystallization from distilled water gave 53.9 mg (51.3%), mp 131–133°, $[\alpha]^{20}D$ −14° (*c* 1, ethanol), after 10 min $[\alpha]^{20}D$ −11°, tlc R_f 0.25 (conditions described above).

Anal. Calcd for $C_{13}H_{17}O_4N$: C, 62.14; H, 6.81; N, 5.57. Found: C, 61.56; H, 6.69; N, 5.50.

***N*-Benzoyl-D-aspartic Acid from *N*-Benzoylristosamine.** *N*-Benzoylristosamine (130 mg) and 135 mg of sodium periodate were dissolved in 4.0 ml of distilled water. The reaction mixture was then allowed to stand for 20 hr at room temperature in the darkness. In the meantime the pH of the mixture was maintained at 4–5 with 0.5 mol of sodium bicarbonate. At the end of the reaction time the solution was evaporated to dryness at a temperature not exceeding 30°. The residue was taken up with 5.0 ml of absolute ethanol and filtered and the solvent was removed. This latter procedure was repeated three times. The residual gum was dissolved in 11 ml of distilled water, and 1 g of calcium carbonate and 14 ml of aqueous bromine were added. The reaction mixture was allowed to stand for 20 hr at room temperature and then filtered. The excess bromine was expelled from the solution by sweeping with nitrogen gas. The mixture was agitated with 1 g of silver carbonate for 5 min and again filtered. The filtrate was acidified to a pH of 1–2 with Dowex 50 (H^+) resin. The solvent was removed to yield a light yellow gum which crystallized from absolute ethanol, 12.0 mg (~10%). Recrystallization from distilled water gave mp 163–165° (lit.[24] mp 163–164°), $[\alpha]^{25}D$ −14.6° (*c* 1.28, H_2O containing 2 equiv of sodium hydroxide) [lit.[24] $[\alpha]^{23}D$ −22.3° (*c* 1.3, H_2O containing 2 equiv of potassium hydroxide)].

The R_f values of 0.34 and 0.76, respectively, on silica gel G tlc in solvent mixtures *n*-propyl alcohol–ammonium hydroxide (70:30) and *sec*-butylalcohol–formic acid–water (75:15:10) were in agreement with those obtained from the *N*-benzoyl-L-aspartic acid prepared by us. The ir spectra were likewise identical.

Acknowledgment. We wish to express our appreciation to Miss Katie Reimer of Arizona State University for the exploratory nmr work at 100 MHz, and to Dr. Frederick Antosz and Professor Kenneth L. Rinehart for their help in securing the 220-MHz spectrum. Helpful discussion with Professor Peter Brown is gratefully acknowledged. We express our gratitude to the Hungarian Academy of Sciences for support of this research and the Analytical Laboratory of the Institute of Organic Chemistry of the Kossuth University for the microanalyses.

Registry No.—**1**, 51869-30-8; **1** picrate, 51869-31-9; **1** HCl, 51869-32-0; **2**, 51869-33-1; **2** HCl, 51869-34-2; **3**, 51869-35-3; **4**, 51869-36-4; **5**, 51869-37-5; **6**, 4915-59-7; ristomycin A, 11021-66-2; ristomycin A sulfate, 51932-11-7.

References and Notes

(1) G. F. Gauze, E. S. Kudrina, R. S. Ukholina, and G. V. Gavrilina, *Antibiotiki*, **8**, 387 (1963).
(2) V. A. Shorin, N. S. Pevzner, and S. P. Shapovalova, *Antibiotiki*, **8**, 396 (1963).
(3) M. G. Brazhnikova, N. N. Lomakina, F. Sztaricskai, M. Puskás, S. Makleit, and R. Bognar, *Kem. Kozlem.*, **27**, 143 (1967).
(4) N. N. Lomakina, L. A. Szpiridonova, R. Bognar, M. Puskás, and F. Sztaricskai, *Antibiotiki*, **13**, 975 (1968).
(5) N. N. Lomakina, R. Bognar, M. G. Brazhnikova, F. Sztaricskai, and L. Muravyeva, Abstracts, Seventh International Symposium on the Chemistry of Natural Products, Zinate, Riga, 1970, p 625.
(6) J. S. Dixon and D. Lipkin, *Anal. Chem.*, **26**, 1092 (1954).
(7) No conflicting structural information derives from the mass spectra of **2** and **3**.
(8) T. Reichstein and E. Weiss, *Advan. Carbohyd. Chem.*, **17**, 65 (1962).
(9) F. Arcamone, G. Cassinelli, P. Orezzi, G. Franceschi, and R. Mondelli, *J. Amer. Chem. Soc.*, **86**, 5335 (1964).
(10) J. F. Stoddart, "Stereochemistry of Carbohydrates," Wiley-Interscience, New York, N. Y., 1971, p 129.
(11) A. W. Johnson, R. H. Smith, and R. D. Guthrie, *J. Chem. Soc., Perkin Trans. 1*, 2153 (1972).
(12) M. Miyamoto, Y. Kawamatsu, M. Shinohara, K. Nakanishi, Y. Nakadaira, and N. S. Bhacca, *Tetrahedron Lett.*, 2371 (1964).
(13) L. D. Hall and J. F. Manville, *Advan. Chem. Ser.*, **74**, 228 (1968).
(14) W. D. Celmer and D. C. Hobbs, *Carbohyd. Res.*, **1**, 137 (1965).
(15) J. S. Brimacombe and D. Portsmouth, *Carbohyd. Res.*, **1**, 128 (1965).
(16) W. Hofheinz, H. Grisebach, and H. Friebolin, *Tetrahedron*, **18**, 1265 (1962).
(17) T. D. Inch, J. R. Plummer, and H. G. Fletcher, Jr., *J. Org. Chem.*, **31**, 1825 (1966); D. Horton, J. B. Hughes, J. S. Jewell, K. D. Philips, and W. N. Turner, *ibid.*, **32**, 1073 (1973); D. Horton, W. E. Mast, and K. D. Philips, *ibid.*, **32**, 1471 (1967); R. J. Cushey, K. A. Watanabe, and J. J. Fox, *J. Amer. Chem. Soc.*, **89**, 394 (1967).
(18) E. A. Davidson, "Carbohydrate Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1967, p 73.
(19) Johnson, *et al.*,[11] found that the nmr spectrum of methyl α-L-vancosaminide in $[^2H_5]$-pyridine provided the *only* example from among ten vancosamine derivatives where H-2e appeared upfield of H-2a. This was also the *only* spectrum run in $[^2H_5]$-pyridine.
(20) In tri-*O*-acetyl-β-D-xylopyranosyl chloride, H-5e is reported to resonate at higher field than H-5a: C. V. Holland, D. Horton, and J. S. Jewell, *J. Org. Chem.*, **32**, 1818 (1967).
(21) R. U. Lemieux and J. C. Stevens, *Can. J. Chem.*, **43**, 2059 (1965).
(22) J. Euw and J. Reichstein, *Helv. Chim. Acta*, **31**, 883 (1948).
(23) J. C. Speck and A. A. Forest, *Anal. Chem.*, **26**, 1942 (1954).
(24) H. H. Baer and F. Kienzle, *Can. J. Chem.*, **43**, 3074 (1965).

Alkaloid Studies. LXVIII.[1] Novel Piperidyl Alkaloids from *Lupinus formosus*

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Three new alkaloids, (+)-*N'*-methylammodendrine (**3**), *N*-acetylhystrine (**4**), and the biogenetically intriguing smipine (**9**), have been isolated from *Lupinus formosus* and their structures determined. Other alkaloids identified were hystrine (**1**), (+)-ammodendrine (**2**), (−)-anabasine (**5**), (−)-*N*-methylanabasine (**6**), lupinine (**7**), and *N*-methylpelletierine (**8**).

In conjunction with an ecological study comparing the predation patterns and alkaloidal contents of several Colorado *Lupinus* species,[2] we undertook an investigation of the alkaloids of a local species, *L. formosus* Greene, collected within a few miles of the Stanford Chemistry Department.

The alkaloids were isolated and identified by standard techniques. The two major alkaloids were hystrine (**1**)[3] and (+)-ammodendrine (**2**).[4] To our knowledge this is the first report of the occurrence of these bipiperidyl alkaloids in a *Lupinus* species,[5] although they have been found together in the related legume genus *Genista*.[6] (+)-Ammodendrine and racemic ammodendrine have been encountered in several genera of the Leguminosae.[7]

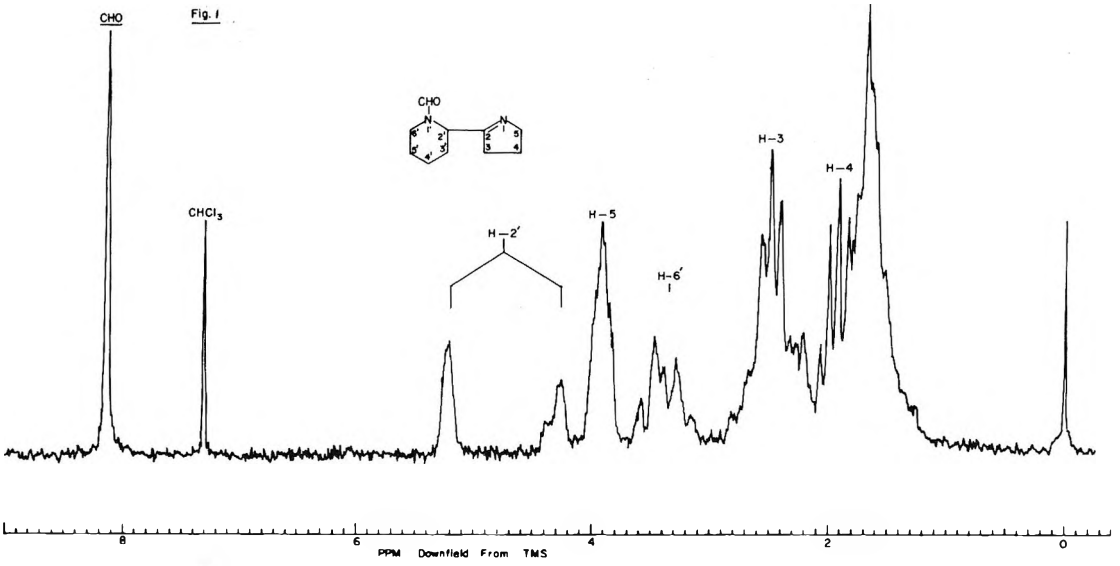
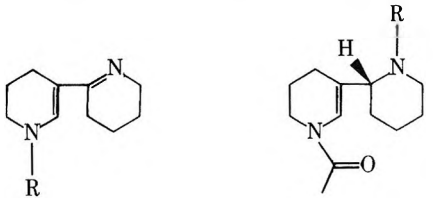


Figure 1. Nmr spectrum of smipine (**9**) at 100 MHz in $CDCl_3$.

The related compounds (+)-*N'*-methylammodendrine (**3**) and *N*-acetylhystrine (**4**) were also isolated from the



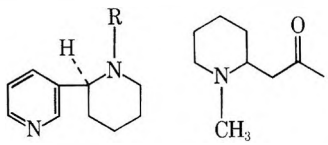
1, R = H
4, R = $COCH_3$

2, R = H
3, R = CH_3

crude basic fraction in reasonable amounts. The former (**3**) was identified by its mass spectrum[8] (M^+ 222), and the similarity of its nmr spectrum with that of ammodendrine (**2**)[9] (excepting an *N*-methyl signal at δ 2.08). Confirmation of the structure was obtained by comparison with a sample prepared by methylation of (+)-ammodendrine.[10] The absolute configurations of (+)-**2** and (+)-**3** have been determined.[11] To our knowledge this is the first description of *N'*-methylammodendrine (**3**) as a natural product.

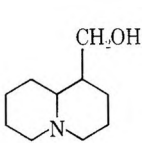
N-Acetylhystrine (**4**) was identified by its mass and nmr spectra. Confirmation was obtained by comparison with a sample synthesized by acetylation of hystrine (**1**).[3] In spite of a thorough search,[12] this fairly unstable alkaloid could not be found in the hystrine-containing plant *Genista hystrix*.

Several alkaloids present in *Lupinus formosus* in only trace amounts were identified by combined gas chromatography-mass spectrometry. These included the "tobacco" alkaloids (−)-anabasine (**5**)[13] and (−)-*N*-methylanabasine (**6**).[14] Also identified were the "pomegranate" alkaloid *N*-methylpelletierine (**7**)[13] and lupinine (**8**), the only conventional "lupine" alkaloid[7] isolated from this plant. These compounds were identified by comparison of their mass spectra and gas chromatographic retention times upon coinjection with authentic samples. It was possible to determine the ORD curves of **5** and **6** on small samples (*ca.* 0.5 mg) obtained by preparative gas chromatography. Unfortunately, sample limitations did not allow for comparable determinations on **7** or **8**. The identification of these trace components would have been impossible without the analytical power of gas chromatography–mass spectrometry.



5, R = H
6, R = CH_3

7



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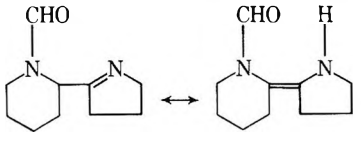
The most interesting alkaloid was named smipine (after the SMIP ranch near Stanford where some of the plant material was collected) and was assigned structure **9** on the basis of spectral evidence. High-resolution mass spectrometry and elemental analysis indicated the molecular formula $C_{10}H_{16}N_2O$. The mass spectrum displayed a small molecular ion (*m/e* 180) with significant peaks at *m/e* 163 (M − OH), 151 (M − CHO), 112 (M − C_4H_6N), 109 (base peak, M − C_3H_5NO), and 96 (M − C_4H_6NO). Diagnostically, the most informative peak was the one at *m/e* 112 which implied the loss of a five-membered nitrogen-containing ring (C_4H_6N) containing one degree of unsaturation. If that moiety and the formyl group (see M − CHO peak and appropriate nmr signal) are subtracted from the molecular formula, a piperidyl ring equivalent remains. Consequently, we started with the hypothesis that smipine was a bicyclic molecule consisting of a piperidine and a pyrroline ring.

Smipine was transparent in the ultraviolet above 210 nm, and optically inactive as evidenced by its optical rotatory dispersion curve. The equilibrium between the imine (**9**) and enamine (**10**) tautomeric forms would explain this lack of optical activity.[17] The infrared spectrum indicated

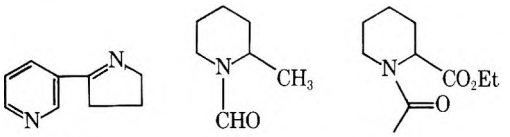


9 10

the presence of a tertiary amide (1670 cm^{-1}) and an isolated imine group (1645 cm^{-1}). No infrared absorption associated with NH, OH, or vinyl groups was observed.

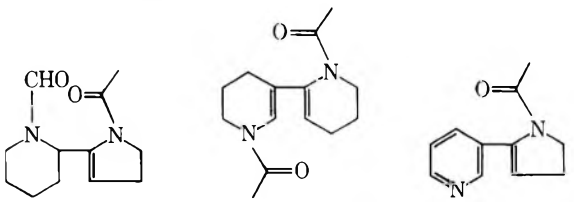
The nmr spectrum (Figure 1) of smipine indicated the presence of an *N*-formyl group (δ 8.15) as well as a 2-substituted 1-pyrroline [a two-hydrogen broad multiplet at δ 3.90, a broadened two-hydrogen triplet (J = 8 Hz) at δ 2.45, and a sharp two-hydrogen multiplet (J = 8 Hz) at δ 1.95]. The pyrroline assignment is supported by decoupling experiments as well as comparison with the nmr spectrum of myosmine (**11**).[18]

A complex set of broad peaks centered at δ 5.21, 4.25, and 3.35 and integrating for three protons is assigned to the α protons in a 2-substituted 1-acylpiperidine structure. This assignment is supported by comparison with the spectra of 1-formyl-2-methylpiperidine (**12**)[19] and ethyl 1-acetylpipecolinate (**13**) (see Experimental Section). The complex nature of these absorptions is due to restricted rotation about the amide bond.[19]



11 **12** **13**

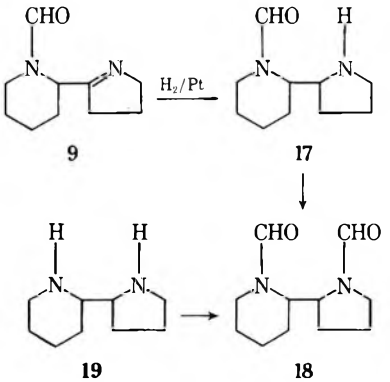
Acetic anhydride–pyridine acetylation of smipine yielded a monoacetyl derivative which was assigned structure **14** by analogy to the products **15** and **16** obtained by similar



14 **15** **16**

treatment of hystrine (**1**)[8] and myosmine (**11**).[20] The mass spectrum of acetylsmipine (**14**) (M^+ 222) displayed losses of 29 (M − CHO) and 43 (M − C_2H_3O) mass units. The ultraviolet spectrum (λ_{max} 244 nm, ϵ_{max} 7200) was indicative of a vinyl amide grouping [compare ammodendrine (**2**), λ_{max} 242 nm[9]]. The nmr spectrum indicated formyl (δ 8.15) and acetyl (δ 2.10) protons, the same diffuse peaks centered at δ 5.30, 4.10 and 3.50, and the resonances expected for a 2-substituted 1-acyl-2-pyrroline [a sharp one-proton triplet (J = 1–2 Hz) at δ 5.25, a two-proton triplet (J = 8 Hz) at δ 3.90, and a broadened two-proton triplet (J = 8 Hz) at δ 2.45]. These assignments are supported by comparison with the nmr spectrum (see Experimental Section) of acetylmyosmine (**16**).

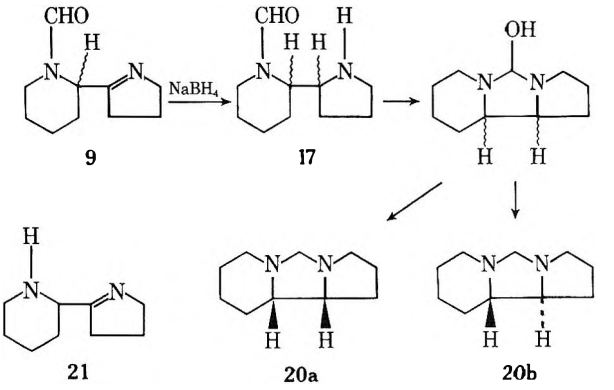
On catalytic hydrogenation (PtO_2–HOAc) smipine quickly took up 1 mol of hydrogen to give a dihydro derivative **17** which was difficult to isolate. It was characterized by formylation to **18**, which proved to be identical with a specimen prepared by diformylation of the known 2-(2-pyrrolidinyl)piperidine (**19**),[22] thus proving the skeletal structure of the alkaloid.



9 **17** **19** **18**

Further chemical support for the structure of smipine was provided by sodium borohydride reduction of the alkaloid, which led to a mixture of isomers shown to be identical with the syn and anti isomers of perhydropyrido[1,2-c]pyrrolo[2,1-*e*]imidazole (**20a** and **20b**).[21] As shown in Scheme I, these isomers can be formed by hydride attack on smipine (**9**) followed by cyclization and further reduction.

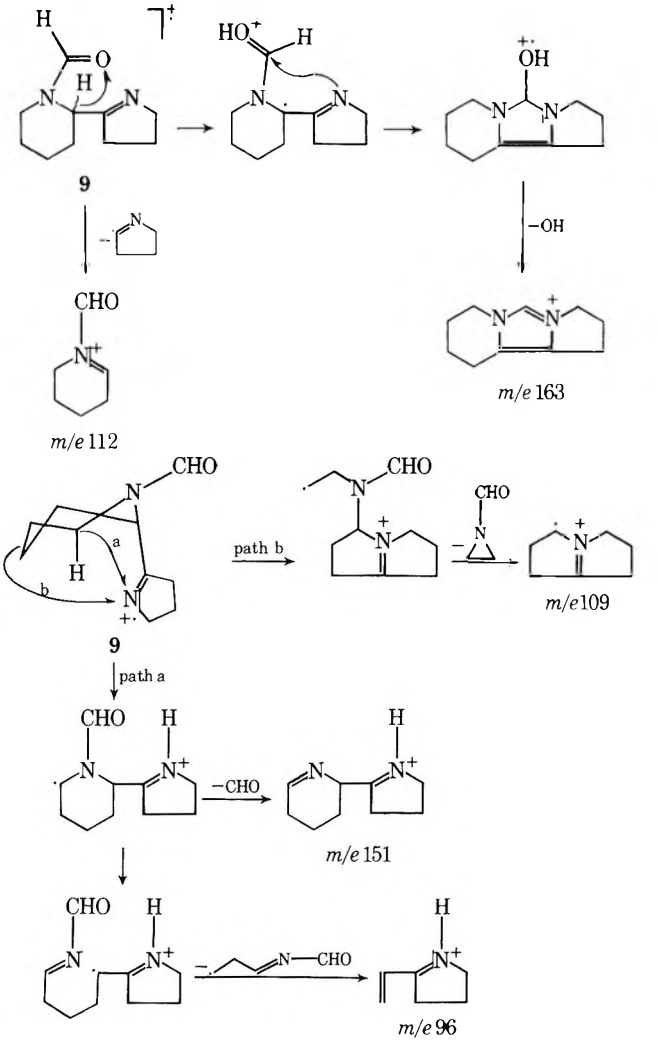
Scheme I



9 **17** **21** **20a** **20b**

With the structure of smipine (**9**) established, it is now possible to rationalize the mass spectral fragmentation in terms of the ion structures listed in Scheme II.

Scheme II

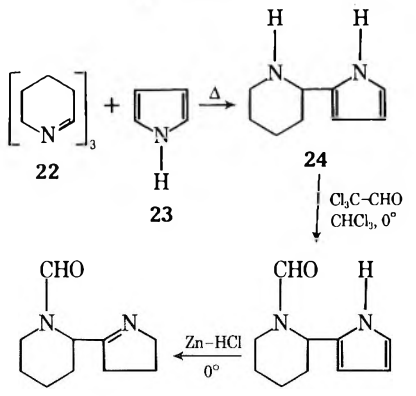


m/e 112 *m/e* 163 *m/e* 109 *m/e* 151 *m/e* 96

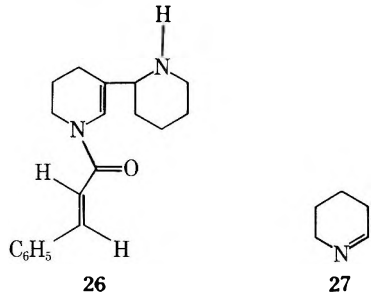
Owing to the unusual chemistry and unprecedented skeleton of smipine, a total synthesis was undertaken to confirm the structure. The logical intermediates **17** and **21** proved too unstable to be converted to smipine. Smipine was finally synthesized by the reactions depicted in Scheme III. Condensation[22] of α-tripiperidine (**22**) with pyrrole (**23**) gave 2-(2-piperidyl)pyrrole (**24**), which on

chloral formylation[23] yielded the formyl derivative **25**. Zinc–hydrochloric acid reduction of pyrroles is known[24] to give mixtures of 1- and 3-pyrrolines. Unfortunately, the strong acid conditions necessary for the reduction also led to considerable hydrolysis of the amide function, and the best yield obtainable was only 10%. This synthetic material was identical in all respects with naturally occurring smipine, thus providing final confirmation for structure **9**.

Scheme III

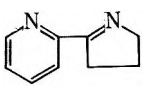


The alkaloids of *Lupinus formosus* all possess a common 2-substituted piperidine ring. In the well-studied cases, including anabasine (**5**),[25] *N*-methylpelletierine (**7**),[26] lupinine (**8**),[27] and the bipiperidyl alkaloid adenocarpine (**26**),[28] these structural units have been shown to arise from lysine, most likely *via* Δ^1-piperideine (**27**).[29] The co-occurrence of



bipiperidyl and lupine alkaloids is well precedented from several plants.[30,31]

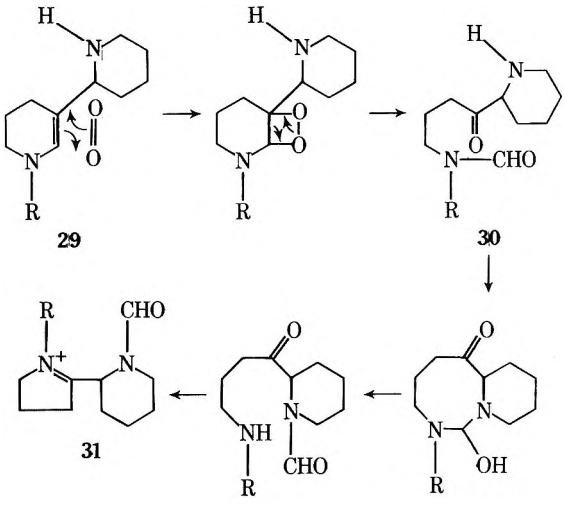
How the unusual alkaloid smipine fits into this scheme is not clear. To our knowledge the only other naturally occurring compound possessing the 2-(2-pyrrolidinyl)piperidine skeleton is the bacterial metabolite, apoferrorosamine (**28**).[32]



As smipine does not easily fit into the common Δ^1-piperideine biosynthetic scheme and considering that its molecular formula, $C_{10}H_{16}N_2O$, corresponds to a hystrine oxide or partially oxidized tetrahydroanabasine, we believe that smipine arises from an oxidative rearrangement of one of the major alkaloids.

One hypothetical scheme for such a transformation (Scheme IV) involves light-induced singlet oxygen cycloaddition to ammodendrine (**2**) or a tetrahydroanabasine analog **29**. Although the singlet oxygen reaction with enamides such as ammodendrine (**2**) has not been studied, $^1O_2$ is known to react with enamines to give dicarbonyl products in high yield.[33] The product from such an oxidative cleavage (**30**) after formyl transfer and recyclization would yield directly a smipine derivative (**31**).

Scheme IV



Experimental Section

Low-resolution mass spectra were recorded on Atlas CH-4 and AEI MS-9 mass spectrometers and are reported as *m/e* values with intensities in parentheses. High-resolution mass spectra were recorded on a Varian MAT-711 mass spectrometer. Combined gas chromatography–mass spectrometry was carried out on a Hewlett-Packard 7610 gas chromatograph (3% OV-17 on Gas-Chrom Q) interfaced through a Watson-Biemann dual stage separator to a Varian MAT-711 mass spectrometer. For infrared spectra, a Perkin-Elmer Model 700 spectrophotometer was used. Nmr spectra were obtained with either a Varian Model T-60 or HA-100 spectrometer, and are recorded in δ values with $CDCl_3$ as solvent unless otherwise stated.

Thin layer chromatograms on silica gel HF-254 as adsorbent were developed with ethyl acetate–hexane–diethylamine (7:7:2). Gas chromatography was carried out on OV-17 (3% on Gas-Chrom Q).

Authentic samples of alkaloids were obtained as follows. (±)-Ammodendrine was a gift from Professor R. R. Arndt, Rand Africaans University, Johannesburg, South Africa. (−)-Anabasine was obtained from Aldrich Chemical Co. (−)-*N*-Methylanabasine,[16] (+)-*N*′-methylammodendrine,[10] hystrine,[3] *N*-acetylhystrine,[3] and (±)-*N*-methylpelletierine[26] were synthesized by standard procedures.

Detailed mass spectral analyses of several of these alkaloids have been published elsewhere.[8]

Extraction and Isolation of Alkaloids. The plant material was collected in September 1971. The dried, ground, whole plants (3.3 kg) were extracted for 1 week with EtOH–CH_2Cl_2 (1:1) at room temperature. After removal of the solvents *in vacuo*, the extract was treated with 1 *N* HCl and washed with several portions of CH_2Cl_2. The aqueous layer was then basified to pH 12 and extracted first with ether and then with $CHCl_3$. The ether extract was evaporated to dryness and treated with acetone to give 7.5 g of a crude precipitate of hystrine hydrochloride (**1**). Purification by chromatography on alumina and recrystallization from MeOH–acetone gave pure hystrine hydrochloride. Chromatography of the acetone-soluble portion of the ether extract on alumina gave 5.5 g of fairly pure *N*′-methylammodendrine (**3**), 12 g of pure ammodendrine (**2**), and an additional 2 g of hystrine hydrochloride. Vacuum distillation of the impure *N*′-methylammodendrine failed to separate it from the contaminating ammodendrine but collection of the first drop of distillate gave a sample enriched in several volatile alkaloids. *N*′-Methylammodendrine could be obtained in a pure state by preparative tlc on silica gel.

N-Acetylhystrine (**4**) was not stable to any extended procedures and was isolated from the fresh crude ether extract by preparative tlc on silica gel followed by preparative gc.

Alumina chromatography of the chloroform extract gave an additional 1.2 g of hystrine hydrochloride as well as a new alkaloid smipine, which was purified by preparative gc.

Hystrine (**1**) was isolated as the hydrochloride (9.2 g, 0.23%), prisms from MeOH–acetone, mp 206–208°. *Anal.* Calcd for

$C_{10}H_{17}N_2Cl$: C, 59.84; H, 8.54; N, 14.00; Cl, 17.66. Found: C, 59.54; H, 8.39; N, 14.00; Cl, 17.71. It was identical with a synthetic sample[3] by mixture melting point and tlc.

(+)-Ammodendrine (2, 13 g, 0.39%) was a colorless oil, $C_{12}H_{20}N_2O$ (calcd mol wt 208.157, obsd 208.159 by high-resolution mass spectrum): $[\alpha]D$ +6.6° (*c* 3.9, EtOH); nmr δ 2.10, 2.14 (singlets split by conformation about N-1, 3 H, $COCH_3$), 2.64 [triplet (J = 11 Hz) of doublets (J = 3 Hz), 1 H, H-6′ axial], 3.05 (m, 2 H, H-2′, -6′ equatorial), 3.60 (m, 2 H, H-2), 6.55, 7.19 (singlets, vinyl hydrogen, two conformations). The perchlorate (from H_2O) had mp 210–211°. **2** was identical by ir, tlc, gc, and mass spectrum with an authentic sample.[9]

(+)-*N*′-Methylammodendrine (3, 2.5 g, 0.08%) was a colorless oil, $C_{13}H_{22}N_2O$ (calcd mol wt 222.173, obsd 222.173 by high-resolution mass spectrum): $[\alpha]D$ −40.5° (*c* 2.0, EtOH); ir (neat) 1640 cm^{-1} (C=O); nmr δ 2.08 (s, 3 H, NCH_3), 2.17, 2.14 (s, 3 H, $COCH_3$), 2.95 [doublet (J = 11 Hz) of triplets (J = 2–3 Hz), 1 H, H-6′ equatorial], 3.65 (m, 2 H, H-2), 6.56, 7.21 (s, 1 H, H-6). It was identical by ir, tlc, gc, and mass spectrum with a synthetic sample.[10]

***N*-Acetylhystrine** (4) (*ca.* 0.01% by gc analysis) was a colorless oil which rapidly yellowed in air, $C_{12}H_{18}N_2O$ (calcd mol wt 206.141, obsd 206.142 by high-resolution mass spectrum), nmr δ 2.20 (s, 3 H, $COCH_3$), 3.65 (m, 4 H, H-2, -6′), 7.18, 7.78 (s, 1 H, H-6). It was identical by gc, mass spectrum, and tlc with a synthetic sample.[3]

Analysis of Volatile Alkaloid Fraction. This fraction (20 mg) obtained as described above, was analyzed by combined gas chromatography–mass spectrometry. Compounds were identified by comparison of mass spectra and coinjection on gc with authentic samples. Small amounts of anabasine and *N*-methylanabasine were present in the crude *N*′-methylammodendrine fraction. By exhaustive preparative gas chromatography small samples (*ca.* 0.5 mg) of these alkaloids were obtained in a pure state. The amounts of lupinine and *N*-methylpelletierine did not allow for similar isolations.

(−)-Anabasine (5), mass spectrum *m/e* (rel intensity) 162 (M^+, 49), 161 (38), 133 (54), 119 (40), 105 (51), 84 (100), 80 (24), ORD (c ~0.01, EtOH) $[\alpha]_{275}$ −490°, $[\alpha]_{255}$ +1050°,[34] was identical by gc, mass spectrum, and ORD with an authentic sample.

(−)-*N*-Methylanabasine (6), mass spectrum *m/e* (rel intensity) 176 (M^+, 19), 175 (12), 147 (9), 133 (9), 119 (21), 98 (100), 42 (11), ORD (c ~0.01, EtOH) $[\alpha]_{275}$ −700°, $[\alpha]_{255}$ + 670°,[34] was identical by gc, mass spectrum, and ORD with a synthetic sample.[16]

***N*-Methylpelletierine (7),** mass spectrum *m/e* (rel intensity) 155 (M^+, 7), 112 (9), 98 (100), 96 (25), 82 (10), 70 (42), 41 (41), was identical by gc and mass spectrum with a synthetic sample.[26]

Lupinine (8), mass spectrum *m/e* (rel intensity) 169 (M^+, 60), 168 (52), 152 (100), 138 (74), 124 (30), 110 (49), 97 (64), 96 (50), 83 (88), 55 (40), 41 (32), was identical by gc and mass spectrum with an authentic sample. In an earlier paper,[2] the lupinine from *Lupinus bakeri* was thought to be epilupinine. However, it has since been shown by optical ($[\alpha]D$ −18.1° (*c* 0.27, EtOH)) and infrared (ν_{max} 3250 cm^{-1} for a dilute $CHCl_3$ solution) measurements to be (−)-lupinine.[36]

Smipine (9) (*ca.* 0.003%) was a colorless oil which rapidly yellowed on standing, $C_{10}H_{16}N_2O$ (calcd mol wt 180.126, obsd 180.126 by high-resolution mass spectrum). *Anal.* Calcd: C, 66.64; H, 8.95; N, 15.54. Found: C, 66.30: H, 8.98; N, 15.26.) Smipine showed no ultraviolet absorption above 230 nm and no optical activity to 200 nm by ORD measurements: ir 1660 (tertiary amide), 1640 cm^{-1} (shoulder, C=N); mass spectrum *m/e* (rel intensity) 180 (M^+, 3), 163 (2), 151 (14), 112 (11), 109 (100), 96 (74); nmr ($CHCl_3$, see Figure 1) (C_6D_6) 1.2–1.8 (8 H), 2.04 (t, 2 H, H-3′), 2.80 (m, 2 H, H-6′), 3.68 (br, 2 H, H-5), 4.44. 5.30 (br, 1 H, H-2′), 7.89 7.92 (s, 1 H, CHO).

Acetylation of Smipine. Treatment of smipine with excess acetic anhydride–pyridine at room temperature for 1 hr gave a monoacetyl derivative isolated by preparative gas chromatography. The colorless oil was assigned structure **14** [1-acetyl-2-(1-formyl-2-piperidyl)-2-pyrroline] on the basis of the spectral evidence: mass spectrum *m/e* (rel intensity) 222 (M^+, 24), 193 (M − CHO, 12), 179 (M − C_2H_3O, 44), 163 (71), 151 (100), 43 (55); ir 1665 cm^{-1}; uv (EtOH) λ_{max} 244 nm (ϵ_{max} 7200); nmr δ 8.15 (s, 1 H, CHO), 5.30 (t, J = 2 Hz, 1 H, H-3), 5.25, 4.10 (br, 1 H, H-2′), 3.90 (t, J = 8 Hz, 2 H, H-5), 3.50 (br, 2 H, H-6′), 2.55 (t, J = 8 Hz, 2 H, H-4), 2.10 (s, 3 H, $COCH_3$), 1.4–1.8 (6 H).

Borohydride Reduction of Smipine. Smipine (65 mg) was dissolved in absolute EtOH (20 ml), sodium borohydride (100 mg) was added, and the solution was refluxed overnight. After removal of the EtOH *in vacuo*, the residue was dissolved in 10% KOH, extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated to yield 45 mg of a colorless oil. Gas chromatography indicated a 3:2 mixture of two products which could be separated on a preparative scale. The two products showed identical mass spectra, *m/e* (rel intensity) 166 (M^+, 18), 165 (14), 97 (67), 96 (10), 83 (100); ir 2800, 2750 cm^{-1} (typical Bohlmann bands[36]), no carbonyl, imine, or NH peaks observed; nmr ($CHCl_3$ solution of the isomer mixture) distinctive doublets at δ 2.82 (J = 4 Hz), 3.10 (J = 7 Hz), 3.60 (J = 7 Hz), and 4.12 (J = 4 Hz), no vinyl peaks present. These products were shown to be identical with the syn and anti isomers of perhydropyrido[1,2-c]-pyrrolo[2,1-*e*]imidizoles **20a** and **20b** by comparison (gc, mass spectrum, nmr, ir) with a synthetic mixture of the isomers.[21]

Catalytic Hydrogenation of Smipine. Smipine (8.4 mg) was hydrogenated at 1 atm with PtO_2 in acetic acid at room temperature. After 1 hr 0.92 ml (0.88 equiv) of H_2 had been absorbed. Filtration and evaporation gave a colorless oil which was dissolved in formic acid (1 ml) and treated with acetic anhydride (0.5 ml). After 2 hr at 60°, the mixture was evaporated to dryness and the product was isolated by preparative gc. This material was identical by ir, gc, and mass spectrum with a sample synthesized as follows. 2-(2-Pyrrolidinyl)piperidine[21] (100 mg) was stirred at 60° for 2 hr with formic acid and acetic anhydride. Evaporation yielded the diformyl derivative **18** as a colorless oil: mass spectrum *m/e* (rel intensity) 210.137 (M^+, calcd for $C_{11}H_{18}N_2O_2$, 210.137, 10), 112 (100), 99 (59), 98 (25), 84 (35), 70 (23); nmr δ 1.3–2.2 (br, 10 H), 3.0–4.5 (complex, 6 H), 8.10 (br, 2 H).

2-(2-Piperidyl)pyrrole (24). Condensation of α-tripiperidine and pyrrole as described[22] gave 2-(2-piperidyl)pyrrole, which was obtained pure after vacuum sublimation and recrystallization from ethyl acetate: mp 96.5–97.5°; mass spectrum *m/e* (rel intensity) 150 (M^+, 100), 134 (34), 121 (86), 107 (38), 94 (96), 93 (67), 80 (38), 67 (30); nmr δ 1.4–2.0 (7 H), 2.5–3.2 (br, 2 H, H-6′), 3.80 (br, 1 H, H-2′), 5.95 (m, 2 H, H-3, -4), 6.52 (m, 1 H, H-5), 10.0 (br, 1 H, H-1).

2-(1-Formyl-2-piperidyl)pyrrole (25). A solution of pure **24** (2.5 g) in $CHCl_3$ (25 ml) was treated dropwise at 0° with chloral (3.0 g).[23] When the addition was complete, the mixture was allowed to warm to room temperature and stirred for 3 hr. It was then evaporated below 40° to a gum which crystallized on addition of a small amount of ether. Filtration and washing with cold ether gave 2.7 g (90%) of crude **25.** After recrystallization from ethyl acetate–hexane the pure material was obtained as colorless needles, mp 113–114°. *Anal.* Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.71. Found: C, 67.19; H, 7.83; N, 15.75. Mass spectrum *m/e* (rel intensity) 178 (M^+, 100), 161 (17), 149 (46), 134 (14), 121 (14), 93 (34), 80 (24); ir 3470, 3300 (NH), 1665 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.5–2.5 (6 H), 2.8–3.6, 4.05 (broad multiplets, 2 H, H-6′), 4.75, 5.60 (br, 1 H, H-2′), 6.05 (m, 2 H, H-3, -4), 6.65 (m, 1 H, H-5), 7.90 (s, 1 H, CHO), 9.7 (br, 1 H, H-1); nmr (C_6D_6) 4.35, 5.75 (br, 1 H, H-2′), 7.70, 7.85 (s, 1 H, CHO).

2-(1-Formyl-2-piperidyl)-1-pyrroline (Smipine 9). Zinc dust (200 mg) was added at 0–5° to 2 ml of 20% HCl. Then **25** (50 mg) was added and the solution was stirred for 0.5 hr, at which time concentrated HCl (2 ml) was added. Stirring at 0° was continued for an additional 4 hr. The cold solution was filtered, neutralized to pH 12 with K_2CO_3 and 30% KOH, and extracted with CH_2Cl_2. After drying and evaporation, 20 mg of reddish oil was obtained. Gc analysis indicated roughly equal amounts of starting material, an unstable product which could not be isolated (possibly the 3-pyrroline), and a peak which corresponded to smipine. Chromatography on neutral alumina (activity II) gave 5 mg of pure 2-(1-formyl-2-piperidyl)-1-pyrroline identical in all respects (gc, tlc, ir, mass spectrum, nmr) with natural smipine.

Acetylmyosmine (16). Myosmine[38] (30 mg) was stirred at room temperature overnight with acetic anhydride and pyridine. Evaporation and normal work-up gave 26 mg of a monoacetyl derivative **16**:[20] mass spectrum *m/e* (rel intensity) 188.095 (M^+, calcd for $C_{11}H_{12}N_2O$, 188.095, 29), 146 (71), 145 (100), 43 (19); nmr δ 1.95 (s, 3 H, $COCH_3$), 2.75 [triplet (J = 8 Hz) of doublets (J = 3 Hz), 2 H, H-4], 4.2 (t, J = 8 Hz, 2 H, H-5), 5.55 (t J = 3 Hz, 1 H, H-3), 7.25 [doublet (J = 8 Hz) of doublets (J = 4 Hz), 1 H, H-5′], 7.54 [doublet (J = 8 Hz) of triplets (J = 2 Hz), 1 H, H-4′], 8.4 (br, 2 H, H-2′, -6′).

Ethyl 1-Acetylpipecolinate (13). This compound was prepared as previously described:[37] nmr δ 2.6–3.9, 4.48, 5.25 (broad, complex, 3 H, H-2, -6), 4.16 (q, 2 H, CH_2CH_3), 1.25 (t, 3 H, CH_2CH_3), 2.05, 2.10 (singlets, 3 H, $COCH_3$); nmr (C_6D_6) 5.45, 4.57, 2.8–3.5 (complex, 3 H).

Acknowledgments. Financial support from the National Institutes of Health (Grants AM-04257 and RR 00612-05A1) is gratefully acknowledged. We also thank the proprietor of the SMIP Shorthorn Ranch (Woodside, Calif.) for facilitating the plant collection on his ranch.

Registry No.—1 HCl, 18017-52-2; **2**, 494-15-5; **3**, 52196-10-8; **4**, 52195-93-4; **5**, 494-52-0; **6**, 24380-92-5; **7**, 40199-45-9; **8**, 486-70-4; **9**, 52196-11-9; **13**, 52195-94-5; **14**, 52196-12-0; **16**, 52195-95-6; **18**, 52195-96-7; **20a**, 23972-23-8; **20b**, 23972-24-9; **24**, 52196-13-1; **25**, 52196-14-2.

References and Notes

(1) For part LXVII see L. J. Durham, C. Djerassi, and J. N. Shoolery, *Proc. Nat. Acad. Sci.*, in press.
(2) P. M. Dolinger, P. R. Ehrlich, W. L. Fitch, and D. E. Breedlove, *Oecologia*, **13**, 191 (1973).
(3) E. Steinegger and P. Weber, *Helv. Chim. Acta*, **51**, 206 (1968).
(4) C. Schöpf and F. Braun, *Naturwissenschaften*, **36**, 377 (1949).
(5) (±)-Ammodendrine was found as the major alkaloid in one of the Colorado species, *Lupinus bakeri*.[2]
(6) E. Steinegger and C. Moser, *Pharm. Acta Helv.*, **42**, 177 (1967).
(7) J. A. Mears and T. J. Mabry in "Chemotaxonomy of the Leguminosae," J. B. Harborne, D. Boulten, and B. L. Turner, Ed., Academic Press, New York, N. Y., 1971, Chapter 3.
(8) The unusual mass spectra of 1–4 and several related molecules have been discussed by W. L. Fitch and C. Djerassi, *J. Amer. Chem. Soc.*, in press.
(9) R. R. Arndt and L. M. DuPlessis, *J. S. Afr. Chem. Inst.*, **21**, 54 (1968).
(10) A. Orechoff and N. Proskurnina, *Chem. Ber.*, **68**, 1807 (1935).
(11) I. Ribas and A. Blanco, *An. Real Soc. Espan. Fis. Quim., Ser. B*, **57**, 781 (1961); *Chem. Abstr.*, **55**, 5738*c* (1961).
(12) E. Steinegger and E. Schnyder, *Pharm. Acta Helv.*, **45**, 156 (1970).
(13) R. F. Raffauf, "A Handbook of Alkaloids and Alkaloid-Containing Plants," Wiley-Interscience, New York, N. Y., 1970.
(14) *N*-Methylanabasine (**6**) appears to be a somewhat elusive compound. The only report of its isolation[15] could not be confirmed.[16]
(15) E. Späth and F. Kesztler, *Chem. Ber.*, **70**, 2450 (1937).
(16) E. Leete and M. R. Chedekel, *Phytochemistry*, **11**, 2751 (1972).
(17) K. Bláha and O.Cervinka, *Advan. Heterocycl. Chem.*, **6**, 0000 (1966).
(18) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 281.
(19) L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, **85**, 3728 (1963).
(20) F. Kuffner and T. Kirchenmayer, *Monatsh. Chem.*, **92**, 701 (1961).
(21) P. J. Chivers, T. A. Crabb, and R. O. Williams, *Tetrahedron*, **25**, 2921 (1969).
(22) D. W. Fuhlhage and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **80**, 6249 (1958).
(23) F. F. Blicke and C. J. Lu, *J. Amer. Chem. Soc.*, **74**, 3933 (1952).
(24) G. G. Evans, *J. Amer. Chem. Soc.*, **73**, 5230 (1951).
(25) E. Leete, *J. Amer. Chem. Soc.*, **91**, 1697 (1969).
(26) M. F. Keough and D. G. O'Donovan, *J. Chem. Soc. C*, 1792 (1972).
(27) H. R. Schütte, H. Hindorf, K. Mothes, and G. Hubner, *Justus Liebigs Ann. Chem.*, **680**, 93 (1964).
(28) H. R. Schütte, K. L. Kelling, D. Knofel, and K. Mothes, *Phytochemistry*, **3**, 249 (1964).
(29) E. Leistner and I. D. Spenser, *J. Amer. Chem. Soc.*, **95**, 4715 (1973).
(30) G. Faugeras, *Ann. Pharm. Fr.*, **29**, 241 (1971).
(31) E. Steinegger and E. Schlunegger, *Pharm. Acta Helv.*, **45**, 369 (1970).
(32) M. Pouteau-Thouvenot, A. Gaudemer, and M. Barbier, *Bull. Soc. Chim. Biol.*, **47**, 2085 (1965).
(33) C. S. Foote and J. Wei-Ping Lin, *Tetrahedron Lett.*, 3267 (1968).
(34) Owing to the small sample size, these values are not accurate, but they compare qualitatively with the published ORD data for anabasine[35] and *N*-methylanabasine.[16]
(35) J. C. Craig and S. K. Roy, *Tetrahedron*, **21**, 401 (1965).
(36) N. J. Leonard in "The Alkaloids," Vol. 7, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960, Chapter 14.
(37) F. P. Doyle, M. D. Mehta, G. S. Sach, R. Ward, and P. S. Sherman, *J. Chem. Soc.*, 578 (1963).
(38) F. Korte and H. Schulze-Steiner, *Chem. Ber.*, **95**, 2444 (1962).

Diamantane. I.[1] Preparation of Diamantane. Physical and Spectral Properties

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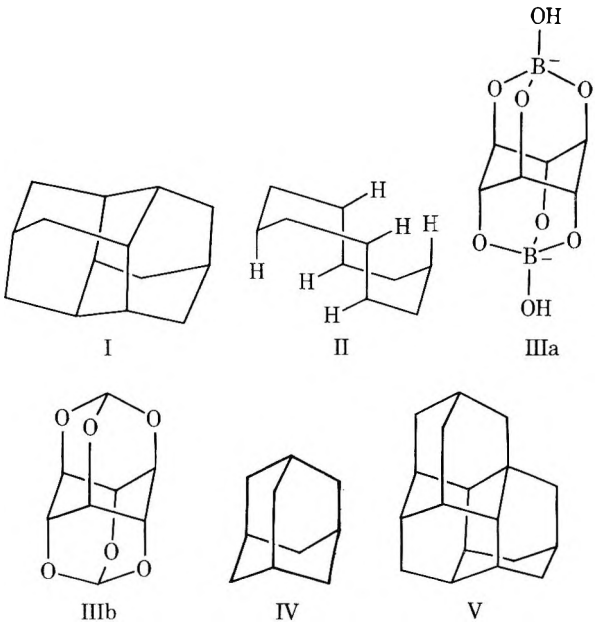
The preparation of diamantane (I) by Lewis acid catalyzed rearrangements of various pentacyclic tetradecanes has been examined. The best yield (84%) was obtained from *trans*-tetrahydro-Binor-S (XXXV). However, the most convenient synthetic procedure involves rearrangement of hydrogenated Binor-S (XXVII/XXVIII), which gives I in ~70% yield. Other more highly strained precursors give I in lower yield (1–47%) owing to disproportionation. The diamond lattice structure of diamantane, confirmed by X-ray analysis, is consistent with high thermodynamic stability. However, I, like adamantane, is not strain free. Molecular mechanics calculations show that this is due to an excess of repulsive over attractive nonbonded interactions in comparison with noncage hydrocarbons. The spectral properties of diamantane are characterized by a single-line proton nmr spectrum, resistance toward mass spectral fragmentation, and a simplified ir spectrum due to high symmetry.

The beautiful three-dimensional array of the diamond lattice has provided many structural insights and synthetic challenges.[3–5] Prelog[4] recognized that cyclodecane in conformation II is such a diamond lattice hydrocarbon and can be deduced from the pentacyclotetradecane I by replacing two CH and two CH_2 by six hydrogens.[6,7] At Prelog's suggestion, I (pentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecane) was chosen as the Congress Emblem of the 1963 London IUPAC meeting, and was featured as a decoration on the cover of abstracts, program, and publicity material. The *Handbook* challenged the Congress participants to synthesize I, and this challenge was reiterated by Cram and Hammond on the end papers of their popular text.[4c] The first preparation of "Congressane" was achieved at Princeton in 1965 in 1% yield by aluminum halide catalyzed isomerization of a mixture of norbornene [2 + 2] photodimers.[8]

Adamantane (IV) is the first and "Congressane" only the second member of an entire family of compounds "whose ultimate is diamond."[7] The synthesis of the third member of the series (V) in 1966[9] emphasized the need for a more general scheme of semitrivial nomenclature. Following the suggestion of Vogl and Anderson,[7] I was renamed "diamantane" and V designated triamantane.[7] The synthesis of tetramantane (three isomers are possible)[10] and of higher "amantanes" has not yet been achieved.

The year 1966 also marked the isolation of diamantane (I) from the high-boiling fractions of the crude oil of Hodonin (from which adamantane was discovered)[11] and the



achievement of a significant improvement in the yield of I (to 10%) by rearrangement.[2c] While this permitted a start to be made in the exploration of the chemistry of diamantane, the hydrocarbon was still difficult to obtain in quantity.

Subsequent work at Princeton explored various alternative precursors for diamantane with increasing success and culminated in a truly convenient high-yield preparation, reported in preliminary form in 1970.[12] Diamantane then became as readily available as adamantane and the chemistry of I could be studied easily. McKervey developed similar preparative improvements; a full report was published in 1972.[13a]

We recount here the preparative studies which led to a convenient synthesis, and summarize the physical properties of diamantane. The following two papers describe the chemical behavior and the functionalization of diamantane. The detailed analysis of the mechanisms of the rearrangements leading to diamantane from various precursors will be published separately.[1e]

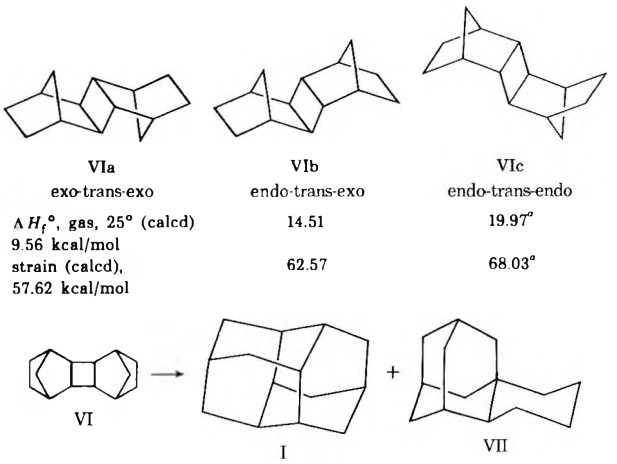
Results and Discussion

Preparation. A convenient preparation of adamantane was achieved in 1956[14] by aluminum halide catalyzed isomerization of the tricyclic $C_{10}H_{16}$ *endo*-tetrahydrodicyclopentadiene.[3,14] Subsequently, it was found that many saturated tricyclic hydrocarbons with ten or more carbon atoms rearrange to the thermodynamically most stable adamantane isomers.[3,14] The generality of these rearrangements suggested that the relatively unstrained diamantane might be obtained by isomerization of pentacyclic $C_{14}H_{20}$ hydrocarbons.

The first $C_{14}H_{20}$ isomers investigated were pentacyclo[8.2.1.1^{4,7}.0^{2,9}.0^{3,8}]tetradecanes, represented by general structure VI (Chart I). Three stereoisomers are now known (VIa–c), and are readily available either by dimerization of norbornene or by hydrogenation of the [2 + 2]-type norbornadiene dimers.[15,16]

Rearrangement of the photodimers of norbornene[15] prepared from acetone-sensitized dimerization[15] (consisting of 12% *exo-trans-exo*-VIa and 88% *endo-trans-exo*-VIb) with $AlCl_3$ gave diamantane in 1% yield.[8] Although the reaction mixture was complex, containing besides tar many fragmentation and disproportionation products, isolation of diamantane (I) was facilitated by its high insolubility and crystallinity.

Chart I



[a] Close to final value (within 0.3 kcal/mol).

Lewis acid catalyzed treatment of strained hydrocarbons often does not give very satisfactory yields of isomerization products.[3] The reason appears to be that excessive strain encourages an alternative mode of strain relief: ring cleavage *via* protonation, followed by disproportionation to give olefin and alkane with one less ring. The former polymerizes to tar under the reaction conditions. It is not difficult to see why VI, a combination of strained norbornane and cyclobutane units, should be especially prone toward disproportionation.

Variation of temperature, concentration, and solvent did not improve yields significantly. Use of a better precursor was indicated. Since the major component of the original mixture was the more strained VIb,[15,17] it was hoped that VIa,[15] available by cuprous chloride sensitized photolysis of norbornene, would give less disproportionation and a better yield of I. However, only a 2% yield was achieved with $AlCl_3$.

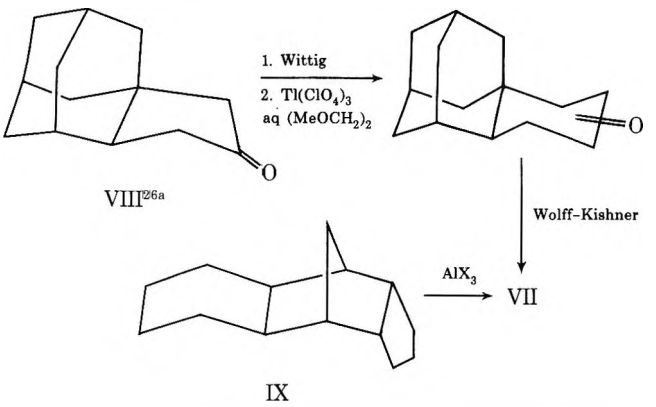
Schneider[18] showed that a "sludge" catalyst, prepared by cracking low molecular weight branched hydrocarbons with an aluminum halide and HX, gave improved yields of substituted adamantanes from perhydrogenated tricyclic aromatic compounds. At Princeton,[2c] a similar "sludge" catalyst system was prepared by adding *tert*-butyl bromide to a suspension of aluminum bromide in cyclohexane. Like the Schneider catalyst,[18] this $AlBr_3$ "sludge" is a yellow, heavy oil possessing an internal initiator and may be stored for longer periods of time under cyclohexane. Activity may be augmented or regenerated by addition of small amounts of $AlBr_3$. The actual composition of the catalyst is not known, but probably consists of polymerized isobutane, formed by elimination of HBr from *tert*-butyl bromide.[2c,18–21] "Sludge" catalysts may also be prepared from *sec*-butyl bromide or from *tert*-butyl chloride with $AlCl_3$.[22]

The activity of "sludge" catalyst was tested first with *endo*-tetrahydrodicyclopentadiene and improved yields of adamantane were obtained.[2c] Robinson and Tarrat[23] subsequently prepared a similar *tert*-butyl bromide catalyst and confirmed its greater efficiency. Yields of adamantane as high as 66% from *endo*-tetrahydrodicyclopentadiene and improved yields of alkyl adamantanes were reported.[23,24]

The rearrangements of the isomeric pentacyclic [8.2.1.1.^{4,7}.0^{2,8}.0^{3,9}]tetradecanes (VI) were reinvestigated with the more active "sludge" catalyst. Significant improvement was achieved. However, the best yield obtained from any of these [2 + 2] dimers was still only ~11%, and this was from the least strained exo-trans-exo isomer (VIa). Sludge catalyst isomerization of hydrogenated commercial

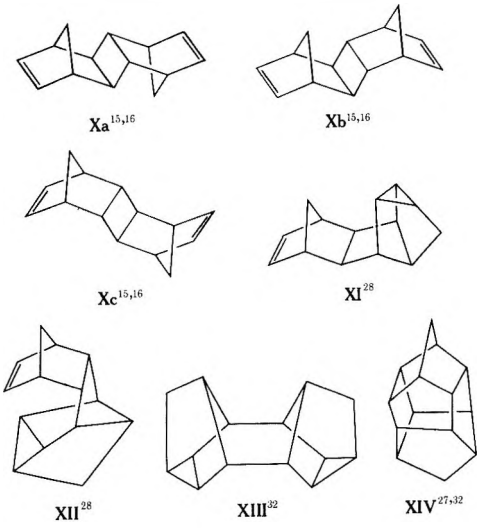
norbornadiene dimer (a mixture of 26% VIa, 71% VIb, and 3% VIc) gives diamantane in not more than 5% yield.

While the yields of diamantane (I) were low from all isomers of VI, a tetracyclic $C_{14}H_{22}$ disproportionation product (VII) was always the major product (yields up to 40%).[25] The structure of this product was initially assigned on the expectation that it should be the most stable $C_{14}H_{22}$ isomer.[17] This assignment has been verified recently; VII is identical in glc retention times, nmr, and ir with a sample prepared unambiguously from VIII.[26a] VII is also identical with the main product of rearrangement of IX, an isomeric starting material with quite a different structure.[26b]



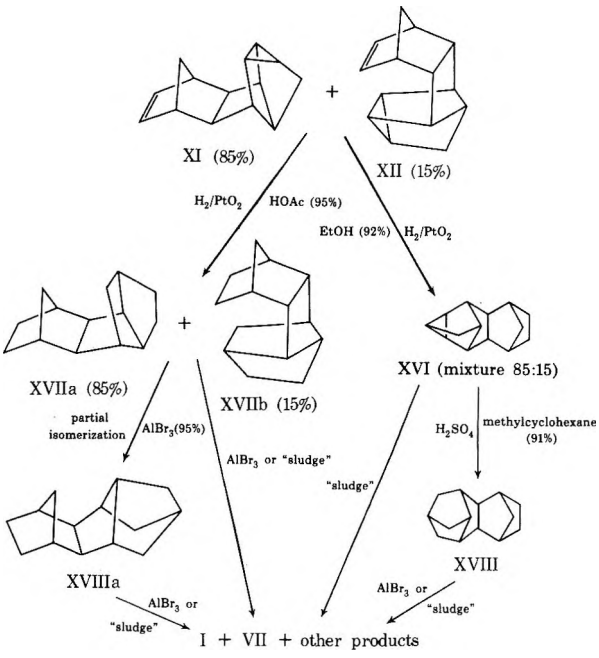
Isomerization of Hydrogenated Katz Dimer. All the [2 + 2] dimers of norbornene (VI) and norbornadiene (X) contain a strained cyclobutane ring which favors disporportionation. Consequently, less strained precursors were sought. Norbornadiene is readily dimerized by various organometallic catalysts.[27,28] Of the seven known dimers[27] (Chart II), three are of the [2 + 2] type (Xa–c),[15,16] two [4 + 2] incorporate one nortricyclene unit (XI, XII),[28] and one [4 + 4] type (XIII) contains two fused nortricyclene units; a cage structure (XIV)[27] completes the list.

Chart II
Known Norbornadiene Dimers



The Katz[28] norbornadiene dimers, consisting of a 7:1 mixture of XI and XII, were obtained from norbornadiene using rhodium/carbon catalyst.[28] Only the double bond hydrogenated under most of the conditions tried, which included even use of Ni catalyst and high pressures. Isomerization of the resulting hexacyclic mixture XVI with sludge catalyst (Scheme I) gave diamantane in up to 16% yield (glc). This result *depended on* disproportionation; in addition, the double disproportionation product (VII) formed in substantial amounts.

Scheme I



Catalytic hydrogenation of the mixture XI and XII in acetic acid with PtO_2 catalyst[29,30] succeeded in reducing both the double bond and the cyclopropane ring to produce two pentacyclic isomers in a 85:15 ratio. By analogy with results of hydrogenation of Binor-S (XIII) and deltacyclane (see later) under similar conditions, structures XVIIa and XVIIb were assigned, the former arising from XI and the latter from XII. Reduction of partially hydrogenated mixture XVI by hydride transfer in concentrated sulfuric acid–methylcyclohexane[31] also gave, in 91% yield, an 85:15 ratio mixture of two cyclopropane cleaved pentacyclic isomers. These differed from XVIIa and XVIIb and were assigned general structure XVIII. A ^{13}C nmr proton decoupled spectrum of the major isomer indicated nine different carbon absorptions and is consistent with structure XVIIIa. Although three other isomers in the set would fit the ^{13}C nmr data, XVIIIa is the lowest energy isomer (see below).

Isomerization of either mixture XVII or XVIII, with aluminum bromide or with sludge catalyst, gave diamantane in up to 25% yields (Table I).

Interestingly XVIIIa appears to be identical with the rearrangement intermediate isolated when AlX_3 isomerization of mixture XVII was interrupted after partial reaction. Such reactions are followed conveniently by gas chromatography. In this way, we demonstrated that intermediate XVIIIa forms diamantane in a yield identical with that from mixture XVIII. Apparently, sulfuric acid effected a similar partial isomerization in giving XVIII.[31]

Courtney, Johnston, McKervey, and Rooney also hydrogenated Katz dimer (XI and XII) in acetic acid and obtained a cyclopropyl-cleaved product which could be isomerized in the gas phase to diamantane in 45% yield employing a chlorinated platinum–alumina catalyst.[13a]

Although the yield it gives is an improvement over that from the [2 + 2] dimers, Katz dimer is not ideal as a diamantane precursor. Examination of the glc trace of a crude $AlBr_3$ isomerized mixture of XVII or XVIII reveals at least 14 products besides diamantane, including a major amount of disproportionation product VII, and other fragmentation products. Furthermore, we have had difficulty

Table I
C_{14} Pentacyclic Precursors Investigated in the Preparation of Diamantane

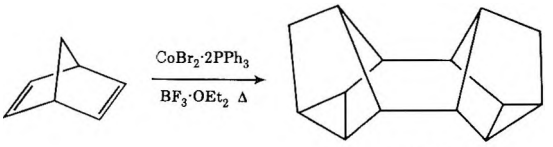
Precursor	Registry no.	Catalyst	% yield diamantane (I)	Ref
VI (12% VIa)	1624-14-2	$AlCl_3$	1	8, *a*
(88% VIb)	1624-16-4	"Sludge"	1–5	
VIa		$AlCl_3$	2	2c
		"Sludge"	10	
XVI	51966-13-3	"Sludge"	10–16	*b*
XVII	51966-14-4	$AlBr_3$	25	*c*
		"Sludge"	20	*c*
		Pt/Cl/alumina	45	13
XVIII	51966-15-5	$AlBr_3$	25	*c*
		"Sludge"	18	
XXI	51982-54-8	"Sludge"	41–47	12
XXIV	51982-55-9	"Sludge"	25	12
XIII	13002-57-8	"Sludge"	10	*c*
		H_2SO_3	30	*c*, 13
XXVII/XXVIII		$AlBr_3$	62–75	12
		"Sludge"	71	12
		$AlCl_3/CH_2Cl_2$	70–90	13
XXXV	51966-16-6	$AlBr_3$	84	*c*

[a] S. Hala, J. Novák, and S. Landa, *Sb. Vys. Chem.-Technol. Praze, Technol. Paliv*, **19**, 9 (1969). [b] Reaction carried out by Dr. Leo Lam. [c] This work.

in obtaining good yields of Katz dimer. The reaction is highly erratic; yields ranged from 0 to 49% and were found to be dependent on the catalyst quality and other unknown factors.

Diamantane from Other Precursors. In our search for other precursors, pentacyclic hydrocarbons XXI and XXIV were prepared as shown in Scheme II. These gave diamantane in 44 and 34% average yields, respectively, upon rearrangement with sludge catalyst (Table I). While diamantane was the main product, 1,3,5,7-tetramethyladamantane (XXV)[18] and 1,3-dimethyl-5-ethyladamantane (XXVI)[18] were identified as components of the reaction mixture. VII and other unidentified products were present in smaller amounts. Although these rearrangements give somewhat better yields of diamantane, the starting materials are cumbersome to prepare and the routes are not convenient.

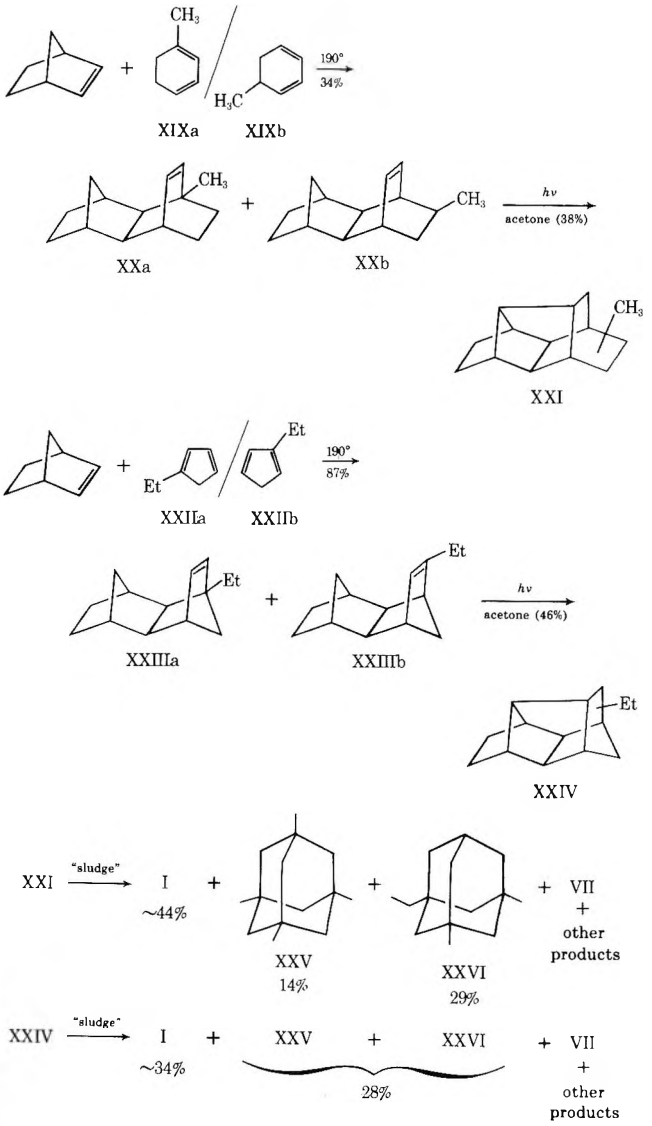
Diamantane from Hydrogenated Binor-S. The availability in almost quantitative yield of a [4 + 4] norbornadiene dimer, "Binor-S" (heptacyclo[8.4.0.0^{2,12}.0^{3,8}.0^{4,6}.0^{5,9}.0^{11,13}]tetradecane, XIII)[27,32] afforded an ideally constituted precursor, especially since the cyclopropane rings can be reduced to give a $C_{14}H_{20}$ pentacyclic hydrocarbon.



XIII

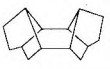
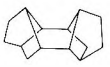
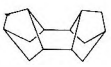
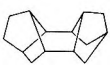
Hydrogenation of Binor-S. Schrauzer[32] has reported that the hydrogenation of Binor-S at 200° with 305 atm hydrogen pressure and Pt catalyst gave a mixture of products consisting of 94% $C_{14}H_{20}$, and 6% $C_{14}H_{18}$ hydrocarbons. The solvent was not indicated, however. We have found that Binor-S did not take up hydrogen in acetic anhydride, even under 102 atm hydrogen pressure with PtO_2 catalyst. However, in agreement with our earlier experience,[29,30] the cyclopropyl rings in Binor-S were readily cleaved by hydrogenation in glacial acetic acid with PtO_2 catalyst.[12] The resulting liquid product [bp 105–110° (1.5 mm)] appears by gas chromatographic analysis on numerous columns to be essentially one material. Cleavage of both cyclopropane rings was confirmed by nmr analysis, which indicated absence of nortricyclene peaks at δ 1.05 and the presence of a more complicated spectrum with peaks in the δ 2.25–0.75 region. These results were verified by McKervey.[13a]

Scheme II



Hydrogenation of Binor-S may, in principle, give rise to four tetrahydro-Binor-S isomers (XXVII–XXX) from the

Table II
Possible Hydrogenation Products of Binor-S,[a,b] Point Group Classifications and Calculated Heats of Formation

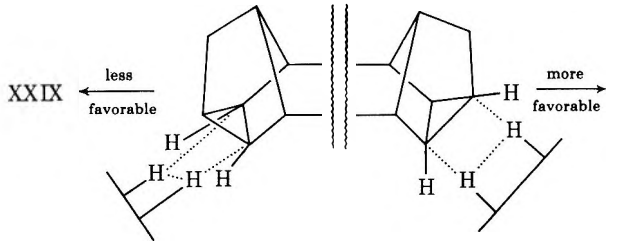
	 XXVII (51966-17-7)	 XXVIII (51966-18-8)	 XXIX (52021-70-0)	 XXX (51966-19-9)
Point group	C_s	C_2	C_{2h}	C_i
Number of different carbon atoms	7	7	5	14
$\Delta H_f°$, gas, 25° (calcd),[c] kcal/mol	14.10	6.09	1.55	2.27
Strain (calcd),[c] kcal/mol	62.16	54.15	49.61	50.33

[a] References 31–33. [b] Registry numbers in parentheses. [c] Reference 17.

various possible cyclopropane ring reductions (Table II). Hydrogenolysis of unactivated cyclopropane rings usually results in the cleavage of the least substituted cyclopropyl ring bonds.[29-31,33] However, in XIII, all cyclopropane bonds are disubstituted. In such strained molecules, hydrogenolysis of the most strained bond seems from literature examples[31] to be a reasonable expectation.

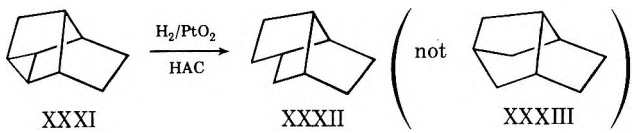
Molecular mechanics calculations showed that XXIX and XXX should be the most stable isomers.[17] However, ^{13}C nmr spectroscopy[34] of the reduction product eliminated these structures from contention, since six signals for seven carbons were observed, there being one coincidence of chemical shift in the single frequency off resonance and noise resonance decoupled spectra. The sharpness of peaks indicated that only one isomer was present. Isomer XXX, possessing no symmetry, should give a 14-line spectrum, whereas the more symmetrical XXIX has only five different kinds of carbon atoms. It is difficult to differentiate between XXVII and XXVIII by ^{13}C nmr, since both isomers possess seven unique carbons of the same general type. A choice may ultimately be possible between the two structures, since XXVIII is chiral while XXVII is not. If strain relief during reduction is a factor, XXVIII should be favored over XXVII on the basis of the molecular mechanics calculations, and we tentatively assign the structure on this basis.

The reduction of XIII to give XXVIII (or XXVII) and not XXIX or XXX is probably influenced by steric inter-



XXVIII (or XXVII)

action during approach of catalyst-bound hydrogen. Other systems containing nortricyclene units behave similarly. For example, deltacyclane (XXXI) gives brexane



XXXI XXXII XXXIII

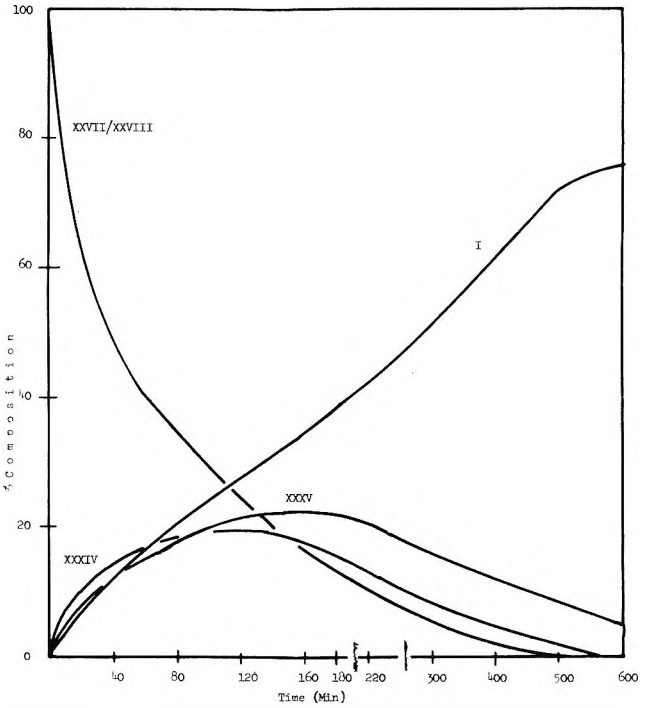
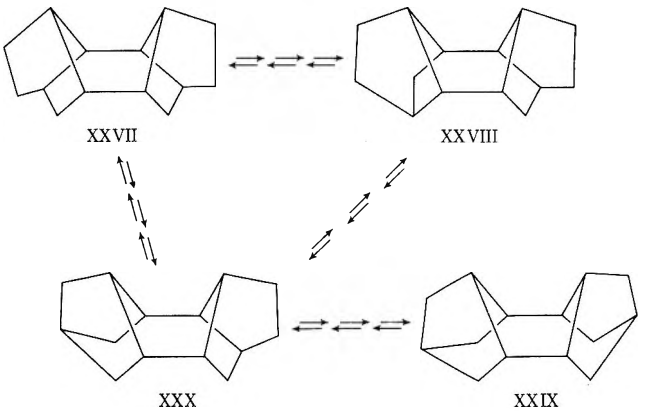


Figure 1. Isomerization of tetrahydro-Binor-S (XXVII/XXVIII) to diamantane (I) at 25° with aluminum bromide in cyclohexane.

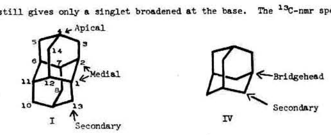
(XXXII).[31,35] On this basis, we assigned structures XVII to the hydrogenated Katz dimers.

Isomers XXVII and XXVIII may be interconverted by simple Wanger–Meerwein 1,2 shifts; either should give diamantane by further rearrangement. In fact, all the tetrahydro-Binor-S type isomers (XXVII–XXX) are, in principle, interconvertible by such 1,2 shifts (the intermediate cations can be generated by hydride abstraction).



Rearrangement of Tetrahydro-Binor-S. The aluminum bromide or "sludge" catalyzed isomerization of tetrahydro-Binor-S in either carbon disulfide or cyclohexane proceeds smoothly and quickly. Careful glc study of the course of the reaction at 0 and 25° indicates that isomerization proceeds with formation of at least two major, and several minor (less than 1%), intermediates. At the end of the reaction, however, only diamantane (over 90% of the product) and tetracyclic disproportionation product VII remain. At 0°, an as yet unidentified $C_{14}H_{20}$ intermediate (XXXIV) is formed initially; this then isomerizes to the major intermediate, which was isolated and could be identified as *trans*-pentacyclo[8.2.1.1.^{2,5}.0^{3,7}.0^{8,12}]tetradecane (XXXV). The concentration of XXXV builds up to a maximum value of over 20%; after several hours, rearrangement proceeds further to form diamantane and VII. Figure 1, a

Structural and Physical Properties. The lower symmetry of diamantane (I) (D_{3d}) compared to adamantane (IV) (T_d) is reflected in its lower melting point (251°[13] vs. 268-269°, Table IV) and in its greater structural complexity. Thus, I possesses not one, but two types of bridgehead positions, designated "medial"[36] (C-1,2,6,7,11,12) and "apical" (C-4 and 9). The six methylene groups in I are equivalent but, unlike those of adamantane, are prochiral. However, despite the three types of hydrogens, the 100 MHz proton nmr spectrum of I consists of a single relatively sharp signal (δ ~ 1.68) whereas that of IV exhibits two partially separated signals (δ ~ 1.78). At 220 MHz, IV displays a cleanly separated two line spectrum (δ 1.87 and 1.74 ppm)[37] due to the two types of hydrogens, whereas I still gives only a singlet broadened at the base. The ^{13}C-nmr spectra of



I[38] and IV[39] are straightforward, consisting of three and two lines, respectively (Table IV). The ir and Raman spectra of I and IV are quite simple, indicating a high degree of symmetry (Table IV).

The mass spectrum of diamantane (I)[8] shows even less fragmentation than that of adamantane (IV)[3c,40] (Table IV). This behavior is due to the interlocking cage framework. As in the case of IV (M+, m/e 136),[40] the parent ion of I (m/e 188)[8] is the most intense but by more than a factor of three than any other peak in the spectrum. Such prominent parent ions are formed from other multicyclic cage molcecules such as ethanoadamantane (m/e 162),[11] ethanodiamantane (both isomers) (m/e 214),[41] triamantane

(m/e 240),[9] bastardane (m/e 292),[10] homoadamantane (m/e 150)[42] etc.; the inherent stability of such molecular frameworks resist fragmentation. Some exceptions in cage molecules have been noted. Noradamantane[35a,b,d] exhibits its base peak at m/e 80 (molecular ion 122), and other strong peaks are present.

The second most intense peak in I, $C_7H_7^+$ (m/e 91), seems characteristic of many diamondoid and cage molecules and is also prominent in ethanoadamantane,[11] ethanodiamantane,[41] triamantane,[9] bastardane,[10] etc. Similar cage molecules, e.g. adamantane[3,40] and homoadamantane[42] exhibit the second most intense peak at m/e 93. In general, both diamantane and adamantane are resistant towards loss of one carbon fragments, while two and especially three and four carbon losses are somewhat more facile.

X-ray analyses of diamantane (I)[43] and adamantane (IV) confirm the expected similarities of these diamond lattice structures: C-C bond lengths ~ 1.54 Å, 60° dihedral angles, and approximately tetrahedral (109.5 ± 1.5°) bond angles (Table IV). These near ideal features are reflected by the high thermodynamic stability of these hydrocarbons; adamantane is the most stable substance of empirical formula $C_{10}H_{16}$ and diamantane is the most stable $C_{14}H_{20}$ structure possible. Despite these favorable features, both adamantane and diamantane are not strain free (Table V). An initial strain estimate based on an experimental heat of formation (ΔH_f^o, gas, 25°) of -32.96 ± 0.19 kcal/mole,[44] and a "strain free" group increment scheme indicated a strain of 6.48 kcal/mole for adamantane.[45] Since then, two new determinations of ΔH_f^o have been reported, -30.65 ± 0.98[46] and -30.57 ± 0.9 kcal/mole.[47] Both differ from the original and indicate a higher strain energy of 8.85 kcal/mole. An initial strain estimate for diamantane (I) of 8.49 kcal/mole, based on an experimental heat of formation (ΔH_f^o gas, 25°) of -39.55 ± 2.0

kcal/mole,[48] suggested that I was strained to approximately the same extent as IV. However, the discovery of two solid-solid phase transitions in I resulted in a corrected heat of formation of -36.64 kcal/mole,[49] raising the total strain energy to 11.42 kcal/mole. Diamantane is thus indicated to be more strained than adamantane but interestingly the strain per carbon seems to be nearly constant (0.8 - 0.9 kcal/mole).

Molecular mechanics calculations[17,45,50] have been employed to determine the origin of the strain in both systems. Calculations by Schleyer, et al.[45] suggested that the strain could be accounted for mainly in terms of C....C non-bonded repulsions. Allinger, et al.[50] came to a different conclusion, attributing the strain to an excessive number of H...H repulsions. While the use of different non-bonded potential functions are responsible for the different interpretations,[17b,50] both calculations agree in their estimated heats of formation and predict diamantane to be more strained than adamantane (Table V).

It is interesting that I and IV violate the conventional principles of conformational analysis which predict these diamond molecules to be strain free. In cage structures, the blend of repulsive and attractive non-bonded interactions is different from that found in acyclic, monocyclic or condensed polycyclic compounds; the repulsive terms became realtively more important in I and IV. It is probably significant in this context that diamond has rather exceptionally long C-C bonds, 1.54452 Å,[51] and actually is less stable than graphite.[51]

TABLE IV. COMPARISON OF STRUCTURAL AND PHYSICAL PROPERTIES OF DIAMANTANE AND ADAMANTANE

	Diamantane	Ref	Adamantane	Ref
Melting Point	244-245.4°, 251°	12, 13	268-269°	a, 14
H-1 Nmr (δ)	1.68 (s) (w_h=3Hz)	8	1.78, 1.74 (d, J ≅ 1.7 Hz) 1.87, 1.74 (two signals due to methine and methylene, 220 MHz)	37
^{13}C-Nmr (δ)[b]	38.47 (medial), 37.76 (secondary), 26.18 (apical)	38	28.6 (bridgehead), 38.0 (methylene)	39
IR (cm^{-1})	2908, 2878, 2851, 1442, 1457, 1047 (w)	8	2907, 2933, 2857, 1453, 1357, 1155, 799, 966, 714	c
Raman (cm^{-1})	2926, 2907, 2880, 2851, 1444, 1308, 1233, 1179, 1086, 1072, 1039, 982, 935, 708	8	2944, 2917, 2895, 2849, 1437, 1315, 122?, 1099, 972, 951, 760, 4?3	3c
Mass spectrum	188 (M^+) (100), 160 (5), 159 (10), 145 (7.5), 131 (12.5), 130 (17.5), 120 (7.5), 105 (15), 91 (C_7H_7,28), 79 (25), 67 (10).	8, 13	136 (M^+) (100), 121, 107, 93 (49), 91 (8), 80 (37) 79 (48) 67	3c, 40
Structure (X-ray)	Space group-Pa3, a=10.109 ± 0.02 Å, Z=4, ρ = 1.210 g/cm³, cubic Bond lengths (± 0.005 Å, see figure) Bond angles ± 25'	43	Space group-Td^2Fm^3m, a=9.426 ± 0.008 Å, ρ = 1.07 g/cm³, cubic Bond lengths C-C = 1.54 ± 0.01 Å Bond angles 109.5 ± 1.5°	d

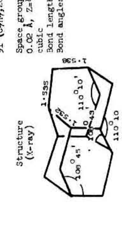


TABLE IV cont.

[a] S. Landa and V. Machacek, Collection Czech. Commun., 5, 1 (1953). [b] Ppm from tetramethylsilane. [c] R. Mecke and H. Spiesecke, Ber., 88, 1997 (1955). [d] J. Donohue and S.H. Goodman, Acta Crystallogr., 22, 352 (1967); cf. C.E. Nordman and D.L. Schmitkons, ibid., 18, 764 (1965).

TABLE V EXPERIMENTAL AND CALCULATED ENTHALPIES AND STRAIN ENERGIES OF ADAMANTANE AND DIAMANTANE

	ΔH_f^o (gas, 25°, kcal/mole)			Strain energy (gas, 25°, kcal/mole)		
		Calcd			Calcd[c]	
	Exptl	Engler Force Field[a]	Allinger Force Field[b]	Exptl	Engler Force Field[a]	Allinger Force Field[b]
Adamantane	-32.96[44]					
	-30.65[46]	-32.50	-33.79	6.48	6.87	6.81
	-30.57[47]			8.85		
Diamantane	(-39.55)[48,d]			(8.49)[d]		
	-36.64[49]	-37.37	-38.04	11.42	10.69	10.34

[a] Reference 17. [b] Reference 50. [c] Calculated from strain free group increments, cf. ref 45. [d] Superseded values, see text.

Experimental Section

Microanalyses were performed at Hoffmann-La Roche, Inc., Nutley, N.J., and by Robertson Laboratories, Florham Park, N.J. Infrared spectra were determined either in KBr pellets or as nujol mulls using a Perkin Elmer 237 or 631 spectrophotometer. Nmr spectra were recorded on Varian A-60A and HA-100 spectrometers. Chemical shifts are reported in units of δ (ppm) relative to internal tetramethyl silane. Gas chromatographic analysis and separations were performed on either a Varian Aerograph 90-P instrument or on a Perkin Elmer 810 gas chromatograph. Melting points were taken on a Mettler FPI apparatus, or in an oil bath, and are not corrected.

Preparation of Precursors. Cobalt dibromide-triphenyl phosphine ($CoBr_2 \cdot 2P\phi_3$ Catalyst.[32a,b] Benzene (200 ml), containing 10 g (0.046 mole) anhydrous cobalt dibromide (ROC/RIC) and 24.4 g (0.092 mole) triphenyl phosphine, was refluxed until a color change from green to blue-green occurred. The blue-green catalyst precipitated upon cooling to room temperature in nearly quantitative yield.

Binor-S (XIII)[32] The procedure of Schrauzer[32] with minor modifications was followed. A 1 liter 3 necked flask equipped with teflon sleeves, two efficient high capacity condensers and a mechanical stirrer, was flushed with N_2 and charged with 200 g of freshly distilled norbornadiene. Then 2.0 g $COBr_2 \cdot 2P\phi_3$ catalyst (see above) and 5 ml of BF_3-etherate (Eastman, distilled within two weeks and kept in the cold) co-catalyst were added. The reaction mixture was heated to 90° until reflux commenced. At this point, the heating mantle was removed as a vigorous exothermic process ensued. This exothermic process must be allowed to proceed as rapidly as possible; only occasional cooling (dry-ice acetone) is desirable (too much cooling results in unwanted polymer formation). After the exothermic process subsided

(5-10 minutes), the brownish-green mixture was allowed to cool to room temperature. Workup included addition of about 100 ml methylene chloride and washing with a saturated sodium bicarbonate solution and with water (~ 100 ml). The methylene chloride solution was dried over $MgSO_4$ and evaporated under reduced pressure to give 164-195 g (86-95%) of low melting solid, mp 59-60°. Distillation (bp 90°/1.5 mm) gave upon cooling 160-170 g (80-85% yield) of a white solid, mp 63-64° (lit.[27] 65-66°).

The reaction may also be carried out in hot toluene as suggested by McKervey.[13a] This avoidsthe overly vigorous reaction.[12]

Tetrahydro-Binor-S (XXVII/XXVIII) by Catalytic Hydrogenation of Binor-S in Acetic Acid. Binor-S (236 g, 0.78 mole) was partially dissolved in hot glacial acetic acid (900 ml) containing 10 ml conc. HCl; PtO_2 (1.5 g) catalyst was added and the mixture was shaken in a Parr apparatus under 3 atm hydrogen pressure for three hours at 70°. After cooling to room temperature, the catalyst was filtered, water was added, the top layer was separated, and the bottom layer extracted with methylene chloride. The combined organic layers were washed with water, dried, and evaporated. The crude tetrahydro-Binor-S was further purified by distillation under reduced pressure, bp 105-110° (1.5 mm), to give 212-231 g (90-97%) of a colorless liquid; glc (15% Apiezon L, 6m X 3mm column, 200°) indicated mainly one peak. Small amounts (< 1%) of other products were present. Sometimes fractions of bp above 130° are obtained when heating is prolonged during distillation. The rearrangement to diamantane is generally carried out using the middle fraction, which appears to be essentially one isomer (XXVII or XXVIII); mass spectrum m/e (rel intensity) 188 (M^+) (100), 173, 159, 147, 146, 145 (51), 134, 133, 131, 119, 105, 93, 92, 91 (55), 80, 79 (44), 77, 67; nmr

($CDCl_3$) complex spectrum in the range δ 2.25-0.75 and absence of cyclopropyl protons at δ1.05; ^{13}C nmr (ppm from TMS) 49.3 $(CH)_2$, 39.0 $(CH)_2$, 37.5 $(CH)_2$, 36.7 $(CH)_2$, 31.9 $(CH_2)_4$, 27.5 $(CH_2)_2$.[34] This compound has also been prepared and characterized by McKervey.[13]

Trans-Pentacyclo[8.2.1.1.^{2,5}.$0^{3,7}$.$0^{8,12}$]tetradecane (XXXV) from Binor-S in Sulfuric Acid-Methylcyclohexane. To 50 ml of 97% sulfuric acid was added dropwise with cooling and stirring 20.0 g Binor-S dissolved in 100 ml methylcyclohexane. A color change from yellow to red was observed and after 1/2 hour, and methylcyclohexane layer was separated. The acid layer was further extracted with methylcyclohexane and the combined organic layers were washed with water, dried over $MgSO_4$ and evaporated. A residue, a combination of oil and solid, was obtained (17.6 g); glc (10% carbowax, 20 M, 3 m x 3 mm column, 170°) indicated four peaks with retention times 10 min (34%), 11.5 min (51%), 12.8 min (5%), and 13.9 min (6%) corresponding to XXXVI (structure undetermined), trans-pentacyclo[8.2.1.1^{2,5}.$0^{3,7}$.$0^{8,12}$]tetradecane (XXXV), diamantane (I), and unreacted Binor-S (XIII). XXXV was isolated from the reaction mixture by recrystallization from petroleum ether (60-70°)/acetone, white crystals, mp 111-112° were obtained; mass spectrum m/e (rel intensity) 188 (M^+) (100), 173, 159, 147, 146, 145, 134, 133, 132, 131, 119, 117, 105, 93, 92, 91, 79, 67; nmr (CCl_4) δ 1.0 (d, J ≅ 10 Hz, 3H), 1.4 (s, 5H) 1.7 (m, 2H), 2.1 (d, br, J ≅ 10 Hz); ^{13}C-nmr (CCl_4, ppm from TMS) 40.1 $(CH_2)_2$, 37.8 $(CH)_2$, 37.5 $(CH)_4$, 35.4 $(CH_2)_4$, 33.2 $(CH)_2$.

Anal. Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 89.50, H, 10.70.

Reaction at room temperature produces the same four compounds in the following ratios: XXXVI (36.5%), XXXV (37.6%), diamantane (15%) and unreacted Binor-S (3%). A portion (1.82 g) of this mixture gave diamantane in 70% yield upon rearrangement with $AlBr_3$ in cyclohexane (see below).

Katz Dimer (XI, XII).[28] Norbornadiene dimerization to give a mixture of XI and XII (7:1 ratio) was accomplished with 5% Rh/C catalyst according to the procedure of Mrowca and Katz.[28] Yields ranged from 0-49% and were dependent on the batch of catalyst used and other unknown variables.

Hydrogenation of Pentacyclo[?.1.1.1^{4,7}.$0^{2,9}$ $0^{3,8}$]Tetradeca-5,11-diene (Norbornadiene Dimer) (X)[15]. Commercial norbornadiene dimer mixture (Aldrich) (104.0 g) (consisting of 26% Xa, 71% Xb, 3% Xc) (Table II) was partially dissolved in 106 g of absolute ethanol. To this 0.5 g of PtO_2 catalyst was added and the mixture was hydrogenated on a Parr apparatus at 3 atm hydrogen pressure at room temperature for 1.5 hours. The solution was diluted with water and extracted with pentane. The combined organic layers were dried over $MgSO_4$ and evaporated to give 98.0 g of an oil which solidified upon standing; glc analysis on a 10% Carbowax 20 M column (3 m x 6 mm, 200°) indicated a mixture consisting of 26% VIa, 71% VIb and 3% VIc. The compounds were not further purified or separated. Arnold, Trecker and Whipple[15] describe the preparation of VIa and VIb by hydrogenation from Xa and Xb. Both are low melting solids. Nmr of our hydrogenated mixture indicated loss of vinyl protons.

Partial Hydrogenation of Katz Dimer (XI, XII) in Ethanol. A solution containing 100 ml absolute ethanol, 16.8 g (0.082 mole) XI, XII (bp 76-77°/0.8 mm) and 0.05 g PtO_2 catalyst was shaken in a Parr apparatus at room temperature under 2.8 atm hydrogen pressure. After 1 hour, the uptake of hydrogen ceased and the mixture was worked up as above. Removal of solvent left 16.5 g of oil which was distilled, bp 150°/5 mm; glc (10% Apiezon-L, 3 m x 3 mm, 200°), indicated 1 major peak with the same retention time (8.1 min) as starting material XI, XII; mass spectrum m/e (rel intensity) 186 (M^+) (100), 171, 158, 157, 145, 132, 131, 130, 129, 121, 120, 119, 118, 117, 106, 105, 98, 95, 93, 92, 91, 83, 79, 66, 65, 64; nmr ($CDCl_3$) showed the absence of vinyl protons in δ 4.0-6.0 region, but

the presence of cyclopropyl protons at δ 0.75 (d); other resonances were at δ 0.91 (s), 1.05 (m), 1.32 (s-br), 1.88 (d J ≅ 2Hz), 2.33 (br).

Hydrogenation of Katz Dimer (XI, XII) in Acetic Acid. Katz dimer (XI, XII) (5.0 g) in 150 ml of glacial acetic acid with 0.5 g PtO_2 catalyst was shaken in a Parr hydrogenator under 3 atm hydrogen pressure at room temperature until the uptake of hydrogen ceased (about 3 hours). The catalyst was removed by filtration and the mixture diluted with 100 ml of water and extracted with 3 x 100 ml methylene chloride. The organic layers were collected and dried over $MgSO_4$. Removal of solvent left 4.9 g of oil which was distilled at 85-88°/1.2 mm; glc (15% Apiezon L, 6 m x 3 mm column, 200°) revealed two peaks with retention times of 19.5 min (15%) and 23.5 min (85%) corresponding to compounds XVIIb and XVIIa. The mixture was not further separated; mass spectrum m/e (rel intensity) 188 (M^+) (100), 186, 181, 160, 159, 148, 147, 145, 134, 131, 122, 121, 120, 119, 118, 117, 107, 106, 105, 95, 94, 93, 92, 91, 79, 78, 77, 67; nmr ($CDCl_3$) shows absence of vinyl and cyclopropyl protons and gives only complex splitting between δ 0.7-2.45. This material has also been prepared by McKervey[13] similarly.

Reaction of Dihydro Katz Dimer (XVI) With Sulfuric Acid and Methylcyclohexane. To 200 ml of 97% sulfuric acid was added dropwise with cooling 8.0 g of XVI dissolved in 100 ml of methylcyclohexane. After stirring overnight at room temperature, the layers were separated. The methylcyclohexane layer was washed with 100 ml H_2O and dried over $MgSO_4$. Removal of solvent left 7.36 g of oil (91% yield) which was distilled and three fractions collected all boiling at 1 mm in the range 80-85°. Low melting solid separated in the last two fractions. The glc spectra on a 15% Apiezon L (6 m x 3 mm column, 200°) of fractions were virtually identical and showed 2 peaks with retention times

20.8 min (85%) and 22.1 min (15%); mass spectrum m/e (rel intensity) 188 (M^+) (100), 179, 173, 160, 159, 147, 146, 145, 134, 131, 109, 105, 97, 95, 93, 92, 91; nmr ($CDCl_3$) shows absence of cyclopropyl protons, δ 0.86 (d, br), 1.13 (br), 1.36 (d, br), 1.87 (d), 2.0 (m), 2.47 (br); ^{13}C-nmr (CCl_4, ppm from TMS) 57.5 $(CH)_2$, 48.0 (CH), 44.8 (CH) + (CH_2) or $(CH)_2$, 41.6 $(CH)_3$ + (CH_2) or $(CH)_2$ + $(CH_2)_2$, 40.1 (CH_2), 34.4 (CH) + (CH_2), 29.1 $(CH_2)_2$.[34] Nine different carbon atoms are indicated with two degeneracies and are consistent with cleavage of one of the two equivalent cyclopropane bonds to give XVIII.

Bromination of 4-Methylcyclohexene.[52] 4-Methylcyclohexene (Aldrich, 48 g, 0.5 mole) and N-bromosuccinimide (Aldrich, 18.5 g, 0.1 mole) in 75 ml

(52) S.W. Staley, Ph.D. Thesis, Yale University, 1964.

of carbon tetrachloride were heated to reflux under magnetic stirring for 20 minutes. After keeping the mixture in a refrigerator overnight, precipitated succinimide was collected (9.7 g, 93%). The filtrate was evaporated to give a dark colored oil, which upon distillation gave 12.6 g of pale yellow green liquid, bp 55-58°/10 mm; glc, (DC 710, copper column 6 m x 6 mm, 210°), indicated two main components; mass spectrum m/e 176, 174, 96, 79; nmr (CCl_4) δ 5.64 (d, J ≅ 2Hz, 2H), 4.65 (m, 1H, CHBr), 2.5-1.25 (complex, 6H), 1.2-0.9 (complex 3H, CH_3). The mixture was not further characterized.

1- and 6-Methyl-1,3-cyclohexadiene (XIXa) (XIXb). A mixture of 330 g (ca. 1.83 moles) of the above brominated 4-methylcyclohexene and 500 g (4 moles) of quinoline was heated at 130-180° under a stream of nitrogen. The distillate was collected in a receiver cooled by ice, washed with dil HCl and water,

dried over $CaCl_2$ and distilled to give 87.6 g (70%) of colorless hydrocarbon, bp 99-105°; mass spectrum m/e (rel intensity) 110 (M^+) (100) 94, 92, 91; 79 and 77; nmr (CCl_4) δ 6.0-5.3 (4.5 H), 2.5-1.6 (8.5 H), 1.03 (d, J ≅ 7 H, 2.9 H); the product appears to be a mixture of XIXa and XIXb.

Anal. Calcd for C_7H_{10}: C, 89.29; H, 10.71. Found: C, 89.50; H, 10.40.

Preparation of XX. The Diels Alder reaction was carried out under similar conditions as reported by Soloway[53] for the preparation of the parent

(53) S.B. Soloway, J. Amer. Chem. Soc., 74, 1027 (1952).

hydrocarbon of XXXVII. A mixture of 87.6 g (0.40 mole) of XIXa/XIXb and 497 g (5.30 mole) of norbornene was heated with a small amount of hydroquinone in a glass pressure bottle at 170-180° for 24 hours. Distillation of the reaction mixture gave 29.7 g of milky, high boiling product, bp 64-66°/ 1 mm; glc, two components of equal intensity, possibly XXa and XXb; mass spectrum, m/e (rel intensity) 188 (M^+) (10), 173 (2), 146 (26), 94, 79 (37), 77 (11); nmr (CCl_4) δ 6.2-5.4 (complex, olefinic, 2H), 2.6-0.4 (complex , aliphatic, 19 H), 1.12 (s, methyl at bridgehead), 0.69 (d, J ≅ 7 Hz, methyl at non-bridgehead).

Anal. Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 89.25; H, 10.90.

Preparation of XXIa/XXIb. Under conditions similar to those used by Scharf[54] for the preparation of the parent hydrocarbon of XXIV, precursor XX (28.92 g) in 1.22 liters of acetone (ACS grade) was irradiated with a 450 W.

(54) H.D. Scharf, Tetrahedron, 23, 3057 (1967).

Hanovia medium pressure mercury lamp with a pyrex filter under nitrogen and with magnetic stirring for 209 hours at room temperature. Evaporation of

solvent left 13.1 g of liquid which upon distillation gave 8.8 g of an oil, bp 75-80°/1 mm; glc indicated at least eight peaks, of which the three major ones were XX (18%), XXIa-XXIb (38%), and XXXVII (40%). The mass spectrum of the mixture (m/e 190 (M^+) (40)), indicates that reduction had taken place to a large extent during irradiation, consistent with the assignment of structure XXXVII.

XXXVIIa XXXVIIb

Anal. Calcd for 0.7 $C_{14}H_{20}$ and 0.3 $C_{14}H_{22}$: C, 89.01; H, 10.89. Found: C, 89.09; H, 10.90.

Ethylcyclopentadiene (XXII). Prepared according to the procedure of Alder and Ache[55] from sodium cyclopentadienide and ethyl bromide in liquid ammonia.

(55) K. Alder and H.J. Ache, Ber., 95, 503 (1962).

Ethyl-exo-endo tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodec-10-ene (XXIII).[53] Essentially the same conditions as for the preparation of XX were employed. Freshly distilled norbornene (bp 95°, 300 g) was heated with 151 g of ethylcyclopentadiene in a glass pressure bottle in the presence of a trace of hydroquinone at 191-3° for 15 hours. Distillation of the reaction mixture gave 223.8 g of a clear liquid (bp 99-108°/4 mm); glc indicated higher boiling impurities, but not the dimer of ethyl cyclopentadiene; nmr δ 0.54

(d, J ≅ 10 Hz, inner proton of methylene bridge),[56] 2.60 (d, J ≅ 10 Hz, outer protons of methylene bridge).

(56) L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd Ed., Pergamon Press, New York, 1969.

Preparation of XXIV.[54] Tetracyclic hydrocarbon mixture XXIII (204 g) in 5 liters of acetone was irradiated under the same conditions as XX for 113 hours. Direct distillation of the photolyzed mixture gave 176 g of colorless product, bp 65-87°/ 1 mm. The pot residue contained 44.1 g of viscous oil, which could be the acetone adduct.[54] The mass spectrum of the distilled product indicated 40% reduction of $C_{14}H_{20}$ to $C_{14}H_{22}$ (m/e 188: 190: 53-39); the nmr indicated the presence of olefinic protons. The process must sometimes be repeated to complete the reaction.

Sludge Catalyst.[26, 18-23] To a solution of 20 g (0.075 mole) of $AlBr_3$ in 50 ml of cyclohexane in a flask fitted with a reflux condenser, dropping funnel and drying tube was added dropwise 7 g (0.05 mole) of t-butyl bromide, diluted with an equal volume of cyclohexane. The reaction was left stirring overnight at room temperature. However, the reaction may be accelerated by slight warming of the reaction vessel. The reaction is usually over after evolution of HBr ceases and the clear yellow catalyst (about 20 g) separates. This catalyst may be kept for prolonged periods under cyclohexane in a vessel stopped with a drying tube and may be reactivated, if necessary, by addition of small amounts of $AlBr_3$.

Preparation of Diamantane. From Tetrahydro-Binor-S (XXVII/XXVIII) With Aluminum Bromide. Tetrahydro-Binor-S (XXVII/XXVIII)(100 g, 0.54 mole)

was added from a dropping funnel to a cyclohexane solution (100 ml) containing 27 g aluminum bromide. After the exothermic reaction subsided, the reaction was refluxed gently for an additional two to three hours. The cyclohexane layer was decanted carefully. The catalyst was washed several times with hot cyclohexane. The combined extracts were then washed with water and dried over $MgSO_4$. Evaporation of solvent left a semisolid residue which was partially dissolved in about 100 ml of pentane. The white solid was filtered and the solution was further concentrated until diamantane no longer precipitated. The total amount of diamantane obtained upon drying was 62-75 g (62-75%), mp 240-241° ; glc (10% Carbowax 20 M, 3 m x 3 mm column 180°) of precipitated material indicated only one peak; the mother liquor contained mostly disproportionation product VII; relative retention times are 8.5 and 11 min for VII and I, respectively; nmr ($CDCl_3$) of I showed a single peak δ 1.68. The diamantane so obtained may be used without further purification for further conversions. Recrystallization from pentane gives white crystals, mp 244.0-245.0° (lit.[13] mp 251° after purification by zone refining).

From Tetrahydro-Binor-S (XXVII/XXVIII) with Sludge Catalyst. To 20 ml of sludge catalyst was added dropwise 1.0 g of XXVII/XXVIII dissolved in 5 ml of cyclohexane. Heat was evolved. After refluxing for five hours, all of the starting material had reacted. The product was diluted with 15 ml cyclohexane and decanted. The catalyst was washed several times with hot cyclohexane. The combined organic layers (150 ml) were washed twice with water (100 ml), dried over $MgSO_4$, and the solvent evaporated. To the semisolid residue, consisting of 90% diamantane, 7% VII, and 3% other unidentified products, acetone was added; upon cooling the white crystals which formed were collected. Total yield of diamantane was 0.71 g (71%).

General Isomerization Procedure For Starting Materials VI, VIa, XIII XVI, XVII, XVIII, XXI, XXIV, XXXV. Each precursor was dissolved in carbon disulfide or cyclohexane in a flask equipped with a condenser and stirrer. The catalyst was then added slowly. The flask was cooled to moderate the initial exothermic process. The reaction was allowed to warm to room temperature and was then heated at the temperatures and for the periods of time indicated in Table VI. Workup involved decanting the organic layer and extracting the catalyst layer with either carbon disulfide or hot cyclohexane. The decanted layer and extracts were combined, washed with water, dried over $MgSO_4$ and evaporated. If an oil was obtained, this was generally taken up in a small amount of pentane and diamantane was crystallized from a dry ice-acetone bath. Sometimes a rapid filtration through alumina was necessary before any crystals of diamantane were obtained.

From Binor-S (XIII) with Sulfuric Acid. Binor-S (2.0 g) was added slowly with stirring to 10 ml of 97% sulfuric acid. After the initial exothermic reaction had subsided, the reaction mixture (which had turned dark red) was stirred for 48 hours. The mixture was poured into ice water, separated, and the aqueous layer extracted with ethyl ether. The combined ether extracts were washed with water and dried over $MgSO_4$. The solvent was then evaporated under reduced pressure to give an oily residue consisting of diamantane (I), diamantanone, and other products. This residue was dissolved in petroleum ether and chromatographed on alumina. Diamantane was the first to elute with pentane (0.6 g, 30% yield). After all the diamantane had eluted, the solvent was changed to benzene (a small amount of unidentified material was obtained), and finally to ethyl ether. The ether fraction contained 0.3 g of material (15% yield), which had identical ir and nmr spectra with those of diamantanone. Characterization and identification of other products were not pursued.

TABLE VI

SUMMARY OF DIAMANTANE PREPARATIONS FROM VARIOUS PRECURSORS

Starting Material	g	Solvent (ml)	Catalyst[b]	Temp	Time, hrs	Products: Diamantane (Isolated)	Products: Other
XXVII/XXVIII	1.0	C_6H_{12} (5)	Sludge (2.0 ml)	Reflux	5	0.71 g (71%)	VII (6-7%)
XXVII/XXVIII	100.0	C_6H_{12} (100)	$AlBr_3$ (27 g)	Reflux	2-3	62-75 g (62-75%)	VII (6-7%)
XXXV	0.5	C_6H_{12} (5)	$AlBr_3$ (0.25 g)	Reflux	2-3	0.42 g (84%)	VII (0.32 g, 6.4%)
XXXVI + XXXV + I + XIII[c]	1.82	C_6H_{12} (10)	$AlBr_3$ (0.5 g)	Reflux	2-3	1.27 g (70%)	VII (6-7%)
XIII	11.0	C_6H_{12} (25)	Sludge (2 ml)	Reflux	4-5	3.5 g (10%)	VII
XIII	2.0	none	97% H_2SO_4 (10 ml)	25°	48	0.6 g (30%)	Diamantanone (0.3 g, 15%)
XVII	1.0	C_6H_{12} (5)	$AlBr_3$ (1.0 g)	Reflux	24	0.25 g (25%)	VII
XVII	1.0	C_6H_{12} (5)	Sludge (2 ml)	Reflux	24	0.20 g (20%)	VII
XVIII	1.0	C_6H_{12} (5)	$AlBr_3$ (2 ml)	Reflux	24	0.25 g (25%)	VII
XVIII	1.0	C_6H_{12} (5)	Sludge (2 ml)	Reflux	24	0.18 g (18%)	VII

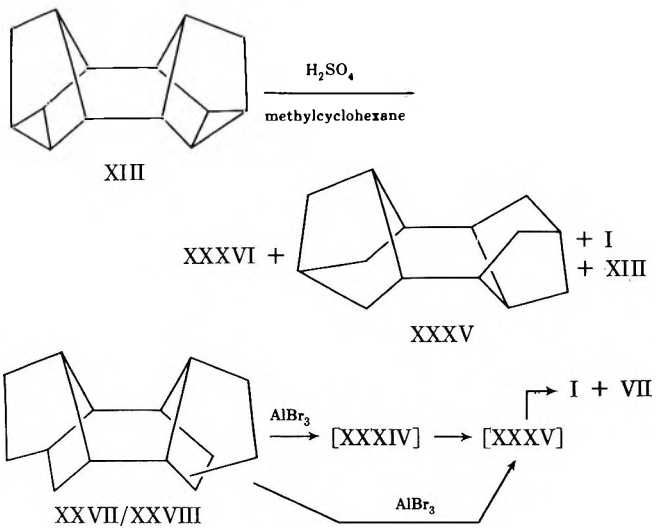
TABLE VI cont.

Starting Material	g	Solvent (ml)	Catalyst[b]	Temp	Time, hrs	Products: Diamantane (Isolated)	Products: Other
XVI	18.5	CS_2 (25)	Sludge (20 ml)	70-100°	4-24	10-16%	VII and alkyl adamantanes
XVI	18.5	none	Sludge (20 ml)	70-100°	4-24	~16%	VII and alkyl adamantanes
VIa[d]	10.0	none	Sludge (7 ml)	65°	72	1.0 g (10%)	VII
VI[e]	10.0	CS_2 (20)	Sludge (10 ml)	100°	19	< 5%	VII (4.0 g, 40%)
VI[f]	10.0	CS_2 (20)	Sludge (10 ml)	80°	48	1-5%	VII (4.0 g, 40%)
XXI	1.66	none	Sludge (3 ml)	85°	6-10	47% by glc	(XXVI)
XXI	0.3	CS_2 (20)	Sludge (0.5 ml)	90-100°	6-10	41% by glc	(XXV)
XXIV	123.3	none	Sludge (215 ml)	89-95°	4.5	31.6 g (25%)	36.0 g (29%) alkyl adamantanes

[a] In all instances besides VII, other fragmentation products were obtained which ranged from small to large amounts. [b] "Sludge" refers to catalyst prepared from t-butyl bromide-aluminum bromide, (see experimental). [c] Mixture from reaction of XIII with H_2SO_4-methylcyclohexane consisting of XXXVI (36.5%), XXXV (37.6%), I (15%) and XIII (3%). [d] From Cu_2Cl_2 sensitized photolysis of norbornene, cf. refs 15 and 16. [e] From hydrogenation of commercial (Aldrich) 2+2 norbornadiene dimer mixture; the hydrogenated material consists of 26% VIa, 71% VIb, and 3% VIc. [f] From acetone sensitized photodimerization of norbornene consisting of 12% VIa, and 38% VIb, cf. refs 15 and 16.

graphical representation of product composition *vs.* time, illustrates the course of a typical rearrangement.

We have also isolated XXXV by hydride transfer reduction of Binor-S (XIII) by the sulfuric acid–methylcyclohexane method[31] at 0°. After 0.5 hr under the conditions used, two major components, XXXVI (34%) (which has not been identified) and XXXV (51%), as well as diamantane (5%) and unreacted Binor-S (6%), were observed by gas chromatographic analysis. XXXV was isolated by crystallization and shown to be identical with the second intermediate observed in the aluminum bromide isomerization. The ^{13}C nmr spectrum[34] of XXXV consisted of five lines. Although XXIX also has five unique carbons, XXXV is more compatible with the chemical shift data[34] and is less strained [$\Delta H_f°$ (calcd) = −13.21 kcal/mol, strain (calcd) = 34.85 kcal/mol].[17] *trans*-Pentacyclo[8.2.1.1.^{2,5}.0^{3,7}.0^{8,12}]tetradecane (XXXV) isomerizes without intervention of other glc-detectable intermediates to diamantane (I) and VII in 84 and 6.4% yields, respectively.



The mechanism of the rearrangement of XXVIII to I has been analyzed exhaustively by graph theoretical techniques involving generation and energetic evaluation of possible routes. A complete account of this treatment will be published separately.[1e]

The diamantane obtained from precursor XXVII or XXVIII is quite pure. Yields of diamantane were as high as 75%, and average overall yields from Binor-S are about 65–70%.[12] McKervey[13] has verified our results independently and has used dichloromethane as solvent with even higher yields, although some chlorinated by-product is formed as a result. Diamantane is now readily available in greater than 50% overall yield in three steps from norbornadiene, and is almost as easy to obtain as adamantane.

Conclusion

Diamantane (I) is readily prepared from Lewis acid catalyzed rearrangement of hydrogenated Binor-S (XXVII/XXVIII) in ~70% yield, and in three steps from commercial norbornadiene in an overall yield of >50%. Other $C_{14}H_{20}$ pentacyclic precursors give lower yields, with the exception of *trans*-tetrahydro-Binor-S (XXXV); however, the preparation of pure XXXV is more cumbersome. In all cases, in addition to diamantane (I), there was isolated a disproportionation product (VII), and the proportions of I to VII varied with the type of precursor. Other catalysts such as the aluminum bromide–*tert*-butyl bromide "sludge" catalyst did not markedly affect the yield, nor did varying the solvent. The large variation of yield with starting material may be explained by mechanistic considerations, as is discussed in a separate paper.[1e]

The structural and spectral properties of I are summarized and are in agreement with expectations for a diamond lattice hydrocarbon.

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Registry No.—I, 2292-79-7; X, 5307-65-3; XI, 17926-99-7; XII, 17926-98-6; XIXa, 1489-56-1; XIXb, 19656-98-5; XXa, 51966-20-2; XXb, 52032-36-7; XXIII, 51982-56-0; XXXVIIa, 52032-37-8; XXXVIIb, 52032-38-9; 4-methylcyclohexene, 591-47-9.

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References and Notes.

(1) For preliminary communications pertinent to this series, see ref 8, 9, 10, 12, 41, and (a) T. M. Gund, M. Nomura, V. Z. Williams, Jr., P. v. R. Schleyer, and C. Hoogzand, *Tetrahedron Lett.*, 4875 (1970); (b) T. M. Gund, P. v. R. Schleyer, and C. Hoogzand, *ibid.*, 1583 (1971); (c) I. Tabushi, Y. Aoyama, N. Takahashi, T. M. Gund, and P. v. R. Schleyer, *ibid.*, 107 (1973); (d) T. M. Gund and P. v. R. Schleyer, *ibid.*, 1959 (1973); (e) T. M. Gund, P. v. R. Schleyer, P. H. Gund, and W. T. Wipke, *J. Amer. Chem. Soc.*, in press; (f) I. Tabushi, S. Kojo, P. v. R. Schleyer, and T. M. Gund, *Chem. Commun.*, 591 (1974).

(2) (a) Ph.D. Thesis, Princeton University, 1973; (b) Department of Chemistry, Faculty of Science, Hokkaido University, Kita 10-jo, Nishi-8 chome, Sapporo-060, Japan; (c) A.B. Thesis, Princeton University, 1965.

(3) Reviews: (a) H. Stetter, *Angew. Chem.*, **66**, 217 (1954); (b) H. Stetter, *ibid.*, **74**, 361 (1962); (c) R. Fort and P. v. R. Schleyer, *Chem. Rev.*, **64**, 277 (1964); (d) V. V. Sevost'yanova, M. M. Krayushkin, and A. G. Yurchenko, *Russ. Chem. Rev.*, **39**, 817 (1970); (e) R. C. Bingham and P. v. R. Schleyer, *Fortschr. Chem. Forsch.*, **18**, 1 (1971); (f) Z. Weidenhoffer and S. Hála, *Sb. Vys. Sk. Chem.-Technol. Praze, Technol. Paliv*, D **22**, 5 (1971); (g) E. M. Engler and P. v. R. Schleyer, *MTP (Med. Tech. Publ. Co.) Int. Rev. Sci.: Org. Chem., Ser. One. 1973*, 239 (1973).

(4) (a) V. Prelog, *Bull Soc. Chim. Fr.*, 1433 (1960); (b) V. Prelog, *Pure Appl. Chem.*, **6**, 545 (1963); (c) G. M. Blackburn, D. W. Cameron, A. R. Katritzky, and R. H. Prince, *Chem. Ind. (London)*, 1349 (1963); (c) D. J. Cram and G. S. Hammond, "Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1964.

(5) M. Saunders, *Tetrahedron*, **23**, 2105 (1967).

(6) Even earlier, Weissbach considered IIIa to be the structure of scyllitol diborate. Although the substance may actually be a polymer,[7] IIIa is the first representation of the basic diamantane structure we have been able to find in the literature: A. Weissbach, *J. Org. Chem.*, **23**, 329 (1958). Authentic scyllitol derivatives, such as hexaoxadiamantane (IIIb), have been prepared.[7]

(7) O. Vogl, B. C. Anderson, and D. M. Simons, *Tetrahedron Lett.*, 415 (1966).

(8) C. Cupas, P. v. R. Schleyer, and D. J. Trecker, *J. Amer. Chem. Soc.*, **87**, 917 (1965).

(9) V. Z. Williams, Jr., P. v. R. Schleyer, G. J. Gleicher, and L. B. Rodewald, *J. Amer. Chem. Soc.*, **88**, 3862 (1966).

(10) A nondiamondoid isomer of the tetramantanes, "bastardane," has been prepared by rearrangement: P. v. R. Schleyer, E. Osawa, and M. G. B. Drew, *J. Amer. Chem. Soc.*, **90**, 5034 (1968).

(11) S. Hála, S. Landa, and V. Hanus, *Angew. Chem.*, **78**, 1060 (1966); *Angew. Chem., Int. Ed. Engl.*, **5**, 1045 (1966).

(12) T. M. Gund, V. Z. Williams, Jr., E. Osawa, and P. v. R. Schleyer, *Tetrahedron Lett.*, 3877 (1970); T. M. Gund, W. Thielecke, and P. v. R. Schleyer, *Org. Syn.*, **53**, 30 (1973).

(13) (a) T. Courtney, D. E. Johnston, M. A. McKervey, and J. J. Rooney, *J. Chem. Soc., Perkin Trans. 1*, 2691 (1972); also see (b) D. Faulkner, R.

A. Glendinning, D. E. Johnston, and M. A. McKervey, *Tetrahedron Lett.*, 1671 (1971); (c) M. A. McKervey, D. E. Johnston, and J. J. Rooney, *ibid.*, 1547 (1972); (d) D. E. Johnston, M. A. McKervey, and J. J. Rooney, *Chem. Commun.*, **29** (1972), and ref 48 and 49.
(14) (a) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **79**, 3292 (1957); (b) P. v. R. Schleyer and M. M. Donaldson, *ibid.*, **82**, 4645 (1960).
(15) D. R. Arnold, D. J. Trecker, and E. B. Whipple, *J. Amer. Chem. Soc.*, **87**, 2596 (1965).
(16) E. B. Whipple and M. Ruta, *J. Amer. Chem. Soc.*, **87**, 3060 (1965).
(17) Confirmed by molecular mechanics calculations. See (a) J. L. Fry, E. M. Engler, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **94**, 4628 (1972); (b) E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *ibid.*, in press.
(18) A. Schneider, R. W. Warren, and E. J. Janoski, *J. Org. Chem.*, **31**, 1617 (1966).
(19) (a) H. Pines, C. T. Chen, and A. W. Shaw, *J. Amer. Chem. Soc.*, **80**, 1930 (1958); (b) H. Pines, F. J. Pavlick, and V. N. Ipatieff, *ibid.*, **73**, 5738 (1951).
(20) For a general review of Lewis acid catalyzed hydrocarbon reactions, see H. Pines and J. Mavity in B. G. Brooks, *et al.*, Ed., "The Chemistry of Petroleum Hydrocarbons," Vol. III, Reinhold, New York, N. Y., 1955, Chapter 39, pp 9–58.
(21) H. C. Brown and W. J. Wallace, *J. Amer. Chem. Soc.*, **75**, 6279 (1953); H. Pines and R. W. Meyerhalz, Jr., *ibid.*, **77**, 5392 (1955).
(22) M. Nomura, P. v. R. Schleyer, and A. A. Arz, *J. Amer. Chem. Soc.*, **89**, 3657 (1967).
(23) M. J. T. Robinson and H. J. F. Tarrat, *Tetrahedron Lett.*, 5 (1968).
(24) H. Koch and J. Franken, *Brennst.-Chem.*, **42**, 90 (1961); *Chem. Abstr.*, **55**, 21059*i* (1961).
(25) Such disproportionation reactions occur frequently in such Lewis acid catalyzed processes.[20] For example, the isomerization of *endo*-tetrahydrodicyclopentadiene to adamantane can give up to 87% disproportionation to *trans*-decalin depending on conditions.[24]
(26) (a) D. Farcasiu, P. v. R. Schleyer, and D. Ledlie, *J. Org. Chem.*, **38**, 3455 (1973); (b) D. Farcasiu, unpublished results.
(27) (a) G. N. Schrauzer, *Advan. Catal.*, **18**, 373 (1968); also see ref 32; (b) H. D. Scharf, G. Weisgerber, and H. Hover, *Tetrahedron Lett.*, 4227 (1967).
(28) (a) J. J. Mrowca and T. J. Katz, *J. Amer. Chem. Soc.*, **88**, 4012 (1966); (b) T. J. Katz and N. Acton, *Tetrahedron Lett.*, 2601 (1967); (c) N. Acton, R. J. Roth, T. J. Katz, J. K. Frank, C. A. Maier, and I. C. Paul, *J. Amer. Chem. Soc.*, **94**, 5446 (1972).
(29) C. W. Woodworth, V. Buss, and P. v. R. Schleyer, *Chem. Commun.*, 569 (1968).
(30) Z. Majerski and P. v. R. Schleyer, *Tetrahedron Lett.*, 6195 (1968).
(31) *Cf.* J. S. Wishnok, P. v. R. Schleyer, E. Funke, G. D. Pandit, R. O. Williams, and A. Nickon, *J. Org. Chem.*, **38**, 539 (1973).
(32) (a) G. N. Schrauzer, B. N. Bastian, and G. A. Fosselius, *J. Amer. Chem. Soc.*, **88**, 4890 (1966). (b) G. N. Schrauzer, R. K. Y. Ho, and G. Schlesinger, *Tetrahedron Lett.*, 543 (1970). (c) The originally proposed[32a] von Baeyer IUPAC name for "Binor-S" is incorrect.[12] See, however, D. von Bimmendylo and A. C. Mackay, *Can. J. Chem.*, **51**, 718 (1973).
(33) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965, pp 133–134.
(34) We thank Dr. E. Hagaman and Professor E. Wenkert for the ^{13}C spectra and spectral analyses reported in this paper.
(35) (a) P. v. R. Schleyer and E. Wiskott, *Tetrahedron Lett.*, 2845 (1967); (b) A. Nickon, G. D. Pandit, and R. O. Williams, *ibid.*, 2851 (1967); (c) A. Nickon, H. Kwasnik, T. Schwartz, R. O. Williams, and J. B. Di Giorgio, *J. Amer. Chem. Soc.*, **87**, 1613, 1615 (1967); (d) B. R. Vogt and J. E. Hoover, *Tetrahedron Lett.*, 2841 (1967).
(36) The original colloquial "belt" designation given to the 1, 2, 6, 7, 11, and 12 positions of diamantane[3e,9] is not adjectival. We now prefer "medial," which seems to us to describe these positions better than the recently employed "zonal."[13] We thank Professor C. W. Jefford for this suggestion.
(37) S. H. Liggero, P. v. R. Schleyer, and K. C. Ramey, *Spectrosc. Lett.*, **2**, 197 (1969).
(38) The ^{13}C nmr spectrum was determined by Professor T. M. Grant, University of Utah, private communication.
(39) T. Pehk, E. Lippmaa, V. V. Sevost'janova, M. M. Krayuschkin, and A. I. Tarasova, *Org. Magn. Resonance*, **3**, 783 (1971).
(40) Z. Dolejsek, S. Hála, V. Hanuš, and S. Landa, *Collect. Czech. Chem. Commun.*, **31**, 435 (1966).
(41) S. T. Rao, M. Sundaralingam, E. Osawa, E. Wiscott, and P. v. R. Schleyer, *Chem. Commun.*, 861 (1970).
(42) A. G. Yurchenko, F. N. Stepanov, S. S. Isaeva, B. M. Zolotarev, V. I. Kadentsev, and O. S. Chezhov, *Org. Mass Spectrom.*, **3**, 1401 (1970).
(43) I. L. Karle and J. Karle, *J. Amer. Chem. Soc.*, **87**, 919 (1965).
(44) M. Mansson, N. Rapport, and E. F. Westrum, Jr., *J. Amer. Chem. Soc.*, **92**, 7296 (1970).
(45) P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Amer. Chem. Soc.*, **92**, 2377 (1970).
(46) R. H. Boyd, S. N. Sanwal, S. Shary-Tehrany, and D. McNally, *J. Phys. Chem.*, **75**, 1264 (1971).
(47) S. R. Butler, A. S. Carson, P. G. Laye, and W. V. Steele, *J. Chem. Thermodyn.*, **3**, 277 (1971).
(48) A. S. Carson, P. G. Laye, W. V. Stelle, D. E. Johnston, and M. A. McKervey, *J. Chem. Thermodyn.*, **3**, 915 (1971).
(49) T. Clark, D. E. Johnston, H. Markle, M. A. McKervey, and J. J. Rooney, *J. Chem. Soc., Chem. Commun.*, 1042 (1972).
(50) N. L. Allinger, M. T. Tribble, M. A. Miller, and D. W. Wertz, *J. Amer. Chem. Soc.*, **93**, 1637 (1971).
(51) "Tables of Interatomic Distances and Configuration in Molecules and Ions," *Chem. Soc., Spec. Publ.*, **No. 11**, M-102 (1958); C–C bond length in graphite = 1.4210 ± 0.0001.

Diamantane. II.[1] Preparation of Derivatives of Diamantane

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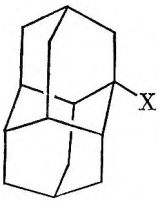
Methods have been developed for the conversion of diamantane (I) to the three possible types of monofunctional derivatives: 1- (medial), 3- (secondary), and 4- (apical). The 1-diamantyl cation is the most stable and most readily generated by hydride abstraction. Kinetically controlled nucleophilic attack on this cation can be made to give 1-bromodiamantane (III) and 1-diamantanecarboxylic acid (V) in liquid bromine and under Koch–Haaf conditions, respectively. Sulfuric acid oxidation of I affords 3-diamantanone (X), a convenient source of other 3-diamantyl derivatives. The secondary 3-diamantyl tosylate (XII) solvolyzes about 3.5 times faster than 2-adamantyl tosylate. Under equilibrium conditions apical adamantyl derivatives are favored by enthalpy over their medial isomers, but the entropy effect is opposite. The enthalpy term for relatively large groups such as methyl dominates. Thus, 4-methyldiamantane (XXIII) can be synthesized by isomerization of the other methyldiamantanes or of other pentacyclotetradecanes, such as XXII, XXV, or XXVI. The equilibrium is less one-sided for smaller substituents, *e.g.*, halide and alcohols, and preparations of apical products require chromatographic separation since they are seriously contaminated by their medial isomers. ^1H nmr chemical shifts of the various types of diamantane derivatives can be predicted satisfactorily by using additivity increments obtained from similarly constituted adamantanes.

The preparation of functional derivatives of diamantane (I) depended on the availability of the parent hydrocarbon.[1a] When the yield of I was improved to 10% by employing the exo-trans-exo norbornene dimer as precursor and aluminum bromide sludge catalyst,[3] the study of the chemistry of diamantane began.[3–5] The reactions employed were modeled after those which had been used successfully on the first member of the diamondoid series, adamantane (II).[6]

Bromination of diamantane by neat bromine led to bridgehead substitution, but, unlike adamantane, two isomers, medial[7] (1-) and apical[7] (4-), were possible. Nmr

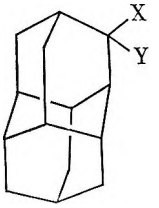
Table I
1-Substituted (Medial) Diamantanes



Compd	X	Starting material	Method	Ref	Diamantane registry no.
III	Br	X = H	Br_2 or *t*-BuBr–$AlBr_3$	1b, 12, 13b	30545-17-6
IV	Cl	X = H	CH_3COCl–$AlCl_3$ $ClSO_2Cl$–$AlCl_3$	13	32401-16-4
V	CO_2H	X = H	Koch–Haaf	9, *a*	30545-18-7
VI	OH	X = Br	Hydrolysis	1b, 9, *a*	30545-19-8
VII	CH_3	X = Br	CH_3MgBr	*b*	26460-76-4
VIII	$NHCOCH_3$	X = Br	CH_3CN–H_2SO_4 (Ritter)	9, *a*	30545-21-2
IX	$NH_3^+Cl^-$	X = $NHCOCH_3$	Hydrolysis	9, *a*	30545-22-3

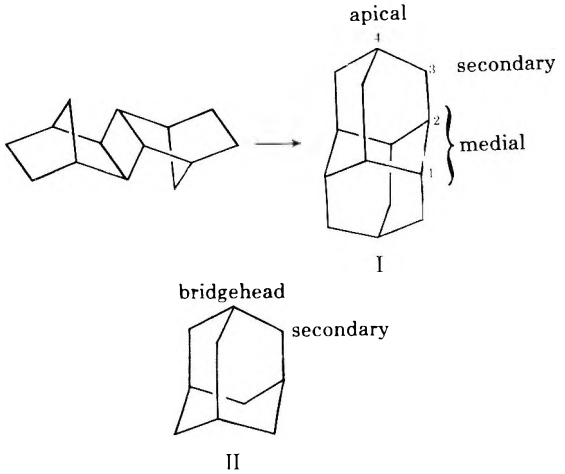
[a] This work. [b] E. Osawa, Z. Majerski, and P. v. R. Schleyer, *J. Org. Chem.*, **36**, 205 (1971).

Table II
3-Substituted (Secondary) Diamantanes



Compd	X	Y	Starting material	Method	Ref	Diamantane registry no.
X	=O		X, Y = H	H_2SO_4	9, 13, *a*	30545-23-4
XI	OH	H	X, Y = O	$LiAlH_4$	9, *a*	30545-24-5
XII	OTs	H	X = OH; Y = H	*p*-$C_7H_7SO_2Cl$	9, *a*	30651-00-4
XIII	Br	H	X = OH; Y = H	PBr_5	9, *a*	30545-25-6
XIV	Cl	H	X = OH, Y = H	$SOCl_2$	9, *a*	30651-01-5
XV	CH_3	OH	X, Y = O	CH_3MgBr	9, *a*	30545-26-7
XVI	$=CH_2$		X = CH_3; Y = OH	H_3PO_4	9, *a*	30545-27-8
XVII	CH_3	H	X, Y = CH_2	H_2/PtO_2	9, *a*	30545-28-9

[a] This work.



I

II

spectroscopy revealed that the product was 1-bromodiamantane (III, Table I) and this provided a synthetic entry to other medial derivatives.[3-5,6e,g]

Likewise, the discovery by Geluk and Schlatmann[8] of a convenient oxidation procedure for forming 2-adamantanone from II prompted the application of this reaction to diamantane. The 3-diamantanone (X, Table II) obtained by the action of sulfuric acid was readily converted to other 3-substituted derivatives.[6e,9]

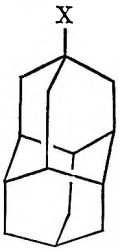
Functionalization of the 4 position (apical) was less straightforward, although 4-methyl- and 4,9-dimethyldiamantane (XXIII, Table III, and XXVII, respectively) had been prepared by rearrangement of C_{15} and C_{16} pentacyclic precursors.[6e,g,9-11] 4-Bromodiamantane (XVIII) was first synthesized as a component of a complex bromination mixture and by partial reduction of the 4,9-dibromide XXVIII.[1b,6e,12] McKervey, who independently studied the preparation and functionalization of diamantane,[13] found that 4 derivatives can be obtained more easily by equilibration, although mixtures of products result.[14] Preferential attack of the less hindered apical bridgehead has been achieved,[15] and recent improvement of this approach provides an even better entry to apical diamantanes.[16]

This paper describes the preparation and physical and nmr spectroscopic properties of the three different kinds of diamantane derivatives. A full discussion of the bromination and polybromination of diamantane is presented in the following paper.[1b]

Results and Discussion

Tables I–III summarize all of the monosubstituted diamantanes which have been prepared to date. Interchange of functional groups was generally accomplished by standard methods not requiring detailed comment. The principles involved in the direct functionalization of diamantane

Table III
4-Substituted (Apical) Diamantanes

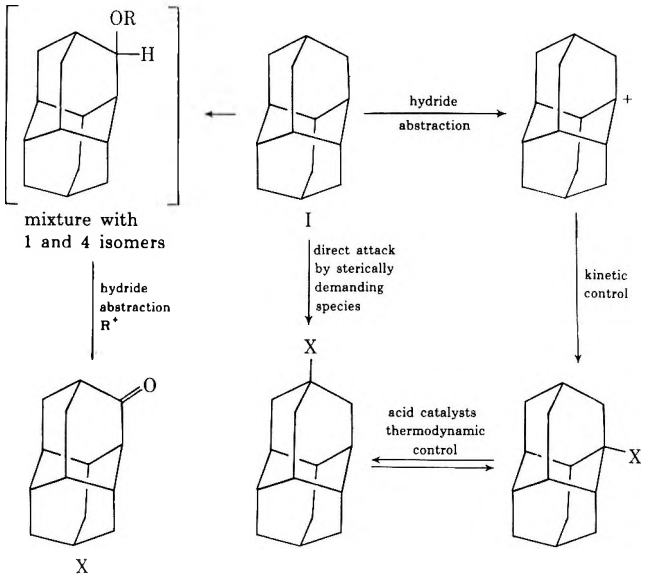


Compd	X	Starting material	Method	Ref	Diamantane registry no.
XVIII	Br	X = H	*t*-BuBr–$AlBr_3$ or Br_2–$AlBr_3$ or	1b	30545-30-3
	1-Bromodiamantane (III)		equilibration	12	
XIX	Cl	X = H	CH_3COCl–$AlCl_3$	13	32401-17-5
XX	OH	X = Br	Hydrolysis	1b, 9	30651-03-7
XXI	CO_2H	X = Br	Koch–Haaf	9, *a*	30651-04-8
XXIII	CH_3	XXII XXV	Rearrangement, $AlBr_3$ or sludge catalyst[b]	1a, 9, *a*	28375-86-2

[a] This work. [b] Prepared from *tert*-butyl bromide–aluminum bromide; *cf.* ref 1a and 3.

at the three types of positions are of greater interest and are summarized in Chart I.

Chart I



Medial Substitution. The 1 position was functionalized directly either by bromination at room temperature to form III,[12] or by the Koch-Haaf[9] reaction to give carboxylic acid V. Both these reactions depended on the greater ease of formation and greater stability of the 1-diamantyl cation over the 4 and 3 cations;[1b] the products are derived by kinetic control.

Secondary Substitution. Sulfuric acid oxidation of diamondoid hydrocarbons such as I and II involves generation of carbocations and the equilibration of alcohols or their sulfate esters.[8] Secondary alcohols, even though less stable than tertiary, can be further oxidized to ketone by hydride abstractions, and this explains the unique course of such reactions.[8] In actual fact, diamantane (I) was converted to 3-diamantanone (X) in 61% yield by 97% H_2SO_4.[9]

3-Diamantanone (X) may also be prepared by rearrangement. Treatment of Binor-S (XXIX) with concentrated sulfuric acid gave a 15% yield of X, along with some diamantane. Similar results have been obtained by McKervey from rearrangement of tetrahydro-Binor-S (XXX) in sulfuric acid.[13]

Acetolysis of 3-diamantyl tosylate (XII) gave the following rate constants and activation parameters: $k_{100°} = 3.52 \pm 0.00 \times 10^{-4}$ sec^{-1}, $k_{75.0°} = 2.20 \pm 0.08 \times 10^{-5}$ sec^{-1}, $\Delta H^* = 27.9$ kcal/mol, $\Delta S^* = 0.0$ eu. The calculated rate constant at 25°, 2.17×10^{-8} sec^{-1}, is 3.6 times faster than that observed for 2-adamantyl tosylate acetolysis at the same temperature.[17] Δ strain calculations[18] on the 2-adamantyl and the 3-diamantyl cations give essentially the same results suggesting that the origin of the enhanced 3-diamantyl rate is electronic rather than steric in origin; the γ branching afforded by the attached adamantane unit evidently is responsible.

Apical Substitution. 4-Substituted diamantanes, because of their equatorial character, have lower enthalpies than their 3 or 1 isomers.[13b,14] The degree of branching favors substitution at either bridgehead over the secondary position. While entropy disfavors apical substitution due to higher symmetry, this factor should be less important than enthalpy in magnitude unless the substituents are small. The symmetry contribution to the $T\Delta S$ term at 25° is 0.65 kcal/mol favoring apical to medial and 1.06 kcal/mol for apical to secondary isomerization. Thus, thermodynamically controlled reactions should generally favor apical substitution.

The first realization of this expectation was achieved not by direct substitution, but by isomerization of pentacyclopentadecanes and pentacyclohexadecanes. Rearrangement of *exo*-tetrahydrotricyclopentadiene (XXII) with aluminum bromide "sludge" catalyst gave a complex mixture from which 4-methyldiamantane (XXIII) was isolated in 3% yield. The other isomers, 1-methyldiamantane (VII) and 3-methyldiamantane (XVII), being of lower thermodynamic stability, were not detected in this reaction. The order of thermodynamic stability of the methyldiamantanes has been determined by empirical force field calculations[18,19] and by experiment;[14b] these results indicate that the equilibrium composition should consist of 93–98% apical (XXIII), 1.3–4.7% medial (VII), and 0.7–2.4% secondary (XVII) methyldiamantanes at 25°. Both homodiamantane isomers XXVIa and XXVIb are expected to be of considerably lower thermodynamic stability than the three methyldiamantanes, and were not observed in any of the above experiments. XXVIa, independently synthesized with aluminum bromide in refluxing cyclohexane, gave a mixture of the three methyldiamantanes, with the 4 isomer (XXIII) comprising >95% of the product mixture (Chart II).[15]

NMR of Substituted Diamantanes. In the following paper of this series[1] we show that the ^{1}H-nmr spectra of diamantyl mono- and polybromides may be calculated by assuming additivity using a set of substituent parameters derived from 1- and 2-substituted adamantanes. To a first approximation, good correlation is observed, but even better agreement was obtained by using "refined" additivity increments derived from 220 MHz nmr spectra of 4- and 1-diamantane bromides.

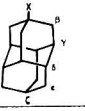
We report here the calculation and observed nmr spectra of some 3-, 3,5-, and 1-substituted diamantanes, and compare shift parameters obtained from 1- and 2-adamantanes to those derived from observed spectra. Tables VI, VII, and VIII summarize the data.

3-Substituted Diamantanes. The spectra of four 3-diamantanes studied (Table VI), were relatively simple with absorptions in the δ 1.4 to 2.3 region and were predictable reasonably well using the adamantane chemical shift increments. The five types of protons give overlapping peaks; in all cases, δ, ϵ, and ζ proton chemical shifts vary only by 0.07 ppm, are not separable by 60 MHz nmr, and are least affected by substituents. β and γ proton chemical shifts may be shielded or deshielded and range over 0.8δ and 0.2δ ppm, respectively, with changes in substituents; sometimes the signals are resolved (Br, OH, CH_3) and sometimes not (COOH). The range of chemical shifts is comparable to those reported for 1-adamantanes[24] which give variations in β protons of 0.8δ ppm, γ of 0.1δ ppm, and δ of 0.1δ ppm.

Of the four substituents, bromine exhibits the largest chemical shift differences with the β protons being most deshielded. The hydroxy group deshields the γ protons most and has only a slight effect on the others. The carboxylic acid group deshields both β and γ protons to a similar extent, while the methyl group shields the β protons (~0.2γ ppm) and has relatively little effect on the other protons which appear as a singlet.

TABLE VI

CHEMICAL SHIFTS IN 4-SUBSTITUTED DIAMANTANES[a] (δ)



Substituent X	Proton Type	Area	δ(calc)	δ(observed)	Area	Shift from Diamantane[b] (ppm)	Increments[c] used for calculation
Br[d]	δ,ϵ,ζ	10	1.63	1.73 (s)	13	+0.05	-0.05
	γ	3	1.88	1.80 (m)		+0.12	+0.20
	β	6	2.20	2.30 (d,J~1.9Hz)	6	+0.62	+0.52
OH	OH	1	1.5-2.0[e]				
	δ,ϵ,ζ	10	1.54	1.65(s)	17	-0.03	-0.14
	β	6	1.59	1.72(d)		+0.04	-0.09
	γ	3	1.92	1.9 (b)	3	+0.22	+0.24

[a] In $CDCl_3$ solution with internal standard. [b] Positive value indicates a downfield shift and negative value an upfield shift from the diamantane resonance at δ 1.68. [c] Substituent shifts for corresponding adamantane derivatives, cf. ref 24. [d] CCl_4 solution. [e] Value for 1-adamantane derivative.

TABLE VII

CHEMICAL SHIFTS IN 3-SUBSTITUTED DIAMANTANES[a] (δ)

Substituents X	Substituents Y	Proton Type	Area	δ (calcd)	δ (observed)	Area	Shift from Diamantane[b]	Increments used for calculation[b,c]
		e	1	1.55				-0.13
		i,j,m,n,o,p,q,r	8	1.63	1.72(s)	14	+0.04	-0.05
		k,l	2	1.70				+0.02
Br	N	f,g,h	3	1.84				+0.16
		a,b	2	1.96	1.95(m)	2	+0.27	+0.28
		c,d	2	2.26	2.32(AB)	2	+0.64	+0.58
		Y	1	4.58[d]	4.48(b)	1		
		e	1	1.50				-0.18
		k,l,m,n	4	1.69				+0.01
					1.75(s)	14	+0.07	
		i,j,o,p,q,r	6	1.73				+0.05
Cl	H	f,g,h	3	1.79				+0.11
		a,b	2	1.88	1.90(br)	2	+0.22	+0.20
Cl	H	c,d	2	2.20	2.25(br)	2	+0.57	+0.52
		Y	1	4.29[d]	4.25(br-s)	1		

TABLE VII

CHEMICAL SHIFTS IN 3-SUBSTITUTED DIAMANTANES[a] (δ) (cont.)

Substituents X	Substituents Y	Proton Type	Area	δ (calc)	δ (observed)	Area	Shift from Diamantane[b]	Increments used for Calculation[b,c]
		e	1	1.46			-0.26	-0.22
		h	1	1.62	1.42	16		-0.06
		a,b	2	1.72	1.73		+0.05	+0.04
		i,j,m,n,o,p,q,r	8	1.73				+0.05
OH	H	e,g	2	1.75				+0.07
		k,l	2	1.78			+0.27	+0.10
		c,d	2	1.99	1.95	2		+0.31
		Y	1	3.75[d]	3.75 (b,s)	1		
		OH	1		1.58(s)	1		
=O		c-r	16	1.90	1.88(t)	16	+0.20	+0.22
		a,b	2	2.31	2.45(br,s)	2	+0.77	+0.65
		c-r	16	1.78	1.78(s)	16	+0.10	+0.10
$=CH_2$		a,b	2	2.28	2.30(br,s)	2	+0.62	+0.60
		$=CH_2$	2	4.38	4.42(s)	2		+2.70

TABLE VII

CHEMICAL SHIFTS IN 3-SUBSTITUTED DIAMANTANES[a] (δ) (cont.)

Substituents X	Substituents Y	Proton Type	Area	δ (calc)	δ (observed)	Area	Shift from Diamantane[b]	Increments used for Calculation[b,c]
		CH_3	3	1.05[d]	1.0(d,J~7Hz)	3		
CH_3	H	Y a,b	2	1.10[e]				
		c,d	2	1.95[e]	1.52(b)	19	-0.16	
		All others	15	1.6-1.8[f]	1.68(s)		~0	
		CH_3	3	1.3[d]	1.3(s)	4		
CH_3	OH	OH	1	1.22[d]				
			1	1.45[d]	1.5(s)			
		Others	16	1.78	1.7(b)	16	+0.02	
		c,f	2	2.22[d,g]	2.2(b)	2	+0.52	

[a] In CCl_4 solution with internal TMS. [b] Positive value indicates a downfield shift and a negative value an upfield shift from diamantane resonance of δ 1.68. [c] Substituent shifts for corresponding 2-adamantane derivatives, cf. ref 25. [d] Value for 2-adamantane derivative. [e] Calculated from 220 MHz nmr spectrum of 2,2-dimethyl adamantane. [f] Value extrapolated from 2-methyl adamantane. [g] Assignment tentative since decoupling experiments were not performed. The effect of an axial methyl on a γ-equatorial proton has not been determined.

TABLE VIII

CHEMICAL SHIFTS IN 1-SUBSTITUTED DIAMANTANES[a] (δ)

Substituent X	Proton Type	Area	δ (calc)	δ (observed)	Area	Shift from Diamantane[b]	Increments used for calculation[c]
	d	2	1.55	1.40(AB-J~12)	10	-0.28	-0.13
	e,g,δ	6	1.63	1.60(br-s)		-0.08	-0.05
	f	2	1.70				+0.02
Br[d]	γ(b)	3	1.88[e]	1.90(br-s)	5	+0.22	+0.20
	a	2	1.96				+0.28
	β	2	2.20	2.20(d)	4	+0.52	+0.52
	c	2	2.26	2.30(AB,J~12)		+0.62	+0.58
	d	2	1.46	1.32(br)		-0.36	-0.22
	δ	4	1.54				-0.14
	β	2	1.59		14		-0.09
	a	2	1.72	1.68(br-s)		0	+0.04
OH	e,g	2	1.73				+0.05
	f	2	1.78			+0.32	+0.10

TABLE VIII

CHEMICAL SHIFTS IN 1-SUBSTITUTED DIAMANTANES[a] (δ) (cont.)

Substituent X	Proton Type	Area	δ (calc)	δ (observed)	Area	Shift from Diamantane[b]	Increments used for calculation[c]
	γ,b	3	1.72	2.0(br)	5		+0.24
OH	c	2	1.99	2.25(AB-J~12)		+0.57	+0.31
	OH	1		1.50(s)	1		
	d	2	1.42	1.48		-0.20	-0.26
	δ	4	1.64	1.78(m)	17	+0.10	-0.04
	e,f,g	4	~1.68				~0
COOH	γ (b)	3	1.83				+0.15
	β	2	1.84				+0.16
	a	2	~1.90				+0.22
	c	2	2.30	2.15(br)	2	+0.47	+0.62
	COOH	1		10.41	1		

TABLE VIII

CHEMICAL SHIFTS IN 1-SUBSTITUTED DIAMANTANES[a] (δ) (cont.)

Substituent X	Proton Type	Area	δ (calcd)	δ (observed)	Area	Shift from[b] Diamantane	Increments used for calculation[c]
	CH_3	3	1.05[f]	0.93 (s)	3		
	β	2	1.38	1.42(d,J=2.5)	6	-0.26	-0.30
	a	2	1.40				-0.28
	f	2	1.52				-0.16
CH_3[g]	d	2	~1.40-1.50	1.68(d,J=2.5)	9	~0	-0.10
	δ	4	1.58				+0.04
	γ (b)[g]	3	1.72				+0.12
	e, g	2	1.80	2.0 (d)	2	+0.32	
	c	2	1.95	2.2 (AB-J=12)	2	+0.52	+0.27

[a] In $CDCl_3$ solution with TMS internal standard. [b] A positive value indicates a downfield shift and a negative value an upfield shift from the diamantane resonance of δ 1.68. [c] Substituent shifts for corresponding 1- and 2-adamantane derivatives, cf. refs 24 and 25. [d] CCl_4 solution. [e] If assumed to be a γ position as in 1-adamantane; but if calculated as a δ position in 2-adamantane, the calculated value is δ 1.84. [f] Calculated values from 1-methyladamantane for β, γ, δ protons; other values derived from 60 mnr spectrum of 2-methyl-adamantane and the 220 MHz nmr spectrum of 2,2-dimethyladamantane. [g] Value for 2-methyladamantane.

3-Substituted Diamantanes. The spectra of the 3-substituted diamantanes listed in Table VII are less complex than expected, with maxima falling between δ 1.90-2.5. The most intense resonance appears as a singlet between δ 1.68-1.88. The calculated shifts in Table VII are based on 2-adamantyl substituent additivity increments.[25] Electronegative substituents facilitate identification since larger variations in chemical shifts are observed. β-Bridgehead protons are deshielded for Br and Cl, but are shielded for OH and methyl. AB quartets resulting from the 1,3-diaxial relationship between the substituent and the methylene proton, d, are observed for Br, Cl, and OH, but are not very intense. This could be due to an interference by proton c which is also axially oriented and is deshielded to about the same extent.

Musher and Segre[26] have determined that an axial methyl is deshielded with respect to an equatorial methyl by 0.14 ppm. Thus, the axial methyl resonance in 3-methyldiamantane at δ 1.0 is deshielded relative to that of 4-methyl diamantane (δ 0.80).

3-Diamantanone and 3-methylenediamantane display essentially two-line spectra; the downfield absorptions are due to the vicinal bridgehead protons. Yurchenko and Isaev[27] found that the deshielding in 2-adamantanone, in the presence of europium shift reagent, decreases with distance from the substituent. This suggests that deshielding of protons in a 1,3 diaxial arrangement for Br, Cl, OH and CH_3 may be a result of a through space[26] and not a through bond inductive interaction.[29]

1-Substituted Diamantanes. The spectra of 1-substituted diamantanes are most complex and display characteristics of both the bridgehead and secondary adamantane derivatives. For the substituents studied (Table VIII), absorptions were observed in the δ 1.32 to 2.3 region, the lowest absorptions being due to 1,3 diaxial substituent-proton interactions, irrespective of the electronegativity of the substituent (e.g., Br and CH_3). A strong resonance in the diamantane absorption region (δ 1.60-1.78), was usually observed; theother resonances were either deshielded (Br, OH, COOH) or shielded (CH_3). In general, 1,3 diaxial interactions are enhanced in 1-diamantanes compared to 3-diamantanes and 2-adamantanes, as seen in greater deshielding of the γ protons. This may reflect the closer proximity to the axial substituent in the 1-position. Surprisingly, the axial methyl resonance in 1-methyldiamantane occurs at δ 0.93 and is therefore deshielded with respect to 4-methyldiamantane (δ 0.80, CH_3 equatorial), but shielded relative to 3-methyldiamantane (δ 1.0 CH_3 axial).

Experimental Section

General. Microanalyses were performed by Robertson Laboratories, Florham Park, N.J., and by Hoffmann-La Roche, Inc., Nutley, N.J. Infrared spectra were determined on a Perkin-Elmer 237-B spectrophotometer. Nmr spectra were taken on a Varian Model A-60A spectrometer using tetramethyl silane as internal standard. Gas chromatographic analyses were performed on either a Varian Aerograph 90-P instrument or a Perkin-Elmer 810 flame ionization gas chromatograph, with columns as reported in individual preparations.

1-Bromodiamantane (III). The preparation from diamantane by treatment with bromine at room temperature for two hours has been published in preliminary form.[12] A detailed account will be given in the following paper.[1b]

1-Methyldiamantane (VII). The preparation from 1-bromodiamantane by a Grignard coupling reaction has been described by Osawa, Majerski and Schleyer.[30]

(30) See Table I, ref b.

4-Bromodiamantane (XVIII). The preparation from diamantane by reaction with bromine-aluminum bromide has been published in preliminary form.[12] The preparation from diamantane with t-butyl bromide-aluminum bromide will be described in a following paper.[1b]

1-Diamantane Carboxylic Acid (V) [Koch-Haaf Reaction[22,31]]. A flask equipped with stirrer, thermometer, dropping funnel, and gas outlet tube was charged with 130 ml of 97.2% sulfuric acid, 50 ml of carbon tetrachloride, and 9.4 g (0.050 mole) of diamantane. The mixture was cooled to 17-19° and 0.5 ml of 98-100% formic acid was added. Then a solution of 19 ml of t-butyl alcohol in 28 g of 98-100% formic acid was added dropwise (about 2 hrs). The reaction mixture was stirred for an additional 30 minutes and then

(31) Cf. H. Koch and W. Haaf, Org. Syn., 44, 1 (1964).

poured onto 350 g of crushed ice. The layers were separated, and the upper acid layer was extracted with three 100 ml portions of CCl_4. The combined CCl_4 layers were shaken with 55 ml of 15 N ammonium hydroxide, and the precipitated ammonium diamantane carboxylate was collected and washed with 20 ml of cold acetone and suspended in about 100 ml of water. The suspension was made strongly acid with concentrated HCl and extracted with chloroform. The organic layer was separated, dried over $MgSO_4$, and evaporated. The residue (3.70 g, 0.0123 mole) of crude 1-diamantane carboxylic acid (V) (25% yield) was crystallized from methanol-water. From the carbon tetrachloride solution (mother liquor) of ammonium salt, 4.0 g of unreacted diamantane was isolated. The acid was purified for analysis by recrystallization from benzene; while fluffy crystals, mp 201.5-202.2°, were obtained; ir (nujol) 1695, 1410, 1275, 1250, 1230 (w), 1100, 1075, 1055 (s), 1040 (w), 935 (b) and 710 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.28; H, 8.97.

1- and 4-Diamantane Carboxylic Acids (V and XXI) [Koch-Haaf Reaction-Mixed Acid Method[22c-i]]. A flask was charged with 140 ml of 1:1 mixture of 97.2% and fuming sulfuric acids, 50 ml of CCl_4 and 10.0 g (0.054 mole) of diamantane. After cooling to 15°, 0.5 ml 98% formic acid was added. Then a solution of 19 ml t-butanol containing 28 g (98%) formic acid was added dropwise within 1/2 hour. Stirring was continued at 15° for 30 minutes and then at room temperature for four hours. Upon workup, as for 1-diamantane carboxylic acid (V), 1.09 g (8.8%) of an acid mixture consisting of 1-diamantane carboxylic acid (V) and 4-diamantane carboxylic acid (XXI) was obtained. The acid composition was determined by conversion of 200 mg of acid to their corresponding methyl esters via reaction with diazomethane in ether. Gas chromatographic analysis on a 1m x 3 mm FFAP column at 190° indicated the ratio of esters with retention times of 6 and 7.5 min to be 76% 1-diamantane methyl carboxylate, and 24% 4-diamantane methyl carboxylate. Retention times were verified by coinjection with authentic esters prepared by diazomethane reaction of pure 1- and 4-diamantane carboxylic acids.

The Koch-Haaf reaction was repeated as above on 5.0 g (0.027 mole) diamantane and stirred at room temperature for 24 hours. Upon the usual workup, 0.175 g (1.4%) of acid mixture consisting of 89% 1-diamantane-carboxylic acid and 11% 4-diamantane carboxylic was obtained. The composition was determined in the same manner as above.

1-Diamantane Carboxylic Acid (V) from 3-Diamantanol (XI) [Koch-Haaf Reaction].[31,32] A Koch-Haaf reaction carried out on 0.4 g (1.9 moles)

(32) This reaction was carried out by Dr. L. Lan.

3-diamantanol with 20 ml carbon tetrachloride, 10 ml 98% sulfuric acid and 5 ml formic acid in the cold, gave after workup what appeared to be 1-diamantane carboxylic acid by nmr analysis. However, the melting point of the acid was not sharp, ca 160°.

1-Diamantanol (VI). 1-Bromodiamantane (III) (1.0 g, 3.8 mmoles) was refluxed overnight with 100 ml of 10% K_2CO_3 solution, 50 ml of acetone, and 0.5 g of $AgNO_3$. The reaction mixture was extracted with 3 x 100 ml of ether. The collected extracts were washed with water until neutral and dried over Na_2SO_4. The solvent was evaporated and the residue crystallized from acetone to give white crystals, 0.63 g (3.01 mmoles, 81% yield), mp 285-288° (sealed capillary). Recrystallization gave an analytical sample, mp 291-292° (lit. mp 292.5-294°); ir (nujol) 3240 (OH), 1115, 1032, and 940 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.00; H, 9.94.

1-Acetamidodiamantane (VIII) [Ritter Reaction][33,34] 1-Bromodiamantane (III)

(33) Cf. L.I. Krimen and D.J. Cota, "Organic Reactions," Vol. 17, John Wiley and Sons, Inc., New York, New York, 1969, p. 213.

(34) This reaction was carried out by C. Hoogzand.

(2.67 g, 10 mmoles) was dissolved in a mixture of 9 ml of cyclohexane and 12 ml of acetonitrile. Then 5.3 ml of concentrated H_2SO_4 was added. The temperature of the reaction mixture rose slightly (ca 10°) and stirring was continued overnight. After 16 hrs the mixture had become a thick orange suspension. Water and ice were added, stirring was continued for 15 minutes, and the white precipitate filtered, washed with 10% aqueous Na_2CO_3 solution and subsequently with water. After drying, 2.2g of white powder was obtained and recrystallized from acetone. White crystals, 1.9 g (78% yield), mp 167-168°, of 1-acetamidodiamantane (VIII) was obtained; ir (KBr) 3283 (NH), 1646 (amide band I), 1572 and 1549 cm^{-1} (amide bands II).

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.31; H, 9.45; N, 5.71. Found: C, 78.18; H, 9.73; N, 5.40.

1-Aminodiamantane Hydrochloride (IX).[34] 1-Acetamidodiamantane (VIII) (1.3 g, 5.3 mmoles) was refluxed in a solution of 2.2 g NaOH in 30 ml diethyleneglycol for 5 hours. The reaction mixture changed color to yellow and then orange-brown. After the reaction was completed, the mixture was poured onto crushed ice, and extracted three times with diethyl ether, dried over KOH pellets and the solvent evaporated. An oily product (1.79 g) was left, which was taken up in 50 ml of anhydrous diethyl ether. Gaseous HCl was introduced and the precipitated solid was filtered and washed twice with ether; 0.90 g (71%) of 1-aminodiamantane hydrochloride (IX) was obtained. A sample for analysis, mp ca 360°, was recrystallized from ethanol/ether.

Anal. Calcd for $C_{14}H_{22}NCl$: C, 70.12; H, 9.25; N, 5.84; Cl, 14.78. Found: C, 69.49; H, 9.30; N, 6.19; Cl, 14.72.

3-Diamantanone (X). To 2.0 g of diamantane was added 100 ml of 96.6% sulfuric acid; the reaction mixture was then heated for four hours at 75° with vigorous stirring. Stirring was continued at room temperature for one additional hour. The black reaction mixture was poured over ice and steam distilled. The steam distillate was extracted with ether, and the combined ether extracts were washed with water and dried over $MgSO_4$. Evaporation of solvent left 1.4 g (70% yield) of crude diamantanone (X). The product may be further purified by chromatography on alumina. The second fraction, eluted with benzene ether (1:1) contained pure diamantanone, 0.8 g (37%). Recrystallization from petroleum ether gave white crystals, mp 249-250° (lit.[13b] 248-249°); ir (nujol) 1745, 1720, 1295, 1245, 1045 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.50; H, 9.43.

3-Diamantanol (XI). A solution containing 0.55 g (2.7 mmoles) of diamantane in 15 ml of anhydrous ethyl ether was added within 1/2 hour to 20 ml of anhydrous diethyl ether containing 0.093 g (2.4 mmole) lithium aluminum hydride. After refluxing for 1 1/2 hours, and stirring at room temperature for an additional 1/2 hour, the reaction mixture was cooled in an ice bath, and 7 ml of 10% sulfuric acid was added slowly. The reaction mixture was worked up in the usual way[35] and evaporation of solvent left 0.4 g (73% yield) of white solid. Recrystallization from petroleum ether gave white fluffy crystals, mp 256-257°; ir (CCl_4) 3150 (OH), 2950, 1065, cm^{-1}.

(35) Cf. L.F. Fieser and M. Fieser, "Reagents for Organic Syntheses," Vol. 1, John Wiley and Sons, Inc., New York, N.Y. 1967, p. 581.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.14; H, 9.78.

3-Diamantyl Tosylate (XII). Diamantanol (XI) (0.180 g) was stirred with tosyl chloride (0.415 g) in pyridine[36] (4.8 g) for 3 days. After the usual workup procedure,[36] 0.301 g (95.6% yield) of white crystalline product was obtained. Recrystallization from petroleum ether gave white crystals, mp 124.2-124.6°; ir (CS_2) 2895, 2855, 2825, 2775, 2275, 2150, 1185, 1175, 945 cm^{-1}.

Anal. Calcd for $C_{21}H_{26}SO_3$: C, 70.35; H, 7.31; S, 8.94. Found: C, 70.55; H, 7.57; S, 8.66.

3-Bromodiamantane (XIII).[37] A mixture of 0.310 g (1.5 mmoles) 3-diamantanol (XI), and 1.15 g (2.7 mmoles) phosphorus pentabromide in 10 ml of anhydrous ether was heated at 45° with stirring for two hours. The reaction mixture was treated with water; the resulting layers were separated, and the ether layer was dried over $MgSO_4$ and evaporated. The white crystalline residue, 0.405 g (99.5% yield) was recrystallized from petroleum-ether to give pure 3-bromodiamantane, mp 93-94°.

Anal. Calcd for $C_{14}H_{19}Br$: C, 62.92; H, 7.17; Br, 29.91. Found: C, 63.20; H, 7.38; Br, 29.69.

(36) Reference 35, p. 1179.

(37) Reference 35, p. 865.

3-Chlorodiamantane (XIV).[38] Thionyl chloride (0.58 g, 4.9 mmoles, 0.35 ml) in 5 ml of chloroform was added rather rapidly to 200 mg (0.98 mmoles) of 3-diamantanol in 2 ml of chloroform. After refluxing for 4 hours, the reaction mixture was cooled, and the solvent evaporated. The residue was sublimed at 70°/20 mm pressure. White crystals, 105.2 mg (49% yield), mp 153-156°, of crude 3-chlorodiamantane were obtained. The compound was recrystallized from MeOH-H_2O, and upon cooling, white fluffy crystals, mp 157-158° (sealed capillary), were collected.

Anal. Calcd for $C_{14}H_{19}Cl$: C, 75.44; H, 8.62: Found: C, 75.44; H, 8.68.

(38) Reference 35, p. 1160.

3-Methyl-3-diamantanol (XV). A solution of 3-diamantanone (X), 0.5 g (2.5 mmoles) in 25 ml of ethyl ether, was added to 30 ml of an anhydrous ethereal solution containing the Grignard reagent prepared from 2.13 g (15 mmoles) methyl iodide and 0.36 g magnesium. After approximately 1 hour, the excess Grignard reagent was decomposed with saturated ammonium chloride solution and the ether layer separated. The aqueous solution was washed three more times with ether and the combined ether solution dried over $MgSO_4$ and evaporated. A white solid remained, 0.45 g, 82% yield. Recrystallization from petroleum-ether gave white crystals, mp 149-150°; ir (CCl_4) 3600, 2890 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16 Found: C, 82.70; H, 10.21.

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3-Methylenediamantane (XVI). 3-Methyl-3-diamantanol (XV) (0.33 g) was heated with 5 g of 85% H_3PO_4 at 135° for 20 min. The mixture was diluted with water and extracted with petroleum-ether. The combined petroleum ether extracts were washed with H_2O, and dried over $MgSO_4$. Removal of solvent left 0.26 g (86% yield) of waxy white solid which was sublimed at 120°/1 atm and recrystallized from petroleum-ether to give product, mp 125-126°; ir (CCl_4) 3050, 1650, 880 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found: C, 89.85; H, 10.03.

3-Methyldiamantane (XVII). 3-Methylenediamantane (XVI), 0.21 g (1.0 mmoles) was dissolved in 30 ml of anhydrous ether containing 0.2 g PtO_2 catalyst, and hydrogenated with a Parr apparatus at room temperature under 3 atm hydrogen pressure. After workup, 0.180 g (0.9 mmoles) (85% yield) of white crystalline 3-methyldiamantane was obtained. Recrystallization from ethanol yielded white crystals, mp 117-118°.

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 88.82; H, 10.82.

4-Diamantanol (XX). A mixture of 1-(III) and 4-bromodiamantanes (XVIII) (1.0 g, 3.8 mmoles) prepared from bromination of diamantane with 2-butyl-bromide/aluminum bromide and equilibrated overnight at 0°,[1b] was hydrolyzed as described for 1-diamantanol above. After workup, 0.60 g (78% yield) of white crystalline material remained; glc on a 5% DC710, 1.5 m x 3 mm column, 195° indicated two peaks of retention time 4.0 and 4.5 min corresponding to VI (41%) and 4-diamantanol (XX) (59%). Separation of the two alcohols was achieved by chromatography on alumina; 1-diamantanol (VI) elutes first with benzene-ether 1:1 and 4-diamantanol (XX) next. 4-Diamantanol (XX) was recrystallized from acetone to give white crystals, mp 204-206° (lit.[39] 206-208°); ir (nujol) 3300 (OH), 1105, 1040 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.02; H, 10.07.

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4-Diamantane carboxylic acid (XXI). [Koch-Haaf reaction - High Dilution Method][23] A 2000 ml flask was charged with 450 ml of 97% sulfuric acid which was cooled in an ice-salt bath to -5°. Then, 15 ml 90% formic acid was added slowly. The temperature rose to +5°, and the mixture was stirred at this temperature for an additional 15 minutes until foamy. Then 1.0 g (3.7 mmoles) 4-bromodiamantane (XVIII) dissolved in 300 ml of carbon tetrachloride was added rapidly. At the same time, 15 ml of 90% formic acid was added slowly. The temperature rose to +10°, the ice bath was removed after 1 hour and the reaction mixture allowed to come to room temperature and stirred for additional four hours. The yellow mixture was poured onto 900 g of ice slowly, and the CCl_4 layer separated. The aqueous layer was washed several times with carbon tetrachloride. The combined carbon tetrachloride layers (about 800 ml) were treated with 30 ml ammonium hydroxide and the solids which formed were filtered and suspended in about 30 ml of water and acidified with 30 ml of 3N HCl. The solution was then extracted with chloroform, and the chloroform extract washed with saturated sodium chloride and dried over $MgSO_4$. Removal of solvent left a white solid which was recrystallized from benzene to give 450 mg (52% yield) of crystalline 4-diamantane carboxylic acid (XXI), mp 273.5-274.1°. Further recrystallization from benzene gave white crystals, mp 278.5-279.9°; ir (nujol) 3100, 1700, 1300, 1250, 1100, 1050, 950 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.83; H, 8.90.

Tetrahydro-tricyclopentadiene (XXII). Exo-tricyclopentadiene (50 g, 2.25 mole, gift from Union Carbide) dissolved in 140 ml glacial acetic acid with 0.15 g PtO_2 catalyst (or Pd/C), was shaken in a Parr apparatus at 3 atm hydrogen pressure for 24 hrs at room temperature. Workup gave a quantitative

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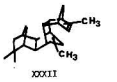
yield of desired product, which was recrystallized from acetone to give white crystals, mp 92°, (lit.[39] mp 100°). Further purification of the material may be achieved by distillation to give 30.5 g (60.7% yield) of tetrahydro-tricyclopentadiene, mp 93.0-95.1°, bp 144-48°/8 mm (lit.[39] bp 287°/766 mm).

(39) K. Alder and G. Stein, Ber., 67, 613 (1934).

Methylcyclopentadiene-6,6-Dimethylnorbornene Adduct (XXIV).[18] Methylcyclopentadiene (83 g, 1.04 moles; prepared by dropping dimethylcyclopentadiene (Aldrich) on mineral oil at 240-270°),[40] and 141 g (1.16 moles) of 5,5-dimethylnorbornene[41] (gift from Union Carbide, bp 51-8° at 50 mm Hg, n_D^{30} 1.4596-63, solid at 25°) were heated with a trace amount of hydroquinone at 180-205° for 17.5 hrs in a glass pressure bottle. The reaction mixture was distilled and 75.6 g (53.6%) of unreacted 5,5-dimethylnorbornene was recovered. The main fraction, 115 g, bp 55-82°/0.5-1 mm, was a mixture with XXIV the major component. The lightly colored pot residue contained 29.0 g of 1:2 adduct XXXII. Redistillation of the main fraction gave about 20 ml of forerun, bp 50-67°/1 mm, and 86 g (41% yield), bp 67-81°/1 mm, of a mixture of three main components of which over 70% was the desired XXIV; ir 3044, 2946, 2862, 1471, 1443, and 803 cm^{-1}; mass spectrum m/e 202, 160, 91, 80, and 66, nmr δ 0.99 (methyl at C_4), 1.71 (methyl at C_9 or C_{10}), 5.37 (s) and 6.0-5.55 (complex-olefinic which disappears on irradiation).

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96 Found: C, 88.98; H, 10.69.



XXXII

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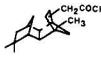
(40) M. Korach, D.R. Nielsen, and W.H. Rideout, Org. Syn., 42, 50 (1962); cf. A. Wilkinson, Org. Syn. Coll., 4, 298, (1963).

(41) N.A. Belikova, L.I. Kovalenko, M.A. Moskaleva, M. Ordubadi, A.F. Plate, E. Kh. Sterin, and R. Jagminas, Zh. Org. Khim., 4, 1363 (1968); Chem. Abstr., 69, 86462m (1968).

Irradiation Product of XXIV (XXV).[18] A solution of 80.7 g of XXIV from the preceeding experiment in 5 liters of acetone (ACS grade) was irradiated with a 450 W Hanovia medium pressure mercury lamp with pyrex filter under agitation by bubbling nitrogen and with magnetic stirring for 1 week. The reaction mixture was distilled directly and two fractions were collected: (1) 57.7 g (bp 56-69°/1 mm); and (2) 112 g (bp 95-126°/1 mm). Fraction I was a mixture containing XXV as the major component (56-69%); ir 2950, 2858, 1448, and 1359 cm^{-1}; mass spectrum m/e 202, 187 (-CH_3), 131, 107, 105, 95, 94, 93, 91, 80; nmr (CCl_4) δ 2.5-0.5 (complex), 0.95 and 0.89 (methyl). Fraction II is thought to be the acetone adduct[42] XXXIII; ir 1718 cm^{-1} (C=O); mass spectrum m/e 260, 202. Nmr (CCl_4) δ 2.01 (acetyl methyl), 1.0-0.6, 0.99 and 0.94 (other methyls).

XXV



XXXIII

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(42) Cf. H.D. Scharf, Tetrahedron, 23, 3057 (1967).

4-Methyldiamantane (XXIII). A. From tetrahydro-tricyclopentadiene (XXII). Sludge catalyst [prepared from 2-butyl bromide-aluminum bromide],[18] 15 ml, was added to 15 g (0.08 mole) of XXII dissolved in 25 ml of carbon disulfide while under a stream of hydrogen bromide gas, and stirred at room temperature for 48 hrs. In cases where starting material was still present, the reaction mixture was treated with more catalyst and heated at 100° without solvent. Following the same workup as described for rearrangement of XXV, an oily material which was a mixture of at least six components was obtained. The volatile materials (mostly alkyl adamantanes) were removed by distillation at 78-108°/10 mm; the residue which crystallized upon standing was recrystallized twice from acetone and gave 0.5 g (3.3% yield) of 4-methyldiamantane (XXIII), mp 91.6-94.0° (sealed tube), identical by nmr and ir to material obtained from XXV.[11]

B. From XXV. Freshly prepared aluminum bromide sludge catalyst,[18] 50 ml, was added in small portions (5-10 ml) over a period of 1 hour to 27 g of C_{15} pentacyclic precursor mixture (XXV) under a stream of hydrogen bromide gas and with vigorous stirring. Vigorous gas evolution, an exothermic process (warming to 50°), and formation of tarry material was observed. After the initial exothermic process subsided, the reaction mixture was

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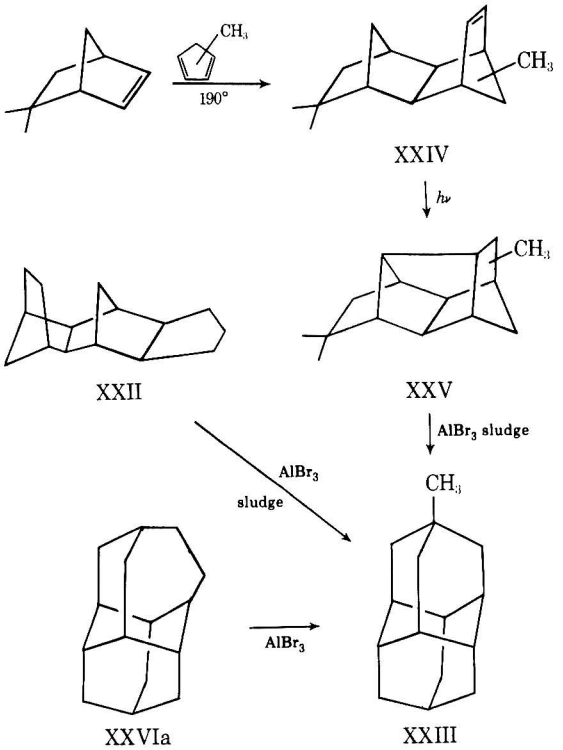
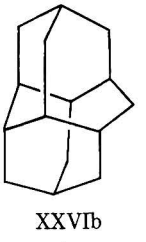
heated at 88-93° for 21 hours and then extracted eight times with 15 ml portions of carbon disulfide. The combined extract was washed with water three times, dried over $CaCl_2$ and evaporated to give 8.41 g (31% yield) of an oil; glc, SE 30 capillary column, 45 m x 0.25 mm, 138°, indicated seven peaks with retention times of 2.6, 3.0, 4.0, 5.5, 5.9, 6.6 and 7.1 minutes corresponding to 1,3,5-trimethyl-7-ethyladamantane, (4%), 1-methyl-3,5-diethyladamantane (14%), unreacted XXV (6%), diamantane (5%), 4-methyldiamantane (55%), 1-methyldiamantane (10%) and 3-methyldiamantane (6%), respectively. 4-Methyldiamantane (XXIII) was separated by preparative gas chromatography on a Carbowax 20M 7.5 m x 9 mm column at 195° and further purified by recrystallization from acetone. Large plate-like crystals, mp 99-100.5°, were obtained; ir (KBr) 2950-2850, 1446, 1375, 1317, and 1047 cm^{-1}; mass spectrum m/e (rel intensity) 202 (M+) (45.7), 187 (loss of CH_3, 100), 91 (1.06).

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.00; H, 11.06.

Chart II

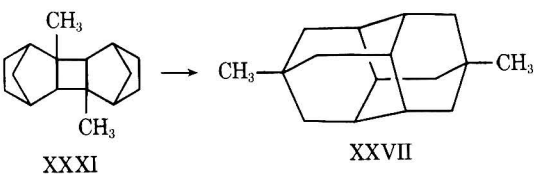




XXVIb

Isomerization of pentacyclic precursor XXV with $AlBr_3$ sludge catalyst at ~90° gave a complex mixture; final equilibrium composition was not achieved. The glc spectrum indicated the components to be diamantane (5%), 4-methyldiamantane (XXIII, 55%), 1-methyldiamantane (VII, 10%), 3-methyldiamantane (XV, 6%), various alkyl adamantanes (18%), and recovered XXV (6%). No evidence for homodiamantane (XXVIa) was found upon glc comparison with an authentic sample. The rearrangement results are summarized in Chart II.

Similar Lewis acid catalyzed rearrangement of 2-methylnorbornene dimer (XXXI) gave 4,9-dimethyldiamantane (XXVII) as the major product isolable only in small quantity.[10]



XXXI XXVII

Table IV
Axial–Equatorial Energy Differences, Liquid

Substituent	ΔH axial → equatorial cyclohexane derivatives, kcal/mol	ΔH medial → apical diamantane derivatives, kcal/mol
Br	0.476[a,b]	0.60[e]
Cl	0.528[a,b]	0.68[e,f]
OH	1.09–1.18[c]	1.1[g]
CH_3	1.73[c]	2.14,[h] 3.0[i]
COOH	1.6–1.7[a,b,d]	*j*
CO^+	*k*	*k*

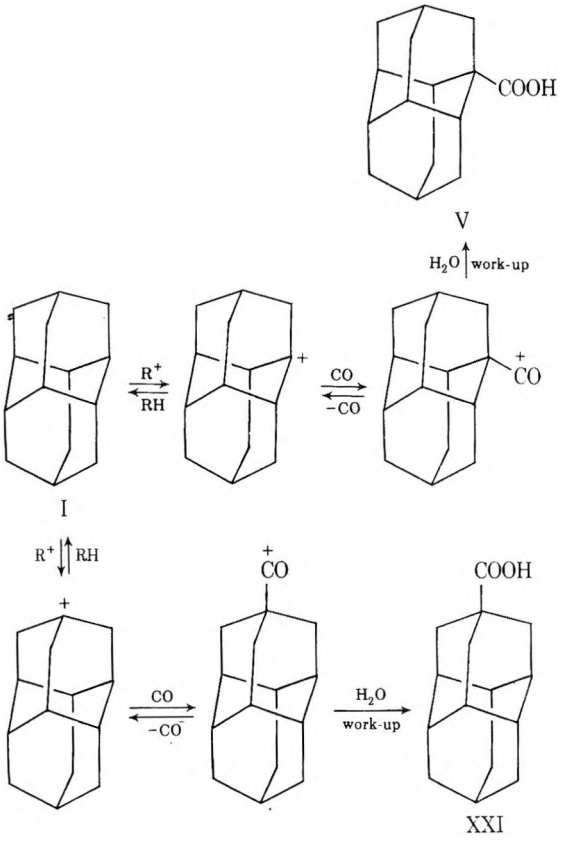
[a] ΔG; ΔS assumed to be zero. [b] F. R. Jensen, C. H. Bushweller, and B. H. Berk, *J. Amer. Chem. Soc.*, **91**, 344 (1969). [c] E. L. Eliel and E. C. Gilbert, *ibid.*, **91**, 5487 (1969). [d] Reference 20. [e] Reference 13 . [f] Reference 14a. [g] Reference 14c. [h] Reference 14b. [i] Calculated by empirical force field calculations, ref 18. [j] *Cf.* data for the adamantanecarboxylic acids: W. V. Steele, A. S. Carson, P. G. Laye, and C. A. Rosser, *J. Chem. Thermodyn.*, **5**, 1257 (1973). [k] A low value is expected; *cf.* ref *b* (ΔG for –CN and –NC = 0.24 and 0.21 kcal/mol, respectively).

Functional substituents can similarly be introduced into the 4 position by rearrangement. We observed that the bromination of diamantane in the presence of traces of $AlBr_3$ at reflux gave a bromide mixture containing 4-bromodiamantane and 4,9-dibromodiamantane; these products were not observed in the absence of the catalyst.[1b] While 4-bromodiamantane could be obtained by separation from the mixture or by selective reduction of 4,9-dibromodiamantane with tri-*n*-butyltin hydride, neither route was very convenient preparatively.[1b]

McKervey demonstrated that not only 1-diamantyl bromide, but also the 1-alcohol and 1-chloride could be equilibrated with acid catalysts to provide mixtures containing roughly comparable amounts of 1 and 4 isomers (owing to a fortuitous balancing of entropy and enthalpy factors; see Table IV).[13b,14] The individual apical and medial halides can be isolated by column chromatography, or else their mixture can be hydrolyzed to the corresponding alcohols VI and XX, which are easier to separate.

Direct bromination of diamantane with *tert*-butyl bromide–aluminum bromide at 0° affords the currently most convenient method of derivatizing the 4 position, since substitution and equilibration are achieved in the same process.[1b] Still, the monobromide product contains ~40% of 1-bromodiamantane (III), which must be separated from the 4-bromide (XVIII).

Since the axial–equatorial ΔG value for the carboxyl group[20] in cyclohexane is about as large as that of a methyl[20,21] (Table IV), we examined the equilibration of the bridgehead diamantanecarboxylic acids (Table V). The use of fuming sulfuric acid, while decreasing the overall yield, did allow equilibration to occur. However, the highest percentage of 4-carboxylic acid in the acid product was only ~25%. It seems likely that the acylium ions, rather than the carboxylic acids, are actually the species undergoing equilibration under those conditions.[22] The low steric demand of the $-CO^+$ group (Table IV) evidently is responsible for the observed result.[22e-j]



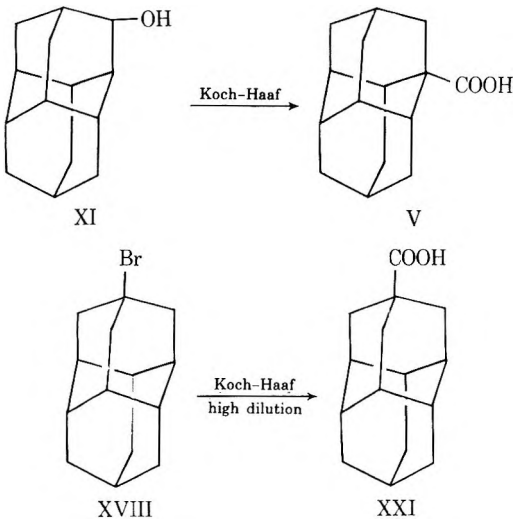
When 3-diamantanol was subjected to ordinary Koch–Haaf conditions, the main product was the 1-carboxylic acid.[9] The 4-carbocylic acid can be prepared from the 4-bromide by the Koch–Haaf procedure, providing that high dilution conditions which preclude intramolecular hydride shifts are employed.[23]

The direct and high-yield conversion of diamantane to 4-diamantyl derivatives relatively free from isomeric contaminants has recently been achieved by reagents with high steric sensitivity.[16]

Table V
Koch–Haaf Reaction on Diamantane[a]

Starting material	Conditions concn	Solvent	Time	% 1-diamantanecarboxylic acid	% 4-diamantanecarboxylic acid	Total yield acid, %[b]
Diamantane	97% H_2SO_4	CCl_4 *t*-BuOH	30 min	Only product by nmr		28
Diamantane	1:1 mixture of 97% H_2SO_4 and fuming H_2SO_4	CCl_4 *t*-BuOH	4 hr	76	24	8.8
Diamantane	1:1 mixture of 97% H_2SO_4 and fuming H_2SO_4	CCl_4 *t*-BuOH	24 hr	88	12	1.4
3-Diamantanol	97% H_2SO_4	CCl_4	30 min	Only product by nmr		
4-Bromodiamantane	97% H_2SO_4 High dilution	CCl_4	3 hr	Small amount	Major	52

[a] *Cf.* ref 9, 22, and 23. [b] Diamantane was recovered in varying amounts in all cases.



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Registry No.—I. 2292-79-7; XXII, 51965-76-5; XXIV, 51966-02-0; XXV, 51966-03-1; XXXII, 51966-04-2; XXXIII, 51966-05-3.

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References and Notes

(1) (a) Part I: T. M. Gund, E. Osawa, V. Z. Williams, Jr., and P. v. R. Schleyer, *J. Org. Chem.*, **38**, 2979 (1974). (b) Part III: T. M. Gund, P. v. R. Schleyer, G. D. Unruh, and G. J. Gleicher, *ibid.*, **38**, 2995 (1974). For preliminary comunications describing aspects of this work, see ref 5, 6c,e,g, 9, 12, and 15 and T. M. Gund and P. v. R. Schleyer, *Tetrahedron Lett.*, 1959 (1973).
(2) (a) Ph.D. Thesis, Princeton University, 1973; (b) on leave from Kyoto Technical University, 1967.
(3) V. Z. Williams, Jr., A.B. Thesis, Princeton University, 1965.
(4) R. C. Fort, Jr., unpublished observations, 1965.
(5) R. C. Fort, Jr., and P. v. R. Schleyer, *Advan. Alicyclic Chem.*, **1**, 283 (1966).
(6) Reviews: (a) H. Stetter, *Angew. Chem.*, **66**, 217 (1954); (b) H. Stetter, *ibid.*, **74**, 361 (1962); (c) R. Fort and P. v. R. Schleyer, *Chem. Rev.*, **64**, 277 (1964); (d) V. V. Sevost'yanova, M. M. Krayushkin, and A. G. Yorchenko, *Russ. Chem. Rev.*, **39**, 817 (1970); (e) R. C. Bingham and P. v. R. Schleyer, *Fortschr. Chem. Forsch.* **18**, 1 (1971); (f) Z. Weidenhoffer and S. Hála, *Sb. Vys. Sk. Chem.-Technol. Praze, Technol. Paliv*, **22**, 5 (1971); (g) E. M. Engler and P. v. R. Schleyer, *MTP (Med. Tech. Publ. Co.) Int. Rev. Sci.: Org. Chem., Ser. One. 1973*, 239 (1973).
(7) For nomenclature, see ref 1a, footnote 36.
(8) H. W. Geluk and J. L. M. A. Schlatmann, *Chem. Commun.*, 426 (1967); *Tetrahedron*, **24**, 5361 (1968).
(9) T. M. Gund, M. Nomura, V. Z. Williams, Jr., P. v. R. Schleyer, and C. Hoogzand, *Tetrahedron Lett.*, 4875 (1970).
(10) S. A. Goscin, A.B. Thesis, Princeton University, 1966.
(11) Statistical substitution by methylene insertion gave a ≈6:12:2 statistical mixture of 1-, 3-, and 4-methyldiamantane characterized by gas chromatographic retention indices: S. Hála, J. Novak, and S. Landa, *Sb. Vys. Sk. Chem.-Technol. Praze, Technol. Paliv*, **19**, 19 (1969). The rearrangement of XXII to 4-methyldiamantane (XXIII) was investigated independently at Prague: S. Landa, private communication.
(12) T. M. Gund, P. v. R. Schleyer, and C. Hoogzand, *Tetrahedron Lett.*, 1583 (1971).
(13) (a) D. Faulkner, R. A. Glendinning, D. E. Johnston, and M. A. McKervey, *Tetrahedron Lett.*, 1671 (1971); (b) T. Courtney, D. E. Johnston, M. A. McKervey, and J. J. Rooney, *J. Chem. Soc., Perkin Trans. 1*, 2691 (1972).
(14) (a) M. A. McKervey, D. E. Johnston, and J. J. Rooney, *Tetrahedron Lett.*, 1547 (1972); (b) R. Hamilton, D. E. Johnston, M. A. McKervey, and J. J. Rooney, *J. Chem. Soc., Chem. Commun.*, 1209 (1972); (c) D. E. Johnston, M. A. McKervey, and J. J. Rooney, *ibid.*, 29 (1972).
(15) I. Tabushi, Y. Aoyama, N. Takahashi, T. M. Gund, and P. v. R. Schleyer, *Tetrahedron Lett.*, 107 (1973).
(16) I. Tabushi, S. Kojo, P. v. R. Schleyer, and T. M. Gund, *Chem. Commun.*, 591 (1974).
(17) P. v. R. Schleyer, J. L. Fry, L. K. M. Lam, and C. J. Lancelot, *J. Amer. Chem. Soc.*, **92**, 2538 (1970).
(18) The force field used is described by E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **95**, 8005 (1973). (Data for 3-methyl and 4-methyldiamantane in this paper should be transposed.)
(19) E. M. Engler, K. R. Blanchard, and P. v. R. Schleyer, *J. Chem. Soc., Chem. Commun.*, 1210 (1972).
(20) R. D. Stolow, *J. Amer. Chem. Soc.*, **81**, 5806 (1959).
(21) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1967.
(22) (a) H. Koch and W. Haaf, *Angew, Chem.*, **70**, 311 (1958); (b) *Justus Liebigs Ann. Chem.*, **618**, 251 (1958); W. Haaf and H. Koch, *ibid.*, **638**, 122 (1960); (c) H. Christol and G. Solladié, *Bull. Soc. Chim., Fr.*, 1307 (1966); (d) W. Haaf, *Angew, Chem.*, **73**, 144 (1961); (e) R. E. Pincock, E. Grigat, and P. D. Bartlett, *J. Amer. Chem. Soc.*, **81**, 6332 (1959); (g) A. Lundeen, *ibid.*, **82**, 3228 (1960); (h) W. Haaf, *Chem. Ber.*, **96**, 3359 (1963); (i) H. Hogeveen and C. F. Roobeck, *Tetrahedron Lett.*, 4941 (1969); (j) H. Hogeveen, *Advan. Phys. Org. Chem.*, **10**, 29 (1973).
(23) D. J. Raber, R. C. Fort, E. Wiskott, C. W. Woodworth, and P. v. R. Schleyer, *Tetrahedron*, **27**, 3 (1971).
(24) (a) R. C. Fort, Jr., and P. v. R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965); (b) R. C. Fort, Jr., and T. R. Lindstrom, *Tetrahedron*, **23**, 3227 (1967).
(25) (a) F. W. V. Deursen and P. K. Korver, *Tetrahedron Lett.*, 3923 (1967); (b) F. W. V. Deursen and A. C. Udding, *Recl. Trav. Chim. Pays-Bas*, **87**, 1243 (1968); (c) F. W. V. Deursen and J. Bakker, *Tetrahedron*, **27**, 4593 (1971).
(26) A. Segre and J. I. Musher, *J. Amer. Chem. Soc.*, **89**, 706 (1967).
(27) A. G. Yurchenko and S. D. Isaev, *Zh. Org. Khim.*, **7**, 2628 (1971).
(28) C. L. Liotta, F. W. Fisher, G. H. Greene, Jr., and B. L. Joyner, *J. Amer. Chem. Soc.*, **94**, 4891 (1972); L. M. Stock, *J. Chem. Educ.*, **49**, 400 (1972), and references cited therein.
(29) R. Hoffmann, *Accounts Chem. Res.*, **4**, 1 (1971).

Diamantane. III[1] Preparation and Solvolysis of Diamantyl Bromides

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The bromination of diamantane (I) may be controlled to give mono-, di-, or polybrominated derivatives. At 25° in neat bromine, 1-bromodiamantane (III) is obtained in high yield. In refluxing bromine, 1,6- and 1,4-dibromodiamantane (V and VI) predominate. 4-Bromodiamantane (IV) is best prepared as a 59:41 equilibrium mixture with III, by reaction of I with *tert*-butyl bromide–aluminum bromide at 0°. Reaction of I in neat bromine with trace amounts of $AlBr_3$ gives 4,9-dibromodiamantane (VII) as the major product together with dibromides V and VI. Addition of larger quantities of Lewis acid produces 1,4,9-tribromodiamantane (VIII) and 1,4,6,9-tetrabromodiamantane (IX). The structure of the various bromides can be determined from their nmr spectra, as a chemical shift additivity relationship holds. The monobromides and dibromides were solvolyzed in 80% aqueous ethanol. The relative rates at 75° follow: III, 1.0; IV, 3.2×10^{-2}; V, 2×10^{-3}; VI, 8×10^{-3}; VII, 7×10^{-4}. 1-Bromodiamantane (III) solvolyzes eight times faster than 1-bromoadamantane (II), and IV three times slower. Although carbocation strain is less favorable for III and IV than for II, III is accelerated by relief of axial leaving group strain and by the greater stability of the 1-cation owing to β-chain branching. No detectable hydroxy bromide intermediates formed during solvolysis of V and VI. The solvolysis rates of dibromides V, VI, and VII were analyzed in terms of two limiting models for the transmission of nonconjugative substituent effects—σ inductive (through bond) and field models. The field effect contribution was evaluated by calculations based on the Tanford modification of the Kirkwood–Westheimer ellipsoidal model. The magnitude of each transmission mode is independent on the geometrical relationship between the two bromines. Through-bond coupling is favored by the parallel arrangements found in V and VII, and contributes factors in the range of $\frac{1}{2}$–$\frac{1}{45}$ to the rate depressions observed.

Diamantane (I), first prepared[3] in 1965, became readily available in 1970.[4,5] Initial chemical studies of this second member of the diamondoid family centered on methods of functionalization,[6-10] substituent interchange,[7-10] relative reactivity of the two bridgehead positions,[6] and equilibration studies of substituent preferences for the three different positions.[11]

Ionic bromination of adamantane proceeds in a relatively uncomplicated manner to give only the bridgehead monosubstituted derivative;[12] no polybrominated compounds are obtained even after prolonged reflux.[12,13] However, by addition of greater amounts of Lewis acid catalysts and increasing the severity of the reaction conditions, adamantane may be selectively di-, tri-, or tetrabrominated at the bridgehead positions.[13-16] The reaction is thought to proceed by an ionic pathway with intermediate formation of bridgehead carbocations.[12,13,17] These adamantane bromides are versatile starting materials for a variety of syntheses leading both to substituted adamantanes and to unusual ring skeletons.[13-15,18-20] It was expected that diamantane also might be selectively brominated. However, owing to its lower symmetry, two types of bridgehead positions, termed "medial"[21] (C-1, -2, -6, -7, -10, -11) and "apical" (C-4, -9) are available for substitution. We have found that the bromination of diamantane may be controlled to give a variety of mono- and polybromides. The solvolysis rates of these compounds provide insight into relative reactivities of the substituent positions.[6]

Results

Preparation of Diamantyl Bromides. Scheme I summarizes the bromination results and Table I provides greater detail. In neat bromine, after only 2 hr at room temperature, diamantane gives 1-bromodiamantane (III) in 80% yield. Refluxing I in bromine for longer periods results in mixture of the 1,6- and 1,4-dibromides (V and VI). Addition of catalytic amounts of aluminum bromide to a diamantane–bromine solution gives mixtures of 1- and 4-bromodiamantane (III and IV) and 1,6- 1,4- and 4,9-dibromodiamantane (V, VI, and VII). The monobromide/dibromide ratio is determined by the amount of catalyst, the temperature, and the reaction time. It is difficult to control the bromine–aluminum bromide reactions to obtain 4-bromodiamantane but the dibromo derivatives VI and VII are best prepared in this manner. The optimum preparation of 1,6-dibromodiamantane (V) utilized refluxing bromine without added $AlBr_3$ catalyst. By successively increasing the amount of aluminum bromide added to the reaction mixture, 1,4,9-tribromodiamantane (VIII) and 1,4,6,9-tetrabromodiamantane (IX) were obtained selectively as major

Scheme I

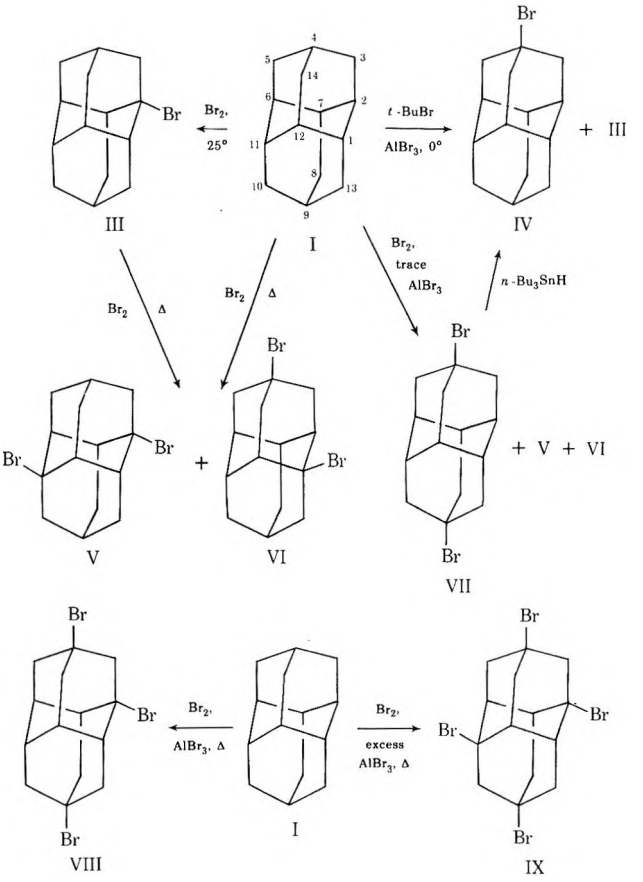


Table I
Bromination of Diamantane. Effect of Temperature, Catalyst, and Brominating Agent on Product Distribution

I, g	Br_2, ml	*t*-BuBr, g	$AlBr_3$, g	Temp, °C	Time, hr	Products, % III	IV	V	VI	VII	VIII	IX	Unidentified products, %
2.0	10			25	2	80[a]		*b*	*b*				
10.0	50			Reflux	16	19[c]		48[c]	7.7[c]				25.3[c]
1.0	5		0.10	0	5		4[c]	6[c]	38[c]	48[c]			*b*
2.0	10		0.08	Reflux	2			40[d]			53[a]		*b*
2.0	10		2.0	Reflux	1	*b*	*b*	*b*	*b*	*b*	*b*	41[a]	*b*
2.0		2.0	0.1	0	24	40[e]	58[e]	*b*	*b*	*b*			

[a] Per cent yield, determined after work-up and purification. [b] Present, but amounts were not determined. [c] Composition of product determined by glc before separation. [d] Mixture was not separated. [e] Composition of product determined by glc analysis of the hydrolyzed mixture.

Table II
Solvolysis Rate Constants of Adamantyl and Diamantyl Bromides in 80% (v/v) Aqueous Ethanol

Compd	Temp, °C	k, sec^{-1} [a]	k_{rel} 75°	ΔH^*, kcal/mol	ΔS^*, eu	Ref	Registry No.
1-Bromoadamantane (II)	25.0	5.1×10^{-7} [b]		22.4	−12.3	*d*	768-90-1
	70.0	8.3×10^{-5} [b]					
	75.0	1.35×10^{-4} [b]					
2-Bromo-2-methyladamantane (XVII)	75.0	7.4×10^{-1}				*e*	27852-61-5
1-Bromo-3-methyladamantane (XVIII)	75.0	9.76×10^{-5}		24.0	−10.1	*f*	702-77-2
1-Bromodiamantane (III)	25.0	3.67×10^{-6} [b]					30545-17-6
	49.8	$7.64 \pm 0.025 \times 10^{-5}$		22.8	−6.8	*g*	
	70.0	6.62×10^{-4} [b]					
	75.0	1.09×10^{-3} [b]	1				
	75.4	$1.13 \pm 0.025 \times 10^{-3}$					
4-Bromodiamantane (IV)	25.0	$1.05 \times 10^{-}$ [b]					30545-30-3
	70.0	2.16×10^{-5} [b]					
	75.0	3.60×10^{-5} [b]	3.2×10^{-2}	23.4	−11.9	*g*	
	75.3	$3.69 \pm 0.13 \times 10^{-2}$					
	100.8	4.29×10^{-4}					
	103.0	4.53×10^{-4}					
1,6-Dibromodiamantane (V)	25.0	1.13×10^{-8} [b]					32401-10-8
	70.0	2.18×10^{-6} [b]					
	75.0	4.51×10^{-6} [b]	2×10^{-3} [i]				
	88.9	$1.97 \pm 0.11 \times 10^{-5}$		24.1	−14.2	*g*	
	100.2	$4.39 \pm 0.025 \times 10^{-5}$					
	123.5	3.14×10^{-4} [c]					
	125.8	5.42×10^{-4}					
1,4-Dibromodiamantane (VI)	25.0	1.91×10^{-8} [b]					32401-09-5
	70.0	5.17×10^{-6} [b]					
	75.0	8.82×10^{-6} [b]	8×10^{-3}	24.7	−11.1	*g*	
	75.2	$8.98 \pm 0.10 \times 10^{-6}$					
	100.4	$1.08 \pm 0.10 \times 10^{-4}$ [h]					
4,9-Dibromodiamantane (VII)	25.0	4.41×10^{-9} [b]					30651-02-6
	70.0	9.11×10^{-7} [b]					
	75.0	1.51×10^{-6} [b]	7×10^{-4}	23.5	−18.1	*g*	
	100.20	$1.60 \pm 0.01 \times 10^{-5}$					
	115.50	$5.78 \pm 0.10 \times 10^{-5}$					
1,3-Dibromoadamantane (X)	25.0	3.20×10^{-10} [b]					876-53-9
	70.0	9.22×10^{-8} [b]					
	75.0	1.58×10^{-7} [b]					
	100.4	$1.98 \pm 0.05 \times 10^{-6}$		25.0	−18.3	*g*	
	125.1	1.70×10^{-5} [c]					
	126.0	1.82×10^{-5} [c]					

[a] Determined conductometrically unless otherwise noted. Average of duplicate determinations. [b] Calculated from other temperatures. [c] Determined titrimetrically. [d] Reference 28c. [e] Rate constant determined by Dr. J. L. Fry. [f] Reference 37. [g] This work. [h] Average of three runs. [i] Statistically corrected.

reaction products. All the bromo and polybromo derivatives are readily separable by column chromatography on alumina.

Alternatively, bromination can be achieved by reaction of diamantane with a slight excess of *tert*-butyl bromide and catalytic amounts of aluminum bromide. After 24 hr at 0°, a mixture of monobromides (40% III, and 58% IV) and trace amounts of dibromides V, VI, and VII were obtained. 4-Bromodiamantane (IV) was also prepared by selective reduction of 4,9-dibromodiamantane (VII) with 1 mol of tri-*n*-butyltin hydride,[6] but this is less convenient than the preparation of the III–IV mixture from *tert*-butyl bromide–aluminum bromide isomerization, and separation of the two components either directly or after conversion to alcohols by column chromatography on alumina.

Solvolysis Reactions. Solvolysis rate constants for III, IV, V, VI, VII, and 1,3-dibromoadamantane (X) were measured in 80% ethanol either conductometrically or titrimetrically (Table II). Product studies to detect the presence of monobromo intermediates were undertaken for dibrom-

ides V and VI. In both cases, solvolyses were carried out in 60% acetone for half of one half-life. The products were analyzed by gas chromatography but no evidence for the build-up of intermediates was found.

Discussion

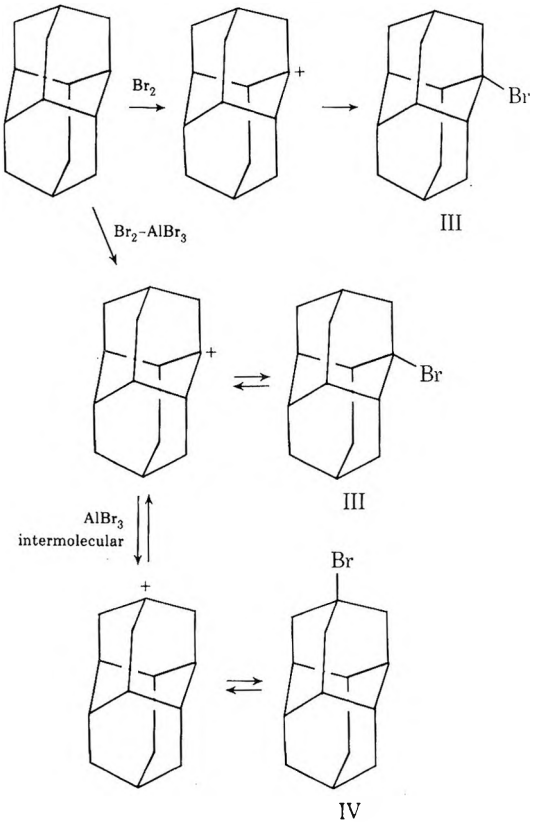
Preparation of Monobromides. Diamantane (I) is more reactive toward bromination than adamantane, since I reacts rapidly at room temperature. Furthermore, the medial bridgehead (C-1) is substituted more readily than the apical (C-4); in the absence of Lewis acid catalyst the 4-monobromo derivative is not formed in significant amounts. This is quite understandable when one considers the 3:1 statistical advantage for medial over apical attack and the inherently greater stability of the medial over the apical cation.

The 24-fold greater solvolysis rate of 1-bromodiamantane (III) over 4-bromodiamantane (IV) at 25° (Table II) provides documentation for the greater stability of the 1 cation. The solvolysis rate of 1-diamantyl bromide (III) also is eight times faster than that of 1-adamantyl bromide (II), consonant with the greater ease of bromination of diamantane than that of adamantane. Furthermore, diamantane in SbF_5–FSO_3H at −78° gives the 1- and not the 4-diamantyl cation, the structure being readily assigned from the proton nmr spectrum.[22]

Apical (4) derivatives are expected to be thermodynamically more stable owing to their equatorial character and more favorable enthalpy; however, medial (1) derivatives, while axial, nonetheless have a statistical advantage (greater entropy owing to lower symmetry, $\Delta\Delta S = R \ln 3/1$), but this effect is of lesser magnitude except when the substituents are small. Apical products would thus tend to result from thermodynamic control by equilibration.[5c]

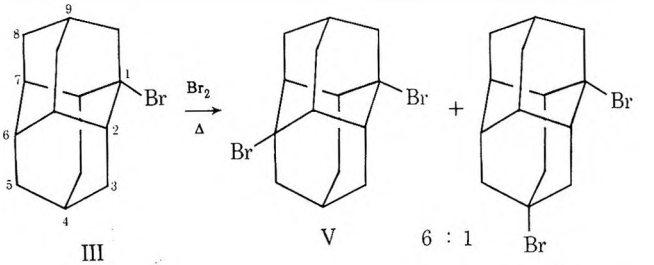
Addition of trace amounts of $AlBr_3$ to the diamantane bromination produces much 4-substituted product by equilibration of the first formed 1-bromodiamantane (III) (Scheme II). Primary formation of 1-bromodiamantane (III) was indicated by following the reaction of I with *tert*-butyl bromide–aluminum bromide at 0° for 24 hr. After 1 hr, III predominated, but at the end, the reaction mixture was richer in IV than III (59:41). This ratio is in agreement with that obtained by McKervey by direct equilibration of III and IV.[5c]

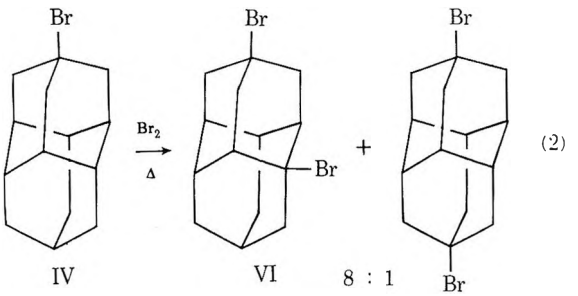
Scheme II



4-Bromodiamantane (point group C_{3v}) has symmetry number 3, which lowers its entropy by $R \ln 3$ or 2.18 cal/deg mol relative to 1-bromodiamantane (point group C_s, symmetry number 1). This would contribute −0.65 kcal/mol ($-T\Delta S$) to the equilibration free energy at 25°.[23] The enthalpy difference between axial and equatorial cyclohexyl halides is rather small (0.28–0.53 kcal/mol)[23] and the entropy term is of comparable importance in the III ⇄ IV equilibration. The entropy term becomes more important at higher temperatures and the formation of the 1 isomer is favored under such conditions.[5c,11,24]

Preparation of Dibromides. Formation of the dibromo derivatives is governed not only by the relative reactivity of the apical and medial positions but also by the position of attachment and the inductive effect of the bromine already present in the precursor monobromide. For 1-bromodiamantane (III) further uncatalyzed bromination occurs at C-4 and C-6 (ratio VI:V 1:6) since both are four carbon atoms away (eq 1). The greater amount of C-6 attack is due to the greater reactivity at the medial position. We expected 4-bromodiamantane (IV) to react preferentially at C-9, since it is the only available bridgehead six carbons removed. In fact, uncatalyzed bromination of IV gave a mixture of 1,4-dibromide (VI) and 4,9-dibromide (VII) in an 8:1 ratio (eq 2) instead of the statistical 3:1. Here the medial position was again preferentially attacked despite its smaller separation from the 4-bromine originally present. This suggests the possibility of the operation of a specific ("through-bond")[25] net effect enhancing the inductive interaction between the 4 and 9 positions (see below).

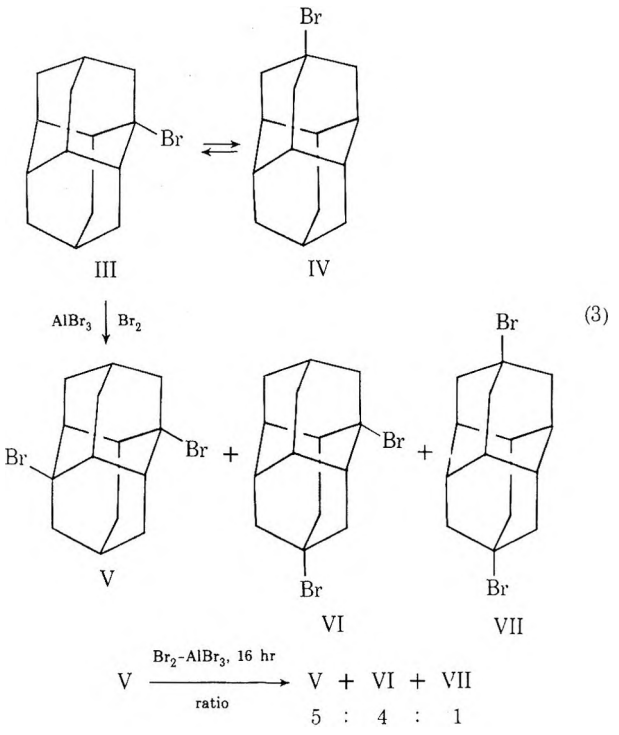




In the presence of aluminum bromide, equilibration of the initially formed monobromides or product dibromides may occur. This is shown most directly by the obtention of VII as one of the products from III (eq 3).

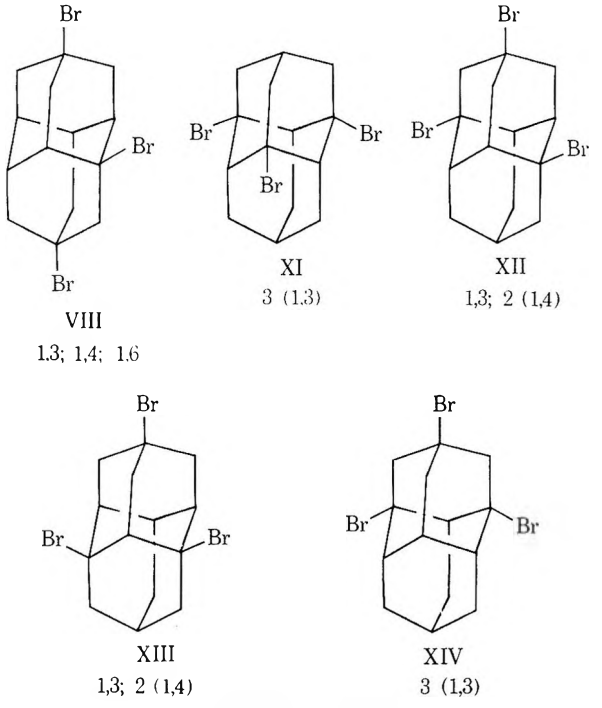
1,6-Dibromodiamantane (V) when treated with traces of aluminum bromide in bromine gives a mixture of V, VI, and VII, but it is not clear that complete equilibration was obtained under the conditions employed.

Preparation of Polybromides. By increasing the severity of the bromination conditions, a tribromide (VIII) and



tetrabromide (IX) were obtained from diamantane (I). Assignment of structures was made by nmr analysis (discussed below) and by synthesis from dibromides.

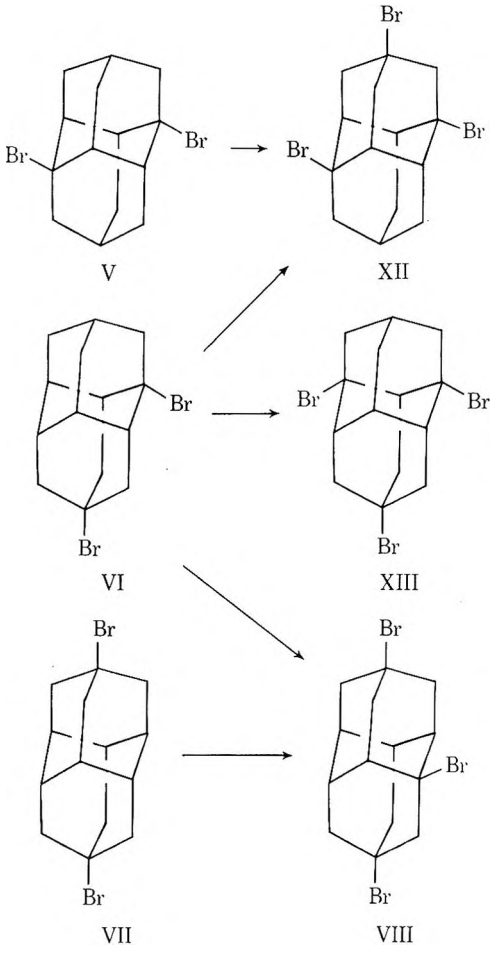
Excluding unlikely vicinal dibromides, five bridgehead tribromides, VIII and XI–XIV, are possible. Tribromides



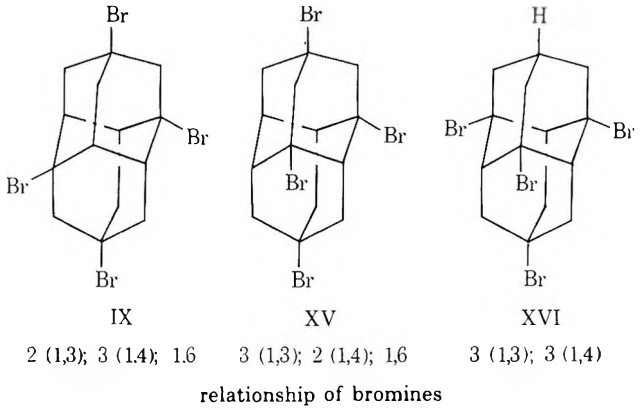
XI and XIV are less likely candidates however, owing to the three 1,3 bromide–bromine relationships. No vicinal or 1,3-type dibromodiamantanes have ever been observed as bromination or even as rearrangement products, suggesting that substitution is strongly inhibited at positions close to bromines already present.

Of the remaining three isomers (VIII, XII, and XIII), VIII seemed most likely since two of the bromines have a 1,6 relationship. Furthermore, the observed nmr spectrum was in closest agreement to that calculated for VIII. Isomer VIII could result directly from bromination of VI and VII; XII can be produced from V and VI but XIII only from VI (Chart I). Bromination of VII in the presence of aluminum bromide gave a product identical by nmr, ir, and melting point with the tribromide VIII isolated by direct polybromination of I (Chart I). Gas chromatographic analysis of the progress of the reaction revealed that equilibration of VII prior to reaction with bromine did not occur. Moreover, bromination of V under similar conditions produced after 16 hr only an equilibrium mixture of V, VI, and VII with only a small amount of tribromide.

Chart I



The tetrabromide isolated by addition of large quantities of aluminum bromide to bromination of I seemed likely to have one of the structures IX, XV, or XVI.



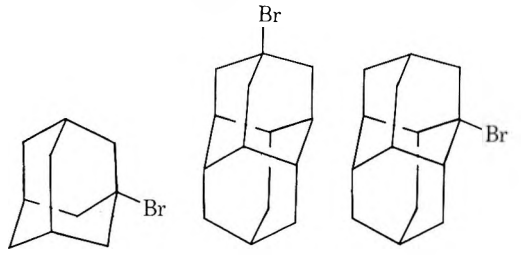
The observed nmr spectrum was in closest agreement to that calculated for IX (see below). Furthermore, IX was

produced by bromination of VII with larger quantities of aluminum bromide. Equilibration of VII prior to reaction with bromine and equilibration of tetrabromide after reaction were excluded by careful glc monitoring of reaction progress.

Solvolysis of Monobromo Derivatives. Since elimination and back-side solvent attack do not occur, diamantane derivatives, like their adamantane analogs,[15,28] undergo mechanistically uncomplicated solvolysis. It might be expected that the apical 4-bromodiamantane (IV) would be about as reactive as 1-bromoadamantane (II) and the medial isomer (III) two to three times faster owing to relief of 1,3-diaxial Br···H interactions destabilizing the starting material.[5c,23,29]

In actual fact, the diamantyl bromides exhibit a 24-fold rate difference between the bridgehead positions, favoring the "medial" isomer. Apical 4-bromodiamantane (IV) solvolyzes three times slower and the medial isomer (III) eight times faster than 1-bromoadamantane (II) (Chart II).

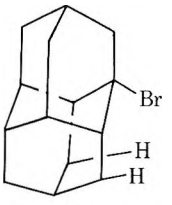
Chart II



	II	IV	III
k_{rel}, 75°, 80% EtOH	1	0.34	8.0

Molecular mechanics calculations[30-32] were carried out to assess the steric contributions to these rate differences (Table V).[33] The method utilizes the hydrocarbon as a model for the ground-state strain, and the free carbocation as a model for strain in the transition state.[33-36] This approach has been applied successfully to other bridgehead systems whose solvolysis rates vary nearly 20 powers of ten; the average deviation is only a factor of 3.[33-36]

From these calculations, the effect of strain on solvolysis was expected to be a small rate deceleration for both 1- and 4-bromodiamantane (*ca.* 0.5 and 0.4) compared to 1-bromoadamantane[33] (Table V). Diamantane is more rigid than adamantane, and resistance toward flattening of the bridgehead cations is greater. Agreement of calculations and experiment for the apical isomer (IV) is excellent, but the higher reactivity of III is not explained.



III

These calculations neglect the greater steric requirement of bromine compared to hydrogen. Winstein[29] has invoked ground-state steric strain relief to explain the three- to fourfold solvolysis rate difference between *cis*- and *trans*-4-*tert*-butylcyclohexane *p*-toluenesulfonate; despite mechanistic differences, these appear to be reasonable models for axial and equatorial substrates. This effect may be neglected for 1-bromoadamantane (II) with 4-bromodiamantane (IV), since in both cases the bromines are equatorial with respect to all composite cyclohexane rings. However, for 1-bromodiamantane (III) the bromine is axial with respect to one cyclohexane ring. Consequently, the diamantane is inaccurate as a model for the ground state. The effect of the diaxial interactions may be estimated from the enthalpy difference between 1- and 4-bromodiamantane, 0.6 kcal/mol[5c,11b] (slightly larger than the axial strain in the more flexible bromocyclohexane, 0.5 kcal/mol).[23]

This ground-state steric effect, not taken into account in the calculations of Table V, should result in a ~2.8-fold rate enhancement for medial bromide (III) if the strain is completely relieved in the transition state. On this basis, III should be 1.4 times more reactive than 1-adamantyl bromide (II), still less than the experimental eightfold effect. We attribute the remaining difference, a factor of 5.7 (8/1.4), to electronic effects (inductive and hyperconjugative) due to differences in chain branching, particularly on two at the β carbons.

The magnitude of this effect is in agreement with that observed experimentally in acyclic compounds. Streitwieser has shown that the 80% ethanolyses of tertiary halides correlate with $\Sigma\sigma^*_{CH_2}$ of the substituents with $\rho^* = -3.29$.[37] Assuming that the difference between III and IV is equivalent to substitution by two ethyl groups ($\Sigma\sigma^*_{CH_2} = 0.230$), a rate enhancement of 5.7 is calculated. Table VI summarizes our rate analysis. That β branching is capable of preferentially stabilizing diamondoid carbocations is shown by the obtention in superacid media of only the 1-diamantyl cation from diamantane[22] or either 1- and 4-bromodiamantane;[38] triamantane (XVII)[39] similarly gives the 2-triamantyl cation. In both cases, the most highly β-branched cation is formed (eq 4-6).

Table V
Calculated Steric Energies of Adamantane and Diamantane and Their Bridgehead Carbocations[a,b]

	Hydrocarbon	Cation	Δ strain	k_{rel} (calcd)[c]	k_{rel} (obsd)
Adamantane	8.91	21.18	12.27	1	1
Diamantane	13.50	26.93 (apical)	13.43	0.4	0.3
		26.51 (medial)	13.01	0.5	8.0

[a] In kilocalories per mole. Reference 33. [b] Calculations with a revised force field. *Cf.* J. L. Fry, E. M. Engler, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **94**, 4628 (1972); and E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *ibid.*, **95**, 8005 (1973), give comparable results. [c] Calculated from the linear free energy relationship $-\log k$ bromide (80% EtOH, 70°) = 0.41 Δ strain − 0.12; *cf.* ref 35.

Table VI
Contributions to Solvolysis of Monobromides

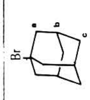
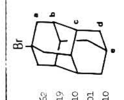
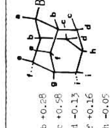
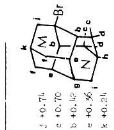
	1-Adamantyl (II)	4-Diamantyl (IV)	1-Diamantyl (III)
Δ strain effect relative rates	1	0.4	0.5
Relief of leaving group strain factor	1	1	2.8[b]
β-Alkyl branching factor	1	1	5.7[c]
Total k_{rel} (calcd)[d]	1	0.4	8.0
Experimental k_{rel} (25°)	1	0.34	8.0

[a] Molecular mechanics calculations (Table V). [b] Corresponds to an enthalpy difference of 0.6 kcal/mol for IV and III.[5c] [c] Based on acyclic models; see ref 37 and text. [d] Product of the three factors.

Nmr Spectra of Diamantyl Bromides. Adamantane derivatives have been shown to obey additivity relationships which make their nmr spectra readily interpretable.[20,27] From 1- and 2-substituted adamantanes, sets of substituent shielding and deshielding parameters have been derived which can be used to accurately predict the spectra of di and polysubstituted adamantanes (Table III). We have found that these shift parameters may also be used to predict diamantane spectra to a first approximation. As illustrated in Table III, the method simply equates the 4-position (apical) of diamantane with an adamantane bridgehead, but the diamantane 1-position (medial) is treated as a bridgehead with respect to one adamantane unit (M) and as a secondary position with respect to the other adamantane moiety, N. Although this approximate procedure is useful for structure elucidation of di- and even polysubstituted diamantanes, better agreement between calculated and observed spectra may be obtained by using a refined set of shift parameters derived from the 220 MHz nmr spectra of 4- and 1-bromodiamantane (Table III). As illustrated in Table IV, superior agreement is found for di and polysubstituted diamantyl bromides using these refined parameters, and isomers are readily differentiated.

In general, 4- (apical) diamantane derivatives give simpler nmr spectra than 1- (medial) isomers and therefore are easier to interpret. 4-Bromodiamantane (IV) behaves like 1-adamantyl bromide, with deshielding effects caused by the bromine substituent generally decreasing with increasing distance. However, the remote C-9 bridgehead hydrogen is deshielded more than the adjacent secondary hydrogens at C-8. The 1-bromodiamantane (III) displays a more complicated spectrum; however, interpretation is facilitated by characteristic AB quartets (at δ 2.38 and 1.56, J ≅ 12 Hz, C_3 and C_{14} methylene H's) due to 1,3-diaxial and 1,3-axial-equatorial interactions between the axial bromine and corresponding protons.

TABLE III. COMPARISON OF ADAMANTANE NMR SHIFT INCREMENTS WITH REFINED DIAMANTANE SHIFT INCREMENTS FOR BROMINE SUBSTITUTION AND SAMPLE CALCULATIONS OF BROMODIAMANTANE SPECTRA USING ADAMANTANE INCREMENTS.

1-Bromoadamantane[a,b]	4-Bromodiamantane[b,c]	2-Bromoadamantane[b,d]	1-Bromodiamantane[b,c]
			
a +0.52	a +0.62	b +0.28	j +0.74
b +0.20	b +0.19	c +0.58	c +0.70
c -0.05	c +0.10	d -0.13	b +0.42
	d +0.01	e,f +0.16	e +0.36
	e +0.10	g,h -0.05	k +0.24
		i +0.02	g +0.09
			h +0.04
			f,i +0.02
			d -0.12

Sample Calculations[e]

4-Bromodiamantane (Found)	1-Bromodiamantane (Found)	
a 1.68+0.52 = 2.20 (2.30)[f](2.30)[g]	j 1.68+0.52 = 2.20 (2.50)[f](2.42)[g]	i 1.68+0.02 = 1.70 (1.58)[f](1.70)[g]
b 1.68+0.20 = 1.88 (1.85)(1.87)	c 1.68+0.52 = 2.26 (2.40) (2.38)	f 1.68-0.05 = 1.63 (1.58) (1.70)
c 1.68-0.05 = 1.63 (1.73)(1.78)	b 1.68+0.28 = 1.96 (2.10) (2.10)	g 1.68-0.05 = 1.63 (1.58) (1.77)
d 1.68+0.00 = 1.68 (1.73)(1.69)	e 1.68+0.20 = 1.88 (1.75) (2.04)	h 1.68-0.05 = 1.63 (1.58) (1.70)
e 1.68+0.00 = 1.68 (1.73)(1.78)	k 1.68+0.20 = 1.88 (1.75) (1.92)	d 1.68-0.13 = 1.55 (1.58) (1.56)

[a] Reference 23a. [b] A positive value represents a downfield shift from the methylene and bridgehead adamantane resonances at δ1.88 and 1.78, and from the single diamantane absorption at δ1.68 for all three kinds of protons. [c] Values derived by calculation from observed 220 MHz nmr spectrum. [d] Reference 24a. [e] 1- and 2-bromoadamantane increments. [f] Observed 60 MHz spectra. [g] Observed 220 MHz spectra taken by E. Hagaman, Indiana University.

Of the three dibromides, diapical VII gave the simplest spectrum consisting of two lines at 60 MHz in a 12:6 downfield:upfield ratio. Dimedial-1,6-dibromide (V) displayed AB quartets at δ 2.50 and 1.69, while medial-apical, 1,4-dibromide (VI) displayed AB patterns further downfield (δ 3.00 and 1.91) than those of V. Of the three most probable tribromide structures, VIII, XII, and XIII, the observed 220 MHz nmr spectrum was most consistent with that calculated for VIII. Tribromide XII would be expected to exhibit two downfield (δ 3.02 and 2.41) and two upfield (δ 2.20 and 1.59) AB patterns, while only one AB pattern (δ 3.00 and 1.91) is actually observed. Similarly tribromide XIII should have three AB protons absorbing at about δ 3.02 and near δ 2.20, while only two protons actually appear at δ 3.02. Also, the proton singlet at δ 1.90 is in better agreement with structure VIII (calc. 2.06-2.21), than XII (calc. 2.11-2.19); XIII is not expected to display such an upfield absorption.

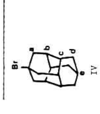
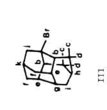
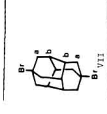
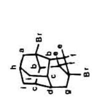
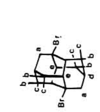
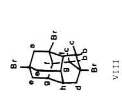
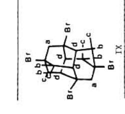
Similar arguments lead to the assignment of structure IX to the tetrabromide.

Experimental Section

Microanalyses were performed at Hoffmann-La Roche, Nutley, N.J., and Robertson Laboratories, Florham Park, N.J. Infrared spectra (Table IX) were taken on a Perkin Elmer 237-B spectrophotometer. Nmr spectra were recorded on Varian A-60-A or HA-100 spectrometers. Chemical shifts are recorded in δ units (parts per million) relative to tetramethylsilane. Gas chromatographic analysis and separations were performed on either a Varian-Aerograph 90-P or a Perkin Elmer 820 flame ionization gas chromatograph unit.

Preparation of Monobromides. A. In Neat Bromine at Room Temperature. Bromine (10 ml) was added dropwise to 2.0 g (0.011 mole) of diamantane with stirring and cooling in an ice bath. After addition was completed, the ice bath was removed and the reaction mixture was stirred about two hours at room temperature. The bromine solution was diluted with CCl_4 or $CHCl_3$ and poured onto ice. Excess bromine was decomposed by addition of solid sodium

TABLE IV. CALCULATED AND OBSERVED 60 AND 220 MHz Nmr SPECTRA OF MONO-, DI-, AND POLYBROMODIAMANTANES

Compd	Proton Type	Area	δ (Calc)[a]	δ (Calc)[b]	δ Found[c] 60 MHz (Type)	Area	Appearance	δ Found[c,d] 220 MHz (Type)	Area	Appearance
 IV	a	6	2.20		2.30 (a)	6	s	2.30 (a)	6	d
	b	3	1.88		1.85 (b)	13		1.87 (b)	3	s
	c,e	3,1	1.68		1.73			1.78 (c,e)	4	s
	d	6	1.63					1.69 (d)	6	d
 III	j	2	2.20		2.50	2		2.42 (j)	2	d
	c	2	2.26		2.40	2	AB J ≅ 12	2.38 (c)	2	AB, J ≅ 12 Hz
	b	2	1.96		2.10	15		2.10 (b)	2	s
	e,k	3	1.88		1.75			2.04 (e)	2	s
	i	2	1.66		1.58		AB J ≅ 12 Hz	1.92 (k)	1	s
								1.77 (g)		
	g,h	6	1.63					1.72 (h)	1	s
	d	2	1.55					1.70 (f,i)	6	s
								1.56 (d)	2	AB, J ≅ 12 Hz
 VII	a	12	2.20	2.30	2.30	12	s			
	b	6	1.83	1.87	1.99	6	s			
 VI	e	2	2.78	3.00	3.03	2	d	3.00 (e)	2	AB J ≅ 12
	a	2	2.20	2.44	2.43	2	d	2.41 (a)	2	d J ≅ 5
	g	2	2.18	2.33	2.25	10	m	2.30 (g)	2	m
	b	2	2.16	2.29	2.05			2.24 (b,h)	3	s
	f	2	2.07	2.18	1.79	4	m	2.14 (c,d)	3	m
	c	2	1.88	2.14			d	1.91 (f)	2	AB J ≅ 12
	h	1		2.02						
	d	1	1.83	1.96				1.73 (i)	4	d J ≅ 5
	i	4	1.63	1.71						
 V	c	4	2.21	2.44	2.62	4	AB J ≅ 12Hz	2.50 (c)	4	AB J ≅ 12
	a	4	2.20	2.40	2.42	4	d	2.48 (a)	4	d
	e	4	2.12	2.46	2.28	4	br	2.33 (e)	4	s
	d	2	1.83	1.96	1.78	2	br	1.94 (d)	2	s
	b	4	1.50	1.58	1.58	4	AB J ≅ 12Hz	1.69 (b)	4	AB J ≅ 12
 VIII	c	2	2.78	3.00	3.0	2	AB J ≅ 12Hz	3.03 (c)	2	AB J ≅ 12
	a	2	2.72	3.05	2.92	2	s	2.92 (a)	2	s
	f	2	2.11	2.39				2.30 (d,e)	6	s
	d	2	2.20	2.33	2.28	13				
	g	2	2.07	2.33	2.25			2.18 (f,g)	4	s
	e	4	2.15	2.33	2.15		AB J ≅ 12			
	b	2	2.07	2.14				2.14 (b)	2	AB J ≅ 12
	h	1	1.78	2.06				1.90 (h)	1	s
 IX	c	4	2.73	3.03	3.10	4	AB J ≅ 12Hz			
	a	4	2.72	3.07	2.90	4	s			
	d	4	2.31	2.75	2.25	4	s			
	b	4	2.02	2.21	2.10	4	AB J ≅ 12Hz			

[a] Calculated using adamantane increments, see Table III. [b] Calculated using refined diamantane values, see Table III. [c] In $CDCl_3$. [d] Taken by E. Hagaman, Indiana University.

TABLE IX

MP, IR, AND ANALYTICAL DATA OF DIAMANTYL BROMIDES

Compound	mp, °C	IR Bands, cm^{-1}	Calculated % C	H	Br	Found % C	H	Br
III	222 - 224	1340, 1280, 1070, 1050, 970, 880, 800, 740, 710	62.92	7.17		62.62	7.25	
IV	127 - 128.2	1325, 1260, 1060, 980, 825, 762	62.92	7.17	29.91	63.16	7.47	30.07
V	272 - 273	1335, 1295, 1280, 1218, 1170, 1110, 1068, 980, 940, 810, 792 690	48.58	5.24	46.18	48.59	5.31	46.26
VI	107.4 - 109.1	1340, 1320, 1280, 1250, 1225, 1090, 1080, 1040, 980, 955 880, 815, 795, 715, 700	48.58	5.24	46.18	48.65	5.50	46.45
VII	324 - 326	1330, 1320, 1260, 1240, 1015, 980, 825, 712	48.58	5.24		48.21	5.37	
VIII	193.2 - 194.8	1332, 1302, 1291, 1265, 1250, 1221, 1118, 1080, 1055, 995, 972, 960, 895, 825, 725	39.50	4.04	56.41	39.76	4.01	56.32
IX	354 - 356	1330, 1290, 1265, 1120, 1050, 1000, 960, 830, 808, 728	33.35	3.17	63.46	33.58	3.22	63.69

bisulfite in small portions and stirring until the bromine color disappeared and the solution turned light yellow or colorless. The carbon tetrachloride (or chloroform) solution was then washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The semi-solid which was obtained was sublimed and recrystallized from pentane; 2.4 g (80%) of white crystalline 1-bromodiamantane (III), mp 217.5-220°, were obtained. Further recrystallization from hexane gave white crystals, mp 222-224°. See Table IX for further data.

B. With t-Butyl Bromide-Aluminum Bromide at 0°C. Freshly sublimed aluminum bromide (0.1 g) was added to a mixture of 2.0 g (0.011 mole) diamantane and 2.0 g (0.015 mole) t-butyl bromide in 10 ml of anhydrous cyclohexane at 0°. After stirring overnight at the same temperature, the reaction mixture was added to ice and extracted with 3 x 100 ml of hexane. The hexane layers were combined, washed with water and dried over $MgSO_4$. Evaporation of solvent left 3.0 g of semi-solid material which was 98% a mixture of monobromodiamantanes III and IV. The rest was comprised of dibromides V, VI and VII. A sample of this material (1.0 g) was hydrolyzed by refluxing in 100 ml of a solution of 10% K_2CO_3, 50 ml acetone, and 0.5 g $AgNO_3$. Gas chromatographic analysis on a 1.5 m X 3 mm 5% DC 710 column, at 190° indicated a mixture of hydrolysis products to be 41% 1-hydroxy and 59% 4-hydroxy diamantane (retention times 3.5 and 4.25 min respectively). 1- and 4-bromodiamantanes III and IV are separable by column chromatography on Woelm neutral alumina or silica gel. The first to elute with hexane was III; IV followed. Recrystallization of IV from hexane yielded white crystals, mp 127-128.2° (lit.[5c] 127-129°).

Preparation of Dibromides. A. In Neat Bromine at Reflux. Diamantane (10.0 g , 0.054 mole) was refluxed in 50 ml of bromine overnight. Workup as in A (above) gave 19.0 g of semi-solid crude product which was shown by gas chromatographic analysis on a (5% carbowax 20 M, 3 m x 3 mm column at 220°) to be a mixture of III (15%), V (48%), VI (9%), and other non-bromide products 28%. Pure white crystalline 1,6-dibromodiamantane (V), mp 272-273°, was obtained by recrystallization from chloroform.

B. In Neat Bromine With Added Aluminum Bromide. Ratio of Diamantane: Aluminum Bromide (10:1) at 0°C. To 1.0 g (0.0054 mole) diamantane mixed with 0.05 g of aluminum bromide was added with ice-cooling 5 ml of bromine slowly. After 3 hours, another 0.05 g of aluminum bromide was added and the reaction mixture left at 0° for an additional two hours. The excess bromine was decomposed and the reaction worked up in the usual manner. A white solid, 2.0 g was obtained. Gas chromatographic analysis (5% DC 710, 3 m x 3 mm, 200°, He = 1.3 atm), indicated a mixture of VII (48%), VI (38%), V (6%) monobromide III and IV (4%) and other unidentified materials (4%). A small amount of petroelum ether was added, and the insoluble 4,9 dibromodiamantane (VII), 0.6 g was collected. The soluble portion was chromatographed on silica gel and eluted with hexane. The order of elution was as follows: monobromides III and IV, followed by dibromides V, VI and VII. Analytically pure white crystalline VI, mp 107.4-109.1°, was obtained by recrystallization of the chromatographed material from hexane. Pure VII, also white and crystalline, mp 324-326°, was obtained by recrystallization from hexane: benzene (1:1).

Preparation of 1,4,9-tribromodiamantane (VIII). To a mixture of 10 ml bromine and 80 mg aluminum bromide was added in small portions 2.0 g (0.011 mole) diamantane. After stirring at reflux for two hours, the usual workup procedure was employed. Evaporation of solvent ($CHCl_3$) left 3.7 g of solid. Addition of a small amount of pentane left 2.5 g (53%) of insoluble material characterized as 1,4,9-tribromodiamantane (VIII). The soluble fraction contained a mixture of mono and dibromodiamantanes which were not separated. The crude, insoluble VIII was chromatographed on 200 g of alumina and eluted first with hexane and then benzene. Pure VIII (2.0 g) was obtained by evaporating the benzene fractions. Recrystallization from benzene-acetone (1:1) gave white crystals, mp 194-195.5°.

Preparation of 1,4,6,9-tetrabromodiamantane (IX). Diamantane (2.0 g, 0.011 mole) was added in small portions to 10 ml of bromine containing 2.0 g

aluminum bromide. An exothermic reaction ensued. Refluxing was continued for an additional hour after which the usual workup procedure was followed. The crude solid thus obtained was washed with pentane leaving 2.25 g (41%) of crude 1,4,6,9-tetrabromodiamantane (IX). The soluble fraction, a mixture of mono- di- and tribromides, was not separated. IX was recrystallized from chloroform; white crystals, mp 354–356° were obtained. IX may also be prepared by adding about 20 mg of aluminum bromide to 100 mg of 4,9-dibromodiamantane (VII) in 1 ml of refluxing neat bromine.

Tri-n-butyltin Hydride Reduction of 4,9-Dibromodiamantane (VII). To 2.2 g of VII dissolved in 25 ml of benzene was added through a dropping funnel 2.5 g of tri-n-butyltin hydride[6] in 10 ml of benzene. The reaction mixture was refluxed for 25 hrs. Evaporation of the solvent left an oily residue. Upon addition of a small amount of hexane, 600 mg of unreacted 4,9-dibromodiamantane (VII) precipitated. The filtrate, a mixture of diamantane, 4-bromodiamantane (IV), 4,9-dibromodiamantane (VII) and tri-n-butyltin bromide, was separated by preparative thin layer chromatography. Three bands were observed by ultraviolet light upon elution with hexane. The first band contained diamantane and tri-n-butyltin bromide, the second was extracted with hexane and gave 565 mg of IV, and the third fraction contained VII.

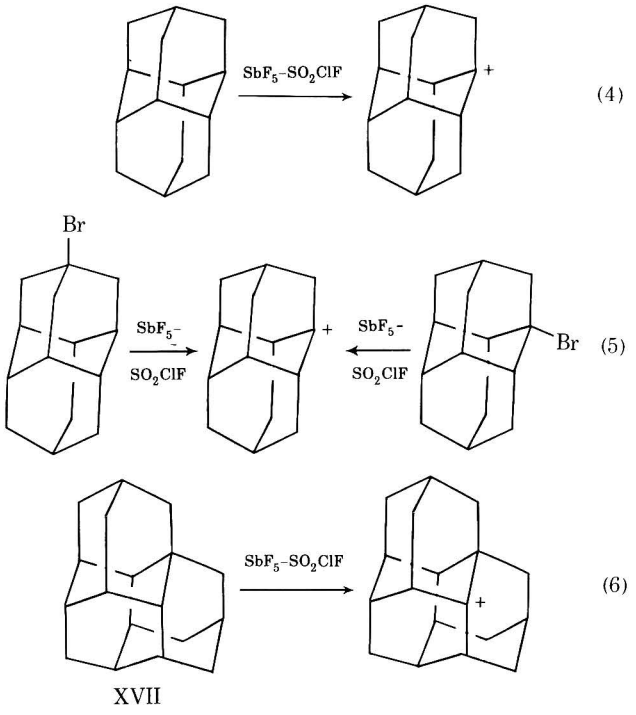
Solvolysis Reactions. A. Kinetic Measurements. Rate measurements were performed in 80% aqueous ethanol (by volume). The ethanol was purified by standard procedures. Conductimetric rates were followed using either a recording conductivity bridge or a Wayne-Kerr Universal Conductance bridge B-641. In each case, the sample was made about 10^{-3} M in a conductance cell having bright platinum electrodes and a capacity of about 20 ml. Titrimetric rates were determined using a Beckman automatic titrator. At least two runs per sample were made, and good first-order rate plots were obtained in all cases.

B. Product Studies from Solvolysis of 1,6-Dibromodiamantane (V). Dibromide V (2.0 g) was partially dissolved in 125 ml of 60% aqueous acetone and heated in a sealed ampoule at 102.31° for 76.3 minutes (one half life at 102.60° is 81.3 minutes). The reaction was quenched and diluted with water and extracted with chloroform and ether. Gas chromatographic analysis of the product mixture on a glass column (5% DC710, 3 m × 6 mm) did not indicate build up of intermediate 1-hydroxy-6-bromodiamantane. Authentic 1,6-dihydroxy compound was prepared by solvolysis to 99% reaction and had retention time of 11 min. Unreacted dibromide had retention time of 30 min. The intermediate, if present, would be expected to show a peak between 11 and 30 minutes.

C. Product Studies from Solvolysis of 1,4-Dibromodiamantane (VI). As above, 2.0 g of VI was partially dissolved in 125 ml of 60% aqueous acetone and heated at 102.6° (solution was complete at this temperature) for 10.45 min (one half life at 100.8° is 18.6 minutes). Following the same workup procedures as above, glc analysis on a 5% carbowax 4 m × 3 mm column did not reveal any significant build up of intermediate. Authentic 1,4-dihydroxydiamantane (retention time 7 min) was prepared by solvolysis to 99% reaction, for product identification. Unreacted 1,4-dibromide had retention time 19.5 min. The intermediate (1-hydroxy-4-bromodiamantane) would be expected to have a retention time between the two. A very small peak (< 1% of retention time 12 min) was observed, but not isolated.

Kirkwood-Westheimer Calculations. The method used has been described in general.[49] Both sets of calculations used point charge models for the cationic centers and the leaving groups were ignored. In the first set, a diamantane structure with tetrahedral angles, C-C bond lengths of 1.535 Å and normal aliphatic C-H and C-Br bond lengths were employed. The second set assumed a flattened carbonation site; distances were reduced accordingly. Standard bond or group moments were employed.[50]

(49) C.P. Smyth, "Dielectric Behavior and Structure," McGraw-Hill Book Co., Inc., New York, N.Y., 1955 p. 4 1.



(4) (5) (6)

XVII

Solvolysis of Dibromides. Rate-Determining Step. Solvolyses of compounds containing two leaving groups can well be expected to be complicated. Nevertheless, all of the diamantane dibromides solvolyzed exhibited apparent first-order behavior over at least 2.5 half-lives. Product analyses after partial solvolysis (0.5 half-life) of V and VI did not reveal significant build-up of intermediates; very small glc peaks (<1%) believed to be due to hydroxybromodiamantanes were observed, but isolation attempts failed.

A large build-up of hydroxyl bromide intermediate is not to be expected during solvolysis of the symmetrical dibromides V and VII. Replacing one bromine ($\sigma^*_{CH_2Br}$ = 1.0)[40–42] by a less electron-withdrawing hydroxyl group ($\sigma^*_{CH_2OH}$ = 0.555)[40–42] should result in a hydroxy bromide more reactive than the original dibromide, despite the statistical advantage of the latter. Analysis of such sequential processes[43] show that if loss of the first bromine (k_1) is ten times slower than loss of the second (k_2), then the maximum build-up of intermediate should only be 8%. The kinetics are complex, but the observed rate approximates k_1. If $k_2 > 10k_1$, then the concentration of intermediate would be undetectable by the methods employed.

To assess the rate enhancement to be expected from replacement of one bromine by a hydroxy substituent, we applied a rough two-point (H and Br) Taft–Hammett treatment[44] to experimental data of VII, V, and X, and interpolated a relative rate for the hydroxy bromo intermediate (Table VII). For a check, we also supplied a Taft–Hammett treatment to published data of some 1,3-disubstituted adamantanes[37,45] and interpolated a relative rate for the hydroxy substituent (Table VII); satisfactory agreement was obtained.

Table VII

Relative Rates of Hydroxy Bromo Compounds Extrapolated from Graph of Log k_R/k_H vs. Taft $\sigma^*_{CH_2}$ Constants

Positions of substitution	Dibromide	Bromo alcohol	Temp, °C	Ref
4,9-Diamantane (VII)	1	5.6	70	*a*
1,6-Diamantane (V)	1	17.4	70	*a*
1,3-Adamantane (X)	1	28.6	70	*a*
	1	36	75	*b*
	1	51	100	*c*

[a] This work; two points used, H and Br; OH derived from graphical interpolation. [b] Extrapolated from data of P. v. R. Schleyer and C. W. Woodworth, *J. Amer. Chem. Soc.*, **90,** 6528 (1968); $\rho^*_{CH_2}$ = −2.70 from plot of log k_R/k_H vs. $\sigma^*_{CH_2}$. [c] Data were taken from ref 45.

The hydroxy substituent retards the rate less than bromine. The roughly estimated 5.6 rate acceleration for 9-OH relative to 9-Br and VII indicates that ~14% maximum build-up of intermediate should have occurred and the measured rate constant should be complicated by contributions from k_2. In V, the calculated rate acceleration for OH is >10 (17.4) and therefore build-up of intermediate is expected to be negligible and k_1 should be the rate-determining step. Solvolysis of VI is the most complicated, since the bromines are at two different types of bridgeheads, which differ 24-fold in reactivity. The medial bromine should solvolyze first, to yield a 1-hydroxy-4-bromodiamantane. A two-point Taft–Hammett treatment here is not possible, and is difficult to assess the exact acceleration for an OH. Although VI is like V in that the two polar substituents are separated by four carbons, the orientations are different. We did not experimentally observe an intermediate from VI, suggesting that the first step (k_1) is rate determining.

Application to Polar Effects Models. Marked rate decelerations with respect to the monobromides were observed for all four dibromides with the effect generally falling off with the distance between the substituents (Table VIII). The decrease is caused by the diminishing electron-withdrawing polar effect of the second bromine.

Two propagation mechanisms for the polar effect are believed to operate. *Through-bond induction* is dependent on the number and orientations of paths between the substituent and reaction site.[25,46] Alternatively, in the *through-space field effect model,*[46] the polar effect is

Table VIII
Calculated and Experimental Solvolysis Rates of Diamantane Dibromides Relative to Diamantane Monobromides in 80% Ethanol (by Volume) at 70°

Compd	Calcd[a] (normal model)	Calcd[b] (flattened model)	Calcd rate deceleration range—normal and flattened models	Obsd
IV	1.0	1.0	1.0	1.0
VII	2.85×10^{-1}	7.46×10^{-2}	1/4–13	2.0×10^{-2}[c] (1/50)
VI		1.66×10^{-2}[d]	1/60	
III	1.0	1.0	1.0	1.0
V	7.23×10^{-2}	2.26×10^{-3}	1/14–442	1.6×10^{-3}[c] (1/625)
VI	1.03×10^{-2}[f]	1.76×10^{-3}[f]	1/98–562	5.2×10^{-3}[e] (1/193)

[a] Kirkwood–Westheimer model with tetrahedral carbons. [b] Kirkwood–Westheimer model with distance between center of cavity and reaction site decreased by flattening to the extent of an adamantane bridgehead carbocation. [c] Statistically corrected by dividing original value by 2. [d] For solvolysis of apical bromine [e] Statistically uncorrected. [f] For solvolysis of medial bromine.

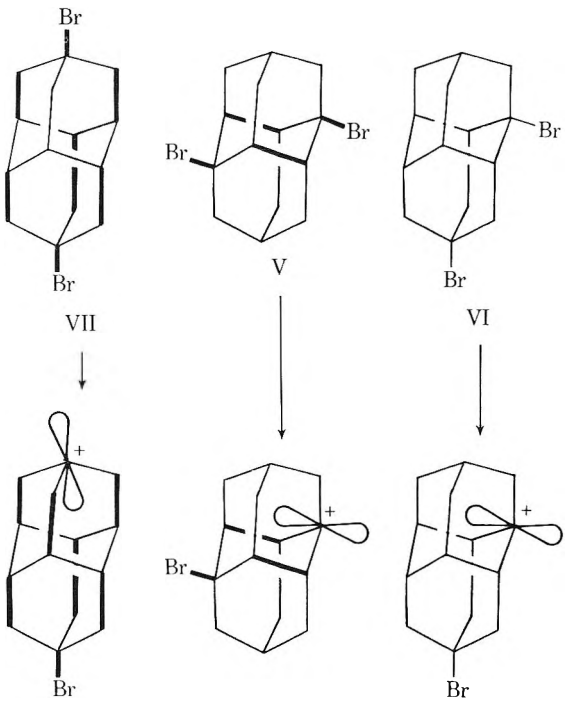
transmitted according to the classical laws of electrostatics, the magnitude being dependent on distance, the angular relationship between the reaction site and substituent, and the nature of the medium between and around them. Most studies of propagation mechanisms have dealt with substituent effects on pK_a's, *e.g.*, of carboxylic acids in rigid systems.[46] Carbonium ion processes would appear to provide even better tests, since charge is created directly upon the molecular framework.[46b]

The rigid diamantyl bromides are ideally constituted for investigation of the two polar mechanisms. Calculations based on the Tanford modification[47] of the Kirkwood–Westheimer elipsoidal cavity model[48] were employed to evaluate the contribution of the field effect to the dibromide rate depressions (Table VIII).[49] Two sets of calculations were performed, both employing the point-charge approximation for the carbocation (the leaving group was ignored). The first set used ground-state geometries but in the second the distance between the reaction site and center of the diamantane molecule was shortened to simulate the flattening expected in such bridgehead cation systems. The calculations predict rate decelerations of 4 (ground-state geometry) to 13 (flattened model) for VII compared to IV, 14–442 for V compared to III, and 98–562 for VI compared to III. These calculations suggest that the rate depressions due to a field effect should be small for VII, and comparable for V and VI. Solvolysis of VI exhibits a 193-fold rate depression relative to III, a magnitude bracketed by the two field model calculations. This is to be expected, since the unsymmetrical dibromide VI does not possess the favorable parallel alignment of bonds and orbitals necessary for optimum operations of the through-bond effect[25] (Chart III).

In contrast, the observed 50-fold rate depression for VII is appreciably larger than that calculated even with the flattened model. We attribute the discrepancy (3–13) to the operation of the through-bond inductive effect.[46] Although the interaction appears to be remarkably large for such a long distance, multiple pathways are available which possess the favorable parallel alignment of the "vacant" cation orbital with the C–C bonds (darkened in Chart III) and the bromine substituent.[25] The inductive model also seems able to account for the 625-fold rate depression of V compared to III which exceeds by 1.4–45 times that calculated by the field effect model. V also possesses a favorable alignment of the "vacant" carbocation orbital with the C–C and C–Br bonds (Chart III).

In summary, it appears that transmission of substituent effects in these diamantyl dibromides may occur by both the through-bond and through-space mechanisms. This is evident in the solvolysis of dibromides V and VII, both of

Chart III



which display rate depressions much greater than that calculated for a direct through-space interaction. The necessary criterion for a strong σ-inductive interaction appears to be a parallel arrangement of orbitals. Effects of other substituents are currently being studied and will be reported later.

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References and Notes

(1) For papers pertinent to this series see ref 3, 4, 5a, 6, 7, and 8 and (a) T. M. Gund and P. v. R. Schleyer, *Tetrahedron Lett.*, 1959 (1973); (b) T. M. Gund, P. v. R. Schleyer, P. H. Gund, and W. T. Wipke, *J. Amer. Chem. Soc.*, in press.
(2) (a) Ph.D. Thesis, Princeton University, 1973; (b) Princeton University; (c) Oregon State University.
(3) C. Cupas, P. v. R. Schleyer, and D. J. Trecker, *J. Amer. Chem. Soc.*, 87, 917 (1965).
(4) T. M. Gund, V. Z. Williams, Jr., E. Osawa, and P. v. R. Schleyer, *Tetrahedron Lett.*, 3877 (1970).
(5) (a) For a full account of the preparative stages see T. M. Gund, E. Osawa, V. Z. Williams, Jr., and P. v. R. Schleyer, *J. Org. Chem.*, **39,** 2979 (1974); (b) T. M. Gund, W. Thielecke, and P. v. R. Schleyer, *Org. Syn.*, **53,** 30 (1973); (c) T. Courtney, D. E. Johnston, M. A. McKervey, and J. J. Rooney, *J. Chem. Soc., Perkin Trans. 1,* 2691 (1972).
(6) T. M. Gund, P. v. R. Schleyer, and C. Hoogzand, *Tetrahedron Lett.*, 1583 (1971).
(7) T. M. Gund, M. Nomura, V. Z. Williams, Jr., P. v. R. Schleyer, and G. Hoogzand, *Tetrahedron Lett.*, 4875 (1970).
(8) I. Tabushi, Y. Aoyama, N. Takahashi, T. M. Gund, and P. v. R. Schleyer, *Tetrahedron Lett.*, 107 (1973).
(9) D. Faulkner, R. A. Glendinning, D. E. Johnston, and M. A. McKervey, *Tetrahedron Lett.*, 1671 (1971).
(10) T. M. Gund, M. Nomura, and P. v. R. Schleyer, *J. Org. Chem.*, **39,** 2987 (1974).
(11) (a) M. A. McKervey, D. E. Johnston, and J. J. Rooney, *Tetrahedron Lett.*, 1547 (1972); (b) C. R. Hamilton, D. E. Johnston, M. A. McKervey, and J. J. Rooney, *J. Chem. Soc., Chem. Commun.*, 1209 (1972); (c) D. E. Johnston, M. A. McKervey, and J. J. Rooney, *ibid.*, 29 (1972).
(12) S. Landa, S. Kriebel, and E. Knobloch, *Chem. Listy,* **48,** 61 (1954); S. Landa and S. Hála, *Collect. Czech. Chem. Commun.*, **24,** 93 (1959).
(13) H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.* **92,** 1629 (1959); H. Stetter and C. Wulff, *ibid.*, **93,** 1366 (1960).
(14) H. Stetter, J. Mayer, M. Schwarz, and K. Wulff, *Chem. Ber.*, **93,** 226 (1960); H. Koch and W. Haaf, *Angew. Chem.*, **72,** 628 (1960); W. Haaf, *ibid.*, **73,** 144 (1961).
(15) Reviews: (a) R. C. Fort, Jr., and P. v. R. Schleyer, *Chem. Rev.*, **64,** 277 (1964); (b) R. C. Bingham and P. v. R. Schleyer, *Fortschr. Chem. Forsch.*, **18,** 1 (1971); (c) V. V. Sevost'yanova, M. M. Krayushkin, and A. G. Yurchenko, *Russ. Chem. Rev.*, **39,** 817 (1970); (d) Z. Weidenhoffer and S. Hála, *Sb. Vys. Sk. Chem.-Technol. Praze, Technol. Paliv,* **22,** 5 (1971); (e) E. Engler and P. v. R. Schleyer, MTP (*Med. Tech. Publ. Co.*) *Int. Rev. Sci.: Org. Chem., Ser. One. 1973,* 239 (1973).
(16) (a) G. L. Baugham, *J. Org. Chem.*, **29,** 238 (1964); (b) E. R. Talaty, A. E. Cancienne, Jr., and A. E. Dupuy, Jr., *J. Chem. Soc. C,* 1902 (1968); (c) T. M. Gorrie and P. v. R. Schleyer, *Org. Prep. Proced. Int.*, **3,** 159 (1971).
(17) H. Stetter, M. Schwarz, and A. Hirschhorn, *Angew. Chem.*, **71,** 429 (1959); H. Stetter and C. Wulff, *ibid.*, **72,** 351 (1960).
(18) A. R. Gagneux and R. Meier, *Tetrahedron Lett.*, 1365 (1969).
(19) H. Stetter, J. Gärtner, and P. Tacke, *Chem. Ber.*, **98,** 3888 (1965); H. Stetter and J. Garnter, *ibid.*, **99,** 925 (1966).
(20) T. Mori, K. Kimoto, M. Kawanisi, and H. Nozaki, *Tetrahedron Lett.*, 3653 (1969); T. Mori, K. H. Yang, K. Kimoto, and H. Nozaki, *ibid.*, 2419 (1970).
(21) "Medial" (proposed by C. Jefford) replaces the original "belt" [6,15b,e] and seems preferable as a general designation to "zonal".[5c]
(22) G. A. Olah and J. Lucas, *J. Amer. Chem. Soc.*, **90,** 933 (1968).
(23) F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Amer. Chem. Soc.*, **91,** 344 (1969).
(24) *Cf.* P. v. R. Schleyer, K. R. Blanchard, and C. D. Woody, *J. Amer. Chem. Soc.*, **85,** 1358 (1963).
(25) R. Hoffmann, *Accounts Chem. Res.*, **4,** 1 (1971).
(26) R. C. Fort, Jr., and P. v. R. Schleyer, *J. Org. Chem.*, **30,** 789 (1965).
(27) (a) F. W. V. Deursen and R. K. Korver, *Tetrahedron Lett.*, 3923 (1967); (b) F. W. V. Deursen and A. C. Udding, *Recl. Trav. Chim. Pays-Bas,* **87,** 1243 (1968); (c) F. W. V. Deursen and J. Bakker, *Tetrahedron,* **27,** 4593 (1971).
(28) For reviews with emphasis on recent work at Princeton, see (a) D. J. Raber and J. M. Harris, *J. Chem. Educ.*, **49,** 60 (1972); (b) P. v. R. Schleyer in J. E. Dubois, Ed., "Reaction Transition States," Gordon and Breach, New York, N. Y., 1972; also (c) D. J. Raber, R. C. Bingham, J. M. Harris, J. L. Fry, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92,** 5977 (1970); (d) D. N. Kevill, K. C. Kolwyck, and F. L. Weitl, *ibid.*, **92,** 7300 (1970); (e) D. J. Raber, J. M. Harris, R. E. Hall, and P. v. R. Schleyer, *ibid.*, **93,** 4821 (1971); (f) D. N. Kevill, K. C. Kolwyck, D. M. Shold, and C.-B. Kim, *ibid.*, **95,** 6022 (1973); J. M. Harris, *Progr. Phys. Org. Chem.*, **11,** 89 (1974).
(29) S. Winstein and N. J. Hollness, *J. Amer. Chem. Soc.*, **77,** 5562 (1955).
(30) Review: J. E. Williams, Jr., P. J. Stang, and P. v. R. Schleyer, *Annu. Rev. Phys. Chem.*, **19,** 531 (1968).
(31) K. B. Wiberg, *J. Amer. Chem. Soc.*, **87,** 1070 (1965); H. A. Harris, Ph.D. Thesis, Yale University, 1966.
(32) N. L. Allinger, M. A. Miller, F. A. Van Catledge, and J. A. Hirsh, *J. Amer. Chem. Soc.*, **89,** 4345 (1967); N. L. Allinger, J. A. Hirsh, M. A. Miller, I. J. Tyminski, and F. A. Van Catledge, *ibid.*, **90,** 1199 (1968); N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *ibid.*, **93,** 1637 (1971).
(33) R. C. Bingham, Ph.D. Thesis, Princeton University, 1971.
(34) G. J. Gleicher and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **89,** 582 (1967).
(35) R. C. Bingham and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **93,** 3189 (1971).
(36) R. C. Bingham, W. F. Sliwinski, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92,** 3471 (1970); S. A. Sherrod, R. G. Bergman, G. J. Gleicher, and D. Morris, *ibid.*, **92,** 3469 (1970); P. v. R. Schleyer, P. R. Isele, and R. C. Bingham, *J. Org. Chem.*, **33,** 1239 (1968); W. G. Dauben and C. D. Poulter, *ibid.*, **33,** 1237 (1968); R. C. Bingham and P. v. R. Schleyer, *Tetrahedron Lett.*, 23 (1971); A. Karim, M. A. McKervey, E. M. Engler, and P. v. R. Schleyer, *ibid.*, 3987 (1971); V. R. Koch and G. J. Gleicher, *J. Amer Chem. Soc.*, **93,** 1657 (1971).
(37) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, pp 125–126.
(38) G. Mateescu, Ph.D. Thesis, Case Western Reserve University, 1972.
(39) G. A. Olah, unpublished results, privately communicated.
(40) R. D. Gilliom, "Introduction to Physical Organic Chemistry," Addison-Wesley, Reading, Mass., 1970, p 160.
(41) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13, p 595.
(42) V. A. Palm, *Russ. Chem. Rev.*, **30,** 471 (1961).
(43) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 323.
(44) R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **74,** 2729, 3120 (1952).
(45) M. M. Krayushkin, V. V. Serost'yanova, and G. I. Danilenko, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2678 (1969).
(46) (a) L. M. Stock, *J. Chem. Educ.*, **49,** 400 (1972), and references cited therein; (b) C. L. Liotta, F. W. Fisher, G. H. Greene, Jr., and B. L. Joyner, *J. Amer. Chem. Soc.*, **94,** 4891 (1972); (c) C. L. Liotta, W. F. Fisher, E. L. Slightom, and C. L. Harris, *ibid.*, **94,** 2129 (1972); (d) S. Ehrenson, *Progr. Phys. Org. Chem.*, **2,** 195 (1964); (e) F. W. Baker, R. C. Parish, and L. M. Stock, *J. Amer. Chem. Soc.*, **89,** 5677 (1967); (f) G. F. Wilcox and C. Leung, *ibid.*, **90,** 336 (1968); (g) J. D. Roberts and W. T. Moreland, *ibid.*, **75,** 2167 (1953); (h) Table VII, footnote *b*.
(47) C. Tanford, *J. Amer. Chem. Soc.*, **79,** 5348 (1957).
(48) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6,** 506 (1938); F. H. Westheimer and J. G. Kirkwood, *ibid.*, **6,** 513 (1938).
(49) For a general description of the calculation method, see P. H. Owens, G. J. Gleicher, and L. M. Smith, Jr., *J. Amer. Chem. Soc.*, **90,** 4122 (1968); L. Harvey, G. J. Gleicher, and W. D. Totherow, *Tetrahedron,* **25,** 5019 (1969).

Bufadienolides. 28. Marinobufotoxin[1]

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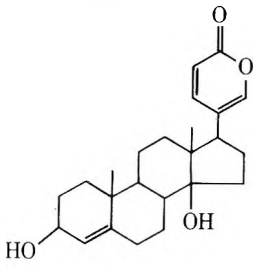
Syntheses of marinobufagin (**5b**) and marinobufotoxin (**5e**) have been achieved. The principal synthetic transformations involved selective dehydration of telocinobufagin (**2**) and addition of hypohalous acid to the resulting olefin (**2** → **3** → **4**) followed by dehydrohalogenation to yield marinobufagin (**5b**). Application of a carefully developed mixed carbonic anhydride reaction to the condensation of marinobufagin suberate (**5c**) with arginine monohydrochloride provided marinobufotoxin (**5e**).

Almost 50 years elapsed between isolation[2] of marinobufagin (**5b**) from the American toad, *Bufo marinus*, and assignment[3] of structure **5b**. Nearly 40 years passed before the structure of marinobufotoxin (**5e**)[4] was firmly estab-

lished.[1b] The suberylarginine side chain of marinobufotoxin is characteristic of the toad venom bufadienolide constituents generally known as "bufotoxins." Of the nine such substances which have been reported, only the structures of marinobufotoxin and bufotoxin[5] are known with certainty.[6]

The formal total synthesis of scillarenin (1)[7] offered in principle a good possibility of extension to telocinobufagin



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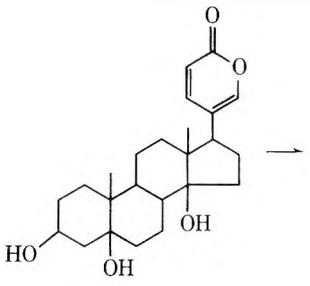
(2)[8] and thence to marinobufagin (**5a**) and marinobufotoxin (**5e**). By attainment of this synthetic outline it was



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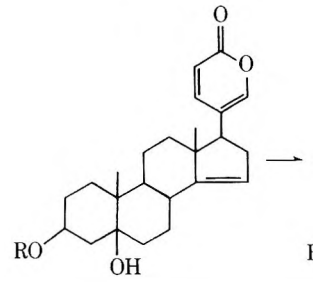
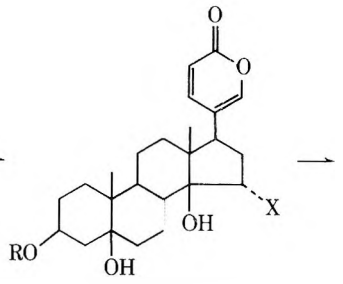
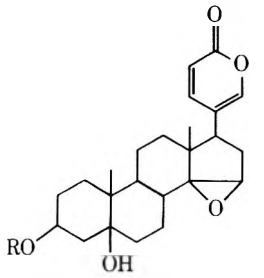


3a, R = H
b, R = $COCH_3$



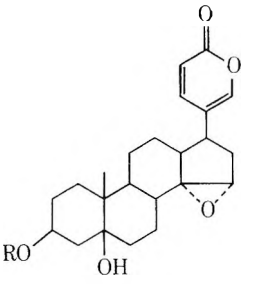
4a, R = $COCH_3$; X = I
b, R = $COCH_3$; X = Br
c, R = H; X = Br
d, R = H; X = I



5a, R = $COCH_3$
b, R = H
c, R = $CO(CH_2)_6CO_2H$
d, R = $CO(CH_2)_6CO_2CH_3$
e, R = $CO(CH_2)_6CONHCH(CH_2)_3NHCNH_2$ (CO$_2$H; NH)

hoped that these bufadienolides would be made more readily available for biological evaluation[9] and that the structure of marinobufotoxin would be unequivocally established. As noted in a preliminary report[1b] we recently confirmed the structure of marinobufotoxin (**5e**) by partial synthesis from telocinobufagin (2). Subsequently we succeeded in obtaining telocinobufagin (2) by a formal total synthetic route employing bufalin and scillarenin as relays.[7,10] Accordingly, the pathway from telocinobufagin (2) *via* marinobufagin (**5b**) to marinobufotoxin (**5e**) which will now be described in detail comprises the first formal total synthesis of a bufotoxin.

The first step planned for conversion of telocinobufagin (2) to marinobufagin (**5b**) involved selective elimination of the 14β-hydroxyl group. Here, our prior experience with such steroid D-ring systems suggested that partial release of steric compression by removal of the 14β-hydroxyl group might favor a selective elimination. In practice, the 14β-hydroxyl group was readily and selectively (51% yield) removed by treating telocinobufagin (2) with hydrochloric acid in methanol.[11a] The resulting 14-olefin **3a** was selectively (92% yield) acetylated to provide 3β-acetate **3b**. Reaction of 3β-acetoxy-14-dehydrotelocinobufagin (**3b**) with hypoiodous acid, prepared *in situ*, readily gave iodohydrin **4a** which, upon contact with pyridine, afforded marinobufagin acetate (**5a**) in 70% overall yield. An analogous reaction sequence was performed employing hypobromous acid to obtain the bromohydrin intermediate **4b**. Preparation of the hypohalous acid from either *N*-bromosuccinimide or *N*-bromoacetamide led to 60% yields of marinobufagin 3β-acetate (**5a**). For purposes of chemical and biological comparison, 14-dehydrotelocinobufagin (**3a**) and its acetate derivative (**3b**) were each oxidized with *m*-chloroperbenzoic acid to yield 14α,15α-epoxides **6a** and **6b**.



6a, R = H
b, R = $COCH_3$

Application of the hypohalous acid reactions to 14-dehydrotelocinobufagin resulted in a convenient synthesis of marinobufagin (**5b**)[11b] in about 45% yields by way of the iodohydrin (**4d**) and in about 30% yields by way of the bromohydrin intermediate. The synthetic specimen of marinobufagin (**5b**) was found to be identical with an authentic specimen isolated from Ch'an Su.

The following experiments leading to marinobufotoxin (**5e**) are based on an extensive series of experiments developed (over a number of years) for the partial synthesis of bufotoxin.[5] Over this period a variety of synthetic approaches[12] and selective protection methods for elaborating the bufadienolide suberylarginine side chain were explored and this accumulated experience finally led to selection of the general and convenient procedure which now follows. By condensing marinobufagin (**5b**) with suberic α-anhydride the corresponding 3-suberate ester **5c** was obtained (92% yield). The methyl ester derivative **5e** was prepared in nearly quantitative conversion by methylating acid **5c** with diazomethane. Methyl ester **5d** was found to be identical with an authentic sample prepared from a specimen of carboxylic acid **5c** isolated from Ch'an Su.

The mixed carbonic anhydride prepared from suberic acid derivative **5c** and isobutyl chloroformate was added, in the cold, to L-arginine monohydrochloride and 88% conversion to marinobufotoxin was realized. Thus, the simple ex-

pedient of selectively protecting the guanidino unit of arginine by protonation obviated the necessity for more extensive protection which upon removal would generally involve the bufadienolide system in unwanted side reactions.[13] The synthetic specimen[14] of marinobufotoxin (**5e**) was found identical with an authentic specimen of the natural product kindly provided by Professor K. Meyer.

Experimental Section[15]

14-Dehydrotelocinobufagin (3a). A solution of telocinobufagin (**2**, 200 mg), methanol (35 ml), and 35% hydrochloric acid (0.04 ml) was heated at reflux for 1.5 hr, poured into ice–water and extracted with chloroform. The solvent extract was washed with water and evaporated to dryness. The crude product was chromatographed on a column of silica gel and the fraction eluted with ligroin–acetone (3:1) was recrystallized from acetone to give 14-dehydrotelocinobufagin (**3a**, 105 mg) as prisms, mp 198–200°. Recovered starting material, telocinobufagin, weighed 85 mg. The pure specimen of olefin **3a** showed λ_{max} (95% EtOH) 300 nm (log ϵ 3.76); ν_{max} (KBr) 3450, 3420 (OH), 1720–1700 (conjugated CO), 1634 (conjugated C=C), 1667 (R_2C=CHR), 1537 (conjugated C=C), 958 (C=C), 836, 814 (R_2C=CHR), 755, 745, cm^{-1} (C=C); pmr (10% solution in $CDCl_3$) δ 0.73 (3 H, s, 18-CH_3), 0.97 (3 H, s, 19-CH_3), 3.44 (1 H, broad peak, 5-OH), 4.17 (1 H, broad s, 3-H), 5.25 (1 H, s, R_2C=CHR), 6.29 (1 H, d, J = 10.5 Hz, 23-H), 7.28 (1 H, d, J = 3 Hz, 21-H), 7.37 (1 H, dd, J = 10.5 and 3 Hz, 22-H); mass spectrum m/e 384 (M^+), 366 ($M^+ - 18$), 348 ($M^+ - 36$), 333 ($M^+ - 51$), 312 ($M^+ - 72$).

Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 75.01; H, 8.24.

The 3β-acetate derivative (**3b**) of 14-dehydrotelocinobufagin was prepared by acetylating 0.18 g of 14-dehydrotelocinobufagin (**3a**) with acetic anhydride (2.7 ml)–pyridine (3.6 ml) at room temperature for 24 hr. Column chromatography (silica gel) of the crude product and elution with ligroin–acetone (9:1) provided 0.17 g of **3β-acetoxy-14-dehydrotelocinobufagin (3b)** as an amorphous solid: λ_{max} 300 nm (log ϵ 3.75); ν_{max} (KBr) 3520 (OH), 1760–1720 (ester CO and conjugated CO), 1635, 1535 (conjugated C=C), 1670 (R_2C=CHR), 1240, 1220 (ester CO), 950 (C=C), 850, 828 (R_2C=CHR), 753, 742, cm^{-1} (C=C); pmr (10% solution in $CDCl_3$) δ 0.74 (3 H, s, 18-CH_3), 0.99 (3 H, s, 19-CH_3), 2.09 (3 H, s, 3-$OCOCH_3$), 3.05 (1 H, broad peak, 5-OH), 5.29 and 5.24 (2 H, overlapped broad peak, 3-H, and 15-H), 6.28 (1 H, d, J = 10 Hz, 23-H), 7.27 (1 H, d, J = 2.5 Hz, 21-H), 7.32 (1 H, dd, J = 10 and 2.5 Hz, 22-H); mass spectrum m/e 426 (M^+), 408 ($M^+ - 18$), 366 ($M^+ - 60$), 348 ($M^+ - 78$), 312 ($M^+ - 114$), 294 ($M^+ - 132$).

Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.04. Found: C, 73.35; H, 8.06.

Marinobufagin 3β-Acetate (5a). Method A. In a typical experiment, a solution of *N*-iodosuccinimide (20 mg) in acetone (2 ml)–water (2 ml) was added to 14-dehydrotelocinobufagin acetate (**3b**, 20 mg) in acetone (3.2 ml). Before a solution prepared from sodium sulfite (20 mg) and water (0.5 ml) was added, the mixture was stirred for 20 hr at room temperature. The solution was concentrated to approximately one-third of the original volume, poured into ice-water with stirring, and extracted with chloroform. The combined extract was washed with water, solvent was removed, and the crude iodohydrin (**4a**, 22 mg) was stirred in pyridine (1 ml) for 2 hr at room temperature. After evaporation of solvent the product was column chromatographed (silica gel) and the fraction eluted with ligroin–acetone (9:1) was recrystallized from acetone–*n*-hexane to afford 14 mg of marinobufagin acetate (**5a**) as prisms melting at 198–216°.

Method B. When *N*-bromosuccinimide (20 mg) was substituted for *N*-iodosuccinimide as described in method A, olefin **3b** (20 mg) led to 21 mg of the crude bromohydrin **4b.** Conversion of the bromohydrin to marinobufagin acetate (**5a**) with pyridine resulted in a 12-mg (mp 194–215°) yield.

Method C. The preceding reaction (method A or B) was repeated using 18 mg of olefin **3b** and 18 mg of *N*-bromoacetamide. Similar treatment of the crude bromohydrin (20 mg) with pyridine led to 11 mg of marinobufagin acetate (**5a**) melting at 198–215°.

The samples of marinobufagin acetate (**5a**) prepared by methods A–C were found identical with acetate **5a** prepared from natural marinobufagin (**5b**).

3β,5β,Dihydroxy-14α,15α-epoxy-5β-bufa-20,22-dienolide (14α,15α-*epi*-Marinobufagin, 6a). To 70 mg of 14-dehydrotelocinobufagin (**3a**) in chloroform (3 ml) was added *m*-chloroperbenzoic acid (50 mg). After 2 hr at room temperature and dilution with chloroform, the solution was poured into ice–water. The chloroform layer was washed with water, dilute sodium thiosulfate solution, and water. Solvent was removed and the residue (68 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone (5:1) provided 60 mg of 14α,15α-*epi*-marinobufagin, mp 209–212° (from acetone), as colorless needles: λ_{max} 298 nm (log ϵ 3.74); ν_{max} (KBr) 3530, 3480 (OH), 1720–1700 (conjugated CO), 1655, 1550 (conjugated C=C), 1245 (epoxy CO), 960 (C=C), 830 (epoxy CO), 760 cm^{-1} (C=C); pmr δ 0.68 (3 H, s, 18-CH_3), 0.97 (3 H, s, 19-CH_3), 3.53 (1 H, s, 15β-H), 4.19 (1 H, broad s, 3α-H), 6.29 (1 H, d, J = 10 Hz, C-23 H), 7.18 (1 H, d, J = 3 Hz, C-21 H), 7.49 (1 H, q, C-22 H), J = 10 and 3 Hz; mass spectrum m/e 400 (M^+), 382 ($M^+ - H_2O$), 364 ($M^+ - 2H_2O$), 346 ($M^+ - 54$).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.92; H, 8.08.

3β-Acetoxy-5β-hydroxy-14α,15α-epoxy-5β-bufa-20,22-dienolide (14α,15α-*epi*-Marinobufagin, 6b). Method A. A solution of 14-dehydrotelocinobufagin acetate (**3b**, 25 mg) in chloroform (1.5 ml) was treated with *m*-chloroperbenzoic acid (18 mg) as described for the preparation of α-epoxide **6a.** After chromatography and elution with ligroin–acetone (9:1) 21 mg (amorphous solid) of 14α,15α-*epi*-marinobufagin acetate (**6b**) was obtained and found identical with the material prepared as follows.

Method B. Alcohol **6a** (60 mg) was acetylated with acetic anhydride (0.85 ml)–pyridine (1.2 ml) and the product was isolated as described in method A to yield 51 mg of 14α,15α-*epi*-marinobufagin acetate (**6b**) as an amorphous solid: λ_{max} 298 nm (log ϵ 3.72); ν_{max} (KBr) 3680 (OH), 3030 (CH), 1760, 1740, 1720 (conjugated CO and ester CO), 1650, 1550 (conjugated C=C), 1260, 1240, 1220 (ester and epoxy CO), 955 (C=C), 830 (epoxy CO), 740 cm^{-1} (C=C); pmr (10% solution in $CDCl_3$) δ 0.78 (3 H, s, 18-CH_3), 1.08 (3 H, s, 19-CH_3), 2.15 (3 H, s, 3-$OCOCH_3$), 3.12 (1 H, broad peak, 5-OH), 3.60 (1 H, s, 15-H), 5.29 (1 H, broad peak, 3-H), 6.31 (1 H, d, J = 10 Hz, 23-H), 7.22 (1 H, d, J = 2.5 Hz, 21-H), 7.25 (1 H, dd, J = 2.5 and 10 Hz, 22-H); mass spectrum m/e 442 (M^+), 424 ($M^+ - H_2O$), 406 ($M^+ - 36$), 382 ($M^+ - 60$), 364 ($M^+ - 78$), 346 ($M^+ - 96$), 331 ($M^+ - 111$), 328 ($M^+ - 114$).

Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.63; H, 7.73.

Marinobufagin (5b). Reaction of 14-dehydrotelocinobufagin (**2a**, 20 mg) with hypobromous acid prepared from *N*-bromosuccinimide (20 mg) was executed as described above for the preparation of iodohydrin **4b.** The crude bromohydrin **4c** upon treatment with pyridine and chromatographic purification (elution with 3:1 ligroin–acetone and recrystallization from acetone) led to marinobufagin (**5b**, 6.5 mg) as prisms melting at 223–225°.

When the reaction was repeated with 15 mg of olefin **3a** and *N*-bromo-acetamide (15 mg) the crude bromohydrin (**4c**, 18 mg) gave, after treatment with pyridine (1.5 ml), 5 mg of marinobufagin (prisms, mp 222–224°). The yield of marinobufagin was higher when the *N*-iodosuccinimide (20 mg) method was applied to olefin **3a** (20 mg). Following isolation by chromatography and recrystallization from acetone, 8.4 mg of prisms (**5b**) was obtained. In each case the synthetic sample of marinobufagin was found identical with the natural product isolated from Ch'an Su.

Marinobufagin 3β-Suberate (5c). A mixture prepared from marinobufagin (**5b**, 50 mg), suberic α-anhydride (mp 65–66°, 110 mg),[16] and pyridine (2 ml) was heated at reflux for 6 hr. The reaction mixture was brought (under reduced pressure) to dryness, water was added, and the mixture was extracted with chloroform. The extract was washed with water, dilute potassium bicarbonate solution, dilute hydrochloric acid, and water. After removal of the solvent the residue (56 mg) was submitted to preparative thin layer chromatography using dichloromethane–methanol–ammonium hydroxide (7:3:1) as developing solvent. The substance corresponding to R_f 0.65 (located by aid of ultraviolet light) was eluted with chloroform–methanol (4:1) to give marinobufagin 3-suberate (**5c**, 46 mg, 92% yield) as a colorless, oily material: tlc R_f 0.34 with chloroform–ethyl acetate–formic acid (3:4:0.5), 0.40 with chloroform–methanol (9:1); color, purple to greenish pink with sulfuric acid spray. The structure was confirmed by preparation and analysis of the methyl ester (**5d**) derivative as summarized in the following experiment.

Marinobufagin 3-Suberate Methyl Ester (5d). An ethereal solution of acid **5c** (20 mg) was methylated with diazomethane in ether. The product was purified by silica gel column chromatography using acetone–ligroin (1:6) to give 19.2 mg of methyl ester **5d** (96% yield), mp 107–112°, as colorless needles from acetone–ether. The melting point, tlc R_f values, and spectral data (uv, ir, nmr, and

mass spectrum as described below) were identical with those of an authentic sample[17] prepared from acid **5c** which was isolated from the Japanese toad, *Bufo formosus* Boulenger. Also, the data are in good agreement with those for methyl ester **5d** reported by Linde-Tempel:[14] tlc R_f 0.46 using acetone–chloroform–ligroin (3:3:4), 0.61 using chloroform–methanol (9:1), 0.44 using chloroform–ethyl acetate–formic acid (3:4:0.5); color with sulfuric acid spray, light greenish pink → purple; λ_{max} (MeOH) 300 nm (log ϵ 3.72) ν_{max} (KBr) 3580, 3460 (OH), 3040 (CH), 1740 (ester CO), 1720–1700 (conjugated CO), 1645, 1545 (conjugated C=C), 1260, 1230 (ester CO), 957 (C=C), 830 (epoxy CO), 795 cm^{-1} (C=C); pmr (10% solution in $CDCl_3$) δ 0.78 (3 H, s, 18-CH_3), 1.01 (3 H, s, 19-CH_3), 3.51 (1 H, s, 15-H), 3.64 (3 H, s, -$COOCH_3$), 4.28 (2 H, t, -CH_2COR), 5.24 (1 H, broad s, 3-H), 6.19 (1 H, d, J = 10 Hz, 23-H), 7.23 (1 H, d, J = 3 Hz, 21-H), 7.74 (1 H, t, J = 10 and 3 Hz, 22-H); mass spectrum *m/e* 570 (M^+), 552 ($M^+ - 18$), 534 ($M^+ - 36$), 401, 382, 364, 346, 328, 213, 171, 157, 145, 138, 129, 123, 105.

Marinobufotoxin (5e). A solution of suberate half ester **5c** (19 mg) in tetrahydrofuran (2 ml) containing triethylamine (0.03 ml) was stirred for 15 min at −10°. Then a solution of isobutyl chloroformate (0.02 ml) in tetrahydrofuran (0.2 ml) was added and stirring was continued for 40 min. Methanol (1 ml) was added, followed by a solution of arginine monohydrochloride (freshly prepared from arginine and concentrated hydrochloric acid in methanol) in methanol (1.5 ml)–water (0.07 ml). The solution was added dropwise over an approximate 3-min period. Stirring was continued for 2 hr at −5 to 0°. The mixture was concentrated under reduced pressure (below 40°) to an oily residue which was dissolved in a small amount of methanol and subjected to preparative thin layer chromatography using dichloromethane–methanol–ammonium hydroxide (7:3:1) as eluant. The product corresponding to R_f 0.24 was located with the aid of ultraviolet light and extracted with chloroform–methanol (4:1). Recrystallization of the bufotoxin from 80% ethanol provided marinobufotoxin (**5e**, 17 mg, 88% yield), mp 176–185°, as colorless, fine prisms: color on tlc, light greenish pink → light purple with sulfuric acid and bluish purple with ninhydrin; λ_{max} (MeOH) 300 nm (log ϵ 3.73); ν_{max} (KBr) 3590, 3380, 3200 (OH), 2800–2400 (broad, -COOH, NH_2,NH, and -C=NH), 1750 (ester CO and -COOH), 1730–1720 (conjugated CO), 1680 (CONH), 1650–1630 (conjugated C=C and ONH), 1540 (conjugated C=C), 1260, 1230 (ester CO), 954 (C=C), 830 (epoxy CO), 797 cm^{-1} (C=C).

Anal. Calcd for $C_{38}H_{56}O_9N_4$: C, 64.16; H, 8.05; N, 7.86. Found: C, 64.22; H, 8.08; N, 7.93.

The compound was found to be identical with an authentic sample of natural marinobufotoxin (mp 174–181°)[14] from Professor Meyer.

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Registry No.—**2a,** 472-26-4; **3a,** 38672-78-5; **3b,** 51876-75-6; **5a,** 4029-68-9; **5b,** 470-42-8; **5c,** 38672-81-0; **5d,** 38672-82-1; **5e,** 30685-91-7; **6a,** 51921-23-4; **6b,** 51921-24-5; arginine monohydrochloride, 1119-34-2.

References and Notes

(1) (a) Contribution 87 of the series Steroids and Related Natural Products. For the preceding part see G. R. Pettit and Y. Kamano, *J. Org. Chem.*, **39,** 2632 (1974). (b) A preliminary report of the present study has been summarized by Y. Kamano and G. R. Pettit, *Experientia*, **28,** 768 (1972).
(2) J. J. Abel and D. J. Macht, *J. Pharmacol. Exp. Ther.*, **3,** 319 (1911).
(3) For leading references to the excellent structural studies of Meyer and colleagues see P. Hofer, H. Linde, and K. Meyer, *Helv. Chim. Acta*, **43,** 1955 (1960).
(4) H. Jensen and E. A. Evans, *J. Biol. Chem.*, **104,** 307 (1934); H. Jensen and K. K. Chen, *J. Amer. Chem. Soc.*, **59,** 767 (1937); V. Deulofeu and J. R. Mendive, *Justus Liebigs Ann. Chem.*, **534,** 288 (1938); V. Deulofeu, E. Duprat, and R. Lobriols, *Nature (London)*, **145,** 671 (1940).
(5) G. R. Pettit and Y. Kamano, *J. Chem. Soc., Chem. Commun.*, 45 (1972).
(6) Quite likely the remaining seven bufotoxins also have the 3-suberylarginine structure analogous to bufotoxin and marinobufotoxin. Specifically, the seven other bufotoxins are alvarobufotoxin, fowlerobufotoxin, arenobufotoxin, cinobufotoxin, gamabufotoxin, regularobufotoxin, and viridobufotoxin. See respectively K. K. Chen and A. L. Chen, *J. Pharmacol. Exp. Ther.*, **49,** 7 (1933); K. K. Chen and A. L. Chen, *ibid.*, **49,** 26, 307, **503,** 514, 529, (1933); K. K. Chen, H. Jensen, and A. L. Chen, *ibid.*, 43, 13 (1931); S. Ohno and M. Komatsu, *Yakugaku Zasshi*, **73,** 651, 796 (1953); H. Wieland and H. Behringer, *Justus Liebigs Ann. Chem.*, **549,** 209 (1941); H. Wieland and F. Vocke, *ibid.*, **481,** 215 (1930); H. Jensen, *J. Amer. Chem. Soc.*, **57,** 1765 (1935); K. K. Chen, H. Jensen, and A. L. Chen, *J. Pharmacol. Exp. Ther.*, **49,** 14 (1933). Unfortunately, we have been unable to obtain authentic samples corresponding to any of these bufotoxins. Thus, definite structural assignments will apparently have to await the reisolation of these substances from the respective toad venoms.
(7) U. Stache, K. Radscheit, W. Fritsch, H. Kohl, W. Haede, and H. Ruschig, *Justus Liebigs Ann. Chem.*, **750,** 149 (1971); Y. Kamano and G. R. Pettit, *J. Org. Chem.*, **39,** 2629 (1974); G. R. Pettit and Y. Kamano, *J. Amer. Chem. Soc.*, **94,** 8592 (1972).
(8) This toad venom component was accorded a structural assignment by K. Meyer, *Helv. Chim. Acta*, **32,** 1593 (1949).
(9) Both telocinobufagin and marinobufagin have been isolated from the Chinese preparation Ch'an Su and, for example, the latter is known to have pronounced cardiac activity: K. Meyer, *Pharm. Acta Helv.*, **24,** 222 (1949); Y. Kamano, H. Yamamoto, K. Hatayama, T. Tanaka, M. Shinohara, and M. Komatsu, *Tetrahedron Lett.*, 5668 (1968).
(10) Y. Kamano and G. R. Pettit, *J. Org. Chem.*, **38,** 2202 (1973); G. R. Pettit and Y. Kamano, *ibid.*, **39,** 0000 (1974).
(11) (a) We wish to thank a referee for locating an analogous reaction involving strophantidinic acid methyl ester described by Jacobs and Gustus, *J. Biol. Chem.*, **74,** 795 (1927). (b) The reverse transformation, namely conversion of marinobufagin to telocinobufagin, has been reported by M. Bharucha, H. Jäger, K. Meyer, T. Reichstein, and O. Schindler, *Helv. Chim. Acta*, **42,** 1395 (1959).
(12) We gratefully acknowledge (in chronological order) the contributions of Miss V. Thiele and Drs. K. Jaeggi, J. C. Knight, and S. Gabriel in these preliminary studies.
(13) G. R. Pettit and S. K. Gupta, *Can. J. Chem.*, **45,** 567 (1967); R. E. Plapinger, M. M. Nachlas, M. L. Seligman, and A. M. Seligman, *J. Org. Chem.*, **30,** 1781 (1965). See also G. R. Pettit, "Synthetic Peptides," Vol. 1, Van Nostrand-Reinhold, Princeton, N. J., 1970, and Vol. 2, 1971.
(14) H. O. Linde-Tempel, *Helv. Chim. Acta*, **53,** 2188 (1970).
(15) Introduction to the experimental section of part 27[1] provides an explanation of the general experimental (for example, melting points uncorrected and chromatography with silica gel columns and silica gel HF_{254} thin layer and preparative layer plates) and instrumental (by Dr. P. Brown, Messrs. R. Scott and E. Kelley, and Miss K. Reimer) techniques employed in the present study. The mutual identity of synthetic with natural specimens was established by mixture melting point determination and comparison thin layer chromatography and infrared spectra.
(16) J. W. Hill and W. H. Carothers, *J. Amer. Chem. Soc.*, **55,** 5023 (1933).
(17) Y. Kamano, H. Yamamoto, Y. Tanaka, and M. Komatsu, 12th Symposium on the Chemistry of Natural Products of Japan, Sendai, Oct 8, 1968, Abstracts of Papers, p 166.

Bufadienolides. 29. Synthetic Routes to Bufotalin[1]

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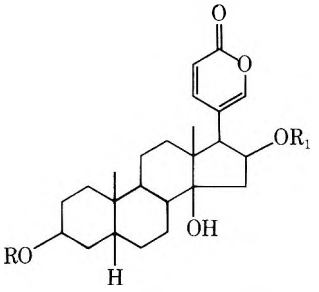
Two partial syntheses of bufotalin (**1a**) were developed as follows. The 16-ketone **3** was prepared from cinobufagin and the 14,15β-epoxide group was reduced with chromous acetate to yield β-hydroxy ketone **4** (61%) and α,β-unsaturated ketone **5** (27%). Selective reduction of β-ketone **4** with Urushibara nickel A afforded alcohol **1b**, which was acetylated to provide diacetate **1c**. Treatment of diacetate **1c** with hydrochloric acid in methanol gave bufotalin (**1a**) accompanied by lesser amounts of other hydrolysis products (**1b**, **1d**, and **6a**). In an alternative approach, α,β-unsaturated ketone **5** was first reduced with Urushibara nickel A to allylic alcohol **6a**. After acetylation (to **6b**) the olefin was subjected to reaction with hypoiodous acid or hypobromous acid and the resulting halohydrin (**7a** or **7b**) was treated with Urushibara nickel A. The product of hydrogenolysis was bufotalin 3β-acetate (**1c**).

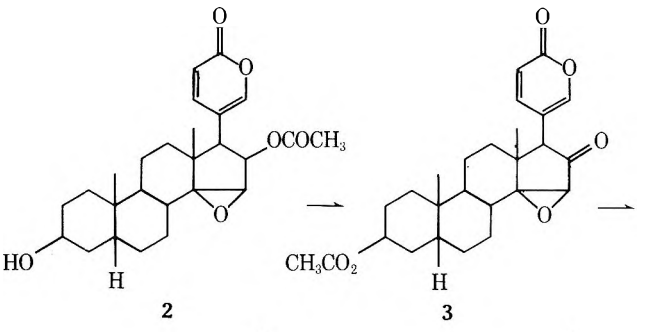
Bufotalin (**1a**) is one of the more widely known and thoroughly characterized constituents of the Chinese medicinal



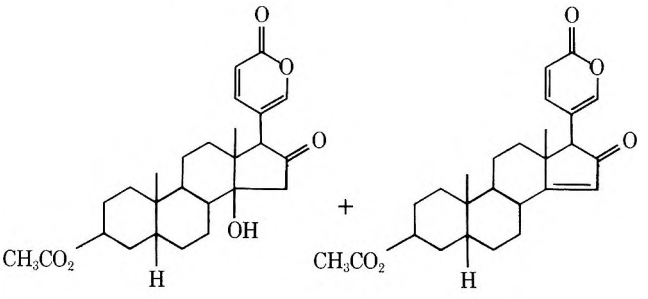
1a, R = H; R_1 = $COCH_3$
b, R = CH_3CO; R_1 = H
c, R = R_1 = $COCH_3$
d, R = R_1 = H

preparation, Ch'an Su. This common toad venom component has been shown to be a potent cytotoxic agent (KB, ED_{50} 0.026)[3] and to exhibit cardiac activity.[4] In prior studies we have reconfirmed the structure of bufotalin (**1a**)[5] and employed this interesting substance as starting material for partial syntheses of cinobufagin (**2**)[6] and bufotoxin.[7] As the next step in an effort to extend our earlier total synthesis of bufalin[8] to bufotalin it became necessary to explore preparation of this bufadienolide from cinobufagin (**2** → **1a**). Two usable synthetic routes from cinobufagin to bufotalin were uncovered and are herein summarized.

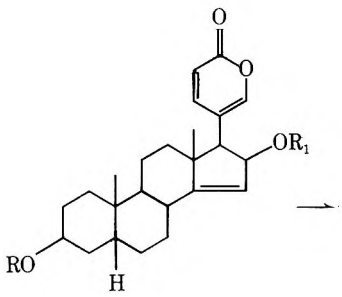
Cinobufagin (**2**, KB, ED_{50} 0.011)[3] was isolated from Ch'an Su and converted to ketone **3** as previously described.[6] The last step in this transformation, namely oxidation of desacetylcinobufagin 3β-acetate to ketone **3**, was found easily reversible by sodium borohydride reduction. Interestingly, the 16β-alcohol was the major product. Next, ketone **3** was subjected to the chromium(II) acetate reduction reaction analogous to that employed as the key step in our recent synthesis of telocinobufagin.[9] Column chromatographic separation of the reduction product provided hydroxy ketone **4** (61%) and α,β-unsaturated ketone **5** (27%). The structural assignments of both products easily followed from the known course[10] of such reduction reactions combined with the results of mass, ultraviolet, and proton magnetic resonance measurements. Under a variety of conditions (hydrochloric acid, oxalic acid, acetic acid, and acidic exchange resin) hydroxy ketone **4** was easily dehydrated to olefin **5**. At this point reduction of hydroxy ketone **4** was found quite convenient using Urushibara nickel A.[8,11] After purification by chromatography and recrystallization diol **1b** was obtained to 70% yield. Gentle oxidation with the chromium trioxide–pyridine complex easily reversed the reduction step and ketone **4** was obtained in 63%



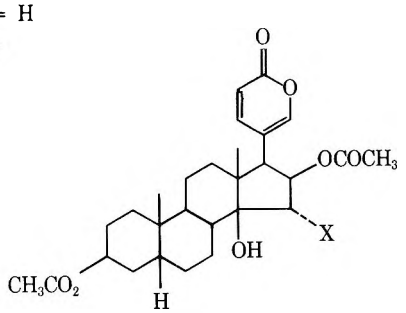
2 **3**



4 **5**



6a, R = CH_3CO; R_1 = H
b, R = R_1 = $COCH_3$



7a, X = I
b, X = Br

yield. Lesser yields (56 and 47%, respectively) were obtained using *N*-bromoacetamide and chromium trioxide–acetic acid procedures.

Mild acetylation of diol **1b** afforded bufotalin acetate (**1c**). Once the structure of diacetate **1c** was confirmed by comparison with authentic bufotalin acetate the partial synthesis of bufotalin seemed close at hand. However, selective hydrolysis of bufotalin acetate proved more challenging than expected. Eventually, acid-catalyzed hydrolysis employing short (10 min) contact with hydrochloric acid in methanol or with an acidic ion exchange resin was found to produce bufotalin in somewhat less than 20% conversion. Application of a basic ion exchange resin or use of potassium bicarbonate was less effective. The major result of both the acid- and base-catalyzed hydrolysis reactions was simply a mixture of recovered starting material accompanied by diol **1b**, triol **1d**, and allylic alcohol **6a**. However, the yield of bufotalin could be substantially increased by recycling diol **1b** and triol **1d** through the acetylation sequence. Further, the yield of bufotalin was more directly increased by selective acetylation of triol **1d** employing acetic acid to afford bufotalin (**1a**) accompanied by bufotalin acetate (**1c**) and diol **1b**.

A second partial synthesis of bufotalin was developed utilizing olefin **5**. First, conditions were found for specific nickel-catalyzed reduction of the 16-carbonyl group of bufadienolide **5** to yield allylic alcohol **6a**. The structure and stereochemistry of alcohol **6a** were confirmed as follows. Bufotalin acetate was dehydrated[6] to olefin **6b**. Selective saponification of the 16β-acetate was performed in good yield using potassium bicarbonate as base. The product, allylic alcohol **6a**, was identical with the same substance obtained from cinobufagin. Mutually identical specimens were again obtained by acetylation of alcohol **6a** derived from cinobufagin and comparing the product with diacetate **6b** prepared from bufotalin acetate. In addition, allylic alcohol **6a** was easily oxidized by active manganese dioxide, chromium trioxide–pyridine complex, or chromium trioxide–acetic acid to ketone **5**.

Treatment[8] of olefin **6b** with hypoiodous acid or with hypobromous acid led respectively to halohydrins **7a** and **7b**. Hydrogenolysis of each halohydrin with Urushibara nickel A afforded bufotalin acetate (**1a**). As diacetate **1c** had already been used to obtain bufotalin (**1a**, see above) the alternative approach from cinobufagin was thereby complete.

The plausibility of extending prior total syntheses of 14-dehydrobufalin (16-desacetoxy-**6a**) or resibufogenin (16-desacetoxy-**2**) to bufotalin (**1a**) received much encouragement from successful completion of the preceding series of experiments. Presently we are attempting to complete the necessary connecting transformations.

Experimental Section

The bufotalin and cinobufagin employed in these experiments were both isolated from the Chinese medicinal preparation, Ch'an Su. Chromium(II) acetate was prepared essentially as described by Balthis and Bailar.[12]

General experimental procedures including materials and methods for thin layer chromatography (3:3:4 acetone–chloroform–hexane as solvent unless otherwise noted) and column chromatography (silica gel) have been summarized in the corresponding section of part 27 of this series.[9] As before, the mutual identity of synthetic with natural specimens was established by mixture melting point determination, comparison thin layer chromatography, and comparison infrared spectra.

All infrared spectra were obtained using potassium bromide pellets. Except for melting points (uncorrected) all instrumental measurements were obtained by Messrs. R. Scott and E. Kelley or Miss K. Reimer.

3β-Acetoxy-16-oxo-14β,15β-epoxy-5β-bufa-20,22-dienolide (3). Ketone **3** was prepared from cinobufagin (**2**) as described in part 21 of this series.[6] Reconversion of ketone **3** to its immediate alcohol precursor was conducted as follows. Sodium borohydride (48 mg) in dioxane (2.4 ml)–water (0.8 ml) was added to a solution of ketone **3** (50 mg, mp 226–228°) in dioxane (5 ml)–water (1.8 ml). After 2 hr at room temperature the mixture was poured into ice–water, acidified with dilute sulfuric acid, and extracted with chloroform. The combined extract was washed with water and concentrated to dryness. The residue (55 mg) was chromatographed on a column of silica gel. A fraction eluted by hexane–acetone (5:1) was recrystallized from methanol to provide 33 mg of 3β-acetoxy-16β-hydroxy-14β,15β-epoxy-5β-bufa-20,22-dienolide as needles melting at 205–208°. The alcohol was identical with authentic specimens prepared from cinobufagin.[6]

Chromium(II) Acetate Reduction of 3β-Acetoxy-16-oxo-14β,15β-epoxy-5β-bufa-20,22-dienolide (3). Chromium(II) acetate (0.70 g) was added to a solution of ketone **3** (0.105 g) in ethyl alcohol (18 ml). After 1 hr at room temperature the mixture was diluted with chloroform and poured into ice–water. The chloroform layer was washed with water, dried, and concentrated to dryness and the residue (0.125 g) was separated by column chromatography with 5:1 hexane–acetone as eluent. Two significant fractions were obtained. The more polar fraction was recrystallized from methanol–hexane to provide 64 mg of **3β-acetoxy-14β-hydroxy-16-oxo-5β-bufa-20,22-dienolide (4)** as needles melting at 229–235°: tlc R_f 0.31; λ_{max} (CH_3OH) 296 nm (log ϵ 4.25); ν_{max} 3420 (OH), 1740, 1720, 1710 (conjugated C=O and ester C=O), 1630, 1535 (conjugated C=C), 1260, 1240 (ester C=O), 1030, 960, 830, 807, 748 cm^{-1}; pmr (10% deuteriopyridine) δ 0.96 (3 H, s, 18-CH_3), 1.11 (3 H, s, 19-CH_3), 2.09 (3 H, s, 3-OAc), 3.12 (1 H, s, 17α-H), 2.56 and 3.23 (2 H, q, J = 17 Hz, 15-CH_2), 5.24 (1 H, broad peak, 3α-H), 6.3 (1 H, d, J = 9.5 Hz, 23-H), 7.65 (1 H, d, J = 3 Hz, 21-H), 7.95 (1 H, dd, J = 9.5 and 3 Hz, 22-H); mass spectrum m/e 442 (M^+), 424 ($M^+ - H_2O$), 382 (M^+ – AcOH), 364 ($M^+ - H_2O$ – AcOH), 231, 213, and 203.

Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.49; H, 7.75.

The less polar fraction was recrystallized from methanol to yield 28 mg of **3β-acetoxy-16-oxo-5β-bufa-14,20,22-trienolide (5)** as needles melting at 211–214°: tlc R_f 0.43; λ_{max} (CH_3OH) 232 nm (log ϵ 4.25) and 295 (3.84); ν_{max} 1750, 1730, 1720, 1700 (conjugated C=O and ester C=O), 1640, 1610, 1538 (conjugated C=C), 1250, 1230 (ester C=O), 1030, 955, 905, 865, 750 cm^{-1}; pmr (10% solution in deuteriochloroform) δ 0.94 (3 H, s, 18-CH_3), 1.05 (3 H, s, 19-CH_3), 2.02 (3 H, s, 3-OAc), 3.12 (1 H, s, 17α-H), 5.06 (1 H, broad peak, 3α-H), 5.83 (1 H, s, 15-H), 6.25 (1 H, d, J = 10 Hz, 23-H), 6.96 (1 H, d, J = 3 Hz, 21-H), 7.22 (1 H, dd, J = 10 and 3 Hz, 22-H); mass spectrum m/e 424 (M^+), 409 ($M^+ - CH_3$), 396 (M^+ – CO), 381, 364 (M^+ – AcOH), 349, 335, 321, 255, 202.

Anal. Calcd for $C_{26}H_{32}O_5$: C, 73.56; H, 7.60. Found: C, 73.47; H, 7.69.

Dehydration of 3β-Acetoxy-14β-hydroxy-16-oxo-5β-bufa-20,22-dienolide (4). Method A. With Hydrochloric Acid. A solution prepared from hydroxy ketone **4** (40 mg), ethyl alcohol (2 ml), and 35% hydrochloric acid (0.1 ml) was heated at reflux for 15 min and poured into ice–water. A chloroform extract of the mixture was washed with water, dried, and evaporated to dryness. Column chromatographic separation (elution with 7:1 hexane–acetone) and recrystallization from methanol gave 34 mg of α,β-unsaturated ketone **5** as needles melting at 212–215°.

Method B. With Oxalic Acid. The preceding experiment was repeated using 30 mg of ketone **4**, 1.8 ml of methyl alcohol, and 10 mg of oxalic acid. In this example the mixture was heated at reflux for 30 min. Isolation of product as above led to 26 mg of ketone **5** melting at 210–213°.

Method C. With Acetic Acid. A solution of ketone **4** (15 mg) in acetic acid (1 ml) was heated at reflux for 15 min. Product was isolated as described in method A and found to weigh 12 mg (mp 210–213°).

Method D. With Amberlite CG-120 (H^+ Form). A mixture prepared from ketone **4** (25 mg), methyl alcohol (2 ml), and 0.125 g of Amberlite CG-120 (H^+ form) was stirred at room temperature for 8 hr. The solution was filtered and evaporated to dryness. The crude product was purified as indicated in method A to provide 19 mg of ketone **5** melting at 212–215°. Essentially the same yield (16 mg) of ketone **5** was obtained employing Dowex 50 W-X8 (H^+ form) and ethyl alcohol as solvent.

The specimens of ketone **5** obtained using methods A–D were mutually identical and identical with the specimen obtained by chromium(II) acetate reduction of ketone **3**.

3β-Acetoxy-14β,16β-dihydroxy-5β-bufa-20,22-dienolide (1b). Method A. Using Urushibara Nickel A. A large excess of freshly prepared Urushibara nickel A[11] was added to a solution of ketone **4** (40 mg) in ethyl alcohol (4 ml). The solution was heated at reflux 1 hr, filtered, and evaporated to dryness and the residue

(45 mg) was chromatographed on a column of silica gel. Elution with hexane–acetone (5:1 to 3:1) and recrystallization from acetone–hexane provided 28 mg of diol **1b** as needles melting at 255–256°.

Method B. Using Raney Nickel (W-2). The preceding experiment was repeated using 20 mg of ketone **4** and an excess of freshly prepared Raney nickel (W-2). The product weighed 11 mg and melted at 253–255°: tlc R_f 0.18; λ_{max} (CH_3CH_2OH) 295 nm (log ϵ 4.22); ν_{max} 3580, 3520 (OH), 1730, 1715, 1705, 1700, 1630, 1535, 1265, 1235, 1135, 1030, 950, 830, 745 cm^{-1}; pmr (10% solution in deuteriopyridine) δ 0.92 (3 H, s, 18-CH_3), 1.02 (3 H, s, 19-CH_3), 2.06 (3 H, s, 3-OAc), *ca.* 2.50 (*ca.* 2 H, broad d, J = 7 Hz, CH_2), 2.80 (1 H, d, J = 7 Hz, 17α-H), 4.81 (1 H, t, J = 7 Hz, 16α-H), 5.21 (1 H, broad peak, 3α-H), 6.28 (1 H, d, J = 10 Hz, 23-H), 7.47 (1 H, d, J = 3 Hz, 21-H), 8.45 (1 H, dd, J = 10 and 3 Hz, 22-H); mass spectrum *m/e* 444 (M^+), 426 ($M^+ - H_2O$), 408 ($M^+ - 2H_2O$), 400, 384, 366, 351, 348, 323, 261, 229, 214, 204.

Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.33; H, 8.14.

Oxidation of 3β-Acetoxy-14β,16β-dihydroxy-5β-bufa-20,22-dienolide (1b). Method A. Using Chromium Trioxide–Pyridine Complex. A 24-mg specimen of diol **1b** was treated with chromium trioxide (22 mg)–pyridine (2.2 ml) at 15–20° for 24 hr. Excess reagent was removed with methanol and the mixture was poured into ice–water and extracted with methylene chloride. The extract was washed with water, dried, and evaporated to a 44-mg residue which was chromatographed. The fractions eluted by 5:1 to 3:1 hexane–acetone recrystallized from methanol–hexane to afford hydroxy ketone **4** as needles (15 mg) melting at 228–233°.

When the oxidation was repeated employing 40 mg of diol **1b** in acetic acid (2.0 ml)–water (2 drops) with chromium trioxide (10 mg) at 0–5° for 20 hr two products were obtained, namely, 19 mg of hydroxy ketone **4** melting at 228–233° and 12 mg of α,β-unsaturated ketone **5** melting at 200–213° (from methanol). In each case the product was identical with the corresponding specimen prepared from ketone **3**.

Method B. Using *N*-Bromoacetamide. To a solution (at 10°) of diol **1b** (25 mg) in methanol (3 ml)–pyridine (1 ml)–water (0.1 ml) was added *N*-bromoacetamide (23 mg). The mixture was allowed to stand in the dark at 10–15° for 20 hr. After pouring the mixture into water and extraction with chloroform the combined extract was washed with water and evaporated to dryness. The crude product (28 mg) was purified as described in method A above to afford 14 mg of hydroxy ketone **4** melting at 229–233°.

3β,16β-Diacetoxy-14β-hydroxy-5β-bufa-20,22-dienolide (1c, Bufotalin Acetate). Selective acetylation of diol **1b** (30 mg) with acetic anhydride (0.5 ml)–pyridine (0.9 ml) was conducted at room temperature over 18 hr. The crude product (32 mg) was recrystallized from acetone–hexane to afford 25 mg of bufotalin acetate (**1c**) as prisms melting at 265–270°. The specimen of bufotalin acetate was identical with a sample prepared by analogous acetylation of natural bufotalin.

Bufotalin (1a). Method A. Hydrolysis with Hydrochloric Acid. A solution of bufotalin acetate (**1c**, 0.10 g) in methanol (4 ml) containing 35% hydrochloric acid (0.22 ml) was heated at reflux for 10 min. The reaction mixture was poured into ice–water and extracted with chloroform. The combined extract was washed with water and solvent was removed to give a 0.102-g residue. The mixture was separated by careful column chromatography. Successive elution with 19:1, 9:1, 7:1, 5:1, and 3:1 hexane–acetone mixtures and recrystallization of each fraction from acetone–hexane led to 15 mg of **bufotalin (1a,** needles melting at 215–220°), 12 mg of **3β-acetoxy-14β,16β-dihydroxy-5β-bufa-20,22-dienolide (1b,** needles melting at 253–255°), 10 mg of **desacetylbufotalin (1d,** prisms melting at 194–221°), 7 mg of **3β-acetoxy-16-hydroxy-5β-bufa-14,20,22-trienolide (6a,** prisms melting at 223–234°), and 35 mg of starting material (**1c**).

Method B. Hydrolysis with Amberlite CG-120 (H^+ Form). A mixture prepared from bufotalin acetate (**1c,** 0.10 g), ethyl alcohol (12 ml)–water (3.5 ml), and 1 g of Amberlite CG-120 (H^+ form) was stirred at room temperature for 38 hr. The solution was filtered and solvent was removed. The crude product was separated as described in the preceding experiment (method A) and led to 14 mg of bufotalin (**1a,** mp 217–221°), 10 mg of diol **1b** (mp 255–256°), 9 mg of desacetylbufotalin (**1d,** mp 199–215°), 5 mg of olefin **6a** (mp 223–234°), and 43 mg of recovered starting material (**1c**).

Method C. By Hydrolysis with Amberlite CG-400 (OH^- Form). The procedure of method B was repeated with 40 mg of bufotalin acetate (**1c**), methyl alcohol (10 ml)–water (1 ml), and 0.20 g of Amberlite CG-400 (OH^- form). In this case the mixture was stirred at room temperature for 8 hr. Separation of the crude product (45 mg) gave 4.8 mg of bufotalin (**1a,** mp 215–220°), 11 mg of diol **1b** (mp 253–255°), 2.6 mg of triol **1d** (mp 195–222°), and 16 mg of starting material (**1c**).

Method D. Hydrolysis by Potassium Bicarbonate. Potassium bicarbonate (0.19 g) in water (6.5 ml) was added to a solution of bufotalin acetate (**1c,** 0.17 g) in methanol (14 ml) and the solution was allowed to stand at room temperature for 10 days. After acidification (to pH 3.0) with dilute sulfuric acid the mixture was extracted with chloroform and the extract was washed with water. Removal of solvent gave a 0.18-g residue which was separated as summarized in method A. By this means 10 mg of bufotalin (**1a,** mp 219–226°), 50 mg of diol **1b** (mp 254–257°), 8.5 mg of desacetylbufotalin (**1d,** mp 201–219°), and 79 mg of recovered bufotalin diacetate (**1c**) were obtained.

Acetylation of Desacetylbufotalin (1d). A solution of desacetylbufotalin (**1d,** 50 mg) in glacial acetic acid (1 ml) was heated at reflux for 1 hr. Solvent was removed and the residue was chromatographed. Elution with the solvent sequence 19:1, 9:1, 7:1, and 5:1 hexane–acetone led to 14 mg of bufotalin acetate (**1c,** mp 266–270°), 9 mg of bufotalin (**1a,** mp 217–220°), 12 mg of diol **1b** (mp 253–256°), and 10 mg of recovered desacetylbufotalin (**1d**).

3β-Acetoxy-16β-hydroxy-5β-bufa-14,20,22-trienolide (6a). Method A. Reduction with Urushibara Nickel A. A large excess of freshly prepared Urushibara nickel A[11] was added to a solution of ketone **5** (40 mg) in ethyl alcohol (4 ml). The mixture was heated at reflux for 1 hr and the solution was filtered. After removal of solvent the residue was chromatographed using 5:1 hexane–acetone as eluent. The principal fraction recrystallized from acetone–hexane to afford 20 mg of alcohol **6a** as prisms melting at 229–237°.

Method B. Reduction with Raney Nickel (W-2). The preceding reduction reaction was repeated employing 20 mg of ketone **5** and a large excess of freshly prepared Raney nickel (W-2). By this means an 8-mg specimen of alcohol **6a** melting at 227–235° was obtained.

Method C. From Bufotalin Acetate (1c). Dehydration of bufotalin acetate (**1c**) was repeated as reported in Part 21.[6] The product, olefin **6b** (0.10 g), was dissolved in methyl alcohol (10ml) and a solution of potassium bicarbonate (0.10 g) in water (38 ml) was added. The saponification mixture was heated at 50° for 10 min and allowed to remain at room temperature for 4 days. Following acidification (to pH 3.0) with dilute sulfuric acid and extraction with chloroform the combined extract was washed with water and concentrated to dryness. The residue (97 mg) was chromatographed with 5:1 hexane–acetone as eluting solvent. The specimens of olefin **6a** prepared by methods A–C were found mutually identical. The major fraction was recrystallized from acetone–hexane to yield 67 mg of allylic alcohol **6a** as prisms melting at 228–237°: tlc R_f 0.31; λ_{max} (MeOH) 299 nm (log ϵ 4.22); ν_{max} 3520, 3480 (OH), 1750, 1720, 1710, 1690, 1635, 1538, 1260, 1230, 1030, 955. 910, 865, 750 cm^{-1}; pmr (10% solution in deuteriochloroform) δ 0.81 (3 H, s, 18-CH_3), 0.98 (3 H, s, 19-CH_3), 2.04 (3 H, s, 3-OAc), 2.53 (1 H, **d**, J = 8 Hz, 17-H), *ca.* 5.0 (1 H, broad m, 16α-H), 5.00 (*ca.* 2 H, m, 3α-H and 16α-H), 5.30 (1 H, broad s, 15-H), 6.30 (1 H, d, J = 11 Hz, 23-H), 7.33 (1 H, d, J = 3 Hz, 21-H), 7.86, (1 H, dd, J = 11 and 3 Hz, 22-H); mass spectrum *m/e* 426 (M^+), 408 ($M^+ - H_2O$), 366 (M^+ – AcOH), 348 ($M^+ - H_2O$ – AcOH), 241, 215, 202, 187.

Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.2; H, 7.04. Found: 73.37; H, 8.03.

3β,16β-Diacetoxy-5β-bufa-14,20,22-trienolide (6b, 3β-Acetoxy-14-dehydrobufotalin). Alcohol **6a** (50 ml) was treated with acetic anhydride (0.7 ml)–pyridine (1.0 ml) at room temperature for 18 hr. The crude product (53 mg) recrystallized from acetone–hexane to give 44 mg of 3β-acetoxy-14-dehydrobufotalin as prisms melting at 204–106°. The diacetate was identical with an authentic sample prepared from natural bufotalin.

Oxidation of 3β-Acetoxy-16β-hydroxy-5β-bufa-14,20,22-trienolide (6a). Method A. With Manganese Dioxide. Active (freshly prepared) manganese dioxide (0.10 g) was added to a solution of allylic alcohol **6a** (20 mg) in chloroform (2.0 ml) and the mixture was stirred at room temperature for 8 hr. The solution was filtered and concentrated to dryness. The crude product was separated by preparative thin layer chromatography on silica gel using 3:3:4 acetone–chloroform–hexane as mobile phase. The zone corresponding to R_f 0.43 was eluted with 3:1 methylene chloride–methanol. The eluted fraction was recrystallized from methanol to provide 15 mg of ketone **5** as needls melting at 211–215°.

Method B. With Chromium Trioxide. The oxidation reaction described to method A directly above was repeated employing 30

mg of allylic alcohol **6a** and the chromium trioxide (30 mg)–pyridine (2 ml) reagent (room temperature, 18 hr). The yield of ketone **5** melting at 211–213° was 22 mg. The yield (20 mg) was somewhat less employing 2% chromium trioxide in acetic acid (room temperature, 4 hr).

Bufotalin Acetate (1c). Method A. From Iodohydrin 7a. A solution of *N*-iodosuccinimide (25 mg) in acetone (0.5 ml)–water (0.5 ml) was added to an acetone (4 ml) solution of 3β-acetoxy-14-dehydrobufotalin (**6b**, 25 mg). The mixture was stirred for 30 min and allowed to remain at room temperature for 20 hr. The mixture was then diluted with sodium sulfite (25 mg in 1 ml of water), poured into ice–water, and extracted with chloroform. The combined extract was washed with water and concentrated to dryness to yield 24 mg of iodohydrin **7a**. A solution of the crude iodohydrin in methylene chloride was allowed to react with excess Urushibara nickel A with stirring (nitrogen atmosphere) at room temperature for 4 hr. The solution was filtered, solvent was evaporated, and the residue was chromatographed. Elution with 9:1 hexane–acetone led to 19 mg of bufotalin acetate as prisms melting at 263–269°.

Method B. From Bromohydrin 7b. The procedure of method A was repeated employing 20 mg of olefin **6b** and 20 mg of *N*-bromosuccinimide. In this experiment the reaction time was 19 hr and 12 mg of bufotalin acetate (**1c**, mp 265–269°) was realized. The overall yield of bufotalin acetate was essentially unchanged using *N*-bromoacetamide in place of *N*-bromosuccinimide.

Method D. From 3β,14β,16β-Trihydroxy-5β-bufa-20,22-dienolide (1d). A 20-mg sample of triol **1b** obtained *via* the ketone **4** route (**4** → **1b** → **1c** → **1d**) was acetylated with acidic anhydride (0.28 ml)–pyridine (0.4 ml) at room temperature over 18 hr. The crude acetone (22 mg) was recrystallized from acetone–hexane to yield 17 mg of bufotalin acetate (**1c**) melting at 263–269°. The specimens of bufotalin acetate prepared by methods A–C were found mutually identical.

Acknowledgments. We are pleased to acknowledge support of this investigation by the National Cancer Institute (performed pursuant to Contract No. N01-CM-12308 with the Division of Cancer Treatment, National Cancer Institute, Department of Health, Education and Welfare), the J. W. Kieckhefer Foundation, The Fannie E. Rippel Foundation, Mrs. Virginia L. Bayless, The Salt River Project of Arizona, The Arizona Public Service Co., and The Motorola Co.

Registry No.—**1a**, 471-95-4; **1b**, 4026-98-6; **1c**, 4029-69-0; **1d**, 465-19-0; **2**, 470-37-1; **3**, 36615-16-4; **4**, 35602-94-9; **5**, 51869-38-6; **6a**, 51869-39-7; **6b**, 36615-06-2; **7a**, 51869-40-0; **7b**, 51869-41-1; 3β-acetoxy-16β-hydroxy-14β,15β-epoxy-5β-bufa-20,22-dienolide, 4026-96-4.

References and Notes

(1) Part 89 of the series Steroids and Related Natural Products. For the prior contribution see Y. Kamano, G. R. Pettit, and M. Tozawa, *J. Org. Chem.*, **39**, 2319 (1974).
(2) Department of Chemistry, Faculty of Science, Tokyo Metropolitan University, Tokyo, Japan.
(3) J. L. Hartwell and B. J. Abbott *Advan. Pharmacol. Chemother.*, **7**, 117 (1969).
(4) *Cf.* K. K. Chen and A. Kovaříková, *J. Pharm. Sci.*, **56**, 1535 (1967).
(5) G. R. Pettit, P. Brown, F. Bruschweiler, and L. E. Houghton, *Chem. Commun.*, 1566 (1970).
(6) G. R. Pettit and Y. Kamano, *J. Org. Chem.*, **37**, 4040 (1972).
(7) G. R. Pettit and Y. Kamano, *J. Chem. Soc., Chem. Commun.*, 45 (1972).
(8) Y. Kamano and G. R. Pettit, *J. Org. Chem.*, **38**, 2202 (1973).
(9) G. R. Pettit and Y. Kamano, *J. Org. Chem.*, **39**, 2632 (1974).
(10) C. H. Robinson and R. Henderson, *J. Org. Chem.*, **37**, 565 (1972).
(11) Y. Urushibara, S. Nishimura, and H. Uehara, *Bull. Chem. Soc. Jap.*, **28**, 446 (1955); K. Hata, "Urushibara Catalyst," University of Tokyo Press, Tokyo, 1971, p 39. For a recent summary of experimental methods, see K. Hata, I. Motoyama, and K. Sakai, *Org. Prep. Proced.*, **4**, 179 (1973).
(12) J. H. Balthis and J. C. Bailar, *Inorg. Syn.*, **1**, 122 (1939).

Deoxygenation of 1,4-Epoxy-1,4-dihydronaphthalenes, a Possible Cheletropic Removal of Oxygen[1]

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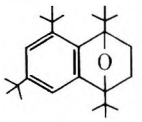
The one-step aromatization of benzyne–furan Diels–Alder adducts has been carried out in two ways. An apparent photochemical extrusion of atomic oxygen in triethylamine afforded a low yield of naphthalene. The use of naphthalene anion radical with substituted adducts proved to be a useful synthetic procedure.

In earlier work in our laboratory,[2] the acid-catalyzed dehydration of endoxide **1** afforded both the desired naphthalene **2** and the unexpected dealkylated naphthalene **3**.



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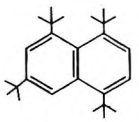

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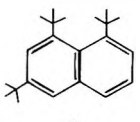

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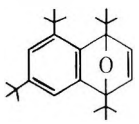
In addition, other dealkylations were observed, but the subject case was the most sensitive one. At the time, new routes to sensistive naphthalenes which would avoid acidic conditions were sought in our laboratory. One approach would be the direct deoxygenation of a benzyne–furan Diels–Alder adduct **4**. The proposed direct deoxygenation



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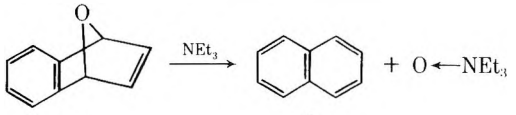
of endoxides such as **4** to form naphthalene **2**, is formally an *extrusion reaction*, examples of which are well known.[3] An approximate order of ease of extrusion is $N_2 > CO_2 > CO \geq$ "SO" $> SO_2 > O_2 \geq S > O$. Woodward and Hoffmann[4] describe a reaction and selection rules in which a tertiary amine reacts with a cyclic allyl ether so as to remove "atomic" oxygen resulting in the formation of an *N*-oxide and a polyene. An analysis of structures with the use



5 **6**

of models shows that the bridgehead protons of **5** obstruct the "linear" approach of the tertiary amine (one of the alkyl groups of the amine) so that oxygen abstraction cannot occur. Thus, a "nonlinear" disrotatory reaction requiring photochemical activation is predicted as necessary for our desired synthesis.[5]

The photolysis of 1,4-dihydronaphthalene-1,4-endoxide

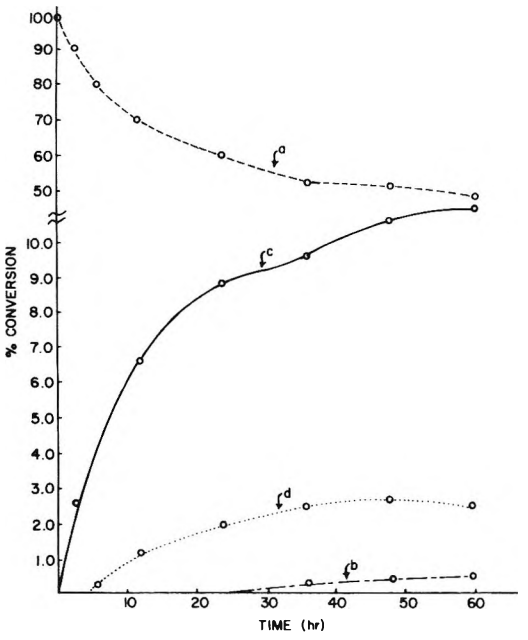
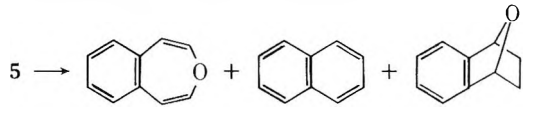


Figure 1. Irradiation of endoxide **5** at 2537 Å in ethanol: (a) endoxide **5**, (b) naphthalene (**6**), (c) benzoxepine **7**, (d) dihydroendoxide **9**.

(**5**) has been reported by Hammond and Ziegler.[6] They report that irradiation of an ethanol or ether solution of endoxide **5** afforded a 4–6% yield of the yellow benz[*l*]oxepine (**7**). The proposed intermediacy of a 7-oxaquadricyclane (**8**), which thermally rearranged to form **7**, was the first example of a $[_{\pi}2_3 + _{\pi}6_s]$ intramolecular cycloaddition.

5 8 7

For this work, a reinvestigation of this reaction, monitored by glpc, revealed the formation of benzoxepine (**7**) and two other products, **9** and **6**. These products were found in 1–4% ether or ethanol solutions of starting endoxide **5** after irradiations for a significant period of time. What is most interesting is the observation of the formation of naphthalene (**6**) and reduced endoxide **9**. These



7 6 9

products were previously undetected, since they do not absorb radiation at 445 nm, at which wavelength the concentrations of benzoxepine **7** were determined by Ziegler and Hammond (Figure 1). Irradiation of the endoxide **5** as a solution in triethylamine at 253.7 nm produced a photolysate with the same products but different proportions. (Figure 2). The starting material is consumed at a much slower rate, so that at the same period of irradiation (60 hr) less than half of starting endoxide **5** is consumed in the amine solution as compared with the ethanol solution. The yield of benzoxepine **7** has been halved while the yield of naphthalene (**6**) has been increased 14-fold. The yield of reduced endoxide **9** has been multiplied by approximately 2.5. In going from ethanol to triethylamine, the total conversion of endoxide has diminished from 13.9 to 4.4%, yet the total yield of products, **6**, **7**, and **9**, has not changed significantly (27.5 to 26.0%).

Investigations into the nature of the excited state in tri-

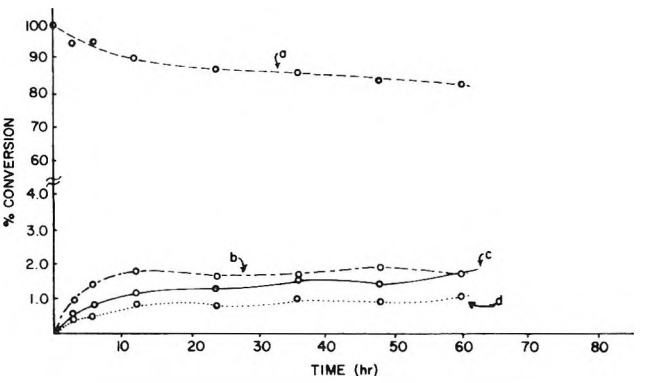


Figure 2. Irradiation of endoxide **5** at 2537 Å in triethylamine: (a) endoxide **5**, (b) naphthalene (**6**), (c) benzoxepine **7**, (d) dihydroendoxide **9**.

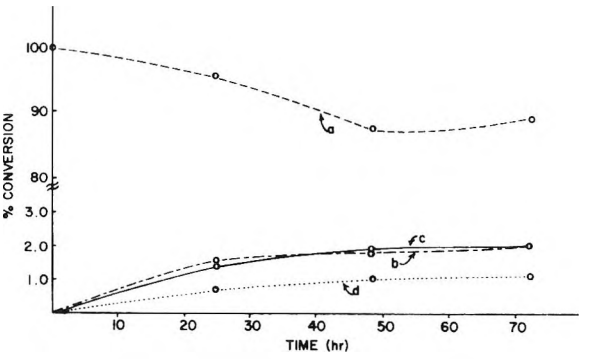


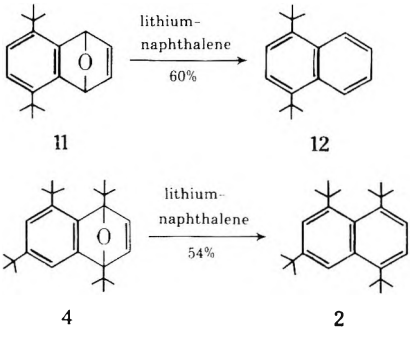
Figure 3. Irradiation of endoxide **5** at 2537 Å in triethylamine with added naphthalene: (a) endoxide **5**, (b) naphthalene formed in photolysis, (c) benzoxepine **7**, (d) dihydroendoxide **9**.

ethylamine were limited to the use of the lower energy triplet sensitizer, triphenylene (E_T = 67.2 kcal/mol; acetophenone, E_T = 76.3 kcal/mol). This was done to avoid the known reaction of aromatic ketones with tertiary amines in solution.[7] The photolysis of endoxide **5** in triethylamine in the presence of triphenylene produced only gummy, intractable material and no formation of **7**, **9**, or **6** was detected. Therefore, we assume that naphthalene (**6**) in addition to benzoxepine **7** and reduced endoxide **9** came from the singlet state of endoxide **5**. As the concentration of naphthalene (**6**) increases in triethylamine solution during the course of the reaction, it should compete with the other products and starting material for absorption of the available ultraviolet light. If this is true and the aromatic products do not react further, the overall disappearance of starting endoxide **5** should proceed more slowly. A solution of endoxide **5** in triethylamine was irradiated in the presence of the quantity of naphthalene which would have been the final amount produced. Figure 3 describes the progress of the reaction. At 60 hr, only 12% of the endoxide was consumed compared to 18% in the absence of naphthalene (Figure 3). Actual product distribution was not changed greatly in the presence of this aromatic hydrocarbon.

Several questions may arise pertaining to the actual source of naphthalene (**6**) in these photolyses. When the reduced endoxide **9** is treated with acid,[8] an excellent yield of naphthalene is obtained. If this dehydration could occur in the photolysate of endoxide **5**, this process might be the main source of naphthalene (**6**). An authentic sample of reduced endoxide **9** was irradiated in triethylamine under the same conditions as irradiation of endoxide **5**. After 48 hr, only 1.8% yield of naphthalene was detected while 71% of the starting reduced endoxide **9** was consumed. Compound **9** is, therefore, only a very minor source of naphthalene.

Since the yield of benzoxepine **7** was decreased in triethylamine while that of naphthalene (**6**) was increased, it might be argued that benzoxepine was the source of naphthalene.[9] Benzoxepine **7** was irradiated with a low-pressure mercury lamp under conditions comparable to the triethylamine–endoxide **5** photolysis. No naphthalene was detected even after irradiation for 107 hr. As a result, benzoxepine **7** is not considered to be a source of naphthalene (**6**). In addition, the products, **7**, **9**, and **6**, of photolysis are not the result of a thermal reaction of endoxide **5**. A solution of endoxide **5** in the amine was warmed at 90° for 77 hr and no trace of **7**, **9**, or **6** could be detected. Thus, our photochemical experiments demonstrate a deoxygenation process. We cannot specify the actual intermediate that is being deoxygenated. It could be the singlet excited state of **5**, quadricyclic **8**, or some electron-rich species which would account for both deoxygenation to form naphthalene and hydrogen abstraction to form reduction product **9**.

Our experiments focused on the use of anion radicals for the following reasons. Double bonds, both isolated and conjugated, can be photoreduced.[10] Furthermore, many mechanistic explanations for this reduction include charge transfer, exciplex formation, and/or radical anion intermediacy.[11] It was therefore conceivable that our photochemistry was simply serving as a fairly inefficient technique for forming the radical anion of **5**, only one of the several possibilities for deactivation of the excited singlet of **5**. Therefore, the production of the radical anion, which would bypass the undesirable photochemical products, was investigated.[12] We used lithium naphthalenide as our electron source and endoxides **4** and **11** as substrates. In clean conversions, the desired substituted naphthalenes were produced.



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4 2

Experimental Section

General. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer Models 137 and 337 spectrometers. Ultraviolet spectra were determined on a Cary 15 spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian A-60A instrument at probe (38°) temperature. Signals are reported downfield from tetramethylsilane. An F & M 810 gas chromatograph with flame ionization detectors and a Honeywell 16 recorder with a disk integrator was used for qualitative and quantitative determinations. The carrier gas was nitrogen at a flow rate 30–40 ml/min. The columns used in this work were A, 6 ft × 0.125 in., 10% silicone gum rubber SE-30 on 80–100 mesh Chromosorb WAW-DMCS; B, 6 ft × 0.25 in., 10% polyphenyl ether (six ring) on 60–80 mesh Chromosorb WAW-DMCS; C, 5 ft × 0.125 in., 15% XF-1150 on 60–80 mesh Chromosorb W; D, 8 ft × 0.125 in., 15% XF-1150 on 60–80 mesh Chromosorb W; E, 8 ft × 0.125 in., 5% Carbowax 20M on 80–100 mesh Chromosorb WAW; F, 8 ft × 0.125 in., 10% XE-60 on 50–100 mesh Anakrom ABS; G, 5 ft × 0.125 in., 10% QF-1 on 60–80 mesh Chromosorb W.

Calibration curves were determined by measuring the glpc response of a known with respect to that of a known quantity of 1-menthol and subjecting these ratios to a least-squares analysis for fitting a straight line to a series of points.[13] Errors in yields and conversions are within a 10% relative standard deviation. The calibration curves for 1,4-dihydronaphthalene-1,4-endoxide (**5**), naphthalene (**6**), and 1,2,3,4-tetrahydronaphthalene-1,4-endoxide (**9**) were prepared by this method. Benzoxepine (**7**) could not be isolated in pure enough state to prepare such a curve. Calibration curves were checked every few months for the correlation, within experimental error, of known *vs.* calculated data.

Photolysis of 1,4-Dihydronaphthalene-1,4-endoxide (5). A. Triethylamine. (1) A 1% solution of endoxide **5** in distilled triethylamine[14,15] was irradiated[16] for 194 hr in a water-jacketed quartz-well photolysis apparatus under a nitrogen atmosphere and magnetically stirred. The resulting amber, cloudy solution was evaporated to give an amber oil. A vpc on column B (200°) indicated the major constituent to be the starting endoxide with minor amounts of materials with retention times of benzoxepine and naphthalene. The dark green solid which adhered to the immersion well was scraped off and this amounted to 5% by weight of starting material. It was insoluble in benzene, hexane, acetone, ethyl ether, and water but soluble in methylene chloride and chloroform. Its melting point was above 350° and it had weak and broad absorptions in the infrared spectrum (KBr) at 2890, 1620, 1580, 1440, 800, 752, and 685 cm^{-1}.

The amber oil above was chromatographed on a column of silica gel and eluted with a gradient of hexane to ether. The fractions were each analyzed by glpc (column B) and combined on this basis. The later fractions (25–40% v/v ether in hexane) contained mainly starting endoxide. This was sublimed and recrystallized from pentane.[17] Thirty-six per cent of the starting endoxide (**5**) could be recovered.

The earlier fractions (20–25% v/v ether in hexane) contained mixtures of naphthalene (**6**), benzoxepine **7**, and endoxide **5**. These were combined and submitted to preparative gas–liquid partition chromatography. Naphthalene (**6**) was isolated in a yield of 0.80% and was confirmed by its infrared spectrum and by peak enhancement techniques in glpc. After two sublimations (low vacuum), the melting point was 78–81° (lit. mp 80.2°).

The yellow benzoxepine **7** was also isolated by this preparative glpc and sublimed in 0.67% yield: mp 82–83° (lit. mp 83–84°);[18] ir (CCl_4) 1658 and 1631 (enol ether), 1486, 1431, 1049 cm^{-1}.

(2) A quartz nmr tube was filled with a 2–6.5% solution of endoxide **5** (*ca.* 100–200 mg) in distilled triethylamine (*ca.* 2.5 ml) and was stoppered with a serum cap. This solution also contained menthol as a standard in amounts equal to 10% of the weight of endoxide. The air above the solution was exchanged for nitrogen or argon *via* a hypodermic syringe. The tube was inverted several times to ensure homogeneity. It was suspended 3 cm from a low-pressure Hg lamp and irradiated.

Samples were withdrawn with a hypodermic syringe through the septum at various time intervals. Each sample was analyzed several times by glpc on column C or D at 100–120°. A significant number of analyses were taken so that the relative standard deviation of R (the ratio of $area_i$ to $area_{standard}$) was less than 10% (usually less than 5%).

(3) A 5.1% solution of endoxide **5** in distilled triethylamine (0.71 mmol in 2.0 ml) containing 0.0094 g of menthol was placed in a quartz nmr tube. This solution contained 0.041 mmol of naphthalene (**6**), an amount which reflected the final per cent conversion (*ca.* 6%) expected in its absence. The analytical procedure was as stated above.

(4) Repeating the procedure with the quartz nmr tube described above, a 6.5% solution of 0.1629 g (1.13 mmol) of endoxide **5** and 0.0161 g of menthol was irradiated by a low-pressure Hg lamp for 60 hr. Analysis of the reaction mixture was made by glpc (column D, 150°) and the amount of naphthalene (**6**) was carefully determined. Infrared spectra were taken of the reaction mixture at time zero and 60 hr. A sample of triethylamine N-oxide (3.45 mg) was added to the irradiated reaction mixture. Infrared spectra were taken of this new reaction mixture and the spectra before and after addition were compared.

B. In Ether or Ethanol. (1) A solution of 1.122 g (7.8 mmol) of endoxide **5** in 110 ml of anhydrous ethyl ether was irradiated for 48 hr under nitrogen with a low-pressure Hg lamp in a quartz photolysis vessel.

Evaporation of the yellow solution gave 1.193 g of an amber syrup. The glpc on column B verified the presence of starting endoxide **5**, naphthalene (**6**), and benzoxepine **7**. This oil was chromatographed on a column of 60 g of activated silica gel and eluted with a gradient of hexane to 5% ether in hexane (v/v). The fractions were each analyzed by glpc. Those which contained benzoxepine also contained naphthalene and endoxide. They were com-

bined to give 0.238 g of a yellow solid, mp 50–65°). Recrystallization from MeOH–H_2O gave 0.112 g of a yellow solid, mp 80–83° (lit. mp 83–84°[18]). The mother liquor was extracted with ether and dried over sodium sulfate. This was subjected to two 1-g columns of silica gel to increase the isolated yield to 11.1%: ir (CCl_4) 1664 and 1631 (enol ether), 1486, 1431, 1311, 1049 cm^{-1}.

In another attempt to obtain pure benzoxepine, the crude reaction mixture was chromatographed by dry column technique on alumina (CCl_4 eluent). The yellow band was extracted and rechromatographed on silica gel by dry-column technique using pentane as eluent. This gave a 6.4% yield of a yellow solid which was only approximately half benzoxepine by glpc analysis (column C, 165°).

(2) A 4% solution of 0.1056 g (0.733 mmol) of endoxide **5** and 0.0175 g of menthol in 2.5 ml of absolute ethanol was used to fill a quartz nmr tube. The tube was stoppered with a serum cap and the air above the solution was exchanged for argon *via* a syringe. The tube was inverted several times to ensure the homogeneity of the solution and irradiated at a distance of 3 cm from a low-pressure Hg lamp. Samples were removed at various time intervals and subjected to glpc analysis on column C at 110°.

C. In the Presence of a Sensitizer. In a quartz nmr tube described above, a 4.4% solution of endoxide **5** in distilled triethylamine was irradiated in the presence of triphenylene (0.15%) with a 450-W Hanovia medium-pressure mercury-arc lamp with a Kimex filter. After 48 hr, the solution was filtered and the residue was washed with benzene. Washings were added to the filtrate, which was then concentrated and a known amount of standard added.

Deoxygenation with Radical Anion Naphthalene. The stock solution of lithium radical anion naphthalene was prepared in both dry THF and 1,2-dimethoxyethane.[19] Small strips of lithium wire (0.0104 mol) were added to a solution of 0.0111 mol of naphthalene in 30 ml of dry solvent under an argon atmosphere. The blue-green color of the radical anion appeared within 2 hr. The solution was stirred (glass-covered stirring bar) overnight. This mixture was used in the deoxygenations of two endoxides.

A. 1,4,5,7-Tetra-*tert*-butyl-1,4-dihydronaphthalene-1,4-endoxide (4). A 4.20-mg portion of this endoxide (4) was stirred in 1 ml of dry DME under an argon atmosphere. One milliliter of the stock radical anion solution was injected dropwise from a syringe over 10 min. Coloration persisted for 2 hr at ambient temperatures. The dark green mixture was decomposed with an iodine crystal and the resulting colorless, cloudy suspension was evaporated *in vacuo*. The residue was suspended in 10 ml of ether and then washed with 5 ml of 1 *N* sodium thiosulfate solution. The organic layer was then washed with 5 ml of water and 5 ml of saturated sodium chloride solution and dried over sodium sulfate.

Evaporation gave 83 mg of a semisolid which was sublimed at 45° (10 mm) for 1.5 hr to remove naphthalene. The amber residue (7 mg) was chromatographed by thin layer chromatography on magnesium silicate (20 × 20 cm plate, 0.1-mm thickness, eluent pentane). The major spot (R_f 0.90–0.74) was extracted with benzene and methylene chloride to give 3 mg of an oily solid. This was rechromatographed on a quarter plate of magnesium silicate to give 2.15 mg (53.5% yield) of a semisolid which was pure by glpc (column A, 230°) and which proved to be 1,4,5,7-tetra-*tert*-butylnaphthalene (**2**) by peak enhancement and comparison of the infrared spectrum with that of authentic samples.

B. 5,8-Di-*tert*-butyl-1,4-dihydronaphthalene-1,4-endoxide (11).[20] A 10.5-mg portion of this endoxide (11) was stirred (glass-covered stirring bar) in 2 ml of dry DME under an atmosphere of argon. The radical anion solution in DME was injected slowly until the blue-green color did not discharge (*ca.* 2 ml). The mixture was allowed to stir for 1 hr at room temperature. A sample was removed, decomposed with water, and extracted with ether. The organic layer was concentrated and subjected to glpc analysis (column C, 175°). The presence of naphthalene and 1,4-di-*tert*-butylnaphthalene (**12**) was confirmed by peak enhancement. No starting endoxide was evident.

The reaction mixture was decomposed with an iodine crystal and evaporated. The residue was taken up in ether, washed with 5 ml of 1 *N* sodium thiosulfate solution, water, and saturated brine, and dried over magnesium sulfate. Evaporation of solvent gave 20 mg of semisolid.

This was sublimed at room temperature at 14 mm to remove naphthalene. The yellowish residue (12 mg) was chromatographed by thin layer technique on magnesium silicate (20 × 20 cm plate, 0.1-mm thickness, eluent CCl_4). the major spot (R_f 0.75–0.60) was extracted with methylene chloride. Evaporation of solvent gave 6 mg (61% yield) of a semisolid which was 1,4-di-*tert*-butylnaphthalene (**12**) by peak enhancement of glpc and by comparison of ir of authentic samples. A similar procedure in THF gave only 50% yield.

Registry No.—**4**, 22495-83-6; **5**, 573-57-9; **11**, 10565-41-0.

References and Notes

(1) (a) Portions of this work have been presented at the Autumn Meeting of the Chemical Society, London, Oct 1970, Abstracts, A 10. (b) Taken from the Ph.D. Thesis of S. B. P., Fordham University, 1973. (c) Acknowledgment for partial financial support is made to the National Science Foundation (Grant GP 7754), the National Institutes of Health (CA 11421), and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

(2) R. W. Franck and E. G. Leser, *J. Org. Chem.*, **35**, 3932 (1970); *J. Amer. Chem. Soc.*, **91**, 1577 (1969).

(3) B. P. Stark and A. J. Duke, "Extrusion Reactions," Pergamon Press, Elmsford, N. Y., 1967.

(4) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

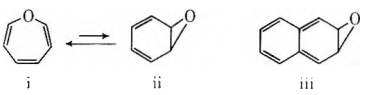
(5) For a complete discussion of selection rules, correlation diagrams, and state diagrams, see S. B. Polovsky, Ph.D. Thesis, Fordham University, 1973.

(6) G. R. Ziegler, *J. Amer. Chem. Soc.*, **91**, 446 (1969); G. S. Hammond and G. R. Ziegler, *ibid.*, **90**, 513 (1968).

(7) (a) S. G. Cohen and H. M. Chao, *J. Amer. Chem. Soc.*, **90**, 165 (1968); (b) R. S. Davidson, P. F. Lambeth, F. A. Younis, and R. Wilson, *J. Chem. Soc. C*, 2203 (1969); (c) S. G. Cohen and J. B. Guttenplan, *Tetrahedron Lett.*, 5353 (1968).

(8) G. Wittig, *Angew. Chem.*, **69**, 245 (1957); G. Wittig and L. Pohmer, *Chem. Ber.*, **89**, 1334 (1956).

(9) It has been found that oxepin (i) is in equilibrium with oxonorcaradiene (ii). It is conceivable that benzoxepine **7** is in equilibrium with or convertible to iii, which on deoxygenation would afford naphthalene. E. Vogel and H. Gunther, *Angew. Chem., Int. Ed. Engl.*, **6**, 385 (1967).



i ii iii

(10) (a) P. S. Engler and H. Ziffer, *Tetrahedron Lett.*, 5181 (1969); (b) A. Gilbert, "Photochemistry," Vol. 2, D. Bryce-Smith, Ed., Chemical Society, London, 1973; (c) W. M. Horspool, *ibid.* p 439; (d) R. C. Cookson, J. Hudec, and N. A. Mirza, *Chem. Commun.*, 180 (1968); (e) R. C. Cookson, S. M. De B. Costa, and J. Hudec, *ibid.*, 753 (1969).

(11) (a) A. Weller, *Pure Appl. Chem.*, **16**, 115 (1968); (b) M. G. Kuzim and L. N. Guseva, *Chem. Phys. Lett.*, **3**, 71 (1969); (c) J. A. Barltrop and R. J. Owers, *Chem. Commun.*, 1462 (1970); (d) see ref 7b. (e) R. F. Bartholomew, D. R. G. Brimage, and R. S. Davidson, *J. Chem. Soc. C*, 3482 (1971).

(12) There are conflicting precedents for this reaction. (a) The original preparation of endoxide **5** was done in the presence of lithium amalgam, and no deoxygenation was detected; see ref 8. (b) In the analogous preparation of an endoxide from phenanthryne and furan, deoxygenation to triphenylene was observed: G. Wittig, W. Uhlenbrock, and P. Weinhold, *Chem. Ber.*, **95**, 1692 (1962). (c) The tetrafluorobenzyne adduct with furan is not deoxygenated by lithium amalgam: P. L. Cole, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 3227 (1962). (d) Hetaryne–furan adducts are deoxygenated: T. Kaufmann and F. Boettcher, *Chem. Ber.*, **95**, 949 (1962); R. J. Martens and H. J. den Hertog, *Tetrahedron Lett.*, 643 (1962). (e) The adduct of furan and diisopropylacetylene dicarboxylate is deoxygenated by lithium naphthalenide: S. F. Nelsen and E. F. Travecedo, *Tetrahedron Lett.*, 2685 (1969). (f) After this work was completed, a preliminary communication describing experiments that convert unsubstituted endoxide **5** to naphthalene (**6**) using sodium naphthalenide was reported: J. G. Krause and S. Perreault, *J. Chem. Soc., Chem. Commun.*, 591 (1972). (g) A possible analogous reaction is the reported isolation of naphthalene and triphenylsilylnaphthalene from the reaction of endoxide **5** and triphenylsilyllithium: D. Wittenberg, D. Aoki, and H. Gilman, *J. Amer. Chem. Soc.*, **80**, 5933 (1958).

(13) W. J. Youden, "Statistic! Methods for Chemists," Wiley, New York, N. Y.. 1964, pp 40–49.

(14) (a) L. Friedman and F. M. Logullo, *J. Amer. Chem. Soc.*, **85**, 1549 (1963); L. F. Fieser and M. J. Haddadin, *Can. J. Chem.*, **43**, 1599 (1965); L. Friedman and F. M. Logullo, *J. Org. Chem.*, **34**, 3089 (1969); (b) E. Wolthius, *ibid.*, **26**, 2215 (1961); H. Gilman and R. Gorsich, *J. Amer. Chem. Soc.*, **79**, 2628 (1957); (c) ref 8.

(15) Dried over potassium hydroxide and distilled from a 2% solution of naphthyl or phenyl isocyanate (triethylamine bp 89°).

(16) Low-pressure mercury-arc lamp whose output is greater than 90% at 2537 Å.

(17) A solid which was insoluble in pentane; proved to be α-naphthol by infrared spectrum and glpc retention time.

(18) K. Dimroth, G. Pohl, and H. Follmann, *Chem. Ber.*, **99**, 634 (1966); K. Dimroth and G. Pohl, *Angew. Chem.*, **73**, 436 (1961).

(19) K. Suga, S. Watanabe, and K. Kamma, *Can. J. Chem.*, **45**, 933 (1967); W. D. Closson, P. Wreide, and S. Bank, *J. Amer. Chem. Soc.*, **88**, 1582 (1966).

(20) R. W. Franck and K. Yanagi, *J. Org. Chem.*, **33**, 811 (1968); *Tetrahedron Lett.*, 2905 (1966).

Effect of Solvent, Temperature, and Nature of the Sulfonate Group on the Azide Displacement Reaction of Sugar Sulfonates

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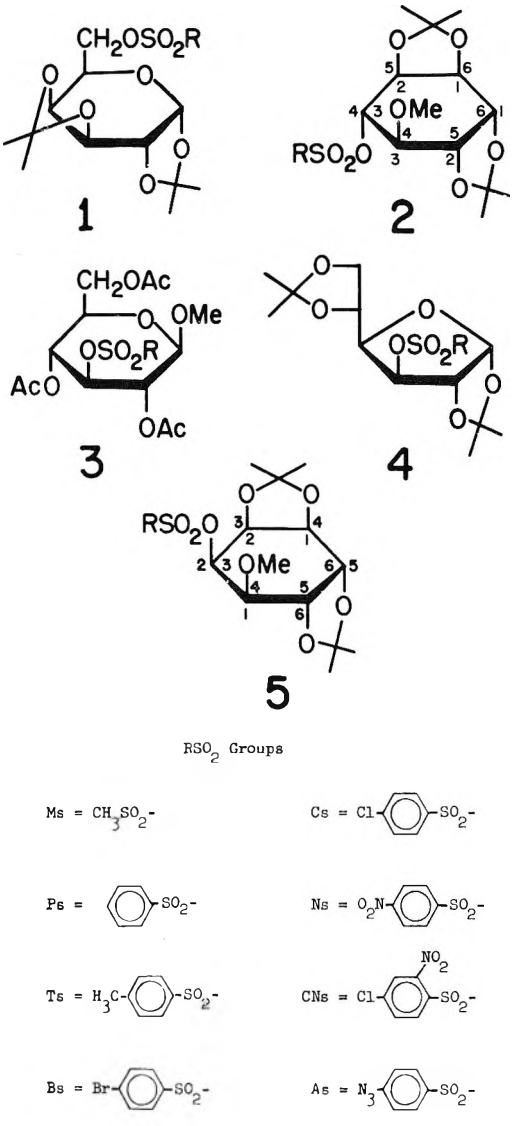
The effect of variation in the solvent, temperature, and nature of the sulfonate group on the rate of the azide–sulfonate displacement reaction was studied with series of sulfonate esters of diisopropylidenegalactose, diisopropylidenepinitol, and methyl tri-*O*-acetyl-D-gluco- and D-galactopyranosides. The order of rates with respect to solvent, calculated for pseudo-first-order conditions, is HMPT > DMSO > DMF. For four primary *p*-toluenesulfonates in DMF ΔH^* ranges from 16.7 to 20.3 kcal/mol, and ΔS^* from −16 to −21.5 eu. The order of rates with respect to sulfonate group is *p*-bromobenzenesulfonate > benzenesulfonate > *p*-toluenesulfonate > methanesulfonate. *p*-Nitrobenzenesulfonates in part give the parent alcohols and *p*-azidonitrobenzene, which is converted by inorganic azide to *p*-nitroaniline. Both direct attack by N_3^- on the aromatic ring and an indirect path beginning with attack on the sulfur must be considered as possible routes to *p*-azidonitrobenzene. The ready replacement by azide of the bromine in *p*-bromobenzenesulfonates was demonstrated.

The displacement of sulfonate groups by azide ion has been much used during the past decade as a means of introducing eventual amino groups into carbohydrate molecules.[1] The method is widely but not universally applicable, being subject to the restrictions which generally govern the displacement of secondary sulfonate groups. These restrictions, which involve conformational and electronic factors, have been particularly well delineated by Richardson[2a] and by Ball and Parrish.[2b]

Among the successful cases of displacement by azide there is great variation in the time required to complete the reaction and in the yield of product obtained. Such variations must be due in part to subtle steric and electronic effects, and in part to factors readily subject to control by the investigator, including the solvent used, the temperature, and the nature of the sulfonate leaving group. There is a body of qualitative knowledge about the effects of these latter variables,[2b] but they have had little systematic investigation. In the present paper quantitative data are given which should aid the synthetic chemist, in the carbohydrate and other fields, in choosing the sulfonate ester to be employed and arranging optimal reaction conditions.



Results

Effect of the Solvent. It is well known that the rates of the displacement of sulfonate groups by azide, like those of other bimolecular displacements involving anionic nucleophiles, are enhanced in dipolar aprotic solvents.[3] Thus, *N*,*N*-dimethylformamide (DMF) and methyl sulfoxide (DMSO) are frequently used in the preparation of carbohydrate azides. Also used is hexamethylphosphortriamide (HMPT), which is regarded as a superior medium for displacement reactions,[4,5] and 2-methoxyethanol, a protonic solvent. Some workers employ the anhydrous solvents, while others add water.

To study the effects of these variations in the solvent the rates of reaction with sodium azide were measured at 110° for two sulfonate esters which undergo displacement with moderate difficulty. One of these, 1,2:3,4-di-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-galactopyranose (1-Ts), is a primary sulfonate; the other, 1D-1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-4-*O*-*p*-tolylsulfonyl-*chiro*-inositol ("diisopropylidenetosylpinitol," 2-Ts), is a secondary sulfonate. Measurements were made in the nominally dry solvents, and in the presence of 1 and 10% (v/v) added water.

In Table I it may be seen that for each substrate the second-order rate constants are about the same in dry DMF and DMSO, and about tenfold greater in HMPT. The addition of water depressed the rates in all cases, the effect being greatest with HMPT. For the most part the data appear to fit the relationship log *k* proportional to the mole fraction of organic solvent.[6] Qualitative tests showed that, with both sulfonates, the reaction proceeds much more slowly in 2-methoxyethanol than in the dipolar aprotic solvents.

The observed second-order rate constants are measures

Table I
Second-Order Rate Constants for the Azide Displacement Reaction of Tosylates 1-Ts and 2-Ts in the Common Dipolar Aprotic Solvents

Sulfonate	Solvent	$10^2 k_2$, M^{-1} min^{-1}, at 110° [a] Dry	1% H_2O	10% H_2O
Gal (1-Ts)	DMF	2.60 ± 0.07	1.98 ± 0.10	0.83 ± 0.05
	DMSO	2.30 ± 0.10	2.00 ± 0.10	0.98 ± 0.03
	HMPT	20.0 ± 0.5	14.9 ± 0.4	3.4 ± 0.4
Pin (2-Ts)	DMF	0.97 ± 0.03	0.86 ± 0	0.36 ± 0.01
	DMSO	0.84 ± 0.02	0.56 ± 0.06	0.35 ± 0
	HMPT	8.2 ± 0.2	6.7 ± 0.1	1.74 ± 0.11

[a] Values are means ± range or, where three or more runs were made, ± standard deviation.

Table II
Solubility of Sodium Azide in the Solvents Used for Sulfonate Displacements

Solvent	Solubility, mol/l. Dry	1% H_2O (110°)	5% H_2O (110°)	10% H_2O (110°)
2-Methoxyethanol	0.31 (124°)			
DMF	0.10–0.12 (25–150°)	0.17	0.28	0.48
DMSO	1.5–1.6 (95–150°)	1.6	1.8	1.9
HMPT	0.43 (110–150°)	0.45	0.48	0.51

Table III
Pseudo-First-Order Rate Constants and Times Required for 97% Completion of the Azide Displacement of Tosylates 1-Ts and 2-Ts at 110°

Sulfonate	Solvent	Dry $10^3 k_1$, min^{-1}	Dry $t_{97\%}$, hr	10% H_2O $10^3 k_1$, min^{-1}	10% H_2O $t_{97\%}$, hr
Gal (1-Ts)	DMF	2.6	22	4.0	14
	DMSO	39	1.5	18	3.2
	HMPT	86	0.67	17	3.3
Pin (2-Ts)	DMF	1.0	59	1.7	33
	DMSO	13	4.4	6.5	8.8
	HMPT	35	1.6	8.9	6.5

of the ability of the respective solvents to promote the azide displacement. However, the reaction is frequently run with excess solid sodium azide present, making it a pseudo-first-order process. Under these conditions the rate is also a function of the solubility of the reagent. Measurements of solubility show that sodium azide is much more soluble in DMSO than in the other two solvents (Table II). For the dry solvents, at least, there is remarkably little variation in solubility with temperature. The addition of water up to 10% greatly increases the solubility of the reagent in DMF, but has only a small effect with DMSO and HMPT.

When the observed second-order rate constants are converted to pseudo-first-order constants by reckoning in the solubility, the values shown in Table III are obtained. The times required for 97% completion of the reaction are also shown. Under pseudo-first-order conditions the reaction proceeds 13–15 times more rapidly in dry DMSO than in dry DMF. An additional two- to threefold gain in rate is achieved by going to dry HMPT. In DMF containing 10% water the rate is 1.5–2 times greater than in the dry solvent, but the addition of water decreases the first-order rates in the other two solvents.

Effect of Temperature. The variation of the rate of the azide displacement reaction with temperature was studied on a series of primary *p*-toluenesulfonates in DMF. The compounds examined and the activation parameters calculated from the data are listed in Table IV. Since this part of the study was designed to provide numbers for the synthetic chemist to use in approximating the effect of temperature on the rate of the reaction, the data are not as extensive or as precise as in the usual physical organic study. Nevertheless they permit qualitative comparisons with the activation parameters of related reactions.

Effect of the Sulfonate Group. In synthetic work in the carbohydrate field methanesulfonate (mesylate) and *p*-toluenesulfonate (tosylate) esters are the most commonly used substrates for displacement reactions. It is generally recognized that toluenesulfonate is a better leaving group

Table IV
Activation Parameters for the Azide Displacement of Some Primary Sugar Tosylates in DMF at 80°

Sulfonate	Registry no.	$10^4 k_2$, M^{-1} sec^{-1}	Measurements made at °C	ΔH^*, kcal/mol[a]	ΔS^*, eu/mol[b]
Methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside	23661-33-8	166	60, 70, 80	16.7	−19.6
Methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranoside	13032-69-4	120	60, 70, 80, 100	18.5	−15.9
Methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside	52109-81-6	5.2	80, 100, 110	20	−17
1,2:3,4-Di-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-galactopyranose (1-Ts)		0.42	80, 100, 110	20.3	−21.5

[a] Estimated accuracy ±1 kcal/mol. [b] Estimated accuracy ±3 eu.

Table V
Variation of the Rate of the Azide Displacement Reaction with Variation of the Sulfonate Group

Sulfonate group	Diisopropylidene-galactose sulfonates (1), $10^2 k_2$, M^{-1} min^{-1}, at 110° in DMF [a]	Diisopropylidene-pinitol sulfonates (2), $10^2 k_2$, M^{-1} min^{-1}, at 110° in DMF [a]	Methyl 2,4,6-tri-O-acetyl-β-D-glucopyranoside sulfonates (3), $10^2 k_2$, M^{-1} min^{-1}, at 110° in DMF [a]
Methanesulfonate	1.1 ± 0.1		
p-Toluenesulfonate	2.6 ± 0.1	0.97 ± 0.03	7.9 ± 0.6
Benzenesulfonate	3.4 ± 0.1		
p-Bromobenzenesulfonate	12 ± 0	3.0 ± 0.1	30.4 ± 0.8
p-Chlorobenzenesulfonate		3.6 ± 0.1	

[a] Values are means ± range or, where three or more runs were made, ± standard deviation.

than methanesulfonate. The use of *p*-bromobenzenesulfonates (brosylates) is occasionally reported, and displacements of *p*-nitrobenzenesulfonates (nosylates) have also been attempted.

To compare the efficacy of the various sulfonate groups in the azide displacement reaction, series of sulfonate esters, **1**, of diisopropylidene-α-D-galactopyranose and **2**, of diisopropylidenepinitol, were prepared. Rate measurements were then carried out on all the esters which appeared to be transformed cleanly to azido products. Two sulfonates (**3**) of methyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside were also included in the study. The measurements were made in DMF at 110°.

It would be expected on theoretical grounds that the rate of the bimolecular displacement of sulfonate groups, RSO_3^-, would increase with increasing electron-withdrawing power of the R group. Indeed this has been demonstrated in the case of the alkoxide displacement of ethyl sulfonates.[7] The results of the present work (Table V) are also in accord with these expectations. In the diisopropylidenegalactose series the tosylate reacted 2.4 times faster than the mesylate, and the brosylate was 11 times faster. A comparison of tosylate with brosylate can be made for all three of the parent sugars, whereupon the rates of displacement of the brosylate group are seen to be 3.0–4.6 times those of tosylate. The *p*-chlorobenzenesulfonate of diisopropylidenepinitol had a slight rate advantage over the corresponding brosylate. No rate measurements were made with the nitrobenzenesulfonates **1**-Ns, **2**-Ns, and **2**-CNs because these compounds reacted with azide ion in two ways, giving the parent alcohols in addition to the normal displacement products. The nature of the side reaction is further discussed below.

In view of the notorious resistance to displacement of the tosylate group in 1,2:5,6-di-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (**4**-Ts) it seemed of interest to study the corresponding brosylate and nosylate. It had been shown[8] that when the brosylate **4**-Bs is treated with dimethylamine the bromine is displaced from the aromatic ring. Also, it had been reported[9] that the nosylate **4**-Ns gave much tar and some of the parent alcohol (diisopropylideneglucose) on treatment with methanolic ammonia at 165°. In our hands the reaction of **4**-Bs with sodium azide under the conditions used for the kinetic measurements gave a crystalline product which could be characterized, by its spectral properties and elemental analysis, as 3-*O*-*p*-azidophenylsulfonyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. The reaction of the nosylate **4**-Ns with azide also gave some of the *p*-azidobenzenesulfonate, as well as the parent alcohol.

The foregoing results raised the question whether the displacement of the brosylates **1**-Bs, **2**-Bs, and **3**-Bs might be proceeding, in part, *via* azidobenzenesulfonates. On refinement of the tlc system used for following the reaction we could demonstrate the formation of some *p*-azidobenzenesulfonate during the displacement of **1**-Bs, and enough of the compound was isolated for a single measurement of its displacement rate. A value of 0.06 M^{-1} min^{-1} in DMF at 110° was found, which is about half the overall rate measured for **1**-Bs. We could not detect azidobenzenesulfonates from **2**-Bs and **3**-Bs, but since the displacement rate for **2**-Bs is lower than that for **1**-Bs, **2**-Bs probably also undergoes some replacement of bromine.

The complexity of the reaction of the brosylates with azide did not strongly affect the kinetic measurements, for plots of 1/substrate concentration *vs.* time were linear out to 2 half-lives. Beyond that point the precision of our analyses was too low to permit any conclusions as to whether the kinetics were complex. Nevertheless the measured rate constants must be considered as composite constants for the direct displacement of brosylate and the simultaneous displacement of azidobenzenesulfonate formed from a portion of the brosylate.

It seemed of interest to investigate the process whereby the nitrobenzenesulfonates are converted, in part, to parent alcohols during attempted displacement with azide ion. Under solvolysis conditions some sugar nosylates have given products suggestive of dissociation to nosylate and sugar carbonium ions.[10,11] If this were happening in the present case the carbonium ions might combine with the solvent to give labile intermediates which would be hydrolyzed to parent alcohols on work-up. To test this possibility compound **1**-Ns and the cyclitol nosylate **5**-Ns were prepared with ^{18}O in the ester oxygen. The labeled compounds were then treated with sodium azide in DMF at 110° for 24 hr, and the alcoholic products were isolated. These products retained all of the ^{18}O of the nosylates from which they were derived. The product from **1**-Ns was identified as 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (formula **1**, H in place of SO_2R). The pmr spectrum of the product from **5**-Ns was identical with that of 1D-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*allo*-inositol (formula **5**, H in place of RSO_2) and the product from (unlabeled) **2**-Ns was rigorously characterized as the pinitol derivative (formula **2**, H in place of RSO_2). These cyclitols are indeed the parent alcohols of **5**-Ns and **2**-Ns; hence there was retention of configuration at the sulfonate-bearing carbons. Compound **1**-Ns gave parent alcohol when heated alone in DMF.

Further investigation of the reactions of the nosylates with azide showed that a major aromatic product was *p*-nitroaniline. In search of immediate precursors of this compound, samples of *p*-azidonitrobenzene and *p*-nitrobenzenesulfonyl azide were synthesized. When the sulfonyl azide was heated for a short time with sodium azide in DMF it was converted to *p*-azidonitrobenzene. The latter, or the sulfonyl azide, when heated for 24 hr with sodium

azide gave *p*-nitroaniline as the principal product. The presence of sodium azide was necessary for the formation of the *p*-nitroaniline. *p*-Nitrobenzenesulfonic acid was unaltered under these conditions, except for salt formation.

In a final experiment the reaction of compound **2**-Ns with sodium azide was interrupted after 3 hr. Chromatographic and pmr spectroscopic examination of the rather complex reaction mixture showed that *p*-azidonitrobenzene, but not *p*-nitrobenzenesulfonyl azide, was present.

Azido Products. Reference samples of all the azido products were obtained by making preparative runs with the respective *p*-toluenesulfonates. The 6-sulfonates gave the expected 6-azido-6-deoxy compounds. Of these, 6-azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[12] and methyl 2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-α-D-glucopyranoside[13] have been reported in the literature. The product from **3**-Ts and **3**-Bs is assumed to be methyl 2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-β-D-allopyranoside on the basis that, in view of its second-order kinetics, the displacement took place with inversion of configuration.

Inversion of configuration was demonstrated to occur in the formation of azidocyclitols from sulfonates of series **2** and **5**. The characterization of these products will be described in a forthcoming paper.

Discussion

The data reported here reveal the extent to which the rates of azide–sulfonate displacements are affected by changes in the sulfonate group and the solvent used as reaction medium. For the compounds studied, with sodium azide as reagent under pseudo-first-order conditions in the common dipolar aprotic solvents, a *ca.* 35-fold range of variation could be shown to result from variation of the solvent, and an 11-fold change from variation of the sulfonate group. Combination of these two factors gives an overall variation in rates, at a given temperature, of nearly 400-fold. It is thus evident that considerable savings in the time required to prepare azido carbohydrate derivatives may be realized by proper choice of solvent and sulfonate ester. These savings will be significant in cases where the parent sugar structure is one which makes displacement inherently slow.

Our results confirm the superiority of HMPT as a solvent for azide–sulfonate displacements. The advantage of HMPT over DMSO is not great, however, owing to the better solubility of the reagent in DMSO. Accordingly DMSO may well be chosen when it is more readily available, or if it is found to be more easily removed from the reaction mixture during work-up. Where maximal rates are not required DMF is to be preferred because it is more easily removed than either of the other two solvents. The addition of up to 10% (perhaps more) of water to DMF increases the solubility of the reagent enough to more than offset the intrinsic rate-depressing effect of the water, and hence is to be recommended. Both DMSO and HMPT give better rates when dry.

Among the sulfonate groups brosylate has a clear advantage over mesylate and tosylate. The fact that a portion of a brosylate may be converted to azidobenzenesulfonate is not a drawback, for it appears that azidobenzenesulfonates undergo displacement at good rates. Under the conditions of our experiments the reaction of the very resistant diisopropylideneglucose derivative **4**-Bs stopped at the azidobenzenesulfonate stage. However, the azide displacement of the tosylate of diisopropylideneglucose has recently been accomplished by prolonged reaction at 115° in DMF,[14] or by treatment for 18 hr at 120° in HMPT.[15] Much elimination product was formed in the latter case.

The hope of achieving further gains in rate by using the still more electron-withdrawing nitrophenyl group in the sulfonate moiety was frustrated by the tendency of the nitrobenzenesulfonates to undergo a side reaction which regenerates the parent alcohols. This reaction was found to proceed with retention of configuration and, when ^{18}O-labeled nosylates were used, retention of label. These findings rule out mechanisms involving C–O cleavage, such as dissociation to *p*-nitrobenzenesulfonate and carbonium ions, or attack by the solvent on the esterified carbon. Since parent alcohol is generated in the absence of sodium azide, there may be some attack by the solvent (or traces of water therein) on the sulfonate sulfur, with the eventual formation of *p*-nitrobenzenesulfonate ion. However, this cannot be the major pathway when azide is present, for it does not explain the formation of *p*-nitroaniline (nosylate ion is inert to sodium azide). Rather, what is indicated is attack by N_3^- either on the sulfur or on the aromatic ring carbon bonded to sulfur. In the former case *p*-nitrobenzenesulfonyl azide would be formed, and the SO_2N_3 group would be displaced by a second N_3^- ion as shown in the present work to give the observed intermediate *p*-azidonitrobenzene. In the second case the *p*-azidonitrobenzene would be produced directly. The final conversion to *p*-nitroaniline may be rationalized as a reduction of *p*-azidonitrobenzene by azide ion.

In summary, the use in a contemplated azide displacement of a sulfonate with a too strongly electron-withdrawing R group can divert the attack of the azide to the sulfonate moiety. In the nitrobenzenesulfonate case, in addition to the points of attack just cited, the nitro group may also suffer displacement, as seen with **4**-Ns. This side reaction, unlike the others, may be followed by the normal displacement of the sulfonate group from the carbon to which it is esterified. Another case of the displacement of the nitro group from **4**-Ns is that observed by Rosenthal and Nguyen,[16] where the alkoxide of diisopropylideneglucose was the displacing species.

A virtue of choosing the solvent and sulfonate group which will give the maximal rate of azide displacement is that this permits lowering the reaction temperature. Since carbohydrate sulfonates and azides are both subject to elimination and other reactions of decomposition at high temperature, the best yields should in general be obtained by operating at the lowest temperature that gives a reasonable reaction rate. Thus, the yield of displacement product from diisopropylideneglucose sulfonates (**4**) could probably be improved by using the brosylate in DMSO (less basic then HMPT) at a temperature somewhat lower than 115°. An estimate of the effect of a change in temperature may be made from the data in Table IV or, more conveniently, by taking 2.2 as the factor by which the reaction rate increases with a 10° increase in temperature (the "Q_{10}" of the older literature).

Our data on the enthalpies and entropies of activation of the azide–sulfonate displacement reaction show no marked differences from other types of bimolecular displacements.[17] In a study of a closely related reaction, the displacement of primary sugar benzenesulfonates by iodide ion in 2,5-hexanedione, Sugihara and Teerlink[18] found 20–25 kcal/mol for ΔH^* and −6 to −15 eu for ΔS^*. These values are, respectively, a little higher and a little less negative than those found in Table IV.

It will be noted that although the diisopropylidenegalactose derivatives (**1**) are primary sulfonates, their reaction rates are in the same range as those of the secondary sulfonates **2** and **3** (Table V). The contrast between **1**-Ts and the more typical primary tosyl derivatives of glucose is

highlighted in Table IV, which also shows a comparatively low reaction rate for the 6-tosylate of methyl tri-*O*-acetyl-α-D-galactopyranoside. This low reactivity of the galactose primary sulfonates, particularly those derived from diisopropylidenegalactose,has been known for many years.[19] It has been attributed both to steric effects[20] and to field effects.[18,21] An explanation based on the interaction of dipoles in the transition state has also been advanced.[2b]

Experimental Section

General. Thin layer chromatography plates were prepared from silica gel G (Merck) and column chromatography was performed on silica gel (Merck). Chromatograms of both types were developed with ethanol–Skellysolve B, 1:9, v/v (solvent A) or benzene–acetone–ether, 14:3:1, v/v/v (solvent B). Compounds and reaction mixtures were routinely checked by tlc in solvent A; solvent B was used only as expressly noted. Melting points were determined in Pyrex glass capillaries immersed in a heated oil bath equipped with a calibrated thermometer. Proton magnetic resonance spectra were recorded with Varian A-60 or T-60 spectrometers, and are referenced to tetramethylsilane as internal standard. Infrared spectra were recorded on a Beckman IR-5. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Mass spectra were obtained with an AEI MS-902 instrument.

2-Methoxyethanol and hexamethylphosphortriamide from Eastman Organic Chemicals were redistilled, the latter under reduced pressure. Methyl sulfoxide, anhydrous grade, and *N,N*-dimethylformamide, spectroquality grade, were from Matheson Chemicals. All these solvents were stored over Linde type 4A molecular sieves.

Sulfonate Esters. Diisopropylidenegalactose,[22] diisopropylidenepinitol,[23] and diisopropylideneglucose were treated with sulfonyl chlorides under the conditions described by Tipson.[22] The acetylated 3-sulfonates of methyl β-D-glucopyranoside were prepared from the corresponding diisopropylideneglucose sulfonates according to Ahluwahlia, *et al.*[24] The following were recrystallized until their melting points and specific rotations agreed closely with those in the literature: 1-Ms,[25] 1-Ps,[18] 1-Ts,[26,27] 2-Ts,[28] 4-Ts,[29] 4-Bs,[8] 4-Ns,[9] and 3-Ts.[30] The acetylated 6-*p*-toluenesulfonates of methyl α-D-glucopyranoside,[31] methyl β-D-glucopyranoside,[32] and methyl α-D-galactopyranoside[33] were prepared by Cramer's procedure.[34]

6-*O*-*p*-Bromophenylsulfonyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (1-Bs) was recrystallized from ethanol: yield 92%; mp 92–93°; $[\alpha]_{589}$ −45.8° (c 2, DMF); pmr ($CDCl_3$) τ 2.23 and 2.32 ppm (q_{AB}, 4, J = 9 Hz, aromatic H).

Anal. Calcd for $BrC_{18}H_{23}O_8S$ (479.35): C, 45.10; H, 4.84. Found: C, 45.37; H, 4.90.

1,2:3,4-Di-*O*-Isopropylidene-6-*O*-*p*-nitrophenylsulfonyl-α-D-galaetopyranose (1-Ns) was recrystallized from ethanol: yield 78%; mp 101–102°; $[\alpha]_{589}$ −48.9° (c 2, DMF); pmr ($CDCl_3$) τ 1.60 and 1.85 ppm (q_{AB}, 4, J = 9 Hz, aromatic H).

Anal. Calcd for $C_{18}H_{23}NO_{10}S$ (445.44): C, 48.53; H, 5.20. Found: C, 48.59; H, 5.19.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-*p*-nitrophenylsulfonyl-[6-^{18}O]-α-D-galactopyranose ([6-^{18}O]-1-Ns). [^{18}O]Benzoic acid was prepared by treating 0.75 ml of $H_2{}^{18}O$ (40 atom %) in 25 ml of dry pyridine with a 0.96 molar portion of benzoyl chloride (78% yield). Sodium [^{18}O]benzoate made by neutralizing the acid with sodium hydroxide was recrystallized from ethanol–water. Compound 1-Ts (1.27 g, 3.1 mmol) and the labeled sodium benzoate (0.89 g, 6.2 mmol) were refluxed in 25 ml of dry DMF for 65 hr. The reaction mixture was then diluted with 50 ml of water and extracted twice with ether (50 ml each). The ether extract, washed twice with water and dried ($MgSO_4$), was evaporated to dryness under vacuum. The syrupy product was identical (tlc in solvent B, pmr) with the substance obtained by benzoylating 1,2:3,4-di-*O*-isopropylidenegalactose with benzoyl chloride, and the pmr spectra had the expected features. Hence the compound was **1-[^{18}O]benzoyl-1,2:3,4-di-*O*-isopropylidene-[6-^{18}O]-α-D-galactopyranose** (yield 0.95 g, 85%).

The labeled benzoate ester was catalytically saponified (sodium methoxide, methanol) to **1,2:3,4-di-*O*-isopropylidene-[6-^{18}O]-α-D-galactopyranose** containing, according to mass spectrometric analysis, 17.1 atom % excess ^{18}O in the labeled position (expected, 20 atom %). The calculations[35] were based on the peaks at *m/e* 245 and 247 (M − 15). The **bulk** (0.65 g, 2.5 mmol) of the [^{18}O]diisopropylidenegalactose was converted to **[6-^{18}O]-1-Ns** by treatment with two molar portions of *p*-nitrobenzenesulfonyl chloride according to the Tipson method,[22] yield 0.82 g (73%), mp 103–104°.

6-*O*-*p*-Azidophenylsulfonyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (1-As). To a solution of 1-Bs (4.8 g, 10 mmol) in HMPT (50 ml), excess sodium azide (5 g) was added. The solution was heated at 110° for 30 min, then distilled under high vacuum (80°, 0.05 Torr) to remove all the solvent. The residue was extracted with chloroform and the extract was evaporated to a thick syrup. Tlc in solvent A showed three spots, R_f 0.8 (6-azido-6-deoxydiisopropylidenegalactose), 0.55 (starting material), and 0.53 (title compound). These components were separated by column chromatography (solvent A), which yielded 0.2 g of pure title compound as a yellowish syrup: ir (film) 2100 cm^{-1} (N_3); pmr ($CDCl_3$) τ 2.19 and 2.82 ppm (q_{AB}, 4, J = 9 Hz, aromatic H).

Anal. Calcd for $C_{18}H_{23}N_3O_8S$ (441.45): C, 48.97; H, 5.25; N, 9.52. Found: C, 49.03; H, 5.49; N, 9.25.

1D-3-*O*-*p*-Bromophenylsulfonyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*chiro*-inositol (2-Bs)[36] was recrystallized from ethanol: yield 90%; mp 115–116°; $[\alpha]_{589}$ +22.7° (c 2, DMF); pmr ($CDCl_3$) τ 2.21 and 2.36 ppm (q_{AB}, 4, J = 9 Hz, aromatic H).

Anal. Calcd for $BrC_{19}H_{25}O_8S$ (493.37): C, 46.25; H, 5.11. Found: C, 46.55; H, 5.37.

1D-3-*O*-*p*-Chlorophenylsulfonyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*chiro*-inositol (2-Cs) was recrystallized from ethanol: yield 80%; mp 110–111°; $[\alpha]_{589}$ +59.7° (c 1, $CHCl_3$); pmr ($CDCl_3$) τ 2.12 and 2.53 ppm (q_{AB}, 4, J = 9 Hz, aromatic H).

Anal. Calcd for $ClC_{19}H_{25}O_8S$ (448.91): C, 50.83; H, 5.61. Found: C, 50.22; H, 5.52.

1D-1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-4-*O*-*p*-nitrophenylsulfonyl-*chiro*-inositol (2-Ns) was recrystallized from ethanol: yield 89%; mp 129–131°; $[\alpha]_{589}$ +64.5° (c 1, $CHCl_3$); pmr ($CDCl_3$) τ 1.64 and 1.89 ppm (q_{AB}, 4, J = 9 Hz, aromatic H).

Anal. Calcd for $C_{19}H_{25}NO_{10}S$ (459.46): C, 49.66; H, 5.48. Found: C, 49.61; H, 5.36.

1D-3-*O*-(4-Chloro-2-nitrophenylsulfonyl)-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*chiro*-inositol (2-CNs) was recrystallized from ethanol: yield 80%; mp 118–119°; $[\alpha]_{589}$ +49.3° (c 1, $CHCl_3$); pmr ($CDCl_3$) τ 1.87–2.38 ppm (m, 3, aromatic H).

Anal. Calcd for $ClC_{19}H_{24}NO_{10}S$ (493.91): C, 46.20; H, 4.90. Found: C, 46.75; H, 5.29.

Methyl 2,4,6-tri-*O*-acetyl-3-*O*-*p*-bromophenylsulfonyl-β-D-glucopyranoside (3-Bs) was recrystallized from ethanol: yield 35%; mp 102–103°; $[\alpha]_{589}$ −15.1° (c 2, $CHCl_3$); pmr ($CDCl_3$) τ 7.93 (s, 3), 8.00 (s, 3), and 8.03 (s, 3) ($COCH_3$), 6.50 (s, 3, OCH_3), and 2.35 ppm (s, 4, aromatic H).

Anal. Calcd for $BrC_{19}H_{23}O_{11}S$ (539.36): C, 42.31; H, 4.30. Found: C, 42.85; H, 4.50.

3-*O*-*p*-Azidophenylsulfonyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (4-As) was obtained from 3-*O*-*p*-bromophenylsulfonyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (4-Bs) by a procedure similar to that used for the preparation of compound 1-As. Recrystallized from ethanol, it had mp 109–110°; $[\alpha]_{589}$ −77.7° (c 1, $CHCl_3$); ir (KBr) 2100 cm^{-1} (N_3); pmr ($CDCl_3$) τ 8.53 (s, 3), 8.70 (s, 3), 8.79 (s, 3), and 8.85 (s, 3) (isopropylidene CH_3), 4.10 (d, 1, J = 4 Hz, H-1), 2.19, and 2.82 ppm (q_{AB}, 4, J = 9 Hz, aromatic H).

Anal. Calcd for $C_{18}H_{23}N_3O_8S$ (441.45): C, 48.97; H, 5.25; N, 9.52. Found: C, 48.93; H, 5.31; N, 9.73.

1D-1,2:5,6-Di-*O*-isopropylidene-4-*O*-methyl-3-*O*-*p*-nitrophenylsulfonyl-*allo*-inositol (5-Ns) (Including [3-^{18}O]-5-Ns).[36] 1L-2-*O*-Benzoyl-3,4:5,6-di-*O*-isopropylidene-1-*O*-methyl-*allo*-inositol[37] was catalytically saponified (sodium methoxide, methanol) and 0.54 g of the resulting syrupy hydroxy compound was treated with three molar portions of *p*-nitrobenzenesulfonyl chloride according to the Tipson procedure.[22] The title compound was recrystallized from absolute ethanol: yield 50%; mp 137°; $[\alpha]_{589}$ + 8°, $[\alpha]_{436}$ + 17° (c 0.7, $CHCl_3$); pmr ($CDCl_3$) τ 1.61 and 1.83 ppm (q_{AB}, 4, J = 9.3 Hz, aromatic H).

Anal. Calcd for $C_{19}H_{25}NO_{10}S$ (459.46): C, 49.66; H, 5.48; N, 3.04; S, 6.97. Found: C, 49.40; H, 5.59; N, 2.99; S, 7.01.

An amount of 1.36 g (3.2 mmol) of compound 2-Ts was treated with the above-described sodium [^{18}O]benzoate (0.91 g, 6.3 mmol) by the procedure of Angyal and Stewart.[37] The resulting 1L-2-*O*-**[^{18}O]-benzoyl-3,4:5,6-di*O*-isopropylidene-1-*O*-methyl-[2-^{18}O]-*allo*-inositol** (0.89 g, 74%) was catalytically saponified to **1D-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-[3-^{18}O]-*allo*-inositol** (0.54 g, 84%). Calculation (see above) based on the mass spectral peaks at *m/e* 259 and 261 (M − 15) showed 17.1 atom % excess ^{18}O in this product. Conversion to **[3-^{18}O]-5-Ns** was accomplished as for the unlabeled material. The purity of the intermediate and

the final product was checked by tlc in solvent B.

Reaction Rate Measurements. Bacteriological culture tubes (1.8 × 15 cm) with screw caps, equipped with 0.5-in. magnetic stirring bars, were used as reaction vessels. A solution of sodium azide in the desired solvent was adjusted to 0.100 *M* (titration). Sulfonate sufficient to give a concentration of 0.100 *M* was weighed into a volumetric flask and dissolved in the azide solution. Aliquots (2.00 ml) of the mixture were then distributed to the tubes and these tubes were immersed to 5 cm in a preheated oil bath regulated to ±0.1°. The oil bath was mounted on a magnetic stirrer. Tubes were removed at intervals and quenched by adding 20 ml of ice water, and the remaining azide ion was titrated with 0.010 *M* silver nitrate with potassium chromate as indicator.[38] Two or more runs were made with each ester in each solvent used.

Solubility of Sodium Azide. Sodium azide (5 g) and the solvent (40 ml) were stirred magnetically in a stoppered flask at the desired temperature for 4 hr. Stirring was discontinued, and after the solid sodium azide had settled, 2 ml of the clear solution was taken by a volumetric pipette and titrated with 0.010 *M* silver nitrate.

Azido Products. The desired *p*-toluenesolfonate was heated with excess sodium azide in DMF at 110° for a suitable time. The reaction mixture was then evaporated to dryness under reduced pressure. The residue was extracted with ether, the extract was evaporated, and the crude azide was purified by the appropriate means.

Product from 3-Ts and 3-Bs. The reaction time was 2 days. Purification by column chromatography gave a colorless syrup: $[\alpha]_{589}$ −25° (*c* 2, $CHCl_3$); ir (film) 2100 cm^{-1} (N_3); pmr ($CDCl_3$) τ 7.90 (s, 3) and 8.00 (s, 6) ($COCH_3$), 6.58 (s, 3, OCH_3), and 4.9–6.2 ppm (m, 7, sugar ring H).

Methyl 2,3,4-Tri-*O*-acetyl-6-azido-6-deoxy-β-D-glucopyranoside. The reaction time was 30 min. The product was recrystallized from ethanol: mp 80–82°; $[\alpha]_{589}$ −38.5° (*c* 2, $CHCl_3$); ir (KBr) 2100 cm^{-1} (N_3); pmr ($CDCl_3$) no aromatic H.

Anal. Calcd for $C_{13}H_{19}N_3O_8$ (345.31): C, 45.22; H, 5.55. Found: C, 45.34; H, 5.40.

Methyl 2,3,4-Tri-*O*-acetyl-6-azido-6-deoxy-α-D-galactopyranoside. The reaction time was 30 min. The product was recrystallized from ethanol–Skellysolve B: mp 85–86°; $[\alpha]_{589}$ +137.3° (*c* 2, $CHCl_3$); ir (KBr) 2100 cm^{-1} (N_3); pmr ($CDCl_3$) no aromatic H.

Anal. Calcd for $C_{13}H_{19}N_3O_8$ (345.31): C, 45.22; H, 5.55. Found: C, 45.39; H, 5.07.

Azide Displacement of the *p*-Nitrobenzenesulfonates. Samples (about 0.8 g) of compounds 1-Ns, 2-Ns, and 5-Ns were heated with an eightfold molar excess of sodium azide in 20 ml of dry DMF at 110° for 24 hr. The solutions were diluted with 50 ml of water and extracted thrice with ether (50 ml each). The combined ether extracts were washed twice with water, dried ($MgSO_4$), examined by tlc (solvent B), and concentrated to dryness. Chromatography of the residues on silica gel columns (3.3 × 60 cm, solvent B) gave in each case three fractions. The first fractions to emerge from each column were shown by comparison (tlc, pmr) with authentic samples to be the azidodeoxydi-*O*-isopropylidene derivatives of galactose, 1-*O*-methyl-*allo*-inositol, and pinitol, respectively. The second fraction in each case was identified as *p*-nitroaniline by comparison (tlc, pmr, ir, and mixture melting point) with an authentic sample.

The third fractions were indistinguishable (tlc, pmr) from the respective parent alcohols of 1-Ns, 2-Ns, and 5-Ns. The product from 2-Ns was heated with 50% aqueous acetic acid to hydrolyze off the isopropylidene groups, and the residue was trimethylsilylated and subjected to glc[39] on a column of 5% SE-30 on Chromosorb W. This column clearly separated the TMS ethers of 1-*O*-methyl-*allo*-inositol and pinitol. The product from 2-Ns chromatographed with penta-*O*-trimethylsilylpinitol.

Treatment of [6-^{18}O]-1-Ns and [3-^{18}O]-5-Ns as just described gave parent alcohol fractions which were analyzed by mass spectrometry (see above). Values of 16.8 and 17.6, respectively, were found for the atom per cent excess ^{18}O in the labeled positions.

A sample (0.23 g) of 2-Ns was heated for 3.5 hr with sodium azide in DMF and worked up as just described. Tlc (solvent B) of the ether extract showed five components, with the R_f's, respectively, of *p*-azidonitrobenzene, unknown, the azidocyclitol product, *p*-nitroaniline, and the parent alcohol. Partial separation of the mixture was accomplished by column chromatography. In the aromatic region of the pmr spectrum of the residue from the early fractions the characteristic doublets (τ 1.71, 2.83, $CDCl_3$) due to *p*-azidonitrobenzene were clearly evident.

Conversion of Aromatic Intermediates to *p*-Nitroaniline. Samples of *p*-azidonitrobenzene[40] (0.064 g) and *p*-nitrobenzenesulfonyl azide[41] (0.11 g) were heated in 5 ml of dry DMF at 110° for 24 hr. After evaporation of the solvent under vacuum the residues were examined by tlc (solvent B) and pmr. The *p*-azidonitrobenzene was recovered unchanged. The *p*-nitrobenzenesulfonyl azide was converted to a product which was not *p*-azidonitrobenzene or *p*-nitroaniline, but which was not further characterized.

These experiments were repeated with the addition of sodium azide (eightfold molar excess) to the reaction mixtures. Ether extracts were obtained as described in the previous section. The residue in both cases was primarily *p*-nitroaniline (tlc, pmr).

p-Nitrobenzenesulfonyl azide was treated with sodium azide as just described for 1 hr. Examination (tlc, pmr) of the residue from the ether extract showed complete disappearance of the starting material. The major product was *p*-azidonitrobenzene, accompanied by a substantial portion of *p*-nitroaniline.

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Registry No.—1-Bs, 52109-71-4; 1-Ns, 52109-72-5; 1-Ns (6-^{18}O), 52109-73-6; 1-Ts, 4478-43-7; 1-As, 52109-74-7; 2-Bs, 52109-75-8; 2-Cs, 52109-76-9; 2-Ns, 52109-77-0; 2-CNs, 52109-78-1; 2-Ts, 18391-45-2; 3-Bs, 52109-79-2; 4-As, 52109-80-5; 4-Bs, 20581-78-6; 5-Ns, 52154-18-4; methyl 2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-β-D-glucopyranoside, 52109-82-7; methyl 2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-α-D-galactopyranoside, 52109-83-8.

References and Notes

(1) A. K. Chatterjee, D. Horton, and J. S. Jewell, *Carbohyd. Res.*, **7**, 212 (1968).
(2) (a) A. C. Richardson, *Carbohyd. Res.*, **10**, 395 (1969); (b) D. H. Ball and F. W. Parrish, *Advan. Carbohyd. Chem.*, **24**, 139 (1969).
(3) A. C. Richardson, *Annu. Rep. Progr. Chem.*, **63**, 493 (1966).
(4) J.-J. Delpuech, *Tetrahedron Lett.*, 2111 (1965); *Bull. Soc. Chim. Fr.*, 1624 (1966).
(5) Y. All and A. C. Richardson, *J. Chem. Soc. C*, 1764 (1968).
(6) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).
(7) M. S. Morgan and L. H. Cretcher, *J. Amer. Chem. Soc.*, **70**, 375 (1948).
(8) D. Horton, J. S. Jewell, and H. S. Prihar, *Can. J. Chem.*, **46**, 1580 (1968).
(9) B. Coxon and L. Hough, *J. Chem. Soc.*, 1643 (1961).
(10) P. W. Austin, J. G. Buchanan, and R. M. Saunders, *J. Chem. Soc. C*, 372 (1967).
(11) P. W. Austin, J. G. Buchanan, and D. G. Large, *Chem. Commun.*, 418 (1967).
(12) W. A. Szarek and J. K. N. Jones, *Can. J. Chem.*, **43**, 2345 (1965).
(13) F. Cramer, H. Otterbach, and H. Springmann, *Chem. Ber.*, **92**, 384 (1959).
(14) U. G. Nayak and R. L. Whistler, *J. Org. Chem.*, **34**, 3819 (1969).
(15) R. L. Whistler and L. W. Doner, *J. Org. Chem.*, **35**, 3562 (1970).
(16) A. Rosenthal and L. Nguyen, *Can. J. Chem.*, **46**, 3751 (1968).
(17) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 22.
(18) J. M. Sugihara and W. J. Teerlink, *J. Org. Chem.*, **29**, 550 (1964).
(19) R. S. Tipson, *Advan. Carbohyd. Chem.*, **8**, 107 (1953).
(20) M. Akagi, S. Tejima, and M. Haga, *Chem. Pharm. Bull.*, **11**, 559 (1963).
(21) S. Nadkarni and N. R. Williams, *J. Chem. Soc.*, 3496 (1965).
(22) R. S. Tipson, *Methods Carbohyd. Chem.*, **2**, 246 (1963).
(23) S. J. Angyal and C. G. Macdonald, *J. Chem. Soc.*, 686 (1952). Prepared by the procedure of S. J. Angyal and R. M. Hoskinson, *J. Chem. Soc.*, 2985 (1962), using dimethoxypropane as reagent.
(24) R. Ahluwahlia, S. J. Angyal, and M. H. Randall, *Carbohyd. Res.*, **4**, 478 (1967).
(25) B. Helferich, H. Dressier, and R. Griebel, *J. Prakt. Chem.*, **261**, 285 (1939).
(26) K. Freudenberg and R. M. Hixon, *Ber.*, **56**, 2119 (1923).
(27) A. B. Foster, W. G. Overend, M. Stacey, and L. F. Wiggins, *J. Chem. Soc.*, 2542 (1949).
(28) S. J. Angyal and N. K. Matheson, *J. Amer. Chem. Soc.*, **77**, 4343 (1955).
(29) K. Freudenberg and O. Ivers, *Ber.*, **55**, 929 (1922).
(30) S. Peat and L. F. Wiggins, *J. Chem. Soc.*, 1088 (1938).
(31) B. Helferich and E. Himmen, *Ber.*, **61**, 1825 (1928).
(32) J. Compton, *J. Amer. Chem. Soc.*, **60**, 395 (1938).
(33) H. Ohle and H. Thiel, *Ber.*, **66**, 525 (1933).
(34) F. D. Cramer, *Methods Carbohyd. Chem.*, **2**, 244 (1963).
(35) S. R. Thorpe and C. C. Sweeley, *Biochemistry*, **6**, 887 (1967).
(36) The cyclitol derivatives described here are named and numbered according to the IUPAC-IUB Tentative Cyclitol Nomenclature Rules, *J. Biol. Chem.*, **243**, 5809 (1968). It will be noted that in some cases the methy-

lated position of pinitol is assigned the number 3, and the sulfonylated position the number 4, while in other cases the opposite is true. Similar numbering shifts occur with the *allo*-inositol derivatives, accompanied by a change in the designation of configurational series (D or L). These unfortunate variations result from the necessity of choosing between the two equivalent numberings inherent in the stereochemistry of each of the parent inositols. The choice is made by the principle of "lowest number to the substituent first in alphabetical order," which seems the least undesirable of the alternatives available for dealing with this situation. Confusion is best avoided by constant reference to formulas **2** and **5**.

(37) S. J. Angyal and T. S. Stewart, *Aust. J. Chem.*, **20**, 2117 (1967).
(38) J. W. Arnold, *Ind. Eng. Chem., Anal. Ed.*, **17**, 215 (1945). We did not find it necessary to remove the bulk of the precipitated silver azide by filtration before completing the titration.
(39) F. Loewus and R. H. Shah, *Methods Carbohyd. Chem.*, **6**, 14 (1972).
(40) H. H. Hodgson and W. H. H. Norris, *J. Chem. Soc.*, 762 (1949).
(41) M. T. Reagan and A. Nickon, *J. Amer. Chem. Soc.*, **90**, 4096 (1968).

Kinetics and Mechanism of Alkyl Ether Oxidation by Peroxydisulfate Ion

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The oxidation of three ethers (*p*-dioxane, tetrahydrofuran, and diethyl ether) by peroxydisulfate ion in aqueous solution has been investigated. The rate law is $-d[S_2O_8^{2-}]/dt = k_{obsd}[S_2O_8^{2-}]^{3/2}$ with the value of k_{obsd} depending on the nature of the ether. The rate law, rate constants, influences of oxygen gas and cupric ion, and activation energies indicate a radical chain mechanism closely similar to that known for the oxidation of primary alcohols by peroxydisulfate. Chain lengths have been evaluated, and the influences of aldehydes on rates were investigated. Some of the products of ether oxidation (vinyl ethers and their oligomers) are different from those found in alcohol oxidation. Similarities in and differences between the reactions for the two classes of organic oxygen compounds are discussed.

The general features of the peroxydisulfate oxidation of primary and secondary alcohols have been elucidated in the work of this group[2,3] and in other laboratories.[4] Evidence was reported for a free-radical chain mechanism which involves as initiation step the unimolecular homolytic dissociation of $S_2O_8^{2-}$

$$S_2O_8^{2-} \xrightarrow[\Delta]{k_1} 2SO_4^{\cdot-} \qquad (1)$$

and the following as propagation steps

$$SO_4^{\cdot-} + H-\underset{\displaystyle R}{\overset{\displaystyle R'}{\overset{|}{\underset{|}{C}}}}-OH \xrightarrow{k_2} HSO_4^- + \cdot\underset{\displaystyle R}{\overset{\displaystyle R'}{\overset{|}{\underset{|}{C}}}}-OH \qquad (2)$$

$$\cdot\underset{\displaystyle R}{\overset{\displaystyle R'}{\overset{|}{\underset{|}{C}}}}-OH + S_2O_8^{2-} \xrightarrow{k_3} \underset{\displaystyle R}{\overset{\displaystyle R'}{\diagdown\!\!\diagup}}C=O + HSO_4^- + SO_4^{\cdot-} \qquad (3)$$

where R′ = R′ = H; R = H and R′ = CH_3; and R = R′ = CH_3. Nevertheless, the exact nature of the third step of the chain was not understood because two reasonable transition state configurations can be visualized. Both of these two pathways seem consistent with the formation of the observed products. One pathway involves the formation of an hemiacetal-like intermediate by carbon attack on peroxide oxygen

$$S_2O_8^{2-} + \cdot\underset{\displaystyle R}{\overset{\displaystyle R'}{\overset{|}{\underset{|}{C}}}}-OH \longrightarrow {}^-OS(=O)_2-O-\underset{\displaystyle R}{\overset{\displaystyle R'}{\overset{|}{\underset{|}{C}}}}-OH + SO_4^{\cdot-} \qquad (3a)$$

and its subsequent breakdown.

$$^-OS(=O)_2-O-\underset{\displaystyle R}{\overset{\displaystyle R'}{\overset{|}{\underset{|}{C}}}}-OH \xrightarrow[H_2O]{k_4} HSO_4^- + \underset{\displaystyle R}{\overset{\displaystyle R'}{\diagdown\!\!\diagup}}C=O \qquad (4)$$

The other mechanism involves the direct breaking of the oxygen–hydrogen bond (*i.e.*, hydrogen atom transfer) during attack on peroxide oxygen.

$$S_2O_8^{2-} + H-O-\underset{\displaystyle R}{\overset{\displaystyle R'}{\overset{|}{\underset{|}{C}}}}\cdot \xrightarrow{k_{3b}} SO_4^{\cdot-} + HSO_4^- + \underset{\displaystyle R}{\overset{\displaystyle R'}{\diagdown\!\!\diagup}}C=O \qquad (3b)$$

The termination step for ethanol involves two organic radicals (reacting by either disproportionation or dimerization).

$$2CH_3\dot{C}HOH \longrightarrow \text{products} \qquad (5)$$

It was deemed worthwhile to carry out a kinetic study of the peroxydisulfate oxidations of ethers. Assuming that the alcohol and ether oxidations proceed by analogous mechanisms, in the case of the ethers the latter pathway (eq 3b) proposed for the third step is clearly impossible. A comparison of the relative rates for alcohols and ethers could then lead to better understanding of the behavior of the reaction of the α-oxyalkyl radical and the peroxydisulfate anion.

Moreover, in the general field of peroxide oxidation of the ethers, very interesting characteristics have been found.[5] A free-radical chain mechanism for the ether-induced decomposition of benzoyl peroxide has been demonstrated. The propagation steps are believed to be the formation of an α-oxyalkyl radical from the ether and the reaction of this radical with the peroxide.

The production of dioxanyl radicals by reaction of the sulfate radical ion $SO_4^{\cdot-}$ (from peroxydisulfate ion) with dioxane and the subsequent dioxanylation of some heteroaromatic bases have been recently reported by Minisci and coworkers,[6] and a kinetic study of the peroxydisulfate oxidation in the presence of silver ion has been carried out by Mishra and Ghosh.[7]

On the other hand, the kinetic behavior of the reaction of ethers and peroxydisulfate alone has never been studied extensively. This investigation was undertaken in order to elucidate the general features of the reaction mechanism as well as to compare the results with those obtained for the peroxydisulfate oxidation of alcohols.

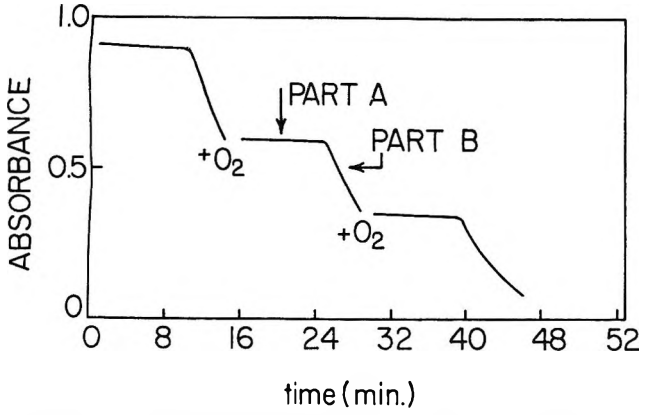


Figure 1. A schematic line drawing showing the behavior of absorbance (due to peroxydisulfate ion) as a function of time. Part A (reaction under oxygen inhibition) is followed by part B (when oxygen is consumed); also part A can be reestablished if the spectrophotometer cell is opened and oxygen is admitted.

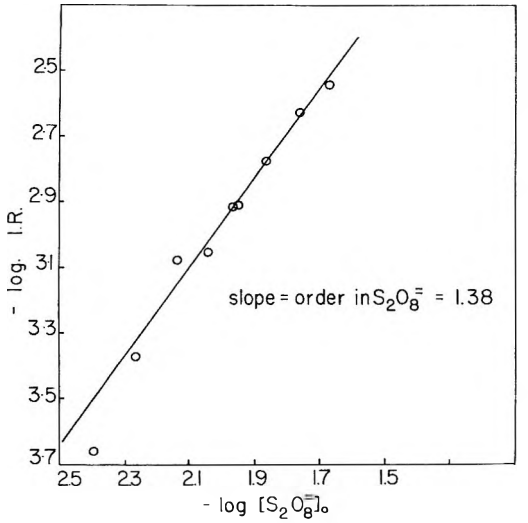


Figure 2. A plot of log (initial rate) against log $[S_2O_8^{2-}]_0$ at 70° to obtain the kinetic order in peroxydisulfate ion. A similar plot for the same reaction (dioxane oxidation) but at 60° gave a slope of 1.58.

Results

General. When the oxidation of an ether was started in a stoppered cell or in a vessel under a nitrogen atmosphere, a small increase in the absorbance was usually observed at the beginning. This increase was paralleled by a small increase in the amount of peroxide (as shown by iodometric analysis). The absorbance increase was, therefore, ascribed to a minor temperature effect plus peroxide being formed by the induced reduction of oxygen. When the solutions were not kept under nitrogen, both effects were enhanced and dissolved oxygen is clearly implicated. Further, the runs were followed by absorbance at 230 mμ, which is a wavelength where all peroxides absorb.[8] This effect due to dissolved oxygen was obvious for dioxane and tetrahydrofuran but small for diethyl ether. The peroxide concentration quickly reached a maximum and little further variation of the concentration was observed for several minutes. Then, a relatively rapid loss of peroxydisulfate begins and the rate of this reaction is considerably larger than the thermal decomposition of peroxydisulfate ion alone at the same temperature.

The rapid reaction is immediately quenched if a small amount of air is introduced in the reacting system (see Figure 1). The effect of the addition of allyl acetate in low concentration to the reagents was studied in the case of dioxane oxidation and the results indicated that the reaction rate (as evidenced by peroxydisulfate concentration change) is lowered to that observed in the thermal decomposition of peroxydisulfate ion alone. In general characteristics, this behavior is similar to that observed in the peroxydisulfate oxidation of the alcohols.

Using the same nomenclature as employed earlier[2,3] we designate the first portion of the reaction as path A and its length as τ, and the second fast portion as path B. As in the oxidation of the alcohols, path A was evidenced by a very slow loss of peroxydisulfate; the observed increase of the total peroxide concentration in the ether oxidations (also reported in the benzoyl peroxide oxidations of organic compounds[8]) is probably due to the formation, in the reaction medium, of relatively stable peroxides derived from the ethers by reaction of the dissolved oxygen with organic radicals.

Product Compositions. For all three ethers, olefins, aldehydes, and oligomeric products were observed. The vinyl compounds and their oligomers were detected by mass spectrometry. A number of peaks, some of which are parent peaks for the olefins and others of which appear as parent peaks in the molecular weight range from 200 to 300, were observed. The latter set is due to oligomers. The amount of vinyl ether decreased slowly on standing with simultaneous increase in amounts of oligomer. Acids (HSO_4^- in our case) are known to bring about slow polymerization of vinyl ethers.

The amounts of aldehyde as indicated by the characteristic carbonyl absorption were very small for dioxane and tetrahydrofuran. In fact, there was too little change in absorption near 280 mμ to allow quantitative evaluation. On the other hand, acetaldehyde seems to be the predominant product in the ethyl ether oxidation. It was isolated as the 2,4-dinitrophenylhydrazone. In the reaction mixture, quantitative evaluation of acetaldehyde was possible in the ultraviolet spectra. Some results are given in Table I. The

Table I
Yield of Acetaldehyde in the Peroxydisulfate Oxidation of Ethyl Ether

$[S_2O_8^{2-}]_0 \times 10^3$, M	$[Et_2O]_0$, M	$[CH_3CHO] \times 10^3$, M	Temp, °C	Yield, %
13.60	0.132	9.5	60	69
6.80	0.132	4.5	60	67
6.80	0.264	5.0	60	73
6.80	0.066	4.3	60	64
6.80	0.132	4.6	71	67
6.80	0.132	5.8	81	86

yields run from 64 to 86%. As expected from the alcohol oxidations, the yield of carbonyl compound was greater when the amount of ether increased. It appears that the yield of carbonyl product also increased with temperature.

It is worthy of note here that carbon–carbon double bonds are also formed in the peroxydisulfate oxidation of tertiary amines.[9]

Rate Law. The kinetic dependence of the path B reaction on peroxydisulfate concentration was determined by varying the amount of peroxide, at fixed ether concentration, and observing the changes in initial rate (IR) of path B. Independent sets of data are given in Table II, which has two parts showing the results obtained in our two laboratories. Also presented are two figures showing some of the

Table II
Dependence of Rates on Peroxydisulfate Concentration

Ether	$[S_2O_8^{2-}]_0 \times 10^3$, M	IR[d] $\times 10^5$, M sec^{-1}	$k_{3/2} \times 10^2$, $M^{-1/2}$ sec^{-1}
Ethyl ether[a]	13.6	5.01	4.5
	6.8	1.80	4.9
	2.7	0.20	4.4
	1.4	0.15	4.2
Tetrahydrofuran[b]	33.1	6.19	1.0
	26.5	3.74	1.0
	13.2	1.46	1.1
	6.6	0.41	1.0
	2.6	0.22	
Dioxane[c]	33.0	2.07	0.44
	22.6	1.47	0.48
	16.9	1.03	0.60
	11.8	0.60	
	8.4	0.39	0.63
	6.5	0.25	0.66
	4.2	0.11	
	3.4	0.08	
Dioxane[e]	20.8	4.80	1.60
	17.2	3.88	1.72
	14.0	2.82	1.70
	10.8	2.08	1.86
	9.0	1.48	1.73
	7.2	1.39	2.27
	5.4	0.70	1.79
	4.0	0.37	1.49

[a] $[\text{Ethyl ether}]_0 = 0.132$ M, temperature 60°. [b] $[\text{Tetrahydrofuran}]_0 = 0.57$ M, temperature 60°. [c] $[\text{Dioxane}]_0 = 0.68$ M, temperature 60°. [d] IR = initial rate of loss of $S_2O_8^{2-}$. [e] Temperature 70°, $[\text{dioxane}]_0 = 0.74$ M.

Table III
Dependence of Rate on Ether Concentration

Ether	$[\text{Ether}]_0$, M	IR[d] $\times 10^5$, M sec^{-1}	$k_{3/2} \times 10^2$, $M^{-1/2}$ sec^{-1}
Ethyl ether[a]	0.066	1.66	4.6
	0.132	1.80	4.9
	0.264	1.92	4.7
Tetrahydrofuran[b]	0.24	2.60	1.5
	0.36	1.95	1.3
	0.48	2.60	1.5
	0.96	3.26	2.1
	1.20	3.10	1.7
	1.44	3.58	2.1
	1.80	3.42	1.7
	2.40	4.23	1.9
Dioxane[c]	0.34	1.12	0.57
	0.54	1.20	0.57
	0.69	1.03	0.60
	0.92	0.87	
Dioxane[e]	0.37	1.62	2.35
	0.74	1.87	2.72
	1.11	1.53	2.24
	1.48	1.38	2.02
	1.85	1.53	2.24
	2.22	1.53	2.24
	2.59	1.30	1.90

[a] $[S_2O_8^{2-}]_0 = 6.80 \times 10^{-3}$ M, temperature 60°. [b] $[S_2O_8^{2-}]_0 = 1.74 \times 10^{-2}$ M, temperature 60°. [c] $[S_2O_8^{2-}]_0 = 1.70 \times 10^{-2}$ M, temperature 60°. [d] IR = initial rate of loss of $S_2O_8^{2-}$. [e] Temperature 70°, $[S_2O_8^{2-}]_0 = 7.8 \times 10^{-3}$ M.

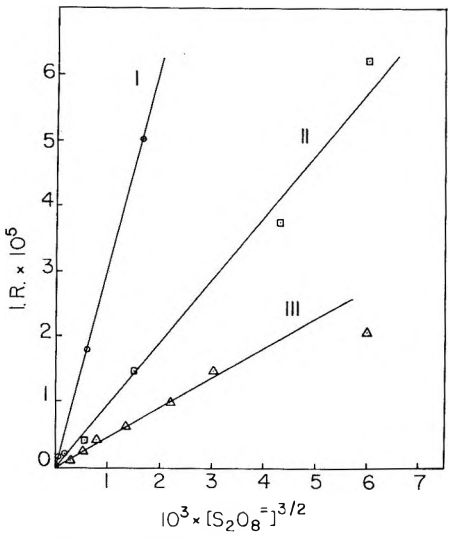


Figure 3. Plots of initial rate as a function of the three-halves power of $[S_2O_8^{2-}]_0$ to show the linear dependence (thus three-halves order) and zero intercept (thus no competing path). Data for three ethers (I, ethyl ether; II, tetrahydrofuran; and III, dioxane) at 60°.

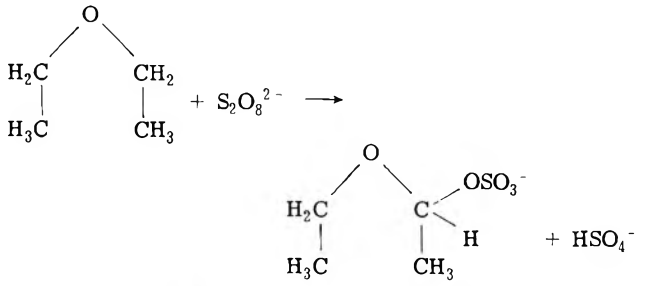
order dependence data. These results plus the linearity of integrated three-halves-order plots indicate that the exponent on the peroxide concentration in the rate law is three-halves.

By varying the initial concentration of the ethers (Table III), a zero-order dependence (*i.e.*, independence) of the rate on ether was found. Therefore, the experimentally determined rate law for the B portion of the reaction, for the concentration ranges explored, is

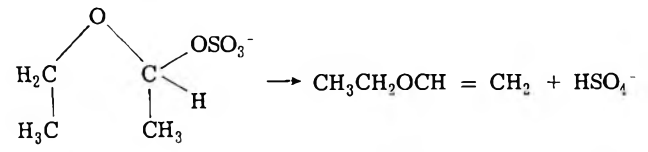
$$\frac{-d[S_2O_8^{2-}]}{dt} = k[S_2O_8^{2-}]^{3/2}$$

Activation Energies. In Table IV are listed the values of the rate constants as a function of temperature for the dioxane and ethyl ether oxidations. The activation energies are 24 and 17 kcal mol^{-1} for dioxane and ethyl ether, respectively.

Effects of the Products. The oxidation of alcohols had a simple stoichiometry with carbonyl compounds being the predominant organic product. It was expected that the ether oxidation would go to acetal-like products, which



would then hydrolyze with production of carbonyl compound. In fact, it turned out that significant quantities of olefinic products are formed. These presumably are derived by elimination of HSO_4^- from the acetal. In the case



of ethyl ether above, vinyl ethyl ether is therefore the specific ether predicted and has been found to be one product;

Table IV
Temperature Dependence of Path B

Ether	Temp, °C	$k_{3/2} \times 10^2$, $M^{-1/2}$ sec^{-1}
Ethyl ether[a]	60.0	4.9[c]
	71.0	15.6[c]
	81.0	29.4[c]
Dioxane[b]	60.0	0.56[c]
	70.0	2.1[c,d]
	80.5	4.7[c]

[a] $[S_2O_8^{2-}]_0 = 6.80 \times 10^{-3}$ *M*, [ethyl ether]$_0$ = 0.132. [b] $[S_2O_8^{2-}]_0 = 5.5 \times 10^{-3}$ *M*, [dioxane]$_0$ = 0.68 *M*. [c] Average of three independent determinations. [d] This value is from B. U.; the value from M. S. C. obtained independently is 2.2.

Table V
Comparison of the $k_{3/2}$ Values Obtained by Extrapolation from the Initial Rates and the $k_{3/2}$ Values Obtained from the Integrated Plots[a,b]

Ether	$k_{3/2}$ (extr) $\times 10^2$	$k_{3/2}$ (int) $\times 10^2$
Ethyl ether	3.2	4.6
Tetrahydrofuran	0.9	1.6
Dioxane	0.47	0.56

[a] The $k_{3/2}$ values are averages taken from kinetic runs under conditions and with concentrations similar to those in Tables II and III. The $k_{3/2}$ (extr) are values obtained from initial slopes and the $k_{3/2}$ (int) values come from slopes of integrated plots. [b] Data for 60°, and the units of $k_{3/2}$ are $M^{-1/2}$ sec^{-1}.

acetaldehyde has also been isolated and identified (see above). In view of these results, some influence of product on rate of ether oxidation is expected. For the three ethers, the values of $k_{3/2}$ obtained by extrapolation from the initial rates (Table V) are smaller than the $k_{3/2}$ values obtained from the three-halves-order integrated plots. This behavior can be rationalized as a catalytic effect of the product of the reaction. By way of comparison, in the ethanol oxidation the product acetaldehyde was found to act as an inhibitor of the oxidation; the aldehyde can be easily oxidized and inhibits the alcohol oxidation by changing the nature of the termination step.[3]

Some experiments were therefore performed in order to evaluate the effect of aldehydes on dioxane oxidation. Small changes in rate were observed but no serious inhibiting effect of glyoxal on the reaction and no hydroxyacetaldehyde were observed. In the case of acetaldehyde, there is an enhancement of the rate of loss of peroxydisulfate. At higher concentrations of acetaldehyde, the catalytic effect ceases and the incursion of an inhibitory effect is observed. Further details of these results may be obtained on request; however, the conclusions we arrive at are not changed due to these minor influences of aldehydes.

Influence of Copper. It was found in the alcohol oxidations that cupric ion has an effect on rate and mechanism.[2,3] We deemed it important to see if this metal ion would influence the ether oxidation in a similar manner.

The effect of copper was of less importance for dioxane than was found for ethanol,[3c] but the difference was not great. The order in peroxydisulfate dropped from three-halves for the uncatalyzed path to one; the data are presented in Table VI and these form an order slope of 1.04. The order in copper was about 0.4 in the range of $[Cu^{2+}]$ from 2×10^{-5} to 2×10^{-4} *M*, and some results are given in Table VII. The rate depended slightly on concentration of dioxane at low concentrations, but at concentrations near 1

M there was no further change; we feel that the changes are so small that they cannot be considered evidence for a true kinetic order. Thus the rate law for the copper-catalyzed path is considered to be

$$\text{rate} = k[S_2O_8^{2-}][Cu^{2+}]^{1/2}$$

This is the same rate law that was found for the copper-catalyzed oxidation of ethanol.[3c]

Discussion and Conclusions

The ether oxidation reactions clearly proceed by a free-radical chain mechanism. The evidence supporting this conclusion is as follows: (a) inhibition by oxygen (which is known to react rapidly with organic radicals), (b) inhibition by allyl acetate (known to react rapidly with sulfate radical ions), (c) sensitivity of rates to low concentrations of additives such as Cu^{2+} and aldehydes, (d) fractional orders (*i.e.*, nonintegral dependence of rates on reagent concentrations), and (e) activation energy values between $E_a'/2$ and E_a' (where E_a' is the activation energy, 33.5 kcal mol^{-1}, for the k_1 step).

All of these results were also seen in the alcohol oxidations, and there are some quantitative similarities as well. The rate law for ethyl ether oxidation is the same as that observed for ethyl alcohol oxidation. Also the rate constants and activation energies are very similar for oxidation of these two structurally related compounds (see ref 3c).

The products in the ether oxidation are dramatically different from those obtained in the oxidation of alcohols wherein the yields of carbonyl compounds were nearly quantitative when $[CH_3CH_2OH] \gg [S_2O_8^{2-}]$. Both the kinetic similarities and the stoichiometric differences must be explained in any suggested mechanism. Therefore, using ethyl ether as example, we propose the following mechanism.

$$S_2O_8^{2-} \xrightarrow{k_1} 2SO_4^{\cdot-} \quad (1)$$

$$SO_4^{\cdot-} + H-\underset{\displaystyle O-CH_2CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-H \xrightarrow{k_{2'}} HSO_4^- + \cdot\underset{\displaystyle O-CH_2CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{CH}}}} \quad (2')$$

$$\underset{\displaystyle O-CH_2CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{\cdot CH}}}} + S_2O_8^{2-} \xrightarrow{k_{3'}} \underset{\displaystyle O-CH_2CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{H-C-OSO_3^-}}}} + SO_4^{\cdot-} \quad (3'a)$$

$$\underset{\displaystyle O-CH_2CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{H-C-OSO_3^-}}}} \xrightarrow{H_2O} CH_2{=}CHOCH_2CH_3 + HSO_4^- \quad \text{or} \quad CH_3C(=O)H + HSO_4^- + CH_3CH_2OH \quad (4')$$

$$2\ \underset{\displaystyle O-CH_2CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{\cdot CH}}}} \xrightarrow{k_{5'}} \text{products} \quad (5')$$

Steps 2′, 3′a, and 5′ are analogous to steps 2, 3a, and 5 of the alcohol oxidation. Step 1 is, of course, identical since it does not involve any organic particle. Step 4′ is given as two separate paths for breakdown of the acetal-like intermediate; for step 4, only one path is given because only aldehyde is observed (as a primary product) in alcohol oxidation.

Table VI
Determination of Order in Peroxydisulfate Concentration[a]

$[S_2O_8^{2-}] \times 10^{-2}$, M	Nm[b]	IR[c] $\times 10^{-3}$
2.72	247	3.92
1.97	242	3.25
1.60	239	2.27
1.00	232	1.50
0.69	227	1.05
0.41	221	0.62

[a] [Dioxane] = 0.72 M, [Cu(II)] = 1.0×10^{-4} M, temperature 60°. [b] Wavelength of analysis, chosen to give full scale deflection. [c] Initial rate in units of mol l.$^{-1}$ min^{-1}.

Table VII
Determination of Order in Copper(II) Concentration[a]

[Cu(II)], M	IR[b]	[Cu(II)], M	IR[b]
2×10^{-4}	1.26×10^{-3}	6×10^{-5}	1.08×10^{-3}
1×10^{-4}	1.19×10^{-3}	4×10^{-5}	0.90×10^{-3}
8×10^{-5}	1.19×10^{-3}	2×10^{-5}	0.67×10^{-3}

[a] $[S_2O_8^{2-}] = 1.2 \times 10^{-2}$ M, [dioxane] = 0.36 M, temperature, 60°. [b] Initial rate in units of mol l.$^{-1}$ min^{-1}.

Assuming steady-state conditions, the mechanism leads to the derived rate law

$$\frac{-d[S_2O_8^{2-}]}{dt} = k_{3'a}\left(\frac{k_1}{k_{5'}}\right)^{1/2}[S_2O_8^{2-}]^{3/2}$$

in agreement with the experimental law. Thus $k_{3/2} = k_{3'a}(k_1/k_{5'})^{1/2}$.

At 60° with $[S_2O_8^{2-}] \simeq 0.02$ M and [ether] $\simeq 0.4$ M, the estimated chain lengths are as follows: for ethyl ether, 1000; for dioxane, 100; and for tetrahydrofuran, 250. These can be compared with the value of 600 for ethyl alcohol at 70° and roughly similar concentrations. The termination step is the reaction of two α-oxyalkyl radicals, but the kinetics are consistent with either a dimerization or a disproportionation in this step.

The presence of both acetaldehyde and vinyl ethyl ether in the oxidation of ethyl ether suggests that the two different products are formed by breakdown of a common intermediate: the pseudoacetal formed in step 3′. This is reasonable if one considers that the reaction of an α-oxyalkyl radical and the peroxydisulfate ion leads, in the case of the alcohols, to the formation of a pseudohemiacetal, readily hydrolyzed to the carbonyl compound, but, for the ethers, involves the formation of a pseudoacetal, certainly more stable, making possible the simultaneous process of elimination of the β hydrogen.

The elimination seems to be favored in the cyclic ethers, where the carbonyl compound is recovered only in very small quantity and where the formation of aldehyde would require the opening of a ring. As mentioned above, the yields of acetaldehyde obtained in ethyl ether oxidation vary with conditions. They are higher at higher temperature, suggesting that the breakdown paths in eq 4′ do not have the same activation energy. They are higher at higher ether concentrations, presumably because the step $k_{2'}$ competes with the step

$$SO_4^{\cdot-} + CH_3CHO \longrightarrow HSO_4^- + CH_3\dot{C}O$$

known from alcohol oxidations to occur readily.

It is worthy of note here that Sosnovsky[11] has reported

that the cuprous bromide catalyzed reaction of *tert*-butyl peresters with ethers leads to the formation of acyloxy intermediates which decompose under the experimental conditions to the corresponding organic acids and unsaturated ethers.

The implication of our results can therefore be summarized.

I. A common type of mechanism is involved in the peroxydisulfate oxidation of alcohols and ethers.

II. The reaction of the α-oxyalkyl radicals with peroxydisulfate leads to the formation of pseudohemiacetal (from alcohols) or pseudoacetal (from ethers) intermediates. Therefore, the question concerning the transition state structure for k_3 seems to be answered; the chain lengths and rate laws are sufficiently similar as to lead to the conclusion that attack on peroxydisulfate by the α-oxyalkyl radical involves the carbon center.

III. The natures of the final products are related to the characteristics of the intermediates and to the experimental conditions. Yet, at the same time, the reaction kinetics are little influenced by the nature of the products.

Experimental Section

All chemicals not described below were reagent grade. Experiments carried out at B. U. utilized distilled water. Those carried out at M. S. C. utilized distilled–deionized water. B. & A. reagent $K_2S_2O_8$ was recrystallized twice from deionized water. Spectrophotometric grade dioxane (Aldrich) was used without further purification at B. U., whereas at M. S. C. Fisher reagent was purified as suggested by Fieser and Fieser.[12] Tetrahydrofuran (Mallinckrodt Analytical Reagent) was refluxed over KOH pellets and distilled before use. Ethyl ether (Allied, Reagent ACS) was distilled before use.

Kinetics were followed with a Cary 15 spectrophotometer (B. U.) or Beckman Acta V spectrophotometer (M. S. C.), or by the usual iodometric analysis. Rate constants were calculated as previously reported.[2,3] Rate constants calculated for duplicate runs with integrated plots usually agreed to ±5% and rate constants obtained from initial slopes varied by ±8%.

Products. The reaction mixture (an aqueous solution of $K_2S_2O_8$ and a tenfold molar excess of ether in a rubber-stoppered flask) was maintained at 60° in a thermostatic bath. Aliquots of the reacting solutions were withdrawn with a syringe, to prevent contact with air, at suitable time intervals and analyzed by vpc (Aerograph 200, F.I.D., column 15% SE-30 on 80/100 mesh A/W, DMCS Treste Chromosorb, 15 ft × 0.25 in. o.d.) and mass spectral (Hitachi Perkin-Elmer, RMU-6D single focusing, ionization 50 eV) techniques. The mass spectrometer and gas chromatograph were connected.

Compounds isolated were the 2,4-dinitrophenylhydrazone of acetaldehyde from ethyl ether oxidation and the osazone of glyoxal from the dioxane oxidation. Vinyl ethyl ether, *p*-dioxene, and 2,3-dihydrofuran (from ethyl ether, dioxane, and tetrahydrofuran, respectively) were identified by mass spectra. Both the mass spectra and gas chromatography showed abundant peaks not common to the reactant ethers. Details may be obtained on request.

Acknowledgments. We are pleased to acknowledge the support of the U. S. Air Force Office of Scientific Research (Grant 71-1961A) for continuing financial aid, of the Committee on International Exchange of Persons (Italy) for a travel grant (to R. C.), of Montclair State College for purchase of the Acta V spectrophotometer, and of the University of Padova for leaves of absence (to R. C. and F. D. F.). Mr. R. Campbell and Mr. G. Bida assisted with some of the measurements.

Registry No.—Peroxydisulfate, 15092-81-6; ethyl ether, 60-29-7; tetrahydrofuran, 109-99-9; dioxane, 123-91-1; copper, 7440-50-8.

References and Notes

(1) (a) Brown University (B. U.); (b) Montclair State College (M. S. C.).
(2) D. L. Ball, M. M. Crutchfield, and J. O. Edwards, *J. Org. Chem.*, **25**, 1599 (1960).
(3) (a) J. O. Edwards, A. R. Gallopo, and J. E. McIsaac, Jr., *J. Amer. Chem. Soc.*, **88**, 3891 (1966); (b) J. E. McIsaac, Jr., and J. O. Edwards, *J. Org. Chex.*, **34**, 2565 (1969); (c) A. R. Gallopo and J. O. Edwards, *ibid.*, **36**, 4089 (1971).
(4) For reviews on peroxydisulfate mechanisms, see (a) A. Haim and W. K. Wilmarth in "Peroxide Reaction Mechanisms," J. O. Edwards, Ed., Wiley-Interscience, New York, N. Y., 1962, p 176 ff; (b) D. A. House, *Chem. Rev.*, **62**, 185 (1972); (c) E. J. Behrman and J. E. McIsaac, Jr., *Mech. React. Sulfur Compounds*, **2**, 193 (1968); (d) E. P. Crematy, Ph.D. Thesis, University of Sydney, Australia, 1970.
(5) *Cf.* K. U. Ingold and B. P. Roberts, "Free-Radical Substitution Reactions," Wiley-Interscience, New York, N. Y., 1971, pp 148–200, and references cited therein.
(6) W. Buratti, G. P. Gardini, F. Minisci, F. Bertini, R. Galli, and M. Perchinunno, *Tetrahedron*, **27**, 3655 (1971).
(7) D. D. Mishra and S. Ghosh, *Proc. Nat. Inst. Sci. India, Part A*, **31**, 119 (1965).
(8) C. J. Battaglia, Ph.D. Thesis, Brown University, 1962.
(9) R. Curci, F. DiFuria, and J. O. Edwards, unpublished study at Brown Universtiy.
(10) The bulk of the data on the copper-catalyzed path is to be found in the M.A. Thesis of George M. Delano, Montclair State College, 1973.
(11) G. Sosnovsky, *Tetrahedron*, **13**, 241 (1961).
(12) L. F. Fieser and M. Fieser, "Reagents for Organic Chexistry," Wiley, New York, N. Y., 1967, p 333.

Reaction Kinetics of 2- and 3-Furoyl Chlorides with Anilines in Benzene

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The reaction rates of 2- and 3-furoyl chlorides with substituted anilines have been measured in benzene at different temperatures. The reactions follow second-order kinetics. 2-Furoyl chloride reacts faster and 3-furoyl chloride slower than benzoyl chloride. The activation parameters and the slopes of the Hammett and Bronsted plots are similar to those of the reactions of benzoyl and 2- and 3-thenoyl chlorides with aniline. The reaction mechanism of 2- and 3-furoyl chlorides with aniline is the same as for the benzoylation reaction. A linear relationship is obtained plotting the log k for the reactions of 2-thenoyl, 3-thenoyl, 3-furoyl, and benzoyl chlorides with aniline against the infrared carbonyl stretching bands in CCl_4 of the acid chlorides.

Several studies have been carried out with the purpose of comparing the furan and thiophene rings reactivity with that of the benzene nucleus.

The acid-catalyzed rearrangement of substituted allyl alcohols shows that the furyl and thienyl groups behave as electron-donating substituents.[1] The carboxylic acids of furan and thiophene are stronger than unsubstituted benzoic acid indicating that the inductive electron-withdrawing effect of the heteroatoms is prevailing here.[2] In the esterification of the two isomeric 2- and 3-furoic acids,[3] in the acid-catalyzed hydrolysis of furan and thiophene carboxylic acid esters,[4] and in the alkaline hydrolysis of 2- and 3-

Table I
Second-Order Rate Constants and Activation Parameters for the Reaction of 2-Furoyl Chloride with Meta- and Para-Substituted Anilines in Benzene

No.	Registry no.	Substituent	pK_a[c]	$k_2 \times 10^2$, l. mol^{-1} sec^{-1} 10°	15°	17.5°	25°	30°	35°	45°	E_A[a]	Log A	ΔS^*[b]
1	62-53-3	H[13]	4.58		8.74		13.3		19.0		6.85	4.14	−41.6
2	108-44-1	*m*-CH_3	4.69	11.9		15.8	21.4		30.4		6.54	4.12	−41.6
3	106-49-0	*p*-CH_3	5.12	36.4		48.1	63.0	74.9			6.15	4.31	−40.8
4	536-90-3	*m*-CH_3O	4.20		6.32		9.18		14.0		7.00	4.11	−41.7
5	108-42-9	*m*-Cl	3.34				0.740		1.24	1.79	8.33	3.98	−42.3
6	106-47-8	*p*-Cl	3.98		2.15		3.50		5.04		7.52	4.04	−42.0
7	99-09-2	*m*-NO_2	2.50				0.0783		0.132	0.221	9.77	4.05	−41.9

[a] In units of kcal/mol. [b] At 25°, in cal mol^{-1} °K^{-1}. [c] Reference 18.

Table II
Second-Order Rate Constants and Activation Parameters for the Reaction of 3-Furoyl Chloride with Meta- and Para-Substituted Anilines in Benzene

No.	Substituent	pK_a[c]	$k_2 \times 10^2$, l. mol^{-1} sec^{-1} 15°	25°	35°	45°	E_A[a]	Log A	ΔS^*[b]
1	H[13]	4.58	2.53	4.09	6.35		8.11	4.56	−39.6
2	*m*-CH_3	4.69	3.95	6.92	9.50		7.76	4.50	−39.9
3	*p*-CH_3	5.12	10.6	16.3	23.7		7.10	4.41	−40.3
4	*m*-CH_3O	4.20	1.54	2.50	3.98		8.37	4.53	−39.8
5	*m*-Cl	3.34		0.218	0.371	0.590	9.38	4.22	−41.2
6	*p*-Cl	3.98		0.883	1.450	2.210	8.64	4.29	−40.9
7	*m*-NO_2	2.50		0.0219	0.0395	0.0698	10.92	4.34	−40.6

[a] In units of kcal/mol. [b] At 25°, in cal mol^{-1} °K^{-1}. [c] Reference 18.

thenoates and 3-furoates both the heteroaromatic nuclei are electron donating, whereas in the alkaline hydrolysis of 2-furoates the furyl group behaves as electron withdrawing.[4-7] The solvolysis of 1-arylethyl acetates[8] and of ethyl *p*-nitrobenzoates[9] and the isomerization of *cis*-2-styrylthiophene in aqueous sulfuric acid[10] all indicate that the furan and thiophene nuclei are electron donating, whereas the rearrangement of 2-2′-thenil is a clear manifestation of the electron-withdrawing nature of this nucleus.[11]

In summary, from the above discussion, it is evident that the furan and thiophene nuclei possess a dual electronic nature: electron donating or electron withdrawing.

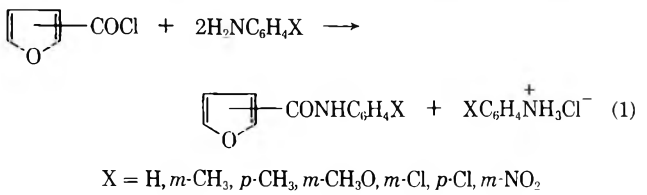
Recently we have undertaken an investigation of the reactions between 2-[12] and 3-thenoyl chlorides[13,14] and meta- and para-substituted anilines in benzene. We have found that 2- and 3-thenoyl chlorides reacted more slowly than benzoyl chloride, indicating the donating effect of the thienyl group.

In our preliminary note we reported the data relating to the reactions of 2- and 3-furoyl chlorides with aniline.[13] The reaction of 2-furoyl chloride was faster than that of benzoyl chloride, whereas 3-furoyl chloride reacted more slowly than the phenylic derivative. Thus, these results indicate that the furyl group behaves as electron withdrawing in the 2-furoyl chloride but as electron donating in the 3 analog compared to phenyl.

The purpose of the present paper is to amplify the study of the reactions of 2- and 3-furoyl chlorides with meta- and para-substituted anilines in benzene.

Results and Discussion

The reactions of the 2- and 3-furoyl chlorides with meta- and para-substituted anilines take place quantitatively according to the stoichiometric eq 1. The reactions were followed kinetically as previously described,[13,14] and in all cases the compounds gave excellent second-order kinetics.



(1)

X = H, *m*-CH_3, *p*-CH_3, *m*-CH_3O, *m*-Cl, *p*-Cl, *m*-NO_2

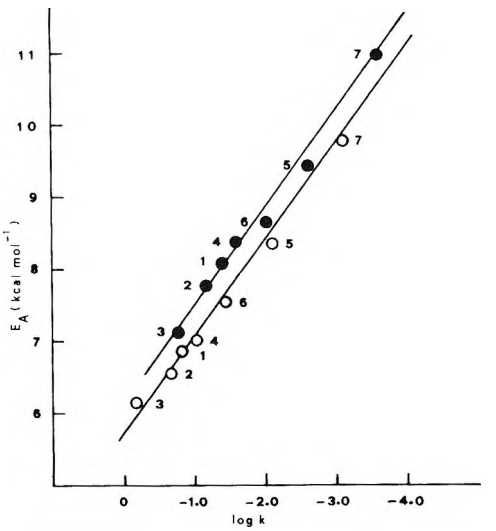


Figure 1. Plots of the experimental values of E_A against log k_{25} for the reactions of 2- and 3-furoyl chlorides with anilines. The lines are of theoretical slopes $-2.303RT$.

The second-order rate constants, reported in Tables I and II, show that electron-donating substituents accelerate and electron-withdrawing groups retard the reactions: the 2-furoyl chloride reaction is faster than that of 3-furoyl chloride. The results compared with those of benzoyl chloride reaction[15-17] indicate that 2-furoyl chloride (Table I) reacts faster and 3-furoyl chloride slower (Table II) than benzoyl chloride.

The activation parameters, listed in Tables I and II, show a regular variation with the substituent in the aniline. In the 2- and 3-furoyl chloride reactions, as previously noted,[14] the effect of the substituents in the aniline is to modify the activation energy while log A remains approximately constant. This is evident from Figure 1 where log k at 25° for 2- and 3-furoyl chlorides is plotted against the experimental values of E_A. All the points lie close to the

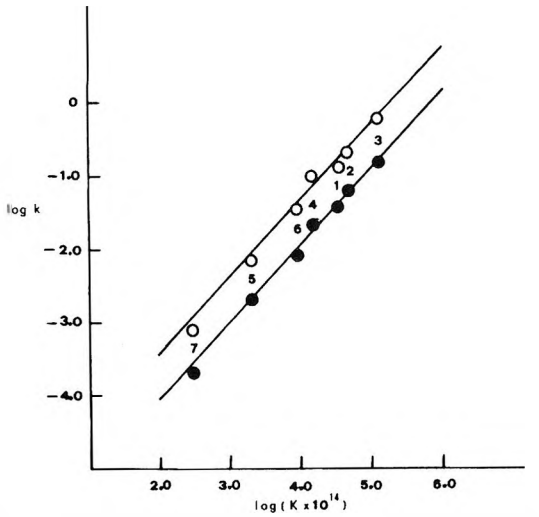


Figure 2. Plots of log k_{25} for the reactions of 2- and 3-furoyl chlorides with anilines in benzene against the logarithm of their dissociation constants in water at 25° (Brønsted plots).

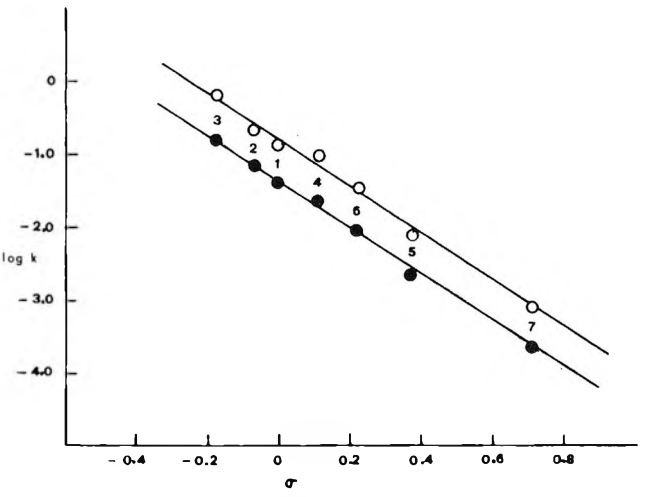


Figure 3. Hammett plots for the reactions of 2- and 3-furoyl chlorides with anilines at 25°.

Table III
Infrared Carbonyl Frequencies of the Acid Chlorides in CCl_4 and Log k at 25° for the Reaction with Aniline

Acid chloride	Registry no.	$\nu C{=}O$, cm^{-1}	Log k
Benzoyl	98-88-4	1777[a]	−1.2027[e]
2-Thenoyl	5271-67-0	1753[b]	−1.5986[f]
3-Thenoyl	41507-35-1	1766[c]	−1.3585[g]
2-Furoyl	527-69-5	1758, 1782[d]	−0.8761
3-Furoyl	26214-65-3	1765[c]	−1.3883

[a] C. Garrigou-Lagrange, N. Claveire, J. M. Lebas, and J. M. Jonen, *J. Chim. Phys.*, **58**, 559 (1961). [b] J. J. Peron and P. Saumagne, *Spectrochim. Acta, Part A*, **26**, 1651 (1970). [c] This work. [d] Reference 22. [e] Reference 17. [f] Reference 12. [g] Reference 14.

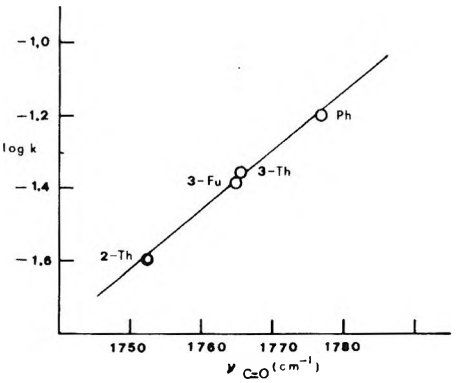


Figure 4. Plots of log k_{25} for the reactions of 2-thenoyl, 3-thenoyl, 3-furoyl, and benzoyl chlorides with aniline in benzene against the carbonyl stretching bands in CCl_4 of the acid chlorides.

theoretical line of slope $-2.303RT$ drawn through the point representing the unsubstituted aniline. The large negative entropies of activation are as expected in reactions involving polar transition states and similar to those found for the 2-[12] and 3-thenoyl[13,14] chloride reactions.

As for the 2-[12] and 3-thenoyl chlorides[14] linear relationships were also found in the reactions of 2- and 3-furoyl chlorides between log k at 25° and the pK_a values at 25° in water of the corresponding protonated anilines[18] (Figure 2) indicating that the reaction rates of 2- and 3-furoyl chlorides depend on the electron density on the nitrogen atom. The slopes of the Brønsted plots, 1.10 (r = 0.997) for 2-furoyl chloride, 1.11 (r = 0.997) for 3-furoyl chloride, are similar to those found for the benzoylation, 2-[12] and 3-thenoyl chloride[14] reactions.

The plots of log k at 25° for the reactions of 2- and 3-furoyl chlorides against Hammett's σ constants are linear with slopes of −3.26 (r = 0.995) and −3.28 (r = 0.997) respectively (Figure 3). These values are comparable to those found for benzoylation, 2-[12] and 3-thenoyl chloride[14] reactions.

From these results it is clear that the 2- and 3-furoyl chlorides react with aniline in benzene with the same mechanism as the reaction of benzoylation[19] involving the attack of the lone pair of the electrons of the amino group on the carbonyl carbon atom. The reported results show that the furyl group functions as electron donating in 3-furoyl chloride and electron withdrawing in the 2-analog relative to the phenyl group in benzoyl chloride. This rate behavior of the 2- and 3-furyl derivatives has been also noted in the saponification of 2- and 3-furoates.[4-7]

Although the infrared carbonyl absorption is property of the ground state only, whereas the reactivity data refer to both reactants and the transition states, a number of examples of linear relationships between the carbonyl stretching bands and the reactivity constants are reported in the literature.[20,21]

In the Table III are listed the log k at 25° for the reactions of 2-[12] and 3-thenoyl,[13] 2- and 3-furoyl, and benzoyl chlorides[17] and the infrared carbonyl stretching bands in CCl_4 of the acid chlorides.

A linear relationship is obtained plotting the log k against the carbonyl stretching bands for the reactions of 2- and 3-thenoyl, 3-furoyl, and benzoyl chlorides which demonstrates that the same combination of factors is responsible for both the shift in carbonyl stretching frequency and the reactivity (Figure 4). It is not possible to correlate the log k and the carbonyl frequencies of 2-furoyl chloride. In fact in this compound the presence of both s-cis and s-trans rotational isomers has been pointed out.[22,23]

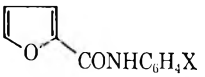
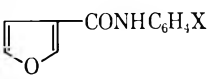
Experimental Section

Materials. The 2- and 3-furoyl chlorides were prepared by refluxing 2 g of 2- or 3-furoic acid (Fluka commercial products) with 10 ml of thionyl chloride for several hours. The excess thionyl chloride was removed by water bath distillation, and the acid chlorides were purified under reduced pressure: 2-furoyl chloride, bp 173–174,[24] 3-furoyl chloride, bp 78–80° (55 mm).[25]

The anilines (Carlo Erba commercial products) were purified to constant melting point or boiling point by recrystallization or fractionation.

The solvent was benzene (R. P. Carlo Erba); no special purification was undertaken.[12]

Table IV
Physical Constants of 2- and 3-Furanilides[a,b]

No.	X =	 Mp, °C	Registry no.	 Mp, °C	Registry no.
1	H	124[e]	1929-89-1	125	52109-86-1
2	*m*-CH_3	87[f]	1982-61-2	117	52109-87-2
3	*p*-CH_3	108[g]	1982-62-3	148	52109-88-3
4	*m*-CH_3O	168[c,h]	52109-84-9	140	52109-89-4
5	*m*-Cl	116[i]	2008-49-3	129	52109-90-7
6	*p*-Cl	146[i]	1982-59-8	152	52109-91-8
7	*m*-NO_2	145[d,h]	52109-85-0	128	52109-92-9

[a] All the compounds were crystallized from aqueous ethanol. [b] Satisfactory analytical data for N (±0.2%) were reported for 3-furanilides. [c] *Anal.* Calcd for $C_{12}H_{11}NO_3$: N, 6.45. Found: N, 6.41. [d] *Anal.* Calcd for $C_{11}H_8N_2O_4$: N, 12.06. Found: N, 11.95. [e] P. Grammaticakis, *Bull. Soc. Chim. Fr.*, 979 (1948). [f] J. Heilbron and H. M. Bumbury, "Dictionary of Organic Compounds," p 560, Eyre and Spottiwoode (1946). [g] C. Tsuchiya, *Nippon Kagaku Zasshi*, **82**, 1395 (1961); *Chem. Abstr.*, **59**, 2751 (1963). [h] This work. [i] Buu-Hoi and Ngugen Hoan, *Recl. Trav. Chim. Pays-Bas*, **68**, 5 (1949).

Infrared Spectra. Spectra of 3-thenoyl[14] and 3-furoyl chlorides were measured on a Hitachi Perkin-Elmer EPS-3T spectrometer using cell of 0.1 mm thickness. The solvent was CCl_4 of spectroscopic grade. In Table III are listed the infrared carbonyl bands of the acid chlorides.

Kinetic Procedure. The reactions were followed kinetically, as previously,[14] by filtering the completely insoluble aniline hydrochloride, dissolving it in water, and estimating the chloride with 0.01 mercury(II) nitrate, using diphenylcarbazone as indicator, in the presence of bromophenol blue.

The second-order rate constants were derived from the formula

$$k_2 = \frac{1}{2 \times 60t}\left(\frac{1}{100 - X} - \frac{1}{100}\right)\frac{100}{a}$$

where t is the time in minutes, X is the percentage change, k_2 is the velocity constant (liters/mole seconds), and a is the initial concentration of the acid chloride in moles/liter.[14]

The second-order rate constants were calculated with constant molar ratios of the reactants (1:2): 1 mol of acid chloride with 2 mol of aniline, in agreement with eq 1. For the 2-furoyl chloride reaction and compounds no. 2 and 3 for the 3-furoyl chloride reaction the initial concentration of the reactants after mixing were acid chloride 0.0025 *M*, aniline 0.005 *M*. For other compounds in Table II the initial concentrations were 0.005 *M* 3-furoyl chloride and 0.01 *M* aniline.

All compounds gave excellent second-order kinetics. All rates were run in duplicate to the least 80% completion with less than 3% deviation between the two rate constants. At temperatures other than 15 or 25°, rate coefficients were corrected for thermal expansion or contraction of the solvent. All rate constants were calculated by a least-squares computer program with a Hewlett-Packard 9100 B. The activation parameters were calculated from a least-squares treatment of log k against T^{-1}. The estimated precision is *ca.* ±0.5 kcal mol^{-1} in E_A and ±2 cal mol^{-1} $°K^{-1}$ in ΔS^*.

Product Analysis. Standard solutions of the appropriate aniline and 2- or 3-furoyl chloride in benzene were placed in a glass-stoppered bottle and maintained at the kinetic temperature until completion. After concentration of the benzenic solution to small volume, the 2- or 3-furanilide was filtered, washed free from aniline hydrochloride with water, dried, and recrystallized from aqueous ethanol.

In all cases the amount of the furoanilide was ≥95% of that expected from the formation of 1 mol of anilide per mol of acid chloride consumed. Physical constants and analytical data of furanilides are reported in Table IV.

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References and Notes

(1) E. A. Braude and J. S. Fawcett, *J. Chem. Soc.*, 4158 (1952).
(2) G. Marino, *Advan. Heterocycl. Chem.*, **13**, 242 (1971).
(3) H. A. Smith, J. B. Conley, and W. H. King, *J. Amer. Chem. Soc.*, **73**, 4633 (1951).
(4) P. A. Ten Thije and M. J. Janssen, *Recl. Trav. Chim. Pays-Bas*, **84**, 1169 (1965).
(5) E. Imoto, Y. Otsuji, T. Hirai, and H. Inoue, *J. Chem. Soc. Jap., Pure Chem. Sect.*, **77**, 804, 809 (1956).
(6) S. Oae and C. C. Price, *J. Amer. Chem. Soc.*, **79**, 2457 (1957).
(7) Y. Otsuji, Y. Koda, M. Kubo, M. Furukawa, and E. Imoto, *Nippon Kagaku Zasshi*, **80**, 1293 (1959).
(8) E. A. Hill, M. L. Gross, M. Stasiewicz, and M. Manion, *J. Amer. Chem. Soc.*, **91**, 7381 (1969).
(9) D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, **34**, 1008 (1969); D. S. Noyce, C. A. Lipinski, and R. W. Nichols, *ibid.*, **37**, 2615 (1972); D. S. Noyce and H. J. Pavez, *ibid.*, **37**, 2620 (1972).
(10) D. S. Noyce, C. A. Lipinski, and G. M. Loudon, *J. Org. Chem.*, **35**, 1718 (1970).
(11) G. P. Nilles and R. D. Schuetz, *J. Org. Chem.*, **36**, 2489 (1971).
(12) A. Arcoria, S. Fisichella, G. Scarlata, and D. Sciotto, *J. Org. Chem.*, **38**, 32 (1973).
(13) A. Arcoria and S. Fisichella, *Gazz. Chim. Ital.*, **103**, 813 (1973).
(14) A. Arcoria and S. Fisichella, *J. Org. Chem.*, **38**, 3774 (1973).
(15) E. G. Williams and C. N. Hinshelwood, *J. Chem. Soc.*, 1079 (1934).
(16) F. J. Stubbs and C. N. Hinshelwood, *J. Chem. Soc.*, 71 (1949).
(17) E. Tommila and T. Vihavainen, *Acta Chem. Scand.*, **22**, 3224 (1968).
(18) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962, p 144.
(19) J. G. Mather and J. Shorter, *J. Chem. Soc.*, 4744 (1961); A. R. Katritzky and A. P. Ambler, "Physical Methods in Heterocyclic Chemistry," Vol. II, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, p 312.
(20) R. N. Jones, W. F. Forbes, and W. A. Mueller, *Can. J. Chem.*, **35**, 504 (1957).
(21) H. A. Staab, W. Otting, and A. Uerberle, *Z. Elektrochem.*, **61**, 1000 (1957).
(22) M. Senechal and P. Saumagne, *J. Chim. Phys.*, **69**, 1246 (1972).
(23) C. Pigenet, I. P. Morizur, Y. Pascal, and H. Lumbroso, *Bull. Soc. Chim. Fr.*, 361 (1969).
(24) N. T. Bogert and A. Stull, *J. Amer. Chem. Soc.*, **48**, 248 (1926).
(25) P. Grunanger and A. Montegani, *Gazz. Chim. Ital.*, **89**, 916 (1959).

The E2C Mechanism in Elimination Reactions. VII.[1a] Secondary Kinetic Hydrogen Isotope Effects in E2 Reactions of Alicyclics

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Secondary kinetic hydrogen isotope effects on the rates of some base-induced dehydrotosylations and dehydrobrominations of cyclohexyl derivatives (E2C-like reactions) have been studied. Secondary hydrogen isotope effects at C_α (13–15%) and at C_β (15–25%) indicate that significant hybridization changes occur at both C_α and C_β in reactions leading to E2C-like transition states. Secondary hydrogen isotope effects (11–22%) at C_γ (adjacent to C_α and allylic to the site of double-bond development) arise most probably from hyperconjugative interactions and suggest either a well-developed double bond between C_α and C_β, or a well-developed positive charge at C_α in E2C-like transition states. The observed secondary hydrogen isotope effects are *not* consistent with those paene-carbonium E2 transition states in which there is very little change in hybridization taking place at C_β. For the SN2 reactions which accompany E2C-like reactions, secondary β-hydrogen isotope effects are of the same order of magnitude as those for the elimination reactions, whereas, in contrast, it appears that secondary α-hydrogen isotope effects are much smaller for SN2 reactions than they are for E2C-like reactions. The nature of the transition states for E2C-like reactions and their concomitant SN2 reactions are discussed in the light of these findings.

Primary hydrogen isotope effects on the rates of bimolecular β-elimination (E2) reactions have now been studied over the spectrum of transition states available for E2 reactions.[1-6] However, the much smaller secondary hydrogen isotope effects on the rates of E2 reactions have received scant attention. In this paper we examine the kinetic hydrogen isotope effects, primary and secondary, arising in the bimolecular reactions (E2, SN2) of cyclohexyl tosylate and cyclohexyl bromide with selected bases.

There have been studies, which have been well reviewed,[3,6-11] of secondary hydrogen isotope effects in solvolytic processes (E1, SN1 reactions). These arise from hybridization changes, hyperconjugative effects, or nonbonded steric interactions. Secondary kinetic hydrogen isotope effects in solvolytic processes (*i.e.*, those using carbonium ion-like transition states) are by no means negligible, and may run to as much as 10–30% retardation in rate per deuterium atom.[8] In contrast, SN2 reactions usually show much smaller secondary isotope effects[12-14] and in some cases inverse isotope effects have been reported.[15,16]

It is generally accepted that E2 reactions have variable transition states depending upon the particular reaction, but a variety of sets of transition states have been proposed.[5,17-20] As usual, we choose to discuss our results in terms of the E2C–E2H spectrum of transition states,[18-20] but isotope effects tell us nothing about whether the base bonds to C_α in the E2C transition state. The information obtained here does, however, tell us that there are substantial bonding changes at C_α and C_β in the transition states for the reactions of cyclohexyl tosylate with bases. Secondary kinetic hydrogen isotope effects in these systems are not only measurable, but have significant magnitude and cannot be ignored. If they are not recognized, errors in evaluating primary kinetic hydrogen isotope effects occur.[21]

It has been clearly established that the type of reaction studied here is an anti elimination so that one can distinguish between effects due to hydrogen or deuterium cis or trans to the leaving group in cyclohexyl derivatives.[20]

Results

The product ratios of the cyclohexenes from the E2 reactions of *trans*-cyclohexyl-2-*d* tosylate (II-OTs), *trans*-cyclohexyl-2-*d* bromide (II-Br), and cyclohexyl-2,2-d_2 tosylate (III-OTs) with a variety of bases are shown in Table I. Also shown in Table I for the same series of bases are the cyclohexene product ratios obtained from intermolecular competition experiments during the first 10% of the E2 reactions of an equimolar mixture of cyclohexyl tosylate (I-OTs) and cyclohexyl-2,2,6,6-d_4 tosylate (V-OTs), as well as of an equimolar mixture of the corresponding bromides (I-Br, V-Br). The product ratios are governed by kinetic hydrogen isotope effects. These reactions, together with the symbolism distinguishing the rate constants for the various elimination routes are shown in Chart I. The data in Table I were derived from mass spectrometric analyses of the olefinic product mixtures arising from the various intramolecular and intermolecular competition experiments.

Rate constants for the total reaction (E2 + SN2) of variously deuterated cyclohexyl tosylates and bromides with NBu_4OAc in acetone containing 2,6-lutidine at 50° are reported in Table II. Specific rate constants for elimination along each pathway illustrated in Chart I were evaluated from the rate constant combinations in Tables I and II, and are collected in Table III. Primary and secondary kinetic hydrogen isotope effects in the reactions of the isotopically substituted cyclohexyl tosylate and cyclohexyl bromide systems are recorded in Table IV. They were evaluated in the following manner.

Primary Isotope Effects (1°). The "true" primary kinetic hydrogen isotope effect for elimination is given by k_H^H/k_D^D in Table IV (*cf.* pathways 1 and 2b in Chart I).

Secondary Isotope Effects. These are of two types which Streitweiser[22] distinguishes as secondary isotope effects of the first and second kind. The criterion for distinction is whether or not the bonds to the isotopic atoms undergo spatial reorientation. In this paper, we use more descriptive terminology for the two sources of secondary isotope effects. Isotope effects of the first kind, *i.e.*, those arising due to hydridization changes at the labeled carbon atom (C_α or C_β), are referred to as hybridization isotope effects. Isotope effects of the second kind arising from isotopic substitution at carbon atoms one removed from those where double-bond formation occurs (*i.e.*, at C_γ in the cyclohexyl system) are referred to as hyperconjugative isotope effects.

i. Secondary Hybridization Isotope Effects at C_α ($2°C_\alpha$). The secondary isotope effect of a hydrogen atom relative to a deuterium atom at C_α on the leaving tendency of the expelled group X as the hybridization at C_α changes from sp^3 in the ground state to increasing sp^2 character in the transition state, is given by $k_H^H/k_{D_\alpha}^H$ in Table IV (*cf.* pathways 1 and 4 in Chart I).

ii. Secondary Hybridization Isotope Effects at C_β

Table I
Isotope Effects for Elimination from Cyclohexyl Tosylates and Cyclohexyl Bromides with Various Base/Solvent Systems, as Measured by Mass Spectral Analysis of Intra- and Intermolecular Competitive Reactions

Base[a]	Registry no.	Solvent	Temp, °C	II-OTs, [c] k_D^H/k_D^D[d]	III-OTs, [c] $k_{D_2}^H/k_{D_2}^D$[d]	V-OTs, [c] $k_H^H/k_{D_4}^D$[e]	Temp, °C	II-Br, [c] k_D^H/k_D^D[d]	V-Br, [c] $k_H^H/k_{D_4}^D$
NBu_4OPh	16909-23-2	Acetone	50	3.1	3.0	3.8	75	4.0	5.6
NBu_4OAc	10534-59-5	Acetone[b]	50	2.7_4	2.9	3.5[h]	75	3.9 (4.4)[g]	5.1[i]
NBu_4SAr	20627-93-4	Acetone[b]	75	2.4	2.4	3.0	75	3.5	4.7
NBu_4Cl	1112-67-0	Acetone[b]	50	2.6	2.6	4.0[f]	75	3.2	4.6
NBu_4Br	1643-19-2	Acetone[b]	75	2.2	2.4	3.5	75		4.7
NaOEt	141-52-6	EtOH	75	2.3	2.3	2.3	75	3.2	3.9[h]
KO-*t*-Bu	865-47-4	Bu-*t*-OH	75	2.8	2.7	3.2	75	3.8	4.8[h]

[a] NBu_4 is the tetra-*n*-butylammonium cation, OPh is phenoxide, OAc is acetate, and SAr is *p*-nitrothiophenoxide. Base concentrations <0.1 *M*. [b] Solvent contained 0.04–0.10 *M* 2,6-lutidine. [c] Substrate numbers and notation for *k* refer to Chart I. Allowance was made for imperfect deuteration of substrates. [d] This is an intramolecular isotope effect obtained by mass spectral analysis of the proportions of the two possible olefins formed from the single substrate shown (see Chart I and text). [e] This is an intermolecular isotope effect obtained by mass spectral analysis of the ratio of the two olefins formed from the reaction of an equimolar mixture of the substrate shown with its undeuterated analog (see Chart I and text). Analysis was made during the first 10% of reaction. [f] Extrapolated from a value of 3.7 measured at 75°.[23] [g] At 50°. [h] These intermolecular isotope values were also determined from a direct comparison of the measured rate constants for the individual reactions of the tetradeuterated and undeuterated substrates. Isotope values determined by the kinetic method agreed to within 6% with the values shown in the table. [i] A value of 7.1 at 50° was obtained by the kinetic method (see footnote *h*).

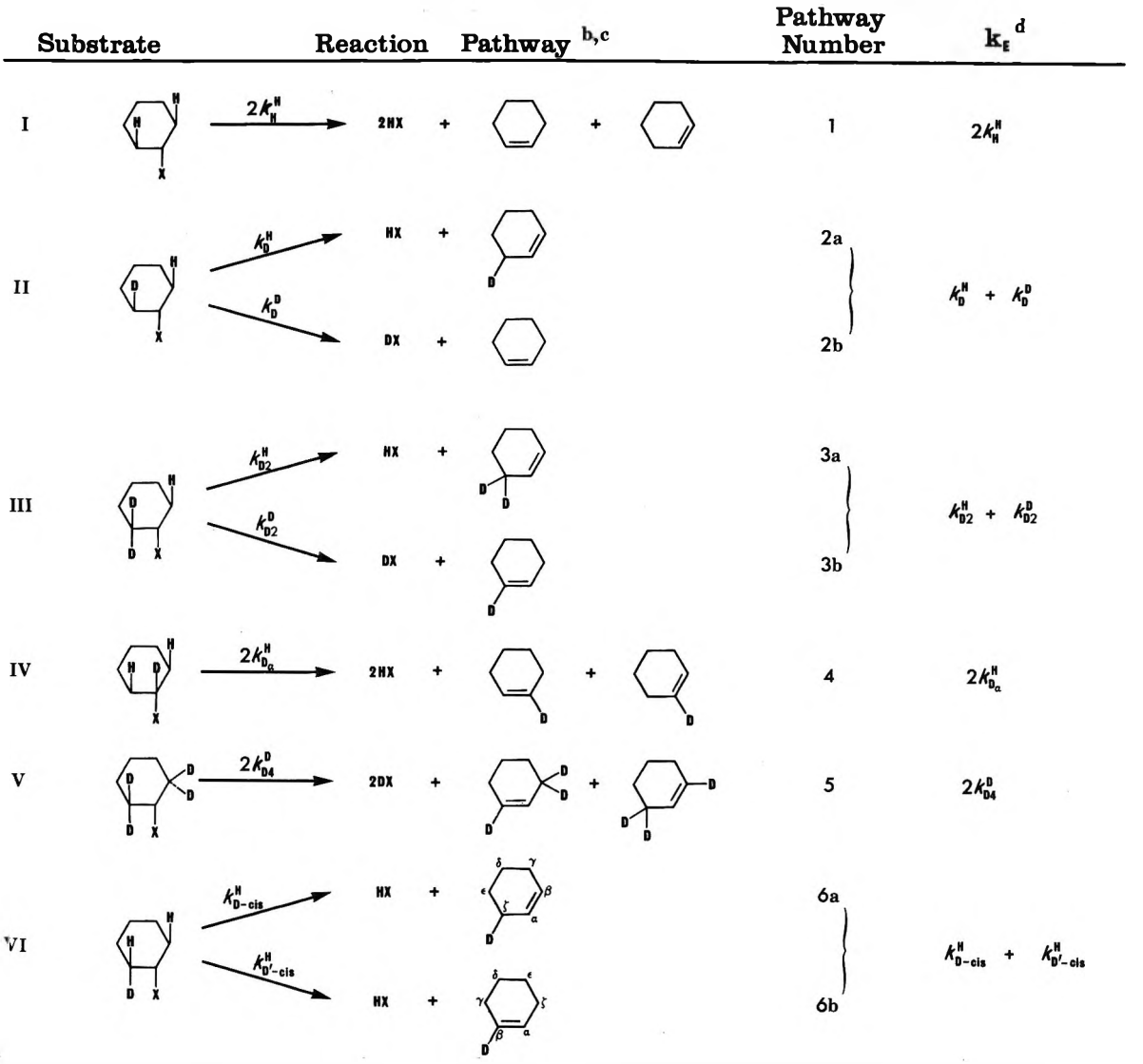
Table II
Kinetic Data for the Reactions of Variously Deuterated Cyclohexyl Tosylates and Bromides at 50° with NBu_4OAc in Acetone Containing 0.15 *M* 2,6-Lutidine

Substrate[a]	Registry no.	10^4k, [b] $dm^3\ mol^{-1}\ sec^{-1}$	F_E[c]	10^4k_S, [d,e] $dm^3\ mol^{-1}\ sec^{-1}$	10^4k_E, [e,f] $dm^3\ mol^{-1}\ sec^{-1}$	E2[g] components
I-OTs	953-91-3	$15.1 \pm 0.1_5$	0.693 ± 0.006	4.6 ± 0.1	10.5 ± 0.2	$2k_H^H$
II-OTs	1085-94-5	10.0 ± 0.12	0.641 ± 0.006	3.6 ± 0.1	6.4 ± 0.1	$k_D^H + k_D^D$
III-OTs	51933-07-4	9.17 ± 0.12	0.621 ± 0.005	3.5 ± 0.1	5.7 ± 0.1	$k_{D_2}^H + k_{D_2}^D$
IV-OTs	957-27-7	13.8 ± 0.1	0.673 ± 0.006	4.5 ± 0.1	$9.3 \pm 0.1_5$	$2k_{D_\alpha}^H$
V-OTs	967-93-1	6.67 ± 0.03	0.434 ± 0.013	3.8 ± 0.1	2.9 ± 0.1	$2k_{D_4}^D$
I-Br	108-85-0	$14.2 \pm 0.1_5$	0.910 ± 0.006	1.3 ± 0.1	12.9 ± 0.2	$2k_H^H$
II-Br	51933-08-5	7.50 ± 0.04	0.870 ± 0.006	0.98 ± 0.05	6.5 ± 0.1	$k_D^H + k_D^D$
V-Br	768-97-8	2.55 ± 0.01	0.711 ± 0.007	0.74 ± 0.02	$1.8 \pm 0.0_5$	$2k_{D_4}^D$

[a] Numbers refer to compounds in Chart I. [b] *k* is the second-order rate constant for total reaction (E2 + Sn2) of substrate. [ROTs] or [RBr] ~ 0.01 *M*; [NBu_4OAc] ~ 0.03 *M* in the presence of 0.015 *M* 2,6-lutidine. Values are the average of two or more determinations with average deviations. [c] F_E is the fraction of the total reaction which is bimolecular elimination. Determined from ratio of acid produced to substrate consumed and found to be constant throughout reaction. Values are the mean of six or more determinations with average deviations. [d] k_S is the second-order rate constant for the Sn2 portion of the total reaction. [e] Derived values are shown together with estimated error limits. [f] k_E is the second-order rate constant for total E2 component of reaction. [g] Indicates the individual E2 rate constants which make up k_E as shown in Chart I.

Chart I

Reaction Pathways for Bimolecular Anti Elimination from Variously Deuterated Cyclohexyl Derivatives[a]



[a] X = *p*-toluenesulphonate or bromide. [b] Symbolism for rate constants: superscript indicates whether H or D is eliminated (as HX or DX, respectively) in an anti elimination; subscript refers to the nature of the deuteration in the substrate. The notation is not intended to be general, but has been simplified as much as possible with reference to the compounds shown in Chart I. The notation for compound VI is necessary to distinguish the two pathways 6a and 6b from each other as well as from pathway 2a of compound II. [c] The labeling system used in this paper to define the positions where various isotope effects arise is as illustrated for the E2 reaction products of substrate VI. The labeling is such that the α carbon (C_α) is always that from which the leaving group X is lost, the β carbon (C_β) is always that from which hydrogen or deuterium is lost, and the ζ carbon (C) is adjacent to C_α but allylic to the developing double bond. The labeling of the carbon atoms clearly depends upon the direction of elimination from the substrate. Double-bond formation always occurs between C_α and C_β. [d] k_E represents the sum of all the E2 rate constants for production of cyclohexenes from a given substrate.

Table III

Partitioned Second-Order Rate Constants (dm^3 mol^{-1} sec^{-1}) for the E2 Reactions of Cyclohexyl Tosylates and Cyclohexyl Bromides[a]

X in cyclohexyl X	Base	Solvent	Temp, °C	k_E[b]	$k_H{}^H$[c]	$k_D{}^H$[d]	$k_D{}^D$[d]	$k_{D_2}{}^H$[e]	$k_{D_2}{}^D$[e]	$k_{D_\alpha}{}^H$[c]	$k_{D_4}{}^D$[c]	$k_{D\text{-cis}}{}^H$[f]	$k_{D'\text{-cis}}{}^H$[g]
Br	NBu_4OAc	Me_2CO	50.0	10^4	6.4_5	5.3	1.1				0.9		
OTs	NBu_4OAc	Me_2CO	50.0	10^4	5.2_5	4.7	1.7	4.2	1.4_5	4.6_5	1.4_5		
OTs	NaOEt	EtOH	49.9	10^{5h}	6.7	5.9[i]	2.3[i]			6.5[j]	1.6	5.9	6.0
OTs	KO-*t*-Bu	Bu-*t*-OH	49.9	10^{5h}	4.3_5	3.7_5[i]	1.2[i]			3.8	0.7	3.7_5	3.5

[a] Symbolism is defined in Chart I. [b] These values are all derived from rate constants reported in Table II. [c] $k_H{}^H$ and $k_{D(4)}{}^H$ are half the observed E2 rate constants for the reactions of I, IV, and V, respectively, as shown in Chart I. [d] $k_D{}^H$ and $k_D{}^D$ are calculated from the observed E2 rate constants for the reactions of II (see Chart I) and the appropriate intramolecular isotope values ($k_D{}^H/k_D{}^D$) recorded in Table I. [e] $k_{D(2)}{}^H$ and $k_{D(2)}{}^D$ are calculated from the observed E2 rate constant ($k_{D(2)}{}^H + k_{D(2)}{}^D$) for the reaction of III (see Chart I) and the appropriate intramolecular isotope value ($k_{D(2)}{}^H/k_{D(2)}{}^D$) recorded in Table I. [f] $k_{D\text{-cis}}{}^H$ is assumed to be the same as corresponding value of $k_D{}^H$ (see text and Chart I). [g] $k_{D'\text{-cis}}{}^H$ is determined from the observed E2 rate constants ($k_{D\text{-cis}}{}^H + k_{D'\text{-cis}}{}^H$) for the reactions of VI, minus $k_{D\text{-cis}}{}^H$ (see text and Chart I). [h] These values are all derived from rate constants reported by Finley and Saunders.[21] [i] These values were derived using intramolecular isotope values ($k_D{}^H/k_D{}^D$) of 2.6 and 3.1 for the reactions of II-OTs with NaOEt and KO-*t*-Bu, respectively, at 50°. These intramolecular isotope values were extrapolated from the corresponding values recorded in Table I for 75° using temperature data reported by Melander.[23] [j] Measured at 50.0°. The corresponding value of $k_H{}^H$ at 50.0° is 7.4×10^{-5} dm^3 mol^{-1} sec^{-1} (see footnote *c* and ref 21).

Table IV
Primary and Secondary Kinetic Hydrogen Isotope Effects for E2 Reactions of Cyclohexyl Tosylate and Cyclohexyl Bromide with Bases at 50°

X in cyclohexyl X	Base	Solvent	k_H^H/k_D^D, primary[a]	$k_H^H/k_{D_\alpha}^H$ Secondary[a,b] C_α[c]	C_β[d]	C_ζ[e]
	NBu_4OAc[f]	Me_2CO	$3.0_5 \pm 0.1_5$	1.13 ± 0.04	1.17 ± 0.06	1.11 ± 0.05
OTs	NaOEt	EtOH	2.9 ± 0.1	1.14 ± 0.02[g]	1.15 ± 0.06	1.13 ± 0.03
	KO-*t*-Bu	Bu-*t*-OH	3.6 ± 0.1	1.15 ± 0.01[g]	1.25 ± 0.04	1.17 ± 0.02
Br	NBu_4OAc[f]	Me_2CO	5.4 ± 0.2			1.22 ± 0.04

[a] All isotope effects are calculated from the partitioned second-order rate constants recorded in Table III, as described in the text. Estimated error limits are also recorded. [b] The labeling of carbon atoms is as defined in Chart I. [c] C_α-H hybridization isotope effect. [d] C_β-H hybridization isotope effect. Evaluated as described in the text. [e] C -H hyperconjugative isotope effect. Evaluated as shown in text. [f] In the presence of 0.015 *M* 2,6-lutidine. [g] As reported by Finley and Saunders.[21]

(2°C_β). In the E2 reaction pathways 3b, 5, and 6b shown in Chart I, anti elimination occurs into the branch containing a deuterium atom at C_β cis to the leaving group X. The secondary hydrogen isotope effect arising in this situation, as the hybridization at C_β changes from sp^3 in the ground state to increasing sp^2 character in the transition state, may be evaluated by either of the following ways: (a) from $k_D^D/k_{D_2}^D$ (*cf.* pathways 2b and 3b in Chart I); (b) from $k_H^H/k_{D_2}^D$ (*cf.* pathways 1 and 3b in Chart I) which gives the product of this secondary isotope effect and the primary isotope effect (evaluated as shown above), *i.e.*, $k_H^H/k_{D_2}^D = k_H^H/k_D^D \times k_D^D/k_{D_2}^D \equiv 1° \times 2°C_\beta$ isotope effects (since k_H^H/k_D^D can be found independently, $k_D^D/k_{D_2}^D$ can be calculated); (c) from $k_H^H/k_{D\text{-cis}}^H$ (*cf.* pathways 1 and 6b in Chart I).

iii. Secondary Hyperconjugative Isotope Effects at C_ζ (2°C_ζ). In the E2 pathways 2a, 3a, 5, and 6a shown in Chart I, anti elimination occurs into the branch away from a site of deuteration at C_ζ. The magnitude of the secondary hydrogen isotope effect arising in this situation due to hyperconjugative interactions (*vide infra*) may be evaluated as follows: (a) from k_H^H/k_D^H (*cf.* pathways 1 and 2a in Chart I) which gives the isotope effect arising when deuteration at C_ζ is initially trans to the leaving group X; (b) from $k_D^H/k_{D_2}^H$ (*cf.* pathways 2a and 3a in Chart I) which gives the isotope effect arising when deuteration at C_ζ is initially cis to the leaving group X; (c) from $k_H^H/k_{D_2}^H$ (*cf.* pathways 1 and 3a in Chart I) which gives the cumulative (*i.e.*, multiplicative) effect arising from dideuteration at C_ζ, cis and trans to the leaving group X.

The magnitude of this hyperconjugative isotope effect was evaluated by all three of the above methods from the reactions of I-OTs, II-OTs and III-OTs with NBu_4OAc in acetone at 50°. The isotope effect was the same, *i.e.*, 11% in magnitude, regardless of the stereochemistry (cis or trans) of the substituent deuterium atom relative to the tosylate leaving group.

In addition to the hydrogen isotope effects evaluated for the reactions of cyclohexyl tosylate and cyclohexyl bromide with NBu_4OAc in acetone, we also include in Table IV for comparison the corresponding primary and secondary isotope effects for the reactions of cyclohexyl tosylate with NaOEt/EtOH and KO-*t*Bu/Bu-*t*-OH. These latter data are derived using the methods outlined above from the partitioned E2 rate constants recorded in Table III. The partitioned E2 rate constants for the NaOEt/EtOH and KO-*t*-Bu/Bu-*t*-OH reactions at 50° were in turn derived from rate constants reported by Finley and Saunders[21] in conjunction with intramolecular data extrapolated[23] from values at 75° reported in Table I (see Table III).

The rate constants for the two E2 reaction routes of *cis*-cyclohexyl-2-*d* tosylate (pathways 6a and 6b in Chart I) could not be separated using intramolecular techniques since the two monodeuterated olefins, which are produced, cannot be distinguished by mass spectrometry. The rate constants can be separated however if it is assumed that $k_{D\text{-cis}}^H = k_D^H$ (*cf.* pathways 6a and 2a). This is not an unreasonable assumption. It has been already shown above, for the reaction of cyclohexyl tosylate with NBu_4OAc, that the stereochemistry (cis or trans) of a substituent deuterium at C_ζ relative to the leaving group at C_α has little or no effect on the magnitude of the secondary hyperconjugative isotope effect when elimination occurs into the branch remote from the site of deuteration.

Discussion

Our first attempts[1] to evaluate primary kinetic hydrogen isotope effects for E2 reactions in alicyclic systems were based in some instances upon the results of intramolecular competition reactions and included effects due to secondary isotope effects. For example, *trans*-cyclohexyl-2-*d* tosylate can undergo anti elimination along two routes (pathways 2a and 2b in Chart I). The olefin product ratio, as determined by mass spectrometry, gives the ratio of the rate constants for the two intramolecular processes, *i.e.*, k_D^H/k_D^D. We had assumed[1] that this "intramolecular" isotope effect was a reflection of the "true" primary hydrogen isotope effect for this system (*i.e.*, $k_D^H/k_D^D = k_H^H/k_D^D$). The "intramolecular" value is lower than the "true" primary value however since it can be expanded to

$$\frac{k_D^H}{k_D^D} = \frac{k_H^H}{k_D^D} \times \frac{k_D^H}{k_H^H} \equiv \frac{1° \text{ isotope effect}}{2° \text{ hyperconjugative isotope effect at } C_\zeta}$$

The secondary hydrogen isotope effect involved in this instance is that arising from hyperconjugation and is ~10–20% in magnitude. Like other workers in this area,[21] we initially assumed that secondary hydrogen isotope effects were negligible relative to the magnitude of the associated primary isotope effects. The danger in making such an assumption is clearly demonstrated by the discrepancies between our reported[1] primary hydrogen isotope effects (k_D^H/k_D^D) for the reactions of *trans*-cyclohexyl-2-*d* tosylate with both NaOEt in ethanol and KO-*t*-Bu in *tert*-butyl alcohol *vs.* those reported by Finley and Saunders.[21] Finley and Saunders reported values of 4.47 and 7.53, respectively, at 50°, whereas we found 2.6 and 3.1 at 50°. Professor Saunders[24] has since pointed out to us that the results can

be reconciled if it is realized that the Finley and Saunders values are derived from an intermolecular rate comparison [*i.e.*, from $k_H^H/(k_D^H + k_D^D - k_H^H)$] whereas our values ($k_D^H/k_D^D$) are derived from an intramolecular product comparison. We both assumed that sources of secondary isotope effects are negligible (*i.e.*, that $k_D^H = k_H^H$) but the error arising from this assumption is much more serious when using the Finley and Saunders expression than it is with ours. This can readily be seen by comparison of the two sets of assumed primary isotope effects (2.6 and 3.1 from part VI[1] and 4.5 and 7.5 from Finley and Saunders[21]) with the "true" primary isotope values of 2.9 and 3.6, respectively, for reaction with NaOEt/EtOH and KO-*t*-Bu/Bu-*t*-OH as reported in Table IV.

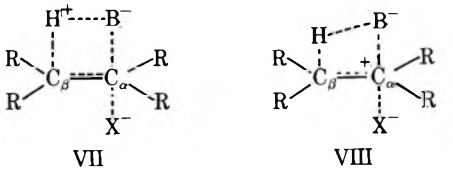
The "intramolecular" isotope effects recorded in Table I for the reactions of *trans*-cyclohexyl-2-*d* tosylate and *trans*-cyclohexyl-2-*d* bromide with a variety of bases have been discussed in part VI.[1] They provide a reasonable reflection of "true" primary hydrogen isotope effects, provided it is realized that these values are probably about 10–20% too low (as judged from the magnitudes of the secondary hyperconjugative isotope effects at C_ζ reported in Table IV).

We show in Table I that the "intramolecular" isotope values for the reactions of cyclohexyl-2,2-d_2 tosylate (*i.e.*, $k_{D_2}^H/k_{D_2}^D$; see Chart I) with a series of bases is remarkably similar to the corresponding set of values for the reactions of *trans*-cyclohexyl-2-*d* tosylate (k_D^H/k_D^D) and thus close to the true primary isotope effect. The similarity is because the two different types of secondary isotope effect at play in these systems, *i.e.* the hybridization effect at C_β and the hyperconjugative effect at C_ζ, are similar in magnitude. Thus

$$\frac{k_D^H/k_D^D}{k_{D_2}^H/k_{D_2}^D} = \frac{k_D^H}{k_{D_2}^H} \times \frac{k_{D_2}^D}{k_D^D} = \frac{2^\circ \text{ hyperconjugative isotope effect at } C_\zeta}{2^\circ \text{ hybridization isotope effect at } C_\beta}$$

The sets of intramolecular isotope effects in Table I give little indication that secondary isotope effects are significant. However, compared with the sets of *inter*molecular isotope effects in Table I which show the relative E2 rates for the cyclohexyl and cyclohexyl-2,2,6,6-d_4 systems, we do get an indication of the distortion produced by the cumulative effect of several secondary isotope effects.

The secondary hydrogen isotope effects for the E2 reactions of cyclohexyl tosylate and cyclohexyl bromide with NBu_4OAc in acetone, NaOEt in ethanol and KO-*t*-Bu in *tert*-butyl alcohol are substantial, *i.e.*, 11–25% (see Table IV). This reflects the fact that a great deal of change has taken place at both C_α and C_β in forming the E2 transition states of these reactions. We have shown elsewhere[18,20,25] that the E2 reactions of cyclohexyl tosylate with a wide range of bases are E2C-like in character; *i.e.*, they may use transition states like VII or VIII.[1] E2 reactions of cyclohexyl bromide are less E2C like, but have considerable E2C character relative to reactions of more acidic substrates with the same bases. These classifications as E2C like are supported by the low primary hydrogen isotope effects exhibited by most eliminations from these two substrates (see Tables I and IV), as discussed elsewhere.[1]



VII VIII

The E2C–E2H spectrum of transition states has been described in previous publications[18,20] in terms of structure VII. More recently we reported[1] that we cannot reject structures like VIII as being descriptive of E2C-like transition states. With regard to the influence of secondary hydrogen isotope effects, the important feature of transition state structures like VII and VIII is that C_α and C_β are both considerably sp^2 hybridized. In VII there is $p\pi$–$p\pi$ orbital overlap to give a well-developed double bond. In VIII there is considerable positive charge formation at C_α, which is stabilized by interaction with the attacking anion and leaving group anion in an ion-triplet arrangement. Despite the rehybridization at C_β in VIII, there is little C_β–H bond breaking, no negative charge at C_β, and as a result a very poorly developed double bond. We prefer VII, but cannot exclude VIII, on existing evidence.

For transition states like VII or VIII, significant secondary hydrogen isotope effects, arising from the extensive hybridization changes at C_α and C_β, are therefore expected. In this work we find that such hybridization isotope effects lie in the range of 13–25% (see Table IV). Is this a large effect? C_α–H isotope effects in solvolysis reactions provide a guide to the magnitude of the secondary hybridization isotope effects that one may expect for reactions using transition states with extensive C_α rehybridization. Streitweiser and Dafforn[26] claim a limiting value of 22% for the α-hydrogen secondary isotope effect arising in the trifluoroacetolysis of isopropyl tosylate. Saunders and Finley[27] have also reported a value of 22% for the α-hydrogen isotope effect in the acetolysis of cyclohexyl tosylate. These values reflect the limiting magnitude of the secondary α-hydrogen isotope effect that one may expect for reactions of secondary tosylates in which carbonium ion character, and consequently the extent of sp^2 hybridization at C_α, is at a maximum, with solvent nucleophilicity at a minimum.[3] The 13–25% secondary hybridization isotope effects observed in this work for the E2 reactions of cyclohexyl tosylate are, we feel, indicative that C_α and C_β have considerable sp^2 character in the transition state, and are consistent with the fact that E2C-like transition states are very product-like.

In other E2 reaction systems, Burton and de la Mare[28] report an α-hydrogen hybridization isotope effect of 12% for the dehydrochlorination of 1,1,2,3,4-pentachlorotetralin with methoxide ion in methanol–acetone. Other evidence suggests that this reaction uses a transition state with a well-developed double bond. In contrast, Cockerill[29] reports low α-hydrogen secondary isotope effects (2–5%) for the reactions of para-X-substituted 2-phenylethyl tosylates (X = MeO, H, and Cl) with KO-*t*-Bu in *tert*-butyl alcohol. The low isotope effects observed in this case are consistent with the E2H-like nature of these reactions in which there is little rehybridization at C_α in the transition state. This contention is supported by the low (<1) tosylate/bromide leaving group tendencies reported for these reactions,[29] a criterion which we have previously shown[1] to be indicative of the E2H-like nature of a reaction.

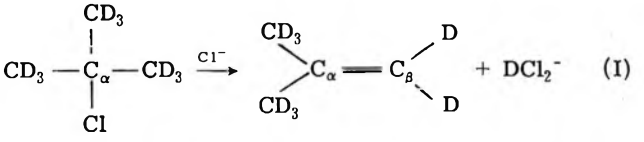
Secondary hyperconjugative hydrogen isotope effects for the reactions studied in this work are 11–22% (see Table IV). Whether these isotope effects arise from the differing hyperconjugative interactions of hydrogen relative to deuterium with sp^2-hybridized C_α, either as a well-developed double bond as in transition states like VII or as a well-developed positive charge at C_α as in VIII, we are unable to decide, but alternatives to either of these are hard to imagine. The magnitudes of the effects however suggest that E2C-like reactions have C_α much changed in the transition state. The concept of a secondary hyperconjugative isotope

Table V
Intermolecular Isotope Effects for the E2 Reactions of Cyclohexyl X and Cyclohexyl-2,2,6,6,-d_4 X with Bases at 50°

X	Base	Solvent	Total isotope effect: Obsd[a] $k_H^H/k_{D_4}^D$	Total isotope effect: Calcd[b] $k_H^H/k_{D_4}^D$	Total secondary isotope effect[c] $k_H^H/k_{D_4}^D \times k_D^D/k_H^H$
OTs	NBu_4OAc[d]	Me_2CO	3.6 ± 0.2[e]	4.4 ± 0.9	1.2 ± 0.1[e]
OTs	NaOEt	EtOH	4.2 ± 0.2[f]	4.3 ± 0.6	1.4_5 ± 0.1
OTs	KO-*t*-Bu	Bu-*t*-OH	6.3 ± 0.1[f]	6.2 ± 0.6	1.7_5 ± 0.0_5
Br	NBu_4OAc[d]	Me_2CO	7.1 ± 0.2		1.3 ± 0.1

[a] Determined from the observed values of k_H^H and $k_{D(4)}^D$ reported in Table III. [b] Evaluated from the product of the component isotope effects (see Table IV). The total isotope effect is composed of a primary isotope effect, a secondary hybridization isotope effect at C_β, and two secondary hyperconjugative isotope effects at C_γ. The somewhat large error limits shown here arise from the addition of percentage errors for the four component isotope effects. [c] Determined by dividing the observed total isotope effect ($k_H^H/k_{D(4)}^D$) by the primary isotope effect (k_H^H/k_D^D) found for the system (see Table IV). [d] In the presence of 2,6-lutidine. [e] See ref 36 and text. [f] As reported by Finley and Saunders.[21]

effect in E2C-like reactions seems to be new. Kevill and Dorsey[30,31] have reported some interesting data for the reactions of *tert*-butyl chloride and *tert*-butyl-d_9 chloride in acetonitrile. They observed[30] for the "E1-reaction" a β-deuterium isotope effect of 2.62 at 45°. This corresponds to a secondary hyperconjugative isotope effect of ~11% per deuterium. For the E2 reaction with NEt_4Cl Kevill and Dorsey[31] observed a β-deuterium isotope effect of 3.81 at 45°. This latter isotope effect is larger than we would expect for a primary hydrogen isotope effect (*cf.* Table I and part VI) in a reaction which we consider to be very E2C like in nature.[32] The observed value of 3.81 is understandable, however, if it is realized that it represents a primary isotope effect inflated by secondary isotope effects. As the reaction sequence (eq I) shows, the E2 reaction involves eight secon-



(I)

dary hydrogen isotope effects (six due to hyperconjugative interactions and two due to hybridization changes at C_β) in addition to the primary isotope effect. If one assumes that the magnitude of the secondary isotope effects for this system is ~10% per deuterium (*cf.* the 11% effect per deuterium in the E1 reaction), the total secondary isotope effect component would amount to 2.1 (*i.e.*, $[1.1]^8$), yielding a primary isotope effect of 3.81/2.1 = 1.8. This is a much more acceptable value in our view, for a very E2C-like reaction when compared with the less E2C-like reactions of cyclohexyl tosylate which have $k_H^H/k_D^D < 3$.

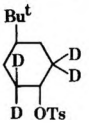
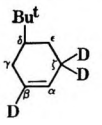
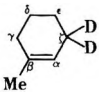
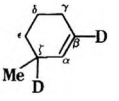
A question arises as to whether one might expect hyperconjugative isotope effects to differ depending upon whether isotopic substitution at C_2 (C_γ in the product) is cis or trans to the leaving group in the ground state. In the solvolysis of cyclopentyl tosylates, Streitweiser[33] has shown that the effect of cis- and trans-2 deuteration is much the same, with the cis-isotope effect marginally larger than the trans-isotope effect. (*i.e.*, 22 *vs.* 16%, respectively). In this work, for the E2 reactions of cyclohexyl tosylates with NBu_4OAc in acetone, the cis- and trans-2-deuterium isotope effects appear to be about the same ($k_D^H/k_{D_2}^H = k_H^H/k_D^H = 1.11$) and the combined effect of cis- and trans-isotope effects gives the expected cumulative effect ($k_H^H/k_{D_2}^H = 1.24 = [1.11]^2$). This suggests that no specific hyperconjugation mechanism is operating in the E2 reactions of the cyclohexyl system, *i.e.*, that a trans-2-hydrogen isotope substituent is in no more favorable position to hyperconjugate with the developing double bond or developing carbonium ion center than is a cis-2-hydrogen isotope substituent (and vice versa). This is consistent with the situation found in many solvolysis reactions studied, particularly in acyclic systems,[34] where conformational restrictions upon hyperconjugating hydrogen isotopes are absent.[35]

Rate constants for the E2 reactions of the tetradeuterated substrates, cyclohexyl-2,2,6,6-d_4 tosylate (V-OTs) and bromide (V-Br), should be retarded relative to the rate constants for their undeuterated analogs owing to a combination of several hydrogen isotope effects. These include a secondary isotope effect due to hybridization changes at C_β and two secondary hyperconjugative isotope effects at C_γ, in addition to the more dominant primary hydrogen isotope effect (see pathway 5 in Chart I). In Table V we compare total isotope effects observed for reactions in these systems with values calculated from the product of all of the component isotope effects. The agreement between observed and calculated total isotope effects is quite good especially for the reactions with NaOEt/EtOH and KO-*t*-Bu/Bu-*t*-OH derived from Finley and Saunders[21] rate data. The observed total isotope effect for the E2 reaction of V-OTs with NBu_4OAc in acetone is ~14% lower than the calculated value, but this may be due to the incomplete deuteration of this substrate.[36] In Table V we also show the magnitudes of the total secondary isotope effects for the reactions indicated. These are determined by dividing the total observed isotope effect by the primary isotope effect for the system (see Table IV). Again, the value of the total secondary isotope effect for the reaction of V-OTs with NBu_4OAc in acetone is lower (1.2) than the value that can be calculated (1.4) from the component secondary isotope effects. With this in mind it can be seen that the magnitude of the total secondary hydrogen isotope effect for these systems is a rather substantial 30–80%.

In part IV[2] we reported the hydrogen isotope effects observed in the E2 and SN2 reactions of some tri- and tetradeuterated alkyl-substituted cyclohexyl tosylates with NBu_4Cl in acetone at 75°. The E2 isotope effects reported were the total observed isotope effects for the specified reactions. In Chart II we re-treat these data and refine from them values for the component isotope effects. Substrates, products, and total E2 isotope effects are shown in Chart II together with an indication of the component isotope effects which are operative in each reaction. If we assume that the magnitudes of the component isotope effects are the same for all three substrates, despite the differing nature of the alkyl substituents, we can set up three equations (1–3) in three unknowns from the information recorded in Chart II. A = primary hydrogen isotope effect, B = secondary C_α–H hyperconjugative isotope effect, and C =

Chart II

Kinetic Hydrogen Isotope Effects on the E2 Reactions of Alkyl-Substituted Cyclohexyl Tosylates with NBu_4Cl in Acetone at 75°[a]

Substrate				$\left(k_E^H/k_E^D\right)$[b]	Component Isotope Effects[c]
IX[d]		DOTs +		3.2	AxBxBxC
X		DOTs +		3.0[e]	AxBxB
XI		DOTs +		2.7	AxBxC

Component Isotope Effects:[f]

A = Primary isotope effect = 1.9

B = Secondary C_ζ–H hyperconjugative isotope effect = 1.19

C = Secondary C_β–H hybridization isotope effect = 1.20

[a] Reactions of 0.035–0.040 *M* NBu_4Cl with 0.015–0.020 *M* alkyl tosylates. [b] k_E^D and k_E^H are the rate constants for elimination from the indicated deuterated substrate and its undeuterated analog. k_E^H/k_E^D represents the total isotope effect observed. [c] Indicates the component isotope effects in each reaction which combine multiplicatively to give the total observed isotope effect. [d] *trans*-4-*tert*-butylcyclohexyl-2,2,6,6-d_4 tosylate. [e] at 50°. [f] From the data in the chart, three equations in the three unknowns *A*, *B*, and *C* can be set up and readily solved. It is assumed that the magnitudes of the component isotope effects are the same for all three substrates despite the differing nature of the alkyl substituents. Allowance is made for the fact that the datum for the reaction of VIII refers to 50° and not 75° (see text).

$$AB^2C = 3.2 \text{ at } 75° \quad (1)$$

$$AB^2 = 3.0 \text{ at } 50° \quad (2)$$

$$ABC = 2.7 \text{ at } 75° \quad (3)$$

secondary C_β–H hybridization isotope effect. From eq 1 and eq 3 we can derive

$$B = 1.19 \text{ at } 75°$$

We note that eq 2 applies to 50°. However, although primary hydrogen isotope effects are certainly temperature dependent,[23] secondary hyperconjugative isotope effects have been found to vary much less with temperature[37] and in some cases to be actually temperature independent.[38] If we assume that secondary isotope effects are the same at 75 and 50° for the reactions in Chart II we can then substitute our value for *B* into eq 2 and obtain

$$A = 2.14 \text{ at } 50°$$

which can be extrapolated to 75° using Melander's data[23] to give

$$A = 1.90 \text{ at } 75°$$

Substitution of A and B in eq 3 leads to

$$C = 1.20 \text{ at } 75°$$

These derived isotope values are not significantly changed even if secondary isotope effects are slightly temperature dependent to the extent observed by other workers.[37] The component isotope effects thus found for the chloride ion promoted E2 reactions shown in Chart II are consistent with the isotope effects found in this work for reactions of cyclohexyl tosylate with other bases (see Table IV). The primary hydrogen isotope effect (A = 2.1 at 50°) for the NBu_4Cl promoted reactions, for instance, is smaller than the value of 3.0 at 50° observed for NBu_4OAc promoted reactions of cyclohexyl tosylate, as would be expected for more E2C-like reactions.[1] Similarly, the secondary hyperconjugative isotope effect (B = 1.19) and secondary C_β hybridization isotope effect (C = 1.20) for the NBu_4Cl reactions of cyclohexyl tosylate are comparable in magnitude to the secondary isotope effects reported in Table IV for other bases.

Isotope Effects in SN2 Reactions. From the data in Table II, secondary hydrogen isotope effects can be evaluated for the SN2 components of the reactions studied with NBu_4OAc as base. These isotope effects are recorded in Table VI together with available isotope effects for the SN2 reactions of other bases with cyclohexyl derivatives. All of the data in Table VI, with the exception of that for the reaction of NBu_4OAc with cyclohexyl-*1-d* tosylate (IV-OTs), refer to β-hydrogen isotope effects. These β-isotope effects (20–75%) are significantly larger than those reported by Shiner[12] (3–13%) for the SN2 reactions of β-deuterated isopropyl bromides with EtO^-/EtOH. This may be due, at least in part, to the fact that SN2 transition states for secondary cyclohexyl tosylates are "looser" and therefore more ionic than the corresponding SN2 transition states for secondary alkyl bromides. That β-hydrogen isotope effects increase in magnitude as the transition state for substitution becomes "looser" has been demonstrated clearly by Leffek and coworkers.[13] They reported small

Table VI
Isotope Effects on the Substitution (SN2) Reactions of Variously Deuterated Cyclohexyl Tosylate and Cyclohexyl Bromides with Bases in Acetone at the Temperatures Shown[a]

	k_S^H/k_S^D[b]				
Substrate[c]	NBu_4OAc,[d,e] 50°	NBu_4Cl,[d] 75°	NBu_4SAr, 75°	NBu_4OPh, 50°	NBu_4N_3, 50°
II-OTs	1.3 ± 0.1				
II-Br	1.3 ± 0.2				
III-OTs	1.3 ± 0.1				
IV-OTs	1.02 ± 0.05				
V-OTs	1.2 ± 0.1[f]	1.3 ± 0.1	1.2 ± 0.1	1.3 ± 0.1	1.2 ± 0.1
V-Br	1.7_5 ± 0.2				
IX-OTs[g]		1.4[j]			
X-OTs[h]		1.1[j]			
XI-OTs[i]		1.1[j]			

[a] Base concentrations are 0.03–0.04 *M* with substrates 0.01–0.02 *M*; NBu_4 is the tetra-*n*-butylammonium cation, OAc is acetate, OPh is phenoxide, and SAr is *p*-nitrothiophenoxide. [b] k_S^H/k_S^D is the rate constant for substitution in the undeuterated substrate (k_S^H) relative to the rate constant for substitution in the indicated deuterated substrate (k_S^D). [c] Numbers refer to substrates indicated in Charts I and II. [d] In the presence of 0.015 *M* 2,6-lutidine. [e] Calculated from data recorded in Table II. [f] See text and ref 36. [g] Registry number 51933-09-6. [h] Registry number 52003-55-1. [i] Registry number 52003-56-2. [j] Calculated from rate constants reported in ref 2.

(2–4%) β-isotope effects for hydrolyses at primary carbon in ethyl derivatives, but large (31–55%) β-isotope effects for hydrolyses at secondary carbon in isopropyl derivatives. In this case, of course, the enhancement of the β-isotope effect is due to a shift in mechanism from SN2 (tight) for the primary substrates to borderline or SN1 (loose) for the secondary substrates.

In contrast to the sizable β-hydrogen SN2 isotope effects reported in Table VI, only a 2% α-hydrogen isotope effect was observed for the SN2 reaction of NBu_4OAc with cyclohexyl-*1-d* tosylate (IV-OTs) in acetone. This low value appears to be quite consistent with α-hydrogen isotope effects reported by other workers. No isotope effect at all was observed for the SN2 reaction of 2-bromopropane-*2-d* with $EtO^-/EtOH$,[12,15] and, indeed, small inverse α-hydrogen isotope effects have been reported[15,16] for SN2 reactions at a primary carbon atom.

Concluding Remarks

The hydrogen isotope effects observed in this work for the E2C-like elimination reactions of cyclohexyl tosylate and cyclohexyl bromide with various bases provide additional evidence to support the view that a great deal of change takes place at both C_α and C_β in reactions leading to E2C-like transition states. The following points emerge.

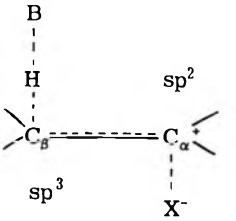
(1) The substantial secondary hybridization hydrogen isotope effects at C_β (15–25%) indicate that there is considerable rehybridization at C_β, from sp^3 in the ground state to sp^2 in the transition state, for E2C-like reactions. This is in agreement with conclusions based on substituent effects, where steric acceleration by bulky β substituents relative to hydrogen, is explicable in terms of changes in bond angles at C_β from tetrahedral to trigonal.[39] In contrast, E2C-like reactions are insensitive to the electronic effects of β substituents,[39,40] which suggests that there is little or no negative charge development at C_β in the transition state.

(2) Secondary hybridization hydrogen isotope effects at C_α (13–15%), as well as secondary hyperconjugative hydrogen isotope effects at C_γ (11–22%), are both substantial and indicate significant hybridization changes at C_α. This again is in agreement with conclusions based on substituent effects,[39] where steric acceleration by bulky α substituents relative to hydrogen occurs for much the same reason as the rate enhancement observed in SN1 processes, *i.e.*, due to release of steric compression as the hybridization of C_α changes from sp^3 to sp^2 from reactants to transition state.

(3) The extensive changes in hybridization at both C_α and C_β, supported by the observed secondary hydrogen isotope effects discussed above, are consistent with E2C-like transition states like VII or VIII. The low primary hydrogen isotope effects observed for E2C-like reactions, in this work, and previously[1,2] are also consistent with VII or VIII, but do not allow us to decide whether the C_β–H bond is very loose as in VII or only slightly broken as in VIII. The insensitivity of E2C-like reactions to electron-withdrawing and electron-releasing substituents at both C_α[39,41] and C_β,[39,40] suggesting that there is little negative charge at C_β or positive charge at C_α, strongly favors E2C-like transition states like VII in which there is a well-developed double bond. This is supported by the similarity of rates of anti-diaxial and anti-diequatorial elimination for E2C-like reactions in alicyclic systems, which is strongly suggestive that very olefin-like transition states are used.[19,20] Similarly, the accelerating effect of α- and β-methyl substituents relative to hydrogen, although explicable in terms of steric effects (*vide supra*), may be due at least in part to stabilizing hyperconjugative interactions with a well-developed double bond as in VII.[20,39]

Transition states like VIII with some positive charge at C_α cannot be ruled out, however. The lack of response which E2C-like reactions exhibit to the inductive effects of substituents at C_α[39,41] may be because there are *two* anions loosely bound to C_α in the transition state, in what is effectively an ion-triplet arrangement.[1] The requirements for positive charge stabilization at C_α by electron-releasing α substituents may therefore be much less than is the case in solvolysis (SN1) transition states[39,41] for instance, which are strongly stabilized by electron-releasing α substituents but which have only one anion (the leaving group) loosely associated with the positive charge center at C_α.

The observed hydrogen isotope effects are not consistent, however, with paene-carbonium transition states like



XII

XII where there is very little change in hybridization taking place at C_β.

We note that, for the SN2 reactions of cyclohexyl tosylates and bromides studies in this work, secondary hydrogen isotope effects at C_β are quite significant. In as much as these β-isotope effects arise from hyperconjugative interactions with C_α, this is consistent with the view that these SN2 reactions use "loose" transition states, and in agreement with the conclusions drawn from solvent effects upon such reactions.[42,43] It is also noteworthy that secondary hydrogen isotope effects at C_β are of the same order of magnitude for both E2C-like reactions and their concomitant SN2 reactions. This is in complete consistency with other observations which have shown that SN2 and E2C-like reactions respond in much the same way to change of leaving group,[25] and of base,[18,44] as well as exhibit very similar enthalpies and entropies of activation.[20]

E2C-like and SN2 reactions differ in two respects as far as isotope effects are concerned. SN2 reactions naturally do not exhibit primary β-hydrogen isotope effects, and any interaction of the base with β hydrogen does not contribute to any stabilization of the SN2 transition state.[45] Also, secondary α-hydrogen isotope effects appear to be much smaller for SN2 reactions than they are for E2C-like reactions. The reaction of NBu_4OAc with cyclohexyl tosylate in acetone for example shows only a 2% hydrogen isotope effect for the SN2 reaction, but a 13% α-hydrogen isotope effect for the E2C reaction. While it is known that increased interaction between a nucleophile and C_α tends to reduce the α-hydrogen isotope effect in solvolysis reactions, as illustrated by the decreasing α-isotope effects observed for hydrolysis of *tert*-butyl, isopropyl, and ethyl derivatives,[13] the discrepancy between loose SN2 and E2C-like reactions is to us a little surprising. However, it does at least emphasize a point we have made before,[19,46] that the bond between the base and C_α in an E2C-like transition state is always looser than that in the concomitant SN2 transition state.

Experimental Section

Mass Spectra. The isotopic compositions of labeled precursors, substrates, and products of the elimination reactions were determined by mass spectrometry. Olefinic products were first isolated by preparative vpc. Compositions of deuterated cyclohexyl tosylates, which could not be determined directly, were equated with those measured for the parent cyclohexanols.

Samples were introduced into an AEI MS9 spectrometer through the heated inlet system, and peak intensities from three slow scans at low ionizing voltage (12–15 eV) in the region of the molecular ion were averaged. Spectra of unlabeled compounds, except cyclohexanol, run under these conditions showed that peaks in the molecular ion region, other than the molecular ion peaks, were negligible. Relative peak intensities of the molecular ions of a partly deuterated compound were therefore a direct measure of the relative amounts of undeuterated, monodeuterated, and polydeuterated compounds, provided that allowance was made for ^{13}C abundance.

The $M - H_2O$ peak from cyclohexanol was isolated and, under conditions of low ionizing voltage, arises principally from 1,3 and 1,4 eliminations.[47] Thus, isotopic compositions of partly deuterated cyclohexanol could be determined. The small amount of 1,2 elimination would cause the deuteration to be underestimated. The isotopic compositions of cyclohexyl-2,2-d_2 tosylate and cyclohexyl-2,2,6,6-d_4 tosylate, besides being determined using the parent alcohols, were also determined from the mass spectra of the derived bromides. There is minor enrichment of deuterium content accompanying the conversion of tosylate to bromide because of the concurrent elimination, and this would cause the deuteration of the tosylates to be overestimated. Repeated enrichment is unlikely because cyclohexyl tosylate reacts more rapidly with bromide ion than does cyclohexyl bromide. The two types of analysis, from the parent alcohols and the derived bromides, thus place upper and lower limits on the isotopic purity of these two tosylates.

Intramolecular Competition Reactions of II and III. Substrates II and III were individually treated with an excess of base at the temperatures shown in Table I. Product olefin mixtures were isolated by preparative vpc and the ratio of the two olefins was analyzed by mass spectrometry in the vicinity of the molecular ion. Allowance was made for incomplete deuteration of the substrates.

Intermolecular Competition Reactions of I and V. Equimolar mixtures of I and V, 0.1 *M* as bromides or tosylates, were prepared with allowance for the incomplete deuteration of V. They were reacted with 0.1 *M* base for only 10% of reaction and the product olefins were separated by preparative vpc from the reaction mixture. The ratio of the two olefins was analyzed by mass spectrometry in the vicinity of the molecular ion.

Kinetics. Rates for the overall reactions (E2 + SN2) of the variously deuterated cyclohexyl tosylates shown in Table II with NBu_4OAc were measured by following consumed acetate base by titration *vs.* *p*-toluenesulfonic acid in acetone with Bromothymol Blue as indicator. Rates of cyclohexyl bromides were followed by potentiometric titration of liberated bromide ion against silver nitrate after acidification of samples with dilute nitric acid. Rates of all deuterated compounds were measured under identical conditions and simultaneously with undeuterated substrates. All reactions with NBu_4OAc were carried out in the presence excess (0.015 *M*) 2,6-lutidine, to prevent formation of the homoconjugate species $H(OAc)_2^-$ as acid developed in the course of the reaction. The fraction of each reaction (F_E) which was bimolecular elimination was determined from the ratio of acid produced to total substrate consumed, and was found to be constant throughout each individual reaction. Developed acid was estimated by titration *vs.* standard sodium methoxide in methanol using Thymol Blue as indicator. The rate constants reported in Table II are the averages of duplicate or triplicate determinations, with average deviations shown.

Materials. Tetra-*n*-butylammonium salts were prepared as previously described.[40] Sodium ethoxide–ethanol and potassium *tert*-butoxide–*tert*-butyl alcohol solutions were prepared by dissolving the appropriate metal in ethanol or *tert*-butyl alcohol, respectively, under nitrogen. The solvents acetone, ethanol, and *tert*-butyl alcohol were purified by standard procedures. Deuterated and undeuterated cyclohexanols and cyclohexyl bromides were purified by distillation and had bp ~60° (20 mm). They were better than 99% pure as determined by vpc. Cyclohexyl tosylates were prepared as previously described,[20,21] mp 44–46° (lit.[21] 42.5–46.5°).

trans-Cyclohexyl-2-*d* bromide (0.8% d_2, 87.3% d_1, 11.9% d_0) and *trans*-cyclohexanol-2-*d* (1.2% d_2, 94.2% d_1, 4.6% d_0) were prepared as previously described.[1]

Cyclohexanol-1-*d* (1.4% d_2, 91.7% d_1, 6.9% d_0) was prepared by reduction of cyclohexanone with lithium aluminium deuteride in the manner reported by Finley and Saunders.[21]

Cyclohexanol-2,2,6,6-d_4 (87 ± 6% d_4, 11.5 ± 4% d_3, 1.5 ± 1.5% d_2, 0% d_1, 0% d_0) was prepared as previously described.[48] The large number of β-deuterium atoms makes the mass spectral analysis of this alcohol slightly unsatisfactory, because of the increased possibility of HOD 1,2 elimination.[47]

Cyclohexyl-2,2,6,6-d_4 bromide (92.6% d_4, 7.4% d_3, 0% d_2, etc.) was prepared from the tosylate using 2 equiv of tetra-*n*-butylammonium bromide (0.3 *M*) and 2,6-lutidine in refluxing acetone for 24 hr. The mixture was poured into pentane, extracted with ice-cold dilute hydrochloric acid, and dried (Na_2SO_4), and the remaining starting material was frozen out and recycled. The combined product from two treatments was dried, concentrated, and distilled from unreacted tosylate at below 40° and 5-mm pressure.

Cyclohexanol-2,2-d_2 (0.7% d_3, 94. d_2, 4.9% d_1, 0% d_0) was prepared from cyclohexanone-2,2-d_2, the reduction being carried out as for the conversion of cyclohexanone-2,2,6,6-d_4 to cyclohexanol-2,2,6,6-d_4.[48] Cyclohexanone-2,2-d_2 was prepared from cyclohexanonecarboxylic acid by deuterium exchange (D_2O) and thermal decarboxylation. A benzene solution of cyclohexanone carboxylic acid (25 g, mainly enol) was briefly shaken with aliquots of D_2O (3 × 5 g). The benzene solution was concentrated at low temperature and twice treated with D_2O in tetrahydrofuran for 7 min at room temperature. After evaporation of solvent at low temperature, the cyclohexanone produced by decarboxylation to this point was removed by pumping at <0.1 mm. The remaining cyclohexanonecarboxylic acid was dissolved in benzene (300 ml) and shaken briefly again with D_2O. The bulk of the D_2O layer was pipetted off, the remainder azeotroped off rapidly, and the solution was refluxed until CO_2 evolution was complete (~1 hr) before washing the benzene solution with ice-cold sodium bicarbonate solution and water. The

solution was dried, concentrated, and distilled to give cyclohexanone-2,2-d_2. Reduction as described above yielded cyclohexanol-2,2-d_2 (41% yield). The low yield was probably the result of too vigorous exchange conditions.

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References and Notes

(1) (a) Part VI: D. Cook, R. E. J. Hutchinson, J. K. MacLeod, and A. J. Parker, *J. Org. Chem.*, **39**, 534 (1974). (b) Author to whom correspondence should be addressed at the School of Chemistry, University of Western Australia, Nedlands, W.A., 6009, Australia.
(2) G. Biale, A. J. Parker, I. D. R. Stevens, J. Takahashi, and S. Winstein, *J. Amer. Chem. Soc.*, **94**, 2235 (1972).
(3) A. Fry, *Chem. Soc. Rev.*, **1**, 163 (1972).
(4) D. V. Banthorpe, "Elimination Reactions," Elsevier, London, 1963.
(5) J. F. Bunnett, *Angew. Chem., Int. Ed. Engl.*, **1**, 225 (1962).
(6) W. H. Saunders, Jr., in "Investigation of Rates and Mechanisms of Reaction," Vol. 8, part I, 2nd ed, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience, New York, N. Y., 1961, p 389.
(7) E. A. Halevi, *Progr. Phys. Org. Chem.*, **1**, 109 (1963).
(8) W. H. Saunders, Jr., *Surv. Progr. Chem.*, **3**, 109 (1966).
(9) H. Simon and D. Palm, *Angew. Chem., Int. Ed. Engl.*, **5**, 920 (1966).
(10) A. Streitweiser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962; *Chem. Rev.*, **56**, 571 (1956).
(11) E. R. Thornton, "Solvolysis Mechanisms," Ronald Press, New York, N. Y., 1964.
(12) V. J. Shiner, Jr., *J. Amer. Chem. Soc.*, **74**, 5285 (1952).
(13) K. T. Leffek, J. A. Llewellyn, and R. E. Robertson, *Can. J. Chem.*, **38**, 2171 (1960).
(14) W. H. Saunders, Jr., S. Asperger, and D. H. Edison, *J. Amer. Chem. Soc.*, **80**, 2421 (1958).
(15) R. R. Johnson and E. S. Lewis, *Proc. Chem. Soc.*, 52 (1958).
(16) H. Simon and D. Palm, *Chem. Ber.*, **92**, 2701 (1959).
(17) J. F. Bunnett, *Surv. Progr. Chem.*, **5**, 53 (1969).
(18) A. J. Parker, M. Ruane, G. Biale, and S. Winstein, *Tetrahedron Lett.*, 2113 (1968).
(19) G. Biale, A. J. Parker, S. G. Smith, I. D. R. Stevens, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 115 (1970).
(20) P. Beltrame, G. Biale, D. J. Lloyd, A. J. Parker, M. Ruane, and S. Winstein, *J. Amer. Chem. Soc.*, **94**, 2240 (1972).
(21) K. T. Finley and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **89**, 898 (1967).
(22) A. Streitweiser, Jr., *Ann. N. Y. Acad. Sci.*, **84**, 576 (1960).
(23) Approximate values of k^H/k^D at a given temperature can be extrapolated from values at other temperatures using data reported by L. Melander in "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y. 1960, p 22.
(24) W. H. Saunders, Jr., private communication.
(25) D. J. Lloyd and A. J. Parker, *Tetrahedron Lett.*, 5183 (1968).
(26) A. Streitweiser, Jr., and A. G. Dafforn, *Tetrahedron Lett.*, 1263 (1969).
(27) W. H. Saunders, Jr., and K. T. Finley, *J. Amer. Chem. Soc.*, **87**, 1384 (1965).
(28) G. W. Burton and P. B. D. de la Mare, *J. Chem. Soc. B*, 897 (1970).
(29) A. F. Cockerill, *Tetrahedron Lett.*, 4913 (1969).
(30) D. N. Kevill and J. E. Dorsey, *Chem. Ind. (London)*, 2174 (1967).
(31) D. N. Kevill and J. E. Dorsey, *J. Org. Chem.*, **34**, 1385 (1969).
(32) Our description of the E2 reaction of NEt_4Cl with *tert*-butyl chloride as E2C like is based upon an abundance of data relating to the E2 reactions of tertiary alkyl halides with bases like NEt_4Cl, which are strong carbon nucleophiles but weak hydrogen bases. See R. Alexander, E. C. F. Ko, A. J. Parker, and T. J. Broxton, *J. Amer. Chem. Soc.*, **90**, 5049 (1968), and ref 39, 40, and 42.
(33) A. Streitweiser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Amer. Chem. Soc.*, **80**, 2326 (1958).
(34) See, for example, the simple mathematical treatment which E. R. Thornton[11] applies to the isotope effects observed in the solvolysis of *tert*-butyl chloride and its d_3, d_6, and d_9 analogs, in 60% aqueous ethanol (v/v) at 25°, to demonstrate the nonstereospecificity of the hyperconjugation mechanism operative in this system.
(35) In contrast Shiner has reported examples of systems in which conformational restrictions give rise to more stereospecific hyperconjugative isotope effects. See V. J. Shiner, Jr., and J. S. Humphrey, Jr., *J. Amer. Chem. Soc.*, **85**, 2416 (1963), and V. J. Shiner, Jr., and J. G. Jewett, *J. Amer. Chem. Soc.*, **86**, 945 (1964), and **87**, 1382, 1383 (1965).
(36) In the preparation of deuterated cyclohexyl tosylates we assume that a lower limit for the extent of deuteration is given by the deuteration pattern of the parent alcohol. For cyclohexanol-2,2,6,6-d_4 the deuteration pattern is 87 ± 6% d_4, 11.5% ± 4% d_3, and 1.5 ± 1.5% d_2 (see Experimental Section) which suggests that the extent of tetradeuteration in the derived tosylates (V-OTs) could be as low as 81%. This may explain why the observed hydrogen isotope effects found in this work for the E2 and SN2 reactions of V-OTs with NBu_4OAc in acetone are somewhat lower than might be expected (see Tables V and VI).
(37) E. S. Lewis and G. M. Coppinger, *J. Amer. Chem. Soc.*, **76**, 4495 (1954); V. J. Shiner, Jr., and C. J. Verbanic, *ibid.*, **79**, 373 (1957).
(38) K. T. Leffek, R. E. Robertson, and S. E. Sugamori, *Can. J. Chem.*, **39**, 1989 (1961).
(39) G. Biale, D. Cook, D. J. Lloyd, A. J. Parker, I. D. R. Stevens, J. Takahashi, and S. Winstein, *J. Amer. Chem. Soc.*, **93**, 4735 (1971).
(40) D. Cook, A. J. Parker, and M. Ruane, *Tetrahedron Lett.*, 5715 (1968).
(41) D. J. Lloyd and A. J. Parker, *Tetrahedron Lett.*, 5029 (1970).
(42) E. C. F. Ko and A. J. Parker, *J. Amer. Chem. Soc.*, **90**, 6447 (1968).
(43) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).
(44) A. J. Parker, M. Ruane, D. A. Palmer, and S. Winstein, *J. Amer. Chem. Soc.*, 94, 2228 (1972).
(45) D. Cook and A. J. Parker, *J. Chem. Soc. B*, 142 (1968).
(46) D. Cook and A. J. Parker, *Tetrahedron Lett.*, 4901 (1969).
(47) R. S. Ward and D. H. Williams, *J. Org. Chem.*, **34**, 3373 (1969).
(48) C. H. DePuy, R. W. King, and D. M. Froemsdorf, *Tetrahedron*, **7**, 123 (1959).

Reactions of Phosphorus Compounds. 35. Reaction of 4-Salicyloxybutyltriphenylphosphonium Bromide with Alcoholic Alkoxide

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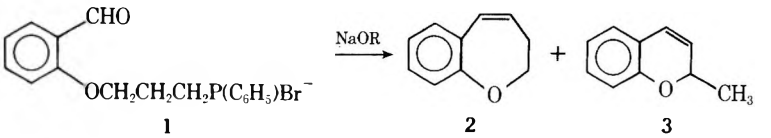
The reaction of 4-salicyloxybutyltriphenylphosphonium bromide (5) with alcoholic alkoxide gave 3,4-dihydro-2*H*-1-benzoxocin (6), 2-ethyl-2*H*-1-benzopyran (7), and 4-(o-α,α-diethoxymethylphenoxy)butyldiphenylphosphine oxide (8a). Mechanisms are proposed for the formation of 7 and 8.

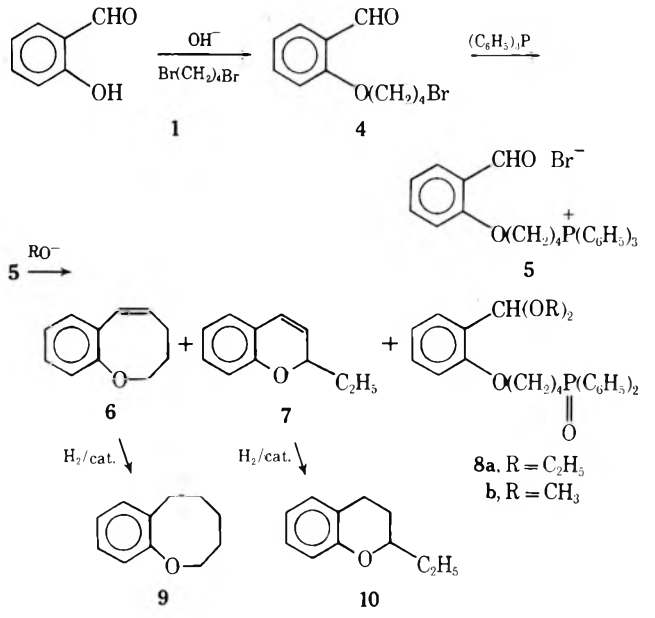
In previous papers[1] we have shown that 3-salicyloxypropyltriphenylphosphonium bromide (1) with base gives either 2,3-dihydro-1-benzoxepin (2) or 2-methyl-2*H*-1-benzopyran (3), depending on the nature of the solvent, and we have proposed a mechanism for the formation of 3 from 1.[1c]



1 2 3

In the present work we wish to report the reactions of 4-salicyloxybutyltriphenylphosphonium bromide (5), under the influence of base, to give the expected 3,4-dihydro-2*H*-1-benzoxocin (6), 2-ethyl-2*H*-1-benzopyran (7), and the unexpected 4-(o-α,α-diethoxymethylphenoxy)butyldiphenylphosphine oxide (8a) [or 4-(o-α,α-dimethoxymethylphenoxy)butyldiphenylphosphine oxide (8b)].

The reaction of salicylaldehyde with 1,4-dibromobutane in aqueous NaOH gave a 62% yield of 4-salicyloxybutyl



bromide (4). The quaternization of triphenylphosphine by halide 4 gave the phosphonium salt 5 (70%).

Reaction of the salt 5 in refluxing ethanolic sodium ethoxide gave a 19% yield of a mixture of 3,4-dihydro-2*H*-1-benzoxocin (6) and 2-ethyl-2*H*-1-benzopyran (7), in a ratio of 64:36, respectively, and a 32% yield of 4-(o-α,α-diethoxymethylphenoxy)butyldiphenylphosphine oxide (8a). The ratio, and yields, of 6 and 7 obtained, using different solvents, are tabulated in Table I. It may be noted, in contrast, that on treating salt 1 in pure MeOH and DMF as solvents the benzopyran 3 and benzoxepin 2, respectively, were obtained (exclusively and in high yield), and no acetal phosphine oxide, comparable to 8, was observed.[1]

Table I
Yields of 6, 7, and 8 from Salt 5

Solvent	Benzoxocin 6 and benzopyran 7 — Temp, °C	Yield, %	Ratio of 6:7[b]	Yield of 8, %
MeOH	Reflux	1–3	63:37	48 (8b)
EtOH	Reflux	19	64:36	33 (8a)
EtOD	Reflux	13	94[c]:6	
DMF[a]	65	19	95:5	
DMF	127	31	98:2	

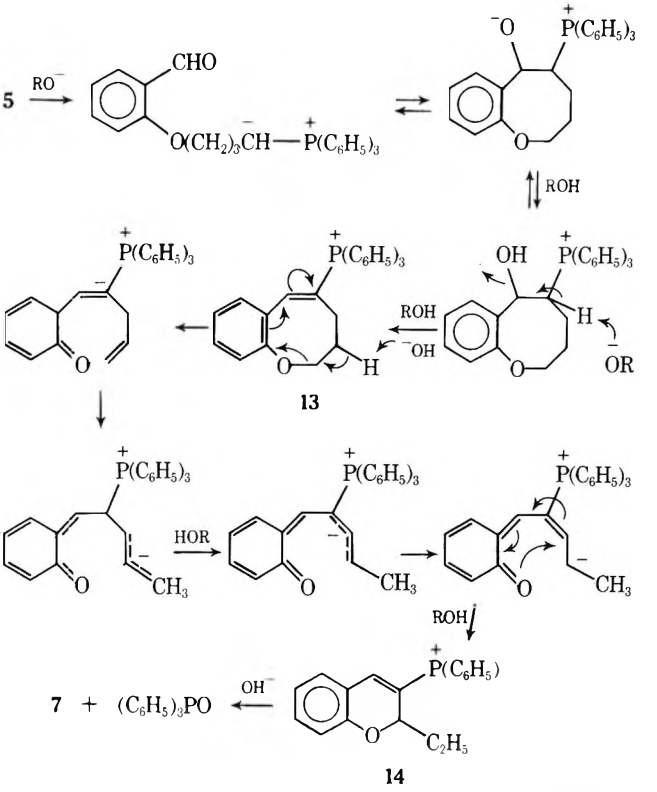
[a] *N*,*N*-Dimethylformamide. [b] By glc. [c] 5-Deuterio substituted 6.

The structure of 3,4-dihydro-2*H*-1-benzoxocin (6) was supported by its reduction to the saturated heterocycle 9, and by examination of the physical data for 6 and 9.

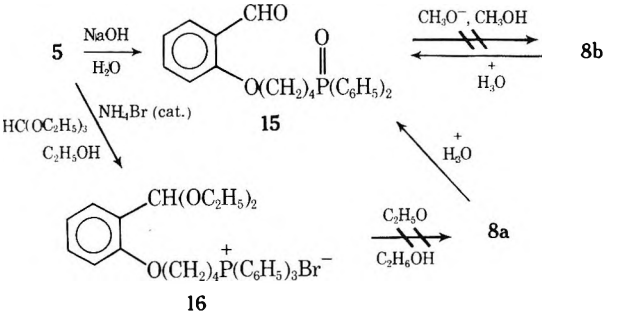
The structure of 2-ethyl-2*H*-1-benzopyran (7) was proven by comparison with an authentic sample prepared in these laboratories[2] from crotyltriphenylphosphonium chloride (11) and sodium salicyloxide (12). Further support for structure 7 was obtained by its reduction to 2-ethylbenzo[*b*]dihydropyran (10), a previously known compound.[3]

We propose that the mechanism for the formation of 2-ethyl-2*H*-1-benzopyran (7) is essentially parallel to that proposed for the formation of 2-methyl-2*H*-1-benzopyran (3) from 3-salicyloxypropyltriphenylphosphonium bromide (1).

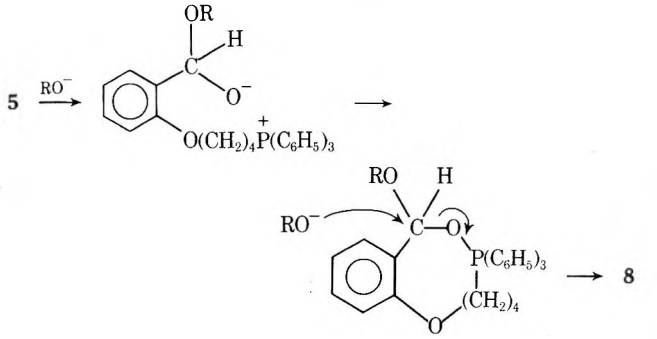
Attempts to isolate intermediate vinylphosphonium salts (13 or 14) under conditions employing catalytic amounts of base, as was accomplished successfully in the series starting with salt 1,[1c] were not successful and yielded only starting material 5. Thus the mechanism rests solely on previous work.[1c]



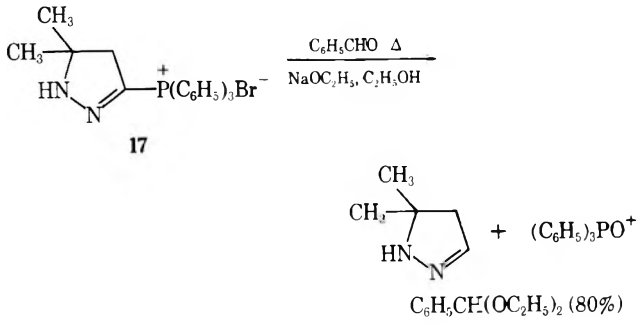
Treatment of 4-(o-α,α-diethoxymethylphenoxy)butyldiphenylphosphine oxide (8a), or the dimethyl acetal 8b, with dilute hydrochloric acid gave an essentially quantitative yield of 4-(o-methylphenoxy)butyldiphenylphosphine oxide (15). An authentic sample of compound 15 was obtained from 4-salicyloxybutyltriphenylphosphonium bromide (5) by aqueous alkaline hydrolysis.



The phosphine oxide 15 did not give the dimethyl acetal 8b on treatment with methanolic sodium methoxide. It was also observed that 4-(o-α,α-diethoxymethylphenoxy)butyltriphenylphosphonium bromide (16), prepared from 5 by its reaction with ethyl orthoformate and a catalytic amount of ammonium bromide, did not give the diethyl acetal 8a on treatment with ethanolic sodium ethoxide. These data suggest the mechanism shown below.



A similar acetal formation was observed[4] on allowing 5,5-dimethyl-2-pyrazolin-3-yltriphenylphosphonium bromide (17) to react with benzaldehyde in alcoholic sodium ethoxide. The search for a suitable simple phosphonium salt which may be used to produce acetals and ketals under basic conditions is underway.



Experimental Section[5]

4-(*o*-Formylphenoxy)butyl Bromide (4). An aqueous solution of NaOH (65.9 g, 1.6 mol) was added over a period of 2 hr to a rapidly stirred refluxing mixture of 454 g (2.1 mol) of 1,4-dibromobutane and 200 g (1.6 mol) of salicylaldehyde in 950 ml of water. After the reaction had continued for 48 hr the mixture was cooled, and the organic phase was separated and added to 500 ml of chloroform. The organic solution was washed with 4 × 300 ml of a 10% NaOH (aqueous) solution, 300 ml of 10% H_2SO_4 (aqueous), and 2 × 300 ml of H_2O. After the organic phase was dried ($MgSO_4$) and the residue was concentrated, distillation gave 220 g (62%) of **4**, bp 140–180° (2 mm), $n^{25}D$ 1.5645.

An analytical sample, from a similar reaction, had bp 140° (0.2 mm); $n^{25}D$ 1.5617; nmr (CCl_4) δ 1.8–2.4 (m, 4, $C_{2,3}$ methylenes), 3.48 (t, 2, C_1 methylene), 4.06 (t, 2, C_4 methylene), 6.8–7.9 (m, 4, C_6H_4), 10.5 ppm (s, 1, CHO).

Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.39; H, 5.06. Found: C, 51.18; H, 5.29.

4-(*o*-Formylphenoxy)butyltriphenylphosphonium Bromide (5). Triphenylphosphine (0.98 mol) and an equimolar amount of **4** were allowed to react for 3 days in refluxing ethyl acetate (1 l.). The mixture was filtered hot and the residue was washed with 2 × 150 ml of hot ethyl acetate and 2 × 150 ml of anhydrous ether to give 353 g (70%) of vacuum oven (80°, 5 mm) dried salt, **5**: mp 157–158°; nmr ($DCCl_3$) δ 1.7–2.5 (m, 4, $C_{2,3}$ methylene), 3.7–4.4 (m, 4, $C_{1,4}$ methylene), 6.77–8.15 (m, 19, aromatic), 10.3 ppm (s, 1, CHO).

Anal. Calcd for $C_{29}H_{28}BrO_2P$: C, 67.17; H, 5.41; P, 5.96. Found: C, 66.92; H, 5.62; P, 601.

Reaction of 4-(*o*-Formylphenoxy)butyltriphenylphosphonium Bromide (5) with Sodium Ethoxide in Ethanol. The salt **5** (42 g, 0.08 mol), dissolved in 250 ml of anhydrous ethanol, was added, over a period of 3 hr, to a refluxing, stirred solution of 0.16 mol of sodium ethoxide in anhydrous ethanol. After the reaction was allowed to proceed for 48 hr the solution was concentrated to 50 ml and added to 2 l. of water. The aqueous mixture was extracted with 4 × 300 ml of ether. The combined organic extracts were washed with 4 × 300 ml of water and then dried ($MgSO_4$). Concentration of the ethereal solution and short-path distillation gave 2.45 g (19.3%) of a 36:64 ratio of 2-ethyl-2*H*-1-benzopyran (**7**) and 3,4-dihydro-2*H*-1-benzoxocin (**6**), bp 80–90° (0.35 mm). The residue was chromatographed over silica gel. Elution with benzene–hexane (1:1) gave 11.8 g (32.6%) of 4-(o-α,α-diethoxymethylphenoxy)butyldiphenylphosphine oxide (**8a**).

The 2-ethyl-2*h*-1-benzopyran (**7**) was shown to be identical (boiling point, ir, nmr) with an authentic sample prepared in these laboratories as previously described.[2]

3,4-Dihydro-2*H*-1-benzoxocin (6). An analytically pure sample (99.5% by glc), obtained from the 127° DMF run (Table I), had bp 77° (0.55 mm); $n^{25}D$ 1.5768; nmr (neat) δ 1.4–1.9 (m, 2, C_3 methylene), 2.0–2.35 (m, 2, C_4 methylene), 3.8 (t, 2, J = 5 Hz), 5.5 (d of triplets, 1, $J_{5,4}$ = 4, $J_{5,6}$ = 11.5 Hz), 5.98 (d of triplets, 1, $J_{6,4}$ = 1, $J_{6,5}$ = 11.5 Hz), 6.5–7.1 (m, 4, C_6H_4).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.75; H, 7.57.

4-(*o*-α,α-Diethoxymethylphenoxy)butyldiphenylphosphine Oxide (8a). An analytically pure sample was obtained by crystallization from benzene–hexane: mp 112–113°; nmr ($CDCl_3$) δ 1.15 (t, 6, CH_3), 1.67–2.68 (m, 6, methylenes), 3.52 (q, 2, $-OCH_2CH_3$), 3.50 (q, 2, $-OCH_2CH_3$), 3.90 (t, 2, $-OCH_2-$), 5.69 [s, 1, -CH(O)(O)], 6.65–7.95 ppm (m, 14, aromatic); ir (KBr) ν 1190 cm^{-1} (P=O); *m/e* 452.

Anal. Calcd for $C_{27}H_{33}O_4P$: C, 71.65; H, 7.35. Found: C, 72.02; H, 7.12.

4-(*o*-α,α-Dimethoxymethylphenoxy)butyldiphenylphosphine oxide (8b) was obtained similarly from the reaction of **5** with methanolic sodium methoxide and purified by crystallization from benzene–hexane: mp 118.5–120°; nmr ($CDCl_3$) δ 1.80–2.67 (m, 6, methylenes), 3.28 (s, 6, $-OCH_3$), 3.96 (t, 2, $-OCH_2-$), 5.57 [s, 1, -CH(O)(O)], 6.70–7.96 ppm (m, 14, aromatic); ir (Nujol) ν 1180 cm^{-1} (P=O); *m/e* 424.

Anal. Calcd for $C_{25}H_{29}O_4P$: C, 70.75; H, 6.84. Found: C, 70.76; H, 6.67.

3,4,5,6-Tetrahydro-2*H*-1-benzoxocin (9). The hydrogenation of 3,4-dihydro-2*H*-1-benzoxocin (**6**) was accomplished quantitatively in 1 hr, in methanol over 10% Pd/C: bp 58–59° (0.6 mm); $n^{25}D$ 1.5321; nmr (neat) δ 1.1–1.7 (m, 6, $C_{3,4,5}$ methylenes), 2.43–2.70 (m, 2, C_6 $-CH_2-$), 3.80 (t, 2, $-OCH_2-$, J = 5 Hz), 6.65–7.1 ppm (m, 4, C_6H_4).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; 8.70. Found: C, 81.44; H, 8.68.

2-Ethyl-2*H*-1-chroman (10) was obtained quantitatively from 2-ethyl-2*H*-1-benzopyran (**7**) as described in the previous experiment for the conversion of **6** to **9**. An analytically pure sample had bp 36–42° (0.1 mm); $n^{25}D$ 1.5252 [lit.[3] bp 116° (16 mm); $n^{25}D$ 1.5250]; nmr (neat) δ 0.9 (split t, 3, $-CH_3$, J = 7 Hz), 1.2–1.9 (m, 4, $-CH_2CH_3$ plus C_3 methylene), 2.35–2.7 (m, 2, C_4 methylene), 3.4–3.82 (m, 1, CH), 6.42–7.07 ppm (m, 4, C_6H_4).

Acid Hydrolysis of 4-(*o*-α,α-Diethoxymethylphenoxy)butyldiphenylphosphine Oxide (8a) to 4-(*o*-Formylphenoxy)butyldiphenylphosphine Oxide (15). The aldehyde **15** was obtained quantitatively by hydrolysis (3 hr) with dilute hydrochloric acid in methanol and crystallization by the addition of ether. Recrystallization from benzene–hexane gave a pure sample: mp 113–114°; ir (KBr) ν 1690 (C=O), 1190 cm^{-1} (P=O); nmr ($CDCl_3$) δ 1.50–2.70 (m, 6, $C_{1,2,3}$ methylenes), 4.05 (t, 2, $-OCH_2-$, J = 5.5 Hz), 6.75–8.05 (m, 14, aromatic), 10.4 ppm (s, 1, -CHO). Reaction of **8b** in the same manner gave the same results.

Basic Hydrolysis of 5 to Give 15. The salt **5** (0.04 mol) was heated at 90–100° for 3 hr in a solution of 0.05 mol of NaOH in 100 ml of water. The cooled reaction mixture was extracted with 3 × 200 ml of benzene. The combined organic extracts were washed with 3 × 200 ml of water, dried ($CaCl_2$), and concentrated. The residue was crystallized from benzene–hexane to give 5.0 g (33%) of pure **15**, mp 113–113.5°, identical in all respects with the sample obtained in the previous experiment.

4-(*o*-α,α-Diethoxymethylphenoxy)butyltriphenylphosphonium Bromide (16). A mixture of 4-salicyloxybutyltriphenylphosphonium bromide (**5**, 10.5 g, 0.02 ml), triethyl orthoformate (3.2 g, 0.022 mol), 0.05 g of powdered ammonium bromide, and 10 ml of anhydrous ethyl alcohol was heated under reflux for 2.5 hr. Ethanol (5 ml) was removed by distillation and the residue was added dropwise, with vigorous stirring, to 250 ml of anhydrous ether. A quantitative yield of the salt **16** was obtained: mp 178–181°; nmr ($CDCl_3$) δ 1.07 (t, 6, $-CH_3$, J = 7 Hz), 1.60–2.55 (m, 4, $C_{2,3}$ methylene), 3.47 [q, 4, $-CH(OCH_2CH_3)_2$], 4.12 (m, 4, $C_{1,4}$ methylene), 5.67 [s, 1, $-CH(OC_2H_5)_2$], 6.75–8.15 ppm (m, 19, aromatic).

Anal. Calcd for $C_{33}H_{38}O_3PBr$: C, 66.78; H, 6.45; P, 5.22. Found: C, 67.07; H, 6.81; P, 5.34.

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Registry No.—**4**, 40359-43-1; **5**, 52032-55-0; **6**, 52032-56-1; **7**, 7734-60-3; **8a**, 52032-57-2; **8b**, 52032-58-3; **9**, 51060-43-6; **10**, 7734-61-4; **15**, 52032-59-4; **16**, 52032-60-7; 1,4-dibromolutane, 110-52-1; salicylaldehyde, 92-02-8; sodium ethoxide, 141-52-6; sodium methoxide, 124-41-4.

References and Notes

(1) (a) E. E. Schweizer and R. Schepers, *Tetrahedron Lett.*, **No. 15**, 979 (1963); (b) E. E. Schweizer, C. J. Berninger, D. M. Crouse, R. A. Davis, and R. Schepers Logothetis, *J. Org. Chem.*, **34**, 207 (1969); (c) E. E. Schweizer, T. Minami, and D. M. Crouse, *ibid.*, **36**, 4033 (1971).
(2) E. E. Schweizer, E. T. Shaffer, C. T. Hughes, and C. J. Berninger, *J. Org. Chem.*, **31**, 2907 (1966).
(3) J. Brugidou and H. Christol, *C. R. Acad. Sci.*, **256**, 3149 (1963).
(4) E. E. Schweizer and C. S. Kim, *J. Org. Chem.*, **36**, 4033 (1971).
(5) The general experimental details are the same as those reported in ref 1.

Competitive Amide *vs.* Thioamide Cyclization. Cyclization of *N*-Allylrhodanine in Strong Acid Media[1]

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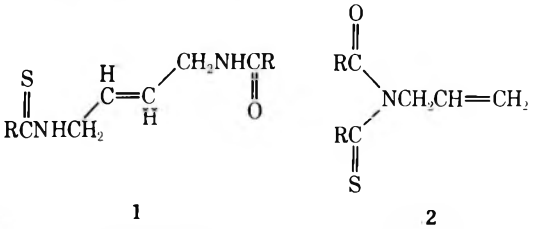
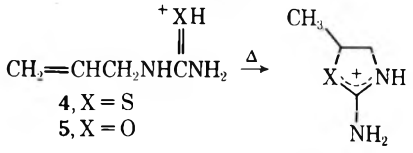
Received April 5, 1974

In a previous report[3] we commented on the relative sluggishness of the cyclization of *N*-allylthiourea as compared to *N*-allylurea. This observation prompted our investigation of the competitive cyclization of an amide group *vs.* a thioamide group. The unavailability of symmetrical model derivatives such as **1** or **2** led us to study the readily available *N*-allylrhodanine (**3**).



1 **2**

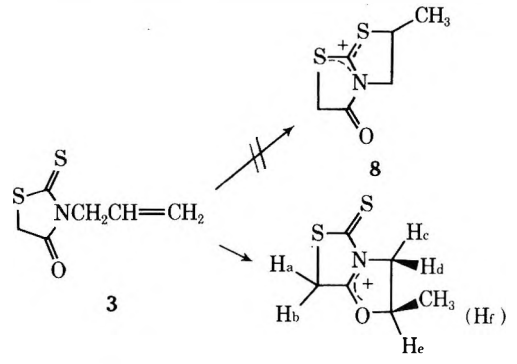
In sulfuric acid solutions (60–96%) at room temperature, *N*-allylthiourea and *N*-allylurea exist in the S-protonated (**4**) and O-protonated (**5**) forms, respectively.[3] Cyclization of **4** and **5** to the respective thiazolinium (**6**) and oxazolinium (**7**) cations occurs, in competition with polymerization, only upon heating of the acid solutions to 70–90°.[3] Usually excellent cyclization yields are achieved.[3]



4, X = S
5, X = O

6, X = S
7, X = O

Unlike **4** and **5**, *N*-allylrhodanine (**3**) cyclized rapidly and quantitatively upon dissolving in concentrated sulfuric acid at 15°. The proton nmr spectrum of the yellow solution revealed a single species which we assumed to be either **8** or



3 **8** **9**

J_{cd} = 12.5 Hz, J_{ce} = 6.5 Hz, J_{de} = 8.5 Hz

9. The 100-MHz spectrum consisted of peaks at δ 2.32 (H_f, 3 protons, doublet), 4.68 (H_c, 1 proton, quartet), 5.08 (H_d, 1 proton, quartet), 5.27 (H_a and H_b, 2 protons, singlet), and 5.58 (H_e, 1 proton, multiplet). Decoupling experiments established that the methyl doublet (H_f, δ 2.32) was coupled with the multiplet (H_e) at δ 5.58. The δ 5.58 multiplet must then be either the proton on carbon bonded to sulfur in **8** or the proton on carbon bearing oxygen in **9**. The chemical shift of this proton is consistent only with its assignment as H_e in **9**. The chemical shift of protons on carbon bonded to sulfur in thiazolinium cations (C-5 in simple cases) has been reported in the region δ 4.17–4.60 while the chemical shift of protons on carbon bonded to oxygen in oxazolinium cations is in the range of δ 4.79–6.30 depending on other substituents.[3–8] Since H_e appears at δ 5.58, a region farther downfield than any known case for C—H adjacent to sulfur in a thiazolinium cation, we are confident that cyclization to oxygen and not sulfur has obtained in the case of **3**.

Since we were somewhat surprised to find only cyclization to oxygen occurring in the presence of the more nucleophilic sulfur, we sought to examine more carefully the cyclization process.

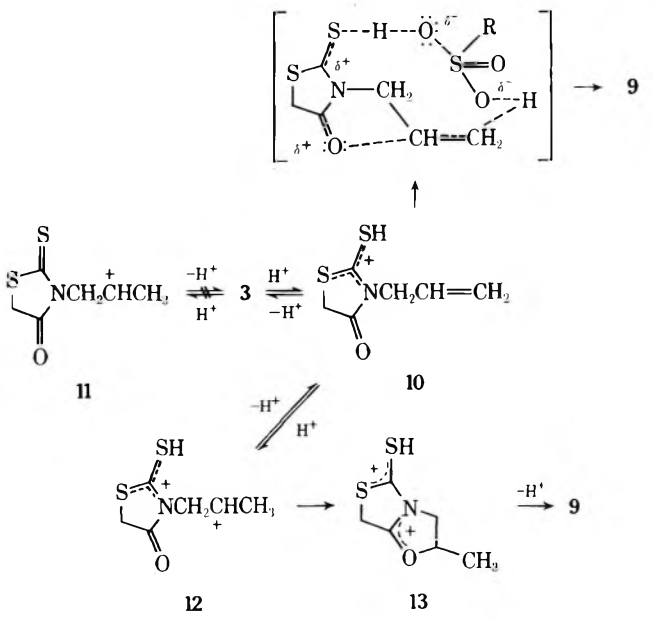
In FSO_3H, a stronger acid than H_2SO_4, cyclization occurred more slowly. Initially, the nmr spectrum contains peaks consistent with C=S protonated allylrhodanine (**10**), with the S–H resonance at δ 6.45.[9] With time the peaks due to **10** decreased (and finally disappeared) and those due to **9** increased. Again, **9** was the sole product of cyclization. In the strongest acid of the series, CF_3SO_3H, the cyclization was slowest. Thus, in both FSO_3H and CF_3SO_3H, C=S protonation is occurring to form **10** and further protonation, if it occurs with **10**, is fast and reversible.

While our experiments do not definitively dissect this complex kinetic process, the results suggest two possible mechanisms for the formation of **9**. First of all, we assume that cation **11** is not involved in this process since it would be difficult to explain why the less nucleophilic oxygen attacks the carbocation, especially in view of the apparent greater resonance stabilization afforded **8** by a second sulfur atom. Additionally, protonation of the C=S bond, even in sulfuric acid must be important; thus **10** or a more highly protonated form is involved. If **12** were the species leading to cyclization, the correct cyclic product would result, but one might expect that cyclization would be faster and not slower in stronger acids. If, however, the formation of the dication **13** were sluggish, then the rate of conversion of **10** into **9** might be dependent of sulfur deprotonation concurrent with cyclization. A possible explanation of how this may occur is shown in Scheme I. This type of proton transfer has many precedents especially where water acts as the bimolecular component.[10,11]

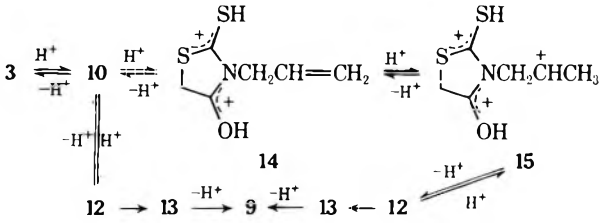
The second possibility is that **10** cyclizes through cation **12**. The observed results could be explained if C=O protonation to form dication **14** occurs more readily than C=C protonation to form **12**. In acids stronger than H_2SO_4, the formation of **9** would then occur more slowly since more and more of **10** is reversibly converted to **14** with that equilibrium slowing formation of **12**; or formation of **9** may require rate-limiting deprotonation of **15** to **12**.[12] These possibilities are shown in Scheme II.

There is no assurance that a single mechanism accounts for the cyclization in all acids, but it appears certain that

Scheme I



Scheme II



the initial protonation of the C=S is the primary reason that cyclization to oxygen rather than sulfur occurs.[13]

Experimental Section

N-Allylrhodanine was purchased from Aldrich Chemical Co., Inc. The acids were used without prior purification. Nmr spectra were determined with a Varian HA-100 MHz or a HFX-10 90 MHz instrument. The decoupling experiments were performed on the latter instrument. Tetramethylsilane was used as the reference (internal capillary) standard for all nmr measurements.

Acknowledgments. Dr. M. T. Emerson is acknowledged for his assistance in the decoupling experiments. This research was supported by a grant (to S. P. M.) from the donors of the Petroleum Research Fund, administered by the American Chemical Society, for which we are grateful. The University of Alabama Research Committee, Project Grant No. 672 (to C. U. P.) is gratefully acknowledged.

Registry No.—**3**, 1457-47-2; **9**, 52123-50-9.

References and Notes

(1) Part XI of the series Acid-Catalyzed Cyclization Reactions; for the previous paper see S. P. McManus, C. U. Pittman, Jr., and P. E. Fanta, *J. Org. Chem.*, **37**, 2353 (1972).
(2) Abstracted, in part, from the M.S. Thesis of K. Y. L., The University of Alabama in Huntsville, May 1973.
(3) S. P. McManus, J. T. Carroll, and C. U. Pittman, Jr., *J. Org. Chem.*, **35**, 3768 (1970); corrections: *ibid.*, **37**, 3752 (1972); *ibid.*, **38**, 4217 (1973).
(4) C. U. Pittman, Jr., S. P. McManus, and J. W. Larsen, *Chem. Rev.*, **72**, 457 (1972).
(5) D. A. Tomalia and J. N. Paige, *J. Org. Chem.*, **38**, 422 (1973).
(6) M. A. Weinberger and R. Greenbalgh, *Can. J. Chem.*, **41**, 1038 (1963).
(7) Tomalia and Paige [*J. Org. Chem.*, **38**, 3949 (1973)] have incorrectly assigned the ring protons of their thiazolinium cation in their recent paper by apparently misreading the assignments of thiazolinium cations in ref 6. The assignments should be reversed. These assignments in no way affect the interesting results presented in that paper.
(8) R. A. Wohl, *J. Org. Chem.*, **38**, 3099 (1973).
(9) G. A. Olah, A. M. White, and D. H. O'Brien, *Chem. Rev.*, **70**, 561 (1970).
(10) M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins," Wiley-Interscience, New York, N. Y., 1971, Chapter 9.
(11) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969.
(12) Formation of the trication **15** is a possibility in very strong acids (see ref 9), but **15** is not expected to be important in H_2SO_4.
(13) The coordination of sulfur by acidic reagents may explain the relatively low yields of cyclic products obtained from *N*-alkenylthioamides; *cf.* P. A. S. Smith and J. M. Sullivan, *J. Org. Chem.*, **26**, 1132 (1961).

Reaction of Hexamethylphosphoric Triamide with Alkyllithiums. *In Situ* Formation of *N*-Methylmethylenimine

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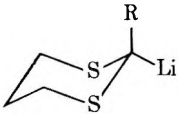
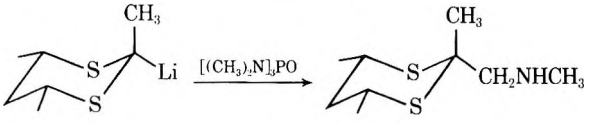
Received April 1, 1974

Hexamethylphosphoric triamide (HMPTA) is a useful solvent of high polarity and low nucleophilic character. We have employed it as a medium for nmr spectral study of 2-dithianyllithium (**1**) and 2-Phenyl-2-dithianyllithium (**2**).[1] When we tried to dissolve *r*-2-lithio-2,*cis*-4,*cis*-6-trimethyl-1,3-dithiane (**3**)[2] in the same solvent, we noted that a reaction occurred; the product, according to elemental analysis and nmr spectral evidence, was *r*-2-methylaminomethyl-2,*cis*-4,*cis*-6-trimethyl-1,3-dithiane (**4**).



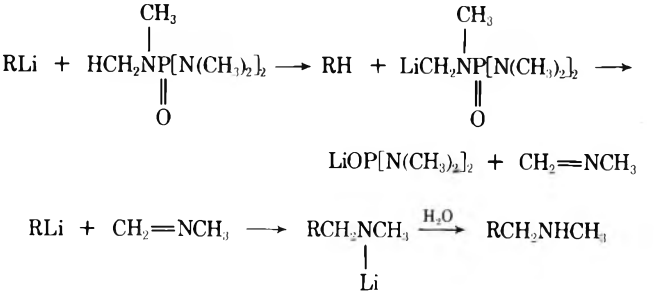
1, R = H
2, R = C_6H_5



3 **4**

About the time we carried out this experiment, a report appeared[3] describing the reaction of dialkoxyphosphoric amides with alkyllithiums to give lithium dialkoxyphosphites and Schiff bases which then react with a second mole of alkyllithium to give the lithium derivative of a secondary amine. It appeared that the reaction we had observed followed a path similar to that postulated by Savignac and Leroux[3] (Scheme I).

Scheme I



In accordance with expectations based on this scheme, we found that *n*-butyllithium, *sec*-butyllithium, and phenyllithium, when allowed to react with hexamethylphospho-

Table I

R in RLi	Solvent, temp, °C	Reaction time, days	Product	Yield, %
n-C_4H_9	Hexane–THF, −30	1	n-$C_5H_{11}NHCH_3$	50
sec-C_4H_9	Hexane–THF, −30	4	$C_2H_5CH(CH_3)CH_2NHCH_3$	68
C_6H_5	7:3 benzene–ether and THF, 0	3	$C_6H_5CH_2NHCH_3$	75

ric triamide in a 2:1 ratio, gave the homologous *N*-methylamines in 50–75% yield, as summarized in Table I.

In addition to being of potential synthetic value, these findings show that HMPTA in the presence of an alkyllithium is an *in situ* source of the very unstable species $CH_3N{=}CH_2$. Although this compound has been prepared[4,5] and studied spectroscopically,[5,6] it polymerizes[4,7] near its boiling point of −35°. Our findings also constitute a *caveat* to investigators who wish to use HMPTA as a solvent for organoalkali reagents, although we must emphasize that the less reactive lithium compounds **1** and **2** are stable in HMPTA for prolonged periods of time at 0°C and room temperature, respectively.

Experimental Section

***N*-Methyl-*N*-(2-methyl)butylamine.** A dry 200-ml round-bottom flask containing a Teflon-coated magnetic stirring bar was capped with a rubber septum and flushed with dry nitrogen using hypodermic needles; then *sec*-butyllithium (50 ml, 0.8 *M* in hexane, 0.04 mol) was introduced into the flask with a syringe. The solution was cooled by immersion in a cooling bath at −30° and diluted with 25 ml of tetrahydrofuran (THF). A solution of 3.6 g (0.02 mol) of HMPTA in 15 ml of THF was then similarly added slowly with cooling and vigorous stirring. The mixture was placed in the deep freeze at −30° for 4 days and then quenched by the addition of several ml of water with continued cooling. The product was extracted from the solution with ether using continuous liquid-liquid extraction. The ether layer was dried over magnesium sulfate, the solvents were removed with a fractionating column, and the residue was distilled, bp 107°, to yield 1.7 g of material of 80% purity (glpc) (68% yield). The material was purified by preparative gas chromatography (10 ft × ⅜ in. 20% SE-30 on 60–80 mesh Chromosorb A): ir 745 cm^{-1} (s, broad), 1110 (m), 1140 (m), 1160 (m), 1385 (m), 1470 (s), 2800 (s), 2885 (s), 2940 (s), 2965 (s), 3290 cm^{-1} (w); nmr 0.65–1 (m, 7 H, reduced to 6 H by D_2O exchange), 0.9–1.7 (m, 3 H), 2.48 ppm (s, and overlapping m, total 5 H). The picrate melted at 102–103° after three recrystallizations from benzene.

Anal. Calcd for $C_{12}H_{18}N_4O_7$: C, 43.64; H, 5.49. Found: C, 43.43; H, 5.55.

An authentic sample of the amine was prepared by treating 2-methylbutanoyl chloride with aqueous methylamine and sodium hydroxide[8] to give the *N*-methylamide, bp 70° (1 mm) [lit.[9] 70° (1 mm)] in 85% yield; reduction of the amide with ethereal lithium aluminum hydride[10] gave *N*-methyl-*N*-(2-methyl)butylamine in 80% yield, bp 107°. The nmr and ir spectra of this sample were identical with those described above.

***N*-Methyl-*N*-amylamine** was similarly prepared from 0.1 mol butyllithium (50 ml, 2*M* in hexane) in 25 ml of THF and 8.95 g (0.05 mol) of HMPTA in 25 ml of THF. The product collected on distillation weighed 2.72 g (50%): bp 116–118° (lit.[11] bp 116–118°); picrate mp 123.5–125.5° (lit.[11] mp 119–120°); nmr 0.6 (s, 1 H, disappears upon D_2O exchange), 0.75–1.08 (m, 3 H), 1.16–1.5 (m, 6 H), 2.38 (s, 3 H), 2.4–2.72 ppm (m, 2 H).

***N*-Methyl-*N*-benzylamine** was prepared from 0.06 mol of phenyllithium (33.3 ml of 1.8 *M* solution in 7:3 benzene–ether) diluted with 20 ml of THF and 5.38 g (0.03 mol) of HMPTA in 20 ml of THF to give 3.2 g of 85% pure material (75% yield): bp 80° (25 mm) [lit.[12] bp 184–185° (749 mm)]; ir (material purified by glpc) identical with that of an authenic sample;[13] nmr 1.38 (s, 1 H, disappears upon D_2O exchange), 2.44 (s, 3 H), 3.74 (s, 2 H), 7.4 ppm (s, 5 H).

***r*-2-Methylaminomethyl-2,*cis*-4,*cis*-6-trimethyl-1,3-dithiane (4).** *r*-2, *cis*-4, *cis*-6-Trimethyl-1,3-dithiane (243 mg, 1.5 mmol) was dissolved in 10 ml of a THF–HMPTA mixture (2:1) contained in a 25-ml round-bottom flask capped with a rubber septum and flushed with nitrogen as described above. Butyllithium (1.3 ml, 2.4 *M* solution in *n*-hexane, 3 mmol) was added and the mixture kept at −30° for 20 hr and then added to rapidly stirred D_2O. The product was extracted three times with 10 ml of hexane, the combined extracts were washed twice with 10-ml portions of water and dried over sodium sulfate, and the solvent was evaporated at water aspirator pressure. The product appeared homogenous upon gas chromatography on a 25 ft × ⅛ in. 25% QF-1 on Chromosorb W column at 120°: ir 730 (m), 780 (m), 1025 (m), 1065 (m), 1105 (m), 1145 (m), 1245 (s), 1370 (m), 1440 (s), 2780 (m), 2860 (s), 2910 (s), 2950 (s), 3300 cm^{-1} (w, broad); nmr 1.25 (d, J = 7 Hz) and 0.83–1.5 (B part of AB, total of foregoing peaks, 7 H), 1.84 (s, 3 H), 2–2.35 (A part of AB) and 2.23 (s) (total of these two peaks 3 H), 2.59 (s, 3 H), 3.0 (s, 2 H), 2.83–3.5 ppm (m, 2 H). The picrate melted at 180.5–182°.

Anal. Calcd for $C_{15}H_{22}N_4O_7S_2$: C, 41.47; H, 5.07. Found: C, 41.42; H, 5.10.

Acknowledgment. This work was supported under NSF Grant GP-35669, and is taken, in part, from the Ph.D. dissertation of Anthony G. Abatjoglou (University of Notre Dame).

Registry No.—**4**, 51932-18-4; **4** picrate, 52019-82-6; HMPTA, 680-31-8; *N*-methyl-*N*-(2-methyl)butylamine, 22431-10-3; *N*-methyl-*N*-(2-methyl)butylamine picrate, 51932-20-8; *N*-methyl-*N*-amylamine, 25419-06-1; *N*-methyl-*N*-amylamine picrate, 51932-21-9; *N*-methyl-*N*-benzylamine, 103-67-3; *r*-2, *cis*-4, *cis*-6-trimethyl-1,3-dithiane, 22452-27-3.

References and Notes

(1) A. G. Abatjoglou, unpublished observations; *cf.* E. L. Eliel, *Tetrahedron*, **30**, 1503 (1974).
(2) E. L. Eliel, A. A. Hartmann, and A. G. Abatjoglou, *J. Amer. Chem. Soc.*, **96**, 1807 (1974).
(3) P. Savignac and Y. Leroux, *J. Organometal. Chem.*, **57**, C47 (1973).
(4) J. L. Anderson, U. S. Patent 2,729,679 (1956); *Chem. Abstr.*, **50**, 12097*d* (1956).
(5) J. Meier, F. Akermann, and Hs. H. Günthard, *Helv. Chim. Acta*, **51**, 1686 (1968).
(6) C. F. Chang, B. J. Fairless, M. R. Willcott, R. F. Curl, Jr., J. Hinze, D. F. Koster, and A. Danti, *J. Mol. Spectrosc.*, **22**, 112 (1967).
(7) W. J. Bailey and R. E. Hartz, *Polym. Prepr., Amer. Chem. Soc., Div. Polym. Chem.*, **9**, 404 (1968); *Chem. Abstr.*, **71**, 125,030g (1968).
(8) S. M. McElvain and C. L. Stevens, *J. Amer. Chem. Soc.*, **69**, 2667 (1947).
(9) W. Dannhauser and G. P. Johari, *Can. J. Chem.*, **46**, 3143 (1968).
(10) C. A. Cope and E. Ciganek, "Organic Syntheses," Collect Vol. IV, Wiley, New York, N. Y., 1963, p 339.
(11) K. Löffler, *Ber.*, **43**, 2040 (1910).
(12) H. Zaunschirm, *Justus Liebigs Ann. Chem.*, **245**, 282 (1888).
(13) Sadtler, Infrared Spectral Catalog, No. 8107.

Novel Synthesis of Substituted Thioacylureas. Reaction of Aryl and Alkyl Thioamides with Aryl Isocyanates

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Received April 22, 1974

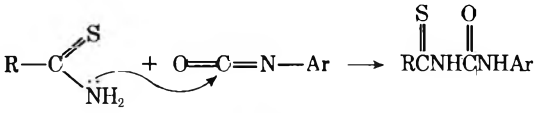
The preparation of acylureas from amides and aryl and alkyl isocyanates has been described by B. Kühn,[1,2] and extended by P. F. Wiley.[3] However, when aliphatic or aromatic thioamides are refluxed with aryl isocyanate in benzene or toluene, loss of H_2S from the thioamide occurs and symmetrical diarylurea is obtained from the reaction of isocyanate and H_2S.[4]

Table I

No.	R	Ar	C=S	C=O	Mp, °C	Crystn solvent	Reflux time, min	Yield, %	Reflux solvent	Formula[a]
1	CH_3	α-$C_{10}H_7$	1240	1702	233	Xylene	1	60	Xylene	$C_{13}H_{10}N_2OS$
2	C_6H_5	C_6H_5	1215	1705	218[b]	1-Butanol	15	70	Xylene, toluene	$C_{14}H_{12}N_2OS$
3	C_6H_5	p-ClC_6H_4	1212	1702	248	1-Butanol	1	65	Xylene	$C_{14}H_{11}ClN_2OS$
4	C_6H_5	α-$C_{10}H_7$	1210	1700	232	Xylene	2	75	Xylene	$C_{18}H_{14}N_2OS$
5	p-$CH_3C_6H_4$	C_6H_5	1215	1700	218	1-Butanol	15	81	Toluene	$C_{15}H_{14}N_2OS$
6	p-$CH_3C_6H_4$	p-ClC_6H_4	1210	1690	262	Anisole	1	70	Xylene	$C_{15}H_{13}ClN_2OS$
7	p-$CH_3C_6H_4$	α-$C_{10}H_7$	1205	1700	232	Methyl ethyl ketone	2	85	Xylene	$C_{19}H_{16}N_2OS$
8	α-$C_{10}H_7$	C_6H_5	1228	1690	233	1-Butanol	5	52	Toluene	$C_{18}H_{14}N_2OS$
9	α-$C_{10}H_7$	p-ClC_6H_4	1220	1690	238	Methyl ethyl ketone	1	48	Xylene	$C_{18}H_{13}ClN_2OS$
10	α-$C_{10}H_7$	α-$C_{10}H_7$	1220	1695	211	1-Butanol	1	84	Toluene, xylene	$C_{22}H_{16}N_2OS$

[a] Analyzed within ±0.4% for C, H, N, and S, except 6. Calcd for 6: C, 59.11; H, 4.29; N, 9.18; S, 10.49. Found: C, 58.75; H, 4.17; N, 9.89; S, 9.25. [b] J. Goerdeler and H. Schenk[5] report mp 214°.

We have now found that in the presence of Cu_2O, the reaction of thioamides and aryl isocyanates provides a satisfactory preparation of thioacylureas for which we propose the following scheme. Cu_2O is specific catalyst for this reaction—perhaps because of its ability to form complex with thioamide C=S bond and permit nitrogen unshared electron pair attack at carbon isocyanate C=N bond.



R = alky or aryl

The spectra of the thioacylureas (Table I) showed a thiocarbonyl absorption band at 1240–1205 cm^{-1} and carbonyl absorption at 1700–1690 cm^{-1}; the intensity ratio $\nu_{C=O}/\nu_{C=S}$ is ~1.4. The related disubstituted ureas show carbonyl absorption at 1650–1610 cm^{-1}.

The reaction of aryl isothiocyanates with alkyl- and arylthioamides provides a general method for preparing substituted thioacylureas. Previous preparation have involved the addition of amines to thiobenzoyl isocyanate[5] or less direct methods.[6-8]

Experimental Section

General. Melting points were measured on a Köfler hotbench apparatus. A Beckman IR-20A spectrophotometer was used for ir spectra, which were run in KBr. Microanalyses were performed by CNRS (Service Central de Microanalyse; 2, rue Henry-Dunant, 94-Thiasis, France).

Commercially available aryl isocyanates and thioacetamide were used as received. Arylthioamides were prepared by established procedures.[9] Useful solvents for the reaction are benzene, toluene, and xylene; 100 mg of Cu_2O as catalyst was used per mole of reactant. To avoid side reactions, dry solvents should be used for reflux and recrystallization. In a typical example a solution of 0.75 g (0.01 mmol) of thioacetamide, 1.6 g (0.01 mol) of α-naphthyl isocyanate, and 10 mg of Cu_2O in 10 ml of anhydrous xylene was heated under reflux for 1 min. The reaction was filtered. Recrystallization from anhydrous xylene gave thioacetyl-3-α-naphthylurea(60%), mp 233°.

Acknowledgment. The author is grateful to Dr. N. Mojdehi the chancellor of the Meshed University for his constant encouragements.

Registry No. 1, 51933-47-2; 2, 3553-47-7; 3, 51933-48-3; 4, 51933-49-4; 5, 51933-50-7; 6, 51933-51-8; 7, 51933-52-9; 8, 4875-18-7; 9, 51933-53-0; 10, 51933-54-1; $RC(S)NH_2$ (R = CH_3), 62-55-5; $RC(S)NH_2$ (R = C_6H_5), 2227-79-4; $RC(S)NH_2$ (R = p-$CH_3C_6H_4$), 2362-62-1; $RC(S)NH_2$ (R = α-$C_{10}H_7$), 20300-10-1; OCNAr (Ar = α-$C_{10}H_7$), 86-84-0; OCNAr (Ar = C_6H_5), 103-71-9; OCNAr (Ar = p-ClC_6H_4), 104-12-1.

References and Notes

(1) B. Kühn, *Ber.*, **17**, 2880 (1884).
(2) B. Kühn, *Ber.*, **18**, 1476 (1885).
(3) P. F. Wiley, *J. Amer. Chem. Soc.*, **71**, 1310 (1949).
(4) J. Goerdeler and H. Horstmann, *Chem. Ber.*, **93**, 663 (1960).
(5) J. Goerdeler and H. Schenk, *Chem. Ber.*, **99**, 782 (1966).
(6) O. Tsuge, M. Tashire, R. Mizuguchi, and S. Kanemasa, *Chem. Pharm. Bull. (Tokyo)*, **14**, 1055 (1966).
(7) J. Goerdeler and H. Schenk, *Chem. Ber.*, **98**, 2954 (1965).
(8) J. Goerdeler and H. Schenk, *Chem. Ber.*, **98**, 3831 (1965).
(9) A. E. S. Fairfull, J. L. Lowe, and D. A. Peak, *J. Chem. Soc.*, 742 (1952).

Pyrolysis of a Tropane Analog of Pethidine. A Novel 7-Azabicyclo[4.2.1]nonane Derivative

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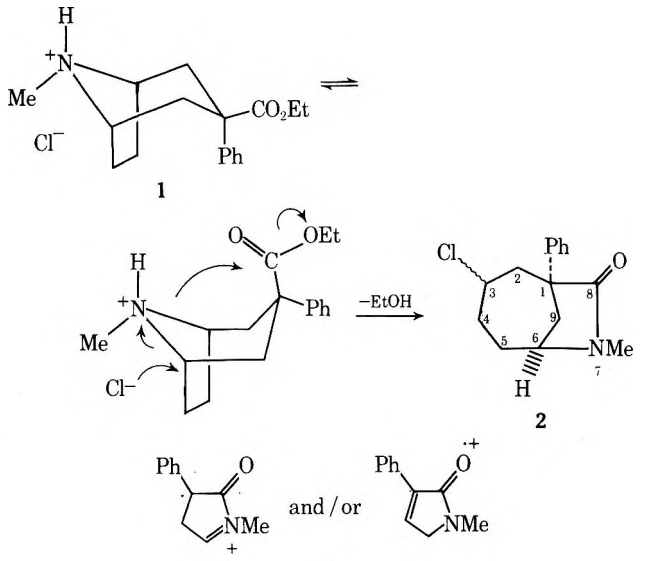
We recently undertook a conformational analysis of 3-β-carbethoxy-3-α-phenyltropane hydrochloride (1),[1] a tropane analog of pethidine, as part of our interest in the stereochemistry of narcotic analgesics based on 4-phenylpiperidine.[2] The ethyl ester hydrochloride 1, prepared from 3-tropinone,[3] melted within the reported range (192.5–193.5°) but with evolution of gas, behavior not originally described. Pyrolysis of 1 was therefore investigated on a larger scale and a nonbasic solid isolated from the thermolysate. This product is assigned the structure 7-aza-3-chloro-7-methyl-1-phenyl-8-oxobicyclo[4.2.1]nonane (2) on the following grounds: (i) elemental analysis; (ii) the M^+ (263) and $M^+ + 2$ (265) ions in its mass spectrum had the

relative abundance ratio of 3:1 characteristic of chlorine-containing derivatives—probable assignments to the base (*m/e* 42) and second most abundant peak (*m/e* 173, 78%) are $H_2C{=}N^+{=}CH_2$ and (3), respectively; (iii) its ir spectrum (Nujol mull) displayed amide carbonyl bands (1670, 1678 cm^{-1}); and (iv) its 100-MHz ^1H nmr spectrum in $CDCl_3$ (TMS reference) showed 1-proton multiplets assigned to methine hydrogens at C-3 and C-6, and an *N*-methyl resonance (s, δ 2.88) typical of an *N*-methyl cyclic amide (*cf.* δ_{NMe} 2.82 for 1-methyl-2-pyrrolidone).[4] The stereochemistry at C-3 is unestablished. Pyrolysis of the amino acid hydrochloride corresponding to 1 gave the same bicyclononane.



The reaction 1 to 2 represents the interconversion of 8-azabicyclo[3.2.1]octane and 7-azabicyclo[4.2.1]nonane derivatives through nucleophilic attack by chloride, and the gas observed when (1) melts must therefore be ethanol vapor.[5]

Experimental Section

Pyrolysis of 3-β-Carbethoxy-3-α-phenyltropane Hydrochloride. The hydrochloride 1 (0.96 g) was heated for 15 min in an oil bath kept at 190–200°. The thermolysate in chloroform was washed with water, and the organic phase dried (Na_2SO_4) and evaporated to leave 7-aza-3-chloro-7-methyl-1-phenyl-8-oxobicyclo[4.2.1]nonane (0.59 g): mp 132–137° (142–144° from benzene–hexane); ^1H nmr δ ($CDCl_3$) 7.46 and 7.22 (2 m, 2 H, 3 H, aryl protons), 4.00 (m, 1 H, $W_{1/2}$ = 22 Hz, 3 CH or 8 CH), 3.70 (m, 1 H, $W_{1/2}$ = 8 Hz, 3 CH or 8 CH), 2.88 (s, 3 H, NMe); 2.86–1.64 (m, 8 H, 2, 4, 5 and 9 CH_2).

Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.30; H, 6.88; Cl, 13.44; N, 5.31. Found: C, 68.39; H, 7.01, Cl, 13.44; N, 5.09.

Similar treatment of the amino acid hydrochloride corresponding with 1 gave a comparable yield of 2.

Acknowledgment. We thank the Medical Research Council for Canada for financial support.

Registry No.—1, 52123-58-7; 2, 52123-59-8.

References and Notes

(1) A. F. Casy and J. E. Coates, *Org. Magn. Resonance*, in press.
((2) A. F. Casy and K. M. J. McErlane, *J. Chem. Soc., Perkin Trans. 1*, 726 (1972); M. A. Iorio, G. Damia, and A. F. Casy, *J. Med. Chem.*, **16**, 592 (1973).
(3) M. R. Bell and S. Archer, *J. Amer. Chem. Soc.*, **82**, 4638 (1960).
(4) J. C. N. Ma and E. W. Warnhoff, *Can. J. Chem.*, **43**, 1849 (1965).
(5) The bicyclic parent of 2 is listed in the "Chemical Abstract Ring Indexes" (1970–1972), but we have traced no specific example.

Synthesis of 1-(6-Aminopurin-9-yl)-2,5-anhydro-1,2-dideoxy-DL-ribitol, a New "Reversed" Amino Nucleoside[1]

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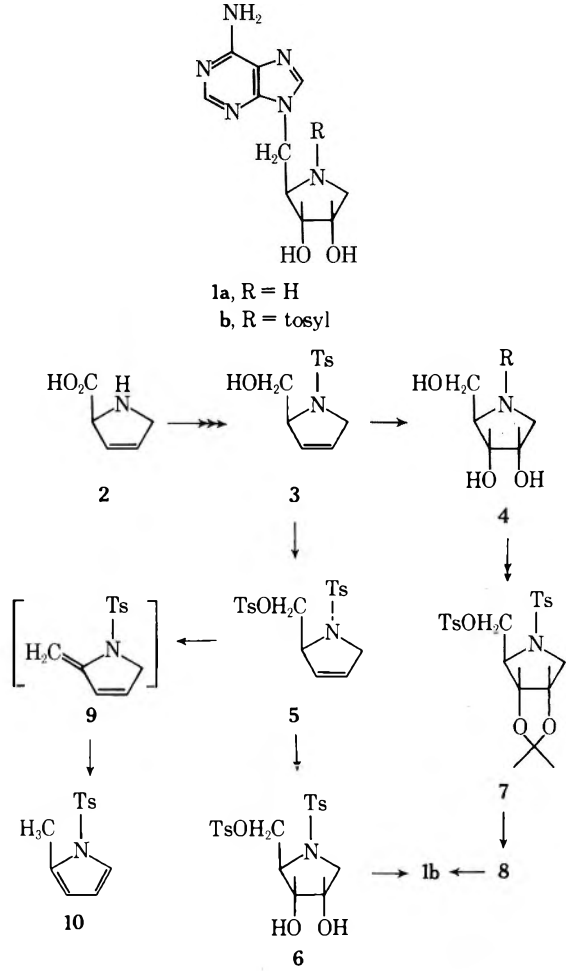
Many nucleosides which are effective agents in inhibiting the growth of malignant cells become ineffective *in vivo* because they are rapidly destroyed by enzymatic cleavage into a purine or pyrimidine and a carbohydrate moiety.[2,3] A reversed nucleoside, however, does not possess the normal linkage between the nitrogen of the base and the anomeric carbon of the sugar, and is more stable with respect to hydrolytic cleavage. A number of reversed nucleosides have already been synthesized.[4–9] Some have elicited interest in connection with cytokinin activity.[10,11] Recently, two patents have been filed which list several reversed nucleosides as antiviral and anticancer drugs.[12,13]

Our research interests in the area of amino and aminoacyl nucleosides prompted the synthesis of 1, the first example of a reversed amino nucleoside. Central to any of the several possible chemical strategies for obtaining 1 is the synthesis of the pyrrolidine sugar 4. The biologically active and synthetic imino acid dehydroproline can be modified by reduction and hydroxylation to give 4 in high yields.[14] Conversion of the amino sugar 4 to 7, subsequent coupling with the sodium salt of adenine, and removal of the isopropylidene group with formic acid gave 1b as a stable, white, crystalline compound, mp 212–213°. The detosylated com-



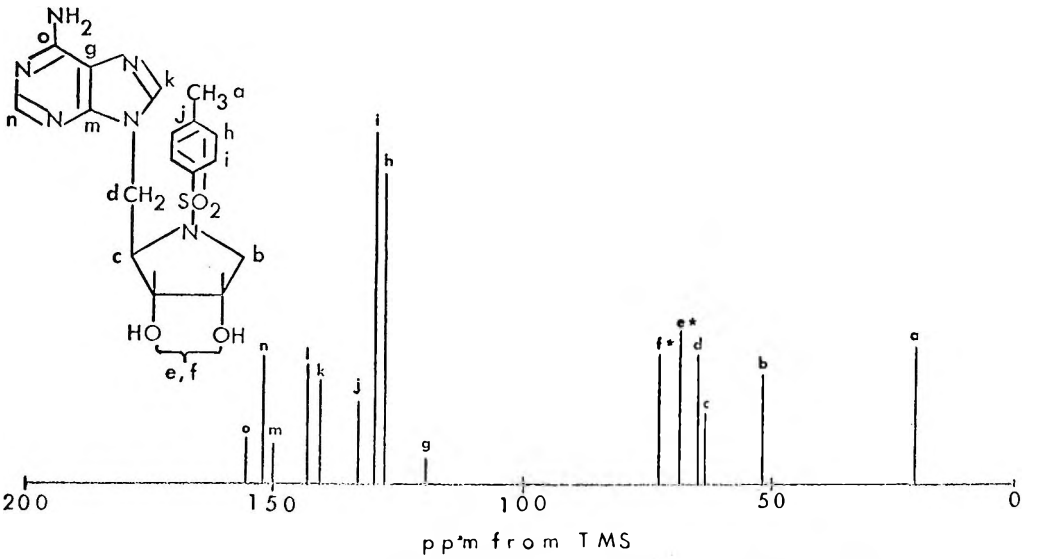


Figure 1. ^{13}C nmr spectrum of 1-(6-aminopurin-9-yl)-2,5-anhydro-1,2-dideoxy-2-(*p*-toluenesulfonamido)-DL-ribitol.

pound **1a** was found to be extremely unstable and difficult to handle. A superior route to the reversed nucleoside is direct coupling of **6** with the sodium salt of adenine, which gives **1b** in 73% yield. Confirmation of the structure of **1b** was provided by its pulsed Fourier transform (PFT) ^{13}C nmr (Figure 1).

Nucleosides containing unsaturation in the sugar moiety have aroused biochemical interest in recent years.[15] Because of this we attempted the displacement of the *p*-toluenesulfonyloxy group of **5** with the sodium salt of adenine. The product of this reaction was *N*-*p*-toluenesulfonyl-2-methylpyrrole (**10**), presumably arising from a base-induced elimination to **9** followed by a facile 1,5-sigmatropic hydrogen shift.

Experimental Section

***N*-Tosyl-3,4-dehydro-DL-prolinol (3)**[14] was prepared as a clear yellow oil from dehydro-DL-proline[17] by tosylation,[18] methylation with diazomethane,[18] and reduction of the *N*-tosyl-3,4-dehydro-DL-proline methyl ester with lithium borohydride.[14]

2,5-Anhydro-2-deoxy-3,4-isopropylidene-2-(*p*-toluenesulfonamido)-1-*O*-(*p*-toluenesulfonyl)-DL-ribitol (7). The dehydroprolinol **3** can be hydroxylated[19] in almost quantitative yield with osmium tetroxide to give **4** as white crystals, mp 139°. The triol **4** can be converted to **7** (mp 143°) by reaction with 2,2-dimethoxypropane and subsequent tosylation with tosyl chloride and pyridine.[14]

1-(6-Aminopurin-9-yl)-2,5-anhydro-1,2-dideoxy-3,4-isopropylidene-2-(*p*-toluenesulfonamido)-DL-ribitol (8). Adenine (233 mg, 1.5 mmol) was dissolved in 10 ml of dry DMF. Sodium hydride (50% in mineral oil, 70 mg, 1.65 mmol) was added to the solution and it was stirred for 0.5 hr. The suspension was then placed in an oil bath at 60° for an additional 0.5 hr to ensure completion of the reaction. After cooling to room temperature 241 mg (0.5 mmol) of 2,5-anhydro-2-deoxy-3,4-isopropylidene-2-(*p*-toluenesulfonamido)-1-*O*-(*p*-toluenesulfonyl)-DL-ribitol in 8 ml of DMF was added to the white suspension of the sodium salt of adenine. This mixture was then stirred at 60° for 12 hr. The DMF was then stripped off to give a light-brown residue that was extracted with methylene chloride. After filtering off the insoluble portion that remained, the methylene chloride was evaporated *in vacuo* to give a yellow oil that was chromatographed on preparative layer silica gel plates to give 104 mg (47%) of product as white crystals: mp 232–233°; nmr spectrum δ_{TMS} ($CDCl_3$) 0.80 (s, 3 H), 1.08 (s, 3 H), 2.41 (s, 3 H), 3.22–3.68 (m, 2 H), 4.02–5.03 (m, 5 H), 6.17–6.38 (br s, 2 H), 7.20–7.90 (m, 4 H), 8.05 (s, 1 H), 8.36 (s, 1 H); mass spectrum (70 eV, direct inlet 200°) *m/e* 444 (M^+).

Anal. Calcd for $C_{20}H_{24}N_6O_4S \cdot 1H_2O$: C, 51.95; H, 5.19; N, 18.18. Found: C, 51.79; H, 5.29; N, 17.98.

2,5-Anhydro-2-deoxy-2-(*p*-toluenesulfonamido-1-*O*-(*p*-toluenesulfonyl)-DL-ribitol (6) was prepared by tosylation of **3** followed by hydroxylation.[14]

1-(6-Aminopurin-9-yl)-2,5-anhydro-1,2-dideoxy-2-(*p*-toluenesulfonamido)-DL-ribitol (1b). Adenine (127 mg, 0.941 mmol) and sodium hydride (50% in mineral oil, 50 mg, 1.035 mmol) were dissolved in 10 ml of dry DMF and stirred for 1.5 hr to form a white suspension of the sodium salt of adenine. To this was added 415 mg (0.941 mmol) of 2,5-anhydro-2-deoxy-2-(*p*-toluenesulfonamido)-1-*O*-(*p*-toluenesulfonyl)-DL-ribitol in 18 ml of DMF. The above mixture was then heated in an oil bath at 60° for 21 hr. The DMF was then stripped off *in vacuo* and further pumped down on a vacuum pump. Addition of a small amount of CH_2Cl_2 resulted in a beige-colored precipitate which was filtered and recrystallized twice from hot methanol to give a 73% yield (279 mg) of the stable, white, crystalline adduct (**1b**): mp 212–213°; uv spectrum λ_{max} (pH 7) 233 nm (ϵ 13,925), 266 (10,735); ^1H nmr spectrum δ_{TMS} (DMSO-d_6) 2.38 (s, 3 H), 3.21–4.63 (m, 9 H), 7.24 (s, 2 H), 7.30–7.95 (m, 4 H), 8.10 (s, 1 H), 8.22 (s, 1 H); ^{13}C nmr spectrum δ_{TMS} (DMSO-d_6) 20.97, 51.78, 63.52, 64.79, 68.47, 72.75, 119.30, 127.79, 129.44, 132.90, 140.90, 143.20, 150.1, 152.4, 155.8; mass spectrum (70 eV, direct inlet 175°) *m/e* 404 (M^+).

Anal. Calcd for $C_{17}H_{20}N_6O_4S$: C, 50.49; H, 4.98; N, 20.86. Found: C, 50.38; H, 5.23; N, 20.95.

***N*-Tosyl-2-methylpyrrole (10).** *N,O*-Ditosyl-3,4-dehydro-DL-prolinol (194 mg, 0.476 mmol) in 3 ml of DMF was added to a suspension of the sodium salt of adenine formed by treating 64 mg (0.476 mmol) of adenine with 71 mg (0.704 mmol) of sodium hydride (50% in mineral oil) in 2 ml DMF for 2.5 hr. After 6 hr of stirred heating at 50°, and an additional 12 hr of reaction time at room temperature, the DMF was removed *in vacuo*. The brown residue remaining was extracted with chloroform (3 × 20 ml) and filtered. After washing the chloroform extracts with water and drying (Na_2SO_4), the solvent was removed to give 99 mg of brown product. This product was purified by preparative layer chromatography on silica gel plates to give 55 mg (49% yield) of the *N*-tosyl-2-methylpyrrole: mp 87.5–89° (lit. mp 93–94°);[16] nmr spectrum δ_{TMS} ($CDCl_3$) 2.29 (s, 3 H), 2.42 (s, 3 H), 5.85–6.03 (m, 1 H), 6.17 (t, 1 H), 7.28 (m, 1 H), 7.20–7.82 (m, 4 H); mass spectrum (70 eV) *m/e* 235 (M^+).

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.55; H, 5.57; N, 5.80.

Acknowledgments. We thank the National Science Foundation for funds toward the purchase of the PFT nmr spectrometer. One of us (R. H. W.) thanks the 3M Co. for a 3M Research Fellowship.

Registry No.—**1b**, 51932-88-8; **3**, 51932-89-9; **4**, 52019-89-3; **5**, 51932-90-2; **6**, 51932-91-3; **7**, 51932-92-4; **8**, 51932-93-5; **10**, 17900-53-7; adenine, 73-24-5.

References and Notes

(1) Abstracted from the Ph.D. Thesis of R. H. W., University of Iowa, 1974. Presented at the 8th Midwest Regional Meeting of the American Chemical Society, Columbia, Mo., Nov 8–10, 1972.
(2) R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970.
(3) J. A. Montgomery, *Progr. Med. Chem.*, 7 (1970).
(4) J. Defaye and T. Reyners, *Bull. Soc. Chim. Biol.*, **50**, 1625 (1968).
(5) J. Defaye and M. Naumburg, Abstracts of Papers, Chemistry of Nucleic Acid Components N-32, The XXI International Congress of IUPAC, Prague, 1967.
(6) N. J. Leonard, F. C. Sciavolino, and V. Nair, *J. Org. Chem.*, **33**, 3169 (1968).
(7) M. Kawazu, T. Kanno, S. Yamamura, T. Mizoguchi, and S. Saito, *J. Org. Chem.*, **38**, 2887 (1973).
(8) N. Takamura, N. Taga, T. Kanno, and M. Kawazu, *J. Org. Chem.*, **38**, 2891 (1973).
(9) S. Fukatsu, Y. Takeda, and S. Umezawa, *Bull. Chem. Soc. Jap.*, **46**, 3165 (1973).
(10) J. Cleophax, J. Defaye, and S. D. Gero, *Bull. Soc. Chim. Fr.*, 104 (1967).
(11) J. Hildesheim, J. Cleophax, S. D. Gero, and R. D. Guthrie, *Tetrahedron Lett.*, 5013 (1967).
(12) M. Kawazu and T. Kanno, Japanese Patent 72 20, 194 (Sept 27, 1972); *Chem. Abstr.*, **78**, 4486w (1973).
(13) M. Kawazu and T. Kanno, Japanese Patent 72 20, 195 (Sept 27, 1972); *Chem. Abstr.*, **78**, 30158k (1973).
(14) V. Nair and R. H. Walsh, *Carbohyd. Res.*, in press.
(15) J. Žemlička, J. V. Freisler, R. Gasser, and J. P. Horwitz, *J. Org. Chem.*, **38**, 990 (1973), and references cited therein.
(16) P. S. Portoghese, A. A. Mikhail, and H. J. Kupferberg, *J. Med. Chem.*, **11**, 219 (1968).
(17) A. Corbella, P. Gariboldi, G. Jommi, and F. Mauri, *Chem. Ind. (London)*, 583 (1969).
(18) N. Izumiya, J. E. Francis, A. V. Robertson, and B. Witkop, *J. Amer. Chem. Soc.*, **84**, 1702 (1962).
(19) J. S. Baran, *J. Org. Chem.*, **25**, 257 (1960).

Bromination of Methyl 3-Oxo-5β-cholanate at C-2

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Molecular bromine is usually used to prepare α-bromo ketones and α-bromo aldehydes. On the other hand, iodine monobromide has been used for this purpose only in a few cases.[1,2]

In the present study **1** was subjected to the action of 2 equiv of iodine monobromide. Two definite stages could be distinguished (Scheme I) by using the nmr technique.

The compound obtained in the first stage, which terminated after about 2 hr, was characterized by its singlet at δ 1.09 and somewhat broad doublet centered at δ 4.98. From the melting point and other physical data this compound proved to be identical with 4β-bromo ketone[3] obtained by the usual bromination of **1** with 1 equiv of bromine.

The second stage extended over a longer period of time (5 days), during which a singlet at δ 1.07 and a quartet centered at δ 4.73 gradually developed at the expense of the previous signals, which eventually completely disappeared (see Experimental Section). The characteristic quartet of the final product **3** unequivocally establishes the location and orientation of the bromine atom in this compound to be 2β (equatorial).[4] The configuration of the hitherto unknown compound **3** was also confirmed by other spectroscopic data.

The carbonyl frequency in the ir spectrum of **3** is higher than that of the parent ketone **1**. The observed shifts of 24 and 17 cm^{-1} for **3** and **2**, respectively, are to be expected for equatorial bromine substituents.[5] Additional evidence for the proposed orientation of the bromine substituent in both **2** and **3** was obtained from the location of the carbonyl absorption in the uv spectrum; the values of their λ_{max} are very close to that of the parent compound **1** (see Experimental Section).

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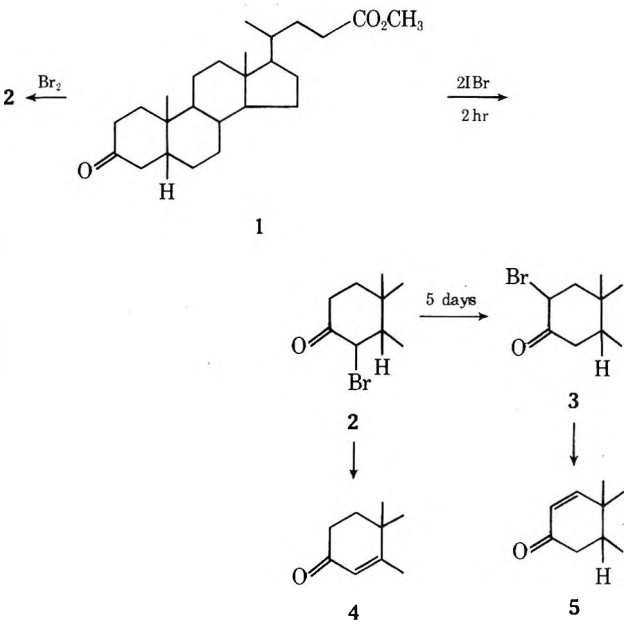
Scheme I



Surprisingly, despite the distinct differences in the other physical constants, the mass spectra of the two bromo compounds **2** and **3** have much in common, indicating possible rearrangement during the fragmentation process.

Chemical evidence for the above assigned structure was provided by the conversion of **3** to the known α,β-unsaturated ketone **5**[3] (~50% yield) by the action of Li_2CO_3 in DMF.[6] The parallel reaction carried out on the isomeric 4β-bromo ketone **2** (Scheme I) proceeded smoothly to give methyl 3-oxo-4-cholenate (**4**)[3] as the major product, but the 2β-bromo isomer **3** reacted much more slowly. The elimination process involved, as expected,[7,8] a partial rearrangement yielding a mixture of methyl 3-oxo-5β-chol-1-enoate (**5**) and methyl 3-oxo-4-cholenate (**4**) in approximately 1:1 ratio. The location of the double bond in **5** was disclosed in the nmr spectrum; the two doublets centered at δ 6.8 and 5.84 are attributable to C-1 and C-2 vinylic protons, respectively. In contrast the single vinylic proton in compound **4** resonates at δ 5.71.

Preliminary experiments showed that complete monobromination could not be achieved with less than 2 equiv of IBr. It was assumed, therefore, that the reaction might be represented stoichiometrically as follows: 1 + 2IBr → 2 + I_2 + HBr. Accordingly, complete rearrangement of the 4β-bromo ketone **2** to 2β-bromo ketone **3** was effected by subjecting the former to the action of 1 equiv of I_2 and a catalytic amount of HBr in acetic acid. Thus, it is evident that the iodine formed during the first stage of the bromination was responsible for the rearrangement in the second stage of the reaction.

The migration of the bromine atom from C-4 to the less hindered C-2 position[9-12] was effected by iodine and hydrogen bromide taken together; in the presence of iodine alone the rearrangement was slower; hydrogen bromide in the absence of iodine proved to be entirely ineffective.

In our opinion the driving force for the migration is the ability of the iodine molecule to form a charge-transfer complex with the carbonyl group of the substrate.[13] The coordinated iodine molecule adjusts itself to the steric and stereoelectronic requirements of the rearrangement reaction. The debromination at C-4 and rebromination at C-2

relieves the strain at the C-4 position[10-12] imposed by the bromine atom.

The tendency of the molecule to part from the bromine atom at C-4 is also reflected by the facile dehydrobromination of 4β-bromo ketone **2** as compared to 2β-bromo isomer **3**.

Another noteworthy observation is that the bromination of **1** to produce 4β-bromo ketone **2** is much slower with IBr (2 hr) than with Br_2 (5 min). Moreover, the slow rate of the monobromination with IBr did not change appreciably when **1**, or even 2, equiv of Br_2 was added to the reaction mixture, implying that in the presence of IBr enolization is depressed. This peculiar behavior could be a result of molecular compound formation between the 3-keto substrate and iodine monobromide.[14-18] The coordinated IBr molecule would then interfere in the process of enolization initiated by the protonation at the oxygen carbonyl group.

The introduction of bromine at C-2 in methyl 3-oxo-5β-cholanate (**1**) is significant, since it is the first reported case in which heterolytic bromination of **1** takes place exclusively at a site unfavorable for enolization.

Experimental Section

Ultraviolet spectra were determined with a Unicam ultraviolet spectrophotometer (Model Sp 300A). Infrared spectra were measured in potassium bromide disks using a Perkin-Elmer spectrophotometer (Model 337). Nmr spectra were recorded on a Jeol C-60-H high-resolution nmr spectrometer with tetramethylsilane as internal standard. CD spectra were obtained using a Cary 60 recording spectropolarimeter. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. Mass spectra were recorded on a CH5 Varian MAT mass spectrometer. IBr was prepared by dissolving 1 g of iodine and 0.614 g of bromine in 50 ml of glacial acetic acid (1 mmol of IBr per 6.35 ml). Column chromatography and tlc were carried out on silica gel (Hopkins and Williams) and Kieselgel GF 254 from Stahl Merck, respectively.

Methyl 3-Oxo-5β-cholanate (1) was prepared according to the procedure of Fieser and Ettorre:[19] mp 119° (lit.[19] mp 119–120°); ir 1706 cm^{-1} (C=O); uv (ethanol) 285 nm (ε 19); nmr ($CDCl_3$) δ 0.70 (s, 3, 18-CH_3), 1.03 (s, 3, 19-CH_3), 3.68 (s, 3, 24-OCH_3); CD (ethanol) $[\theta]_{262}$ 0, $[\theta]_{285}$ −1600, $[\theta]_{318}$ 0; mass spectrum *m/e* (rel intensity) 388 (base peak, M^+), 537 (52, M − 31), 275 (93).

Bromination of 1 with IBr for 2 Hr. To a solution of **1** (388 mg) in acetic acid (10 ml) 2 equiv of IBr (12.7 ml) was added. After standing for 2 hr at room temperature the reaction mixture was diluted with water (100 ml) and sufficient sodium bisulfite was added. The precipitate was filtered, washed with water, and dissolved in chloroform. The solvent was removed and the solid residue was crystallized from methanol to yield pure 4β-bromo ketone **2**: mp 100–100.5° (lit.[3] mp 96–101°); $[\alpha]_D$ ($CHCl_3$) +51.0°; ir 1725 (C=O), 710–700 cm^{-1} (C–Br); uv (ethanol) 280 nm (ε 25); nmr ($CDCl_3$) δ 0.70 (s, 3, 18-CH_3), 1.09 (s, 3, 19-CH_3), 3.67 (s, 3, 24-OCH_3), 4.90 and 5.07 (d, 1, H–C–Br); CD (ethanol) $[\theta]_{250}$ 0, $[\theta]_{282}$ −660, $[\theta]_{300}$ 0, $[\theta]_{310}$ +240, $[\theta]_{330}$ 0; mass spectrum *m/e* (rel intensity) 468, 466 (0, M^+), 355 [base peak, M − (HBr + 31)], 419, 417 (9, M − 49), 387 (60, M − Br), 369 [33, M − (HBr + H_2O)], 337 (33), 55 (66, CH_2=CHC≡O^+).

Anal. Calcd: C, 64.24; H, 8.35; Br, 17.13. Found: C, 64.10; H, 8.25; Br, 17.16.

Bromination of 1 with Br_2 in the Presence of IBr. To a solution of **1** (388 mg) in acetic acid (10 ml), 1 equiv of IBr (6.4 ml) and 1 equiv of Br_2 were added. The product which was isolated after 2 hr by the above procedure proved to be identical in all respects with 4β-bromo ketone **2**. The same result was also obtained when **1** was subjected to the action of 2 equiv of Br_2 in the presence of 1 equiv of IBr under the same conditions.

Methyl 2β-Bromo-3-oxocholanate (3). To a solution of methyl 3-oxo-5β-cholanate (**1**, 500 mg) in acetic acid (10 ml), 2 equiv of IBr solution (16.4 ml) and 2 drops of 10% HBr in acetic acid were added and the reaction mixture was kept for 5 days at 30°. The brown residue which was obtained after the usual work-up was chromatographed and purified by plc (8% acetic acid in benzene). Recrystallization from methanol yielded 300 mg of pure methyl 2β-bromo-3-oxocholanate (**3**): mp 85°; $[\alpha]_D$ ($CHCl_3$) +2.4°; ir 1730 (C=O), 702 cm^{-1} (C–Br); uv (ethanol) 280 nm (ε 25); nmr ($CDCl_3$) δ 0.70 (s, 3, 18-CH_3), 1.07 (s, 3, 19-CH_3), 3.7 (s, 3, 24-OCH_3), 4.57, 4.66, 4.80, and 4.88 (q, 1, H–C–Br); CD (ethanol) $[\theta]_{258}$ 0, $[\theta]_{287}$ −1600, $[\theta]_{332}$ 0; mass spectrum *m/e* (rel intensity) 468, 466 (0, M^+), 355 (base peak), 419, 417 (13), 387 (85), 369 (47), 337 (53), 55 (91).

Anal. Calcd: C, 64.24; H, 8.35; Br, 17.13. Found: C, 64.04; H, 8.17; Br, 17.37.

Table I
Formation of 2β-Bromo Ketone 3

Time, hr	Height of peak at δ 1.07/ height of peak at δ 1.09
12	~0.1
36	~1.2
60	~20
84	~30
120	No peaks at δ 1.09 and 5.07

Bromination of 1 with IBr at Different Intervals of Time. To a solution of **1** (388 mg) in acetic acid (10 ml) 2 equiv of IBr (12.7 ml) and 2 drops of 10% HBr were added and the reaction mixture was kept at 30°. Aliquots of 4 ml were taken after 12, 36, 60, 84, and 120 hr and analyzed by nmr after the usual work-up. The formation of 2β-bromo ketone **3** was followed by the appearance of the peaks at δ 1.07, 4.57, 4.66, 4.80, and 4.88. The results are summarized in Table I.

Rearrangement of 2 to 3. To a solution of 4β-bromo ketone **2** (467 mg) and I_2 (254 mg) in acetic acid (10 ml), 2 drops of 10% HBr in acetic acid was added. The reaction mixture was kept at 30°. Aliquots of 2 ml were taken after 12, 36, 60, 84, and 120 hr and analyzed by nmr. The results were similar to those represented in Table I for the formation of 2β-bromo ketone **3** by the action of iodine monobromide on **1**.

The rearrangement with I_2 was not complete after 5 days in the absence of HBr. HBr alone was found to be ineffective.

Registry No.—**1**, 1173-32-6; **2**, 52032-49-2; **3**, 52032-50-5; IBr, 7789-33-5.

References and Notes

(1) Y. Yanuka, R. Katz, and S. Sarel, *Chem. Commun.*, 849 (1968).
(2) Y. Yanuka and G. Halperin, *J. Org. Chem.*, **38**, 2587 (1973).
(3) M. Fieser and L. F. Fieser, *J. Amer. Chem. Soc.*, **82**, 2002 (1960).
(4) L. Mamlok, *Bull. Soc. Chim. Fr.*, 3466 (1965).
(5) R. N. Jones, D. A. Ramsey, F. Herling, and K. Dobriner, *J. Amer. Chem. Soc.*, **74**, 2828 (1952).
(6) R. Joly, J. Warnant, G. Nominé, and D. Bertin, *Bull. Soc. Chim. Fr.*, **366** (1958).
(7) E. M. Kuehne, *J. Amer. Chem. Soc.*, **83**, 1492 (1961).
(8) E. W. Warnhoff, *J. Org. Chem.*, **27**, 4587 (1962).
(9) E. J. Corey, and R. A. Sneen, *J. Amer. Chem. Soc.*, **77**, 2505 (1955).
(10) A. S. Liston, *J. Org. Chem.*, **31**, 2105 (1966).
(11) B. Berkoz, E. P. Chavez, and C. Djerassi, *J. Chem. Soc.*, 1323 (1962).
(12) L. Velluz, J. Valls, and G. Nominé, *Angew. Chem.*, **77**, 185 (1965).
(13) D. Wobschall and D. A. Norton, *Arch. Biochem. Biophys.*, **122**, 85 (1967).
(14) R. L. Scott, *J. Amer. Chem. Soc.*, **75**, 1550 (1953).
(15) E. Augdal and P. Klaboe, *Acta Chem. Scand.*, **16**, 1637, 1647, 1655 (1962).
(16) W. B. Person, *J. Amer. Chem. Soc.*, **82**, 29 (1960).
(17) L. E. Orgel and R. S. Mulliken, *J. Amer. Chem. Soc.*, **79**, 4839 (1957).
(18) O. Hassel and C. Roemming, *Quart. Rev., Chem. Soc.*, **16**, 1 (1962).
(19) L. F. Fieser and R. Ettorre, *J. Amer. Chem. Soc.*, **75**, 1700 (1953).

Synthesis of Methyloxocyclopentaneacetic Acids

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In studying the synthesis of a carbocyclic analog of muscarone,[1] 4-methyl-3-oxo-1-cyclopentaneacetic acid was required. An attempt was made to synthesize it by a Wittig reaction between 4-methyl-4-cyclopentene-1,3-dione[2] and triphenylcarbethoxymethylenephosphorane[3] using benzoic acid as catalyst.[4] Contrary to reports[5,6] on similar experiments, the reaction took place under mild conditions, yielding ethyl 3-methyl-4-oxo-2-cyclopenten-1-ylideneace-

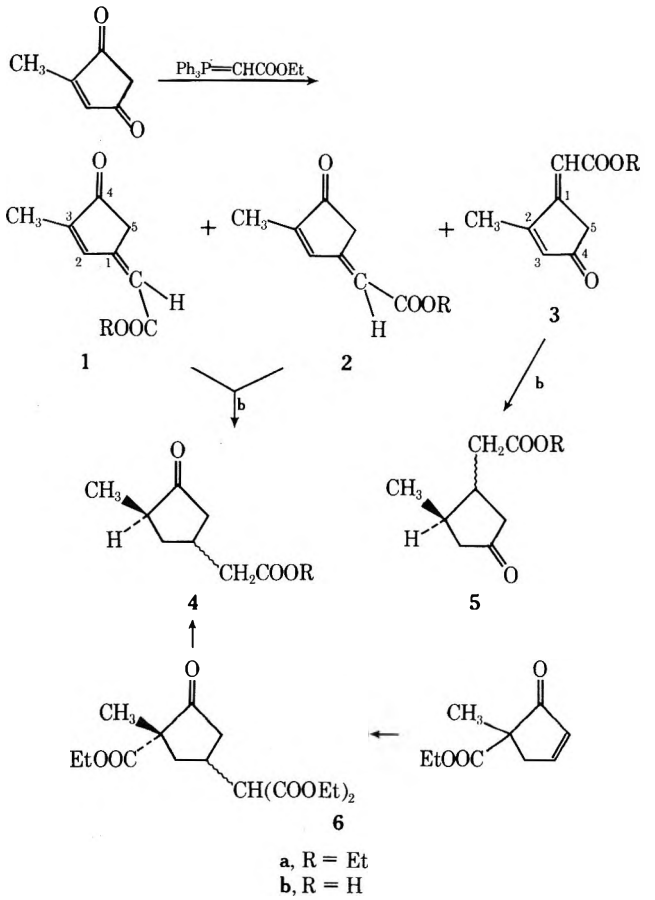
tate (**1a** and **2a**) and 2-methyl-4-oxo-2-cyclopenten-1-ylideneacetate (**3a**) in a 1:1.8 ratio.

The products were isolated by column chromatography and the isomers were identified by their nmr spectra. The C-2 proton in **1a** and **2a** absorbed at lower fields than the C-3 proton in isomer **3a**, consistent with the former being a vinylic proton β to a keto group. Furthermore, the anisotropic effect of the ester group causes a downfield shift of the C-2 proton in the *Z* form, allowing the distinction of the two isomers **1a** and **2a**. It is interesting to note that the nmr spectrum of **2a** showed $J \cong 1.5$ Hz for allylic coupling between the proton α to the ester group and the two protons of C-5. In compound **1a**, the same coupling was definitely smaller in that it resulted in simply a broadening of the C-5 proton signal. This confirms Newsoroff's observations[7] on *J* cisoid and *J* transoid (*J* cisoid < *J* transoid) constants.

Catalytic reduction of **1a**, **2a**, and **3a** led to the esters **4a** and **5a**, which were easily hydrolyzed to the corresponding acids **4b** and **5b**. The nmr spectra showed that compound **5** was a 60:40 mixture of cis and trans isomers.

To avoid obtaining several isomers simultaneously and to verify the assignment of the structures, 3-methyl-4-oxo-1-cyclopentaneacetic acid was also synthesized starting from ethyl 1-methyl-2-oxo-3-cyclopentene-1-carboxylate[8] according to Scheme I. The compound prepared in this manner had the same chemical–physical characteristics as **4b**.

Scheme I



Experimental Section

Melting points (uncorrected) were taken in capillary tubes on a Büchi apparatus. The ir and uv spectra were recorded with Perkin-Elmer 257 and Unicam SP 800 spectrophotometers, respectively. The nmr spectra were measured on a Jeol JMH-MH-60 spectrometer using TMS as internal standard.

Wittig Reaction of 4-Methyl-4-cyclopentene-1,3-dione with Triphenylcarbethoxymethylenephosphorane. A solution of 4-methyl-4-cyclopentene-1,3-dione[2] (2.2 g) in benzene (50 ml) was slowly added to triphenylcarbethoxymethylenephosphorane[3] (6.96 g, 2.0 mmol) and benzoic acid (0.25 g, 2.0 mmol) in benzene (50 ml). The resulting solution was refluxed for 2 hr; then petroleum ether (200 ml) was added and the mixture was cooled. After filtration of triphenylphosphine oxide, the solution was evaporated to yield an oil that was separated into three main fractions through chromatography using a silica gel column and ethyl acetate–cyclohexane (3:7) as the eluting solvent.

The first fraction was ethyl (*Z*)-3-methyl-4-oxo-2-cyclopenten-1-ylideneacetate (**1a**): tlc (silica gel) R_f 0.44; yield 0.4 g (11.1%); mp 50–51° from *n*-hexane; ir (Nujol) 1635 (C=C) and 1705 cm^{-1} (C=O); uv max (95% EtOH) 285.5 nm (ϵ 15,200); nmr (CCl_4) δ 1.20 (t, 3, $-CH_2CH_3$), 1.80 (s, 3, 3-CH_3), 2.75 (s, 2, 5-CH_2), 3.83 (q, 2, $-CH_2CH_3$), 5.20 (s, 1, =CHCOOEt), and 7.64 ppm (s, 1, 2-H).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.46; H, 6.58.

The second fraction was ethyl (*E*)-3-methyl-4-oxo-2-cyclopenten-1-ylideneacetate (**2a**): tlc (silica gel) R_f 0.38; yield 0.4 g (11.1%); mp 68–69° from *n*-hexane; ir (Nujol) 1635 (C=C) and 1700 cm^{-1} (C=O); uv max (95% EtOH) 282 nm (ϵ 20,100); nmr (CCl_4) δ 1.20 (t, 3, $-CH_2CH_3$), 1.80 (s, 3, 3-CH_3), 3.03 (d, $^4J \cong 1.5$ Hz,[7] 2, 5-CH_2), 3.83 (q, 2, $-CH_2CH_3$), 5.29 (s, 1, =CHCOOEt), and 6.73 ppm (s, 1, 2-H).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.54; H, 6.66.

The third fraction was ethyl 2-methyl-4-oxo-2-cyclopenten-1-ylideneacetate (**3a**): tlc (silica gel) R_f 0.26; yield 1.4 g (38.9%); bp 105–108° (8 mm) (with decomposition); ir (neat) 1643 (C=C) and 1705 cm^{-1} (C=O); uv max (95% EtOH) 276 nm (ϵ 9200); nmr (CCl_4) δ 1.22 (t, 3, $-CH_2CH_3$), 2.08 (s, 3, 2-CH_3), 3.01 (s, 2, 5-CH_2), 3.72 (q, 2, $-CH_2CH_3$), 5.42 (s, 1, =CHCOOEt), and 5.71 ppm (s, 1, 3-H).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.80; H, 6.86.

(*Z*)- and (*E*)-3-Methyl-4-oxo-2-cyclopenten-1-ylideneacetic Acid (1b and 2b). A suspension of **1a** (or **2a**) in 4 *N* HCl was refluxed for 30 min. The solution was then evaporated under reduced pressure and the resulting residue was crystallized from water.

Compound **1b** had mp 140–141°; ir (Nujol) 1645 (C=C), 1685, 1715 (C=O), and 2400–3500 cm^{-1} (OH).

Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 62.80; H, 5.51.

Compound **2b** had mp 196–198°; ir (Nujol) 1628 (C=C), 1675, 1715 (C=O), and 2300–3400 cm^{-1} (OH).

Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 62.85; H, 5.26.

2-Methyl-4-oxo-2-cyclopenten-1-ylideneacetic Acid (3b). This compound was prepared from **3a** using the procedure described for **1b**. It was crystallized from water: mp 178–180°; ir (Nujol) 1625 (C=C), 1670, 1690, 1720 (C=O), and 2300–3600 cm^{-1} (OH).

Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 62.95; H, 5.46.

Ethyl 3-Methyl-4-oxo-1-cyclopentaneacetate (4a). A. A solution of **1a** (or **2a**) in anhydrous ethanol was hydrogenated for 20 min over 10% palladium on charcoal at ambient pressure and temperature. The catalyst was filtered and washed with ethanol, and the filtrate was evaporated to yield an oil that was distilled under reduced pressure: bp 74–76° (5 mm); ir (neat) 1735 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.10 (d, $^3J \cong 7.0$ Hz, 3, 3-CH_3), 1.27 (t, 3, $-CH_2CH_3$), 1.60–3.00 (m, 8, cyclopentane protons and $-CH_2COOEt$) and 4.16 ppm (q, 2, $-CH_2CH_3$).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.28; H, 8.81.

B. Esterification of the acid obtained from **6** with anhydrous ethanol and concentrated H_2SO_4 resulted in a product with the same physical characteristics as that obtained from method A.

Ethyl 2-Methyl-4-oxo-1-cyclopentaneacetate (5a). This compound was prepared from **3a** using the procedure described for **4a**. The resulting oil was distilled under reduced pressure: bp 68–72° (6 mm); ir (neat) 1735 cm^{-1} (C=O); nmr (CCl_4) δ 0.92 and 1.12 (2 d, $^3J \cong 6.5$ Hz, 3, 2-CH_3, trans and cis forms), 1.20 (t, 3, $-CH_2CH_3$), 1.50–3.00 (m, 8, cyclopentane protons and $-CH_2COOEt$), and 3.92 ppm (q, 2, $-CH_2CH_3$).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.25; H, 8.68.

3-Methyl-4-oxo-1-cyclopentaneacetic Acid (4b). A. Com-

pound **4a** was refluxed in 4 *N* HCl for 4 hr, and the solution was then evaporated and the resulting oil distilled under reduced pressure: bp 133–134° (0.25 mm); ir ($CHCl_3$) 1712, 1740 (C=O), and 2700–3600 cm^{-1} (OH); nmr ($CDCl_3$) δ 1.11 (d, $^3J \cong 7.0$ Hz, 3, 3-CH_3), 1.70–3.00 (m, 8, cyclopentane protons and $-CH_2COOH$), and 8.58 ppm (s, 1, –OH).

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.45; H, 7.68.

B. A suspension of **6** (4.0 g) in 48% HBr (40 ml) was refluxed for 5 hr. Ammonium chloride was added and the solution was extracted with chloroform to yield 1.5 g of an oil with the same characteristics as that obtained with method A.

2-Methyl-4-oxo-1-cyclopentaneacetic Acid (5b). This compound was obtained from the corresponding ester **5a** using the procedure described for **4b**. The resulting oil was distilled under reduced pressure: bp 135–139° (0.3 mm); ir ($CHCl_3$) 1710, 1740 (C=O), and 2500–3600 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.95 and 1.13 (2 d, $^3J \cong 6.5$ Hz, 3, 2-CH_3, trans and cis forms), 1.50–3.00 (m, 8, cyclopentane protons and $-CH_2COOH$), and 7.75 ppm (s, 1, –OH).

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.62; H, 7.80.

Diethyl 3-Carbethoxy-3-methyl-4-oxo-1-cyclopentanemalonate (6). Diethyl malonate (6.4 g, 0.04 mol) and then ethyl 1-methyl-2-oxo-3-cyclopentene-1-carboxylate[8] (6.8 g, 0.04 mol) were added to a solution of Na (0.23 g, 0.01 mol) in anhydrous ethanol (12 ml) with cooling in a water bath. The reaction mixture was left for 2 hr at room temperature, and then decomposed with water and acidified with acetic acid. Extraction with ether and washing with saturated $NaHCO_3$ solution yielded an oil that was distilled under reduced pressure: bp 142–144° (0.04 mm); yield 9.7 g; ir (neat) 1730, 1740, and 1755 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{24}O_7$: C, 58.52; H, 7.37. Found: C, 58.61; H, 7.49.

Registry No.—**1a**, 51965-77-6; **1b**, 51965-78-7; **2a**, 51965-79-8; **2b**, 51965-80-1; **3a**, 51965-81-2; **3b**, 51965-82-3; **4a**, 51965-83-4; **4b**, 51965-84-5; *cis*-**5a**, 51965-85-6; *trans*-**5a**, 51965-86-7; *cis*-**5b**, 51965-87-8; *trans*-**5b**, 51965-88-9; **6**, 51965-89-0; 4-methyl-4-cyclopentene-1,3-dione, 30268-57-6; triphenylcarbethoxymethylenephosphorane, 1099-45-2; diethyl malonate, 105-53-3; ethyl 1-methyl-2-oxo-3-cyclopentene-1-carboxylate, 51965-90-3.

References and Notes

(1) F. Gualtieri, M. Giannella, C. Melchiorre, and M. Pigini, *J. Med. Chem.*, **17**, 455 (1974).
(2) L. Van Wijnsberghe and M. Vandewalle, *Bull. Soc. Chim. Belg.*, **79**, 699 (1970).
(3) D. B. Denney and S. T. Ross, *J. Org. Chem.*, **27**, 998 (1962).
(4) C. Rüchardt, S. Eichler, and P. Panse, *Angew. Chem.*, **75**, 858 (1963).
(5) S. Sugasawa and H. Matsuo, *Chem. Pharm. Bull.*, **8**, 819 (1960); *Chem. Abstr.*, **55**, 20901a (1961).
(6) G. Fodor and I. Tömösközi, *Tetrahedron Lett.*, 579 (1961).
(7) G. P. Newsoroff and S. Sternhell, *Tetrahedron Lett.*, 6117 (1968).
(8) P. C. Dutta, *J. Indian Chem. Soc.*, **26**, 106 (1949).

Catalytic Reduction. III. Hydrogenation of Unsaturated Compounds over Borohydride Reduced Palladium[1,2]

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Partial reduction of multifunctional unsaturated compounds, using a variety of reagents or catalysts, is of considerable synthetic utility. In all preparatively useful conversions, it is of utmost importance that the reduction be highly selective as to site.

The product from the reaction between sodium borohydride and palladium(II) chloride catalyzes the partial hydrogenation of difunctional unsaturated compounds in a highly selective manner. A partial investigation reveals significant differences in the catalytic activities of this material from other palladium catalysts. In 1962, Polkovnikov, *et al.*,[3] reported that the rates of hydrogen uptake by a series of multifunctional olefins over borohydride reduced palladium were twice those over alkaline-formalin reduced palladium. Brown and Brown[4] in 1966 briefly described the activity of borohydride reduced palladium on some olefinic hydrocarbons.

Borohydride reduced palladium is a very versatile hydrogenation catalyst, as evidenced by the data in Table I. The material effectively and rapidly catalyzes the hydrogenation of carbon–carbon π bonds in a variety of solvents. Neither hydrogenation nor hydrogenolysis of nitrogen or oxygen functions σ bonded to carbon have been observed, with the exception of a slow ring opening of epoxides. Nitrogen–nitrogen and nitrogen–oxygen π bonds were reduced, whereas carbon–nitrogen and carbon–oxygen π bonds were not in the compounds studied. Presumably, the nitrogen–oxygen σ bond does undergo hydrogenolysis.

Experimental Section

Chemicals. All chemicals hydrogenated were reagent grade and were used directly from the bottles without further purification. Hydrogenation media were lower grade solvents. The palladium chloride was from Research Organic Chemicals. All organic chemicals, except the acids, amides, and azobenzene, were analyzed for purity by gas chromatography prior to use.

Catalyst Preparation. To a stirred solution of 0.443 g (2.5 mmol) of palladium chloride in 40 ml of absolute methanol, or other liquid at room temperature, was added 0.19 g (5.0 mmol) of powdered sodium borohydride over a 5–10-min period. Stirring was continued for 20 min, or until the evolution of a gas had ceased. The black reaction product settled rapidly when stirring was stopped.

The catalyst was used directly or stored under a liquid in a stoppered flask. The solvent was changed by decanting and washing twice.

Hydrogenation Procedure. To 2.5 mmol of catalyst and 40 ml of solvent in a Parr hydrogenation flask was added 100 mmol of the material to be hydrogenated. The flask was flushed with hydrogen, connected to a Parr low-pressure hydrogenator, and pressurized to 30 psi. Time and pressure were monitored. The conditions were maintained until no further uptake of hydrogen was observed. Reactions were begun at room temperature and conducted under ambient conditions.

The catalyst settled rapidly upon removing the reaction flask from the hydrogenator. The liquid was decanted for subsequent analysis. Following two washings, the catalyst was ready for reuse.

Product Analysis. All hydrogenation reaction mixtures were analyzed by gas chromatography. Only one product was detected in all cases. It was isolated and its infrared spectrum was taken on a Beckman IR-8. All spectra obtained were compared with those of authentic samples or those in the "Aldrich Library of Infrared Spectra."[5]

Results and Discussion

Applications. The versatility of borohydride reduced palladium as a hydrogenation catalyst can best be seen by a comparison of its activity with those of other catalysts.

No hydrogenolyses of nitrogen and oxygen groups σ bonded to carbon has been detected in alcohols, amides, amines, esters, ethers, or lactones studied. These results are in contrast with many findings that many palladium catalysts do effect hydrogenolysis of allylic and benzylic functions as well as reduction of a wide variety of other functions.[6]

Epoxides are very slowly opened, yielding monoalcohols at the sole products; however, since carbon–carbon π bonds are hydrogenated rapidly, the epoxide group should be unaffected in such a reaction over borohydride reduced palladium. It is of interest to note that the nickel analog did not open epoxides.[7]

Table I
Times of Hydrogenation over Borohydride Reduced Palladium[a]

Reactant[b]	Registry no.	Solvent[c] Methanol	Dimethyl-formamide	Cyclohexane	1,2,-Dime-thoxyethane	Toluene
Allyl alcohol	107-18-6	13	23	51	18	19
Cinnamyl alcohol	104-54-1	27	40	38		
1,4-Butynediol[d]	110-65-6	67				
2-Methyl-3-butyn-2-ol[d]	115-19-5	72	63	46	42	40
Butyl vinyl ether	111-34-2	17	40	20	22	34
Allyl phenyl ether	1746-13-0	16	24	21		
Diallyl ether[d]	557-40-4	44	120	72		
1,2-Epoxybutane[e]	106-88-7	24[f]				
Epoxyethane	75-21-8	26[f]				
α-Methylstyrene	98-83-9	24	40	31	24	34
5-Hexen-2-one	109-49-9	21	35	21	20	32
Mesityl oxide	141-79-7	28	68	38		
Crotonaldehyde	4170-30-3	18	55	36	22	40
Butyraldehyde	123-72-8	*g*	*g*	*g*	*g*	*g*
Cinnamaldehyde	104-55-2	208				
Cinnamic acid	621-82-9	25	58	75	37	67
Crotonic acid	3724-65-0	25				
Maleic anhydride	108-31-6					270
Ethyl cinnamate	103-36-6	27	70	62		
Vinyl acetate	108-05-4	12	30	20	21	28
Acrylamide	79-06-1	20	51			
Methacrylamide	79-39-0	17	52	73		
Allylamine	107-11-9	15	33	22	23	25
Diallylamine[d]	124-02-7	45	55	60		
2-Butenenitrile	4786-20-3	35	28	46		
3-Butenenitrile	109-75-1	10	17	12	9	12
Cinnamonitrile	4360-47-8	80				
2-Acetylbutyrolactone	517-23-7	*g*				
Azobenzene	103-33-3	152	34[h]			
Nitrobenzene[i]	98-95-3	55	147	77	77	104

[a] Time in minutes. [b] 100 mmol, 2.5 mmol of catalyst, 30 psi H_2 initial pressure, ambient temperature. [c] 40 ml. [d] Uptake of 2 equiv of hydrogen. [e] 20 mmol of catalyst. [f] Hours. [g] No hydrogen uptake after 18 hr. [h] 50 mmol of reactant. [i] Uptake of 3 equiv of hydrogen.

Table II
Hydrogenation Times for 5-Hexen-2-one in Various Solvents

Solvent	Time,[a] min: Catalyst prepared and run in	Catalyst prepared in methanol and run in
Methanol	21	21
Dimethylformamide	*b*	35
Cyclohexane	14	21
1,2-Dimethoxyethane	13	20
Toluene	16	32

[a] 100 mmol of reactant, 2.5 mmol of catalyst, 40 ml of solvent. [b] Black material prepared but did not effect reduction in 24 hr.

Rylander[8] has summarized the reduction of carbon–carbon and carbon–nitrogen π bonds over a variety of catalysts. No reduction of the carbonyl function in acids, aldehydes, amides, esters, and lactones was observed over borohydride reduced palladium. The nitrile function was unaffected under normal conditions, by using 20 mmol of catalyst, or by adding Ti(II) to the reaction mixture as suggested by van Tamelen, *et al.*[9] Nitriles[1] and aldehydes[7] yielded primary amines and alcohols, respectively, over borohydride reduced nickel.

Azo compounds undergo hydrogenation and hydrogenolysis simultaneously over Pd/C, yielding amines and anilines.[10] Borohydride reduced palladium catalyst was selective in that it catalyzed only the reduction of the nitrogen–nitrogen π bond in azobenzene. No aniline was detected.

Hydrogenolysis was observed in the reduction of nitrobenzene. Aniline was the only product detected.

Solvents. A wide variety of solvents are available for use with borohydride reduced palladium. Table I lists four aprotic solvents used with the catalyst prepared in methanol—dimethylformamide (DMF), cyclohexane, 1,2-dimethoxyethane (glyme), and toluene. Some differences in reduction times are observed but no differences in products.

Table II lists reduction times of 5-hexen-2-one over borohydride reduced palladium prepared in each of the five solvents. It is interesting to note that DMF was not suitable for use as a catalyst preparation medium but was suitable as a hydrogenation solvent when the catalyst had been prepared in methanol.

Deactivation. As the catalytic material is coarse and settles rapidly upon cessation of agitation, recovery and reuse is a simple matter. In a series of successive reductions of 5-hexen-2-one in methanol, reduction time increased less than 50% after 30 consecutive reactions, from 20 to 29 min. As no effort was made to exclude air from the catalyst (see below), the deactivation may have been due to handling and not catalyst "fatigue."

General. Two other facets of the borohydride reduced palladium catalyst enhance its utility. The material is not pyrophoric as are some hydrogenation catalysts. Apparently, it does not ignite hydrogen in the presence of air, thus eliminating a dangerous element inherent in some other catalysts.

The material was not observed to be sensitive to air under routine handling. In this study, no special effort was made to exclude air from the glassware containing the catalyst. The operations of catalyst preparation, solvent change, product separation from catalyst, and catalyst washing for reuse were done under ambient atmosphere. A purge of air from vessels containing the catalyst was found

to be necessary only when connecting a hydrogenation flask to the Parr apparatus.

Work extending the application of borohydride reduced palladium to heterocyclic and homocyclic rings, halides, and sulfides is currently underway.

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Registry No.—Palladium chloride, 7647-10-1; sodium borohydride, 16940-66-2.

References and Notes

(1) Part II: T. W. Russell, R. C. Hoy, and J. E. Cornelius, *J. Org. Chem.*, **37**, 3552 (1972).
(2) Presented in part at the First Rocky Mountain Regional Meeting of the American Chemical Society, Ft. Collins, Colo., June 1972.
(3) B. D. Polkovnikov, A. A. Balandin, and A. M. Taber, *Dokl. Akad. Nauk SSSR*, **145**, 809 (1962).
(4) H. C. Brown and C. A. Brown, *Tetrahedron, Suppl. 8*, Part I, 149 (1966).
(5) C. Pouchert, Ed., "The Aldrich Library of Infrared Spectra," Aldrich Chemical Co., Milwaukee, Wis., 1970.
(6) See, *inter alia*, S. Mitsui, S. Imaisumi, and Y. Esashi, *Bull. Chem. Soc. Jap.*, **43**, 2143 (1970); S. Nishimura, M. Katagiri, T. Watanabe, and M. Uromota, *ibid.*, **44**, 166 (1971); W. H. Hartung and R. Simonoff, *Org. React.*, **7**, 263 (1953); G. L. Southard, B. R. Zaborowsky, and J. M. Pettee, *J. Amer. Chem. Soc.*, **93**, 3302 (1971).
(7) T. W. Russell and R. C. Hoy, *J. Org. Chem.*, **36**, 2018 (1971).
(8) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press, New York, N. Y., 1967.
(9) E. E. van Tamelen, R. B. Fechter, S. W. Schneller, G. Boche, and R. H. Greely, *J. Amer. Chem. Soc.*, **91**, 1551 (1969).
(10) M. Friefelder, "Practical Catalytic Hydrogenation," Wiley, New York, N. Y., 1971.

Organic Synthesis Using Borane–Methyl Sulfide. II.[1] Reduction of Aromatic Carboxylic Acids in the Presence of Trimethyl Borate

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Borane–methyl sulfide (BMS) is a concentrated and stable source of BH_3 and we have reported its utility in the hydroboration of alkenes.[1] The stability, commercial availability in pure form, and solubility in a wide variety of solvents makes BMS an attractive alternative to borane–tetrahydrofuran (BH_3–THF).

The approximate rates and stoichiometry for the reaction of BH_3–THF with various organic functional groups has been reported by Brown and coworkers.[2] The reduction of carboxylic acids with BH_3–THF was found to yield the corresponding alcohols rapidly and quantitatively under remarkably mild conditions. The obvious potential of this reaction for selective reductions in multifunctional molecules resulted in a detailed study of the scope of this reduction.[3]

As part of our continuing study on the full potential of BMS as a reagent in organic synthesis, we have investigated the use of this reagent for the reduction of carboxylic acids. Initially, the approximate rates of reduction were determined using *n*-hexanoic and benzoic acid as representative carboxylic acids. When *n*-hexanoic acid was added to a solution of BMS in THF, a quantitative yield of 1-hexanol was observed after 4 hr at 20–25°. Reversing the order of addition resulted in an apparent increase in the rate of reduction; *i.e.*, when BMS was added to a solution of *n*-hexanoic acid in THF, a quantitative yield of 1-hexanol was observed after only 30 min at 20–25°. Surprisingly, the reduction of benzoic acid was appreciably slower and gave only a 40–50% yield of benzyl alcohol after 4 hr at 20–25°, irrespective of the order of addition. The use of either ethyl ether or hexane as the solvent in place of THF had essentially no effect upon the rate of reduction of benzoic acid. In all cases, instantaneous hydrogen evolution was observed due to the initial reaction of BH_3 with the acidic hydrogen of the carboxylic acid. The complete results of this preliminary investigation on the BMS reduction of *n*-hexanoic and benzoic acid are summarized in Table I.

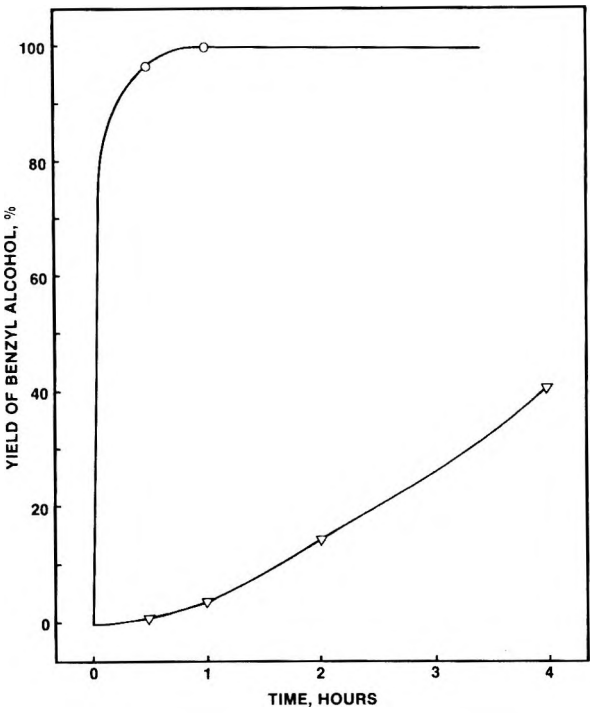

Figure 1. The effect of trimethyl borate on the reduction of benzoic acid (30 mmol) with BMS (33 mmol) at 20–25°: ▽, THF (30 ml) alone; ○, THF (20 ml) plus trimethyl borate (10 ml).

The reduction of both *n*-hexanoic and benzoic acid with BH_3–THF at 25° has been reported to give the corresponding alcohols rapidly and nearly quantitatively.[3] We have duplicated these results.

Although many questions exist concerning the mechanism of the reduction of carboxylic acids with BH_3–THF,[3,4] the first step probably involves the formation of an acyloxyborane (eq 1). The carbonyl group of this acyloxyborane

$$RCOOH + BH_3 \xrightarrow{\text{fast}} RCOB\!\!<\!\!\begin{matrix}O\\ \\ \end{matrix} + H_2 \qquad (1)$$

has been postulated to be "activated" toward attack by borane because of possible resonance interaction of the electron pairs on the acyloxy oxygen with the electron-deficient boron atom.[3] We reasoned that a similar activation might be possible in the presence of excess trimethyl borate as a result of a disproportionation reaction (eq 2).

$$RCOH + B(OCH_3)_3 \text{ (excess)} \longrightarrow RCOB(OCH_3)_2 + CH_3OH \qquad (2)$$

Irrespective of the precise reasons, a pronounced increase in the rate of reduction of benzoic acid with BMS was observed when the reaction was conducted in the presence of excess trimethyl borate, as illustrated in Figure 1.

Triacyloxyboranes are unstable and are known to undergo a dismutation to acid anhydride and an oxybisdiacyloxyborane (eq 3).[4] Pelter has shown that for both *n*-hexanoic

Table I
Reduction of Carboxylic Acids with BMS. Effect of Order of Addition and Solvent

Acid	Solvent	Procedure[a]	Reduction,[b] % 0.5 hr	1.0 hr	2.0 hr	4.0 hr
n-Hexanoic	Tetrahydrofuran	A	59	87	96	100
n-Hexanoic	Tetrahydrofuran	B	100			
Benzoic	Tetrahydrofuran	C	2.6	5.2	13	41
Benzoic	Tetrahydrofuran	B	1.9	3.7	14	48
Benzoic	Ethyl ether	C[c]				54[d]
Benzoic	Ethyl ether	B				53[d]
Benzoic	Hexane	B				43

[a] Procedure A: *n*-hexanoic acid (30 mmol) was added dropwise to BMS (33 mmol) in 30 ml of THF at 0–5° over a 5-min period. The reaction mixture was then allowed to stir in a 20–25° water bath. Procedure B: BMS (33 mmol) was added dropwise to the acid (30 mmol) in 30 ml of solvent with stirring in a 20–25° water bath. Procedure C: benzoic acid (30 mmol) dissolved in 15 ml of solvent was added dropwise to BMS (33 mmol) in 15 ml of solvent at 0–5° over a 5-min period. The reaction mixture was then allowed to stir in a 20–25° water bath. [b] Yield of 1-hexanol or benzyl alcohol by gc analysis using an internal standard. Aliquots of reaction mixture were removed, after stirring for time indicated at 20–25°, and hydrolyzed with water prior to analysis. [c] Benzoic acid dissolved in 25 ml of ethyl ether. [d] Solid material precipitated and the rate could not be followed by removal of a homogeneous aliquot. Entire reaction mixture was hydrolyzed after 4 hr.

Table II
Reduction of Substituted Benzoic Acids with BMS in the Presence of Trimethyl Borate

Benzoic acid, 300 mmol	Registry no.	BMS, mmol	Reduction[a] Time, hr	Temp, °C	Benzyl alcohol[b] yield, %	Registry no.
o-Chloro-	118-91-2	330	4	20–25	94	17849-38-6
o-Bromo-	88-65-3	330	4	20–25	88	18982-54-2
o-Iodo-	88-67-5	330	4	20–25	100	5159-41-1
m-Hydroxy-[c]	99-06-9	440	17	20–25	99	620-24-6
o-Amino-	118-92-3	870	2	Reflux	94	5344-90-1
p-Nitro-	62-23-7	330	3	Reflux	98	619-73-8
4,4′-Sulfonyldi-	2449-35-6	660	4	20–25	99[d]	52123-62-3

[a] The BMS was added dropwise to the substituted benzoic acid dissolved in THF (200 ml) and trimethyl borate (100 ml) at the temperature indicated. When addition of BMS was complete, the reaction mixture was stirred for the time indicated. The temperature necessary and time required for complete reduction were dependent upon both the position and the electron-withdrawing power of the substituent. [b] See Experimental Section for a detailed description of the isolation procedures. [c] The *m*-hydroxybenzoic acid was dissolved in THF and added to the BMS–THF–trimethyl borate. The normal order of addition (see footnote *a*) resulted in the formation of a polymeric precipitate. [d] Isolated product was 4,4′-sulfonyldibenzyl alcohol.

$$2(RCO)_3B \longrightarrow RCOCR + (RCO)_2BOB(OCR)_2 \qquad (3)$$

and benzoic acid, both the acid anhydride and the oxybisborane derivative are satisfactorily reduced with BH_3–THF.[4] A similar investigation using BMS was beyond the scope of the present study.[5] However, interestingly, the reduction of *n*-hexanoic anhydride with BMS gave a quantitative yield of 1-hexanol after just 30 min at 20–25° while benzoic anhydride gave only a 54% yield of benzyl alcohol after 4 hr at 20–25°.

This striking rate enhancement for the BMS reduction of aromatic carboxylic acids in the presence of the trimethyl borate may eventually provide some important insight into the mechanism of borane reduction of carboxylic acids.[5] However, since our interests are primarily directed toward developing the synthetic utility of BMS, this new method was applied to the reduction of a number of functionally substituted benzoic acids on a preparative scale. The results of this study are summarized in Table II.

The wide variety of functional groups that can be tolerated, mild conditions that are required, ease of experimental work-up, and excellent yield and high purity of the isolated product indicate that reduction of benzoic acids with BMS in the presence of trimethyl borate is a useful and convenient method for the preparation of benzyl alcohols.

Experimental Section

All starting materials were used directly as obtained from Aldrich Chemical Co. Since BMS is slowly decomposed by atmospheric moisture, all manipulations of liquid BMS and the reduction reactions were carried out in dry glassware under a nitrogen atmosphere. A detailed description of the techniques necessary in handling air-sensitive solutions has been given elsewhere.[6]

***o*-Chlorobenzyl Alcohol.** A dry, 1-l. flask equipped with a pressure-equalizing addition funnel, magnetic stirring bar, and reflux condenser vented to a bubbler was charged with 47 g (300 mmol) of o-chlorobenzoic acid. After flushing the system with nitrogen, 200 ml of tetrahydrofuran and 100 ml of trimethyl borate were added. The resulting solution was stirred in a 20–25° water bath as 33 ml (~330 mmol) of BMS was added dropwise over a 1-hr period. The hydrogen evolved was vented through the bubbler to a hood. Following the BMS addition, the reaction mixture was stirred for an additional 4 hr at 20–25°. Methanol (100 ml) was then added dropwise over a 1-hr period at 20–25°. After stirring for 0.5 hr, the reaction mixture was concentrated to dryness on a rotary evaporator. The residue was dissolved in 1 l. of ethyl ether and washed with 400 ml of water, 400 ml of saturated aqueous sodium bicarbonate, and 400 ml of saturated aqueous sodium chloride. The ether layer was then dried over anhydrous potassium carbonate, filtered, and concentrated to dryness on a rotary evaporator, giving 40.0 g (93.5%) of *o*-chlorobenzyl alcohol, mp 68–70° (lit.[7] mp 70°), with an ir spectrum identical with that reported for the authentic material.[8] Recrystallization from hexane gave colorless needles, mp 69.5–70.5°.

***o*-Bromobenzyl Alcohol.** The reduction of 56.2 g (300 mmol) of *o*-bromobenzoic acid was carried out using the procedure de-

scribed for o-chlorobenzoic acid. Isolation by the same procedure gave 49 g (88%) of o-bromobenzyl alcohol, mp 78–80° (lit.[9] mp 79.5–80°), with ir and nmr spectra in accordance with the assigned structure. Recrystallization from hexane gave 46.4 g of off-white needles, mp 79–80°.

o-**Iodobenzyl Alcohol.** The reduction of 74.5 g (300 mmol) of o-iodobenzoic acid was carried out using the procedure described for o-chlorobenzoic acid. Following methanolysis, the reaction mixture was concentrated to dryness on a rotary evaporator. The residue contained traces of boron as shown by a flame test. This boron-containing impurity was easily removed by dissolving the solid in 150 ml of methanol and concentrating to dryness on a rotary evaporator.[10] Further drying in a vacuum oven gave 70 g (100%) of o-iodobenzyl alcohol, mp 88–89° (lit.[11] mp 91°), with ir and nmr spectra in accordance with the assigned structure.

m-**Hydroxybenzyl Alcohol.** A dry, 1-l. flask equipped with a pressure-equalizing addition funnel, magnetic stirring bar, and reflux condenser was flushed with nitrogen and charged with 100 ml of THF, 100 ml of trimethyl borate, and 44 ml (440 mmol) of BMS. This solution was then stirred in a 20–25° water bath as 41.4 g (300 mmol) of *m*-hydroxybenzoic acid dissolved in 150 ml of THF was added dropwise over a 1-hr period.[12] Instantaneous hydrogen evolution occurred throughout the addition. After stirring for 17 hr at 20–25°, methanol (200 ml) was added dropwise and the solution was filtered *via* nitrogen pressure through a fritted glass funnel charged with diatomaceous earth to remove a minor amount of suspended solid. The clear, light-yellow filtrate was concentrated to dryness on the rotary evaporator, giving a brown oil. This oil was dissolved in 100 ml of methanol, concentrated to dryness, redissolved in 100 ml of methanol, and again concentrated to dryness, giving 36.9 g (99%) of *m*-hydroxybenzyl alcohol as a brown oil, which was free of boron-containing impurities by a flame test. The oil rapidly crystallized at room temperature, giving tan crystals, mp 69–71° (lit.[13] mp 73°), with an ir spectrum identical with that reported for the authentic material.[14]

o-**Aminobenzyl Alcohol.** A dry, 1-l. flask equipped as usual was charged with 41 g (300 mmol) of anthranilic acid, 200 ml of THF, and 40 ml of trimethyl borate. The resulting solution was heated at reflux as 87 ml (870 mmol) of BMS was added dropwise over a 1-hr period. Vigorous hydrogen evolution occurred during the BMS addition. The reaction mixture was maintained at reflux with stirring for an additional 2 hr. After cooling to 20–25°, the light-yellow supernate was removed *via* nitrogen pressure, leaving behind a small amount of black precipitate. Methanol (280 ml) was then added dropwise over a 1-hr period at 20–25°. The reaction mixture was then heated to a gentle reflux for a few minutes with stirring and concentrated on a rotary evaporator to a red oil. This oil was dissolved in 150 ml of ethyl ether and treated with 200 ml of 6 *N* aqueous sodium hydroxide. After heating at reflux for 2 hr and then cooling to 20–25°, the organic layer was removed and the aqueous layer was saturated with potassium carbonate and extracted with ethyl ether (3 × 50 ml). The combined organic layers were dried over anhydrous potassium carbonate, filtered, and concentrated to dryness on a rotary evaporator. Further drying in a vacuum oven gave 34.6 g (94%) of o-aminobenzyl alcohol as a light-tan, crystalline solid, mp 81–82° (lit.[13] mp 84°), with an ir spectrum identical with that reported for the authentic material.[15]

p-**Nitrobenzyl Alcohol.** The reduction of 50.2 g (300 mmol) of *p*-nitrobenzoic acid was carried out using the procedure described for o-chlorobenzoic acid. However, the THF solution of the acid and trimethyl borate was heated at reflux as 33 ml (330 mmol) of BMS was added dropwise over a 1-hr period. Vigorous hydrogen evolution occurred during the BMS addition. The reaction mixture was then heated at reflux with stirring for an additional 3 hr. Methanolysis and isolation of the product, using the procedure described for o-iodobenzyl alcohol, gave 48 g (>100% yield) of a light-yellow, crystalline solid. This solid was washed with hot hexane, filtered, and dried in a vacuum oven, giving 44.8 g (97.6%) of *p*-nitrobenzyl alcohol, mp 93–94.5° (lit.[16] mp 93°), with an ir spectrum identical with that reported for the authentic material.[17]

4,4′-Sulfonyldibenzyl Alcohol. The reduction of 91.8 g (300 mmol) of 4,4′-sulfonyldibenzoic acid with 66 ml (660 mmol) of BMS was carried out using the procedure described for o-chlorobenzoic acid. Methanolysis and isolation of the product, using the procedure described for *m*-hydroxybenzyl alcohol, gave 83.3 g (99%) of 4,4′-sulfonyldibenzyl alcohol: mp 133–135°; ir (mineral oil mull) 3401 (s), 3311 (s), 2933 (vs), 2865 (vs), 1597 (w), 1458 (m), 1412 (w), 1376 (w), 1309 (m), 1290 (m), 1267 (w), 1202 (w), 1151 (s), 1103 (m), 1070 (w), 1030 (s), 1012 (m), 986 (w); nmr ($CDCl_3$ plus DMSO-d_6) δ 4.58 (s, 4 H), 5.11 (s, 2 H), 7.47 (d, 4 H), 7.76 (d, 4 H).

Registry No.—BMS, 13292-87-0; trimethyl borate, 121-43-7; hexanoic acid, 142-62-1; benzoic acid, 65-85-0.

References and Notes

(1) Part I: C. F. Lane, *J. Org. Chem.*, **39**, 1437 (1974).
(2) (a) For a recent, excellent review of organic reductions using boron hydrides, see H. C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1972, pp 209–251; (b) for a summary of organic reductions using BH_3–THF, see H. C. Brown, P. Heim, and N. M. Yoon, *J. Amer. Chem. Soc.*, **92**, 1637 (1970).
(3) N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.*, **38**, 2786 (1973).
(4) A. Pelter, M. G. Hutchings, T. E. Levitt, and K. Smith, *Chem. Commun.*, 347 (1970).
(5) A detailed mechanistic study of the reduction of carboxylic acids with both BH_3–THF and BMS is currently in progress at Purdue University: H. C. Brown and T. P. Stocky, private communication, 1973.
(6) The bulletin "Handling Air-Sensitive Solutions" is available upon request from Aldrich Chemical Co., Milwaukee, Wis.
(7) J. B. Shoesmith and R. H. Slater, *J. Chem. Soc.*, 218 (1926).
(8) C. J. Pouchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Co., Milwaukee, Wis., 1970, p 512f.
(9) R. C. Fuson and B. Freedman, *J. Org. Chem.*, **23**, 1161 (1958).
(10) This simple isolation procedure failed to remove boron-containing residues completely in the preparation of o-chlorobenzyl alcohol and *o*-bromobenzyl alcohol. In these cases, the washing with aqueous bicarbonate was necessary and may have been due to impurities present in the starting benzoic acid.
(11) R. G. R. Bacon and W. S. Lindsay, *J. Chem. Soc.*, 1375 (1958).
(12) This order of addition was necessary because when BMS was added to a solution of the acid and trimethyl borate in THF an insoluble polymeric intermediate formed.
(13) C. Mettler, *Chem. Ber.*, **38**, 1751 (1905).
(14) Reference 8, p 513a.
(15) Reference 8, p 535f.
(16) B. M. Bogoslovskii and Z. S. Kazakova, *Zh. Prikl. Khim.*, **21**, 1183 (1948); *Chem. Abstr.*, **43**, 6182a (1949).
(17) Reference 8, p 600d.

O-Benzylmonoperoxycarbonic Acid. A New Oxygenating Reagent[1]

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Although the peroxycarboxylic acids are a well known and widely used group of oxygenating agents,[3-5] the corresponding peroxycarbonic acids (*e.g.*, **2**) have been little studied. The parent member of this family, monoperoxycarbonic acid (H_2CO_4) has been suggested as a transient intermediate[6] and a number of its metal salts have been reported.[7] Dialkyl esters of monoperoxycarbonic acid ($ROCO_3R'$) have been prepared.[8]

However, there seems to be no mention of an *O*-alkylmonoperoxycarbonic acid ($ROCO_3H$) in the literature, although such compounds would be expected to be reasonably stable and readily prepared by perhydrolysis of the well-known dialkyl peroxydicarbonates.[8,9] It is possible that the active oxidizing agents formed by the reaction of hydrogen peroxide and aryl isocyanates are, in fact, *N*-arylperoxycarbamic acids ($ArNHCO_3H$), nitrogen analogs of *O*-alkylperoxycarbonic acids.[10,11]

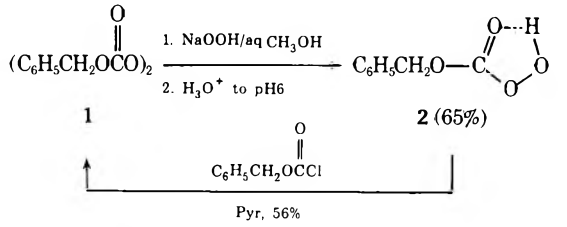
We have prepared *O*-benzylmonoperoxycarbonic acid (**2**) by perhydrolysis[12] of dibenzyl peroxydicarbonate (**1**),[8] a crystalline, relatively stable peroxydicarbonate which is easily obtained from the reaction of benzyl chloroformate and alkaline hydrogen peroxide.[8,13]

The structure of **2** is based upon its reconversion to dibenzyl peroxydicarbonate (**1**) upon reaction with benzyl chloroformate in pyridine, its high peroxide content (>97% of theoretical amount by iodometric titration), its acidic

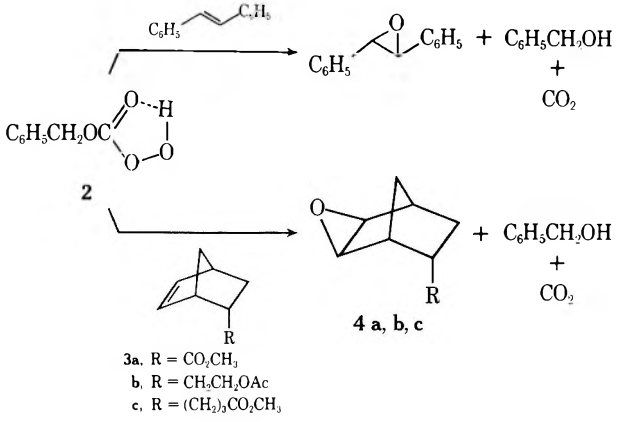
Table I
Comparison of Rates of Epoxidation of *trans*-Stilbene by *O*-Benzylmonoperoxycarbonic Acid (2) and Selected Aromatic Peroxycarboxylic Acids, with the Acidity of the Parent Acid

Peroxy acid	$10^4 k_2^{25°}$, l./mol sec[a]	k_{rel}	pK_a of parent acid[b]	−Log k_2/pK_a
O-Benzylmonoperoxycarbonic acid (**2**)	7.12 ± 0.04[c]	1.7	3.76[d]	0.84
Peroxybenzoic acid	4.27[e]	(1.0)	4.21	0.80
m-Chloroperoxybenzoic acid	15.0[e]	3.5	3.82	0.74

[a] In benzene solution. [b] Data from ref 15. [c] Average of three separate runs with measured rate constants ($10^4 k_2$) 6.67, 7.00, and 7.68. Error indicates deviation of individual rate constants from the average. [d] pK_a of carbonic acid. [e] Data from ref 14.



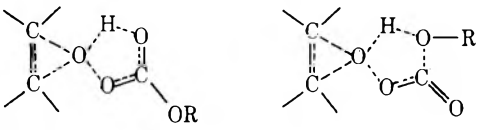
character (extraction of the alkaline reaction mixture prior to acidification affords only a small amount of recovered **1**), and its spectral properties [ir (film) ν_{max} 3700–2700 and 1775 (C=O, br) cm^{-1}; nmr (CCl_4, −22°) δ 12.17 (s, 1 H, OCO_3H), 7.25 (s, 5 H, Ar H), and 5.08 (s, 2 H, CH_2)]. *O*-Benzylmonoperoxycarbonic acid (**2**) reacts with olefins to afford moderate to good yields of epoxides and the by-products benzyl alcohol and carbon dioxide (assumed).



O-Benzylmonoperoxycarbonic acid (**2**) could be stored in the cold with relatively little decomposition, *i.e.*, loss in peroxide content according to iodometric titration [approximate decomposition rates: ~4%/week at −20° (neat); ~7%/week at 1° (benzene solution)]. The rate of decomposition at room temperature is appreciable (~50% loss of peroxide content after 2½ days at 23° in benzene solution).

Since the log of the rate of olefin epoxidation (k_2) of various peroxybenzoic acids correlates rather precisely with the σ constant (pK_a) of the corresponding normal acid,[14] it was of interest to determine the rate of epoxidation with *O*-benzylmonoperoxycarbonic acid (**2**). The rate of epoxidation of stilbene with **2** (0.069 *M* in benzene at 25 ± 0.5°) was followed to ~60% completion by iodometric titration giving a second-order rate constant $k_2 = 7.1 \pm 0.4 \times 10^{-4}$ l./mol sec (average of three runs). Thus, *O*-benzylmonoperoxycarbonic acid (**2**) is a more reactive epoxidizing reagent toward *trans*-stilbene than peroxybenzoic acid but is less reactive than *m*-chloroperoxybenzoic acid (see Table I). Although the acidity of the parent acid, *O*-benzylcarbonic acid, is unknown, it should be approximated by the acidity of carbonic acid (pK_a = 3.76).[15] The data in Table I indicate that the epoxidative reactivity of **2** toward *trans*-stilbene is rather close to, though apparently somewhat less than, that predicted on the basis of the acidity of carbonic acid.

Two alternative transition states (A and B) for olefin epoxidation with an *O*-alkylmonoperoxycarbonic acid may be



considered. The first (A), analogous to that usually suggested for epoxidation with peroxycarboxylic acids,[3,4,16] would initially form an *O*-alkylcarbonic acid which would subsequently collapse to the alcohol and carbon dioxide. The second (B) suggests that epoxidation and decarboxylation may be concerted. Since the epoxidative reactivity of **2** corresponds rather closely to that expected on the basis of the acidity of carbonic acid, we assume that the transition state very likely resembles that for peroxycarboxylic acid epoxidation (A).

O-Benzylmonoperoxycarbonic acid (**2**), as well as other peroxycarbonic acids, should provide a useful alternative reagent to peroxycarboxylic acids for epoxidation and other oxygen transfer reactions. This type of peroxy acid has the potential advantage that the reaction medium remains essentially neutral during the oxidation reaction.[17] Side reactions are sometimes catalyzed by the carboxylic acid formed in the reactions of peroxycarboxylic acids.[3b,4,19] However, for slow reactions self-decomposition of the reagent may become competitive. It is also necessary to be able to separate the desired product from benzyl alcohol.

Experimental Section[20]

***O*-Benzylmonoperoxycarbonic Acid (2).** Dibenzylperoxydicarbonate (**1**, 5.01 g, 16.6 mmol)[8,13] was suspended in a solution containing 30% hydrogen peroxide (8.03 ml, 75.0 mmol) and magnesium sulfate (heptahydrate, 0.22 g, 0.83 mmol) in alkaline, aqueous methanol [3.00 g (75.0 mmol) of sodium hydroxide, 75 ml of methanol, and 67 ml of distilled water].[12] The mixture was stirred vigorously for 10 min, diluted with 80 ml of cold distilled water, and extracted with cold chloroform (2 × 50 ml) to remove neutral products (<1% recovery of dibenzyl peroxydicarbonate by iodometric titration[21]). Acidification with 10% sulfuric acid (to ~pH 6) of the aqueous reaction solution and extraction with cold benzene (3 × 50 ml) gave the peroxycarbonic acid **2** in 65% yield (determined by iodometric titration) in benzene solution.

Evaporation (*in vacuo* without heat) of a 5.0-ml aliquot of the cold benzene solution (0.129 *M* in peroxycarbonic acid **2**) gave a clear, colorless oil (111 mg): ir (film) ν_{max} 3700–2700, 1775 (br) cm^{-1}; nmr (100 MHz, CCl_4, −22°) δ 12.17 (s, 1 H, $-OCO_3H$), 7.25 (s, 5 H, Ar H), 5.08 (s, 2 H, CH_2); iodometric titration showed the oil product to contain >97% theoretical peroxide content for peroxycarbonic acid **2**.

In a separate experiment, benzyl chloroformate (0.6100 g, 3.58 mmol) and pyridine (0.2830 g, 3.58 mmol) were placed in a flask and cooled to 5–10°.[22] A benzene solution of peroxycarbonic acid **2** (75 ml of a 4.76×10^{-2} *M* solution; 0.6015 g, 3.58 mmol of **2**) was added to the flask, and the resulting solution was stirred for 5 min and placed in a refrigerator (+1°) overnight. The solution was then washed with distilled water (3 × 50 ml), dried ($MgSO_4$), and evaporated to yield 1.268 g of an oily, white precipitate (~100% peroxide content, according to initial peroxycarbonic acid titer). Recrystallization from acetone–water (−20°) gave dibenzyl peroxydicarbonate **1** in 56% yield as powdery, white crystals: mp 99–100° with

gas evolution (lit.[8] mp 101–102° dec); nmr (CCl_4) δ (CH_2) 7.37 (s, 10 H, Ar H), 5.30 (s, 4 H, CH_2); peroxide content 97% of theoretical amount for 1 by iodometric titration.

The peroxycarbonic acid 2 was stored at −20°, with only 4% decomposition after 7 days (by titration). The peroxycarbonic acid was determined (by titration) to decompose at a rate of ~7% per week in benzene solution when kept cold (+1°). The half-life of peroxycarbonic acid 2 in benzene solution at room temperature (~23°) was found, in two independent determinations, to be ~61 hr, with an average rate of decomposition of ~0.09 mg/hr.

Epoxidation of *trans*-Stilbene with *O*-Benzylmonoperoxycarbonic Acid (2). A. Preparative Run.[14] *trans*-Stilbene (~4.4 mmol) was added to a solution of the peroxycarbonic acid 2 (~4.8 mmol) in benzene (~80 ml). The reaction mixture was stirred to dissolve the olefin and then allowed to stand at room temperature (23–24°) for 2–3 days. The benzene solution was then extracted with 5% sodium bicarbonate (2 × 50 ml), washed with distilled water (1 × 50 ml), dried ($MgSO_4$), and evaporated to yield a mixture of benzyl alcohol and *trans*-stilbene epoxide. The solid epoxide was obtained in highest yield (85%) by column chromatography (silica gel, ether–hexane) of the product mixture (benzyl alcohol was also obtained in 66% recovery, based on the initial concentration of 2 in the solution; four other unidentified minor products were obtained, accounting for 11% of the weight of crude product placed on the column). Recrystallization from absolute ethanol gave white crystals: mp 68–69° (lit.[14] mp 69°); ir ($CHCl_3$) 870 cm^{-1}; δ (CCl_4) 7.25 (s, 10 H, Ar H), 3.70 (s, 2 H, epoxide H). Direct recrystallization of the crude product mixture from absolute ethanol gave the epoxide in ~75% yield.

B. Kinetics.[14] A benzene solution of the peroxycarbonic acid 2 (~6.9×10^{-2} *M*) was brought to temperature equilibrium (25 ± 0.5°) in a water bath. *trans*-Stilbene was then added with stirring to make the solution initially ~5.5×10^{-2} *M* in olefin. Aliquots were removed at set intervals and titrated iodometrically, thus following the reaction from 0–60% completion. The rate constant was determined from data obtained in three independent runs, assuming second-order kinetics. After correcting for the decomposition of peroxycarbonic acid 2 in benzene solution at room temperature, the values obtained (k_2 = 6.67×10^{-4}, 7.68×10^{-4}, and 7.00×10^{-4} l. mol^{-1} sec^{-1}) gave an average rate constant of k_2 = 7.12×10^{-4} l. mol^{-1} sec^{-1}.

Epoxidation of Substituted Norbornenes (3a, 3b, and 3c) with *O*-Benzylmonoperoxycarbonic Acid (2).[23] A typical procedure for the epoxidation of the norbornenes **3a, 3b,** and **3c**[23] is as follows.

The olefin was added to a cooled (0–5°) benzene solution containing a 25% excess of peroxycarbonic acid 2 (~4.5×10^{-2} *M* in 2). The homogenous solution was then allowed to warm to room temperature and stand for an average of 3 days. The solution was then extracted with 5% sodium bicarbonate solution, washed with distilled water, dried ($MgSO_4$), and evaporated *in vacuo* to yield a mixture of benzyl alcohol and the epoxide.

Analysis of the crude product mixture by glpc (column *A*, 155–195°) showed the yields of epoxides to be ~70% in the cases of norbornene analogs **3a** and **3c**. Preparative glpc (column B, 155–195°) gave the pure epoxides (**4a** and **4c**) in 39% average yield. Column chromatography (silica gel, ether–hexane) of the crude product mixture obtained with the acetate **3b** gave the pure epoxide (**4b**) in 53% yield.

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Registry No.—**1,** 2144-45-8; **2,** 52123-51-0; **3a,** 6203-08-3; **3b,** 52123-52-1; **3c,** 52123-53-2; *trans*-stilbene, 103-30-0.

References and Notes

(1) Taken in part from Ph.D. thesis of J. W. W., University of Illinois, 1973.
(2) A. P. Sloan Foundation Fellow, 1971–1973.
(3) D. Swern, Ed., "Organic Peroxides," Wiley-Interscience, New York, N. Y.: (a) Vol. I, 1970, Chapters VI and VII; (b) Vol. II, 197771, Chapter V.
(4) H. O. House, "Modern Synthetic Reactions," Second ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 6.
(5) J. B. Lee and B. C. Uff, *Quart. Rev.*, **21,** 429 (1967).
(6) (a) P. Günther and L. Holzapfel, *Z. Phys. Chem.*, **49,** 303 (1941). (b) K. Schmidt, *Nature,* **187,** 931 (1960). (c) A. Vaskelis and A. Prokopcikas, *Lietuvos TSR Mokslu Akad. Darbai, Ser. B.*, 75 (1963); *Chem. Abstr.*, **60,** 10215 (1964).
(7) (a) J. R. Partington and A. H. Fatballah, *J. Chem. Soc.*, 1934 (1950); (b) M. Gutierrez de Celis and J. R. Masaquer, *Anal. Reale Soc. Espan. Fis. Quim. (Madrid)*, **51B,** 693 (1955); *Chem. Abstr.* **50,** 6237 (1956).
(8) F. Strain, W. E. Bissinger, W. R. Dial, H. Rudoff, B. J. DeWitt, H. C. Stevens, and J. H. Langston, *J. Amer. Chem. Soc.*, **72,** 1254 (1950).
(9) Ref 3: Vol. I, p 68; Vol. II, pp 863–867.
(10) N. Matsumura, N. Sonoda, and S. Tsutsumi, *Tetrahedron Lett.*, 2029 (1970).
(11) Professor J. Rebek, Jr. (Department of Chemistry, University of California, Los Angeles) has kindly informed us that a number of other peroxycarbamic acids have been prepared in his laboratories.
(12) Y. Ogata and Y. Sawaki, *Tetrahedron,* **23,** 3327 (1967); R. N. MacDonald, R. N. Steppel, and J. E. Dorsey, *Org. Syn.*, **50,** 15 (1970).
(13) Dibenzyl peroxydicarbonate is also commercially available from the Pennwalt Co., Lucidol Division.
(14) B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955).
(15) "Lange's Handbook of Chemistry," Eleventh ed., J. A. Dean, Ed., McGraw-Hill, New York, N. Y., 1973.
(16) P. D. Bartlett, *Rec. Chem. Progr.*, **11,** 47 (1950).
(17) Peroxycarboxylic acids have pK_a values in the range of 7–8.[3,18] It is assumed that the lifetime of the intermediate *O*-benzylcarbonic acid is too short to lower the effective pH of the medium appreciably.
(18) A. J. Everett and G. J. Minkoff, *Trans Faraday Soc.*, **49,** 410 (1953).
(19) A. Rosowsky in "Heterocyclic Compounds," Vol. 19, A. Weissberger, Ed., part 1, Chapter 1.
(20) Melting points were taken in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Spectra were recorded with the following instruments: Perkin-Elmer Model 137 or 237 B ir spectrophotometers; Varian Associates Model A-60A or HA-100 nmr spectrophotometers. All nmr spectra were determined in deuterated chloroform unless otherwise stated and chemical shifts are reported as δ values using tetramethylsilane as internal standard. Microanalyses were performed in the University of Illinois Microanalytical Laboratory. Gas–liquid phase chromatography (glpc) was performed on a Wilkens Aerograph A-90-P3 instrument using one of the following columns: A (5 ft × ¼ in., 15% FFAP on 60/80 mesh Chromosorb W AW/DMCS) or B (5 ft × ⅜ in., 15% FFAP on 60/80 mesh Chromosorb W AW/DMCS). Purifications by column chromatography were carried out with Brinkman 0.02–0.5 mm silica gel eluting with the solvent(s) indicated.
(21) V. R. Kokatnur and M. Jelling, *J. Amer. Chem. Soc.*, **63,** 1432 (1941).
(22) W. Gerrard and A. M. Thrush, *J. Chem. Soc.*, 2117 (1953).
(23) For the methods of preparation of **3a, 3b,** and **3c** and characterization of the corresponding epoxides **4a, 4b,** and **4c,** see the Ph.D. thesis of J. W. W., University of Illinois, Urbana, Ill., 1973.

Rearrangement of the *o*-Tolyl Radical to the Benzyl Radical. A CIDNP Study

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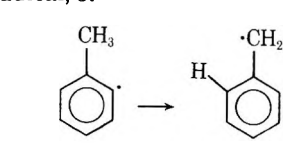
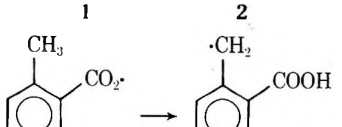
The observation of CIDNP signals in the nmr spectra of solutions in which free-radical reactions occur provides an extremely effective means of probing the mechanisms of such reactions.[1] Since the discovery of CIDNP in the thermolysis of benzoyl peroxide by Bargon and Fischer[2] there have been numerous CIDNP studies of aroyl peroxides.[3] We report here the use of CIDNP techniques to detect the rearrangement of the *o*-tolyl radical, **1,** to the benzyl radical, **2,** during the thermolysis of *o*-toluyl peroxide, **3.** In addition, we have confirmed the postulated[4] intramolecular rearrangement of the *o*-toluoyloxy radical, **4,** to the *o*-carboxybenzyl radical, **5.**



1 2



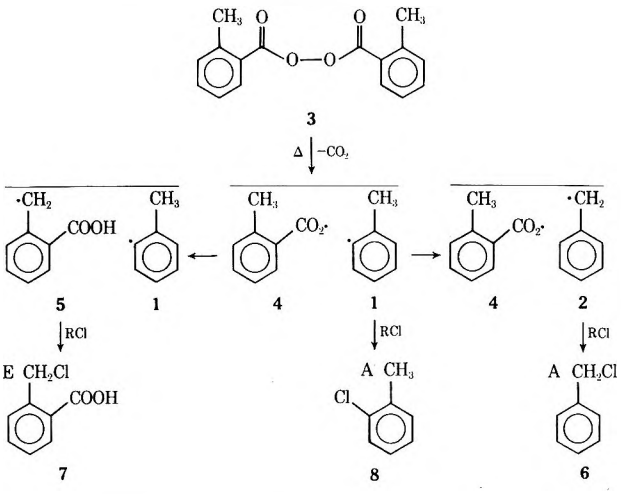
4 5

Prior to the discovery of CIDNP, a thorough investigation of the thermal decomposition of **3** was reported by Greene and coworkers.[4] These authors obtained products resulting from **5** and proposed that rearrangement of **4** to **5** occurs. However, products resulting from **2** were not obtained in sufficient quantity to allow their detection.

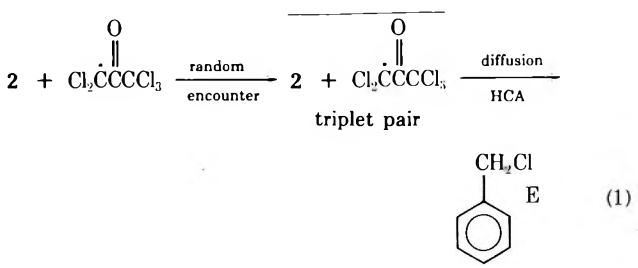
If rearrangement to **1** to **2** generates **2** as a member of a radical pair, the high sensitivity of the CIDNP technique should permit the detection of polarized products resulting from **2**. Accordingly, the nmr spectrum recorded during the 115° thermolysis of **3** in hexachloroacetone (HCA) showed a strong enhanced absorption for the methylene protons of benzyl chloride, **6**. The benzyl protons of α-chlorotoluic acid, **7**, exhibited emission while the methyl protons of o-chlorotoluene showed enhanced absorption.

These CIDNP results along with their mechanistic interpretation are shown in Scheme I. The formation of polarized benzyl chloride is evidence that rearrangement of **1** to **2** is occurring within the solvent cage. Initial cleavage of the O–O bond in **3**, followed by decarboxylation, would produce the radical pair (**1** + **4**). Extensive studies on the analogous benzoyl peroxide system have confirmed that this process produces a singlet radical pair.[3] Rearrangement of **1** to **2** now yields the radical pair (**2** + **4**) also in the singlet state. Hyperfine splitting (hfs) by the methylene protons in **2** should be negative, and the oxygen centered radical **4** should have the higher g value. Hence, enhanced absorption is predicted[5] for the benzyl protons of **6** which arises by diffusion of **2** from the singlet radical pair (**2** + **4**).

Scheme I



An alternative mechanism for the formation of benzyl radicals is *via* hydrogen abstraction from a small amount of toluene produced in the reaction. Benzyl chloride, resulting from **2** generated in this manner, should exhibit polarization only if a random encounter between **2** and a solvent radical (S·) has occurred. Such a random encounter will yield the triplet radical pair (**2** + S·). Diffusion of **2** from this triplet radical pair followed by chlorine abstraction (eq 1) would yield **6** whose benzyl protons would show emission rather enhanced absorption.



(1)

In order to test the hypothesis outlined in eq 1, benzyl radicals must be generated in HCA and the polarization of benzyl chloride measured. We have done this by thermally decomposing benzoyl peroxide with a small amount of toluene in HCA solvent. This reaction produces **6** which exhibits strong emission as predicted by eq 1. This experiment shows that the enhanced absorption observed for the benzyl protons of **6** when o-toluoyl peroxide is decomposed in HCA cannot be the result of a random encounter between **2** and S·. Such encounters ultimately result in emission rather than enhanced absorption for the methylene protons of **6**. The polarization in **6** must result from the singlet radical pair (**2** + **4**) which is formed by rearrangement of **1** to **2**.

The stability of the benzyl radical as compared to a phenyl radical provides the thermodynamic driving force for this rearrangement. An estimate of the ΔH for the rearrangement, using bond dissociation energies for aromatic and benzyl C–H bonds,[6] yields −26.5 kcal/mol. Although this rearrangement is thermodynamically favorable, geometric constraints on the transition state undoubtedly decrease its importance relative to intermolecular reactions of **1**. That this rearrangement is a minor pathway is evidenced by the fact that only a trace of benzyl chloride could be detected by nmr at the conclusion of the reaction. The assignment of enhanced absorption to the methylene protons of **6** was confirmed by adding a small amount of benzyl chloride to a hexachloroacetone solution of **3** before heating. Thermolysis of this sample showed the methylene proton singlet of **6** grow in intensity during the reation and diminish at its conclusion. Benzyl chloride was also detected by gas chromatography.

Greene and coworkers[4] have presented convincing evidence for the rearrangement of **4** to **5**. When they carried out the thermolysis of **3** in carbon tetrachloride, a major product was o-(β,β,β-trichloroethyl)benzoic acid. In the present study, the emission for the benzyl protons of **7** indicates that this rearrangement produces a radical pair consisting of **1** and **5**. If the g factor of **5** is greater than that of **1**, diffusion of **5** from the radical pair followed by chlorine abstraction would result in the observed emission. It is likely that the Δg is in this direction as INDO calculations[7] predict a small amount of unpaired spin density on the oxygens of **5**. Alternately, the polarization in **7** may result from a random encounter of **5** with a solvent radical in the manner outlined in eq 1 for the benzyl radical. Since this process is also expected to result in emission for the benzyl protons in **7**, it cannot be ruled out at this time.

A final point of interest is that the methyl protons of o-chlorotoluene, the major product, show enhanced absorption. This result requires that there be hyperfine splitting (hfs) by the methyl protons in **1** and that the sign of this hfs be negative. An esr study of **1** has confirmed that there is hfs by the methyl protons of less than 3 G.[8] We have carried out INDO molecular orbital calculations[7] on **1** which predict a value of −1 G for this hfs.

Experimental Section

The o-toluoyl peroxide was prepared according to the procedure of Greene and coworkers.[4] All nmr spectra were recorded with a Varian A-60 spectrometer.

CIDNP Studies of 3. An nmr sample tube containing a 0.56 M solution of **3** in HCA was placed in the preheated (115°) probe of the spectrometer. Consecutive spectra were then recorded at a sweep time of 100 sec. After completion of the reaction, a small amount of toluene was added to the hot solution as an internal standard. The positions of the CIDNP signals are reported in ppm downfield from the methyl signals in toluene at 115°. The benzyl protons of **6** exhibited enhanced absorption at 2.27 ppm, the benzyl protons of **7** showed emission at 2.75 ppm, and the methyl peak of o-chlorotoluene exhibited enhanced absorption at 0.05 ppm.

The identity of the above signals was established by adding a small amount of each compound to the hot solution and observing the signal grow in intensity. Benzyl chloride and o-chlorotoluene were also identified by their gc retention times on a 20% SE-30 on 40/60 Chromosorb W column. In addition to the above CIDNP signals, strong polarizations in the aromatic proton region and weak polarizations in the aryl methyl region were observed.

Thermolysis of Benzoyl Peroxide with Toluene in HCA Solution. CIDNP from an HCA solution of 60 mg of benzoyl peroxide and 25 mg of toluene was measured at 115° in the manner described above. The methylene protons of **6** exhibited strong emission signals in this sample.

Registry No.—**1**, 22904-44-5; **2**, 2154-56-5.

References and Notes

(1) H. R. Ward, *Accounts Chem. Res.*, **5**, 18 (1972).
(2) J. Bargon, H. Fischer, and U. Johnsen, *Z. Naturforsch.*, **22a**, 1551 (1967).
(3) H. Fischer in "Chemically Induced Magnetic Polarization," A. R. Lepley and G. L. Closs, Ed., Wiley-Interscience, New York, N. Y., 1973, pp 197–222.
(4) F. D. Greene, G. R. Van Norman, J. C. Cantrill, and R. D. Gilliom, *J. Org. Chem.*, **25**, 1970 (1960).
(5) Rules for predicting CIDNP spectra have been summarized by R. Kaptein, *Chem. Commun.*, 732 (1971).
(6) D. M. Golden and S. W. Benson, *Chem. Rev.*, **69**, 125 (1969).
(7) The INDO molecular orbital calculations [J. A. Pople, D. L. Beveridge, and P. A. Dobosh, *J. Chem. Phys.*, **47**, 2026 (1967)] were performed using the program written by P. A. Dobosh, "CNDO and INDO Molecular Orbital Program," Program 141, Quantum Chemistry Program Exchange, Indiana University.
(8) S. Nagai, S. Ohnishi, and I. Nitta, *J. Phys. Chem.*, **73**, 2438 (1969). (1969).

Ring Opening of Indene Oxide with Benzoic Acid[1]

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A stereochemical study on the ring opening of indene oxide with benzoic acid was recently reported by Gagis, Fusco, and Benedict.[2] We find that in addition to *trans*-1,2-indandiol, *cis*-1,2-indandiol[3] is also formed on hydrolysis of the hydroxy benzoates initially produced. A third product, not hitherto reported in this context, is 2-indanone, which is formed concurrently with the hydroxy benzoates and can be isolated directly from the reaction mixture.[4] This parallels our findings for the reaction of indene oxide with formic acid in chloroform where the cis and trans esters together with 2-indanone are formed in a ratio of about 2:2:1.[5] The least equivocal evidence for the simultaneous formation of the cis and trans benzoates we think lies in the appearance of the nmr doublets at δ 6.32 and 6.17 in the raw reaction mixture. These must almost certainly be assigned to the C_1 proton in the benzoates from the analysis of analogous compounds by Rosen, *et al.*[6]

These results give credence to a carbonium ion or ion-pair mechanism in which positive charge is localized on the benzylic carbon. The formation of both cis and trans benzoates can be associated with the susceptibility of such a benzylic carbon to attack on either side of the ring. The formation of 2-indanone may be attributed to hydride ion transfer.

Our work supports that of Brewster,[7] and of Berti and Bottari.[8]

Experimental Section

All melting points were taken on a Mel-Temp apparatus and are uncorrected. Infrared spectra were taken on a Beckman IR-5 spectrophotometer as Nujol mulls. Nmr spectra were obtained on a Varian A56/60 spectrometer, using tetramethylsilane in $CHCl_3$ as an external standard.

Preparation of Chloroform.[9] To remove the ethyl alcohol which is present as a preservative, 250 ml of Fisher certified grade chloroform was washed with three 100-ml portions of concentrated sulfuric acid followed by 100-ml portions of water until the washings were neutral to litmus. The chloroform was dried over anhydrous calcium chloride and distilled. The chloroform was further dried by passing over Linde 4A molecular sieve just before using.

Preparation of Indene Oxide (1). A solution of 100 g of indene bromohydrin (prepared by the method of Suter and Milne)[10] in 900 ml of 95% ethanol was cooled to 5°. To this was added slowly, with stirring, 55 g of 85% potassium hydroxide in 95% ethanol, keeping the temperature below 10°. The reaction mixture was poured over 2000 g of ice and the crude indene oxide was taken up in ~200 ml of diethyl ether, washed twice with water, and dried over anhydrous sodium sulfate. After removal of the ether on a rotary evaporator the crude oxide was sublimed at 5 Torr with a cold-finger temperature of 0–10°: mp 30–31°; ir 1230, 1005, 986 cm^{-1} (lit.[11] mp 31°).

Reaction of Indene Oxide with Benzoic Acid. A solution of 0.037 mol (4.88 g) of **1** and 0.037 mol (4.51 g) of benzoic acid in 60 ml of chloroform was allowed to stand for about 72 hr at room temperature (25°). The solution was washed with 50 ml of 10% sodium bicarbonate twice and with 50 ml of water and dried over anhydrous sodium sulfate. The chloroform was removed on a rotary evaporator at about 50° and the product was transferred to a sublimation apparatus. Sublimation of the viscous liquid at 5 Torr and with a cold-finger temperature of 0–10° gave in about 3 hr 0.4 g of colorless crystals (**2**) and a residue of 5.3 g of a viscous liquid. Nmr analysis (CCl_4) showed that the separation of indanone was incomplete.

Identification of 2 as 2-Indanone. The nmr spectrum showed only two resonances at δ 7.11 and 3.32 (CCl_4). The melting point was 56–56.5° (lit.[11] mp 57–59°); 2,4-dinitrophenylhydrazone mp 196.5–197.5° (lit.[6] mp 198–198.5°).

Saponification of Benzoate. The 5.3 g of liquid from the reaction of indene oxide with benzoic acid was treated under reflux with 1.3 g of potassium hydroxide in 50 ml of 95% ethanol. The solution quickly turned dark brown and a precipitate gradually formed. After 3 hr the precipitate was removed by filtration,[12] 50 ml of water was added, and the solution was extracted with four 100-ml portions of diethyl ether. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness in a rotary evaporator at about 50°. The solid so obtained was recrystallized from benzene, after treatment with Norite, to yield 1.6 g (40.5%) of crystals, mp 156–157°; the ir spectrum was identical with that of *trans*-1,2-indandiol (mp 158–159°) prepared by the method of Rosen, *et al.*[6] The mother liquor from the recrystallization was evaporated to a viscous liquid which on sublimation at 90° and 5 Torr gave 0.4 g (6.2%) of colorless crystals, mp 92–93°. The ir spectrum of this material was identical with that of authentic sublimed *cis*-1,2-indandiol (mp 93–95°) obtained by the method of Rosen, *et al.*[6]

Nmr Spectrum of Reaction Mixture. A sample of the reaction mixture was withdrawn after about 72 hr and the nmr spectrum ($CHCl_3$) was obtained on the untreated mixture: δ 8.12 (m, ArH), 7.4 (m, ArH), 6.7 (m), 6.32 (d), 6.17 (d), 5.7–4.5 (m), 3.51 (s), 3.3 (m). The relative intensities of the doublets at δ 6.32 and 6.17 and the singlet at δ 3.51 were estimated from the peak heights and half-widths to be roughly in the ratio 15:115:200, respectively. The overall spectrum was that expected from the work of Rosen, *et al.*[6]

Reaction of Indene Oxide with Benzoic Acid.[13] A solution of 0.0378 mol (5.0 g) of **1** and 0.0420 mol (5.13 g) of benzoic acid in 60 ml of chloroform (purified only by distillation and passing over Linde 4A molecular sieve) was allowed to stand for 72 hr at room temperature (25°). The solution was washed with a 5% sodium bicarbonate solution and then with water, dried, and concentrated on a rotary evaporator at about 50° to yield 9.21 g of an oily liquid which proved difficult to crystallize. Sublimation of the viscous liquid at 5 Torr with a cold-finger temperature of 0–10°, water-bath temperature of 35–40°, gave in about 3 hr 0.40 g of colorless crystals (**2**) and a residue of 7.75 g of a viscous liquid.

Reduction of Benzoate. A 250-ml two-necked round-bottomed flask was fitted with a reflux condenser, a dropping funnel, a magnetic stirrer, and a heating mantle. In the flask were placed 2.0 g of pulverized lithium aluminum hydride and 50 ml of tetrahydrofuran which had been dried over lithium aluminum hydride and distilled. A solution of the 7.75 g of residue from the sublimation apparatus in 20 ml of dry tetrahydrofuran was then added slowly

with vigorous stirring at such a rate that the solvent refluxed gently. When the addition was completed and the initial reaction subsided, the mixture was stirred at the reflux temperature for an additional 2 hr. The excess lithium aluminum hydride was then decomposed by the addition of water dropwise with vigorous stirring. This was followed by the addition of 12 ml of 12 *N* HCl, just sufficient to dissolve the precipitate of aluminum hydroxide. The liquid was then extracted for 7 hr with diethyl ether in a continuous extraction apparatus. The extract was stripped of ether at a final temperature of 50° in a rotary evaporator. The precipitation of colorless crystals was aided by the addition of 25 ml of CCl_4. The solid so obtained was filtered and the filtrate was reserved. The crude solid material was recrystallized from benzene to yield 2.30 g (40.5%) of colorless crystals, mp 156–157°; the ir spectrum was identical with that of *trans*-1,2-indandiol (mp 158–159°) prepared by the method of Rosen, *et al.*[6] A mixture melting point with authentic *trans*-1,2-indandiol showed no depression. The filtrate after removal of CCl_4 in a rotary evaporator at 50°, from the filtration of the crude *trans*-1,2-indandiol, was subjected to molecular distillation at 0.63 Torr and 45°. The roof of the still was cooled by ice. In 12 hr approximately 3 ml of distillate collected. The ir spectrum of the distillate was identical with that of benzyl alcohol. The residue was taken up in diethyl ether and evaporated to yield 0.350 g (6.2%) of colorless crystals, mp 94–95°. The ir spectrum of this material was identical with that of authentic *cis*-1,2-indandiol (mp 93–95°) obtained by the method of Rosen, *et al.*[6]

Registry No.—**1**, 768-22-9; **2**, 615-13-4; benzoic acid, 65-85-0; 1-bromo-2-indanol, 52148-02-4; 2-bromo-1-indanol, 5400-80-6; *cis*-1,2-indandiol, 4647-42-1; *trans*-1,2-indandiol, 4647-43-2.

References and Notes

(1) Certain preliminary work bearing on this investigation was done by John A. Hyatt, a National Science Foundation Undergraduate Research Participant (1968), NSF Grant GY 4263.
(2) A. Gagis, A. Fusco, and J. T. Benedict, *J. Org. Chem.*, **37**, 3181 (1972).
(3) The high water solubility (0.066 g/cc) of the *cis*-1,2-indandiol probably accounts for the fact that this compound was not isolated in the previous work.[2]
(4) The nmr spectrum of the crude reaction mixture points unquestionably to the presence of 2-indanone (singlet, δ 3.51) while the two doublets at δ 6.32 and 6.17 can be assigned to H on C_1 of two different hydroxy benzoates.[6] The constitution of the reaction mixture and the structure of the products actually isolated are thus in accord.
(5) S. W. Scott and H. B. Miller, J. Elisha Mitchell Scientific Society, Abstracts of 66th Annual Meeting of the North Carolina Academy of Science, Vol. 85, 1969, p 119.
(6) W. E. Rosen, L. Dorfman, and M. P. Linfield, *J. Org. Chem.*, **29**, 1723 (1964).
(7) J. H. Brewster, *J. Amer. Chem. Soc.*, **78**, 4061 (1956).
(8) G. Berti and F. Bottari, *J. Org. Chem.*, **25**, 1286 (1960).
(9) G. Berti, B. Macchia, and F. Macchia, *Tetrahedron*, **28**, 1299 (1972). The effect of water on the stereochemical coarse of the reaction is noted. However, in our work the presence of ethyl alcohol had no apparent effect on the course of the reaction. The results with benzene as the solvent are substantially the same as with $CHCl_3$ (unpublished work).
(10) C. M. Suter and H. B. Milne, *J. Amer. Chem. Soc.*, **62**, 3473 (1940).
(11) H. Bodot, J. Jullien, and E. LeBlanc, *Bull. Soc. Chim. Fr.*, 41 (1962).
(12) An aqueous solution of the precipitate gave a crystalline solid, mp 118.5–120°, on acidification, identified as benzoic acid.
(13) The lithium aluminum hydride reduction was undertaken at the suggestion of one of the referees.

Determination of Configuration Using Magnetic Nonequivalence of Diastereotopic Benzylic Protons

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In earlier studies it was shown that a diastereotopic relationship between the two protons of an *N*-benzyl group may, if the proper conditions are met, cause them to appear at different chemical shifts.[1] Specifically, this phenomenon has been applied to a qualitative study on the conformational analysis of *N*-benzyl-2-substituted six-membered heterocycles[2] and it has also been shown that a 3-axial, and in some cases a 3-equatorial, alkyl substituent on an *N*-benzylpiperidine causes observable nonequivalence of the benzylic methylene protons.

Table I
Nmr Results on the Determination of Stereochemistry of 1-Benzyl-3-methyl-4-acetoxy-4-Substituted Piperidines (1) Using the Diastereotopic *N*-Benzyl Protons

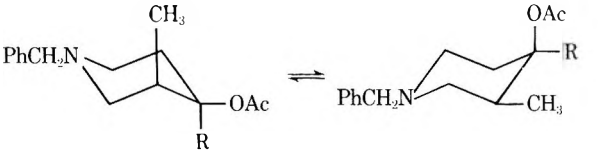
Compd 1	Isomer	*N*-Benzyl protons ($\Delta\nu_{AB}$, ±0.5 Hz)
a R = CH_3	Trans	Singlet
b, R = CH_3	Cis	Singlet
c, R = CH_2CH_3	Trans	Singlet
d, R = CH_2CH_3	Cis	11.7 Hz[a]
e, R = Ph	Trans	Singlet
f, R = Ph	Cis	13.8 Hz[a]
g, R = *o*-tolyl	Trans	Singlet
h, R = *o*-tolyl	Cis	

[a] Calculated from coupling constants obtained on a Jeolco MH-100 at a sweep width of 270 Hz.

To study further the "3-axial alkyl effect," 1-benzyl-3-methyl-4-acetoxy-4-substituted piperidines (1) were prepared to (1) determine the conformational limits for observing benzylic methylene nonequivalence when a third substituent was present on the piperidine ring and (2) determine what effect an anisotropic carbonyl would have on the magnetic nonequivalence. Since the configurational assignments of some 1-alkyl-4-aryl-3-methylpiperidin-4-ols (2) and their corresponding alkoxy esters have been previously determined by X-ray crystallography[3] and other pmr methods,[4] facile verification of stereochemical assignments was possible.

Alkyllithium addition to 1-benzyl-3-methyl-4-piperidone (**3**)[5] followed by acetylation of the resulting tertiary alcohol with acetyl chloride in $CHCl_3$ yielded the desired 4-acetoxy derivatives. In each case a mixture of diastereomers resulted with the trans isomer being predominant. The stereochemistry of each isomer was preliminarily assigned on the basis of its thin layer chromatographic retention time on silica gel, with the trans isomer always being the slower eluate as previously noted by Casy.[6,7]

From steric considerations, the conformational equilibrium for the trans isomers of **1** should favor the equatorial 3-methyl conformer by 1.2–1.4 kcal/mol[8,11] (R = CH_3, the smallest group studied). This prediction was confirmed by their nmr spectra (see Table I), which show singlets for the benzylic protons as expected when the 3-methyl group is equatorial and not axial.

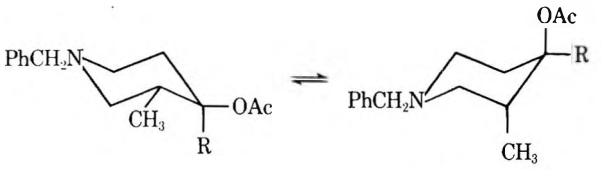


3-axial 3-equatorial

trans-**1a**, R = CH_3
c, R = CH_2CH_3
e, R = Ph
g, R = *o*-tolyl

Steric consideration of the cis isomer **1b** shows that there is very little (0.3–0.5 kcal/mol) difference in free energy between its two conformers. The nmr signal for its benzylic protons appears as a singlet, since the equatorial 3-methyl conformer is present in the conformational equilibrium by as much as 40%. However, for the cis isomer of **1** when R is

larger than a methyl group, the *N*-benzyl protons appear as a detectable AB quartet (see Table I), therefore indicating that the percentage of the axial 3-methyl conformer had increased while that of the equatorial 3-methyl conformer decreased with greater steric bulk at the 4 position. Further



3-equatorial 3-axial

cis-**1b**, R = CH_3
d, R = CH_2CH_3
f, R = Ph
h, R = *o*-tolyl

evaluation of the data presented in Table I also shows that the benzylic nonequivalence is not only detectable, but increases (~2 Hz) as the steric strain caused by the 4 substituent increases. This correlates well with the calculated percentages of ~65 and ~95% for the 3-axial conformer in the equilibrium of **1d** and **1f**, respectively.

To provide an answer for the second objective, the nmr spectrum of *cis*-1-benzyl-3-methyl-4-phenylpiperidine (**4**) shows a chemical shift separation of ~13 Hz for the *N*-benzyl protons (see Experimental Section), the magnitude of which is similar to those observed for the corresponding 4-acetoxy derivatives listed in Table I. This suggests that the 4-acetoxy has very little influence, other than steric, on the nonequivalence of the *N*-benzyl protons.

Experimental Section

Melting points were determined in a Mel-Temp apparatus in open capillaries and are uncorrected. The nmr spectra were obtained on either a Jeolco MH-100, Perkin-Elmer R-32A, Varian T-60, or a Hitachi R-20A in $CDCl_3$ with tetramethylsilane as an internal standard. Infrared absorption spectra were determined using a Perkin-Elmer 237B spectrophotometer. Elementary analyses were performed by Chemalytics, Inc., Tempe, Ariz. Thin layer chromatography (tlc) was done on precoated silica gel GF-254 plates (Analtech, Inc., Newark, Del.); spots were developed in an iodine chamber. Isomeric ratios were determined by nmr electronic integration.

General Procedure for Preparation of 1-Benzyl-3-methyl-4-acetoxy-4-substituted Piperidines (1). The *N*-benzyl-3-methyl-4-piperidone (**3**)[5] (50 mmol) was added dropwise with stirring to a cooled ether solution of the appropriate organometallic reagent (70 mmol). The mixture was stirred under reflux for 24–48 hr and then added to cold dilute hydrochloric acid. The acid solution was washed with ether and then basified with aqueous ammonia and extracted with ether. After drying over K_2CO_3, the ether was removed under reduced pressure to yield the crude mixture of diastereomeric 4-piperidinols which was then distilled and dissolved in $CHCl_3$. The reaction flask was cooled in an ice–water bath and 50 mmol of acetyl chloride was added slowly with stirring. The solution was then allowed to stand for 12 hr, and after concentration under reduced pressure, the resulting residue was basified with K_2CO_3 and extracted with ether (in some cases the residue was recrystallized before basification to yield the pure trans isomer as its hydrochloride salt; see below). The ether extracts were combined and dried over K_2CO_3 and the solvent was removed to yield the crude isomeric mixture of 4-acetoxy derivatives. The following *N*-benzylpiperidines were prepared by this method.

trans-**1-Benzyl-3-methyl-4-acetoxy-4-methylpiperidine (1a)** was the major isomer (80%) and was isolated by recrystallization of its crude esterification mixture from ethanol–ether: mp (HCl) 204–205°, mp (base) 48–50°; ir (neat) 1716 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (d, 3 H, J = 6.0 Hz), 1.5 (s, 3 H), 1.96 (s, 3 H), 1.4–2.8 (m, 7 H), 3.45 (s, 2 H), 7.28 (s, 5 H).

Anal. Calcd for $C_{16}H_{24}ClNO_2$: C, 64.53; H, 8.12; N, 4.70. Found: C, 64.04; H, 8.18; N, 4.50.

cis-**1-Benzyl-3-methyl-4-acetoxy-4-methylpiperidine (1b)** was the minor isomer (20%) and was separated from the slower moving trans isomer **1a** (R_f 0.3) by thick layer chromatography over a 0.5-mm plate of silica gel, R_f 0.5 (90% benzene–10% ethyl acetate): mp (HCl) 201–202°; bp 94° (0.02 mm); ir (neat) 1718 cm^{-1}; nmr ($CDCl_3$) δ 0.90, (d, 3 H, J = 6.4 Hz), 1.26 (s, 3 H), 1.80 (s, 3 H), 1.5–2.6 (m, 7 H), 3.4 (s, 2 H), 7.2 (s, 5 H).

Anal. Calcd for $C_{16}H_{24}ClNO_2$: C, 64.53; H, 8.12; N, 4.70. Found: C, 64.54; H, 8.30; N, 4.64.

trans-**1-Benzyl-3-methyl-4-acetoxy-4-ethylpiperidine (1c)** was the major isomer (68%) and was isolated by recrystallization of its crude esterification mixture from ethanol–ether: mp (HCl) 194–195°, mp (base) 42–45°; ir (neat) 1721 cm^{-1}; nmr ($CDCl_3$) δ 0.90 (m, 6 H), 1.2–2.8 (m, 9 H), 2.0 (s, 3 H), 3.5 (s, 2 H), 7.4 (s, 5 H).

Anal. Calcd for $C_{17}H_{26}ClNO_2$: C, 65.47; H, 8.40; N, 4.49. Found: C, 65.56; H, 8.50; N, 4.40.

cis-**1-Benzyl-3-methyl-4-acetoxy-4-ethylpiperidine (1d)** was the minor isomer (32%) and was separated from the slower moving trans isomer **1c** by column chromatography over neutral alumina using petroleum ether–ether (4:1) as the eluent: mp (HCl) 151–153°; ir (neat) 1717 cm^{-1}; nmr ($CDCl_3$) δ 0.80 (m, 3 H), 1.10 (d, 3 H, J = 6.5 Hz), 1.4–2.7 (m, 9 H), 1.9 (s, 3 H), 3.4 (q, 2 H, J_{AB} = 13.0, $\Delta\nu_{AB}$ = 11.7 Hz), 7.3 (s, 3 H).

Anal. Calcd for $C_{17}H_{26}NO_2$: C, 65.47; H, 8.40; N, 4.49. Found: C, 65.60; H, 8.51; N, 4.73.

trans-**1-Benzyl-3-methyl-4-acetoxy-4-phenylpiperidine (1e)** was the major isomer (72%) and was obtained pure by recrystallization of its crude esterification mixture from ethanol–ether: mp (HCl) 214.5–216°, mp (base) 88–89°; ir (neat) 1724 cm^{-1}; nmr ($CDCl_3$) δ 0.65 (d, 3 H, J = 6.0 Hz), 2.0–3.3 (m, 7 H), 2.10 (s, 3 H), 3.55 (s, 2 H), 7.2–7.5 (m, 10 H).

Anal. Calcd for $C_{21}H_{26}ClNO_2$: C, 70.08; H, 7.28; N, 3.89. Found: C, 70.41; H, 7.15; N, 3.88.

cis-**1-Benzyl-3-methyl-4-acetoxy-4-phenylpiperidine (1f)** was the minor isomer (28%) and was separated from the slower moving trans isomer **1e** (R_f 0.55) by thick layer chromatography over a 0.5-mm plate of silica gel, R_f 0.70 (90% benzene–10% ethyl acetate): mp (HCl) 207–208°; ir (neat) 1718 cm^{-1}; nmr ($CDCl_3$) δ 0.75 (d, 3 H, J = 6.8 Hz), 2.0 (s, 3 H), 2.0–2.7 (m, 7 H), 3.58 (q, 2 H, J_{AB} = 13.5, $\Delta\nu_{AB}$ = 13.8 Hz), 7.4 (s, 5 H).

Anal. Calcd for $C_{21}H_{26}ClNO_2$: C, 70.08; H, 7.28; N, 3.89. Found: C, 69.76; N, 7.03; H, 3.84.

trans-**1-Benzyl-3-methyl-4-acetoxy-4-*o*-tolylpiperidine (1g)** was the major isomer (84%) and was obtained pure by recrystallization of the crude isomeric alcohol mixture from ether–hexane: mp (HCl) 198–199°; ir (neat) 1709 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (s, 3 H), 1.8–3.2 (m, 7 H), 2.05 (s, 3 H), 2.4 (s, 3 H), 3.45 (s, 2 H), 7.0–7.3 (m, 9 H).

Anal. Calcd for $C_{22}H_{28}ClNO_2$: C, 70.67; H, 7.55; N, 3.78. Found: C, 70.60; H, 7.54; N, 4.17.

cis-**1-Benzyl-3-methyl-4-acetoxy-4-*o*-tolylpiperidine (1h)** was the minor isomer (16%) and was separated from the slower moving trans isomer **1g** by column chromatography over neutral alumina using petroleum ether–ether (4:1) as the eluent. However, this material was found to be thermally unstable and an analytically pure sample could not be obtained.

cis-**1-Benzyl-3-methyl-4-phenylpiperidine (4a).** To 5 g (1.8 mmol) of the isomeric mixture of alcohols obtained from the phenyllithium addition to **3** was added 66 ml of concentrated hydrochloric acid and 124 ml of acetic acid. The solution was stirred under reflux for 24 hr and then concentrated to dryness. The resulting residue was dissolved in 50 ml of ethanol and 100 mg of PtO_2 was added to the flask. The reaction vessel was placed on the Parr apparatus, kept under hydrogen at 45–50 psi for 48 hr, and then concentrated to dryness. The residue obtained was basified with aqueous K_2CO_3 and extracted with ether. The combined ether extracts were dried over K_2CO_3 and then concentrated to yield a mixture (by nmr) of 1-benzyl-3-methyl-1,2,5,6-tetrahydropyridine (**5**, 40%), *cis*-**4a** (25%), and *trans*-1-benzyl-3-methyl-4-phenylpiperidine (**4b**, 35%). An examination of the nmr signals for the *N*-benzyl protons in the mixture shows singlets at δ 3.64 and 3.54 for *trans*-**4b** and **5**, respectively, and also a partially obscured AB quartet at δ 3.50 for *cis*-**4a** (J_{AB} = 13, $\Delta\nu$ ~13 Hz). Further attempts to effect complete catalytic hydrogenation of the 3,4 double bond (using Pt) without debenzylation and reduction of the 4-phenyl were futile.

Acknowledgment. The author is grateful to Dr. R. Lyle's research group of the University of New Hampshire,

Dr. E. White, V, of Smith, Kline and French Laboratories, and Dr. Ned Heindel of Lehigh University for nmr spectra. The author is especially grateful to Dr. Lyle for his consultation and encouragement.

Registry No.—**1a**, 52195-27-4; **1a** hydrochloride, 52195-28-5; **1b** hydrochloride, 52195-29-6; **1c**, 52195-30-9; **1c** hydrochloride, 52195-31-0; **1d** hydrochloride, 52195-32-1; **1e**, 52195-33-2; **1e** hydrochlorides, 52195-34-3; **1f** hydrochloride, 52195-35-4; **1g** hydrochloride, 52195-36-5; **1h**, 52195-37-6; **3**, 34737-89-8; **4a**, 52195-38-7; **4b**, 52195-39-8; **5**, 40240-24-2.

References and Notes

(1) R. E. Lyle and L. N. Pridgen, *J. Org. Chem.*, **38**, 1618 (1973), and references cited therein.
(2) L. N. Pridgen, Ph.D. Thesis, University of New Hampshire, 1972.
(3) G. Kartha, F. R. Ahmed, and W. H. Barnes, *Acta Crystallogr.*, **13**, 525 (1960); F. R. Ahmed, W. H. Barnes, and L. DiMarco Masironi, *ibid.*, **16**, 237 (1963).
(4) A. F. Casy, *Tetrahedron*, **22**, 2711 (1966).
(5) P. M. Carabateas and L. Grumbach, *J. Med. Chem.*, **5**, 913 (1962).
(6) (a) A. H. Beckett, A. F. Casy, G. Kirk, and J. Walker, *J. Pharm. Pharmacol.*, **9**, 939(1957); (b) A. H. Beckett, A. F. Casy, and N. J. Harper, *Chem. Ind. (London)*, **78**, 19 (1959); (c) A. F. Casy and M. A. Iorio, *J. Chem. Soc. C*, 135 (1970).
(7) In addition to the nmr methods summarized in ref 4, an X-ray crystallographic analysis[3] of the slower eluting major isomer obtained from phenyllithium addition to 1,3-dimethyl-4-piperidone (**6**) established the 4-Ph/3-Me stereochemistry as trans. Our stereochemical assignments were then made on the warranted assumption that replacement of the *N*-methyl group by *N*-benzyl does not reverse the preferred pathway of lithium reagent attack. Additionally, these stereochemical assignments and nmr results are in accord with those reported earlier for similar piperidines obtained by catalytic hydrogenation of the parent pyridines.[1]
(8) Free-energy differences between conformers were calculated using a decrease of 0.6–0.8 kcal/mol in the unfavorable axial methyl interaction on replacement of one syn-axial hydrogen by the nitrogen free pair[9] and the best $-\Delta G_x$ values listed by Hirsch.[10]
(9) P. J. Brignell, K. Brown, and A. R. Katritzky, *J. Chem. Soc. B*, 1462 (1968); F. G. Ridell, *Quart. Rev., Chem. Soc.*, **21**, 364 (1967).
(10) J. A. Hirsch, *Top. Stereochem.*, **1**, 199 (1967).
(11) As one referee has correctly suggested, there are several hazards in making predictions on conformational equilibria based on additive free energies of substituent groups when two or more are present.[12] In our case, conformational distortions are considered to be negligible.
(12) P. L. Durette and D. Horton, *J. Org. Chem.*, **36**, 2658 (1971), and references cited therein.

Hydration of 3-Methyl-3-buten-2-one (Isopropenyl Methyl Ketone)

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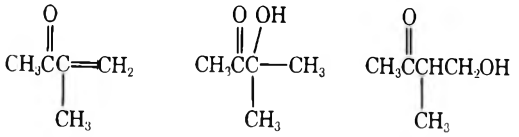
Experience shows that the acid-catalyzed addition of water to a carbon–carbon double bond conjugated with a carbonyl group occurs such that hydrogen appears on the α carbon atom and hydroxyl on the β. Thus methyl vinyl ketone affords 4-hydroxy-2-butanone,[1] and acrylaldehyde and acrylic acid yield respectively 3-hydroxypropionaldehyde and 3-hydroxypropionic acid.[2] This direction of addition can be rationalized in terms of the strong electron-withdrawing influence of the carbonyl group, especially when protonated by the mineral acid catalyst.[2]

It has been reported that 3-methyl-3-buten-2-one (isopropenyl methyl ketone, **1**) behaves abnormally in this reaction, yielding 3-hydroxy-3-methyl-2-butanone (**2**) instead of the anticipated 4-hydroxy-3-methyl-2-butanone (**3**).[3] The formation of this unexpected product has been explained in terms of a possible methyl migration in **1** subsequent to protonation,[3] or of Markovnikov addition of water to the enolic form of **1**.[4]



1 **2** **3**

Since there appeared to be no compelling reason why **1** should be hydrated in this unusual manner, we have carefully reinvestigated the reaction, and our findings show that in fact the sole product of the addition (aside from polymeric material and unchanged ketone) is the expected 4-hydroxy-3-methyl-2-butanone (**3**). None of the isomeric ketol **2** could be detected.

3-Methyl-3-buten-2-one (**1**) was prepared by reaction between ethyl methyl ketone and formaldehyde,[5] leading to **3**, the ir and nmr spectra of which (see Experimental Section) were in complete agreement with the assigned structure; dehydration of the ketol with anhydrous oxalic acid[6] afforded **1**. The structure **1** was in harmony with its spectral properties, and the melting points of the 2,4-dinitrophenylhydrazones of both ketol and enone were in agreement with values in the literature (see Experimental Section).

The hydration of **1** was effected at 100 and at 50°, by simply mixing the ketone and 2 *N* sulfuric acid and heating under reflux at these temperatures. At the higher temperature the major product was polymeric material; volatile material consisted of unchanged ketone and 4-hydroxy-3-methyl-2-butanone (**3**), separable by fractional distillation and identified by their 2,4-dinitrophenylhydrazones and by comparison of their ir and nmr spectra with those of authentic specimens. Glc of the volatile product showed three peaks; two of these had retention times identical with those of authentic samples, and the third small peak was not identified. There was no peak corresponding to 3-hydroxy-3-methyl-2-butanone. At 50° for a longer period a similar result was obtained, except that there was very little polymeric material formed, and most of the ketone was recovered unchanged. Two glc peaks were observed with the volatile product; these corresponded exactly in retention times with unchanged ketone and 4-hydroxy-3-methyl-2-butanone. Neither of the peaks corresponded with 3-hydroxy-3-methyl-2-butanone, which could not be detected in the product.

We conclude that the hydration of isopropenyl methyl ketone occurs in the expected manner, to yield 4-hydroxy-3-methyl-2-butanone (**3**). It would seem almost certain that this was also the product encountered in the original report,[3] since the 2,4-dinitrophenylhydrazone of the product there described had mp 192°, which coincides with that of isopropenyl methyl ketone, and 4-hydroxy-3-methyl-2-butanone is known to yield this derivative under the acid conditions normally used for 2,4-dinitrophenylhydrazone formation.[7] Further, 3-hydroxy-3-methyl-2-butanone (**2**) with 2,4-dinitrophenylhydrazine in alcoholic acid media yields not the simple derivative, but that of the *O*-alkyl ketone $CH_3CO(CH_3)_2OR$.[8] Finally, the *p*-nitrobenzoates of both isomeric alcohols **2** and **3** were prepared. The former had mp 123–123.5°, as opposed to the reported[3] value of 194°, and the latter had mp 54°, in agreement with that reported.[5]

Experimental Section

Gas chromatography was conducted on a Carbowax column at 150°, on an F and M Model 810 apparatus. Nmr measurements were carried out using a Hitachi Perkin-Elmer R-24 Instrument, in deuteriochloroform solution, and using TMS as internal standard. Analyses are by Galbraith Laboratories, Inc., Knoxville, Tenn.

4-Hydroxy-3-methyl-2-butanone (3). This hydroxy ketone was prepared by a modification of Morgan and Holmes' method.[5] Freshly distilled ethyl methyl ketone (500 ml), 40% aqueous formaldehyde (375 ml), and 2 *N* aqueous sodium hydroxide (5 ml) were mixed and stirred at 65°. The temperature rose gradually to 80° and was maintained so, with gentle refluxing, for 2–3 hr. A further quantity (5 ml) of alkali was added and the mixture was stirred at room temperature overnight. Acetic acid (10 ml of 2 *N*) was added, the liquid was distilled until the distillation temperature reached 105°, and the residue was distilled fractionally *in vacuo*. A fraction, bp 86–94° (25–35 mm) (127 g), consisting of 4-hydroxy-3-methyl-2-butanone, was collected. It showed a single peak on glc: ir (film) 3425 (OH) and 1709 cm^{-1} (C=O); nmr δ 1.09 (d, J = 7 Hz, 3 H, $CHCH_3$), 2.19 (s, 3 H, $COCH_3$), 2.80 (m, 1 H, CH), 3.34 (s, 1 H, OH), and 3.69 ppm (d, J = 7 Hz, 2 H, CH_2OH). The 2,4-dinitrophenylhydrazone, prepared under mild conditions in diglyme,[7] had mp 108–109° (lit.[7] mp 107–109°); under strongly acidic conditions the derivative of isopropenyl methyl ketone was formed[7] (see below). The *p*-nitrobenzoate separated from light petroleum (bp 60–90°) in very pale yellow plates, mp 54° (lit.[5] mp 54°).

Isopropenyl Methyl Ketone (3-Methyl-3-buten-2-one[6] 1). The foregoing keto alcohol (107 g, 1.05 mol), anhydrous oxalic acid (2.0 g), and a few crystals of hydroquinone were placed in a distillation flask and distilled slowly until the vapor temperature reached 115°. The heterogeneous distillate was separated, and the upper layer was dried with anhydrous potassium carbonate. The liquid was filtered and distilled, bp 42–45° (85–90 mm), to yield isopropenyl methyl ketone (42 g, 41%): ir (film) 1678 (C=O), 1629 (C=C), and 935 cm^{-1} (=CH_2); nmr δ 1.83 (s, 3 H, =CCH_3), 2.28 (s, 3 H, $COCH_3$), and 5.79 ppm (d, J = 10 Hz, 2 H, =CH_2); uv λ_{max} (EtOH) 220 nm (ϵ 9175). The product showed a single peak on glc. The 2,4-dinitrophenylhydrazone separated from 95% ethanol as red needles, mp 192–193° (lit. mp 190,[9] 192.7–193.7° [7]), uv λ_{max} (EtOH) 372 nm (ϵ 21,800).

Hydration of Isopropenyl Methyl Ketone. A. At 100°. Isopropenyl methyl ketone (12.0 g) and 2 *N* sulfuric acid (240 ml) were heated under reflux at 100° (steam bath) for 3 hr. After being cooled the solution was saturated with anhydrous potassium carbonate and subjected to continuous ether extraction overnight. The extract was dried ($MgSO_4$) and concentrated by flask evaporation. The residue distilled at 92–95° (24 mm) (1.0 g), leaving a large residue of polymeric material. The ir and nmr spectra of the volatile product were identical with those of authentic 4-hydroxy-3-methyl-2-butanone *(vide supra)*. Glc of the product showed one major peak (73%) corresponding in retention time with that of 4-hydroxy-3-methyl-2-butanone. A minor peak corresponded to unchanged isopropenyl methyl ketone (16%); a third peak (11%) was unidentified. None of the peaks corresponded in retention time with authentic 3-hydroxy-3-methyl-2-butanone. The 2,4-dinitrophenylhydrazone of the major product, prepared in diglyme under mild conditions,[7] had mp 108–109°, alone or mixed with an authentic sample *(vide supra)*.

B. At 50°. Isopropenyl methyl ketone (7.5 g) and 2 *N* sulfuric acid (135 ml) were heated under reflux at 50° (internal temperature) for 7 hr. No polymeric material seemed to be formed. The mixture was cooled, saturated with potassium carbonate, and subjected to continuous ether extraction for 22 hr. The extract was dried (K_2CO_3), concentrated, and distilled, bp 90–95° (24 mm) (2.5 g), ir (film) 3425 (OH) and 1709 cm^{-1} (C=O). Glc of the product showed a major peak (73%) corresponding in retention time to authentic 4-hydroxy-3-methyl-2-butanone, and a minor peak (27%) corresponding to unchanged isopropenyl methyl ketone. Both retention times were quite different from that of authentic 3-hydroxy-3-methyl-2-butanone.

3-Hydroxy-3-methyl-2-butanone (2). The commercial product (Aldrich Chemical Co.) was purified by distillation, bp 140°, nmr δ 1.40 [s, 6 H, $C(CH_3)_2$], 2.25 (s, 3 H, $COCH_3$), and 3.95 ppm (s, 1 H, OH); it showed a single peak on glc. The 2,4-dinitrophenylhydrazone, prepared in dilute hydrochloric acid, separated from ethyl acetate as orange prisms, mp 144–145° (lit.[8] mp 138–139°), λ_{max} (EtOH) 359 nm (ϵ 23,300).

Anal. Calcd for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.81; H, 5.00; N, 19.85.

The *p*-nitrobenzoate was prepared by heating the alcohol and *p*-nitrobenzoyl chloride (1.05 mol) in pyridine on the steam bath for 2 hr, and then cooling and adding ether and a slight excess of dilute HCl. The ether layer was separated, washed with water and sodium bicarbonate, dried, and evaporated. The residual crystalline ester separated from light petroleum (bp 60–90°) in very pale yellow plates, mp 123–123.5°.

Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.57. Found: C, 57.33; H, 5.23; N, 5.54.

Registry No.—**1**, 814-78-8; **1** 2,4-DNP, 5077-59-8; **2**, 115-22-0; **2** 2,4-DNP, 52123-60-1; **2** *p*-nitrobenzoate, 52123-61-2; **3**, 3393-64-4; formaldehyde, 50-00-0; ethyl methyl ketone, 78-93-3; *p*-nitrobenzoyl chloride, 122-04-3.

References and Notes

(1) German Patent 717,491 (1942); *Chem. Abstr.*, **38**, 2350[2] (1944).
(2) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, pp 1019–1020, and references cited therein.
(3) N. Thorne, *J. Chem. Soc.*, 2587 (1956).
(4) H. B. Henbest, *Annu. Rep. Progr. Chem.*, **53**, 155 (1956).
(5) G. T. Morgan and E. L. Holmes, *J. Chem. Soc.*, 2667 (1932).
(6) G. T. Morgan, *J. Soc. Chem. Ind., London*, **57**, 885 (1938).
(7) H. J. Shine and J. Y.-F. Tsai, *J. Org. Chem.*, **29**, 443 (1964).
(8) J. G. Aston and R. B. Greenburg, *J. Amer. Chem. Soc.*, **65**, 2590 (1940).
(9) G. Martin, *Ann. Chim. (Paris)*, **4**, 541 (1959).

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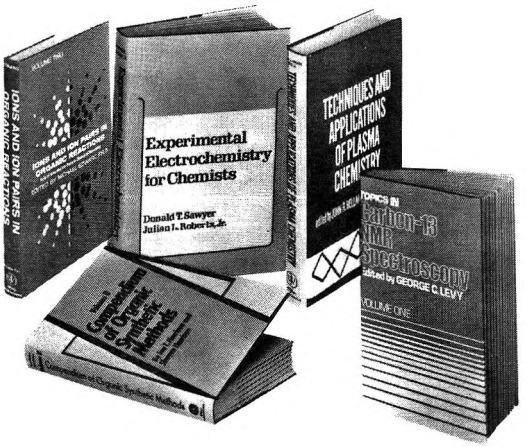

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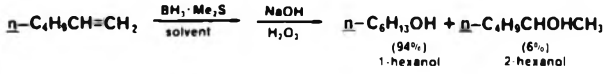

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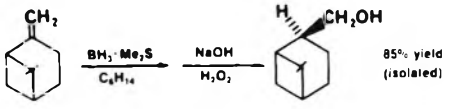

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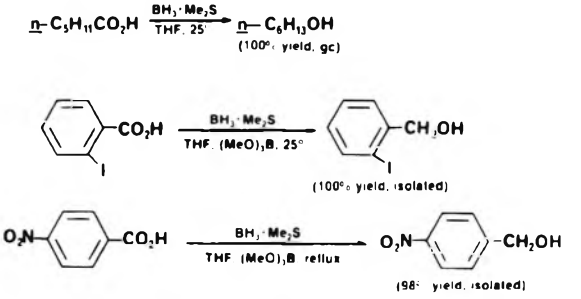

References

1) C.F. Lane, *J. Org. Chem.*, **39**, 1437 (1974).

2) C.F. Lane, H.L. Myatt, J. Daniels and H.B. Hopps, *ibid.*, 39, 3052 (1974), this issue.

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