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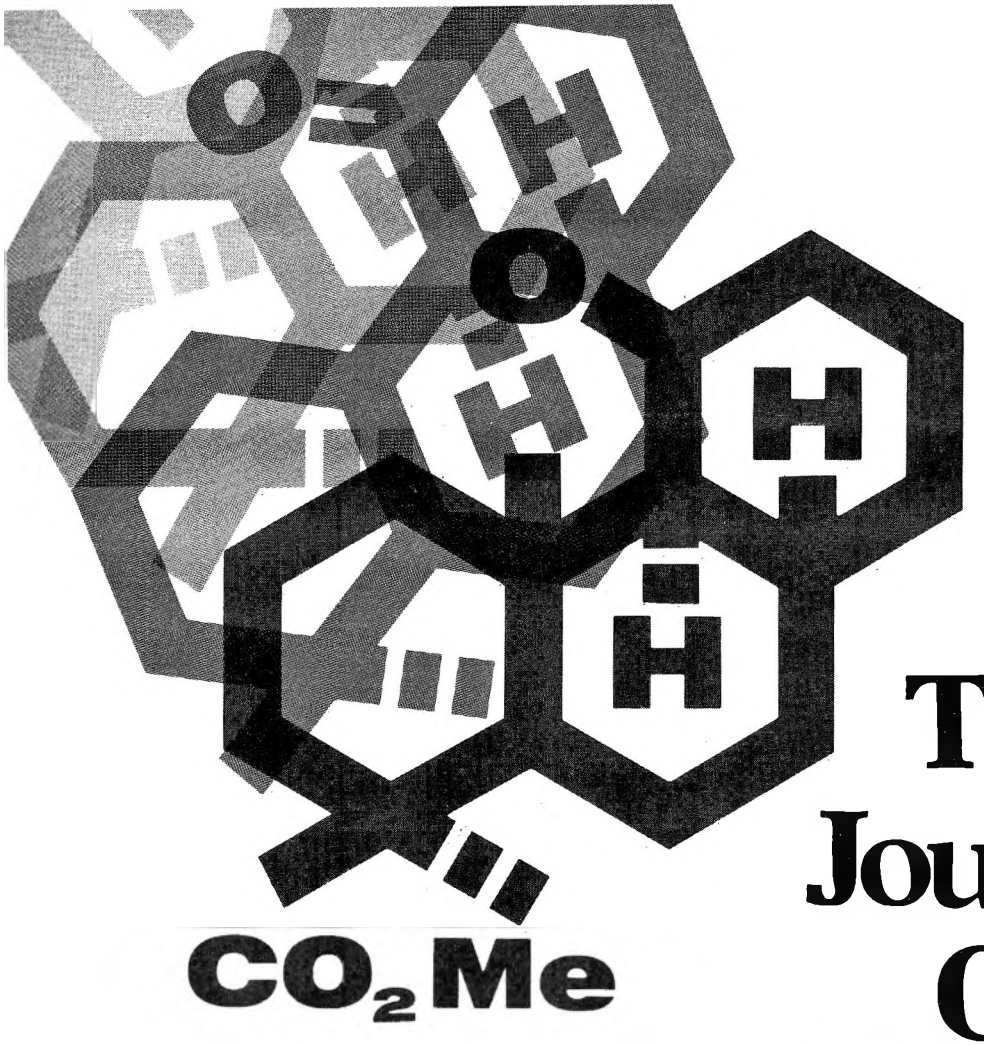

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Carbocyclic Phenylhydrazines in the Fischer Indole Synthesis. 3. Some Rearrangements with 1-Phenyl-5-pyrazolidinones

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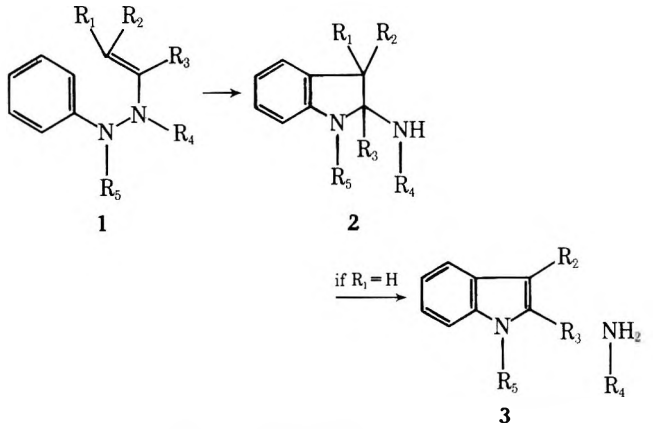
Received November 24, 1975

Reactions of 1-phenyl-5-pyrazolidinone **4a,b** with a variety of carbonyl compounds are described. Cyclohexanone and its higher homologues gave the novel 5-(3-aminopropanoyl)-5*H*-cycloalk[*b*]indoles **5a–g**. The carbonyl group was reduced with diborane to give 5-(3-aminopropyl)-5*H*-cycloalk[*b*]indoles **7a–c**. Loss of the side chain occurred upon treatment of **5a** and **5f** with $LiAlH_4$ to give **6a** and **6b**, respectively. Cyclopentanone and **4a,b** gave the indolines **8a,b**. Upon reduction with $LiAlH_4$, the methyl substituted compound **8b** gave the indoline **9** while the unsubstituted compound **8a** gave the indole **7d**. From the reaction of **4a** with 2,6-dichlorophenylacetaldehyde the enehydrazine **11** was isolated, which underwent thermal rearrangement to the indoline **12**.

According to Robinson and Robinson,[1] the mechanism of the Fischer indole synthesis[2] involves the formation of an enehydrazine from a phenylhydrazone followed by a [3,3] sigmatropic rearrangement to form the respective indole.

Scheme I



During the course of our investigation of the chemistry of 1-phenylpyrazolidine we have isolated[3a] 10,10-dimethyl-1,2,3,4,10,10a-hexahydropyrimido[1,2-*a*]indole [**2**, $R_1 = R_2 = Me$; $R_3 = H$; $R_4R_5 = (CH_2)_3$]. This compound was obtained from the reaction of 1-phenylpyrazolidine with isobutyraldehyde and may be regarded as the equivalent of an intermediate of the classic Fischer indole synthesis—a stable compound because of the presence of two alkyl substituents. We have also demonstrated[4] that under our experimental conditions system **2** was not isolated but underwent further bond reorganization to form indole **3** when one of the substituents R_1 or R_2 was replaced with hydrogen. In all the cases described above, we have not isolated any compounds of the general structure **1**, the postulated precursor of **2**. To our knowledge, the literature contains only three references pertaining to the isolation and characterization of enehydrazines[5a,b,6] **1**. These compounds, when treated under conditions favorable for rearrangement, gave the respective indoles directly.

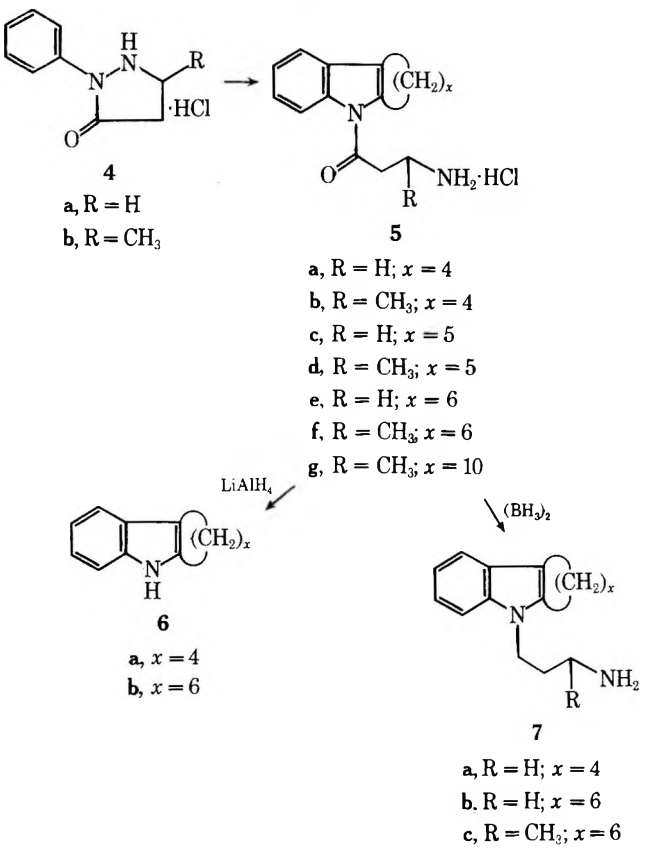
In a recent example,[7] a vinylogous hydrazide was prepared and thermally rearranged to an indoline.

We now wish to report the isolation of three compounds with the general structure **2** ($R_1 = H$) and of an enehydrazine **1**, which rearranged thermally to the indoline **2** ($R_1 = H$). These indolines did not undergo bond reorganization to give the corresponding indoles upon treatment with hydrogen chloride, but formed the indoline hydrochlorides instead.

1-Phenyl-5-pyrazolidinones **4a,b** have been known since the turn of the century as summarized recently by Jacquier et al.[8a,b] We found that their hydrochlorides[9] are capable of reacting with cyclic ketones. Equimolar amounts of 1-phenyl-5-pyrazolidinone hydrochloride (**4a**) and cyclohexanone were heated under reflux in glacial acetic acid. The novel product 9-(3-aminopropanoyl)-1,2,3,4-tetrahydrocarbazole hydrochloride (**5a**) was isolated in 86% yield and characterized by analytical and spectral data. The formation of this product was not observed, however, when the reaction was attempted in the absence of the acid. The free base of the starting material **4a** was recovered unchanged after prolonged heating to reflux with cyclohexanone in toluene. Under similar conditions 1-phenylpyrazolidine and cyclohexanone readily[4] formed the corresponding indole. The difference in reactivity with cyclohexanone parallels the basicity of the corresponding free base. We observed $pK_a = 5.0$ for 1-phenylpyrazolidine hydrochloride compared to $pK_a = 2.0$ for **4a** (CMS), the basicity of the 2-N of **4a** being lowered by the proximity of the amide.

When **5a** was treated with lithium aluminum hydide in THF we isolated tetrahydrocarbazole (**6a**). After treatment of **5a** with diborane,[10] the reduction product was 9-(3-aminopropyl)-1,2,3,4-tetrahydrocarbazole (**7a**). The maleate of

Scheme II

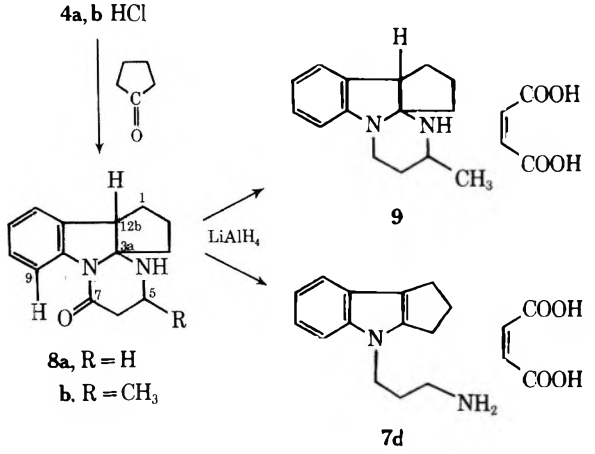


7a was found to be identical in every respect with an authentic sample prepared from cyclohexanone and 1-phenylpyrazolidine,[4] thus proving the structure of **5a**.

When 1-phenyl-3-methyl-5-pyrazolidinone hydrochloride (**4b**) and cyclohexanone were heated together in glacial acetic acid, 9-(3-aminobutanoyl)-1,2,3,4-tetrahydrocarbazole hydrochloride (**5b**) was isolated in 79% yield.

Different products were isolated, however, when cyclopentanone was used as starting material. In this case, a novel indoline **8a** was isolated in moderate yield following the reaction with **4a**, while the methyl substituted analogue **8b** was

Scheme III



isolated in 83% yield from **4b** and the same ketone. Analytical and mass spectral data support the assigned structures. While the uv spectra for both compounds show absorption usually associated with indoles (fine structure), the ^{13}C NMR spectra obtained for both **8a** and **8b** clearly established the presence of an indoline ring.

The NMR spectrum of **8a** shows the presence of a doublet at δ 4.33 ppm (1 H), which was assigned to the proton in position 12b of **8a** with coupling constants of 7 and 1–2 Hz to the vicinal methylene group. A similar doublet was observed for the compound **8b**, which is superimposed on a multiplet assigned to the proton at C-5. When the NMR spectra of the base **8a,b** were recorded in the same solvent, no absorption in the region δ 3.7–6.8 ppm was observed. To clarify the situation with respect to a possible equilibrium between 8 and the ring open tautomer, it was decided to examine the ^{13}C NMR spectra for **8a** (base and hydrochloride) and **8b** (hydrochloride).

Discussion of the ^{13}C NMR Spectra of 8a and 8b. The fully proton decoupled spectrum of **8a** HCl gave a total of 14 peaks, corresponding to the number of carbon atoms. Single-frequency off-resonance decoupling (sford) experiments were used to determine the number of protons attached to each carbon. The results are listed in Table V. These data preclude the presence of an indole in **8a**, since the spectrum displays only six peaks that can be associated with aromatic carbons.[11,12] The spectrum of **8a** compares favorably, however, with spectra[13] obtained for three related indolines which we had prepared[3a] earlier. The peak at 87.7 ppm (singlet) was assigned to the fully substituted C-3a (for the numbering see Scheme III) with two of the substituents being nitrogen. This is in good agreement with the chemical shift observed for the corresponding carbon of the three models [e.g., **2**, $R_1 = R_2 = CH_3$; $R_3 = H$; $R_4R_5 = (CH_2)_3$]. In these cases values between 80.9 and 83.4 ppm were observed. It should be kept in mind that our models were substituted ith R_1R_2 = alkyl and R_3 = H (Figure 1), thus accounting for the shift to lower field observed for **8a**. The peak at 51.6 ppm (doublet) was assigned to the C-12b. The corresponding carbon of our models showed absorptions between ca. 40 [**2**, $R_1 = R_2 = CH_3$; $R_3 = H$; $R_4R_5 = (CH_2)_3$; peak obscured by Me_2SO] and 47.8 ppm. These deviations are attributed to the differences in the substitution patterns. The ^{13}C NMR spectrum of the free base **8a** showed only minor changes in comparison to the spectrum of the hydrochloride. The chemical shifts for the C-3a and C-12b appeared at 90.7 and 52.7 ppm, respectively. For additional support of the above assignment, see below for the ^{13}C NMR spectrum of **12**.

The ^{13}C NMR spectrum of **8b** (see Table VI) shows the expected shifts in comparison to the spectrum of **8a** due to the presence of the additional methyl group. Particularly, the chemical shifts in **8b** assigned to C-3a and C-12b are the same as observed for **8a**. The same is true for the chemical shifts observed for the aromatic carbons. The expected shifts to lower field are observed for C-5 and C-6.

The presence of the methyl group in **8b** can give rise to diastereoisomers. That this is indeed the case is borne out by the ^{13}C NMR spectrum of **8b**. There, every peak is accompanied by a small satellite peak, indicating the presence of a second isomer to the extent of 7–8% after one recrystallization. This stereoisomerism can be attributed to the methyl group, excluding the possibility of isomerism at the juncture of the two five-membered rings, since **8a** consists of a single isomer according to the ^{13}C NMR spectrum of that compound. Further work will be required to determine the stereochemistry of **8b**.

Reduction of the Hexahydrocyclopenta[*b*]pyrimido[1,2-*a*]indol-7(6*H*)-one System (8a and 8b). When the title compound *without* the methyl group (**8a**) was treated with $LiAlH_4$ the known[4] 4-(3-aminopropyl)-1,2,3,4-tetrahydrocyclopent[*b*]indole (**7d**) was isolated and characterized as the maleic acid salt. This was found to identical in every respect with an authentic sample. The structure of this compound was also verified with the aid of its ^{13}C NMR spectrum, which clearly showed the presence of eight aromatic carbons for **7d**. In light of the results discussed above it may be as-

sumed that the lactam group in **8a** was reduced to the corresponding amine followed by opening of the perhydropyrimidine ring to form the indole **7d**, since base alone did not rearrange the skeleton of **8a** (see Experimental Section).

Surprisingly, when the title compound *with* the methyl group (**8b**) was reduced under similar conditions as employed for **8a**, the product was not the indole corresponding to **7d** but the indoline **9**, isolated and characterized as the maleic acid salt. This structure is based on the following spectral data. The NMR spectrum of **9** did not exhibit the expected triplet associated[4] with the methylene group attached to the indole nitrogen near 4.2 ppm. Instead the corresponding signal was observed in the region between 3.0 and 4.0 ppm. From the ^{13}C NMR spectrum of **9** it became clear that the product had to be assigned the cyclic tautomer with the same skeleton as the starting material **8b**. The characteristic peaks for the C-3a and C-12b were observed at 90.4 and 51.8 ppm, respectively, in addition to six low-field peaks assigned to the aromatic carbons. The spectrum also showed that the reduction product consisted of a single isomer with no detectable amount of a second isomer as was present in the starting material **8b**. The isolation of product **9** from the reduction of **8b** also proves the sequence of steps (reduction followed by ring opening) in the reduction of **8a** leading to the indole **7d**.

Additional Examples. For the results of reactions between **4a,b** and cycloheptanone, cyclooctanone, and cyclododecanone, which yielded the corresponding indoles, see Tables II and III.

To demonstrate the generality of the reduction with diborane, both compounds **5e** and **5f** were subjected to this reagent. Reduction of the free base of **5e** and the subsequent treatment with hydrogen chloride lead to the known[4] 5-(3-aminopropyl)-6,7,8,9,10,11-hexahydro-5*H*-cyclooct[*b*]indole hydrochloride (**7b**). Reduction of the free base of **5f** (mp 84–85 °C) gave 5-(3-aminobutyl)-6,7,8,9,10,11-hexahydro-5*H*-cyclooct[*b*]indole (**7c**), which was isolated as the hydrochloride in 65% yield.

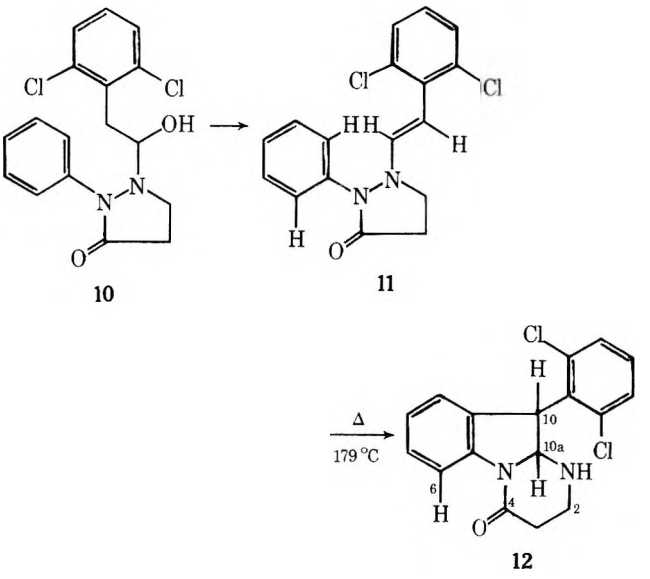
Another reductive cleavage as described above for **5a** was observed when **5f** was treated with $LiAlH_4$. Cyclooctenoindole (**6b**) was isolated and found to be identical with a commercial sample.

Isolation and Rearrangement of an Enehydrazine. Acetaldehydes did not tolerate the presence of the strong acid in attempted reactions with **4a**.

When equimolar amounts of the free base[8] 1-phenyl-5-pyrazolidinone (**4a**) and 2,6-dichlorophenylacetaldehyde[14] were mixed together, a crystalline product $C_{17}H_{16}Cl_2N_2O_2$ was isolated which we assigned structure **10** on the basis of the following data. According to the NMR spectrum of **10**, the amino alcohol seemed to dissociate at least to some degree into its components when dissolved in chloroform. Nevertheless, we were able to secure a correct elemental analysis for **10** and a mass spectrum indicating dehydration of **10** rather than reversal to the starting materials. Water was also lost when **10** was recrystallized from ethanol and a new compound $C_{17}H_{14}Cl_2N_2O$ was isolated. Analytical and spectral data are in agreement with the structure **11**. The NMR spectrum of this enehydrazine exhibits two sets of triplets at 2.82 and 3.80 ppm (J = 7.0 Hz) assigned to the methylene groups of the pyrazolidinone The two vinylic protons of **11** give rise to an AB pattern with two doublets centered at δ 5.60 and 6.73 ppm and a coupling constant of 14 Hz, indicating the presence of a trans double bond[15] in **11**. This interpretation was verified by double resonance experiments. Upon irradiation at 336 Hz, a singlet appeared at δ 6.73 ppm in place of the doublet. Absorption for two of the eight aromatic protons was observed at lower field (δ 7.85 ppm). This is interpreted as being due to the free rotation of the unsubstituted phenyl ring.

We found the enehydrazine **11** recovered unchanged even after prolonged heating to reflux in toluene. A new isomeric substance, however, was isolated after **11** was heated to 179 °C in refluxing 1,2-dichlorobenzene. The ir spectrum of the new compound possesses a NH band indicating that the original hydrazine must have undergone a cleavage. The NMR spectrum of the new compound is compatible with structure **12**. Of a total of *seven* aromatic protons we found only *one* at lower field (δ 8.10 ppm), probably due to its proximity to the carbonyl group. We assigned a broadened singlet at δ 5.44 ppm (2 H) to the protons in position 10 and 10a. Under optimal conditions this signal could be resolved to a quartet with a coupling constant J = 9 Hz and a calculated[16] $\Delta\nu$ = 6.4 Hz. The absorption for the two methylene groups no longer lends itself to first-order analysis. At δ 1.90 ppm we found a broad signal equivalent to *one* proton which could be replaced by deuterium when the sample was treated[17] with D_2O.

Scheme IV



The NMR spectrum of the hydrochloride of **12** exhibits only minor changes compared to the spectrum of the free base. The same observation was made when the NMR spectrum of **12** HCl was taken in CF_3COOH as solvent. From this we conclude that the opening of the pyrimidone ring with concomitant formation of 1-(3-aminopropanoyl)-3-(2,6-dichlorophenyl)-indole hydrochloride is not readily accomplished. This is in contrast to our observation[3a] that **2** [$R_1 = R_2 = CH_3$; $R_3 = H$; $R_4R_5 = (CH_2)_3$] in moderately strong acid exists in the ring open 3*H*-indole tautomeric form. We attribute the stability of **12** to the presence of a bulky substituent at C-10. It seems that not even the 1,4 axis of the 2,6-dichlorophenyl group can reach coplanarity with the phenyl ring of the potential indole. This hypothesis is supported by the ^{13}C NMR spectrum of **12**.

Discussion of the ^{13}C NMR Spectrum of 12. The fully proton decoupled spectrum of **12** gave a total of 17 peaks corresponding to the number of carbon atoms present. This implies the nonequivalency for the positions 2′,6′ and 3′,5′, respectively, of the 2,6-dichlorophenyl ring which is hindered in its free rotation. The results of the ^{13}C NMR spectrum, which are listed in Table VIII, further indicated the presence of only *one* isomer in **12**. Since isomerization is unlikely (see above), it may be concluded that the addition of the amide to the C=N double bond of the nine-membered-ring intermediate occurred in a stereospecific manner, though the stereochemistry of **12** is not known at this time.

Single-frequency off-resonance decoupling experiments (sford) were used to assign the number of protons attached to each carbon. This revealed the presence of *two* methylene

Table I. ^{13}C NMR Spectrum of 5a HCl in Me_2SO

Absorptions observed	Rel intensity	Assignment
170.8	83	C-10
135.8	80	C-8a
135.2	87	C-9a
130.1	94	C-4b
124.3	205	C-6
123.5	189	C-7
118.0	217	C-5
116.1	153	C-4a,8
35.6	156	C-12
34.8	180	C-11
26.1	132	C-1
23.4	149	C-4
21.4	137	C-2
20.7	148	C-3

and *two* methine groups and allowed the assignment of the peaks at 79.7 and 50.1 ppm to the carbons 10a (NCHN) and 10, respectively (see also arguments cited in the discussion of the ^{13}C NMR of **8a**).

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. NMR spectra were measured on either a Varian A-60 and/or T-60 spectrometer and are recorded in δ (ppm) values from Me_4Si as internal standard. ^{13}C NMR spectra were measured on a Varian XL-100 spectrometer and are recorded in parts per million values from Me_4Si as internal standard. Uv absorption spectra were measured in ethanol on a Cary spectrometer Model 14. Ir spectra were taken on a Perkin-Elmer Model 257 or 457. Gas–liquid chromatography was carried out on a Hewlett-Packard 5750 chromatograph. Mass spectra were taken on a LKB 9000 mass spectrometer.

9-(3-Aminopropanoyl)-1,2,3,4-tetrahydrocarbazole Hydrochloride (5a). A mixture of 5.0 g (0.025 mol) of 1-phenyl-5-pyrazolidinone hydrochloride[9] (**4a**) and 3.6 g (0.037 mol) of cyclohexanone was heated under reflux in 50 ml of glacial acetic acid for 3 h under an atmosphere of nitrogen. The product **5a** precipitated from the cold solution, yield 6.0 g (86%), mp 226–228 °C. A sample was recrystallized from ethanol: mp 227–229 °C; *m/e* 242 (M^+); ^{13}C NMR, see Table I; NMR ($CDCl_3$ + Me_2SO) δ 1.4–2.1 (m, 4) 2.3–3.8 (m, 8) 6.9–7.4 (m, 3, C_6H_3) 8.0–8.3 (m, 1, C_6H_1) 7.3–8.8 (broad, 3, NH_3); ir (Nujol) 2500–3400 (NH), 1692 (C=O), 1614 cm^{-1}; uv 244 nm (ϵ 21 760), 266 (11 900), 294 (6100), 301 (6050). Anal. Calcd for $C_{15}H_{18}N_2O.HCl$ (278.8): C, 64.6; H, 6.9; N, 10.0; Cl, 12.7. Found: C, 65.0; H, 6.9; N, 10.0; Cl, 12.7.

Tetrahydrocarbazole (6a). A solution of 1.0 g (0.004 mol) of the free base of **5a** (mp 50–52 °C) in 50 ml of THF was added to a suspension of lithium aluminum hydride (0.5 g) in the same solvent. The mixture was stirred at room temperature overnight under an atmosphere of nitrogen. Excess of the reducing agent was decomposed by slowly adding 1.5 ml of water followed by 100 ml of ether. After filtration the solvent was evaporated to yield 0.5 g (71%) of tetrahydrocarbazole (**6a**), mp 117–118 °C, identical in every respect with a commercial sample (ir, NMR, uv, TLC), mmp 117–118 °C.

Cyclooctenoindole (6b). This compound was obtained from **5f** in 87% yield following th procedures described above. It was found to be identical in every respect with a commercial sample (ir, NMR, TLC, *m/e*, melting point, and mixture melting point).

9-(3-Aminopropyl)-1,2,3,4-tetrahydrocarbazole (7a). To 2.0 g (0.008 mol) of **5a** (free base) in 25 ml of cold THF, 25 ml of a commercial solution of diborane (1 M) was added. The mixture was kept at room temperature overnight. The solution was evaporated under reduced pressure. The residue was dissolved in ether, washed with 2 N sodium carbonate, and worked up in the usual manner to yield 1.4 g (75%) of crude **7a**. A sample was converted into the maleate, mp 194–195 °C after several recrystallizations from methanol/ether. It was identical in every respect with an authentic sample[4] (ir, NMR, uv, TLC), *m/e* 228 (M^+).

5-(3-Aminopropyl)-6,7,8,9,10,11-hexahydro-5*H*-cyclooct-[*b*]indole Hydrochloride (7b) was prepared from 1.0 g (0.003 mol) of **5e** following the procedures described above: yield 0.4 g (42%); mp 210–214 °C; recrystallized from MeOH/ether; mp 242–244 °C; identical in every respect with an authentic sample.[4]

5-(3-Aminobutyl)-6,7,8,9,10,11-hexahydro-5*H*-cyclooct[*b*]-indole hydrochloride (7c) was prepared from **5f** in 65% yield as above: mp 239–240 °C; *m/e* 270 (M^+); NMR ($CDCl_3$ + Me_2SO) δ 1.42 (d, 3, J = 7 Hz, CH_3), 1.1–2.6 (m, 10), 2.6–3.6 (m, 5), 4.24 (t, 2, J = 8 Hz, indole NCH_2), 6.8–7.6 (m, 4, C_6H_4), 8.2–9.0 (3, NH_3); ir (Nujol)

Table II. Physical Properties and Analyses

Compd	St mat.	Yield, %	Mp, °C	*m/e* (M^+)	Empirical formula	Mol wt	Calcd, % C	H	N	Cl	Found, % C	H	N	Cl
5b	**4b**	79	215–217	256	$C_{16}H_{20}N_2O\cdot HCl$	292.8	65.6	7.2	9.6	12.1	65.3	7.0	9.4	11.9
5c	**4a**	48	206–208	256	$C_{16}H_{20}N_2O\cdot HCl$	292.8	65.6	7.2	9.6	12.1	65.3	7.6	9.6	12.3
5d	**4b**	23	177–178	270	$C_{17}H_{22}N_2O\cdot HCl$	306.9	66.5	7.6	9.1		66.2	7.7	9.2	
5e	**4a**	72	195–197	270	$C_{17}H_{22}N_2O\cdot HCl$	306.9	66.5	7.6	9.1	11.6	66.1	7.5	9.3	11.8
5f	**4b**	82	179–180	284	$C_{18}H_{24}N_2O\cdot HCl$	320.9	67.4	7.9	8.7	11.0	67.6	8.0	8.5	11.4
5g	**4b**	65	231–233	340	$C_{22}H_{32}N_2O\cdot HCl$	377.0	70.1	8.8	7.4	9.4	69.9	9.1	7.4	9.4

Table III. Spectral Data

Compd	Ir, cm^{-1} (NH)	(Nujol) (C=O)	Uv, nm (ϵ) in ethanol	^1H NMR in $CDCl_3$ + Me_2SO
5b	3200	1675, 1620	246 (17 100), 266 (9500), 300 (5000)	1.47 (d, 3, J = 7 Hz, CH_3), 1.6–2.2 (m, 4), 2.7–4.2 (m, 7), 7.0–7.5 (m, 3, C_6H_3), 8.0–8.2 (m, 1, C_6H_1), 7.5–8.5 (NH_3)
5c	2700–3300	1700, 1590		1.6–2.1 (m, 6, 3 CH_2), 2.4–2.9 (m, 2, CH_2), 2.9–3.8 (m, 6, 3 CH_2), 7.0–7.6 (m, 3, C_6H_3), 7.6–8.6 (m, 4, C_6H_1 + NH_3)
5d	2500–3400	1695, 1600	249 (14 900), 303 (5800)	1.47 (d, 3, J = 7 Hz, CH_3), 1.6–2.3 (m, 6, 3 CH_2), 2.5–4.3 (m, 7), 7.2–7.8 (m, 3, C_6H_3), 8.0–8.4 (m, 1, C_6H_1), 8.0–9.4 (broad, NH_3)
5e	3500	1680, 1580	248 (15 500), 271 (9500), 298 (4900) 304 (5100)	1.0–2.0 (m, 8), 2.7–3.8 (m, 8), 7.1–7.6 (m, 3, C_6H_3), 7.8–8.2 (m, 1, C_6H_1), 8.3–8.9 (broad, NH_3)
5f	3130	1680, 1600	248 (15 800), 271 (9700), 304 (5400)	1.48 (d, 3, J = 6 Hz, CH_3), 1.0–2.0 (m, 8), 2.6–4.1 (m, 7), 7.1–7.6 (m, 3, C_6H_3), 7.8–8.1 (m, 1, C_6H_1), 8.1–8.5 (NH_3)
5g	3130	1680, 1600	247 (16 300), 294 (5500), 302 (5500)	1.0–2.0 (m, 19), 2.3–4.0 (m, 7), 7.0–7.6 (m, 3, C_6H_3), 7.6–8.0 (m, 1, C_6H_1), 8.0–8.6 (NH_3)

Table IV. ^{13}C NMR Spectrum of 7d $C_4H_4O_4$ in Me_2SO

Absorption observed, ppm	Rel intensity	Assignment
168.5	123	C-1 maleic acid
146.3	70	C-4a
141.1	73	C-3a
136.7	157	C-2 maleic acid
124.5	83	C-8a
120.3	93	C-7
119.3	109	C-6
118.7	111	C-8
117.5	76	C-8b
110.4	97	C-5
41.5	117	C-9
37.1	77	C-11
28.2	138	C-1,3
24.8	102	C-2
24.5	116	C-10

Table V

^{13}C NMR Spectrum of **8a** (Free Base) in Me_2SO

Absorption observed, ppm	Rel intensity	Sford	Assignment
166.9	21		C-7
141.8	16		C-8a
133.6	36		C-12a
127.6	133		C-10
124.3	126		C-12
124.2	190		C-11
116.2	160		C-9
90.7	51		C-3a
52.7	202		C-12b
38.5	203		C-5
37.5	144		C-3
31.2	217		C-1
30.9	215		C-6
24.3	112		C-2

^{13}C NMR Spectrum of **8a** HCl in Me_2SO in Presence of $Fe(AcAc)_3$[18]

164.8	42	s	C-7
141.4	49	s	C-8a
131.2	50	s	C-12a
128.0	60	d	C-10
124.9	69	d	C-12
124.4	67	d	C-11
115.0	65	d	C-9
87.7	54	s	C-3a
51.6	98	d	C-12b
37.6	118	t	C-3
35.3	62	t	C-5
31.8	68	t	C-1
28.3	67	t	C-6
23.8	65	t	C-2

2500–3200 (NH), 1600 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2$·HCl (306.9): C, 70.5; H, 8.9; N, 9.1; Cl, 11.6. Found: C, 69.9; H, 9.1; N, 9.3; Cl, 11.9.

4-(3-Aminopropyl)-1,2,3,4-tetrahydrocyclopent[*b*]indole (7d). This compound was prepared from 0.5 g (0.002 mol) of **8a** HCl in 50 ml of ether in the presence of 1.0 g (0.025 mol) of $LiAlH_4$ and converted to the maleic acid salt, which was found to be identical with an authentic sample,[4] mmp 178–180 °C, ^{13}C NMR spectrum see Table IV.

1,2,3,4,5,12b-Hexahydrocyclopenta[*b*]pyrimido[1,2-*a*]indol-7(6*H*)-one (8a). This compound was prepared from 5.0 g (0.025 mol) of **4a** and 2.5 g (0.03 mol) of cyclopentanone in 30 ml of glacial acetic acid as described above: yield 2.0 g (30%); mp 202–203 °C; *m/e* 228 (M^+); ^{13}C NMR see Table V; NMR ($CDCl_3$ + Me_2SO) δ 1.2–2.7 (m, 6), 2.92 (t, 2, *J* = 7 Hz, O=CCH_2), 3.58 (t, 2, *J* = 7 Hz, CH_2NH_2), 4.33 (d, 1, *J* = 7 Hz, HC-12b), 7.1–7.6 (m, 3, C_6H_3), 7.9–8.2 (m, 1, C_6H_1), 10.7 (broad, 2, NH_2); ir (Nujol) 2400–2800 (NH), 1680 (C=O), 1602 cm^{-1}; uv 251 nm (ε 12 900), 278 (3300), 286 (2900). Anal. Calcd for $C_{14}H_{16}N_2O$·HCl (264.8): C, 63.5; H, 6.5; N, 10.6; Cl, 13.4. Found: C, 63.2; H, 6.6; N, 10.5; Cl, 13.6. The free base was prepred from the hydrochloride as usual: mp 130–132 °C; ^{13}C NMR see Table V; NMR (Me_2SO) δ 1.0–2.2 (m, 4), 2.2–2.6 (m, 2), 2.8–3.7 (m, 6), 6.8–7.3 (m, 3, C_6H_3), 7.7–8.0 (m, 1, C_6H_1).

1,2,3,4,5,12b-Hexahydro-5-methylcyclopenta[*b*]pyrimido-[1,2-*a*]indol-7(6*H*)-one (8b). This compound was prepared from 21.2 g (0.10 mol) of **4b** and 12.5 g (0.15 mol) of cyclopentanone in 200 ml of refluxing glacial acetic acid during 2 h; yield 23.0 g (83%); mp 243–244 °C; recrystallized from ethanol; mp 253–255 °C; *m/e* 242 (M^+); ^{13}C NMR see Table VI; NMR ($CDCl_3$ + Me_2SO) δ 1.48 (d, 3, *J* = 7 Hz, CH_3), 1.0–3.6 (m, 8, 4 CH_2), 3.6–4.4 (broad, 1, $CHCH_3$), 4.20 (d, 1, *J* = 7 Hz, HC-12b), 7.0–7.6 (m, 3, C_6H_3), 7.8–8.2 (m, 1, C_6H_1), below 9.0 (broad, 2, NH_2); ir (Nujol) 2300–2800 (NH), 1672 (C=O), 1602 cm^{-1}; uv 251 nm (ε 12 610), 278 (3230), 286 (2850). Anal. Calcd for $C_{15}H_{18}N_2O$·HCl (278.8): C. 64.6; H, 6.9; N, 10.0; Cl, 12.7. Found: C, 64.8; H, 6.8; N, 10.2; Cl, 12.8. The free base was isolated after a mixture of 0.150 g (0.005 mol) of **8b** HCl and 4 ml (0.08 mol) of 2 N NaOH was heated to reflux for 2 days in 15 ml of methanol: yield 75 mg (57%); mp 116–118 °C; *m/e* 242 (M^+); NMR ($CDCl_3$ + Me_2SO) 1.23 (d, 3, *J* = 6 Hz, CH_3), 3.0 (s, 1, exchangeable with D_2O, NH), 1.4–3.7 (m, 10), 6.8–7.4 (m, 3, C_6H_3), 7.8–8.1 (m, 1, C_6H_1).

1,2,3,4,5,6,7,12b-Octahydro-5-methylcyclopenta[*b*]pyrimido-[1,2-*a*]indole (9). To the suspension of 0.2 g (0.005 mol) of lithium aluminum hydride in 25 ml of anhydrous ether there was added 0.050 g (0.0002 mol) of **8b**. The mixture was stirred at room temperature for 2 h. After the usual workup 0.030 g (73%) of a liquid was obtained which was converted to the maleic acid salt: mp 158–159 °C; *m/e* 228 (M^+); ^{13}C NMR see Table VII; NMR ($CDCl_3$ + Me_2SO) δ 1.20 (d, 3,

Table VI. ^{13}C NMR Spectrum of 8b HCl in Me_2SO

Absorption observed, ppm	Rel intensity	Assignment
164.6	75	C-7
141.8	50	C-8a
131.4	92	C-12a
128.4	190	C-10
125.5	172	C-12
124.6	148	C-11
115.5	126	C-9
87.9	104	C-3a
51.7	216	C-12b
45.5	211	C-5
38.7	185	C-6
36.6	164	C-3
31.7	177	C-1
23.9	175	C-2
19.0	125	CH_3

Table VII. ^{13}C NMR Spectrum of 9 $C_4H_4O_4$ in Me_2SO

Absorption observed, ppm	Rel intensity	Assignment
168.1	26	C-1 maleic acid
149.0	36	C-8a
136.5	217	C-2 maleic acid
130.4	82	C-12a
128.6	140	C-12
124.9	148	C-10
118.3	155	C-11
105.8	140	C-9
90.4	130	C-3a
51.8	203	C-12b
49.4	209	C-5
37.3	160	C-7
33.5	198	C-3
32.7	176	C-6
28.8	159	C-1
25.3	177	C-2
19.0	166	CH_3

Table VIII. ^{13}C NMR Spectrum of 12 in $CHCl_3$

Absorptions observed, ppm	Rel intensity	Sford	Assignment
166.9	101	s	C-4
141.3	63	s	C-5a
138.1	55	s	C-1′
136.1	65	s	C-2′
134.1	50	s	C-6′
131.1	158	d	C-4′
130.5	114	s	C-9a
130.1	171		C-3′
129.3	169		C-5′
128.5	163		C-7
124.9	176		C-9
123.7	182	d	C-8
116.9	142	d	C-6
79.7	174	d	C-10a
50.1	220	d	C-10
41.7	168	t	C-2
31.7	190	t	C-3

J = 6 Hz, $CHCH_3$), 1.4–2.6 (m, 7), 3.0–4.0 (m, 4), 6.00 (s, 2, maleic acid), 6.3–7.3 (m, 4, C_6H_4); ir (Nujol) 2300–3500 (NH), 1618, 1585 cm^{-1}; uv 248 nm (ϵ 11 700), 303 (2500). Anal. Calcd for $C_{15}H_{20}N_2 \cdot C_4H_4O_4$ (344.3): C, 66.3; H, 7.0; N, 8.1. Found: C, 66.0; H, 7.0; N, 7.9.

1-[2-(2,6-Dichlorophenyl)-1-hydroxyethyl]-2-phenyl-3-pyrazolidinone (10). A mixture of 1.6 g (0.01 mol) of 1-phenyl-5-pyrazolidinone[8] and 1.9 g (0.01 mol) of 2,6-dichlorophenylacetaldehyde[14] was warmed in 50 ml of toluene until a clear solution was obtained. Upon cooling the product precipitated as a white solid, mp 119–120 °C, yield 2.6 g (74%). A small sample was recrystallized from ethanol: mp 128–130 °C; m/e 332 ($M^+ - 18$); NMR ($CDCl_3$) δ 2.67 (t, J = 7.5 Hz), 3.1–4.0 (m), 4.11[19] (d, J = 1.5 Hz), 4.5–5.1 (m), 6.9–7.6 (m), 7.7–8.0 (m), 9.7 (t, J = 3 Hz); ir (CH_2Cl_2) 3580 (NH or OH), 1720, 1690, 1590 cm^{-1}. Anal. Calcd for $C_{17}H_{16}Cl_2N_2O_2$ (351.25): C, 58.1; H, 4.6; N, 8.0; Cl, 20.2. Found: C, 58.1; H, 4.6; N, 8.1; Cl, 20.1.

1-(*trans*-2,6-Dichlorostyryl)-2-phenyl-3-pyrazolidinone (11). When the crude compound **10** was recrystallized from hot ethanol/water the product precipitated as a white solid: mp 133–134 °C; m/e 332 (M^+); NMR ($CDCl_3$) δ 2.82 (t, 2, J = 7.0 Hz, $COCH_2$), 3.80 (t, 2, J = 7.0 Hz, NCH_2), 5.60 (d, 1, J = 14 Hz, vinyl H), 6.73 (d, 1, J = 14 Hz, vinyl H), 6.8–7.7 (m, 6, aromatic), 7.7–8.1 (m, 2, 2,6-C_6H_2); ir (CH_2Cl_2) 1710 (C=O), 1645, 1594 cm^{-1}; uv 273 nm (ϵ 16 500). Anal. Calcd for $C_{17}H_{14}Cl_2N_2O$ (333.2): C, 61.3; H, 4.2; N, 8.4; Cl, 21.3. Found: C, 61.2; H, 4.3; N, 8.2; Cl, 20.9.

10-(2,6-Dichlorophenyl)-1,2,10,10a-tetrahydropyrimido-[1,2-*a*]indol-4(3*H*)-one (12). A solution of 4.0 g (0.012 mol) of **11** in 50 ml of *o*-dichlorobenzene was heated to reflux under an atmosphere of nitrogen during 12 h. The solvent was evaporated under reduced pressure. The product solidified upon the addition of ether, mp 201–203 °C, yield 3.6 g (90%). A sample was recrystallized from methylene chloride/hexane: mp 203–205 °C; m/e 332 (M^+); ^{13}C NMR see Table VIII; NMR ($CDCl_3$) δ 1.90 (broad singlet, 1, exchangeable[17] with D_2O, NH), 2.3–2.8 (m, 2, $COCH_2$), 2.8–3.7 (m, 2, $NHCH_2$), 5.44 (q, 2, J = 9 Hz, $\Delta\nu$ = 6.4 Hz, 2 CH), 6.6–7.6 (m, 6, 2 C_6H_3), 7.9–8.3 (m, 1, C_6H); ir (CH_2Cl_2) 3300 (NH), 1655 (C=O), 1600, 1580, 1560 cm^{-1}; uv 265 nm (ϵ 14 500), 301 (3260). Anal. Calcd for $C_{17}H_{14}Cl_2N_2O$ (333.2): C, 61.3; H, 4.2; N, 8.4; Cl, 21.3. Found: C, 60.9; H, 4.5; N, 8.3; Cl, 21.3.

The hydrochloride of **12** was prepared following the usual procedures: mp 258–261 °C (ethanol/ether); NMR ($CDCl_3$ + Me_2SO) δ 2.88 (t,[20] 2, J = 6.7 Hz, $COCH_2$), 3.55 (t,[20] 2, J = 6.7 Hz, NCH_2), 5.96 (q, 2, J = 9 Hz, $\Delta\nu$ = 4.1 Hz, 2 CH), 6.7–7.7 (m, 6, 2 C_6H_3), 7.9–8.2 (m, 1, C_6H), below 8.5 (broad, 2, NH_2); ir (Nujol) 3450 (NH), 1670 cm^{-1} (C=O); uv 249 nm (ϵ 13 700), 279 (3200), 288 (2740). Anal. Calcd for $C_{17}H_{14}Cl_2N_2O \cdot HCl$ (369.69): C, 55.2; H, 4.1; N, 7.6. Found: C, 54.9; H, 4.2; N, 7.6.

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Registry No—**4a,** 60260-53-9; **4a** free base, 16860-34-7; **4b,** 13292-56-3; **5a,** 60260-54-0; **5a** free base, 60260-55-1; **5b,** 60260-56-2; **5c,** 60260-57-3; **5d,** 60260-58-4; **5e,** 60260-59-5; **5f,** 60260-60-8; **5f** free base, 60260-61-9; **5g,** 60260-62-0; **7c** HCl, 60260-63-1; **7d** maleate, 52987-43-6; **8a,** 60260-64-2; **8a** HCl, 60260-65-3; **8b,** 60260-66-4; **8b** HCl, 60260-67-5; **9** maleate, 60260-69-7; **10,** 60260-70-0; **11,** 60260-71-1; **12,** 60260-72-7; **12** HCl, 60260-73-3; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; cyclooctanone, 502-49-8; cyclododecanone, 830-13-7; cyclopentanone, 120-92-3; 2,6-dichlorophenylacetaldehyde, 20973-90-4.

References and Notes

(1) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **113,** 639 (1918); **125,** 827 (1924).
(2) B. Robinson, *Chem. Rev.*, **69,** 227 (1969).
(3) (a) M. K. Eberle and G. Kahle, *Tetrahedron*, **29,** 4049 (1973); (b) P. L. Southwick, J. A. Vida, B. M. Fitzgerald, and S. Ki Lee, *J. Org. Chem.*, **33,** 2051 (1968).
(4) M. K. Eberle, G. Kahle, and S. Talati, *Tetrahedron*, **29,** 4045 (1973).
(5) (a) N. N. Suvorov, N. P. Sorokina, and Yu. N. Sheinker, *J. Gen. Chem. USSR (Engl. Transl.)*, **28,** 1090 (1958); *Chem. Abstr.*, **52,** 18373*d* (1958); (b) R. H. Elgersma and E. Havinga, *Tetrahedron Lett.*, 1735 (1969).
(6) H. Posvic, R. Dombro, H. Ito, and T. Telinski, *J. Org. Chem.*, **39,** 2575 (1974).
(7) G. Kollenz and C. Labes, *Justus Liebigs Ann. Chem.*, 1979 (1975).
(8) (a) P. Bouchet, J. Elguero, and R. Jacquier, *Tetrahedron*, **22,** 2461 (1966); (b) *Bull. Soc. Chim. Fr.*, 3502 (1967).
(9) S. Gaft, N. Zakharova, N. Khromov-Borisov, V. Zaitsev, S. Kozhevnikov, and L. Sinkevich, *Zh. Org. Khim.*, 3, 542 (1967); *Chem. Abstr.*, **67,** 11451g (1967).
(10) While this manuscript was being prepared, a paper appeared describing the reduction of 1-formyl-3-methylindole in the presence of diborane: A. Chatterjee and K. M. Biswas, *J. Org. Chem.*, **40,** 1257 (1975).
(11) J. B. Stothers, "Organic Chemistry", Vol. 24, Academic Press, New York, N.Y., 1972.
(12) E. Wenkert, J. S. Bindra, C. J. Chang, D. W. Chochran, and F. M. Schell, *Acc. Chem. Res.*, **7,** 46 (1974).
(13) Unpublished results.
(14) (a) H. Bredereck, G. Simchen, and R. Wahl, *Chem. Ber.*, **101,** 4048 (1968); (b) J. B. Bream, C. W. Picard, T. G. White, and H. Lauener, *J. Med. Chem.*, **13,** 1051 (1970).
(15) P. Laszlo, and P. v. R. Schleyer, *Bull. Soc. Chim. Fr.*, 87 (1964).
(16) R. H. Bible, "Interpretation of NMR Spectra", Plenum Press, New York, N.Y., 1965.
(17) The sample was filtered through a glass wool filter. Deuterium exchange was reversed when the sample was filtered through a cotton filter. The authors are grateful to Mrs. Nancy Engstrom for conveying this observation.
(18) S. Barcza and N. Engstrom, *J. Am. Chem. Soc.*, **94,** 1762 (1972).
(19) Absorption coincides with the methylene absorption of the 2,6-dichlorophenylacetaldehyde.
(20) K. B. Wiberg and N. J. Nist, "The Interpretation of NMR Spectra", W. A. Benjamin, New York, N.Y., 1962, p 319, no. 5–3.

Pyrimidine Derivatives and Related Compounds. 4. A Route for the Synthesis of Pyrazolo[3,4-*e*]-*as*-triazines, Pyrazolo[3,4-*d*]pyrimidines, and Pyrazolo[1,5-*c*]-*as*-triazines

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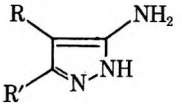
5-Amino-3-phenylpyrazole (**1a**) reacts with benzoyl isothiocyanate (**2**) to yield 5-amino-4-benzoylthiocarbamoyl-3-phenylpyrazole (**1b**). On the other hand, the 5-amino-4-arylazopyrazoles **1c–e** reacted with **2** to yield thiourea derivatives **3b–d** which could be cyclized into the pyrazolo[3,4-*e*]-*as*-triazine derivatives **5a–c**. 5-Amino-4-cyano-3-cyanomethylpyrazole (**1f**) reacted with **2** to yield 4-amino-3-cyanomethyl-6-mercapto-1*H*-pyrazolo[3,4-*d*]pyrimidine (**7**). **1a** was diazotized and the resulting diazonium salt was coupled with a variety of active methylene β functional compounds to afford pyrazolo[1,5-*c*]-*as*-triazine derivatives. The intermediate coupling products could be isolated in some cases. The behavior of the pyrazolo[1,5-c]-*as*-triazine derivatives **11a–c** toward the action of hydroxylamine, ethanolic sodium ethoxide, and acetic–hydrochloric acid mixture is reported.

The considerable biological and medicinal activities of pyrazolopyrimidines[1–4] and of pyrazolotriazines,[5–7] as adenine analogues, antagonists, and antitumor agents[8,9] have stimulated recent interest in the synthesis of derivatives of these ring systems. In continuation of our previous work,[10–15] we have investigated a variety of synthetic routes to pyrazolo[3,4-*d*]pyrimidines, pyrazolo[3,4-*e*]-*as*-triazines, and pyrazolo[1,5-c]-*as*-triazines. This work has led to some new procedures for the synthesis of several known heterocyclic systems from 5-aminopyrazoles in good yields and under milder conditions than previously reported.

The reaction of 5-aminopyrazoles with acetyl isothiocyanate and with ethoxycarbonyl isothiocyanate is straightforward and affords the expected pyrazol-5-ylthiourea derivatives which cyclize readily to pyrazolo[1,5-*a*]-*as*-triazines in base.[16–18] We have found, however, that 5-amino-3-phenylpyrazole (**1a**) reacts with benzoyl isothiocyanate (**2**), in refluxing acetone, to give 5-amino-4-benzoylthiocarbamoyl-3-phenylpyrazole (**1b**) as the only product. The ^{1}H NMR spectrum of this product revealed the absence of a signal at δ 5–7.3 ppm for C_4 proton[19] indicating substitution at this position. Moreover, the chemical behavior of **1b** is different from that expected for pyrazolylthiourea derivatives (cf. possible alternative structure **3a** or **4**) and resembles that of pyrazole-4-carboxylic acid derivatives. Thus, **1b** was recovered largely unchanged when refluxed in pyridine solution or in aqueous 2 N NaOH solution (cf. the hydrolysis of *N*-(pyrazol-5-yl)-*N'*-acetylthioureas under these conditions in ref 16 and 17). When **1b** was heated with Ac_2O, 5-acetamido-3-phenylpyrazole (**3b**) was formed in 90% yield. Compound **3b** was also obtained by the action of Ac_2O on **1a**. These results parallel the facile decarboxylation of 5-aminopyrazole-4-carboxylic acid derivatives under acidic conditions.[20] Although the position of NH_2 signals depends much on solvent and concentration of solutions, the downfield shift of the NH_2 protons of **1b** (8.18 ppm) as compared with previously reported values for NH_2 protons in 5-aminopyrazoles[19] may be attributed to deshielding of these protons by the adjacent benzoylthiocarbamoyl groups at C_4. A similar effect on the NH_2 protons due to action of the adjacent thiocarbamoyl moiety has been observed.[21]

In contrast to the reaction of **1a** with **2** the 5-amino-4-arylazopyrazoles (**1c–e**) reacted with **2** to give the expected pyrazol-5-ylthioureas **3c–e.** When these products were refluxed with acetic acid–hydrochloric acid mixture for a short time, yellow products were obtained in high yields. Structure **5** was suggested for these reaction products on the basis of analytical and spectral data. The reaction of **3c** with hydrazine hydrate in refluxing ethanol give the pyrazolylthiourea derivative **3f.** The cyclization of **3c–e** into **5a–c** constitutes a new, simple, and efficient route for the preparation of pyrazolo[3,4-*e*]-*as*-triazines, only a few of which have been previously reported.[22,23]

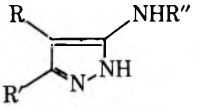
5-Amino-4-cyano-3-cyanomethylpyrazole (**1f**) reacted with **2** to yield the pyrazolo[3,4-*d*]pyrimidine derivative **7.** The formation of **7** from **1f** and **2** may be assumed to take place via the benzoylthiourea derivative which then undergoes cyclization to **6.** The latter then decomposes to the final product **7** during purification. Compound **7** was hydrolyzed into the



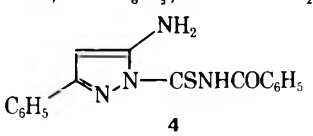
$C_6H_5CON{=}C{=}S$

2

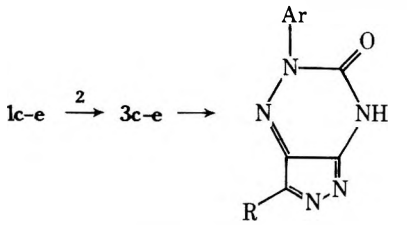
1a, R = H; R′ = C_6H_5
b, R = $C_6H_5CONHCS$; R′ = C_6H_5
c, R = $C_6H_5N{=}N$; R′ = C_6H_5
d, R = *p*-$CH_3C_6H_4N{=}N$; R′ = C_6H_5
e, R = $C_6H_5N{=}N$; R′ = CH_3
f, R = CN; R′ = CH_2CN



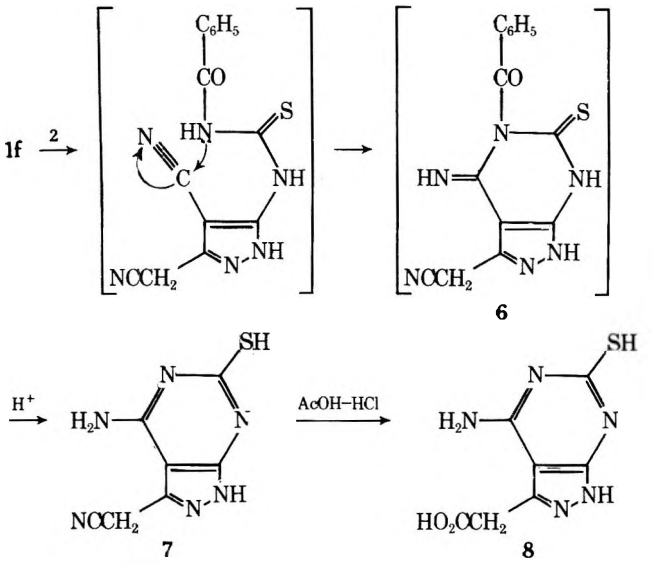
3a, R = H; R′ = C_6H_5; R″ = $CSNHCOC_6H_5$
b, R = H; R′ = C_6H_5; R″ = $COCH_3$
c, R = $C_6H_5N{=}N$; R′ = C_6H_5; R″ = $CSNHCOC_6H_5$
d, R = *p*-$CH_3H_6H_4N{=}N$; R′ = C_6H_5; R″ = $CSNHCOC_6H_5$
e, R = $C_6H_5N{=}N$; R′ = CH_3; R″ = $CSNHCOC_6H_5$
f, R = $C_6H_5N{=}N$; R′ = C_6H_5; R″ = $CSNH_2$



4

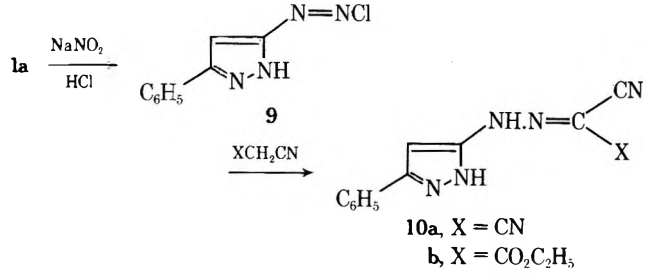


5a, R = Ar = C_6H_5
b, R = C_6H_5; Ar = $C_6H_4CH_3$-*p*
c, R = CH_3; Ar = C_6H_5

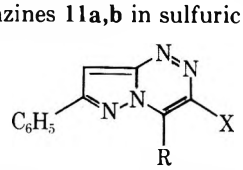


carboxylic acid 8 by the action of acetic acid–hydrochloric acid mixture. The behavior of **1f** toward **2** is similar to that of cyclic enaminonitriles toward the action of isothiocyanates.[24]

Diazotization of 5-aminopyrazoles in strong acids has been reported to afford the corresponding diazonium salts,[25,26] which undergo coupling with phenols to yield pyrazolotriazines by intermolecular condensation.[26] Pyrazole-3-diazonium chloride, when treated with β-keto acids or esters, gave products which spontaneously cyclized to pyrazolo[1,5-c]-*as*-triazines.[27] Coupling with compounds such as ethyl cyanoacetate gave azo compounds which also readily cyclized to pyrazolotriazines.[27] In the present work 3-phenylpyrazole-5-diazonium chloride (**9**) was prepared by diazotization



of **1a** and its reactions with a variety of active methylene reagents were investigated. Thus **9** coupled with malononitrile or with ethyl cyanoacetate to yield the corresponding pyrazol-5-ylhydrazones **10a,b** which readily cyclized to the pyrazolo[1,5-c]-*as*-triazines **11a,b** in sulfuric acid. Compound **9**



11a, X = CN; R = NH_2
b, X = CN; R = OH
c, X = CN; R = CH_3
d, X = $CO_2C_2H_5$; R = CH_3
e, X = (C:NOH)NH_2; R = NH_2
f, X = (C:NOH)NH_2; R = OH
g, X = (C:NOH)NH_2; R = CH_3
h, X = $CONH_2$; R = NH_2
i, X = $CONH_2$; R = OH
j, X = $CONH_2$; R = CH_3
k, X = CO_2H; R = NH_2
l, X = CO_2H; R = OH
m, X = CO_2H; R = CH_3

reacted with 3-iminobutyronitrile or with ethyl acetoacetate to yield directly the pyrazolo[1,5-c]-*as*-triazine derivatives **11c,d**, respectively.

The behavior of **11a–c** toward the action of hydroxylamine, ethanolic sodium ethoxide, and acetic acid–hydrochloric acid mixture was also investigated with the aim of preparing a variety of 6 substituted derivatives of **11**. In this manner, treatment of **11a–c** with hydroxylamine hydrochloride and sodium acetate in refluxing ethanol solution has resulted in the formation of the amidoximes **11e–g**.

Compounds **11a–c** reacted with ethanolic sodium ethoxide to yield the amides **11h–j**.

Treatment of **11a–c** with acetic acid–hydrochloric acid mixture has resulted in the formation of the carboxylic acid derivatives **11k–m**. The ir and ^1H NMR data for all compounds **11a–m** were in good agreement with proposed structures (cf. tables).

Table I. List of the Pyrazolythiourea Derivatives 3c–f

Registry no.	Compd	Crystn solvent	Mp, °C	Yield, %	Formula
60269-77-4	**3c**	EtOH	243	60	$C_{23}H_{18}ON_6S$
60269-78-5	**3d**	AcOH	248	60	$C_{24}H_{20}ON_6S$
59119-57-2	**3e**	EtOH	224	55	$C_{18}H_{16}ON_6S$
60269-79-6	**3f**	AcOH	114	70	$C_{16}H_{14}N_6S$

Table II. List of the Pyrazolo[1,5-c]-*as*-triazine Derivatives 11a–m

Registry no.	Compd	Yield, %	Crystn solvent	Mp, °C	Formula
60269-80-9	**11a**	80	*a*	287	$C_{12}H_8N_6$
60269-81-0	**11b**	75	*b*	246	$C_{12}H_7ON_5$
60269-82-1	**11c**	70	*b*	210	$C_{13}H_9N_5$
60269-83-2	**11d**	65	*b*	149	$C_{15}H_{14}O_2N_4$
60269-84-3	**11e**	45	*c*	300	$C_{12}H_{11}ON_7$
60269-85-4	**11f**	40	*b*	244	$C_{12}H_{10}O_2N_6$
60269-86-5	**11g**	40	*b*	255	$C_{13}H_{12}ON_6$
60269-87-6	**11h**	50	*c*	300	$C_{12}H_{10}ON_6$
60269-88-7	**11i**	53	*d*	222	$C_{12}H_9O_2N_5$
60269-89-8	**11j**	50	*b*	290	$C_{13}H_{11}ON_5$
60269-90-1	**11k**	70	*b*	300	$C_{12}H_9O_2N_5$
60269-91-2	**11l**	75	*c*	300	$C_{12}H_8O_3N_4$
60269-92-3	**11m**	72	*c*	180	$C_{13}H_{10}O_2N_4$

[a] Pyridine. [b] Ethanol. [c] Acetic acid. [d] Methanol.

Experimental Section

All melting points are uncorrected. Infrared spectra were recorded (KBr) on a Perkin-Elmer Model 337 spectrophotometer. Proton magnetic resonance spectra were obtained with a Varian A-60 spectrophotometer using Me_4Si as internal standard and chemical shifts are expressed as δ, parts per million. Satisfactory analytical data (±0.3%) were obtained for all compounds listed in Tables I and II.

Reaction of 1a,c–e with Benzoyl Isothiocyanate (2). General Procedure. To a solution of **2** (prepared from 0.12 mol of NH_4SCN and appropriate quantity of BzCl as has been described by Douglass and Dains[28]), 0.1 mol of the compound in acetone (50 ml) was added. The reaction mixture was refluxed for 2 h and then evaporated in vacuo. The remaining product was washed several times with water and then boiled with 100 ml of ethanol. The solid products, **1b, 3c–e,** were collected by filtration and crystallized from ethanol.

1b: colorless crystals; mp 242 °C; yield 22.5 g (0.07 mol, 70%); ir 1670 (benzoyl C=O) and 2550–3450 cm^{-1} (NH bands); ^1H NMR δ 7.4–8.0 (m, 10 H, 2 C_6H_5), 8.18 (d, 2 H, NH_2 lost after D_2O exchange), 11.68 (br, 1 H, amide NH), and 13.28 (br, 1 H, ring NH).

Anal. Calcd for $C_{17}H_{14}ON_4S$: C, 63.35; H, 4.38; N, 17.38; S, 9.96. Found: C, 63.22; H, 4.41; N, 17.35; S, 9.67.

N-(4-Arylazo-3-substituted-pyrazol-5-yl)-*N'*-benzoylthiourea derivatives (3c–e), listed in Table I, showed ir bands at 1670 (C=O), 3050–3100, and 3320–3340 cm^{-1} (NH groups). The ^1H NMR spectrum of **3c** showed signals at δ 7.2–8.0 (m, 15 H, 3 C_6H_5), 11.67 (br, 1 H, amide NH), and 13.28 (BR= [H, ring NH).

Action of Ac_2O on 1b. A solution of **1b** (3.0 g) in Ac_2O (25 ml) was refluxed for 3 h and then poured onto water (150 ml). The resulting reaction mixture was boiled till complete decomposition of excess Ac_2O and then left to stand. The solid product, so formed, was collected by filtration and crystallized from water.

3b: colorless crystals; mp 147 °C; yield 1.7 g (0.008 mol, 90%); ir 1690 (acyl CO), 3340 cm^{-1} (NH); ^1H NMR δ 2.0 (s, 3 H, CH_3), 6.18 (s, 1 H,

ring NH), 7.2–8.0 (m, 5 H, C_6H_5), 11.9 (s, H, amide NH, lost after D_2O exchange), and 13.6 (br, ring NH, lost after D_2O exchange).

Anal. Calcd for $C_{11}H_{11}ON_5$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.50; N, 5.59; N, 20.68.

Compound **3b** was also obtained as follows. **1a** (1.0 g) was refluxed in Ac_2O solution (10 ml) for 15 min. The resulting solution was poured onto water and excess Ac_2O was decomposed by boiling in water for a short period. The crystals formed on standing were collected by filtration (0.9 g) and the product was identified (melting point, mixture melting point, and ir) as **3b.**

2-Aryl-2,3-dihydro-7-substituted-3-oxo-4*H*-pyrazolo[3,4-*e*]-*as*-triazine (5a–c). To a suspension of each of **3c–e** (3.0 g) in acetic acid (20 ml), 2 ml of concentrated hydrochloric acid was added. The reaction mixture was refluxed for 30 min and then poured onto water. The solid products **5a–c** were collected by filtration and crystallized from acetic acid. Compounds **5a–c** are all buff in color.

5a: mp 230 °C; yield 1.62 g (0.006 mol, 80%).

Anal. Calcd for $C_{16}H_{11}ON_5$: C, 66.42; H, 3.83; N, 24.21. Found: C, 66.44; H, 3.79; N, 24.05.

5b: mp 220 °C; yield 1.73 g (0.006 mol, 82%).

Anal. Calcd for $C_{17}H_{13}ON_5$: C, 67.31; H, 4.32; N, 23.09. Found: C, 67.33; H, 4.39; N, 23.08.

5c: mp 120 °C; yield 7.33 g (0.006 mol, 65%).

Anal. Calcd for $C_{11}H_9ON_5$: C, 58.14; H, 3.99; N, 30.82. Found: C, 58.07; H, 4.10; N, 31.00.

Compounds **5a–c** showed ir bands at 1700 (ring C=O) and 3320 cm^{-1} (NH).

1-(4-Phenylazo-3-phenylpyrazol-5-yl)-2-thiourea (3f). A suspension of **3c** (2.0 g) in ethanol (80 ml) was treated with hydrazine hydrate (2 ml, 80%). The reaction mixture was refluxed for 4 h and then evaporated in vacuo. The remaining product was triturated with water and the resulting solid product was collected by filtration and crystallized from acetic acid. Compound **3f** is listed in Table I.

4-Amino-3-cyanomethyl-6-mercapto-1*H*-pyrazolo[3,4-*d*]pyrimidine (7). A solution of 0.1 mol of **1f** in pyridine (100 ml) was treated with a solution of 0.1 mol of **2** (prepared as described above) in 50 ml of acetone. The reaction mixture was refluxed for 2 h and then evaporated in vacuo. The product, so formed, dissolved in water and the resulting solution was acidified with hydrochloric acid. The resulting solid product was collected by filtration and crystallized from acetic acid to yield 8.0 g (0.04 mol, 40%) of **7.** Recrystallization of this product from acetic acid afforded analytically pure sample.

7: mp 220 °C; ir 1650 (δ NH_2), 2255 (unconjugated CN), 3250 and 3480 cm^{-1} (ν NH_2).

Anal. Calcd for $C_7H_6N_6S$: C, 40.78; H, 2.94; N, 40.77; S, 15.52. Found: C, 40.58; H, 3.21; N, 40.67; S, 15.59.

4-Amino-3-carboxymethyl-6-mercapto-1*H*-pyrazolo[3,4-*d*]pyrimidine (8). To a mixture of acetic acid (30 ml) and hydrochloric acid (8.0 ml), 3.0 g of **7** was added and the mixture was refluxed for 2 h. The solvent was removed in vacuo and the residue was treated with a little water. The solid product, which separated on standing, was collected by filtration and crystallized from acetic acid to yield 1.5 g (0.008 mol, 44%) of **8:** mp 260 °C; ir 1700 (CO) and broad band from 2500 to 3300 cm^{-1} (OH dimer and NH groups).

Anal. Calcd for $C_7H_7O_2N_5S$: C, 37.34; H, 3.13; N, 31.11; S, 14.21. Found: C, 37.51; H, 3.3; N, 31.00; S, 14.27.

3-Phenylpyrazole-5-diazonium Chloride (9). A suspension of **1a** (0.1 mol) in acetic acid (80 ml) was treated with hydrochloric acid (30 ml, 37.5%). The mixture was heated to produce a clear solution and then cooled to 5 °C. A solution of $NaNO_2$ (7.0 g) in 30 ml of water was then gradually added with stirring. The reaction mixture was left in a refrigerator for 2 h, then poured onto cold water. The solid product separated was collected by filtration and washed several times with hot ethanol to afford an analytically pure sample of **9,** mp 168 °C, yield 11.4 g (0.055 mol, 55%).

Anal. Calcd for $C_9H_7N_4Cl$: C, 52.35; H, 3.38; N, 27.10; Cl, 17.19. Found: C, 52.01; H, 3.65; N, 26.89; Cl, 16.97.

3-Phenylpyrazol-5-ylhydrazonomesoxalonitrile (10a). A solution of malononitrile (0.1 mol) in ethanol (100 ml) was treated with a suspension of sodium acetate (10 g) in 50 ml of water. A solution of **9** (0.1 mol) in 50 ml of acetic acid was then added with stirring. The solid product, obtained on standing, was collected by filtration and washed several times with hot water. An analytically pure sample of **10a** was prepared by extracting the solid product (13.0 g, 0.005 mol, 55%) so obtained by hot ethanol and filtration while the solution was hot. **10a:** mp >300 °C; ir 1630 (C=N), 2235 (CN), and 3220, 3330 cm^{-1} (NH groups); ^1H NMR δ 6.2 (1 H, ring CN), 7.4–8.0 (5 H, C_6H_5), 12.7 (1 H, hydrazone NH), and 13.3 (1 H, ring NH).

Anal. Calcd for $C_{12}H_8N_6$: C, 61.00; H, 3.41; N, 35.58. Found: C, 61.22; H, 4.15; N, 35.30.

Ethyl 3-Phenylpyrazol-5-ylhydrazonocyanoglyoxalate (10b). This compound was prepared from ethyl cyanoacetate and **9** in the same manner as **10a** and was obtained as a cream-colored solid in a 60% yield: mp 196 °C; ir 1725 (ester CO), 2190 (conjugated CN), and 3310–3325 cm^{-1} (NH groups); ^1H NMR δ 1.43 (t, 3 H, ester CH_3), 4.45 (q, 2 H, ester CH_2), 6.2 (s, 1 H, ring CH), 7.4–8.0 (m, 5 H, C_6H_5), 12.3 (br, NH), 13.3 (br, NH), and 13.3 (br, 1 H, ring NH).

Anal. Calcd for $C_{14}H_{13}O_2N_5$: C, 59.35; H, 4.63; N, 24.72. Found: C, 59.54; H, 4.61; N, 25.00.

Cyclization of 10a,b. A mixture of each of **10a,b** (3.0 g) and concentrated H_2SO_4 (2.0 ml) was kept at room temperature for 30 min. The mixture was then diluted with water and neutralized by addition of ammonia, and the resulting products were collected by filtration. The reaction products, **11a,b,** are listed in Table II.

6-Cyano-7-methyl-2-phenylpyrazolo[1,5-*c*]-*as*-triazine (11c). This compound was obtained from reaction of 3-iminobutyronitrile and **9** using the same experimental conditions described for coupling of **9** with malononitrile. The reaction product is listed in Table II.

6-Ethoxycarbonyl-7-methyl-2-phenylpyrazolo[1,5-c]-*as*-triazine (11d). This compound was prepared by coupling of **9** and ethyl acetoacetate as described for synthesis of **11c** and is listed in Table II.

Reaction of 11a–c with Hydroxylamine. To a suspension of the nitrile (0.1 mol) in ethanol (100 ml) a solution of NH_2OH·HCl (0.1 mol) in 30 ml of water and 10 g of anhydrous sodium acetate were added. The reaction mixture was refluxed for 3 h and then poured onto water. The solid product formed was collected by filtration and crystallized from the proper solvent. The amidoxime derivatives **11e–g** are listed in Table II.

2-Phenyl-7-substituted-pyrazolo[1,5-*c*]-*as*-triazine-3-carboxyamide (11h–j). To a sodium ethoxide solution (prepared from 1 g of sodium metal and 80 ml of ethanol), 0.02 mol of each of **11a–c** was added. The reaction mixture was then refluxed for 3 h, left to cool, poured over water, and acidified with concentrated hydrochloric acid. The solid product, so formed, was collected by filtrated and crystallized. The reaction products, **11h–j,** are listed in Table II.

2-Phenyl-7-substituted-pyrazolo[1,5-*c*]-*as*-triazine-3-carboxylic Acid (11k–m). To a mixture of acetic acid (30 ml), water (5 ml), and hydrochloric acid (5.0 ml, 35.5%) 3.0 g of each of **11a–c** was added and the mixture was refluxed for 6 h. The solvent was then removed in vacuo and the remaining solid product was purified by dissolution in sodium carbonate, filtration of insoluble impurities, and reprecipitation by acidification. The carboxylic acid derivatives **11k–m,** listed in Table II, were purified by crystallization from the proper solvent.

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Registry No.—**1a,** 1572-10-7; **1b,** 60269-93-4; **1c,** 57695-75-7; **1d,** 60269-94-5; **1e,** 57695-74-6; **1f,** 54711-21-6; **2,** 532-55-8; **3b,** 50671-40-4; **5a,** 60269-95-6; **5b,** 60269-96-7; **5c,** 60269-97-8; **7,** 60269-98-9; **8,** 60269-99-0; **9,** 60270-00-0; **10a,** 60270-01-1; **10b,** 60270-02-2; malononitrile, 109-77-3; ethyl cyanoacetate, 105-56-6; 3-iminobutyronitrile, 1118-60-1.

Supplementary Material Available. Ir and ^1H NMR spectral data (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) G. B. Elion, S. W. Callahan, H. C. Nathan, S. Bieber, R. W. Rundles, and G. H. Hitchings, *Biochem. Pharmacol.*, **12,** 85 (1963).
(2) J. A. Alexander, G. F. Wheeler, D. D. Hill, and H. P. Morris, *Biochem. Pharmacol.*, **15,** 881 (1966).
(3) R. A. Long, J. F. Gerster, and L. B. Townsend, *J. Heterocycl. Chem.*, **3,** 863 (1970), and references cited therein.
(4) T. Novinson, R. Hanson, M. K. Dimitt, L. N. Simon, R. K. Robins, and D. E. O'Brien, *J. Med. Chem.*, **17,** 645 (1974).
(5) T. Novinson, K. Senga, J. Kobe, R. K. Robins, D. E. O'Brien, and A. A. Albert, *J. Hererocycl. Chem.*, **11,** 691 (1974).
(6) M. H. Palmer, P. N. Preston, and M. F. G. Stevens, *Org. Mass Spectrom.*, **5,** 1085 (1971).
(7) K. Pesske, German Patent 92 457 (1972); *Chem. Abstr.*, **78,** 111676 (1973).
(8) B. C. Hinshaw, O. Lconoudakis, and L. B. Townsend, Abstracts, 112d National Meeting of the American Chemical Society, Washington, D.C., Sept 1971, No. MEDI-15.
(9) I. Ito, Japanese Patent 7 030 101 (1970); *Chem. Abstr.*, **74,** 22827 (1971).
(10) M. H. Elnagdi, *Tetrahedron*, **30,** 2791 (1974).

(11) M. H. Elnagdi, D. H. Fleita, and M. R. H. El-Moghayar, *Tetrahedron*, **31**, 63 (1975).
(12) M. H. Elnagdi, S. M. Fahmy, M. R. H. El-Moghayar, and M. A. M. Ilias, *Z. Naturforsch. B*, **30**, 778 (1975).
(13) M. H. Elnagdi, M. M. M. Sallam, and M. A. M. Ilias, *Helv. Chim. Acta*, **58**, 1944 (1975).
(14) M. H. Elnagdi and S. O. Abdallah, *J. Prakt Chem.*, **315**, 1009 (1933).
(15) M. H. Elnagdi and M. Ohta, *Bull. Chem. Soc. Jpn.*, **46**, 1830 (1973).
(16) A. Vogel and F. Troxler, *Helv. Chim. Acta*, **58**, 761 (1975).
(17) L. Capuano and H. J. Schrepfer, *Chem. Ber.*, **104**, 3039 (1971).
(18) J. Kobe, R. K. Robins, and D. E. O'Brien, *J. Heterocycl. Chem.*, **11**, 199 (1974).
(19) Cf. δ values reported for C_4 and NH_2 protons of 5-aminopyrazoles: V. Spiro and S. Plescia, *J. Heterocycl. Chem.*, **9**, 951 (1972); J. D. Ratjcryk and L. R. Swett, *ibid.*, **12**, 517 (1975).
(20) I. Hori, K. Saito, and H. Midorikawa, *Bull. Chem. Soc. Jpn.*, **43**, 849 (1970); N. J. Cusack, G. Shaw, and G. J. Litchfield, *J. Chem. Soc. C*, 1501 (1971).
(21) T. Hirata, L. Twanmoh, H. B. Wood, Jr., A. Goldin, and J. S. Driscoll, *J. Heterocycl. Chem.*, **9**, 99 (1972).
(22) J. H. Lister, D. S. Manners, and G. M. Timmis, *J. Chem. Soc. C*, 1313 (1970).
(23) J. Slouka and P. Pec, *Monatsh. Chem.*, **103**, 1444 (1972).
(24) E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles", Interscience, New York, N.Y., 1970, p 295, and references cited therein.
(25) H. Reimlinger and A. van Overstraeten, *Chem. Ber.*, **94**, 1036 (1961).
(26) H. Reimlinger and A. Van Overstaeten, *Chem. Ber.*, **99**, 3350 (1966).
(27) M. W. Partridge and M. F. G. Stevens, *J. Chem. Soc. C*, 1127 (1966).
(28) I. B. Douglass and F. B. Dains, *J. Am. Chem. Soc.*, **56**, 1408 (1934).

Synthesis of Imidazo[4,5-*b*]pyridines and *v*-Triazolo[4,5-*b*]pyridines. Preparation of 1-Deaza-6-thioguanine Analogues[1]

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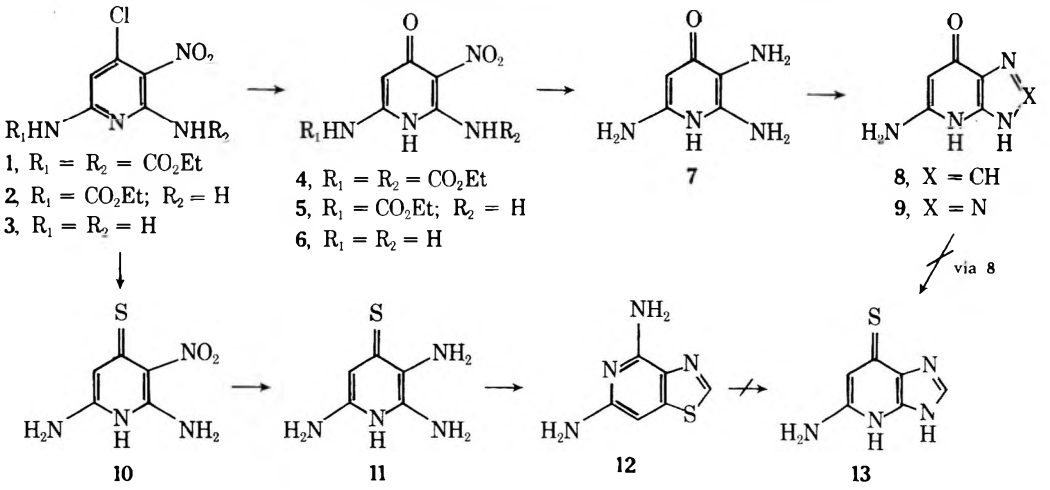
Improved methods for the preparation of 1-deazaguanine (8) and its 8-aza analogue are reported. The preparation of 1-deaza-6-thioguanine (13) either by the thiation of 8 or by the rearrangement of the isomeric 4,6-diaminothiazolo[4,5-*c*]pyridine was unsuccessful. The successful preparation of 13 was accomplished by the removal of the diphenylmethyl group of 2-amino-6-[(diphenylmethyl)thio]-1-deazapurine with refluxing trifluoroacetic acid. 8-Aza-1-deaza-6-thioguanine (26) was prepared by the reaction of the corresponding 6-chloro compound with sodium hydrosulfide. The reversible rearrangement between 26 and 4,6-diamino[1,2,3]thiadiazolo[4,5-c]pyridine was demonstrated. In addition, 2-amino-6-(methylthio)-1-deazapurine and its 8-aza analogue were prepared from 2,3,6-triamino-4-(methylthio)pyridine.

Previously we reported the development of synthetic methods for the preparation of the 5,7-diamino derivatives of imidazo[4,5-*b*]pyridine and *v*-triazolo[4,5-*b*]pyridine, the 1-deaza and 8-aza-1-deaza analogues of 2,6-diaminopurine.[2,3] Further work in this area has resulted in the development of procedures for the preparation of the 5-amino-7-thione derivatives of these ring systems, which are the 1-deaza and 8-aza-1-deaza analogues of 6-thioguanine.

The synthesis of the thione 13 from the corresponding chloro compound 24 was unsuccessful because of the unreactive nature of the chloro group toward nucleophilic displacement with sodium hydrosulfide.[2,4] In addition the direct preparation of 13 by the cyclization of a 2,3-diaminopyridine-4-thione precursor (11) was unlikely since analogous reactions in the pyrimidine series provided thiazolopyrimidines rather than purines.[5,6] However, the thiation of guanine with P_4S_{10} in pyridine has been reported to give 6-thioguanine[7] and it was anticipated that thiation of the known 1-deaza analogues of guanine, 8 and 9, might give the desired target compounds 13 and 26, respectively. Also this route was attractive because both 8 and 9 can be prepared from the common intermediate 7. In the original synthesis, 8 was obtained in 30% yield by hydrolysis of 2-amino-6-ethoxy-1-deazapurine with 48% HBr.[8] In addition, the triaminopyridine 7 was converted with formic acid to 8 in unspecified yield and with aqueous nitrous acid to 9 in 9% yield.[9,10] Modifications of these reactions gave higher yields of 8 and 9. The chloropyridine 1[11] was treated with refluxing 98% HCO_2H to hydrolyze the chloro group. Reaction of the resulting crude pyridin-4-one 4 with ethanolic KOH hydrolyzed the urethane groups to give the intermediate 3-nitropyridine 6 in an overall yield of 75%. Also, the monourethane 2[12] was converted to 5 with refluxing formic acid. When the crude product from this reaction was treated with ethanolic KOH, 6 was obtained in an overall yield of 82%. Catalytic hydrogenation of 6 to give 7 at atmospheric pressure and room temperature in the presence of Raney nickel was slow and required about 20 h for completion.[13] The resulting triaminopyridine 7 was isolated



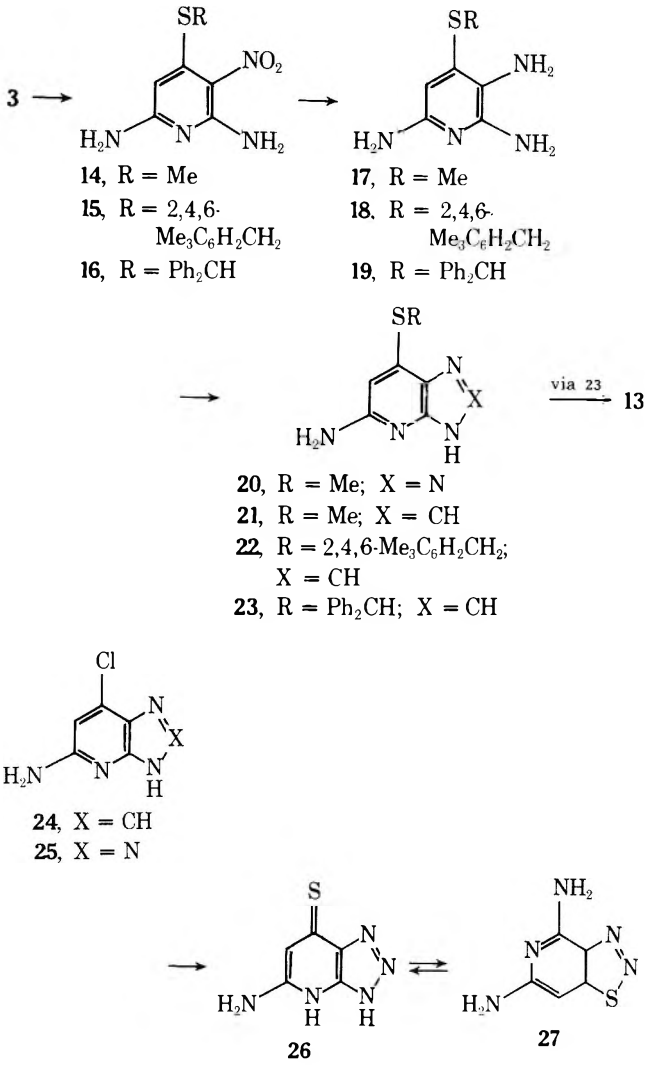
as its dihydrochloride, which was sensitive to air and rapidly changed from a white to a purple solid as has been noted for the free amino compound.[10] However, the dihydrochloride was cyclized to **8** with refluxing HCO_2H in 43% yield and to **9** with aqueous $NaNO_2$ in DMF in 47% yield. Thiation of **8** with P_4S_{10} in refluxing pyridine gave a product that was reprecipitated from a basic solution with acid. Although the ultraviolet spectrum of this product was dissimilar to that of **8**, treatment of the thiation product with hot base led to the recovery of the deazaguanine **8**, indicating that the thiation reaction gave a complex that resulted from the covalent addition of P_4S_{10} to **8**. Because of these results, the preparation and rearrangement of the thiazolopyridine **12** to give **13** was considered.

Treatment of **2** with NaSH was expected to replace the chloro group with a mercapto group and possibly reduce the nitro group to give an amino group. However, purification of the resulting complex reaction mixture gave only a low yield of the nitropyridine **10**, which resulted from replacement of the chloro group and cleavage of the urethane moiety. To avoid the mixtures resulting from partial hydrolysis of the urethane group, **3** was prepared by treatment of **2** with methanolic NaOAc.[14] A crude sample of **3** was also obtained by the chlorodehydroxylation of **6** with $POCl_3$. In contrast to the conversion of **2** to give a low yield of **10**, the reaction of **3** with NaSH gave **11** directly in good yield. The cyclization of **11** with formic acid gave a formylated derivative of the thiazolopyridine **12**, which was readily converted to **12** by hydrolysis of the formyl groups with methanolic HCl. Also, the cyclization of **11** with ethyl orthoformate in the presence of K_2CO_3 was shown by TLC to give mainly **12**. The structure of **12** was supported by its ^1H NMR spectrum and was confirmed by its alkaline insolubility.

Although thiazolopyrimidines in base are rearranged via a ring-opened pyrimidine intermediate to give purines,[5] treatment of **12** either with excess aqueous NaOH at room temperature or with an equivalent amount of base at reflux gave little or no reaction; when **12** was treated with an excess amount of hot base, the ultraviolet spectrum of the product indicated that complete decomposition of the ring system had occurred. Apparently, opening of the thiazolo ring of **12** gave an extremely unstable pyridine intermediate, which was supported by the observation that **11** was unstable in base.

Simultaneously with the work described above, it was found that alkylation of MeSNa with **3** in DMF gave the 4-(methylthio)pyridine **14**. This compound was hydrogenated in the presence of Raney nickel to give **17**, which was converted to the 8-aza-1-deazapurine **20** with nitrous acid in low yield. The mass spectrum of the crude product of this reaction suggested that partial replacement of the amino group of **20** by a chloro group had occurred, indicating that diazotization of the amino group was a side reaction.

Treatment of **17** with refluxing formic acid gave a good yield of the 1-deazapurine **21**. This result indicated that the preparation of an intermediate similar to **21** but containing a removable S-blocking group might provide a route to 1-deaza-6-thioguanine (**13**). Since 2,4,6-trimethylbenzyl esters are cleaved with 2 N HBr in HOAc[15] at room temperature, this group was chosen as the S-blocking group. Alkylation of **3** with the potassium salt of 2,4,6-trimethyl-α-toluenethiol gave **15**, which was hydrogenated in the presence of Raney nickel to give **18**. The cyclization of **18** was effected with formamide at 140 °C to give **22** (mass spectrum), which was not purified when it was found that only partial removal of the benzyl blocking group was obtained on treatment of **22** for a prolonged period of time with hot 30% HBr in HOAc. To obtain a less stable blocking group, **3** was alkylated with the sodium salt of diphenylmethylthiol to give **16**. Hydrogenation of **16** in the presence of Raney nickel gave **19**, which was isolated as the dihydrochloride in 34% yield. For this reduction to proceed, the amount of Raney nickel used was twice the weight of **16**. Under these conditions, over-reduction occurred, suggesting that some of the diphenylmethyl group was reductively removed. In other runs, crude **19** was converted without purification to **23** with formamide at about 160 °C. The diphenylmethyl blocking group of **23** was removed in refluxing CF_3CO_2H to give **13**.[16,17]



In earlier work it was demonstrated that the chloro group of **25** can be displaced with nucleophiles.[3] Treatment of **25** with NaSH in refluxing BuOH gave **26** contaminated with some of the rearrangement product **27**. This crude product was eluted from silica gel to give a pure sample of **26**. In addition, on heating **26** in DMAc, a pure sample of the rearrangement product **27** was obtained. The reverse rearrangement, **27** → **26**, was shown by TLC to be practically complete when **27** was heated in DMAc containing K_2CO_3 at 125 °C.[18]

The ultraviolet, infrared, and ^1H NMR spectral properties of the 1-deaza and 8-aza-1-deaza purines and related compounds are presented in Table I. Of interest is the similarity of the ultraviolet spectra in base of 1-deazaguanine (**8**) and 1-deaza-6-thioguanine (**13**) to those of the corresponding purines. In contrast, the anion of 8-aza-1-deaza-6-thioguanine has a maximum at a lower wavelength than that of 8-aza-6-thioguanine (328 nm).

Experimental Section

Melting points were determined on a Mel-Temp or Kolfer-Heizbank apparatus.

2,6-Diamino-4-chloro-3-nitropyridine (3). A suspension of **2**[12] (10.0 g) and NaOAc (16.4 g) in absolute MeOH (700 ml) was refluxed

Table I. Spectral Properties of 1-Deaza- and 8-Aza-1-deazapurines

Registry no.	Compd	Uv absorption[a] spectra, 0.1 N NaOH	Ir absorption[b] spectra, KBr, selected bands, cm^{-1}	^1H NMR spectral assignments,[c] chemical shifts, δ (rel area)
60282-59-9	8	262 (10.6), 276 (9.41)	1670, 1640, 1610	6.33 (1,6-CH), 8.30 (1,2-CH), ~10 br (6, NH)
60282-60-2	9	282 (15.4), 326 (1.14)	1645, 1595, 1515	5.72 (1,6-CH), 6.37, 9.88, (4, NH)
60282-61-3	12	314 (10.4)	1620, 1605, 1575	5.54 (2, NH_2), 6.14, 6.23 (3,7-CH, NH_2), 8.60 (1,2-CH)
60282-62-4	13	280 (5.83), 317 (9.18)	1640, 1525, 1500	6.98 (1,6-CH), 7.65 (4, NH), 8.84 (1,2-CH)
60282-63-5	20	288 (14.7), 306 sh (11.5)	1610 sh, 1590, 1550	2.59 (CH_3), 6.40 (6-CH), 6.57 (NH_2), ~12 br (NH)
60282-64-6	21	233 sh (15.6), 271 sh (7.10), 277 (7.80), 312 (9.60)	1650 br, 1555, 1520	2.65 (3, CH_3), 6.69 (1,6-CH), 7.42 br (NH), 8.50 (1,2-CH)
60282-65-7	23	273 sh (8.22), 279 (9.20), 318 (10.1)	1615 sh, 1600, 1555	5.68 (2, NH_2), 6.21, 6.43, (1,1,6-CH and Ph_2CH), 7.38 m (10, C_6H_5), 7.86 (1,2-CH)
60282-66-8	26	217 (19.1), 308 (19.7)	1640 br, 1570, 1545	6.46 (1,6-CH), 6.82 (2, NH_2)
60306-33-4	27	241 sh (10.2), 256 (12.3), 310 (4.72), 360 (7.85)	1640, 1610, 1565	6.18, 6.28 (3,7-CH, NH_2), 7.17 (2, NH_2)

[a] Spectra were determined on a Cary Model 17 spectrophotometer. [b] Perkin-Elmer Model 621 spectrophotometer. [c] Spectra were determined on Me_2SO-d_6 solutions (3–7% w/v) on a Varian XL-100-15 spectrometer with Me_4Si as an internal reference; the relative peak areas are given to the nearest whole number.

for 104 h, and evaporated to dryness in vacuo. The residue was washed with H_2O and dried in vacuo over P_2O_5: yield 7.16 g (99%); mp 269–270 °C dec (lit.[14] mp 268 °C dec); λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 224 (10.8), 273 (6.95), 303 (4.17), 397 (14.3).

Also, treatment of **6** (1.0 g) with $POCl_3$ (25 ml) at reflux for 3 h gave crude **3** (0.76 g, 68%), which was identified by TLC.

Ethyl 6-Amino-1,4-dihydro-5-nitro-4-oxo-2-pyridinecarbamate (5). A solution of **2** (1.0 g) in 98% HCO_2H (20 ml) was refluxed for 8 h, and evaporated to dryness in vacuo. The resulting residue was recrystallized from a mixture of EtOH–H_2O and dried in vacuo over P_2O_5 at 78 °C: yield 0.25 g (27%); mp 239–240 °C dec; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 255 (11.8), 333 (9.87).

Anal. Calcd for $C_8H_{10}N_4O_5$: C, 39.67; H, 4.17; N, 23.13. Found: C, 39.88; H, 4.07; N, 23.24.

2,6-Diamino-3-nitro-4(1*H*)-pyridinone (6). A. The crude product of **5** obtained from **2** (12 g) as described above was suspended in a solution of KOH (24 g) in EtOH (220 ml), and the whole was heated in an oil bath at 100 °C for 72 h. The solid material was collected by filtration, dissolved in H_2O (600 ml), and acidified to pH 1 (paper) with concentrated HCl to deposit unreacted crude **5**, yield 1.4 g (13% recovery). The filtrate was adjusted to pH 6 (paper) with 4 N NaOH to give a precipitate of **6**, yield 5.6 g (82%). For analyses a sample was dried in vacuo over P_2O_5 at 56 °C: mp 257–258 °C dec (lit.[10] mp 256–258 °C dec); λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 253 (8.62), 334 (8.66), 388 (8.89).

Anal. Calcd for $C_5H_6N_4O_3$: C, 35.29; H, 3.56; N, 32.93. Found: C, 35.35; H, 3.65; N, 32.71.

B. A solution of **1** (50 g) in 98% HCO_2H (1300 ml) was refluxed for 8 h and evaporated to dryness in vacuo to give crude **4**: yield 46 g; mp 150–155 °C (lit.[10] mp 164–167 °C). A suspension of this material in a solution of KOH (79 g) in EtOH (1000 ml) was refluxed for 86 h. The solid was collected by filtration and treated as described above to give **6**, yield 19 g (75%).

2,3,6-Triamino-4(1*H*)-pyridinone (7).[13] A mixture of **6** (5.0 g) and Raney nickel (8 g, weighed wet, washed with EtOH) in EtOH (80 ml) was hydrogenated at room temperature and atmospheric pressure for 20 h and filtered (Celite) into a flask containing 2.3 N ethanolic HCl (40 ml). A white precipitate was obtained, which rapidly changed to a purple solid. Evaporation of the mixture to dryness under reduced pressure gave a solid that was dried in vacuo over P_2O_5 at 56 °C for 48 h, yield 6.1 g (93%). This sample decomposed from about 200 °C: λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 224 (9.15), 300 (8.52).

Anal. Calcd for $C_5H_8N_4O \cdot 2HCl \cdot 0.2C_2H_6O$: C, 29.15; H, 5.16; Cl, 31.87; N, 25.18. Found: C, 28.90; H, 4.96; Cl, 32.26; N, 25.20.

5-Amino-3*H*-imidazo[4,5-*b*]pyridin-7(4*H*)-one (8).[10] A solution of **7** $2HCl \cdot 0.2C_2H_6O$ (1.0 g) in 98% HCO_2H (20 ml) was refluxed for 4 h and evaporated to dryness in vacuo. The residue was heated at 160 °C (1 mm) for 3 h and extracted with hot H_2O (450 ml). After filtration, the filtrate was evaporated to dryness and the resulting solid was refluxed in 6 N HCl for 1 h. This suspension was evaporated to dryness in vacuo to give an orange solid, which was dried in vacuo over P_2O_5: yield 0.43 g (43%); mp >300 °C.

Anal. Calcd for $C_6H_6N_4O \cdot 2HCl$: C, 32.30; H, 3.62; Cl, 31.79; N, 25.12. Found: C, 31.91; H, 3.83; Cl, 31.64; N, 25.30.

5-Amino-3*H*-triazolo[4,5-*b*]pyridin-7(4*H*)-one (9).[9] Solid $NaNO_2$ (0.33 g) was added with stirring and cooling to a solution of **7** $2HCl \cdot 0.2C_2H_6O$ (1.0 g) in a mixture of DMF (15 ml) and H_2O (5 ml). After 15 min, the ice bath was removed; the solution was stirred at room temperature for 4 h, diluted with H_2O (200 ml), and neutralized by the addition of solid $NaHCO_3$. The solid that deposited was collected by filtration and recrystallized from H_2O, yield 0.33 g (47%). This sample underwent decomposition from about 280 °C.

Anal. Calcd for $C_5H_5N_5O \cdot 0.2H_2O$: C, 38.81; H, 3.52; N, 45.26. Found: C, 38.91; H, 3.26; N, 45.52.

2,6-Diamino-3-nitropyridine-4(1*H*)-thione (10). A mixture of **2** (5.0 g) and hydrated NaSH (20 g) in EtOH (250 ml) was refluxed for 69 h and evaporated to dryness in vacuo. The residue was dissolved in water (170 ml) and acidified with concentrated HCl to pH 2 (paper) to deposit a crude mixture (1.3 g) of **10** and its urethane derivative, based on TLC and elemental analyses. The filtrate from this solid was adjusted to pH 6 with 1 N NaOH and evaporated to dryness. The resulting residue was extracted with boiling EtOH (3 × 300 ml) and evaporated to dryness, and the residue was washed with C_6H_6 to give crude **10**, yield 2.4 g. This sample was extracted with 1 N NaOH (50 ml), and the extract was acidified to pH 5 with 1 N HCl to give pure **10**, which was dried in vacuo at 78 °C for 4 h: yield 0.54 g (15%); mp >300 °C; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 234 (8.61), 267 (sh) (6.70), 338 (4.92).

Anal. Calcd for $C_5H_6N_4O_2S$: C, 32.26; H, 3.25; N, 30.11; S, 17.22. Found: C, 32.12; H, 3.18; N, 29.88; S, 17.46.

2,3,6-Triaminopyridine-4(1*H*)-thione (11). A mixture of **3** (5.0 g) and hydrated NaSH (10 g) in EtOH (250 ml) was refluxed for 24 h and evaporated to dryness in vacuo. The residue was dissolved in 1 N NaOH (40 ml), the solution was adjusted to pH 5 (paper) with concentrated HCl, and the sulfur (1.3 g) that deposited was removed by filtration. The filtrate was evaporated to dryness under reduced pressure, and the solid was washed by stirring in 3 N HCl for 1 h. The product was collected by filtration, washed with C_6H_6, and dried in vacuo over P_2O_5, yield 3.9 g (66%). This sample underwent decomposition from about 222 °C when taken from 200 °C: λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 293 (10.6), 342 (8.91).

Anal. Calcd for $C_5H_8N_4S \cdot 1.8HCl$: C, 27.07; H, 4.45; N, 25.26. Found: C, 27.44; H, 4.29; N, 24.96.

4,6-Diaminothiazolo[4,5-*c*]pyridine (12). A. A solution of **11** 1.8HCl (1.2 g) in 98% HCO_2H (20 ml) was refluxed for 18 h, and evaporated to dryness in vacuo. The residue was suspended in 10% ethanolic HCl and stirred at room temperature for 18 h. The solid was collected by filtration, washed with Et_2O, and dried in vacuo over P_2O_5: yield 0.70 g (61%); mp 235–240 °C dec.

Anal. Calcd for $C_6H_6N_4S \cdot 1.25HCl$: C, 34.02; H, 3.45; Cl, 20.93; N, 26.46. Found: C, 34.23; H, 3.38; Cl, 20.88; N, 26.39.

A solution of the hydrochloride of **12** (200 mg) in H_2O (6 ml) and 1 N NaOH (6 ml) was stirred at room temperature for 16 h to deposit **12**: yield 83 mg (53% recovery); mp 151–152 °C with decomposition from 145 °C when taken from 130 °C; M^+ *m/e* 166.

Anal. Calcd for $C_6H_6N_4S$: C, 43.36; H, 3.64; N, 33.71. Found: C, 43.10; H, 3.53; N, 33.96.

B. A powdered mixture of **11** 1.8HCl (222 mg) and K_2CO_3 (500 mg) in $(EtO)_3CH$ (10 ml) was refluxed for 4 h and evaporated to dryness in vacuo. The resulting residue was suspended in H_2O and acidified

to pH 5 (paper) with dilute HCl to give crude **12**, yield 159 mg (96%).

5-Amino-1,4-dihydro-7*H*-imidazo[4,5-*b*]pyridine-7-thione (13). A solution of **23** (500 mg) and phenol (500 mg) in CF_3CO_2H (20 ml) was refluxed for 3 h and evaporated to dryness in vacuo. The resulting residue was stirred in 9% methanolic HCl (25 ml) for 2 h; the solid was collected by filtration (142 mg), and recrystallized from EtOH to give the HCl, yield 60 mg (20%), mp >265 °C (Mel-Temp).

Anal. Calcd for $C_6H_6N_4S$·HCl: C, 35.56; H, 3.48; N, 27.65. Found: C, 35.65; H, 3.43; N, 27.57.

The residue obtained from the methanolic HCl filtrate was recrystallized from EtOH to give an additional amount of **13** HCl, yield 17 mg (6%). The total yield was 77 mg (26%).

2,6-Diamino-3-nitro-4-(methylthio)pyridine (14). A solution of MeSNa was prepared from NaOMe (3.6 g) in MeOH (190 ml) by saturation of the solution with MeSH at 0 °C. A mixture of the solid obtained by evaporation of this solution to dryness in vacuo and **3** (6.3 g) in DMAC (150 ml) was heated at 50 °C for 24 h and diluted with H_2O (2500 ml). The solid that precipitated was collected by filtration, washed with H_2O, and dried in vacuo over P_2O_5: yield 5.6 g (84%); mp 271–272 °C dec; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 272 (7.92), 347 (9.04), 398 (12.4).

Anal. Calcd for $C_6H_8N_4O_2S$: C, 35.99; H, 4.03; N, 27.98. Found: C, 36.36; H, 3.83; N, 28.01.

2-(2,4,6-Trimethylbenzyl)-2-thiopseudourea Hydrochloride. A solution of 2,4,6-trimethylbenzyl chloride (5.0 g) and thiourea (2.5 g) in EtOH (90 ml) was refluxed for 4 h and chilled. The white solid was collected by filtration and dried in vacuo over P_2O_5: yield 5.2 g (71.5%); mp 242–243 °C.

Anal. Calcd for $C_{11}H_{16}N_2S$·HCl: C, 53.97; H, 7.00; N, 11.44. Found: C, 54.16; H, 6.96; N, 11.60.

Concentration of the filtrate gave an additional amount of product: yield 1.0 g; mp 242–243 °C. The total yield was 6.3 g (86.5%).

2,4,6-Trimethyl-α-toluenethiol. A solution of 2-(2,4,6-trimethylbenzyl)-2-thiopseudourea hydrochloride (26 g) in 2.5 N NaOH (500 ml) was refluxed for 1 h and filtered. The filtrate was cooled in an ice bath and acidified with concentrated HCl. The white precipitate was collected by filtration, washed with H_2O, and dried in vacuo over P_2O_5: yield 15 g (85%): mp 44–45 °C.

Anal. Calcd for $C_{10}H_{14}S$: C, 72.23; H, 8.46. Found: C, 72.18; H, 8.43.

2,6-Diamino-4-[(2,4,6-trimethylbenzyl)thio]-3-nitropyridine (15). A solution of **3** (5.0 g) and 2,4,6-trimethyl-α-toluenethiol (4.6 g) in DMAC (100 ml) and anhydrous K_2CO_3 (3.7 g) was heated at 50 °C for 46 h. TLC of the reaction mixture showed the presence of unreacted **3**. After an additional amount of the thiol (1.2 g) was added, the reaction mixture was heated for 18 h and poured into cold H_2O (3500 ml). The yellow solid was collected by filtration, washed with Et_2O (800 ml), and dried in vacuo over P_2O_5: yield 5.2 g (61%); mp 290 °C dec. For analysis, a sample (100 mg) was recrystallized from propanol: yield 70 mg (70% recovery); mp 293 °C dec; λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 N HCl, 224 (24.8), 296 (7.67), 375 (15.4).

Anal. Calcd for $C_{15}H_{18}N_4O_2S$: C, 56.59: H, 5.70; N, 17.60. Found: C, 56.46; H, 5.65; N, 17.47.

2-(Diphenylmethyl)-2-thiopseudourea Hydrochloride. A solution of thiourea (3.8 g) and diphenylmethyl chloride (8.7 ml) in EtOH (25 ml) was refluxed for 2.5 h and evaporated to dryness in vacuo. The residue was extracted in a hot Soxhlet apparatus with MeCN (1400 ml) for 20 h, and the solid that precipitated from the cooled extract was collected by filtration: yield 9.0 g (65%); mp 196–199 °C.

Anal. Clcd for $C_{14}H_{14}N_2S$·HCl: C, 60.31; H, 5.42; N, 10.05. Found: C, 60.08; H, 5.83; N, 10.27.

2,6-Diamino-4-[(diphenylmethyl)thio]-3-nitropyridine (16). A solution of 2-(diphenylmethyl)-2-thiopseudourea hydrochloride (6.8 g) in 1 N NaOH (122 ml) was heated in an oil bath at 77 °C for 0.5 h, acidified to pH 4 (paper) with dilute HCl, and extracted with $CHCl_3$ (3 × 300 ml). The combined extracts were evaporated to dryness in vacuo; the residue (4.7 g) of crude (diphenylmethyl)thiol[19] was dissolved in MeOH (125 ml) containing NaOMe (1.3 g), and the solution was evaporated to dryness in vacuo to give the crude sodium salt. A mixture of this salt and **3** (3.8 g) in DMAC (100 ml) was heated with stirring at 50 °C for 69 h and diluted with H_2O (1000 ml). The solid was collected by filtration, washed with H_2O, and dried in vacuo over P_2O_5 to give crude **16**, yield 7.6 g. This sample was recrystallized from a large volume of C_6H_6: yield 4.6 g (65%); mp 230–233 °C; λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 N HCl, 255 (27.2), 297 (9.93), 377 (19.5).

Anal. Calcd for $C_{18}H_{16}N_4O_2S$: C, 61.34; H, 4.58; N, 15.90. Found: C, 61.04; H, 4.69; N, 15.86.

2,3,6-Triamino-4-(methylthio)pyridine (17). A suspension of **14** (2.0 g) in EtOH (1000 ml) containing Raney nickel (4 g, weighed wet, washed with EtOH) was hydrogenated at room temperature and atmospheric pressure. After 3 h, the catalyst was removed by filtration (Celite). The filtrate was diluted with concentrated HCl (2 ml), and evaporated to dryness in vacuo: yield 2.2 g (90.5%); mp 248 °C dec; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 222 (sh) (14.4), 236 (18.2), 324 (6.04).

Anal. Calcd for $C_6H_{10}N_4S$·2HCl: C, 29.64; H, 4.97; N, 23.04. Found: C, 30.02; H, 4.82; N, 22.95.

2,3,6-Triamino-4-[(2,4,6-trimethylbenzyl)thio]pyridine (18). A solution of **15** (3.84 g) in a mixture of DMAC (40 ml) and EtOH (350 ml) was hydrogenated in the presence of Raney nickel (4 g, washed with EtOH, weighted wet) at 50 °C for 4.5 h. The catalyst was removed by filtration (Celite), the filtrate was evaporated to dryness in vacuo, and the resulting residue was washed with petroleum ether and dried under reduced pressure at 56 °C: yield 2.80 g (81%); mp 175 °C dec; λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 N HCl, 242 (22.9), 270 (15.3), 333 (9.52).

Anal. Calcd for $C_{15}H_{20}N_4S$: C, 62.47; H, 6.99; N, 19.42. Found: C, 62.21; H, 6.86; N, 19.54.

2,3,6-Triamino-4-[(diphenylmethyl)thio]pyridine (19). A solution of **16** (1.0 g) in EtOH (500 ml) containing Raney nickel (2 g, weighed wet, washed with EtOH) was hydrogenated at room temperature and atmospheric pressure for 5 h. The mixture was filtered (Celite) into a flask containing 1 N HCl (6 ml), and the filtrate was evaporated to dryness in vacuo. The resulting residue was recrystallized from EtOH: yield 0.38 g (34%); mp 209–211 °C dec with presoftening; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 337 (5.76).

Anal. Calcd for $C_{18}H_{18}N_4S$·2HCl: C, 54.69; H, 5.10; N, 14.17. Found: C, 54.53; H, 5.24; N, 13.71.

An additional amount of crude **19** (0.28 g) was obtained from the ethanol filtrate.

5-Amino-7-(methylthio)-1*H*-*v*-triazolo[4,5-*b*]pyridine (20). To a solution of **17** 2HCl (1.48 g) in H_2O (58 ml) containing HOAc (3.05 ml) and NaOAc (1.00 g) was added solid $NaNO_2$ (0.50 g) with stirring. After 2 h the solid was collected by filtration, recrystallized from H_2O, and dried in vacuo over P_2O_5 at 78 °C: yield 0.29 g (20%); mp 279–280 °C with dec from 267 °C.

Anal. Calcd for $C_6H_7N_5S$·0.39H_2O: C, 38.28; H, 4.17; N, 37.20. Found: C, 38.54; H, 4.05; N, 36.86.

5-Amino-7-(methylthio)-1*H*-imidazo[4,5-*b*]pyridine (21). A solution of **17** 2HCl (100 mg) in 98% HCO_2H (5 ml) was refluxed for 4 h and evaporated to dryness in vacuo. The resulting residue was suspended in 10% ethanolic HCl (5 ml), stirred at room temperature for 18 h, collected by filtration, washed with Et_2O, and dried in vacuo over P_2O_5 at 78 °C: yield 89 mg (88%); mp 254 °C dec with premelting from about 180 °C; M^+ *m/e* 180.

Anal. Calcd for $C_7H_8N_4S$·1.8HCl: C, 34.19; H, 4.02; N, 22.79. Found: C, 33.86; H, 3.96; N, 22.79.

5-Amino-7-[(diphenylmethyl)thio]-1*H*-imidazo[4,5-*b*]pyridine (23). A solution of **16** (3.68 g) in EtOH (2,000 ml) containing Raney nickel (8 g, weighted wet, washed with EtOH) was hydrogenated at room temperature and atmospheric pressure for 5.5 h. The H_2 absorbed was 17% in excess of the theoretical amount. The catalyst was removed by filtration under N_2; the filtrate was evaporated to dryness in vacuo, and the residue was heated in $HCONH_2$ (100 ml) at 160 °C for 18 h. The reaction mixture was evaporated to dryness in vacuo. The resulting solid was stirred in 1 N NaOH (64 ml) for 18 h, and the product was collected by filtration: yield 2.44 g (70%); mp ~195 °C dec. A portion (100 mg) of this sample was recrystallized from EtOH to give the analytical sample: yield 46 mg; mp 228–230 °C.

Anal. Calcd for $C_{19}H_{16}N_4S$: C, 68.65; H, 4.85; N, 16.86. Found: C, 68.30; H, 5.01; N, 16.59.

5-Amino-1,4-dihydro-7*H*-*v*-triazolo[4,5-*b*]pyridine-7-thione (26). A solution of **25** (1.50 g)[3] in butanol (75 ml) containing hydrated sodium hydrosulfide (7.50 g) was refluxed for 18 h, and the resulting suspension was evaporated to dryness in vacuo. The residue was dissolved in H_2O, and after acidification with HOAc, the solid was collected by filtration, washed with hot C_6H_6 (2 × 200 ml), and dried in vacuo over P_2O_5 at 110 °C, yield 1.15 g. This solid was dissolved in a minimum amount of 1 N NH_4OH and poured into a fritted glass funnel containing silica gel H (23 g). The whole was washed with 8:2 $CHCl_3$–MeOH and the washings were evaporated to dryness in vacuo to give **26** contaminated with **27**, yield 0.44 g. Next the silica gel was washed with 1 N NH_4OH, and the washings were neutralized with HOAc to give a precipitate of **26**: yield 0.48 g; mp 236–237 °C with decomposition and presoftening from 220 °C.

Anal. Calcd for $C_5H_5N_5S$: C, 35.92; H, 3.01; N, 41.89. Found: C, 35.71; H, 3.25; N, 41.62.

4,6-Diamino[1,2,3]thiadiazolo[4,5-*c*]pyridine (27). A solution of **26** (0.50 g) in DMAC (15 ml) was heated at 125 °C for 30 min, fil-

tered, and evaporated to dryness in vacuo. The residue was washed with Et_2O and recrystallized from MeCN: yield 0.36 g (72%); mp 240 °C dec.

Anal. Calcd for $C_5H_5N_5S$: C, 35.92; H, 3.01; N, 41.89. Found: C, 36.18; H, 3.10; N, 41.81.

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Registry No.—**1**, 53995-21-4; **2**, 6506-86-1; **3**, 40497-64-1; **4**, 60282-67-9; **5**, 60282-68-0; **6**, 60282-69-1; **7** 2HCl, 60282-70-4; **8** 2HCl, 60282-71-5; **10**, 60282-72-6; **10** urethane derivative, 60282-73-7; **11** 1.8HCl, 60282-74-8; **12** 1.25HCl, 60282-75-9; **13** HCl, 60282-76-0; **14**, 60282-77-1; **15**, 60282-78-2; **16**, 60282-79-3; **17** 2HCl, 60282-80-6; **18**, 60282-81-7; **19** 2HCl, 60282-82-8; **21** 1.8HCl, 60282-83-9; **25**, 38359-74-9; 2-(2,4,6-trimethylbenzyl)-2-thiopseudourea HCl, 60282-84-0; 2,4,6-trimethylbenzyl chloride, 1585-16-6; thiourea, 62-56-6; 2,4,6-trimethyl-α-toluenethiol. 21411-42-7; 2-(diphenylmethyl)-2-thiopseudourea HCl, 60282-85-1; diphenylmethyl chloride, 90-99-3; (diphenylmethyl)thiol Na salt, 60282-86-2.

References and Notes

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(2) C. Temple, Jr., B. H. Smith, Jr., and J. A. Montgomery, *J. Org. Chem.*, **38**, 613 (1973).
(3) C. Temple, Jr., B. H. Smith, Jr., and J. A. Montgomery, *J. Org. Chem.*, **38**, 1095 (1973).
(4) J. E. Schelling and C. A. Salemink, *Recl. Trav. Chim. Pays-Bas*, **91**, 650 (1972).
(5) D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 682 (1957).
(6) G. B. Elion, W. H. Lange, and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 2853 (1956).
(7) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **77**, 1676 (1955).
(8) D. G. Markees and G. W. Kidder, *J. Am. Chem. Soc.*, **78**, 4130 (1956).
(9) B. S. Gorton, J. M. Ravel, and W. Shive, *J. Biol. Chem.*, **231**, 331 (1958).
(10) B. S. Gorton and W. Shive, *J. Am. Chem. Soc.*, **79**, 670 (1957).
(11) J. A. Montgomery and N. F. Wood, *J. Org. Chem.*, **29**, 734 (1964).
(12) R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **31**, 1890 (1966).
(13) No elemental analysis was presented for **7** in a previous report. See ref 10.
(14) C. Temple, Jr., B. H. Smith, R. D. Elliott, and J. A. Montgomery, *J. Med. Chem.*, **16**, 292 (1973), reported the obtainment of **3** as a by-product.
(15) F. H. C. Stewart, *Aust. J. Chem.*, **24**, 2739 (1971).
(16) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Med. Chem.*, **15**, 441 (1972).
(17) F. I. Carroll and A. Philip, *J. Org. Chem.*, **33**, 3376 (1968).
(18) C. Temple, Jr., B. H. Smith, and J. A. Montgomery, *J. Org. Chem.*, **37**, 3601 (1972).
(19) H. Staudinger and J. Siegwart, *Ber.*, **49**, 1920 (1916).

Stereochemistry in Trivalent Nitrogen Compounds. 31. Conformational Preferences and Torsional Barriers in *N*-Acylimidazoles[1]

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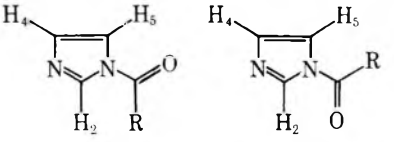
The low temperature ^1H NMR spectra of a series of *N*-acylimidazoles have been examined. All but one exhibited doubling of the resonances of H-2 and H-5 at low temperature reflecting the presence of two diastereomers which differ in configuration at the carbonyl to nitrogen (amide) bond. In all cases, the predominant diastereomer was assigned the *E* configuration. The configurational assignment involved the use of NMR chemical shifts and coupling constants, CNDO/2 calculations, solvent effects, and analogy to imides. Equilibrium constants and free energies of activation for isomerization were determined using variable temperature NMR spectroscopy in methylene chloride: *N*-formylimidazole, 4.6, 11.6 kcal/mol; *N*-acetylimidazole, 1.9, 10.5 kcal/mol; *N*-propionylimidazole, 1.5, 9.9 kcal/mol; *N*-(2-methylpropionyl)imidazole, 1.6, 9.9 kcal/mol; *N*-trifluoroacetylimidazole, 2.2, 10.2 kcal/mol; *N*-trimethylacetylimidazole, no splitting observed. The behavior of the first two of these compounds in three other solvents was also examined and the effects of solvent on NMR chemical shifts, the isomerization equilibrium constant, and the barrier to stereomutation are discussed. The relation between data for *N*-acylimidazoles and those for imides and *N,N*-dimethylamides is discussed.

Among the most informative amide torsional barriers are those for compounds in which the nitrogen lone pair forms part of an aromatic π system. The torsional barriers in such compounds are lower than in the corresponding *N,N*-dialkylamides, and the extent to which the barrier is lowered is related to the delocalization of the nitrogen lone pair and hence to the aromaticity of the heterocyclic ring. Although torsional barriers in amides have been intensively studied over the past 20 years,[3] only few studies have been made on amides of aromatic heterocyclic amines.[4-7] This paper reports our investigation of the variable temperature NMR spectra of a series of *N*-acylimidazoles, **1**, a system which had received no attention when our investigation was begun.

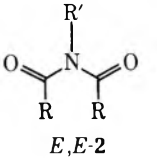
The *N*-acylimidazoles represented an interesting subject for study for another reason as well. The *N*-acylimidazoles can be considered as analogues of imides, a class of compounds whose torsional barriers and configurational preferences have been of interest in our laboratory.[8] Two labile configurational isomers are possible for *N*-acylimidazoles, *E*-**1** and *Z*-**1**, which can be interconverted by torsion about the carbon–nitrogen partial double bond. These two configurations are electronically related to the *E,E* and *E,Z* configurations of the imides **2**. Most imides prefer one of these two configurations when in solution in nonpolar solvents.[8,9] While the parent imide, diformamide, and its *N*-methyl derivative (**2a**, R′ = H, CH_3) prefer the *E,E* configuration, the higher homologues diacetamide and dipropionamide and their *N*-methyl derivatives (**2b**, R′ = H, CH_3 and **2c**, R′ = H, CH_3) adopt the *E,Z* configuration. The unsymmetrical imide *N*-acetylpropionamide



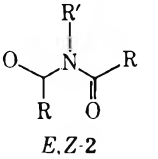
E-**1**

Z-**1**

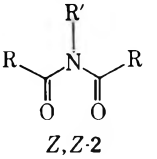
a, R = H
b, R = CH_3
c, R = CH_2CH_3
d, R = $CH(CH_3)_2$
e, R = CF_3
f, R = $C(CH_3)_3$



E,E-**2**



E,Z-**2**



Z,Z-**2**

exists as a mixture of the two possible *E,Z* forms. The reversal in configurational preference between diformamide and its higher homologues was interpreted by considering a balancing between opposing steric and coulombic factors. The *E,E* configuration preferred by **2a** corresponds to the form with the minimum dipole moment and its greater stability seemed to be associated with the decrease in repulsive coulombic interactions reflected in the lower dipole moment. However, the *E,E* form brings the two R groups into close proximity and this leads to significant destabilizing interactions when R is methyl or a larger alkyl group. It was, therefore, of interest to examine configurational preferences in a system in which steric factors could be controlled. We wished to determine whether the preference for the *E,E* configuration in diformamide and *N*-methyldiformamide was the result of coulombic factors alone or whether an H–H attractive interaction might be important. We also wished to learn whether the reversal in configurational preference when R is changed from hydrogen to alkyl might involve coulombic as well as steric factors.

The *N*-acylimidazole system can be considered as a model system for imides in which steric factors are controlled. While the two configurations *E*-**1** and *Z*-**1** are electronically related to *E,E*-**2** and *E,Z*-**2**, steric differences between the two acylimidazole diastereomers are minimized. Thus, the steric interaction between H_2 and R in *E*-**1** is comparable to that between H_5 and R in *Z*-**1**. As a consequence, electrostatic interactions should be the dominant factor controlling the configurational equilibrium in acylimidazoles, **1**.

Results

The ambient and low temperature spectra of acylimidazoles **1** were obtained in methylene chloride solvent. In addition, spectra of **1a** and **1b** were also obtained in tetrahydrofuran, acetone-d_6, $CDCl_3$ (for **1a**), and $CFCl_3$–$CDCl_3$ (for **1b**). The ambient temperature spectra, in all cases, feature three multiplets for the ring protons at nearly the same chemical shifts, ca. δ 8.2, 7.5, and 7.1.[10] Assignment of these three multiplets is relatively straightforward and has been reported by several groups for *N*-acetylimidazole.[7,11,12] The lowest field multiplet derives from H_2, the multiplet at ca. δ 7.5, derives from H_5, while H_4 gives rise to the high-field resonance. Change of solvent from methylene chloride to acetone effects only small changes in the ambient temperature chemical shifts. In **1b** downfield shifts of −0.14 and −0.12 ppm were observed for H_2 and H_5, respectively, the protons flanking the acyl group, as well as for the acetylmethyl group −0.09 ppm. The ring proton furthest away from the acyl group suffered an upfield shift (+0.05 ppm). Very similar behavior was observed for **1a**. Changing the solvent to tetrahydrofuran produced shifts in much the same directions but of much smaller magnitudes. Much larger solvent shifts were observed in the low temperature spectra (vide infra) but they were largely averaged out by rapid torsion about the amide bond in the room temperature spectra.

When the temperature is lowered, two of the resonances derived from the ring protons (those from H_2 and H_5) in **1a–e** broaden and split into pairs of unequally intense peaks (Figure 1) reflecting the presence of two diastereomers, in a ratio of 65/35 for **1b**, which interconvert only slowly on the NMR time scale. The resonance corresponding to H_4, which lies furthest from the acyl group, did not exhibit an observable difference in chemical shift corresponding to the difference in configuration at the amide partial double bond. Of the acylimidazoles **1** examined only the trimethylacetyl (pivaloyl) derivative **1f** failed to exhibit nonequivalence at the lowest temperature at which it was examined (−120 °C).[13]

In the spectrum of **1b** in dichloromethane at −94 −C (Figure 1), the resonance derived from H_5 in the major isomer

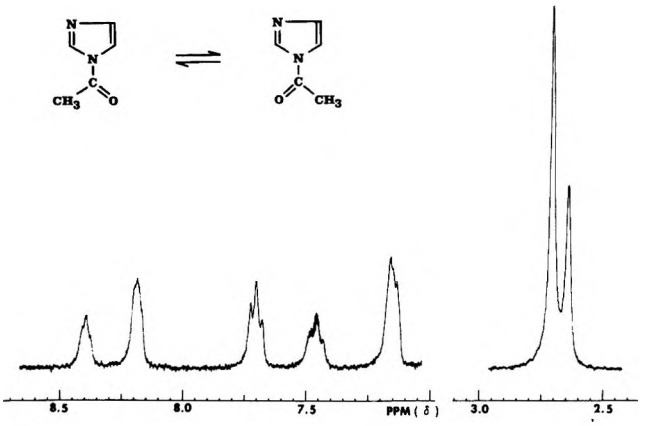


Figure 1. Low temperature (−94 °C) ^1H NMR spectrum of *N*-acetylimidazole (**1b**) in methylene chloride solvent.

appears at lower field (δ 7.69) when compared with that derived from the minor isomer (δ 7.47). By contrast, the multiplet derived from H_2 appears at higher field in the major isomer (δ 8.19) as compared with the minor isomer (δ 8.39). The same qualitative behavior was observed for the other compounds: H_2 always appeared upfield and H_5 always appeared downfield in the major isomer (Table I).

We have assigned the *E* configuration to the major isomer for **1a–e** on several bases. Based upon the analogy with imides we would expect the isomer with the lower dipole moment to be favored. Semiempirical molecular orbital calculations (CNDO/2) indicate that the *E* isomer has a lower dipole moment than the *Z* isomer, supporting the validity of the analogy between *E*-**1** and *E,E*-**2** and between *Z*-**1** and *E,Z*-**2**. The calculated moments for *N*-formylimidazole were *E*-**1a**, 1.76 D; *Z*-**1a**, 3.45 D. The corresponding calculated moments[8] in *N*-methyldiformamide (**2a**, R = CH_3) are strikingly similar considering the differences in the two compounds: *E,E*, 1.75 D; *E,Z*, 3.49 D. The calculated dipole moments in the imide series seemed to agree fairly well with estimates based upon the experimentally obtained dipole moments in imides with known (or fixed) configurations. In analogy with the CNDO/2 calculations for *N*-methylformamide, the difference in energy between *E*-**1a** and *Z*-**1a** was found to be very small.

The chemical shift differences between the resonances for H_2 and H_5 in the two isomers provide further support for our assignment. The reversal of the chemical shift differences for H_2 and H_5, and the negligible difference observed for H_4 indicate that the anisotropy of the acyl group is responsible for the chemical shift difference. The dependence of the ring proton chemical shifts as a function of the R group in the acyl function was relatively small supporting the idea that the configurationally dependent changes in the chemical shifts of H_2 and H_5 are associated with proximity to the acyl oxygen rather than the R group.

Models for the effect of an acyl oxygen in this kind of orientation can be found in the imide series. In diformamide (**2a**, R′ = H), the two diastereotopic formyl protons in the *E,Z* form can be definitively assigned on the basis of the vicinal coupling constants.[8] The formyl proton closest to the carbonyl oxygen atom of the other acyl group appears at lowest field. The low temperature ^1H NMR spectrum of *N*-acetylpropionamide provides a second example.[14] This compound exists as a mixture of two *E,Z* diastereomers. In the major isomer the methyl group is in the more sterically hindered position close to the oxygen atom of the propionyl moiety. It exhibits a downfield shift of 0.65 ppm relative to the resonance of the minor isomer. The propionyl methylene group of the minor diastereomer, which is in a comparable orientation near the acetyl oxygen atom, also appears downfield with respect to the

Table I. Low Temperature NMR Data for *N*-Acylimidazoles, 1

Registry no.	Compd	R	Solvent	Chemical shifts, δ: *E* isomer R	H_2	H_4[b]	H_5	*Z* isomer R	H_2	H_4[b]	H_5	Equilibrium constant (*E*:*Z*)[a]	Temp °C
3197-61-3	1a	H	$CDCl_3$	9.32	8.27	7.27	7.68	9.21	8.44	7.27	7.52	78/22	−70
			Tetrahydrofuran	9.33	8.47	7.21	7.85	9.21	8.47	7.21	7.85	87/13	−94
			CH_2Cl_2	9.29	8.27	7.23	7.69	9.19	8.41	7.23	7.56	82/18	−94
			Acetone-d_6	9.54	8.62	7.35	7.93	9.44	8.62	7.35	7.93	88/12	−94
2466-76-4	1b	CH_3	$CFCl_3$-$CDCl_3$ (2:1)	2.76	8.14	7.17	7.67	2.68	8.41	7.17	7.34	72/28[c]	−94
			Tetrahydrofuran	[e]	8.43	7.07	7.72	[e]	8.35	7.07	7.80	~3/1[f]	−94
			CH_2Cl_2	2.70	8.19	7.16	7.69	2.64	8.39	7.16	7.47	65/35	−94
			Acetone-d_6	2.82	8.68	7.23	7.80	2.73	8.48	7.23	7.96	78/22[d]	−94
4122-52-5	1c	CH_2CH_3	CH_2Cl_2		8.20	7.15	7.71		8.39	7.15	7.48	60/40	−93
4122-53-6	1d	$CH(CH_3)$	CH_2Cl_2		8.26	7.16	7.69		8.38	7.16	7.53	61/39	−97
1546-79-8	1e	CF_3	CH_2Cl_2		8.26	7.26	7.78		8.52	7.26	7.55	69/31	−98

[a] These equilibrium constants are estimated to be accurate to ±2%. The *E* form is favored in all cases. [b] None of the compounds examined exhibited observable chemical shift nonequivalence for H_4. [c] Reported to have an equilibrium constant of 63/37 in $CHFCl_2$. [d] Reported to have an equilibrium constant of 25/75 favoring the *Z* isomer.[7b] The error of this assignment is discussed in text. [e] The solvent peak obscured this resonance. [f] Small chemical shift differences prevented precise determination of the equilibrium constant.

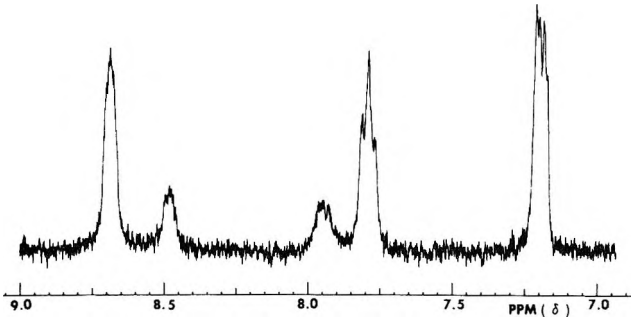
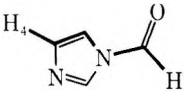


Figure 2. Low temperature (−94 °C) ^1H NMR spectrum of *N*-acetylimidazole (**1b**) in acetone solvent.

methylene group in the major isomer. These observations are in accord with the notion that protons adjacent to and in the nodal plane of an imide carbonyl group should suffer downfield shifts, just as protons adjacent to and in the nodal plane of the carbonyl groups of aldehydes and ketones are shifted downfield as a consequence of the anisotropy of the carbonyl group.[15] On this basis the major isomer is assigned the *E* configuration since in this isomer H_5 is shifted downfield, while H_2 is shifted downfield in the minor isomer. This pattern was observed in the low temperature spectra of all of the acylimidazoles, **1a–e,** in methylene chloride solvent and we have assigned the *E* configuration to the major isomer in all cases. While the chemical shifts were not greatly affected by the nature of the R group, a slightly larger variation in chemical shifts was observed for the protons in closest proximity to the R group (H_2 in *E*-**1** and H_5 in *Z*-**1**), except in the case of **1e.** In this compound, the chemical shifts of these hydrogens show little effect from the replacement of an alkyl group by trifluoromethyl while the other two ring hydrogens (furthest from the CF_3 group) suffer comparable downfield shifts, possibly as the result of the inductive effect of CF_3.

Further evidence supporting the assignment of the *Z* configuration to the minor isomer of *N*-trifluoromethylimidazole (**1e**) was obtained by examination of widths at half height in the low temperature spectrum. The H_2 proton in the major isomer and the H_5 proton in the minor isomer showed extra broadening ($W_{1/2}$ of 5.8 and 7.5 Hz, respectively, as compared with the corresponding protons in the other isomers, $W_{1/2}$ 3.8 and 3.9 Hz), probably due to long-range coupling with the fluorine atoms ($^5J_{HF}$). The through-space mechanism for long-range HF coupling allows the prediction that the proton nearer to the trifluoromethyl group will exhibit the larger coupling constant. In *N*,*N*-dimethyltrifluoroacetamide, the lower field methyl signal has a larger $^5J_{HF}$ coupling (1.60 Hz) than does the methyl resonance at higher field (0.65 Hz).[18–21] Signal assignment has been controversial,[19,20] but the most recent study[21] using lanthanide shift reagents clearly indicated that the lower field signal should be assigned to the methyl group cis to the trifluoromethyl group supporting the operation of through-space coupling for hydrogen and fluorine atoms in this type of system.

Additional broadening was also observed in the spectrum of **1a.** The formyl proton resonance in the major isomer has a greater half width (2.5 Hz) than that in the minor isomer (1.3 Hz). This may be a reflection of long range (5-bond) coupling with H_5, which has a "zig-zag" relationship,[22,23] **3,** with the



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formyl proton only in the *E* configuration. A similar argument based on long-range (5-bond) coupling has been used by Elguero and co-workers[7d] to assign the configuration at the amide bond in *N*-formylindole.

The appearance of the low temperature (−94 °C) spectrum of **1b** in acetone (or tetrahydrofuran) is quite different (Figure 2). The H_2 proton of the major isomer now appears at lower field and the H_5 proton appears at higher field with respect to the resonances of the corresponding protons in the minor isomer, although the ratio of intensities of major to minor resonances was not greatly changed (Table I). This reversal was also noted by Sandstrom and Elguero and co-workers,[7b,c] who concluded that there is a reversal of configurational preference in this solvent rather than attributing the difference to solvent induced changes in chemical shifts.[24] That the explanation based upon reversal of configurational preference is incorrect can be easily demonstrated by examination of spectra in mixtures of dichloromethane and acetone as solvent. Such spectra are expected to be intermediate in either peak intensities or chemical shifts between the extremes recorded in the pure solvents. The spectra in intermediate solvent mixtures show clearly that the ratio of intensities does

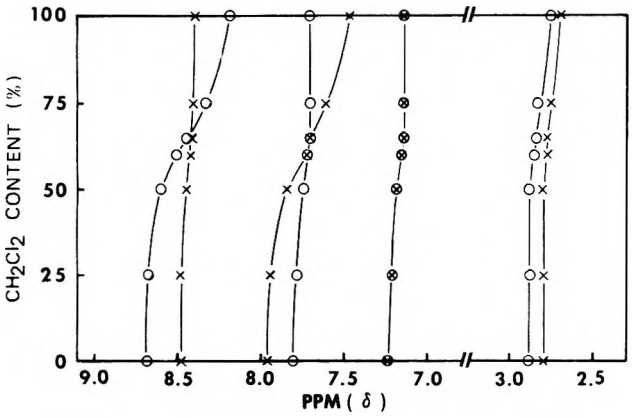
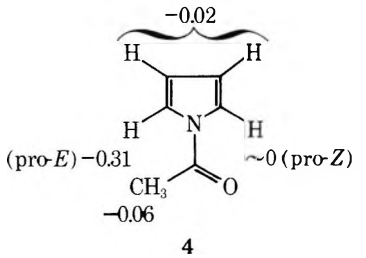


Figure 3. Plot of chemical shifts in *N*-acetylimidazole (**1b**) in mixtures of methylene chloride and acetone as a function of solvent composition: ×, chemical shifts of resonances in *Z*-**1b**; ○, chemical shifts of resonances in *E*-**1b**; the symbol ⊗ indicates that the resonances of the two configurations could not be resolved because of overlap.

not reverse but that the positions of the resonances cross over as the amount of acetone in the solvent mixture is increased. The plot of chemical shifts as a function of solvent composition (Figure 3) indicates that the changes are not linear. Rather, the crossover points, at which the chemical shifts are nearly equivalent, occur with solvent compositions with less than 50% of acetone (about 35% v/v or about 30% when mole percentages are used). This is consistent with the idea, discussed in a succeeding section, that the change is due to specific solvation by acetone rather than a bulk solvent change. Thus, the configuration of the major isomer must be the same in acetone as in dichloromethane. This reversal is caused by very substantial downfield solvent shifts for two protons H_2 in the *E* isomer and H_5 in the *Z* isomer. While the other ring protons, H_5 in the *E* isomer, H_2 in the *Z* isomer, and H_4, are shifted downfield by only ca. 0.1 ppm, H_2 in the *E* isomer and H_5 in the *Z* isomer suffer much greater shifts on the order of 0.5 ppm. Similar but smaller shifts were noted in tetrahydrofuran solvent. The shifts observed in both solvents are illustrated in Figure 4. Formylimidazole (**1a**) also exhibits downfield shifts in these two solvents resulting in coincidence between the resonances in the two diastereomers for all of the ring protons in these solvents. The presence of the two diastereomers is, however, still reflected in the pair of resonances observed for the formyl proton and the population ratio could still be determined by integration of these resonances.

We have observed similar acetone shifts in the low temperature (−61 °C) spectra of *N*-acetylpyrrole (**4**). While the



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low-field signal of the pair assigned to the α protons exhibits no appreciable shift upon change of solvent from dichloromethane to acetone (δ 7.47), the high-field signal is shifted from δ 7.17 to δ 7.48 at −61 °C. The β protons and the acetyl methyl group exhibit small downfield shifts. On the basis of the similarity of the acetone shifts in acetylpyrrole to those in acetylimidazole and formylimidazole, we can assign the low-field signal to the pro-*Z* hydrogen and the high-field signal to the pro-*E* hydrogen. The two groups[4,5] who first investi-

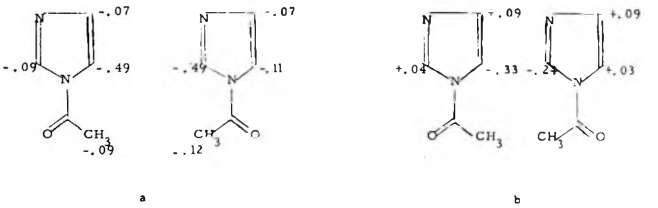


Figure 4. Solvent shifts observed for **1b** in (a) acetone and (b) tetrahydrofuran. Positive shifts (δ units) refer to upfield shifts relative to methylene chloride solvent.

gated slow torsion about the amide bond in *N*-acetylpyrrole made contradictory tentative assignments of the signals from the α protons on the basis of the supposed anisotropy of the amide carbonyl group. Elguero and co-workers[7d] have examined the problem in greater detail and have made assignments in this and other *N*-acylazoles using lanthanide induced shifts and comparison with chemical shifts in configurationally fixed model compounds. They concluded that the ring proton closest to the carbonyl oxygen atom appears upfield from that nearest the R group of the acyl function in this and other azoles. Our results provide further support for this conclusion (except when strong solvent shifts occur). While this generalization seems to be valid for a fairly large number of compounds, including the imides as well as *N*-acylazoles, we agree that assignments of configuration in amides should not be made on the basis of chemical shifts alone.[7d,16]

A small effect of solvent on the configurational equilibrium is evident in the data in Table I. Surprisingly, in the more polar solvents, acetone and tetrahydrofuran, the equilibium is shifted even further in the direction of the less polar isomer. A rationale for this behavior is discussed in a subsequent section of this paper. It is also surprising that the solvent effects on the equilibrium are so small when one compares the behavior of acylimidazoles with that of furfural where the configuration of more stable isomer changes from *E* in CF_2Cl_2 or CCl_4 to *Z* in acetone.[25]

The negligible differences in the equilibrium constants measured in methylene chloride for compounds **1b**, **1c**, and **1d** (1.9, 1.5, and 1.6, respectively) bearing methyl, ethyl, and isopropyl groups at the acyl carbon atom, support our contention that steric factors cannot play a significant role affecting the magnitude of the equilibrium constant and that steric interactions are nearly the same in the two diastereomers. If steric interactions were substantially different in the two forms, the equilibrium constant would be expected to change significantly in this series. The much greater equilibrium constant in formylimidazole (**1a**) (4.6 in methylene chloride), then, cannot be ascribed to a decrease in steric bulk of the R group but rather must result from some type of electronic effect. By implication, then, the reversal in the configurational equilibrium in the imide series may not be due solely to changes in steric interactions but may also reflect the same nonsteric factor which is responsible for the differences in the equilibrium constants of **1a** and of **1b, c.** On the other hand, the change in equilibrium constants is much more dramatic in the imide series implying that while steric repulsion may not be the sole factor accounting for the reversal it must certainly be the major factor.

In order to obtain the free energies of activation for torsion about amide bonds in **1a–e,** the coalescence temperatures (T_c) were measured and the rate constants at the coalescence point (k_c) were calculated using computer assisted complete lineshape analysis. The signal broadening due to coupling was simulated by adjusting the relaxation times (T_2). The relative populations and chemical shift differences were assumed to be essentially independent of temperature within the temperature range in which coalescence occurs. The validity of

Table II. Dynamic NMR Data and Torsional Barriers for *N*-Acylimidazoles, 1

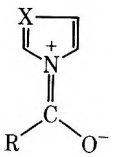
Compd	R	Solvent	Proton obsd	$\Delta\nu$, Hz	T_c, °C	Equilibrium constant (*E*/*Z*)	$\Delta G^{\ddagger}_{E\rightarrow Z}$, kcal/mol	$\Delta G^{\ddagger}_{Z\rightarrow E}$, kcal/mol
1a	H	$CDCl_3$	H_2	9.5	−50	(78/22) = 3.5	12.4	11.8
			H_5	9.8	−50		12.5	11.9
			CHO	6.4	−54		12.3	11.7
		THF	CHO	6.8	−65	(87/13) = 6.7	11.9	11.1
		CH_2Cl_2	H_2	8.2	−56	(82/18) = 4.6	12.2	11.6
			H_5	8.2	−56		12.4	11.7
			CHO	6.2	−59		12.1	11.5
		Acetone-d_6	CHO	6.2	−68	(88/12) = 7.3	11.8	11.0
1b	CH_3	$CFCl_3CDCl_3$ (2:1)	H_2	16.4	−68	(72/28) = 2.6	10.9	10.5
			H_5	19.7	−65		11.0	10.6
			Me	4.6	−76		11.0	10.7
		CH_2Cl_2	H_2	12.1	−73	(65/35) = 1.9	10.6	10.4

Table III. Room Temperature NMR Chemical Shifts (δ) in *N*-Acylimidazoles

		R						
R	Solvent	CH_3	CH_2	CH	H	H_2	H_4	H_5
H	$CDCl_3$				9.16	8.17	7.19	7.53
	THF				9.19	8.20	7.06	7.57
	CH_2Cl_2				9.19	8.16	7.17	7.53
	Acetone-d_6				9.39	8.33	7.14	7.65
CH_3Me	$CFCl_3$–$CDCl_3$	2.57				8.09	7.06	7.44
	THF	2.57				8.22	7.03	7.57
	CH_2Cl_2	2.56				8.12	7.08	7.48
	Acetone-d_6	2.65				8.26	7.03	7.60
CH_2CH_3	CH_2Cl_2	1.29	2.90			8.14	7.07	7.48
$CH(CH_3)_2$	CH_2Cl_2	1.31		3.22		8.17	7.08	7.50
CF_3	CH_2Cl_2					8.24	7.19	7.58
$C(CH_3)_3$	CH_2Cl_2	1.45				8.25	7.02	7.56

this assumption was supported by the finding that changes in $\Delta\nu$ and K_{eq} were within experimental error for **1b** in dichloromethane in the temperature range −80 to −105 °C. In any event, it is well known that moderately large errors in k_c result in errors in the free energy of activation smaller than the error introduced by the experimental uncertainty in the measurement of temperature.[26] The chemical shift differences, coalescence temperatures, and free energies of activation (obtained using the Eyring equation) are collected in Table II. In most cases, the coalescence of more than one set of signals could be used to calculate the torsional barrier. The barriers calculated using signals derived from different protons never differed by more than 0.2 kcal/mol, which is approximately the error derived from the uncertainty in the temperature (about ±2 °C).

The energy barriers for *N*-acetyl- and *N*-formylimidazoles are about 2–3 kcal/mol lower than those for the corresponding pyrrole analogues.[4,5,7] This implies that the ionic canonical structure **5** makes a less important contribution to the structures of imidazoles (X = N) than it does to the structures of the corresponding pyrroles (X = CH). This is in accord with the results of studies on *N*-acylazoles using infrared spectra and molecular orbital calculations.[27,29] The carbonyl stretching absorbtion of the amide group appears at 1734, 1747, 1765, and 1779 cm^{-1} in the *N*-acetyl derivatives of



X = CH, N
R = H, CH_3

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pyrrole, imidazole, triazole, and tetrazole, respectively, and the amide torsional barriers are expected to decrease in this order.

The barriers in the imidazole series are comparable to those in the imide series. Thus the barrier in **1a** (11.8 kcal/mol) is slightly smaller than that in diformamide (12.9 kcal/mol). The replacement of one of the carbonyl oxygen atoms by a less electronegative nitrogen atom would be expected to increase the barrier to torsion about the other amide bond. The aromaticity of the imidazole ring, on the other hand, leads to a lowering of the torsional barrier. Apparently these two factors are nearly balanced and the barrier is not changed appreciably.

The variation of the torsional barriers in compounds **1** parallels that in the corresponding *N*,*N*-dimethylamides, $RCON(CH_3)_2$. A plot of the free energies of activation for the acylimidazoles **1** in methylene chloride as a function of the barriers for the corresponding dimethylamides in nonpolar solvents indicates a good correlation (Figure 5).[30] This suggests that the barriers in both series are dependent on approximately the same mix of steric and electronic effects associated with changes in the acyl moiety.[31] Based upon the correlation illustrated in Figure 5, an approximate torsional barrier for *N*-trimethylacetylimidazole (**1f**) of ca. 7.9 kcal/mol can be predicted. Based on a chemical shift difference of ca. 10 Hz and an equilibrium constant of 1.5, this would correspond to a coalescence temperature of about −130 °C. This prediction is in accord with the failure to detect signal splitting as the result of slow exchange in **1f** at the lowest temperatures attained (−120 °C).

The barriers for **1a** and **1b** measured in the more polar solvent acetone are somewhat smaller than those in the less polar solvent $CDCl_3$ (or $CFCl_3/CDCl_3$ for **1b**). It might have

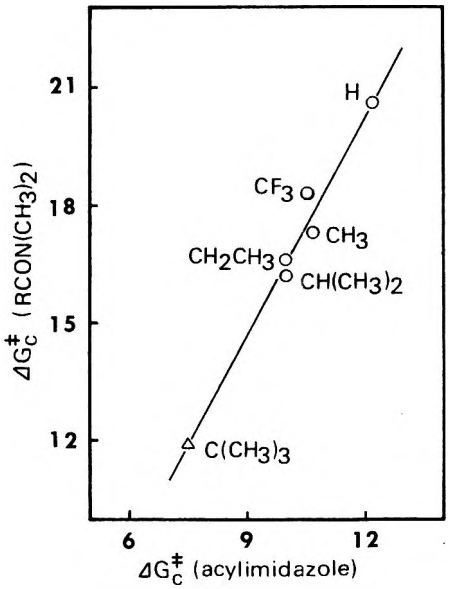

Figure 5. Linear free energy relationship between torsional barriers in *N*-acylimidazoles ($RCONC_3H_3N$) and those in the corresponding *N,N*-dimethylamides [$RCON(CH_3)_2$]. The point, △, for R = $C(CH_3)_3$ is not a data point but was extrapolated from the linear least-squares best fit line from the experimental points, O, using the literature value for the barrier in *N,N*-dimethylpivalamide.

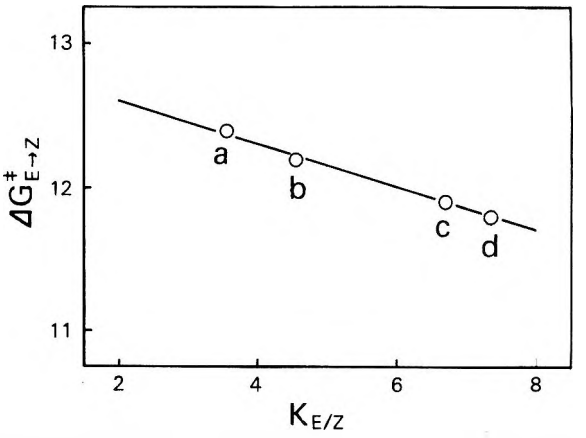

Figure 6. Plot of the free energies of activation for torsion in *N*-formylimidazole (**1a**) as a function of the configurational equilibrium constant in a series of solvents: a, deuteriochloroform; b, methylene chloride; c, tetrahydrofuran; d, deuterated acetone.

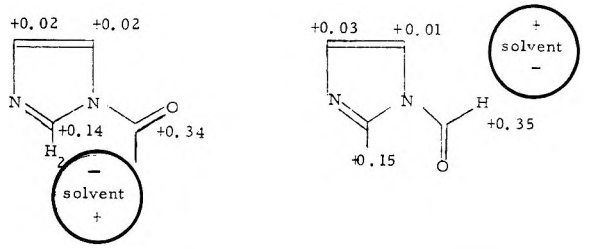

Figure 7. Proposed solvation of **1a** by polar solvents acetone and tetrahydrofuran. The charges on the carbon atoms shown are those obtained by CNDO/2 calculations.

been supposed that polar solvents would stabilize the ground state, in which the polar canonical structure **5** makes a contribution, more than they would in the torsional transition state where amide resonance is not possible. Indeed, this is the direction observed for the simple amides dimethylformamide and dimethylacetamide.[30c] Further, we note that the variations in barriers in **1a** do not correlate quantitatively with solvent bulk dielectric constant. Thus, the barrier for **1a** in tetrahydrofuran (ϵ 10.6 at −60 °C) is considerably lower than that in dichloromethane (ϵ 13.3 at −60 °C), but is not very different from that in acetone (ϵ 30.0 at −60 °C). While we cannot offer a conclusive rationale for this phenomenon, nor for the effect of solvent on the equilibrium constant for the configurational equilibrium, the two may very well be related. A plot of the torsional barrier as a function of the equilibrium constant for **1a** results in a surprisingly good correlation (Figure 6). In those solvents in which the configurational equilibrium is most biased, the torsional barrier is the lowest. If this correlation is not fortuitous, it suggests that the operation of a common factor is involved. The implication is that solvation of a particular region of **1a** by acetone and tetrahydrofuran is more favorable in the *E* isomer of the ground state than in the *Z* isomer and more favorable in the transition state than in either ground-state form. The most positively charged carbon atom, according to our CNDO/2 calculations, is the carbonyl carbon atom of the acyl group which bears a charge of +0.35. It seems most reasonable to suppose that solvation of this carbon atom is involved. This postulate provides a rationale for the solvent effects on chemical shifts described earlier (Figure 4). The greatest shifts observed are those for the ring carbon atoms H_5 in the *Z* isomer and H_2 in the *E* isomer. The protons would be the closest to solvent molecules interacting with the positive end of the carbonyl bond dipole. This solvation would be more favorable in the *E* isomer than in the *Z* isomer, (Figure 7), since solvent is able to interact as well with C_2, which is the most positively charged of the ring carbons, as shown. Solvation even in this form is hindered by the peri-like interaction with H_2 and thus solvation can be more effective in the transition state where this interaction is absent. The more effective solvation of the transition state results in a lowering of the torsional barrier in these solvents. This model also has the virtue of rationalizing the greater effects on chemical shifts, the equilibrium constant, and free energy of activation of tetrahydrofuran as compared with dichloroethane. While the bulk dielectic constant of tetrahydrofuran is slightly smaller than that of dichloromethane, it is better at solvating positive charge.

Experimental Section

N-Acylimidazoles were synthesized and purified as reported by Staab and his co-workers.[32] Physical and spectroscopic properties were in accord with those reported and the assigned structures. *N*-Acetylpyrrole was prepared by transacetylation from *N*-acetylimidazole according to Reddy.[33]

^1H NMR spectra were recorded on a Varian A-60A spectrometer equipped with a V-6040 temperature controller using 2.5 mol % solutions. Temperatures were measured using methanol spectra as described in the Varian users manual and are considered accurate to ±2 °C. Chemical shifts were calibrated by the side band method using a Hewlett-Packard 200CDR audio oscillator, and a Beckman FR 67/U frequency counter.

Molecular orbital calculations (CNDO/2) were carried out using a slightly modified version of the program given in ref 34. Bond lengths and angles used were taken from x-ray crystallographic data for imidazole[35] and microwave spectroscopic data for formamide[36] (subscript f refers to atoms in the formyl moiety): C_f–O, 1.19 Å; C_f–H_f, 1.102 Å; C_f–N_1, 1.376 Å; N_1–C_2, 1.349 Å; N_1–C_5, 1.369 Å; C_2–N_3, 1.326 Å; N_3–C_4, 1.376 Å; C_4–C_5, 1.358 Å; $C_{2(4,5)}$–H, 1.08 Å; bond angles OC_fN_1, 123.8°; $H_fC_fN_1$, 113.2°; $C_fN_1C_2$, 126.4°; $N_1C_2N_3$, 111.3°; $C_2N_1C_5$, 107.2°; $N_1C_5C_4$, 106.3°.

References and Notes

(1) (a) For part 30 in this series on Stereochemistry in Trivalent Nitrogen Compounds, see D. Kost and M. Raban, *J. Am. Chem. Soc.*, in press. (b) This work was supported by the National Science Foundation.
(2) (a) On leave from the University of Tokyo; (b) A. P. Sloan Fellow, 1972–1976.
(3) (a) W. E. Stewart and T. H. Siddall, III. *Chem. Rev.* **70**, 517 (1970); (b) I. O. Sutherland, *Annu. Rep. NMR Spectrosc.*, **4**, 71 (1971).
(4) T. Matsuo and H. Shosenji, *J. Chem. Soc., Chem. Commun.*, 501 (1969).
(5) K.-I. Dahlquist and S. Forsen, *J. Phys. Chem.*, **73**, 4124 (1969).

(6) (a) A. Mannschreck, H. A. Staab, and D. Wurmb-Gerlich, *Tetrahedron Lett.*, 2003 (1963); (b) H. A. Staab and D. Lauer, *Chem. Ber.*, **101**, 864 (1968).
(7) (a) L. Pappalardo, J. Elguero, and C. Marzin, *C. R. Acad. Sci., Ser. C*, **277**, 1163 (1973); (b) J. Elguero, C. Marzin, and L. Pappalardo, *Bull. Soc. Chim. Fr.*, 1137 (1974); (c) J. Elguero, A. Fruchier, L. Knutsson, R. Lazaro, and J. Sandstrom, *Can. J. Chem.*, **52**, 2744 (1974); (d) J. Elguero, C. Marzin, and M. E. Peck, *Org. Magn. Reson.*, **7**, 445 (1975).
(8) E. Noe and M. Raban, *J. Am. Chem. Soc.*, **97**, 5811 (1975).
(9) In methanol a substantial amount of the *Z,Z* isomer (ca. 40%) of diacetamide is observed in equilibrium with the *E,Z* form (E. A. Noe and M. Raban, unpublished results).
(10) Chemical shift data from ambient spectra are given in Table III.
(11) G. S. Reddy, L. Mandell, and J. H. Goldstein, *J. Chem. Soc.*, 1414 (1963).
(12) A. Mannschreck, W. Seitz, and H. A. Staab, *Ber. Bunsenges. Phys. Chem.*, **67**, 470 (1963).
(13) The low temperature spectra of **1f** were taken in a series of solvents, dichloromethane, vinyl chloride, dichloromethane–dimethyl ether, and dichloromethane–bromotrifluoromethane, in order to minimize the possibility that the chemical shift equivalence derived from accidental coincidence of signals from the two diastereomers rather than rapid exchange.
(14) M. Raban and R. Keintz, unpublished results.
(15) The situation in simple *N,N*-dialkylamides is more complicated.[3a,16,17] In *N,N*-dimethylamides, $RCON(CH_3)_2$, the methyl group cis to the carbonyl oxygen atom is shifted *upfield* relative to the trans methyl group. The direction of this shift was rationalized by taking into account the placement of methyl protons out of the plane of the carbonyl group and into a region of shielding by the anisotropic amide group. Perhaps the greater planarity in imides and acylimidazoles leads to results which are more consistent with the well-established model of the magnetic anisotropy of the isolated carbonyl group (in ketones and aldehydes) in which protons near the nodal plane of the carbon–oxygen double bond are deshielded. It may be noted that *N*-acylanilides, which have a similar geometry, exhibit consistent downfield shifts for the ortho protons which are cis to the carbonyl group. The methyl group in *N,N*-diethylamides also exhibits a downfield shift for the methyl cis to the amide oxygen.
(16) A. H. Lewin and M. Frucht, *Org. Magn. Reson.*, **7**, 206 (1975).
(17) (a) H. Paulsen and K. Todt, *Angew. Chem., Int. Ed. Engl.*, **5**, 899 (1966); (b) H. Paulsen and K. Todt, *Z. Anal. Chem.*, **235**, 29 (1968).
(18) L. L. Graham, *Org. Magn. Reson.*, **4**, 335 (1972).
(19) M. T. Rogers and C. W. Woodbrey, *J. Phys. Chem.*, **66**, 540 (1962).
(20) L. W. Reeves, R. C. Shaddick, and K. N. Shaw, *Can. J. Chem.*, **49**, 3683 (1971).
(21) L. R. Isbrandt and M. T. Rogers, *Chem. Commun.*, 1378 (1971).
(22) S. Sternhell, *Q. Rev., Chem. Soc.*, **23**, 236 (1969).
(23) M. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (1969).
(24) P. Laszlo in "Progress in Nuclear Magnetic Resonance Spectroscopy", Vol. 3, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Ed., Pergamon Press, Elmsford, N.Y., 1967, Chapter 6.
(25) (a) R. J. Abraham and T. M. Siverns, *Tetrahedron*, **28**, 3015 (1972); (b) R. J. Abraham and E. Bretschneider in "Internal Rotation in Molecules", W. J. Orville-Thomas, Ed., Wiley, New York, N.Y., 1974, Chapter 13.
(26) D. Kost, E. H. Carlson, and M. Raban, *Chem. Commun.*, 656 (1971).
(27) J. M. Gross, and D. G. Rush, *Chem. Ind. (London)*, 1766 (1968).
(28) H. A. Staab, *Angew. Chem.*, **74**, 407 (1962).
(29) H. W. Thompson and R. J. L. Popplewell, *Z. Electrochem.*, **64**, 746 (1960).
(30) (a) The free energies of activation at coalescence for *N,N*-dimethylamides, $RCON(CH_3)_2$, used in construction of Figure 5 are literature values or were calculated from literature activation parameters for nonpolar solvents (R, $\Delta G_c^{\ddagger}$ in kcal/mol, solvent, reference): H, 20.6, C_2Cl_4, 30b; CH_3, 17.3, CCl_4 (1.7 mol %), 30c; CH_3CH_2, 16.6, CCl_4 (11 mol %), 30d; $CH(CH_3)_2$, 16.2, *o*-$Cl_2C_6H_4$ (33 mol %), 30e; CF_3, 18.3, CCl_4 (11.25 mol %), 20; $C(CH_3)_3$, 11, 9, CH_2Cl_2 (10 mol %), 30f. (b) T. Drakenberg, K.-I. Dahlquist, and S. Forsen, *J. Phys. Chem.*, **76**, 2178 (1972). (c) R. C. Neuman, Jr., and V. Jonas, *J. Org. Chem.*, **39**, 929 (1974). (d) J. C. Woodbrey and M. T. Rogers, *J. Am. Chem. Soc.*, **84**, 13 (1962). (e) G. Isaksson and J. Sanstrom, *Acta Chem. Scand.*, **21**, 1605 (1967). (f) L. L. Graham and R. E. Diel, *J. Phys. Chem.*, **73**, 2696 (1969).
(31) R. C. Neuman, Jr., and V. Jonas, *J. Am. Chem. Soc.*, **90**, 1790 (1968); *J. Org. Chem.*, **39**, 925 (1974).
(32) (a) H. A. Staab and B. Polenski, *Justus Liebigs Ann. Chem.*, **655**, 95 (1962); (b) H. A. Staab, *Chem. Ber.*, **89**, 1927 (1956); (c) *ibid.*, **89**, 2088 (1956); (d) H. A. Staab and G. Walther, *ibid.*, **95**, 2070 (1962).
(33) G. S. Reddy, *Chem. Ind. (London)*, 1426 (1965).
(34) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, N.Y., 1970.
(35) S. Martinez-Carrera, *Acta Crystallogr.*, **20**, 783 (1966).
(36) C. C. Costain and J. M. Dowling, *J. Chem. Phys.*, **32**, 158 (1960).

Reduction of 1,3-Diphenyl-2,2-dihaloaziridines with Tri-*n*-butyltin Hydride

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1,3-Diphenyl-2,2-dihaloaziridines (**1–5**) were prepared by the addition of dihalocarbene (CClF, CBrF, CClBr, CCl_2, and CBr_2) to *N*-benzylideneaniline in *n*-hexane. These aziridine compounds were reduced with tri-*n*-butyltin hydride in *n*-pentane at room temperature to give the corresponding 1,3-diphenyl-2-haloaziridines (**6–8**). The reduction of **1**, **2**, and **3** proceeded stereospecifically, i.e., with retention of configuration, indicating that the intermediate 2-fluoro- and 2-chloro-2-aziridinyl radicals are pyramidal, and configurationally stable enough to abstract hydrogen from tri-*n*-butyltin hydride much more rapidly than invert their configurations.

It is known that the configurational stability of cyclopropyl radicals is strongly dependent on the nature of the α substituent, i.e., the substituent at the radical carbon.[1] The energy barriers for inversion of the cyclopropyl (A), the α-chlorocyclopropyl (B), and the α-fluorocyclopropyl (C) radicals have been calculated to be 0.8, 4.0, and 10.5 kcal/mol, respectively, by use of the CNDO/2 approximation.[2] These calculations indicate that the configurational stability of these radicals increases in the order A < B < C, which is in good agreement with that of the degree of stereospecificity observed in a number of reactions proceeding via these radicals, such as the reduction of cyclopropyl halides with organotin hydrides, the brominative decarboxylation of silver cyclopropanecarboxylates, and the thermal decomposition of cyclopropanepercarboxylic acid esters. Thus, cyclopropyl radical (A)[3] inverts its configuration so fast that it behaves as if it were planar, whereas the α-fluorocyclopropyl radical (C) reacts stereospecifically, i.e., with complete retention of configuration, in many reactions.[1,4,5] The inversion rate of the α-chlorocyclopropyl radical[1,6] is between those of the radicals cited above.

Recently, we have shown that the configurational stability of the α-fluorocyclopropyl radical is also affected by the β substituent.[7] Our findings are again in agreement with the prediction made theoretically by Dewar and Bingham.[8]

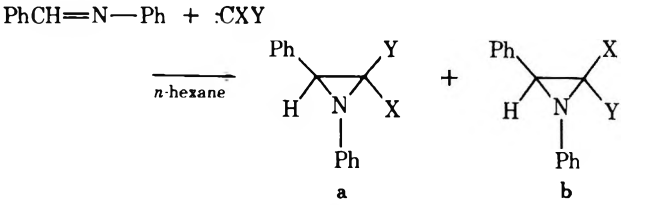
As compared with cyclopropyl radicals, however, there have been very few studies on the configurational stability of other three-membered-ring radicals containing a heteroatom in the ring, such as oxiranyl, 2-aziridinyl, and thiiranyl radicals. Altman and his collaborator have shown both theoretically[2] and experimentally[9] that the energy for inversion of the oxiranyl radical is larger than that of the corresponding cyclopropyl radical.

We have now extended our studies to the hitherto unexa-

mined 2-aziridinyl radical, with the expectation that the 2-aziridinyl radical might have a larger configurational stability than the cyclopropyl radical, as does the oxiranyl radical. In the present paper will be described the results of the studies on the reduction of 1,3-diphenyl-2,2-dihaloaziridines with tri-*n*-butyltin hydride.

Results

Preparation of 1,3-Diphenyl-2,2-dihaloaziridines. The aziridine compounds employed in this study were prepared by the reaction of dihalocarbene with *N*-benzylideneaniline.[10]



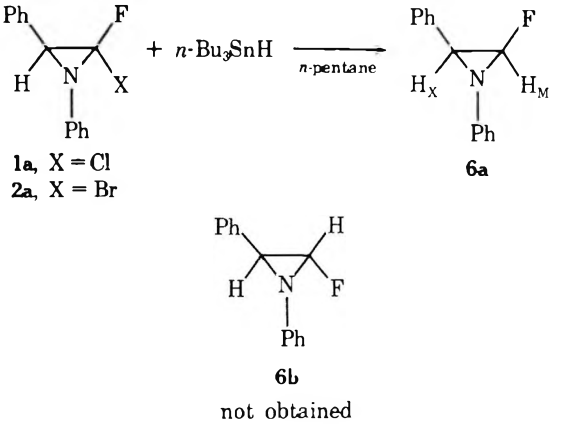
1, X = Cl; Y = F
2, X = Br; Y = F
3, X = Cl; Y = Br
4, X = Y = Cl
5, X = Y = Br

All of the aziridine compounds prepared gave satisfactory elemental analyses as well as ir, NMR, and mass spectra.

Since chlorofluoro-, bromofluoro-, and chlorobromocarbenes and *N*-benzylideneaniline are both unsymmetrical, two isomers of the aziridine should expectedly be formed. In fact, from chlorobromocarbene and the anil, usual treatment of the reaction mixture and recrystallization from *n*-pentane gave a mixture of two isomers (**3a** and **3b**) of 1,3-diphenyl-2-chloro-2-bromoaziridine in 61% yield. The NMR spectrum of the product showed the absorptions at δ 3.50 (singlet), 3.66 (singlet), and 6.90–7.50 (multiplet). Heating the mixture of the two isomers in refluxing *n*-hexane–benzene (1:1) for a week resulted in the decomposition of one isomer (**3a**), with the other isomer (**3b**) left unchanged. The NMR spectrum of the remaining unchanged isomer showed the absorptions at δ 3.66 (singlet, 1 H) and 6.90–7.50 (multiplet, 10 H). Column chromatography (silica gel, *n*-pentane eluent) of the two isomers gave pure **3a** which had the absorptions at δ 3.50 (singlet, 1 H) and 6.90–7.50 (multiplet, 10 H) in its NMR spectrum. The isomer ratio in the product was 2.3/1, with the isomer (**3b**) having the absorption at δ 3.66 predominating. Although neither these NMR data nor the ir and mass spectral data of the isomers were sufficient to determine their configurations (*E* or *Z*), the results of the reduction of each isomer allowed us to assign the *Z* configuration to **3a** and the *E* configuration to **3b**.[11]

In the NMR spectrum of the product obtained from chlorofluorocarbene and the anil, only one doublet (δ 3.48, doublet, J = 3.5 Hz, 1 H) was observed in addition to a complex multiplet due to phenyl protons (δ 6.90–7.58, 10 H). Similarly, the NMR spectrum of the bromofluorocarbene adduct showed one alicyclic hydrogen (δ 3.50, doublet, J = 4.0 Hz) and ten aromatic hydrogens (δ 6.92–7.60, multiplet). These doublets are due to the benzylidene proton coupled with the fluorine on the adjacent carbon. The magnitudes of the coupling constants suggest that these aziridines are the *E* isomers (**a**).[12] The absence of other absorptions which could possibly be attributed to the other isomer (**b**) indicates that these recrystallized products contain only one isomer (**a**) and that the reaction occurs with high stereoselectivity.[14] An analogous stereoselective addition was observed in the reaction of excess $LiCHCl_2$ with *N*-benzylideneaniline in ether at temperatures below −70 °C.[15]

Reduction of 1,3-Diphenyl-2,2-dihaloaziridines with Tri-*n*-butyltin Hydride. 1,3-Diphenyl-2-chloro-2-fluoroaziridine (**1**) was reduced with a small excess of tri-*n*-butyltin hydride in *n*-pentane at room temperature under nitrogen atmosphere for 5 days. The reduction product was isolated by use of column chromatography (alumina). The NMR spectrum of the product proved that only one isomer of 1,3-diphenyl-2-fluoroaziridine (**6a**) was formed. The NMR spectrum in carbon tetrachloride showed the absorptions at δ 5.03 (double doublet, J = 4.0 and 79.0 Hz, 1 H), 3.16 (double doublet, J = 3.5 and 4.0 Hz, 1 H), and 6.90–7.58 (multiplet, 10 H). The smaller coupling constant (4.0 Hz) at δ 5.03 is due to the interaction between H_M and H_X, and the larger one (79.0 Hz), to that between H_M and F. Similarly, the coupling constants of 4.0 and 3.5 Hz at δ 3.16 can be attributed to the interaction between H_X and H_M, and between H_X and F, respectively. These magnitudes of the coupling constantssuggest that the reduction product formed was the isomer (**6a**) whose fluorine atom was trans to the hydrogen (H_X) at the adjacent ring carbon.[12,16] This means that the reduction proceeded with retention of the original configuration.

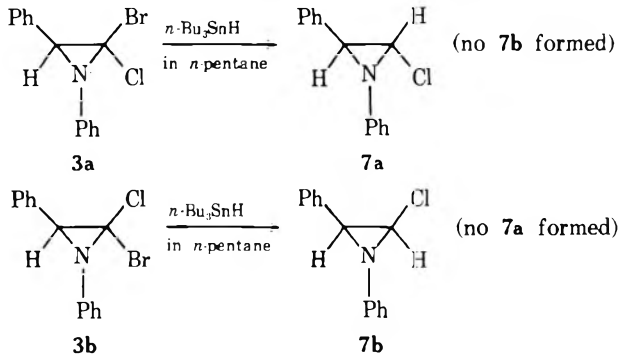


A similar stereospecificity was observed in the reduction of 1,3-diphenyl-2-bromo-2-fluoroaziridine (**2a**). **2a** was converted into **6a**, with no sign of **6b** being formed.

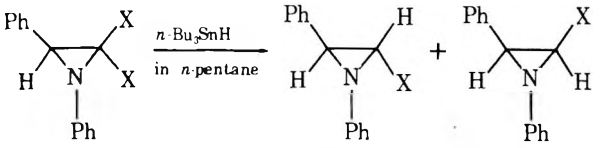
A mixture of isomers (**3a** and **3b**) of 1,3-diphenyl-2-chloro-2-bromoaziridine was similarly reduced in *n*-pentane. An attempt to isolate the reduction product (**7**) by column chromatography was unsuccessful because it was too unstable under the chromatographic conditions.[17] Inspection of the NMR spectrum of the reaction mixture in *n*-pentane revealed the peaks at δ 3.20 (doublet, J = 5.0 Hz), 3.26 (doublet, J = 2.0 Hz), 4.27 (doublet, J = 2.0 Hz), 4.32 (doublet, J = 5.0 Hz), and 7.15–7.80 (multiplet) in addition to the peaks due to *n*-pentane, phenyl group, and the *n*-butyl group of *n*-butyltin bromide. After removal of the *n*-pentane from the reaction mixture, benzene was added to the residue. The NMR spectrum of the benzene solution showed the peaks at δ 2.87 (doublet, J = 5.0 Hz), 3.16 (doublet, J = 2.0 Hz), 4.08 (doublet, J = 2.0 Hz), and 4.11 (doublet, J = 5.0 Hz) in addition to the peaks due to the *n*-butyl group of *n*-butyltin bromide and phenyl group. That these four doublets are due to aziridine ring hydrogens of the reduction product is supported by the comparison of the δ values and the coupling constants with those of 1,3-diphenyl-2-chloroaziridine prepared by Deyrup et al.[15,16] and of other analogous aziridine compounds.[18] The larger coupling constant (J = 5.0 Hz) is attributed to the cis isomer (**7b**), and the smaller one (J = 2.0 Hz) to the trans isomer (**7a**).

Each isomer of **3** was reduced separately under the same conditions. The NMR spectra of the reaction mixture confirmed that only one isomer was formed from each of the isomers (**7a** from **3a**, **7b** from **3b**), which indicated that the reduction of **3** also proceeded stereospecifically.

1,3-Diphenyl-2,2-dichloroaziridine (**4**) and 1,3-diphenyl-2,2-dibromoaziridine (**5**) were similarly reduced in *n*-pentane.



The reduction products (7 and 8) could not be isolated because of their instability under the chromatographic conditions. The NMR spectra (in *n*-pentane and in benzene) of the reaction mixture obtained in the reduction of 4 had the peaks, except a small one due to the unreacted starting material (4), at the



4, X = Cl
5, X = Br

7a, X = Cl
8a, X = Br

7b, X = Cl
8b, X = Br

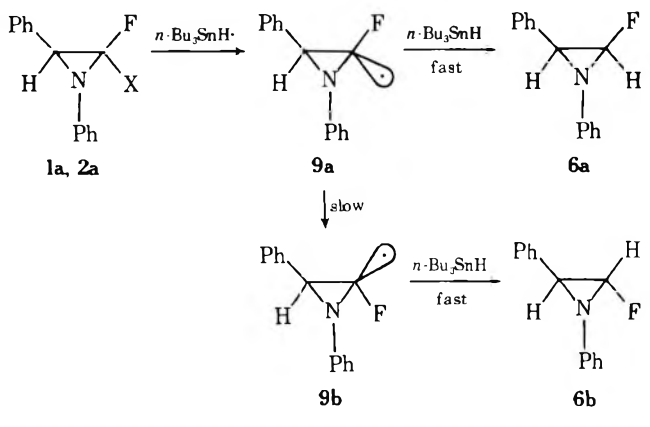
same positions as the reaction mixture obtained from an isomeric mixture of **3**. The isomer ratio of the reduction product (**7b**/**7a**) was calculated from peak areas in NMR to be 1.9/1.

Similarly, the NMR spectrum (in benzene) of the reaction mixture obtained in the reduction of **5** showed complex aromatic peaks and four doublets, two of which (J = 5.0 Hz) centered at δ 2.88 and 4.26, and the other two (J = 2.0 Hz) centered at δ 3.25 and 4.17, in addition to the peaks due to the *n*-butyl group of *n*-butyltin bromide. The isomer ratio (**8b**/**8a**) was 2.0/1.

Discussion

The reduction of organic halides with organotin hydride have been rationalized as a free-radical chain reaction[19] and the intermediacy of a free radical has been postulated also in the reduction of some 7,7-dihalonorcaranes[20] and of some *gem*-dihalocyclopropanes[21] with organotin hydride. It is of little doubt that the reduction of **1**–**5** is a radical chain reaction which involves intermediate formation of the 2-halo-2-aziridinyl radical as one of the chain-propagating steps.

The experimental results obtained in the reduction of **1** and **2** demonstrate that the 2-fluoro-2-aziridinyl radical (**9a**) thus formed is pyramidal and abstracts hydrogen from tri-*n*-butyltin hydride much more rapidly than it inverts its configuration to **9b**; if it is planar, or if the inversion occurs before



hydrogen abstraction, a mixture of the two isomeric 1,3-diphenyl-2-fluoroaziridines (**6a** and **6b**) must be formed. The application of the same argument to the reduction of **3a** and **3b** leads to the conclusion that the 2-chloro-2-aziridinyl radicals are also pyramidal and are configurationally very stable.

A similar stereospecificity was observed in the reduction of *gem*-halofluorocyclopropanes with tri-*n*-butyltin hydride,[4,5] while the other hitherto known α-substituted cyclopropyl radicals, formed in the reduction of α-substituted cyclopropyl halides with organotin hydride or in the Hunsdiecker reaction of α-substituted cyclopropanecarboxylic acids, were found to lose their original configurations completely or partly during the reaction. Thus, 7-cyano-, 7-phenyl-, or 7-methoxycarbonyl-7-norcaryl radical equilibrates between its isomeric configurations before hydrogen abstraction.[22] The 7-chloro-7-norcaryl radical[1,6] can retain its original configuration to some extent, but not completely.

These results demonstrate that the 2-aziridinyl radical has a stronger tendency to retain its configuration than the cyclopropyl radical. One of the possible explanations is to attribute it to the increase of s charactor of the radical orbital of carbon in the aziridinyl radical, caused by the electronegative nitrogen atom.[23]

The **b** isomer of 1,3-diphenyl-2-chloroaziridine (**7**) was preferentially formed in the reduction of 1,3-diphenyl-2,2-dichloroaziridine (**4**). This may be explained by postulating that the sterically less hindered chlorine, i.e., the one trans to the phenyl group at the adjacent carbon, is abstracted by the tri-*n*-butyltin radical more easily than the cis chlorine[24] and that the resulting 2-chloro-2-aziridinyl radical retains its configuration when it abstracts hydrogen from tri-*n*-butyltin hydride. The preferential formation of the **b** isomer of 1,3-diphenyl-2-bromoaziridine (**8**) in the reduction of 1,3-diphenyl-2,2-dibromoaziridine (**5**) might be explained in a similar way, but no definite conclusion can be drawn at present, because the configurational stability of the 2-bromo-2-aziridinyl radical has not been examined so far.

Experimental Section

Infrared spectra were obtained with a Shimadzu IR-400 or a Japan Spectroscopic Co. IR-DS 402G infrared spectrometer. ^{1}H NMR spectra were obtained with a Varian Associates T-60A or a JEOLCO 4H-100 NMR spectrometer in carbon tetrachloride with tetramethylsilane as internal reference. Mass spectra were obtained with a Shimadzu LKB-9000 or a Hitachi RMS-4 mass spectrometer. Isomer distributions were calculated from peak area in NMR spectra. All melting points are uncorrected. All chemicals were reagent grade and used without further purification. Solvents were distilled through a 25-cm Vigreux column and, if necessary, were purified in the usual manner prior to use.

Preparation of 1,3-Diphenyl-2,2-dihaloaziridines. 1,3-Diphenyl-2-chloro-2-fluoroaziridine (1). To a stirred solution of 18.1 g (0.10 mol) of *N*-benzylideneaniline and 4.8 g (0.20 mol) of sodium hydride in 200 ml of *n*-hexane, cooled to 0 °C in an ice bath, was added 32.2 g (0.20 mol) of methyl dichlorofluoroacetate, under a nitrogen atmosphere, at such a rate that the temperature should not rise above 5 °C. After the addition was over, the mixture was warmed up to 20–30 °C and then for 3 h at room temperature. The reaction mixture was suction filtered, the residue was washed three times with *n*-hexane, and the solvent was removed in vacuo from the combined filtrates, leaving a dark brown viscous liquid. *n*-Pentane was added to this liquid and then the solution was filtered again. The filtrate (*n*-pentane solution) was stored for 20 h at −20 °C to give as precipitates 5.7 g (23% yield) of 1,3-diphenyl-2-chloro-2-fluoroaziridine (**1**). Recrystallization from *n*-pentane gave pale yellow crystals: mp 54–55 °C; ir (KBr) 3040 (w), 1600 (vs), 1495 (s), 1410 (s), 1275 (w), 1235 (m), 1130 (s), 1040 (w), 840 (w), 760 (s), 695 cm^{-1} (s); NMR δ 3.48 (d, J_{HF} = 3.5 Hz, 1 H), 6.90–7.58 (m, 10 H); mass spectrum *m/e* 249 (P + 2), 247 (P), 229, 227, 212. Anal. Calcd for $C_{14}H_{11}NClF$: C, 67.89; H, 4.48. Found: C, 67.98; H, 4.37.

1,3-Diphenyl-2-bromo-2-fluoroaziridine (2a). To a stirred solution of 18.1 g (0.10 mol) of *N*-benzylideneaniline and 22.4 g (0.20 mol) of potassium *tert*-butoxide in 200 ml of *n*-hexane, cooled to 0 to −10 °C in an ice–salt bath, was added 38.4 g (0.20 mol) of dibro-

mofluoromethane, under nitrogen atmosphere, over 2 h. After the addition was over, the mixture was stirred for 2 h at 0 to −10 °C and then for 3 h at room temperature. The reaction mixture was worked up as described above. Light-tan crystals of 1,3-diphenyl-2-bromo-2-fluoroaziridine (**2**) were obtained in 28% yield: mp 57–59 °C; ir (KBr) 3035 (w), 1600 (s), 1495 (vs), 1404 (s), 1275 (w), 1230 (w), 1120 (s), 1035 (w), 835 (w), 755 (vs), 695 cm^{-1} (vs); NMR δ 3.50 (d, J_{HF} = 4.0 Hz, 1 H), 6.95–7.55 (m, 10 H); mass spectrum *m/e* 293 (P + 2), 291 (P), 273, 271, 212. Anal. Calcd for $C_{14}H_{11}NBrF$: C, 57.56; H, 3.80. Found: C, 57.59; H, 3.75.

1,3-Diphenyl-2-bromo-2-chloroaziridine (3) was prepared by the same method as described for the preparation of **2.** Dibromochloromethane was used as carbene precusor instead of dibromofluoromethane. The pale yellow crystals of **3** were obtained in 61% yield, mp 89–91 °C. The NMR spectrum of the crystals (in CCl_4) showed absorptions at δ 3.50 (s), 3.66 (s), and 6.90–7.50 (m), indicating the existence of a mixture of isomers of **3** (**a** and **b**). Column chromatography (alumina, *n*-pentane eluent) gave only one isomer (**3a**) (assignment was made from the results of reduction), and the other isomer (**3b**) could not be isolated because of its decomposition. Pure **3b** was obtained by heating a mixture of **3a** and **3b** in refluxing *n*-hexane–benzene (1:1) for a week, which resulted in the decomposition of **3a**, with **3b** left unchanged. The isomer ratio of **3a**/**3b** was 1/2.3.

3a: mp 92–94 °C; ir (KBr) 3045 (w), 1590 (vs), 1305 (s), 1265 (w), 1095 (w), 805 (s), 760 (s), 690 cm^{-1} (s); NMR δ 3.50 (s, 1 H), 6.90–7.50 (m, 10 H). Anal. Calcd for $C_{14}H_{11}NBrCl$: C, 54.49; H, 3.59. Found: C, 54.65; H, 3.50.

3b: mp 94–96 °C; ir (KBr) 3045 (w), 1588 (vs), 1306 (s), 1265 (w), 1100 (w), 805 (s), 760 (s), 690 cm^{-1} (s); NMR δ 3.66 (s, 1 H), 6.90–7.50 (m, 10 H). Anal. Calcd for $C_{14}H_{11}NBrCl$: C, 54.49; H, 3.59. Found: C, 54.73; H, 3.48.

Mass spectrum (a mixture of **3a** and **3b**): *m/e* 311 (P + 4), 309 (P + 2), 307 (P), 274, 272, 230, 228.

1,3-Diphenyl-2,2-dichloroaziridine (4) was prepared in 55% yield according to the method of Cook and Fields:[25] mp 97–99 °C; ir (KBr) 3045 (w), 1590 (vs), 1390 (s), 1265 (w), 1100 (w), 820 (s), 765 (s), 695 cm^{-1} (s); NMR δ 3.95 (s, 1 H), 6.90–7.50 (m, 10 H); mass spectrum *m/e* 267 (P + 4), 265 (P + 2), 263 (P), 230, 228. Anal. Calcd for $C_{14}H_{11}NCl_2$: C, 63.66; H, 4.20. Found: C, 63.41; H, 4.12.

1,3-Diphenyl-2,2-dibromoaziridine (5). To a stirred slurry of *N*-benzylideneaniline (0.10 mol) and potassium *tert*-butoxide (0.20 mol) in *n*-hexane (200 ml), bromoform (0.20 mol) was slowly added at −20 to −30 °C. The reaction mixture was stirred for 3 h at this temperature and then for 5 h at room temperature. The mixture was suction filtered, the residue was washed three times with *n*-hexane, and the solvent was removed in vacuo from the combined filtrates, leaving a crystalline product. Recrystallization from *n*-pentane gave **5** in 35% yield as light-tan crystals: mp 88–90 °C; ir (KBr) 3050 (w), 1605 (vs), 1400 (s), 1280 (w), 1090 (w), 790 (s), 765 (s), 700 cm^{-1} (s); NMR δ 3.58 (s, 1 H), 6.95–7.55 (m, 10 H). Anal. Calcd for $C_{14}H_{11}NBr_2$: C, 47.63; H, 3.14. Found: C, 47.31; H, 3.05.

Reduction of 1,3-Diphenyl-2-chloro-2-fluoroaziridine (1a). In a 50-ml, two-necked flask fitted with an inlet an an outlet tubes for nitrogen and a magnetic stirrer was placed a mixture of 5 mmol of 1,3-diphenyl-2-chloro-2-fluoroaziridine and 6 mmol of tri-*n*-butyltin hydride in *n*-pentane. The mixture was stirred at room temperature until an aliquot from the reaction mixture showed no absorption due to Sn–H stretching (near 1820 cm^{-1}), which took 5 days. The reduction product was isolated in 55% yield by use of column chromatography (alumina, *n*-pentane eluent): mp 66–68 °C; ir (KBr) 3020 (w), 1585 (s), 1480 (s), 1405 (s), 1265 (m), 1110 (s), 1010 (m), 760 (s), 695 cm^{-1} (s); NMR δ 3.16 (q, J_{HH} = 4.0, J_{HF} = 3.5 Hz, 1 H), 5.03 (q, J_{HH} = 4.0, J_{HF} = 79.0 Hz, 1 H), 6.71–7.52 (m, 10 H). The NMR spectrum showed that the reduction product formed was one isomer of **6**, and the magnitudes of the coupling constant suggested that the isomer formed had the configuration (**a**) whose fluorine atom was trans to the hydrogen at the adjacent ring carbon. Mass spectrum: *m/e* 213 (P), 193, 93, 66. Anal. Calcd for $C_{14}H_{12}NF$: C, 78.85; H, 5.67. Found: C, 78.71; H, 5.58.

The same product (**6a**) was obtained in 60% yield in the reduction of 1,3-diphenyl-2-bromo-2-fluoroaziridine (**2a**) with tri-*n*-butyltin hydride at room temperature for 4 days. The NMR spectrum also confirmed the formation of only one isomer (**6a**).

Reduction of 1,3-Diphenyl-2-chloro-2-bromoaziridine (3a,b). The reduction of a mixture of isomers of **3** (**3b**/**3a** = 2.3) was conducted at room temperature for 24 h. Attempts to isolate the product (**7**) by column chromatography (alumina or silica gel, *n*-pentane eluent) or by recrystallization from *n*-pentane were unsuccessful. However, the NMR spectrum of the reaction mixture revealed the formation of a mixture of isomers of **7** (**7b**/**7a** = 2.5). Each isomer of **3** was reduced separately under the same conditions (room temperature, 24 h). The NMR spectrum of the reaction mixture of **3a** in *n*-pentane showed the absorptions at δ 3.25 (d, J = 2.0 Hz) [3.16 (d, J = 2.0 Hz) in benzene] and 4.27 (d, J = 2.0 Hz) [4.08 (d, J = 2.0 Hz) in benzene] in addition to the peaks due to *n*-pentane, phenyl group, and the *n*-butyl group of *n*-butyltin bromide. The NMR spectrum of the reaction mixture of **3b** in *n*-pentane showed the absorptions at δ 3.20 (d, J = 5.0 Hz) [2.87 (d, J = 5.0 Hz) in benzene] and 4.32 (d, J = 5.0 Hz) [4.11 (d, J = 5.0 Hz) in benzene] in addition to the peaks due to *n*-pentane, phenyl group, and *n*-butyl group of *n*-butyltin bromide.

Reduction of 1,3-Diphenyl-2,2-dichloroaziridine (4). The reduction was conducted at room temperature for 4 days. The reduction product (**7**) could not be isolated by column chromatography. The NMR spectrum of the reaction mixture showed the formation of the two isomers of **7** (**7b**/**7a** = 1.9/1).

Reduction of 1,3-Diphenyl-2,2-dibromoaziridine (5). The reduction was conducted at room temperature for 23 h. The starting material (**5**) was completely consumed. The reduction product (**8**) could not be isolated by column chromatography because of its decomposition. The NMR spectrum of the reaction mixture showed the formation of the two isomers of **8** (**8b**/**8a** = 2.0/1).

Registry No.—**1a**, 57500-62-6; **2a**, 57500-63-7; **3a**, 57500-61-5; **3b**, 57500-60-4; **4**, 3543-98-4; **5**, 39072-51-0; **6a**, 60253-62-5; **7a**, 3683-71-4; **7b**, 952-87-4; **8a**, 60253-63-6; **8b**, 60253-64-7; CClF, 1691-88-9; CClBr, 13590-47-1; CBrF, 4539-11-1; CBr_2, 4371-77-1; *N*-benzylideneaniline, 538-51-2; tri-*n*-butyltin hydride, 688-73-3.

References and Notes

(1) T. Ishihara, K. Hayashi, T. Ando, and H. Yamanaka, *J. Org. Chem.*, 40, 3264 (1975).
(2) L. J. Altman and R. C. Baldwin, *Tetrahedron Lett.*, 2531 (1971).
(3) D. E. Applequist and A. A. Peterson, *J. Am. Chem. Soc.*, **82**, 2372 (1960).
(4) T. Ando, F. Namigata, H. Yamanaka, and W. Funasaka, *J. Am. Chem. Soc.*, **89**, 5719 (1967).
(5) T. Ando, H. Yamanaka, F. Namigata, and W. Funasaka, *J. Org. Chem.*, **35**, 33 (1970).
(6) L. A. Singer and J. Chen, *Tetrahedron Lett.*, 939 (1971).
(7) T. Ishihara, E. Ohtani, and T. Ando, *J. Chem. Soc., Chem. Commun.*, 367 (1975).
(8) R. C. Bingham and M. J. S. Dewar, *J. Am. Chem. Soc.*, **95**, 7180, 7182 (1973).
(9) L. J. Altman and R. C. Baldwin, *Tetrahedron Lett.*, 981 (1972).
(10) 1,3-Diphenyl-2,2-dichloroaziridine has already been prepared by this method; e.g., M. K. Meilahn, L. L. Augenstein, and J. L. McManaman, *J. Org. Chem.*, **36**, 3627 (1971).
(11) The configurations of **3a** and **3b** were assigned on the basis of the configurations of the reduction products, **7a** and **7b**, complete retention of configuration during the reduction being assumed. The alternative assignment is very unlikely, because it is implausible that the reduction of **1** and **2** proceed with complete retention while that of **3** proceeds with complete inversion.
(12) There are no data, in the literature, on coupling constants (J_{HF}^{VIC}) between ring hydrogen and fluorine in the aziridine compounds containing ring fluorine. This assignment was tentatively made by comparison of the coupling constants with those of the *gem*-halofluorocyclopropanes; J_{HF}^{cis} is 15.5–17.7 Hz and J_{HF}^{trans} is 3.0–9.4 Hz.[4,13]
(13) K. L. Williamson, Y.-F. Li Hsu, F. H. Hall, S. Swager, and M. S. Coulter, *J. Am. Chem. Soc.*, **90**, 6717 (1968); H. Yamanaka, T. Yagi, K. Teramura, and T. Ando, *Chem. Commun.*, 380 (1971).
(14) The possibility that the **b** isomer was formed but was lost during the workup may be ruled out, since 1,3-diphenyl-2,2-dichloro- (**4**) and -dibromoaziridine (**5**) are relatively stable under similar conditions.
(15) J. A. Deyrup and R. B. Greenwald, *Tetrahedron Lett.*, 321 (1965).
(16) J. A. Deyrup and R. B. Greenwald, *J. Am. Chem. Soc.*, **87**, 4538 (1965).
(17) The instability of **7** was reported by Deyrup et al.[15] They isolated it incompletely from the reaction mixture by column chromatography using inactive alumina, but neither their method nor its modification gave satisfactory results in our hands.
(18) M. Ueyama and K. Tori, *Nippon Kagaku Zasshi*, **92**, 741 (1971); M. Ohtsuru and K. Tori, *J. Mol. Spectrosc.*, **27**, 296 (1968).
(19) H. G. Kuivila, *Acc. Chem. Res.*, **1**, 299 (1968), and references cited therein.
(20) D. Seyferth, H. Yamazaki, and D. L. Alleston, *J. Org. Chem.*, **28**, 703 (1963).
(21) L. J. Altman and T. R. Erdman, *Tetrahedron Lett.*, 4891 (1970).
(22) T. Ando, K. Wakabayashi, H. Yamanaka, and W. Funasaka, *Bull. Chem. Soc. Jpn.*, **45**, 1576 (1972).
(23) L. Pauling, *J. Chem. Phys.*, **51**, 2767 (1969).
(24) The reduction of a mixture of **3a** and **3b** with less than stoichiometric *n*-Bu_3SnH for a shorter period showed that **3b** was more reactive than **3a.** This means that the bromine trans to the phenyl group on the adjacent carbon is more reactive than bromine cis to the phenyl group.
(25) A. G. Cook and E. K. Fields, *J. Org. Chem.*, **27**, 3686 (1962).

Reactions of Amines. 19. Reactions of 1,3-Di-*tert*-butylaziridinone and 2-Bromo-*N*-*tert*-butyl-3,3-dimethylbutanamide with Selected Organometallic Reagents[1]

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1,3-Di-*tert*-butylaziridinone (**1c**) reacts with the phenyl bromide Grignard reagent to give *N*-*tert*-butyl-2-hydroxy-3,3-dimethyl-2-phenylbutanimine (**4cz**) and with phenyllithium to give **4cz** plus 2-*tert*-butylamino-3,3-dimethyl-1-phenyl-1-butanone (**3cz**). α-Lactam **1c** reacts with an excess of the methyl halide Grignard reagents to give mixtures of 2-halo-*N*-*tert*-butyl-3,3-dimethylbutanamide (**2c**), *N*,*N*′,2,3-tetra-*tert*-butylbutanediamide (**7c**), *N*-*tert*-butyl-3,3-dimethylbutanamide (**8c**), *N*-*tert*-butyl-2,3,3-trimethylbutanamide (**9cw**), 3-*tert*-butylamino-4,4-dimethyl-2-pentanone (**3cw**), and *N*-*tert*-butyl-2-hydroxy-2,3,3-trimethylbutanimine (**4cw**). The choice of halide ion in the Grignard reagent appears to determine the relative amounts of the products, the combined yields of **2c** and **8c** decreasing and the yield of **4cw** increasing in the order iodide, bromide, chloride. Dimethylmagnesium reacts with **1c** to give largely **4cw**; and, depending on the conditions, methyllithium reacts to yield either **3cw** or **4cw**, or mixtures of these. The α-halo amide **2c** (X = Br) reacts with the Grignard reagents to give **4c, 7c, 8c,** and **9c** but little or no **3c**. The isomerization of **3c** to **4c** and vice versa is described. The solid-state structure of *N*-*tert*-butyl-2-hydroxy-3,3-dimethyl-2-phenylbutanimine (**4cz**) has been determined by single-crystal x-ray diffraction and has been refined (anisotropically on C, O, and N; isotropically on H) by full-matrix least-squares techniques to R (unweighted) = 0.044 and r (weighted) = 0.048 using 1621 independent diffractometer-recorded reflections having $2\theta_{MoK\alpha} < 55°$ and $I > 3\sigma(I)$. An intramolecular hydrogen bond is observed in the solid state between the hydroxyl oxygen atom and imine nitrogen atom.

A number of papers[3-8] have appeared in the past 5 years describing the reactions of organometallic reagents with the highly sterically stabilized α-lactams **1a–d**. Prior to the publication of these papers we had conducted an exploratory study[9] of the reactions of several α-lactams, including **1c**, with organomagnesium and organolithium reagents as a part of a more general study of the reactions of α-lactams. Inasmuch as our conclusions differed somewhat from those published, we have reexamined and extended our earlier observations. We report here our findings, which we hope will unify and clarify the previous reports which have appeared largely in the form of brief, somewhat contradictory, communications with a minimum of supporting data.

First, it should be noted that the reactions of the highly sterically stabilized α-lactams, such as **1a–d**, should be expected to be no more typical of the class of α-lactams than the reactions of di-*tert*-butyl ketone are typical of the class of ketones. Thus,the subset of reactions of **1a–d** with organometallic reagents appears to be somewhat more limited in scope than the set of all known reactions[9] of α-lactams with a given reagent. This will be demonstrated in later papers in this series.

Second, since we reported nearly 15 years ago[10] how easily α-lactams react with halide ion to give α-halo amides **2**, any conclusions drawn from observations of the reactions of α-lactams with reagents or solutions containing halide ion must take into consideration the possibility that **2** may be an intermediate in the observed reactions.

The first published report of a reaction between an α-lactam and an organometallic reagent was that of Sheehan and Nafissi-V.[3] Although subsequent investigators[4-9] have not been able to confirm either the observations or conclusions of Sheehan and Nafissi-V, the report apparently has stimulated others to examine the behavior of **1a–d** with organometallic reagents. Thus, in separate communications Talaty[6,7] and co-workers reported that **1a–d** react with *tert*-butyllithium at 25–30 °C to give products tentatively identified as α-hydroxy imines[6] (**4ay–dy**) and that **1b** and **1d** react with a variety of alkyllithiums at −78 °C to give the α-amino ketones **3b(x–z)** and **3d(x–z)**. However, Talaty et al.[4,7] reported also that **1d** reacted with the phenyl bromide Grignard reagent (at 0 °C followed by 3 h at room temperature) to give 78% of the α-halo amide **2d** (X = Br). This stands in contrast to a later report by Lengyel, Mark, and Troise[8] that **1b** reacted with the phenyl bromide Grignard reagent at 0 °C to give a 41.2% yield of the α-amino ketone **3bz**. Probably Talaty et al.[4] either used an insufficient amount of Grignard reagent or conditions that led to destruction of some of the reagent. Unless more than 1 equiv is used with most α-lactams, the halide **2** may be the major product. Even so, we believe that the product obtained by Lengyel, Mark, and Troise[8] was more probably the α-hydroxy imine **4bz** and **3bz** and that most of the conclusions of Talaty et al.[6,7] are correct.

In our experiments (Table I) when **1c** was treated with the phenyl bromide Grignard reagent in refluxing ether, the principal product was the α-hydroxy imine **4cz**. The structure of this compound was determined unequivocally by x-ray crystallography (vide infra). When **1c** was treated with excess phenyllithium at room temperature, a mixture of **3cz** and **4cz** in the ratio 2:1 was obtained. These two compounds form an isomeric pair of the type studied quite thoroughly by Stevens[11] and others. As Stevens[11,12] has carefully pointed out, the composition of a mixture of α-amino ketones and α-hydroxy imines of this type will depend on the environment from which they are isolated. The isolation of **4cz** rather than **3cz** in the reaction with the phenyl bromide Grignard reagent probably indicates that, under the conditions of the reaction, the complex **6cz** is more stable than **5cz** and that, in the reaction with excess phenyllithium, either the position of the equilibrium has changed (stabilization by the metallic ion being less significant) or some sort of kinetic control is being exercised.

Since the composition of a mixture of **3cz** and **4cz** will depend on the immediate past history of the pair,[11] it may not be profitable to label one or the other as the *thermally* more stable based on its isolation from the Grignard reaction. Thus, when **4cz** (or a mixture of **3cz** and **4cz**) was heated at 115 °C for 18–72 h, a quantitative conversion to **3cz** resulted, suggesting that in the melt **3cz** is the more stable. Furthermore, when **3cz** was treated with a large excess of the methyl

Table I. Approximate Analysis of Reaction Mixtures[a]

Substrate (S)	Reagent (R)	Mole ratio (S/R)	Temp,[b] °C	Time, h	2c	3cz	4cz	7c	8c	9cz	Other
1c	PhMgBr	1:1.2	RT	3			~100				
	PhLi	1:1.2	RT	8		22	35		Tr		43[c]
		1:2	RT	8		67	33				
2c	PhMgBr	1:1	RT	3	~100		Tr				
		1:2.5	RT	3	1.5	Tr?	55	17[d]	15	12	
		1:2.5	RT	3	6	Tr?	50	20[e]	14	10	
3cz	MeMgCl	1:1	RT	3		~100					
		1:2	RT	3		~100					
		1:31[f]	RT	3		9	50				41[g]
		1:40[f]	RT	3		<1	70				29[g]
4cz	None		~80	18			~100				
			~80	96		~100					
			80, 113	18, 18		~100					
			113	18		67	33				
			115	72		~100					

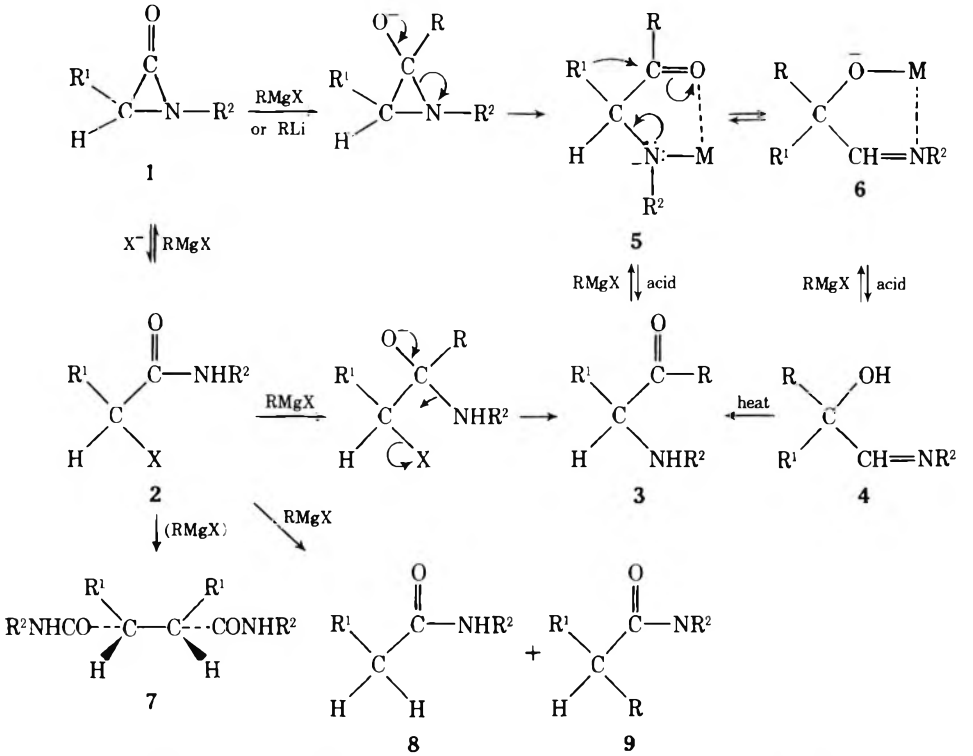
[a] Based on ^{1}H NMR analysis of crude reaction mixture; see Experimental Section. [b] RT = room temperature. [c] Recovered 1c. [d] Two substances in the ratio of ca. 12:5. [e] Two substances in the ratio of ca. 13:7. [f] In tetrahydrofuran. [g] Largely an unidentified product [^{1}H NMR δ ($CDCl_3$) 1.43 (9 H), 2.28 (2 H), 6.99 (1 H); δ (CCl_4) 1.42 (9 H), 2.23 (2 H), 6.85 (1 H)] plus traces of other products with ^{1}H NMR peaks at δ (CCl_4) 1.25, 1.00; δ ($CDCl_3$) 1.30, 1.26, 1.00.

chloride Grignard reagent, **3cz** was converted into a mixture of **4cz** and a frequently encountered by-product of undetermined structure, which appeared to be a cleavage product [^{1}H NMR peaks at δ 1.43 (*t*-Bu) and 1.36 but no peaks in the phenyl region]. This result would appear to support the role of the metal complex (**5** or **6**).

A simplified mechanism is given in the chart for the formation of **4** from **1** or **2**. Presumably, the transition state for the rearrangement step in the sequence **5** → **6** is similar to that proposed by Stevens[11] for the thermal rearrangement except that the hydrogen-bonded proton is replaced by the metallic ion (or complex). Possibly, other α-amino ketones could be isomerized to α-hydroxy imines using magnesium salts or complexes as intermediates.

The ^{1}H NMR spectra of **3cz** and **4cz** are quite different. In particular the spectrum of **4cz** shows the aldimine proton at δ 8.36 (CCl_4). Since the spectrum of the product assigned the structure **3bz** by Lengyel, Mark, and Troise[8] showed a 1 H singlet at δ 8.33 (CCl_4) and since their other spectral data (ir and ^{1}H NMR) are more in accord with those to be expected for **4bz** rather than **3bz** (based on our values for **3cz** and **4cz**), we conclude that their product was indeed **4bz**.

The reaction of the α-halo amide **2c** (X = Br) with the phenyl bromide Grignard reagent also gave **4cz** as the major product; however, the reaction was more complex than that with **1c**. In a careful analysis of the ^{1}H NMR spectrum of the crude reaction mixture (Table I) all of the peaks present could be accounted for on the basis that there were four products in addition to **4cz** and unreacted starting materials. Two of these could be regarded as "dimers" of **1c**. They were not



a, R^1 = 1-adamantyl; R^2 = *t*-Bu
b, R^1 = *t*-Bu; R^2 = 1-adamantyl
c, R^1 = R^2 = *t*-Bu
d, R^1 = R^2 = 1-adamantyl

w, R = Me
x, R = *i*-Pr
y, R = *t*-Bu
z, R = Ph

Table II. Approximate Analysis of Reaction Mixtures[a]

Substrate (S)	Reagent (R)	Mole ratio, S:R	Temp,[b] °C	Time, h	2c[c]	3cw	4cw	7c	8c	9cw	Other substances
1c	MeMgI	1:1	0, RT	3	37		6	6	21	6	24
		1:1	0, RT	3	40		10	7	23	10	10
		1:1	0, RT	3	30		3	4	40	6	20
		1:2.5	RT	3	Tr		18	3	67	13	
		1:1	0, RT	4	4		7	8	67	12	
		1:1	0, RT	3	Tr?		10	7	71	8	4
	MeMgBr	1:0.83	RT	3	~100						
		1:2.5	RT	3	61		22	3	9	4	
		1:1[d]	0, RT	3	42		58	?	?	?	
	MeMgCl	1:1[e]	0, RT	3	53		20		Tr?		27
		1:2.5[f]	RT	3	10		84				6
		1:2.5[e]	RT	3	>9		84				7
		1:2.5[e]	RT	3	>4		84		6		6
		1:6.25[e]	0, RT	3	4		87		Tr		10
		1:5[f]	0, RT	3	5		92		3		
	Me_2Mg	1:3	0, RT	20			~100				
	MeLi	1:1.5	0, RT	30			>95				<5
		1:2	RT	8	8	68	21				3
		1:2	0, −78[g]	2		>95					<5
		1:2	0, −78[g]	2		>95					<5
	$MgBr_2$	1:10	R, RT	3	~100						
2c (X = I)	MeMgI	1:1.67	0, RT	3	27			Tr?	55		18
2c (X = Br)	MeMgBr	1:2.5	RT	3	87		9		6		
		1:2.5	RT	3	20		8	10	51	11	
	MeMgCl	1:2.5[h]	RT	3	55/9		23	Tr?	13	Tr?	
		1:2.5[h]	RT	3	59/10		18	1	6	2	5[i]
		1:2.5[h]	RT	3	48/10		23	4.5	9	2.5	2.5[i]
		1:2.5	RT	3	66/10		13	5	2	4	
		1:2.5	RT	3	7/6		37	26	15	10	
		1:2.5	RT	3	3/6		21	24	5	36	4
		1:4[f,j]	RT	3	31/16		6	Tr	9	34	6
		1:2.5[f,j]	RT	3	32/17		7	Tr	7	30	7
4cw	None		114[k]	96			~100				
			150	19		9	91				
			150	69		52	48				*l*

[a] Based on ^{1}H NMR analysis of crude reaction mixture; see Experimental Section. [b] First temperature is that at which the reagent was added. The reaction was then allowed to warm up or cool down to the second temperature (RT = room temperature; R = reflux temperature). [c] Where two values are given the first is for 2c (X = Br) and the second for 2c (X = Cl). [d] In *n*-butyl ether. Traces of solvent made analysis for 7c, 8c, and 9c infeasible. [e] Reagent in tetrahydrofuran diluted to final volume with ethyl ether. [f] In tetrahydrofuran. [g] Procedure A of ref 7 followed; yield of 3cw, 87%. [h] Compound 2c in solution, concentration 0.2 M. [i] Probably 1c; ^{1}H NMR ($CDCl_3$) δ 2.74, 1.303, 1.002; (CCl_4) δ 2.61, 1.263, 0.987. See note 17. [j] Reagent concentration 0.02 M; anhydrous $FeCl_3$, 3.3 × 10^{-4} M. [k] In refluxing toluene. [l] Small amounts of other substances were formed, ^{1}H NMR δ (CCl_4) 1.43 and 1.18; the amounts could not be estimated from the ^{1}H NMR spectrum.

readily separated from each other by the usual techniques. Since there are several ways in which two units equivalent to **1c** might be linked together and since these could not be distinguished by simple spectral methods, selected crystals of one of the two products from the mixture were analyzed by x-ray crystallographic analysis and shown to be **7c**.[13] Presumably, based on its ^{1}H NMR spectrum, the other "dimer" was the epimer of **7c**, but this has not been established.

The other two products were the reduction product **8c** and the alkylation or cross-coupling product, *N-tert*-butyl-3,3-dimethyl-2-phenylbutanamide (**9cz**). Compounds **7c, 8c,** and **9cz** are the products to be expected from a coupling reaction of an alkyl halide (**2c**) and a Grignard reagent.[14] Traces of **3cz** appeared to be present, but the amounts were too small for certain identification. If compounds **7c, 8c,** and **9cz** were present in the reaction mixtures resulting from the reaction of **1c** and the phenyl bromide Grignard reagent, the amounts were so small as to be difficult to identify. On the basis of this and the methyl halide Grignard reagent results described below we conclude that it is unlikely that **2c** is a *required* intermediate in the conversion of **1c** to **3cz** and **4cz**.

Although organolithium reagents appear to attack all α-lactams preferentially at the carbonyl group to give ketones (or their further addition products, tertiary alcohols), organomagnesium reagents generally attack at the α-carbon atom cleaving the 1–3 bond to give α-alkylation, α-substitution by halide ion, or reduction, depending on the reagent used and the conditions.[9] Thus, the products obtained by us and by Lengyel, Mark, and Troise[8] from the reaction of **1b** and **1c** with the phenyl bromide Grignard reagent are atypical. With these highly sterically stabilized α-lactams the phenyl bromide Grignard reagent appears to react (initially at least) in a manner similar to that of phenyllithium by addition to the carbonyl group. One explanation for the atypical behavior of the Grignard reagents is that the steric requirements of **1c** are such that formation of the required intermediate complex or transition state for attack at the α-carbon atom is inhibited but attack at the somewhat less hindered carbonyl carbon atom is allowed. If this reasoning is correct, the course of the reaction could be dependent on the size and reactivity of the specific organometallic species involved and the reactivity of the corresponding halide (if any) and might be altered by using a smaller reagent (such as the methyl halide Grignard reagent), by using a less nucleophilic halide, or by substituting a dialkylmagnesium for the Grignard reagent. To observe attack at the carbonyl carbon by the methyl halide Grignard reagent, **1c** would have to react with the reagent at a rate at least competitive with the rate of reaction with the magnesium halide (or halide ion) present. Therefore, we compared the reactions of **1c** with the Grignard reagents derived from methyl iodide, methyl bromide, and methyl chloride and with dimethylmagnesium (halide free) (see Table II).

The reaction of the methyl iodide Grignard reagent with **1c** was reported by Sheehan and Nafissi-V[3] to give the unique insertion product, *N*-*tert*-butyl-4,4-dimethylpentamide. Although our earlier experiments[9] had indicated that **2c** (X = I) was the major product,[15] we reran the reaction with the Grignard reagent prepared from magnesium from several commercial sources. Since α-lactam reactions are often dependent on reaction conditions, we tried low and high temperatures, normal and inverse addition, and various solvents. In no case did we obtain significant quantities of products besides **2c** (X = I) or the further reaction products of **2c**. Usually the **2c** (X = I) was accompanied by variable amounts of *N*-*tert*-butyl-3,3-dimethylbutanamide (**8c**) and small amounts of *N*-*tert*-butyl-2-hydroxy-2,3,3-trimethylbutanimine (**4cw**) and of *N*-*tert*-butyl-2,3,3-trimethylbutanamide (**9cw**). The amide **8c** appeared to result from the reduction of **2c** (X = I), and its yield was dependent to some extent on the amount of the excess methyl iodide Grignard reagent used [as shown by separate experiments carried out on **2c** (X = I)]. The origin of the hydroxy imine **4cw** was probably similar to that of **4cz** (vide supra). The α-alkylation product **9cw** may have formed by alkylation of **1c** or, more probably, by cross-coupling between **2c** and the Grignard reagent.[14] Under no set of experimental conditions have we been able to confirm the results and structural assignments of Sheehan and Nafissi-V.[3] As noted above, two other research groups[4,5] have independently reached the same conclusion.[16]

Like the methyl iodide Grignard reagent excess methyl bromide Grignard reagent reacted with **1c** to give a mixture of **2c** (X = Br), **4cw, 7c, 8c,** and **9cw** in which **2c** and **4cw** tended to predominate. The methyl chloride Grignard reagent reacted with **1c** to give principally **4cw** and only small amounts of **2c** (X = Cl) and **8c**, and excess dimethylmagnesium reacted with **1c** to give only **4cw**. Methyllithium reacted with **1c** to give mixtures of **3cw** and **4cw** ranging from approximately 0 to 100% of each product depending on conditions [plus a small amount of **2c** (X = Br) if lithium bromide was present]. Talaty's conditions[7] gave the highest yield of essentially pure **3cw**. Magnesium dibromide reacted readily with **1c** to give a nearly quantitative conversion to **2c** (X = Br). Thus, the α-alkylation product **9cw** was observed only in the experiments with the methyl iodide and methyl bromide Grignard reagents. If **9cw** was present in any of the other reactions of the methyl organometallic reagents with **1c** the amount was such that we could not detect it in the ^{1}H NMR spectra of the crude reaction mixtures.

In contrast to the behavior of **1c, 2c** reacted with the methyl bromide and methyl chloride Grignard reagents to give widely varying yields of **4cw, 7c, 8c, 9cw,** and (possibly) **1c**,[17] even when the conditions were apparently unchanged and the same batch of Grignard reagent was employed (Table II). For want of a better explanation, we attribute these variations to the presence of traces of transition metal ion impurities[14] which could have been introduced not only from the magnesium metal used in preparing the reagent but also from the solvents or apparatus. Those reactions that gave higher yields of **9cw** were visibly more vigorous. Although we have not carried out a systematic study of the effects of transition metal ions on the coupling reactions of **2c** with organometallic reagents, we did observe that 30–34% yields of **9cw** were obtained when catalytic amounts of ferric chloride were added to the reaction of **2c** (X = Br) with a large excess of the methyl chloride Grignard reagent.

The thermal isomerization of **4cw** to **3cw** proceeded much more slowly than that of **4cz** to **3cz** (Table II). After 69 h at 150 °C about half of the **4cw** had been converted to **3cw**. Small amounts of degradation or other isomerization products also formed, possibly including the alternative isomerization product, 2-(*N*-*tert*butylamino)-4,4-dimethylpentanone, formed by migration of the methyl rather than the *tert*-butyl group; however, migration of the *tert*-butyl group was clearly the preferred process as would be expected from the work of Stevens and others.[11]

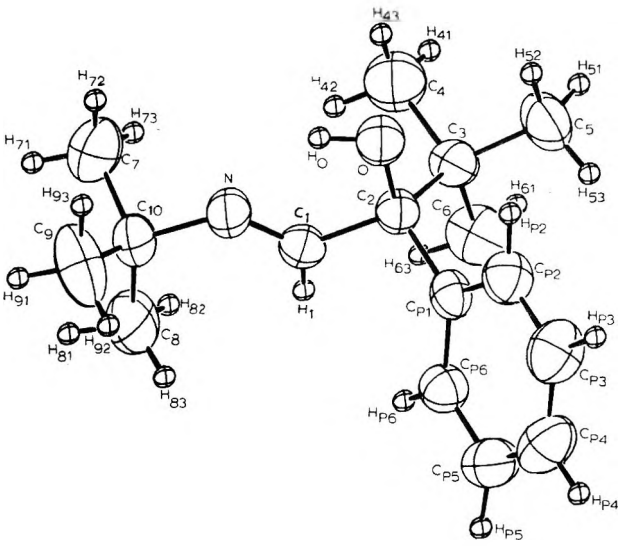


Figure 1. An ORTEP drawing showing the solid-state molecular structure of *N*-*tert*-butyl-2-hydroxy-3,3-dimethyl-2-phenylbutanimine. All atoms except hydrogen are represented by a (50% probability) ellipsoid having the shape, orientation, and relative size consistent with the refined anisotropic thermal parameters listed in Table IV. Hydrogen atoms are represented by arbitrarily small spheres for purposes of clarity.

In summary it would appear that the variety of results obtained from the reaction of the highly sterically stabilized α-lactams with organometallic reagents can be attributed to variations in the choice of anion,[3,4] the amount of reagent,[4] the presence of impurities,[3,16] as well as the nature of the specific organometallic reagent.[18] When the competitive attack by magnesium halide (or halide ion) is suppressed, the characteristic reaction of highly sterically stabilized α-lactams with organomagnesium and organolithium reagents appears to be addition to the carbonyl group, followed in some instances by an amino ketone–hydroxy imine rearrangement.[11]

The labeling scheme used in the x-ray crystallographic analysis to designate the atoms of the *N*-*tert*-butyl-2-hydroxy-3,3-dimethyl-2-phenylbutanimine molecule (**4cz**) is given in Figure 1. The final coordinates and anisotropic thermal parameters for all atoms except hydrogen are given in Tables III and IV, respectively.[19] The final least-squares refined positional and isotropic thermal parameters for the hydrogen atoms are given in Table V.[19] Covalent bond lengths are given in Table VI, and bond angles in Tables VII and VIII.

The crystallographic identification of the compound as a hydroxy-substituted imine was based primarily on the structural and thermal parameters for the $-N{=}C_1{-}C_2{-}O$ grouping and the successful location and refinement of the parameters for the hydrogen atoms. Relevant bond lengths involving these four atoms are shown in Figure 2. The lengths of 1.479 (3)[20] and 1.250 (3) Å for the $N{-}C_{10}$ and $N{=}C_1$ bonds correspond to values for carbon–nitrogen single and double bonds, respectively. The $C_1{-}C_2$ bond length of 1.525 (4) Å is essentially the value expected for an sp^2–sp^3 carbon–carbon single bond. Values of 1.430 (3) and 0.87 (3) Å for the $C_2{-}O$ and $O{-}H_O$ bond lengths are typical x-ray values for single bonds from oxygen to carbon and hydrogen, respectively.[21]

Although the near (to within 0.03 Å) coplanarity of atoms C_{10}, N, C_1, H_1, and C_2 was anticipated from the presence of the $C_1{=}N$ double bond, the near (to within 0.11 Å) inclusion

Table VI. Bond Lengths in Crystalline *N-tert*-Butyl-2-hydroxy-3,3-dimethyl-2-phenylbutanimine[a]

Type[b]	Bond length, Å	Type[b]	Bond length, Å	Type[b]	Bond length, Å
$O-C_2$	1.430 (3)	$C_{p1}-C_{p2}$	1.392 (4)	C_4-H_{41}	0.93 (3)
		$C_{p1}-C_{p6}$	1.391 (4)	C_4-H_{42}	0.98 (3)
$N-C_1$	1.250 (3)	$C_{p2}-C_{p3}$	1.378 (4)	C_4-H_{43}	0.98 (4)
		$C_{p3}-C_{p4}$	1.376 (5)	C_5-H_{51}	1.00 (3)
$N-C_{10}$	1.479 (3)	$C_{p4}-C_{p5}$	1.375 (5)	C_5-H_{52}	0.98 (4)
		$C_{p5}-C_{p6}$	1.386 (4)	C_5-H_{53}	0.99 (3)
C_1-C_2	1.525 (4)			C_6-H_{61}	0.98 (3)
C_2-C_{p1}	1.533 (4)	$O-H_O$	0.87 (3)	C_6-H_{62}	0.95 (3)
				C_6-H_{63}	0.98 (3)
C_2-C_3	1.569 (4)	C_1-H_1	0.98 (3)	C_7-H_{71}	0.94 (4)
C_3-C_4	1.525 (4)	$C_{p2}-H_{p2}$	0.95 (3)	C_7-H_{72}	1.02 (5)
C_3-C_5	1.537 (4)	$C_{p3}-H_{p3}$	0.96 (4)	C_7-H_{73}	1.03 (5)
C_3-C_6	1.526 (4)	$C_{p4}-H_{p4}$	0.92 (3)	C_8-H_{81}	0.96 (4)
$C_{10}-C_7$	1.531 (5)	$C_{p5}-H_{p5}$	0.96 (3)	C_8-H_{82}	1.04 (4)
$C_{10}-C_8$	1.515 (5)	$C_{p6}-H_{p6}$	0.97 (3)	C_8-H_{83}	0.96 (4)
$C_{10}-C_9$	1.516 (5)			C_9-H_{91}	0.95 (4)
				C_9-H_{92}	0.97 (4)
				C_9-H_{93}	1.05 (5)

[a] The number in parentheses following each entry is the estimated standard deviation in the last significant digit. [b] Atoms labeled in agreement with Figure 1. Each symbol for a hydrogen atom which is bonded to a carbon carries the same subscripts as the carbon atom to which it is bonded. In addition, methyl hydrogens carry a second (numerical) subscript to distinguish between hydrogens on the same carbon atom.

Table VII. Bond Angles for Nonhydrogen Atoms in Crystalline *N-tert*-Butyl-2-hydroxy-3,3-dimethyl-2-phenylbutanimine[a]

Type[b]	Bond angle, deg	Type[b]	Bond angle, deg
C_1NC_{10}	122.4 (2)	OC_2C_3	108.0 (2)
NC_1C_2	119.1 (2)	$C_3C_2C_{p1}$	113.1 (2)
$C_2C_{p1}C_{p2}$	119.6 (2)	$C_2C_3C_4$	109.1 (2)
$C_2C_{p1}C_{p6}$	122.5 (2)	$C_2C_3C_5$	109.4 (2)
$C_{p2}C_{p1}C_{p6}$	117.9 (3)	$C_2C_3C_6$	111.6 (2)
$C_{p1}C_{p2}C_{p3}$	120.8 (3)	$C_4C_3C_5$	108.6 (3)
$C_{p2}C_{p3}C_{p4}$	120.6 (3)	$C_4C_3C_6$	109.6 (3)
$C_{p3}C_{p4}C_{p5}$	119.5 (3)	$C_5C_3C_6$	108.6 (3)
$C_{p4}C_{p5}C_{p6}$	120.1 (3)	$NC_{10}C_7$	104.7 (3)
$C_{p5}C_{p6}C_{p1}$	121.0 (3)	$NC_{10}C_8$	114.9 (3)
		$NC_{10}C_9$	105.4 (3)
C_1C_2O	107.6 (2)	$C_7C_{10}C_8$	110.2 (3)
$C_1C_2C_3$	110.1 (2)	$C_7C_{10}C_9$	110.4 (3)
$C_1C_2C_{p1}$	109.5 (2)	$C_8C_{10}C_9$	110.9 (3)
OC_2C_{p1}	108.5 (2)		

[a] The number in parentheses following each entry is the estimated standard deviation in the last significant digit. [b] Atoms labeled in agreement with Figure 1.

of atoms O and H_O in this five-atom mean plane was unexpected. However, with atoms C_2 and C_{10} occupying trans positions relative to the C_1=N double bond, appropriate rotations about the C_1–C_2 and C_2–O single bonds can give the hydroxyl group a favorable orientation for forming an *intramolecular* hydrogen bond between atoms O and N. Atoms N, C_1, C_2, O, and H_O are coplanar to within 0.01 Å and form a five-membered ring which contains a O–H_O···N hydrogen bond. The 2.579 (3) Å O···N and 1.96 (3) Å N···H_O separations are shorter than their van der Waal's contact values[22] by 0.32 and 0.74 Å, respectively.

The six independent sp^2–sp^2 phenyl carbon–carbon bonds have an average length of 1.383 (4, 7, 9) Å[20] while the 24 independent C–H bonds average 0.98 (4, 2, 7) Å.[20] The 0.44 (4) Å elongation of the C_2–C_3 bond relative to the other six sp^3–sp^3 C–C single bonds which average 1.525 (5, 6, 12) Å[20] is presumably the result of steric crowding within the molecule. Crowding between the phenyl ring and the *tert*-butyl group attached to C_2 is reflected in a 3.6 (2)° opening of the C_3–C_2–C_{p1} bond angle from the idealized tetrahedral value of 109.5°.

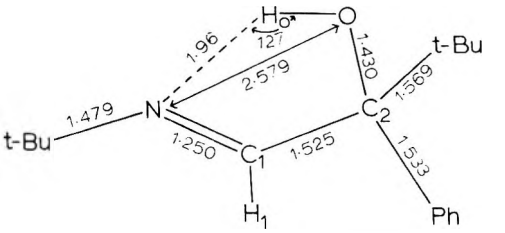


Figure 2. Diagram showing the primary structural features for the planar five-membered ring which contains the intramolecular hydrogen bond in the *N-tert*-butyl-2-hydroxy-3,3-dimethyl-2-phenylbutanimine molecule.

Intramolecular (solid-state) crowding is also evidenced by short contacts involving the two hydrogen atoms of the phenyl group that are ortho to the C_{p1}–C_2 bond. Distances of 2.21 (4) and 2.35 (3) Å for the H_{p6}···H_1 and H_{p2}···O contacts, respectively, are 0.19 and 0.25 Å shorter than the corresponding van der Waal's contact distances.[22]

Experimental Section

The methyl iodide Grignard reagent was prepared in the usual manner using oven-dried Vitro Clear-Seal glassware, flame-dried magnesium (Ventron, 99.9999%; or Research Organic/Inorganic Chemical Co., 99.95%) and a nitrogen atmosphere. Phenyl bromide Grignard reagent was prepared in the same manner using the 99.95% magnesium. Dimethylmagnesium was prepared from dimethylmercury (Ventron) according to the published procedure.[23] Commercial methyl bromide Grignard reagent (Ventron, 3.0 M in ether or 3 M in di-*n*-butyl ether), methyl chloride Grignard reagent (Ventron, 3.2 M in tetrahydrofuran), and methyllithium (Research Organic/Inorganic, 1.7 M in ether, halide free) were diluted with dry solvent before use. Phenyllithium was prepared in the usual manner from bromobenzene.

Analyses were by Micro-Tech Laboratories, Inc., Skokie, Ill. ^{1}H NMR spectra were determined using a Varian A-60D spectrometer, and ^{13}C NMR spectra using a Varian XL-100 spectrometer in the FT mode. Ir spectra were determined with a Perkin-Elmer 237 or 621 spectrometer. All melting and boiling points are uncorrected.

General Reaction Procedure. The following procedure was used for most of the experiments reported.

To the chosen quantity of a solution of the organometallic reagent a solution of 2.4 mmol of 1,3-di-*tert*-butylaziridinone[23] (**1c**) or a solution or suspension of 2.4 mmol of *N-tert*-butyl-2-bromo-3,3-dimethylbutanamide[24] (**2c**, X = Br) in anhydrous ether (or tetrahydrofuran) was added dropwise at the desired temperature under a nitrogen atmosphere. The volume of solvent was such that the concentration of organometallic reagent was 0.1–0.5 M (average, 0.3 M) after addition of the substrate. The concentration of α-lactam **1c** solution was 0.1–0.7 M (average 0.3 M) before addition; the concentration of the **2c** (X = Br) solution was 0.02–0.1 M (average 0.06 M) and of the **2c** (X = Br) suspension was 0.1–0.3 M (average 0.2 M). When addition was complete, the reaction mixture was stirred for an additional 3–30 h at room temperature or as specified in Tables I and II. Saturated aqueous ammonium chloride was added slowly with stirring. The layers were separated, the ethereal layer was washed with additional aqueous ammonium chloride, and the aqueous layers were extracted with ether. The combined ether layers were dried ($MgSO_4$), and the ether was evaporated. In general all crude reaction mixtures were soluble in $CDCl_3$ but some were only partially soluble in CCl_4 [the α-halo amides (**2c**) and the "dimer" **7c** being least soluble in the latter]. The ^{1}H NMR spectra of the soluble portion of all crude reaction mixtures were run in both solvents, as this procedure was found to facilitate analysis of the mixtures. Liquid residues were separated and purified by distillation under vacuum, and solid residues were separated and purified by extraction followed by repeated recrystallizations from appropriate solvents, or occasionally by column chromatography using a Florisil column and 0–15% solutions of ethyl acetate in Skellysolve B as eluent. The results of typical experiments

Table VIII. Bond Angles Involving Hydrogen Atoms in Crystalline *N*-*tert*-Butyl-2-hydroxy-3,3-dimethyl-2-phenylbutanimine[a]

Type[b]	Bond angle, deg	Type[b]	Bond angle, deg	Type[b]	Bond angle, deg
C_2OH_0	104 (2)	$C_3C_4H_{43}$	109 (2)	$C_{10}C_7H_{72}$	105 (3)
		$H_{41}C_4H_{42}$	112 (3)	$C_{10}C_7H_{73}$	110 (3)
NC_1H_1	125 (2)	$H_{41}C_4H_{43}$	109 (3)	$H_{71}C_7H_{72}$	108 (3)
$C_2C_1H_1$	116 (2)	$H_{42}C_4H_{43}$	107 (3)	$H_{71}C_7H_{73}$	110 (4)
$C_{p1}C_{p2}H_{p2}$	115 (2)	$C_3C_5H_{51}$	110 (2)	$H_{72}C_7H_{73}$	116 (4)
$C_{p3}C_{p2}H_{p2}$	124 (2)	$C_3C_5H_{52}$	109 (2)	$C_{10}C_8H_{81}$	109 (2)
$C_{p2}C_{p3}H_{p3}$	118 (2)	$C_3C_5H_{53}$	110 (2)	$C_{10}C_8H_{82}$	112 (2)
$C_{p4}C_{p3}H_{p3}$	121 (2)	$H_{51}C_5H_{52}$	106 (3)	$C_{10}C_8H_{83}$	111 (2)
$C_{p3}C_{p4}H_{p4}$	120 (2)	$H_{51}C_5H_{53}$	107 (3)	$H_{81}C_8H_{82}$	107 (3)
$C_{p5}C_{p4}H_{p4}$	121 (2)	$H_{52}C_5H_{53}$	116 (3)	$H_{81}C_8H_{83}$	114 (3)
$C_{p4}C_{p5}H_{p5}$	122 (2)	$C_3C_6H_{61}$	111 (2)	$H_{82}C_8H_{83}$	104 (3)
$C_{p6}C_{p5}H_{p5}$	118 (2)	$C_3C_6H_{62}$	113 (2)	$C_{10}C_9H_{91}$	106 (2)
$C_{p5}C_{p6}H_{p6}$	121 (2)	$C_3C_6H_{63}$	109 (2)	$C_{10}C_9H_{92}$	103 (3)
$C_{p1}C_{p6}H_{p6}$	119 (2)	$H_{61}C_6H_{62}$	103 (3)	$C_{10}C_9H_{93}$	107 (3)
		$H_{61}C_6H_{63}$	105 (3)	$H_{91}C_9H_{92}$	108 (4)
$C_3C_4H_{41}$	110 (2)	$H_{62}C_6H_{63}$	116 (3)	$H_{91}C_9H_{93}$	111 (4)
$C_3C_4H_{42}$	111 (2)	$C_{10}C_7H_{71}$	107 (2)	$H_{92}C_9H_{93}$	121 (4)

[a] The number in parentheses following each entry is the estimated standard deviation in the last significant digit. [b] Atoms labeled in agreement with Figure 1. Each symbol for a hydrogen atom which is bonded to a carbon carries the same subscripts as the carbon atom to which it is bonded. In addition, methyl hydrogens carry a second (numerical) subscript to distinguish between hydrogens on the same carbon atom.

Table IX. Properties of Reactants and Products[a]

Registry no.	Compd	Mp, °C or bp, °C (Torr)	Ir,[b] cm^{-1}	^1H NMR,[c] δ Solvent	*t*-Bu-C	*t*-Bu-N	CH or CH_2	NH or OH[d]	Ph or Me	Anal. calcd/found C	H	N
14387-89-4	1c	38 (0.4)[e]	1850	$CDCl_3$	1.002	1.303	2.73					
				CCl_4	0.987	1.265	2.62					
14387-96-3	2c (X = Br)	157–157.5[f,g]	3410;	$CDCl_3$	1.150	1.372	4.03	5.97				
			1665	CCl_4	1.122	1.340	3.96					
60294-83-9	2c (X = Cl)	130.5–132[f]	3410;	$CDCl_3$	1.11	1.37	3.99	6.08		58.38	9.80	6.81
			1665	CCl_4	1.08	1.34	3.90			58.00	9.75	6.65
30340-20-6	2c (X = I)	171.5–173[h,i]	3415;	$CDCl_3$	1.18	1.35	4.04	5.65				
			1666	CCl_4		1.34						
60294-84-0	3cw	49 (1.4)	3320;	$CDCl_3$	0.927	0.990	3.07	1.81	2.24	71.30	12.51	7.56
			1703	CCl_4	0.890	0.970	2.97	1.77	2.16	71.11	12.62	7.32
60294-85-1	3cz	98–99.5[j]	3324;	$CDCl_3$	0.880	1.007	4.04	2.11	[k]	77.68	10.19	5.66
			1671	CCl_4	0.867	1.015	3.97	2.09	[l]	77.59	10.12	5.49
60294-86-2	4cw	27 (0.4)	3350;	$CDCl_3$	0.937	1.208	7.74	4.77	1.198	71.30	12.51	7.56
			1665	CCl_4	0.895	1.202	7.71	4.33	1.110	71.35	12.77	7.37
60294-87-3	4cz	70–71[m]	3300;	$CDCl_3$	0.933	1.223	8.39	5.45	[n]	77.68	10.19	5.66
			1665	CCl_4	0.902	1.220	8.36	5.05	[o]	77.52	10.33	5.49
60319-04-2	7c	239–240[a,m,p]	3450,	$CDCl_3$	1.063	1.357	2.21	5.27		70.54	11.84	8.23
			1665	CCl_4	1.012	1.333	2.05			70.58	11.87	8.14
49633-54-7	8c	123.5–125.5[h]	3430;	$CDCl_3$	1.033	1.352	1.953	5.57		70.12	12.36	8.18
			1660	CCl_4	0.998	1.308	1.848	5.61		70.02	12.45	7.98
30340-21-7	9cw	138–140.5	3440,	$CDCl_3$	0.968	1.352	1.80[q]	5.21	1.073[r]			
			1670	CCl_4	0.928	1.308	1.82[q]	5.11	1.020[r]			
60294-88-4	9cz	147.5–149[s]	3450,	$CDCl_3$	1.022	1.303	2.90	5.30	7.32[t]	77.68	10.19	5.66
			1673	CCl_4	0.978	1.270	2.78	5.10	7.28[t]	77.51	10.22	5.58

[a] Satisfactory analytical data (±0.4%) for C, H, N were obtained for all new compounds in this table except 7c, which was obtained as a mixture of diastereomers essentially free of other products (based on ^1H NMR analysis). The structure of 7c was established by an x-ray crystallographic analysis (to be published elsewhere) of single crystals selected by hand from this mixture. The spectral and other data given in the table are for the mixture. [b] In $CHCl_3$. [c] See Experimental Section for procedures used. [d] Position variable; average valve is given. [e] Lit.[17] bp 38°C (0.4 Torr). [f] Recrystallized from petroleum ether (bp 30–60°C). [g] Lit.[17] mp 156–157 °C. [h] Purified by sublimation. [i] Lit.[4a] mp 168–170 °C. [j] Recrystallized from methanol. [k] Phenyl region similar in appearance to phenyl region of acetophenone with two clusters of peaks of 475–486 and 437–457 Hz at 60 MHz. [l] Phenyl region similar in appearance to that of acetophenone with two clusters of peaks at 470–485 and 443–456 Hz at 60 MHz. [m] Recrystallized from methanol–pentane. [n] Complex multiplet at 431–460 Hz at 60 MHz. [o] Complex multiplet at 427–455 Hz at 60 MHz. [p] An apparent diastereomer of 7c (which was not isolated) showed the following NMR spectra: in $CDCl_3$, δ 1.078, 1.377, 2.17; in CCl_4, δ 1.325, 1.002, 2.03. [q] Quartet, J = 6.9 ± 0.1 Hz. [r] Doublet, J = 6.9 ± 0.1 Hz. [s] Lit.[4a] mp 147.5–148 °C. [t] Broad.

are summarized in Tables I and II, and the properties of the purified starting materials and products are given in Tables IX and X.

General Analytical Procedure. The ^1H NMR chemical shifts in the region 0–100 Hz (at 60 MHz) of purified reactants and products were determined as precisely as possible in both $CDCl_3$ and CCl_4 using Me_4Si and cyclohexane as internal standards (sweep width 100 Hz, sweep time 250 s). The values obtained are given in Table IX and are based on cyclohexane, δ 1.436 in both CCl_4[25] and $CDCl_3$.[26] For approximately 100 measurements (covering all compounds) the average deviation was ±0.1 Hz and the maximum deviation was ±0.3 Hz from the values given. Fortuitously there was little overlap of peaks in this region among the various reactants and products; therefore, identification of products was relatively easy.[27] Usually the entire crude reaction mixture was dissolved in $CDCl_3$ and analyzed by ^1H NMR.

Table X. ^{13}C NMR Spectra[a] and Probable Assignments

Compd	C=O or C=N	α-C	$(CH_3)_3CN$	$(CH_3)_3CN$	$(CH_3)_3CC$	$(CH_3)_3CC$	CH_3-α-C	Phenyl C_1	Phenyl C_2	Phenyl C_3	Phenyl C_4
1c	161.07	54.17	55.99	27.78	31.31	27.14					
3cz	172.66	62.02	50.40	30.16	35.28	27.34		138.21	128.49	128.14	132.66
4cw	160.48	75.28	56.15	29.64	37.30	25.40	20.87				
4cz	159.13	77.94	56.55	29.64	38.77	25.56		142.62	126.31	127.14	127.06
8c	170.95	30.75	50.87	29.29	29.80	28.77					

[a] Determined in $CDCl_3$. The chemical shifts are given in parts per million downfield from internal Me_4Si.

The solvent was evaporated, and as much of the residue as possible was dissolved in CCl_4 and analyzed by ^1H NMR. The composition of the reaction mixtures was estimated on the basis of the machine integrals and, wherever possible, through use of a polar planimeter. Because of difficulties encountered due to overlap of the bases of some peaks, the results are considered to be no more accurate than ±10% (relative) for the larger percentages (<40%) and up to ±30% for the smaller values (<10%). The most approximate analysis was that of the **7c** diastereomers, which frequently gave broad peaks that overlapped those of **8c** sufficiently to make accurate analysis of **7c** difficult. In some experiments unidentifiable singlet peaks appeared in the 50-100-Hz region. These were summed and treated as if they were caused by *tert*-butyl groups (the most likely origin based on evaluation of the downfield portion of the spectrum) and are reported as "Other Substances". The results of the analyses are given in Tables I and II.

Isomerization of 4cw. A small amount of **4cw** (about 0.5 g) was heated under reflux in an oil bath held at 150 ± 2 °C. Periodically a sample of material was removed and analyzed by ^1H NMR spectroscopy. In one experiment a solution of **4cw** in a fivefold volume of toluene was heated under reflux and periodically analyzed in the same manner. The results are given in Table II.

Isomerization of 4cz. The first isomerization was unintentional and occurred when a reaction residue (from which most of the **7c** and much of the **4cz** had been removed by fractional extraction) was allowed to stand on the steam bath over the weekend, during which time the flask became filled with long, slender, needlelike crystals. ^1H NMR analysis of these indicated them to be essentially pure **3cz**. Since other materials were present in the residue, they could have had some effect on the rate of isomerization; therefore, 80–200-mg samples of purified **4cz** were heated at selected temperatures on the steam bath or in the oven in a lightly stoppered flask for 18–96 h. The contents of the flasks were analyzed by ^1H NMR. The results are given in Table I.

Isomerization of 3cz. The isomerization of **3cz** and the analysis of the resultant crude reaction mixture were conducted by the general reaction and analytical procedures described above for the reactions of **1c** and **2c** with organometallic reagents. The results are given in Table I.

Crystallographic Analysis of 4cz.[19] Single crystals (mp 70–71 °C) of $C_{16}H_{25}ON$, **4cz**, suitable for x-ray studies were obtained by crystallization from a methanol–pentane solution. They are monoclinic, space group $P2_1/c$-C_{2h}^5 (no. 14)[28] with $a = 13.938 \pm 0.002$ Å, $b = 6.141 \pm 0.001$ Å, $c = 18.793 \pm 0.002$ Å, $\beta = 104.42 \pm 0.01°$, and $Z = 4$ at 20 ± 1 °C [$d_{calcd} = 1.055$ g cm^{-3}, $d_{measd} = 1.044$ g cm^{-3}, μ_a (Mo K$\overline{\alpha}$)[29] = 0.07 mm^{-1}]. Intensity measurements were made on a Syntex $P\bar{1}$ Autodiffractometer for a nearly cube-shaped specimen (0.44 × 0.44 × 0.50 mm) which was sealed under nitrogen gas in a thin-walled glass capillary. A total of 3558 independent reflections having $2\theta_{MoK\overline{\alpha}} < 55°$ (the equivalent of 1.0 limiting Cu K$\overline{\alpha}$ sphere) were collected using 1°-wide ω scans and graphite-monochromated Mo K$\overline{\alpha}$ radiation. A scanning rate of 2°/min was employed for the scan between ω settings 0.50° respectively above and below the calculated K$\overline{\alpha}$ doublet value ($\lambda_{K\overline{\alpha}} = 0.71069$ Å). Each 1° scan was divided into 19 equal (time) intervals and those 13 contiguous intervals which had the highest single accumulated count at their midpoint were used to calculate the net intensity from scanning. Background counts, each lasting for one-fourth the total time used for the net scan (13/19 of the total scan time), were measured at ω settings one degree above and below the calculated K$\overline{\alpha}$ doublet value for each reflection. The data were not corrected for absorption since the absorption of x-rays by a spherical crystal having the same volume as the crystal actually used would be virtually independent of scattering angle[30] ($\mu r = 0.02$) and deviations from this absorption occasioned by the use of the nearly cube-shaped specimen are practically negligible.

The 18 nonhydrogen atoms comprising the asymmetric unit appeared simultaneously on an E map which was calculated from a trial set of statistical direct methods (MULTAN) phases. All 25 chemically anticipated hydrogen atoms were located from a difference Fourier synthesis calculated from a full-matrix least-squares refined structural model [R(unweighted) = 0.102, r(weighted) = 0.112 for 1248 reflections having $2\theta_{MoK\overline{\alpha}} < 43°$ and $I < 3\sigma(I)$] which incorporated unit weighting and anisotropic thermal parameters for all nonhydrogen atoms. All structure factor calculations employed the atomic form factors compiled by Cromer and Mann[31] and a least-squares refineable extinction correction[32] of the form $1/(1 + gI_c)^{1/2}$. The final cycles of empirically weighted full-matrix least-squares refinement which employed isotropic thermal parameters for hydrogen atoms and anisotropic thermal parameters for all others converged to values of 0.044 and 0.048 for R and r, respectively, for 1621 independent reflections having $2\theta_{MoK\overline{\alpha}} < 55°$ and $I > 3\sigma(I)$.

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Registry No.—**7c** diastereomer, 60294-89-5; PhBr, 108-86-1; PhLi, 591-51-5; MeCl, 74-87-3; MeI, 74-88-4; MeBr, 74-83-9; Me_2Mg, 2999-74-8; MeLi, 917-54-4; $MgBr_2$, 7789-48-2.

Supplementary Material Available. Tables III–V, a detailed description of the experimental conditions for the crystallographic study and a listing of observed and calculated structure factor amplitudes (15 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Part 18: H. E. Baumgarten, H. L. Smith, and A. Staklis, *J. Org. Chem.*, **40**, 3554 (1975).
(2) Camille and Henry Dreyfus Teacher–Scholar.
(3) J. C. Sheehan and M. M. Nafissi-V, *J. Am. Chem. Soc.*, **91**, 4596 (1969).
(4) (a) E. R. Talaty, A. E. Dupuy, Jr., C. K. Johnson, T. P. Pirotte, W. A. Fletcher, and R. E. Thompson, *Tetrahedron Lett.*, 4435 (1970); (b) E. R. Talaty, A. E. Dupuy, Jr., and C. M. Utermoehlen, *Chem. Commun.*, 16 (1971).
(5) H. Quast, E. Schmitt, and R. Frank, *Angew. Chem., Int. Ed. Engl.*, **10**, 651 (1971).
(6) E. R. Talaty and C. M. Utermoehlen, *J. Chem. Soc., Chem. Commun.*, 204 (1974).
(7) E. R. Talaty, L. M. Pankow, D. D. Delling, and C. M. Utermoehlen, *Synth. Commun.*, **4**, 143 (1974).
(8) I. Lengyel, R. V. Mark, and C. A. Troise, *Synth. Commun.*, **1**, 153 (1971).
(9) L. D. Hagemeier, M.S. Thesis, University of Nebraska, March 1967; V. J. Elia, Ph.D. Thesis, University of Nebraska, Jan 1970; B. I. Gold, Ph.D. Thesis, University of Nebraska, May 1972. These theses describe exploratory rather than in depth studies and should be read with caution. The physical data given are correct; however, compounds **4cz** and **4cw** were assigned incorrect structures, some minor, but important, reaction products were not identified, and optimum reaction parameters were not always employed. All of the data from these studies were reanalyzed for the present report.
(10) H. E. Baumgarten, R. L. Zey, U. Krolls, W. W. Linstromberg, and J. J. Fuerholzer, Abstracts, 141st National Meeting of the American Chemical Society, Washington, D.C., March 1962, p 9-0.
(11) C. L. Stevens, P. M. Pillai, M. E. Munk, and K. G. Taylor in B. S. Thyagarajan, "Mechanism of Molecular Migrations", Vol. 3, Wiley-Interscience, New York, N.Y., 1971, p 271.
(12) This point is best seen by careful examination of the Experimental Sections of the several papers by Stevens and co-workers listed in ref 11.
(13) Single crystals of dimer **7c** are monoclinic, space group $P2_1/n$ (an alternate setting of $P2_1/n$-C_{2h}^5), with $a = 13.479$ (1) Å, $b = 5.8751$ (7) Å, $c = 13.562$ (1) Å, $\beta = 102.488$ (8)°, and $Z = 2$ (dimers). The structure was solved using direct methods and the resulting structural parameters for the 32 crystallographically independent hydrogen and nonhydrogen atoms have been refined to convergence [$R = 0.039$ for 1668 independent, diffractometer-recorded (graphite-monochromated Mo K$\overline{\alpha}$ radiation with 1°-wide

ω scans) reflections having $2\theta_{MoK\bar{\alpha}} < 55°$ and $I > 3\sigma(I)$] in cycles of empirically weighted least-squares refinement. Anisotropic thermal parameters were utilized for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. The estimated standard deviations for covalent bond lengths are 0.002–0.003 Å for bonds between two nonhydrogen atoms and 0.02–0.03 Å for bonds between a hydrogen and nonhydrogen atom. Full structural details will be published elsewhere.

(14) The coupling and cross-coupling reactions of alkyl halides and Grignard reagents (sometimes called Kharasch couplings) have been the subject of considerable study during the past 10 years. A recent review of much of this chemistry with leading references to other aspects is (a) H. Felkin and G. Swierczewski, *Tetrahedron*, **31**, 2735 (1975). Additional pertinent references are (b) Y. Ohbe and T. Matsuda, *Nippon Kagaku Zasshi*, **89**, 298 (1968) [*Chem. Abstr.*, **69**, 51309q (1968)]; (c) Y. Ohbe and T. Matsuda, *Bull. Chem. Soc. Jpn.*, **45**, 2947 (1972); (d) Y. Ohbe and T. Matsuda, *Tetrahedron*, **29**, 2989 (1973); (e) Y. Ohbe, M. Takagi, and T. Matsuda, *ibid.*, **30**, 2669 (1974); (f) M. Mori, S. Nishimura, and Y. Ban, *Tetrahedron Lett.*, 4951 (1973).

(15) Talaty et al.[4] reported that the ^{1}H NMR spectrum of their crude product showed the presence of two substances, **2c** (X = I) being by far the more abundant. The second product was not identified.

(16) The question remains as to the probable identity of the well-characterized Sheehan–Nafissi-V product. Our experimental observations lead us to conclude that the product may have been an impure sample of the reduction product **8c**, possibly contaminated with **9cw** and the diastereomers of the dimeric coupling product **7c**. The contaminants are required to explain the observed ^{1}H NMR spectrum, elemental analysis, and mass spectrum.

(17) The first preparation of an authentic α-lactam [H. E. Baumgarten, *J. Am. Chem. Soc.*, **84**, 4975 (1962)] involved the cyclization of an *N*-chloro amide with potassium *tert*-butoxide as base. The choice of base was deliberate, based on sound experimental analogies. Later the same base was used in the first successful preparation of an α-lactam through cyclization of an α-chloro amide [H. E. Baumgarten, J. J. Fuerholzer, R. D. Clark, and R. D. Thompson, *J. Am. Chem. Soc.*, **85**, 3303 (1963)]. Here, however, the choice of base was less critical and other bases could have been used (with the appropriate laboratory technique). Most other workers have elected to follow our lead in the choice of base. However, we have experimented with other bases. In fact, one can use (with care) powdered KOH (in THF) to prepare certain α-lactams by cyclization of α-halo amides, but this is *not* recommended. Various Grignard and organolithium reagents were among the bases studied for such cyclizations, and we were able to observe (using ir techniques) but not to prepare α-lactams using these bases. Thus, in two experiments with **2c** (X = Br) and the methyl chloride Grignard reagent (in dilute solution) we did observe the appropriate ^{1}H NMR peaks for **1c** in both $CDCl_3$ and CCl_4. The amount of this product (if it were **1c**) was such (2.5–5%) as to preclude the use of this base for preparative purposes; however, our observation does suggest that, in the devising of mechanistic pathways for the reactions of α-halo amides with bases, one should consider α-lactam-like intermediates. One example where such an intermediate is a reasonable alternative may be found in ref 14f.

(18) A referee has suggested that the results with the methyl halide Grignard reagents which show yields of **4cw** in the order I < Br < Cl (and the high yield of **4cw** with dimethylmagnesium) may be indicative of a single electron transfer mechanism. He suggests further that the effect of ferric chloride may also indicate a SET mechanism and wonders what the reaction with the *tert*-butyl chloride Grignard reaction might reveal. These reasonable suggestions are not new to us; however, we believe that any detailed mechanisms for these reactions will require evidence well beyond what is available to us since small changes in structure seem to have a substantial effect on heterolytic vs. SET mechanisms in the addition of organometallic reagents to the carbonyl group [cf. E. C. Ashby, J. Laemmle, and H. M. Neumann, *Acc. Chem. Res.*, **7**, 272 (1974); T. Holm and I. Crossland, *Acta Chem. Scand.*, **25**, 59 (1971)]. Furthermore, some metal-catalyzed Kharasch-type couplings go by SET mechanisms; others do not.[14] In 1967 we carried out a single experiment in which **1a** was treated with 2 equiv of the *tert*-butyl chloride Grignard reagent. The isolated and purified product in 72% yield was **2c** (X = Cl). Recent experiments on 1-*tert*-butyl-2-phenylaziridinone with this reagent have given similar results, a high yield of the α-chloro amide plus a complex mixture of other products that are still under investigation. In experiments in progress both **1a** and **2a** have reacted with the dimethyllithium cuprate to give high yields (73–83%) of **9cw** together with small amounts of **8c**, but no **4cw**. This reaction is generally regarded as not proceeding by an SET mechanism [cf. H. O. House, *Acc. Chem. Res.*, **9**, 59 (1976)]. On the other hand, some α-lactams *do* appear to react with organometallic reagents preferentially by a SET mechanism, especially 1-*tert*-butyl-3,3-diphenylaziridinone.[9]

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

(20) The first number in parentheses following a given bond length or angle is the root mean square estimated standard deviation of an individual datum. The second and third numbers, when included, are the average and maximum deviations from the average value, respectively.

(21) "International Tables for X-Ray Crystallography", Vol. III, "Physical and Chemical Tables", Kynoch Press, Birmingham, England, 1968, p 276.

(22) L. Pauling, "The Nature of the Chemical Bond", 3d ed, Cornell University Press, Ithaca, N.Y., 1960, p 260.

(23) E. C. Ashby and R. C. Arnot, *J. Organomet. Chem.*, **14**, 1 (1968).

(24) J. C. Sheehan and J. H. Beeson, *J. Am. Chem. Soc.*, **89**, 362 (1967).

(25) G. W. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(26) P. Laszlo, *Prog. Nucl. Magn. Reson. Spectrosc.*, **3**, 241 (1967).

(27) With this procedure the detection of as little as 1% of any product with the possible exception under certain conditions of **7c** and **3cw** was possible.

(28) "International Tables for X-Ray Crystallography", Vol. I, "Symmetry Groups", Kynoch Press, Birmingham, England, 1969, p 99.

(29) Reference 21, p 166.

(30) "International Tables for X-Ray Crystallography", Vol. II, "Mathematical Tables", Kynoch Press, Birmingham, England, 1967, p 302.

(31) D. T. Cromer and J. B. Mann, *Acta Crystallogr., Sect. A*, **24**, 321 (1968).

(32) W. H. Zachariasen, *Acta Crystallogr.*, **23**, 558 (1967).

Reactions of Amines. 20. Syntheses of Racemic and Optically Active Alkylhydrazines and *N*-Acyl-*N*-alkyl- and *N*-Acyl-*N*-arylhydrazines[1,2]

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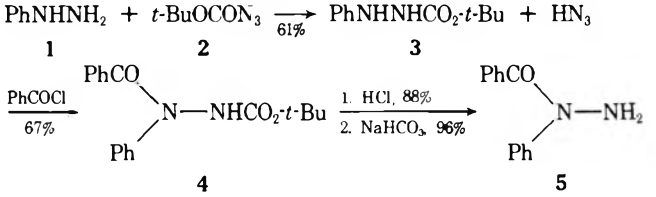
N-Acyl-*N*-alkyl- (**11**) and *N*-acyl-*N*-arylhydrazines (**5**) may be prepared by acylation of *N*-alkyl- (**9**) and *N*-aryl-*N'*-carbo-*tert*-butoxyhydrazines (**3**) followed by cleavage of the *N'*-carbo-*tert*-butoxy group. The intermediate **3** may be prepared by treatment of arylhydrazines with *tert*-butyl azidoformate (**2**). The intermediates **9** may be prepared by reduction of the corresponding ketone carbo-*tert*-butoxyhydrazones (**8**) or by the rearrangement [presumably via the diaziridinone (**17**)] of alkylureas (**15**). Cleavage of **9** prepared by the latter route has been used for the stereospecific synthesis of (*R*)-1-phenylethylhydrazine (**19a**) from (*R*)-1-phenylethylamine (**13a**) (via the urea **15a**).

Recently Moss and Powell[3] reported a new synthesis of hydrazines from alkyl diazotates that is sufficiently stereoselective to convert 1-phenylethylamine (**13a**) into 1-phenylethylhydrazine (**19a**) in 40% yield (as the oxalate) with a reported 54% net inversion of configuration. Like Moss and his coworkers, we have had a need for a simple, useful synthesis of optically active hydrazines but have found that most of the previously reported procedures[4,5] are deficient for our purpose in one respect or another. In addition we have required monosubstituted hydrazines with a *tert*-alkyl substituent and monosubstituted hydrazines acylated on the nonterminal nitrogen (i.e., *N*-aminoamides). This communication describes the procedures we are currently using for the synthesis of these several types of hydrazine derivatives. For this purpose the preparation of *N*-benzoyl-*N*-phenylhydrazine (**5**), several *N*-acyl-*N*-alkylhydrazines (**11**), racemic and optically active 1-phenylethylhydrazine (**19a**), *tert*-butylhydrazine (**22**), and related substances will be described.

Several early syntheses of **5** appear in the literature,[6,7] but none of these is convenient or efficient. Therefore, we have used the sequence shown in Chart I, which appears to be a

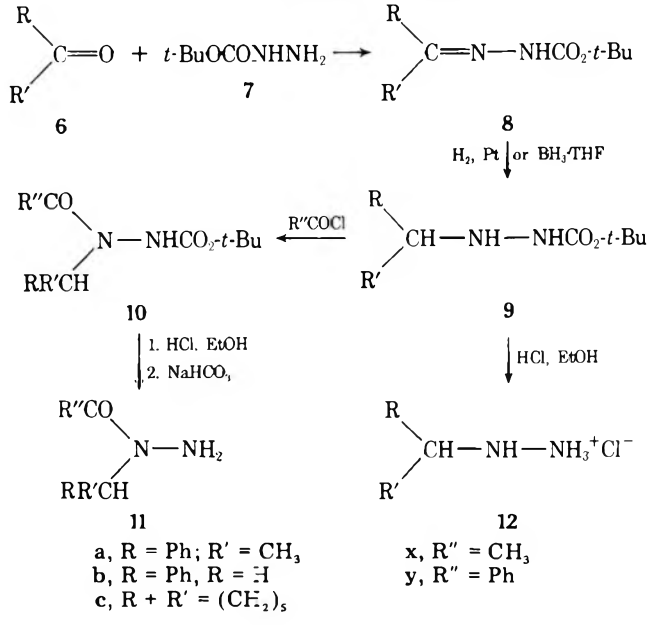
Chart I. Synthesis of *N*-Benzoyl-*N*-phenylhydrazine



potentially general synthesis for *N*-aminoanilides from the readily available arylhydrazines (**1**). The superiority of this synthesis over those used previously results from the use of the easily introduced [via *tert*-butyl azidoformate (**2**)] and easily removed (via mild acidic cleavage) *N*-carbo-*tert*-butoxy blocking group.[8] The overall yield of **5** from phenylhydrazine (**1**) was 35%. The identities of the products **3** and **5** were readily established by the characteristic differences in the ir and ^{1}H NMR spectra of *N*-acyl-*N*-arylhydrazines and *N'*-acyl-*N*-arylhydrazines[9] and confirmed for **5** by comparison with authentic samples made by an established procedure.[6] This identification shows that **1** is preferentially acylated on the terminal nitrogen with **2**.

Although the foregoing procedure should be useful for many arylhydrazines, it might be expected to be less effective with alkylhydrazines, which might react with **2** at either N atom. Therefore, the procedure in Chart II was developed for the

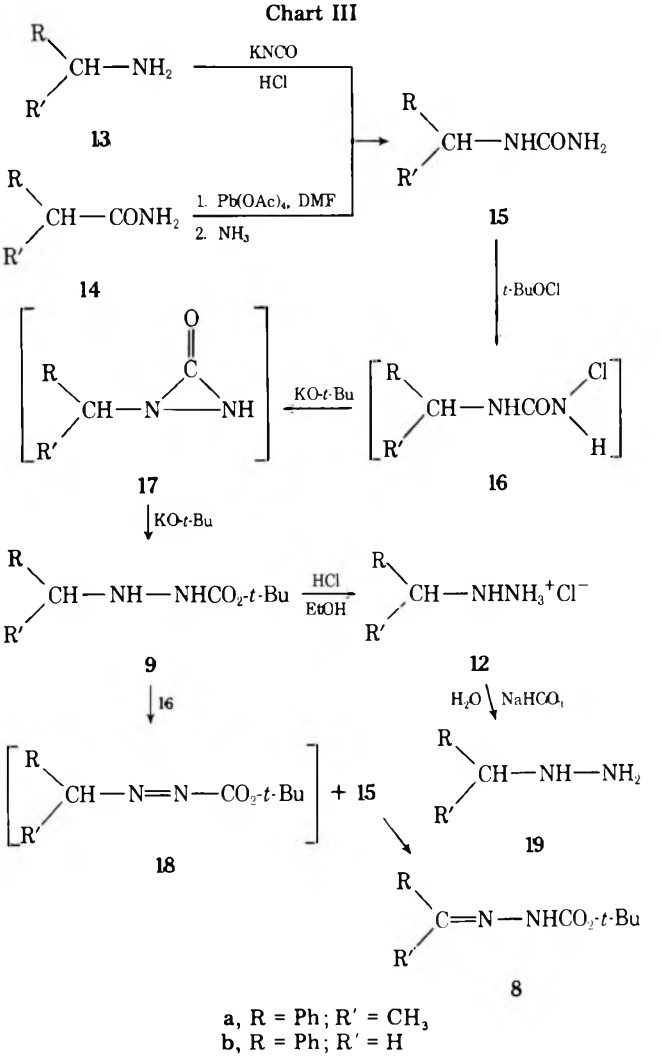
Chart II. Synthesis of *N*-Acyl-*N*-alkylhydrazines



synthesis of **11**. This synthesis could be modified (by elimination of the second acylation step) to afford a convenient variation on the previously reported[10,11] synthesis of alkylhydrazines [as the hydrochloride (**12**)] which used ethyl carbazate rather than *tert*-butyl carbazate (**2**).[12] The results of a number of preparations of **8** and **9** are summarized in Table I. Using the five-step process of Chart II hydrazides **11ax, 11ay,** and **11cy** were prepared in 43, 38, and 39% overall yields, respectively, from the corresponding ketones.

Although the procedure in Chart II is quite general, it cannot be used for optically active hydrazines (because the reductions of **8** to **9** shown are not stereoselective) nor for *tert*-alkylhydrazines. Attempts to bring about the stereoselective reduction of the carbo-*tert*-butoxyhydrazones of 2-methylcyclohexanone with potassium tri-*sec*-butylborane hydride[13] were unsuccessful. Attempts to develop a synthesis of *tert*-alkylhydrazines from **8** were thwarted when the addition of the methyl bromide Grignard reagent or methyllithium across the azomethine bond of **8b** gave at most 1–2% of **9a**. Rather than attempt to circumvent these experimental difficulties, we developed the route to **9** shown in Chart III.

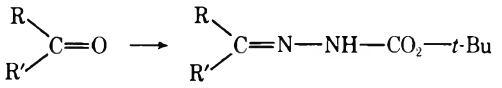
Chart III



This synthesis begins with an *N*-alkylurea (**15**), readily obtained from an amine (**13**) (racemic mixture or a single enantiomer) or a carboxamide[1] (**14**) (racemic mixture or single enantiomer) by the routes shown. Our expectation was that **15** would be converted by procedures well established in α-lactam[14] and diaziridinone[15] chemistry to, successively, the *N*-chloro urea (**16**), the unstable diaziridinone **17**, and finally the ring cleavage product, the *N'*-carbo-*tert*-butoxyhydrazine (**9**).

A similar procedure using sodium hypochlorite and aqueous base and leading directly to the hydrazine (or hydrazine derivative) was first reported by Schestakov[16] and apparently rediscovered recently.[17–19] The Schestakov procedure is described[16–18] as proceeding by halogenation on the terminal nitrogen atom followed by the Hofmann rearrangement (although this mechanistic route has been questioned[20]). Chlorination on the terminal nitrogen is to be expected *in alkaline media* where the reaction may involve displacement on the chlorine atom of the hypochlorite by amide anion. However, in neutral media N-chlorination by *tert*-butyl hypochlorite may involve a four- or six-center transition state[21] (steric factors permitting) and attack at the more basic (internal) nitrogen atom. We have attempted to determine the site of N-chlorination in **15b** and in **20** by comparison of the ^{1}H NMR spectra of the ureas with those of the crude *N*-chloro ureas.

Table I. Carbo-*tert*-butoxyhydrazones[a]



6 **8**

Registry no.	6	Yield, %	Mp, °C	Ir (CH_2Cl_2), cm^{-1} ν(N–H)	Ir (CH_2Cl_2), cm^{-1} ν(C=O)	^1H NMR ($CDCl_3$), δ[b]	Registry no. (8)
98-86-2	Acetophenone	84–94	169–170	3330	1740	2.17 (s 3)	56572-27-1
93-55-0	Propiophenone	72	169–171	3375	1750	2.65 (q 2)	60295-07-0
119-61-9	Benzophenone	92	142–145	3330	1740		60295-08-1
122-00-9	*p*-Methylacetophenone	90	142–144	3355	1735	2.14 (s 3)	60295-09-2
121-97-1	*p*-Methoxypropiophenone	90	163–165	3350	1735	2.60 (q 2)	60295-10-5
108-94-1	Cyclohexanone	91	125–127	3225[d]	1695[d]	0.90–2.50[e,f]	60295-11-6
583-60-8	2-Methylcyclohexanone	96	103–105	3440[g]	1730[g]	1.2–2.5[e]	60295-12-7
78-59-1	Isophorone	97	129–131			2.23 (s 2), 6.0 (m 1)	60295-13-8
98-53-3	4-*tert*-Butylcyclohexanone	100	137–139	3370	1735	1.20–2.75[e]	60295-14-9
1192-62-7	2-Acetylfuran	90	148.5–149.5	3350	1740	2.17 (s 3)	60295-15-0

[a] Satisfactory analytical data (±0.4% for C, H, N) were obtained for all new compounds in the table. [b] For α-CH protons only. *t*-BuO protons appeared at δ 1.50–1.54 except where otherwise noted. Aryl protons appeared as two clusters of peaks, roughly similar to those found in the spectrum of the parent ketone, range δ 6.75–8.00. [c] J = 7.5 Hz. [d] In KBr. [e] All ring protons. [f] *t*-BuO protons appeared at δ 1.50. [g] In CCl_4.

In **15b** the $-CH_2NH-$ moiety appears as a doublet and triplet. The $-CH_2-$ doublet appears to be shifted downfield upon chlorination but the splitting is retained, suggesting chlorination on the terminal N atom. However, there are enough other changes in peak shape, position, and area to render any decision somewhat ambiguous; thus, it is possible that both *N*-chloro species are present (or are in a slow equilibrium).

It is known from earlier studies[15] on *N,N'*-di-*tert*-butylurea, which has a single *tert*-butyl peak at δ 1.27 (in CCl_4), that chlorination gives an unstable *N*-chloro compound with two *tert*-butyl peaks at δ 1.32 and 1.41 (CCl_4) (our data, which are in close agreement with that reported[15]), corresponding to the *t*-BuNH and *t*-BuNCl moieties, respectively. Chlorination of *tert*-butylurea (**20**) [δ 1.37 ($CDCl_3$)] under the same conditions[15] gives a moderately stable crude solid with its principal *tert*-butyl peak at δ 1.39 ($CDCl_3$) (the only other *tert*-butyl peaks being caused by small amounts of unreacted **20** and *tert*-butyl alcohol, both of which are found *upfield* of δ 1.39). The very small shift in the position of the *tert*-butyl ^1H NMR peak upon chlorination suggests that chlorination occurs largely (if not exclusively) on the terminal nitrogen atom, and not on the nitrogen atom bearing the *tert*-butyl group, possibly because of steric inhibition of the transition state for the latter.

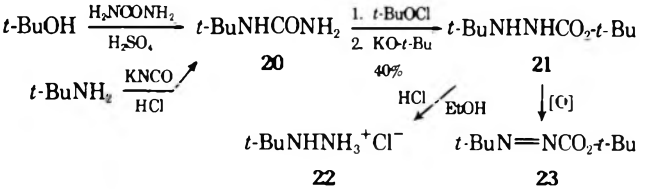
We also attempted to observe the proposed diaziridinone intermediate **17** using ir techniques similar to those we described earlier for the observation of α-lactams.[14] No ir peak in the 1850-cm^{-1} region was observed; therefore, the ring opening of **17** (if it is an intermediate) must be quite rapid. Thus, the question of the mechanism of this rearrangement remains unresolved. Although we prefer the general route shown, it is possible that a Hofmann rearrangement may be involved.

The new sequence, whether from **13, 14,** or **15** to **9,** is short and simple experimentally. Unfortunately, this synthetic sequence is not free from complication. Thus, with **13a** it was necessary to use a large excess (5–10 mol) of potassium *tert*-butoxide and to add **16a** *to the base* in the steps **16a** → **17a** → **9a.** When slightly more than the theoretical amount of base was used, the product was a mixture of **8a** and **9a** in ratios varying from 1:3 to 1:1 depending on other reaction variables. Apparently, the reaction of **16a** with the base is sufficiently slow that the product **9a** may be oxidized by the as yet uncyclized **16a** unless a large excess of base is used to accelerate the removal of **16a.** Presumably **9a** is oxidized to the corresponding azo compound, which then rearranges to **8a.** Of course any **8a** present can be readily hydrogenated back to **9a** (Chart II). This additional step would increase the overall yield of **9a** but would reduce the optical purity of the **9a.** If optical purity is not important, this may be the preferred procedure in some instances. For **13a, 8a** and **9a** could be separated.

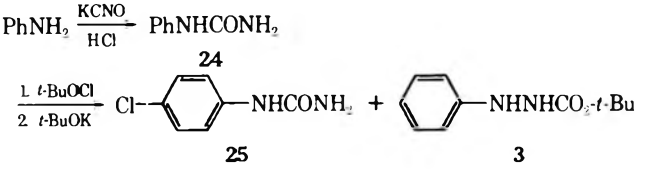
Cleavage of **9a** with hydrogen chloride went fairly easily in ethanol, and subsequent neutralization of the resultant hydrazinium salt (**12a**) gave the free hydrazine **19a.** In our hands the overall yield of **19a** from (*R*)-(+)-**13a** was 56%. Since our observed optical rotation for **19a** was slightly larger than the previously reported value for "pure" **19a,** presumably **19a** was obtained with essentially complete retention of configuration.[22,23]

Application of this synthetic route to benzylurea (**13b**) (using a large excess of base) gave an 82% yield of *N*-benzyl-*N'*-carbo-*tert*-butoxyhydrazine (**9b**) plus a trace of benzaldehyde carbo-*tert*-butoxyhydrazone (**8b**).

The route shown in Chart III could also be used for the synthesis of *tert*-butyl- and phenylhydrazine derivatives; however, the yields were substantially lower. In the synthesis of *tert*-butylhydrazine (**22**) it was again difficult to avoid the formation of the oxidation product **23;** furthermore, even



when a large excess of base was employed the yield of the intermediate hydrazide **21** was only 40%. However, there was also a 52% recovery of **20.** In the synthesis of *N*-phenyl-*N'*-carbo-*tert*-butoxyhydrazine (**3**) the intermediate *N*-chloro urea apparently underwent preferential rearrangement to *p*-chlorophenylurea (**25**) or was directly halogenated by the



tert-butyl hypochlorite, even under the usually favorable conditions of Chalsty and Israelstram.[24] The yield of **3** was 31% and that of **25** was 39% when the latter conditions were employed.

Experimental Section

Dichloromethane was distilled from phosphorus pentoxide under nitrogen. *tert*-Butyl alcohol was refluxed over calcium hydride for 24 h and distilled under nitrogen. Anhydrous ethanol was further dried by distillation with magnesium turnings. Benzene was dried by azeotropic distillation. *tert*-Butyl carbazate, *tert*-butyl azidoformate, and diborane–tetrahydrofuran complex were purchased from the Aldrich Chemical Co. Melting points were obtained with a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were determined with Perkin-Elmer Models 137, 237, or 621 spectrometers. ^{1}H NMR spectra were determined at 60 MHz with a Varian A-60 or A-60D spectrometer. Chemical shifts are given in parts per million downfield from internal Me_4Si except for those determined in D_2O, which are based on the internal DOH peak (4.61 ppm). Mass spectra were taken on a Hitachi Perkin-Elmer RMU-6D mass spectrometer operated at 70 eV. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter using a 1-dm cell (critical values were measured on two different instruments of this type). Microanalyses were obtained from Micro-Tech Laboratories, Skokie, Ill.

***N*-Phenyl-*N'*-carbo-*tert*-butoxyhydrazine [*tert*-Butyl 2-Phenylcarbazate (3)].** A mixture of 11.44 g (0.0796 mol) of *tert*-butyl azidoformate, 8.6 g (0.0796 mol) of phenylhydrazine, 11.1 ml of triethylamine, and 20 ml of water was stirred for 40 h. The solid mass was broken up into small pieces. The yellow-orange solid was filtered, dried, and recrystallized from petroleum ether (bp 60–90 °C) to yield 10.0 g (61.0%) of **3** as white needles: mp 90–92 °C (lit.[25] 91–93 °C); ir (KBr) 3.05 (amide NH), 3.10 (amine NH), 5.80–5.95 (ester C=O), 8.3–8.7 μ (ester C–O–C); ^{1}H NMR ($CDCl_3$) δ 1.44 (9 H, s, *t*-Bu), 5.92 (1 H, s, NH), 6.62–7.37 (6 H, m, Ph + NH).

***N*-Benzoyl-*N*-phenyl-*N'*-carbo-*tert*-butoxyhydrazine (4).** To a solution of 5.0 g (0.024 mol) of **3** in 25 ml of dry pyridine, 3.38 g (0.024 mol) of benzoyl chloride was added dropwise over a period of 10 min. The reaction mixture was stirred for 12 h and was poured into ice and water. The cream colored precipitate was filtered, dried, and recrystallized from ethyl acetate–petroleum ether to yield 5.0 g (67.0%) of **4** as white crystals: mp 139–140 °C; ir (KBr) 3.05 (NH), 5.90 (urethane C=O), 6.05 (amide C=O), 8.50 μ (ester C–O–C); ^{1}H NMR ($CDCl_3$) δ 1.43 (9 H, s, *t*-Bu), 6.88 (1 H, s, NH), 7.05–7.82 (5 H, m, Ph).

Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.36; H, 6.48; N, 9.00.

***N*-Benzoyl-*N*-phenylhydrazine (5).** A solution of 4.9 g (0.0158 mol) of **4** in 50 ml of absolute ethanol was treated with anhydrous hydrogen chloride for 30 min. The white solid was filtered, washed with ether, and dried to yield 3.4 g (88.0%) of crude **5** hydrochloride: mp 196–198 °C; ir (KBr) 3.5–4.0 ($+NH_3$), 6.05 μ (C=O). To a solution of 4.9 g (0.0158 mol) of crude **5** hydrochloride in 25 ml of water a saturated solution of sodium bicarbonate was added until the mixture was basic to litmus. The aqueous solution was extracted with three 25-ml portions of chloroform. The dried extracts ($MgSO_4$) were treated with charcoal and evaporated to yield a light yellow oil. The oil was dissolved in a minimum amount of ethyl acetate and petroleum ether added until the solution became turbid. White crystals were obtained which were recrystallized in the same manner to yield 1.97 g (96.0%) of **5**: mp 63–65 °C (lit.[6] 67–69 °C); ir (KBr) 3.05–3.15 (NH_2), 6.10 μ (amide C=O); ^{1}H NMR ($CDCl_3$) δ 5.03 (2 H, s, NH_2), 7.00–7.50 (10 H, m, Ph + Ph).

Aldehyde and Ketone *tert*-Butoxycarbohydrazones (8). General Procedure. Equimolar amounts of *tert*-butyl carbazate or ethyl carbazate and the corresponding aldehyde or ketone (0.1–0.2 mol) were dissolved in an appropriate amount of absolute ethanol (30–75 ml), and the reaction mixture was stirred at room temperature until a copious precipitate had formed. A few drops of glacial acetic acid were added if the reaction mixture had been stirred for more than 24 h without formation of a precipitate. After filtration of the precipitate usually further precipitate could be obtained by adding small amounts of water to the filtrate. Generally, the combined precipitates were recrystallized by dissolving them in a sufficient amount of hot 95% ethanol and adding water dropwise to the cloud point, then setting the solution aside until recrystallization was completed (2–3 h).

For bulky ketones, such as benzophenone and 2-acetylfluorene, 0.5–1.0 ml of glacial acid was added at the beginning to the stirred mixture and the latter was heated under reflux for several hours. Benzophenone, 4-methoxypropiophenone, and 2-acetylfluorene *tert*-butoxycarbohydrazones were recrystallized from a mixture of 95% ethanol and 1,4-dioxane.

Selected results obtained using this procedure are given in Table I.[26]

N-Substituted *N'*-Carbo-*tert*-butoxyhydrazines (9). General Procedure. A. To a solution of 0.05 mol of **8** in 50–60 ml of 95% ethanol was added 0.3–0.4 g of 10% palladium on carbon.[27] The solution was mixed well and hydrogenated in the Paar shaker hydrogenator (starting pressure 45–50 psi). Generally, it took 2–3 h to complete the hydrogenation of the carbon–nitrogen double bond. Bulky *tert*-butoxycarbohydrazones required a longer reaction time. The reaction mixture was filtered through Celite, the filtrate was evaporated, and the residual solid was recrystallized from ethanol.

B. A dried three-necked round-bottomed flask was equipped with a pressure-equalized funnel, a nitrogen inlet and outlet device, a mechanical stirrer, and a condenser fitted with a calcium chloride tube. A solution of **8** in 60–80 ml of dry tetrahydrofuran was stirred and cooled (ice–salt bath) under a blanket of nitrogen, and twice the molar amount of diborane–tetrahydrofuran complex was transferred with an Aldrich Flex-needle under nitrogen pressure through a rubber septum to the sealed, pressure-equalized funnel. The diborane–tetrahydrofuran complex was then added dropwise through the funnel to the vigorously stirred reaction mixture. The reaction mixture was allowed to stand in the ice–salt bath for 1 h and then was stirred overnight at room temperature. The excess diborane was carefully destroyed by addition of 60 ml of a solution of THF and water (2:1). The resulting mixture was neutralized with dilute K_2CO_3 and extracted with three 40-ml portions of ether. The organic layer was dried ($MgSO_4$) and the solvent was evaporated under water aspirator pressure. The resulting oily material was dissolved in petroleum ether and passed through a silica gel column to remove dissolved inorganic material. The light yellow oily solution either yielded a precipitate on standing or gave an oily product on evaporation. Solid precipitates were recrystallized by dissolving them in a limited amount of 95% ethanol and adding water dropwise to the cloud point.

Selected results using these procedures are given in Table II.[26] All of the examples of **9** shown were prepared by procedure A. Three examples were also prepared by procedure B to compare the two procedures. The yield of **9a** from procedure B was 85%. The ir and ^{1}H NMR spectra of this product were identical with those for the product prepared by procedure A and the mixture melting point was not depressed. The other two compounds prepared by both procedures were oils but gave appropriate ir and ^{1}H NMR spectra.

***N*-Acetyl-*N*-(1-phenylethyl)-*N'*-carbo-*tert*-butoxyhydrazine (10ax).** To a solution of 12.0 g (0.05 mol) of **9a** in 75 ml of dry pyridine 5.1 g (0.05 mol) of acetic anhydride was added; the mixture was heated under reflux for 4 h and poured into ice water. The resulting yellow oil was extracted with three 50-ml portions of ether. The dried extracts ($MgSO_4$) were evaporated to a viscous oil. All attempts to crystallize the oil using chloroform–petroleum ether, ethyl acetate–petroleum ether, and ether–petroleum ether solvents were unsuccessful. The oil appeared to be hygroscopic. The yield of crude **10ax** was 10.1 g (72.5%): ir (neat) 3.10 (NH), 5.80 (C=O), 6.05 μ (C=O); ^{1}H NMR ($CDCl_3$) δ 1.18 (3 H, d, J = 7 Hz, CH_3), 1.48 (9 H, s, *t*-Bu), 2.06 (3 H, s, CH_3), 5.93 (1 H, q, J = 7 Hz, CH), 6.88–7.13 (1 H, s, NH), 7.33 (5 H, m, Ph).

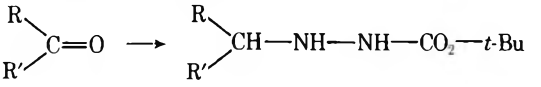
***N*-Acetyl-*N*-(1-phenylethyl)hydrazine (11ax).** A solution of 10.0 g (0.036 mol) of crude **10ax** in 50 ml of absolute ethanol was treated with anhydrous hydrogen chloride for 0.5 h. The ethanol was removed with a rotary evaporator leaving a thick yellow oil. The oil was dissolved in methanol, and ethyl ether was added until the solution became turbid. The mixture was allowed to crystallize to give 5.4 g (76.5%) of crude hydrochloride of **11ax**: mp 125–127 °C; ir (KBr) 3.4–3.8 ($+NH_3$), 6.05 μ (C=O).

A solution of 5.4 g (0.025 mol) of the crude hydrochloride in 25 ml of water was treated with a saturated solution of sodium bicarbonate until the solution was basic to litmus. The aqueous solution was extracted with three 25-ml portions of chloroform. The dried extracts ($MgSO_4$) were treated with charcoal and evaporated to dryness. The white solid remaining was recrystallized from chloroform–petroleum ether to give 3.9 g (87%) of **11ax**: mp 53–54 °C; ir (KBr) 3.05–3.10 (NH_2), 6.20 μ (C=O); ^{1}H NMR ($CDCl_3$) δ 1.48 (3 H, d, J = 7 Hz, CH_3), 2.19 (3 H, s, CH_3) 3.55 (3 H, s, NH_2), 6.11 (1 H, q, J = 7 Hz, CH), 7.32 (5 H, m, Ph).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.25; H, 7.93; N, 15.95.

***N*-Benzoyl-*N*-(1-phenylethyl)-*N'*-carbo-*tert*-butoxyhydrazine (10ay).** To a solution of 5.0 g (0.0212 mol) of **9a** in 50 ml of dry

Table II. Carbo-*tert*-butoxyhydrazines[a,b]



6	Yield, %	Mp, °C	Ir (CCl_4) cm^{-1} ν(NH)	Ir (CCl_4) cm^{-1} ν(C=O)	^1H NMR ($CDCl_3$), δ[c]	Registry no. (9)
Acetophenone	94[d,e]	72–73	3320	1710	4.17 (q 1)[f]	60295-16-1
Propiophenone	75	64–66	3330	1720	3.85 (m 1)	60295-17-2
Benzophenone	93	97–99	3440	1750, 1720	5.30 (s 1)	60295-18-3
p-Methylacetophenone	99	77–78.5	3435	1720	4.16 (q 1)[f]	60295-19-4
p-Methoxypropiophenone	99	60–62	3440	1720	3.5–3.95 (m 1)	60295-20-7
Cyclohexanone	82[g]	76–78	3225[h]	1695[h]	0.90–3.0[i]	60295-21-8
2-Methylcyclohexanone	85	Oil	3380	1710	1.05–3.00[i]	60295-40-1
Isophorone	97	151.5–153	3220	1750, 1700	1.60–2.65[i–k]	60295-41-2
4-*tert*-Butylcyclohexanone	96	Oil	3380	1700	1.0–2.0[i]	60295-42-3

[a] Satisfactory analytical data (±0.4% for C, H, N) were obtained for all new compounds in the table. [b] Made by hydrogenation using Pd/C unless otherwise specified. [c] For CHN protons only. *t*-BuO protons appeared at δ 1.42–1.45 except where otherwise noted. Aryl protons appeared as sharp to broad singlets except for **9** from *p*-methoxyacetophenone which appeared in a distorted AB-like AA'BB' pattern, range 7.2–7.7. Alkyl protons appeared in their normal ranges. [d] Using BF_3·THF complex for reduction, yield was 85%. [e] Using 5% Pt/C (1.0 g/10 g of hydrazone) 73% of product was obtained after recrystallization from ethyl acetate–petroleum ether. [f] J = 6.5 Hz. [g] Obtained with 5% Pt/C (1.0 g/10 g of hydrazone). [h] In KBr. [i] All ring protons. [j] *t*-BuO protons at δ 1.50. [k] Ring double bond also reduced.

pyridine 3.0 g (0.0212 mol) of benzoyl chloride was added dropwise. The reaction mixture was stirred for 15 h and poured into ice cold 4 N hydrochloric acid. The aqueous solution was extracted with three 50-ml portions of chloroform. The dried extracts ($MgSO_4$) were treated with charcoal and evaporated to dryness. The white solid was recrystallized from chloroform–petroleum ether to give 5.3 g (76%) of **10ay**: mp 115–117 °C; ir (KBr) 3.10–3.15 (NH), 5.90 μ (C=O); ^1H NMR ($CDCl_3$) δ 1.18 (9 H, s, *t*-Bu), 1.58 (3 H, d, J = 7 Hz, CH_3), 5.83 (1 H, q, J = 7 Hz, CH), 6.77 (1 H, broad s, NH), 7.03–7.67 (6 H, m, Ph + NH).

Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.50; H, 7.13; N, 8.24.

***N*-Benzoyl-*N*-(1-phenylethyl)hydrazine (11ay).** A solution of 5.3 g (0.0156 mol) of **10ay** in 50 ml of absolute ethanol was treated with anhydrous hydrogen chloride for 0.5 h. The ethanol was removed by evaporation, leaving a thick yellow syrup (the hydrochloride salt was hygroscopic). The syrup was treated with 30 ml of a saturated solution of sodium bicarbonate until basic to litmus and the solution was extracted with three 50-ml portions of chloroform. The dried extracts ($MgSO_4$) were treated with charcoal and evaporated to dryness. The light yellow oil was dissolved in chloroform and petroleum ether added until the solution turned cloudy. White needles of **11ay** were obtained: yield 2.1 g (56%); mp 56–67 °C; ir (KBr) 3.05–3.10 (NH_2), 6.20 μ (C=O); ^1H NMR ($CDCl_3$) δ 1.57 (3 H, d, J = 6.5 Hz, CH_3), 3.91 (2 H, broad s, NH_2), 5.33 (1 H, q, J = 6.5 Hz, CH), 7.30 (5 H, s, PhCH), 7.45 (5 H, s, PhCO).

Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.75; H, 6.80; N, 11.75.

***N*-Benzoyl-*N*-cyclohexylhydrazine (11cy).** To a solution of 10.0 g (0.0467 mol) of **9c** in 30 ml of methylene chloride was added 5.3 ml (0.0467 mol) of benzoyl chloride and the reaction mixture allowed to stir for 5 h. The methylene chloride was removed with a rotary evaporator leaving a white solid which liquefied upon filtration. The hygroscopic substance was redissolved in ethanol and the solution was treated with anhydrous hydrogen chloride for 30 min. The ethanol was evaporated leaving a white solid which was recrystallized from ethanol–water to give 7.2 g (61%) of the crude hydrochloride of **11cy**; mp 176–180 °C; ir (KBr) 3.5–4.0 ($+NH_3$), 6.1 μ (C=O); ^1H NMR ($CDCl_3$) δ 0.68–2.65 (10 H, broad m, C_6H_{10}), 3.45–4.12 (1 H, broad s, CH), 7.60 (5 H, s, Ph), 9.13 (3 H, broad s, $+NH_3$).

To a solution of 10.0 g (0.0392 mol) of the crude hydrochloride in 50 ml of water was added a sufficient amount of saturated sodium bicarbonate to make the solution basic to litmus. The mixture was extracted with three 50-ml portions of chloroform, and the extracts were dried ($MgSO_4$) and evaporated to dryness, leaving a white solid. Recrystallization from water–ethanol gave **11cy** as white platelets, yield 7.3 g (86%): mp 118–119 °C; ir (KBr) 3.0–3.1 (NH_2), 6.1 (amide C=O), 6.3 (NH in plane bend), 13.3 (NH_2 out of plane bend), in $CHCl_3$ 2.9–3.0 (NH_2), 6.1 (C=O), 6.3 μ (NH_2 deformation); ^1H NMR ($CDCl_3$) δ 0.92–2.08 (10 H, broad m, C_6H_{10}), 3.51–3.91 (1 H, broad m, CH), 4.00–4.33 (2 H, broad s, NH_2), 7.55 (5 H, s, Ph); mass spectrum (80 eV) *m/e* rel intensity and pertinent metastables) 218 (27.6), 202 (1), 136 (24.8), 105 (100), 77 (39), 84.8 (218 → 136), 50.6 (218 → 105), 81.1 (136 → 105), 56.5 (105 → 77).

Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.40; H, 8.36; N, 12.72.

N-Substituted Ureas. General Procedure. A solution of 0.10 mol of the amine in a mixture of 8.3 ml of concentrated hydrochloric acid and 100 ml of water was added to a solution of 8.1 g (0.10 mol) of potassium cyanate in 100 ml of water. The mixture was stirred at room temperature for 6 h. The white precipitate was collected by filtration and washed with water. For *N*-*tert*-butylurea (**20**) it was necessary to remove the water (rotary evaporator) because of the solubility of the product in water. The ureas were recrystallized from ethanol.

The yield of **1-phenylethylurea (15a)** was 83%: mp 110–112 °C (lit.[28] mp 112–113.5 °C); ^1H NMR (Me_2SO-d_6) δ 1.31 (3 H, d, J = 6.5 Hz, CH_3), 4.73 (1 H, q, J = 6.5 Hz, CH), 5.46 (2 H, broad s, NH_2), 6.43 (1 H, d, J = 6.5 Hz, NH), 7.28 (5 H, s, Ph).

***(R)*-(+)-1-Phenylethylurea (15a)** was prepared from (*R*)-(+)-1-phenylethylamine [^1H NMR (CCl_4) δ 1.29 (3 H, d, J = 6.5 Hz, CH_3), 1.47 (2 H, s, NH_2), 3.99 (1 H, q, J = 6.5 Hz, CH), 7.22 (5 H, s, Ph); $[\alpha]^{25}_{589}$ +36.47° (neat), $[\alpha]^{25}_{589}$ +38.28°,[27] $[\alpha]^{25}_{589}$ +28.32° (*c* 2.020, EtOH), 94.3% optically pure (lit.[29] $\alpha^{22}D$ −38.30° (neat, 1 dm); $[\alpha]^{25}D$ +40.6° (neat))]: yield 84%; mp 118–120 °C [lit.[30] mp for (*S*)-(−)-urea 123.5–124 °C]; ^1H NMR (Me_2SO-d_6) δ 1.30 (3 H, d, J = 6.5 Hz, CH_3), 4.73 (1 H, q, J = 6.5 Hz, CH), 5.48 (2 H, broad s, NH_2), 6.46 (1 H, d, J = 7 Hz, NH), 7.28 (5 H, s, Ph).

The yield of ***tert*-butylurea**[31] **(20)** was 50%: mp 182–184 °C (lit.[32] mp 183 °C); ^1H NMR (Me_2SO-d_6) δ 1.21 (9 H, s, *t*-Bu), 5.23 (2 H, broad s, $-NH_2$), 5.82 (1 H, broad s, –NH); ^1H NMR ($CDCl_3$) δ 1.37 (s, *t*-Bu).

The yield of **benzylurea (15b)** was 93%: mp 145–146 °C (lit.[33] mp 146.6 °C); ^1H NMR (Me_2SO-d_6) δ 4.20 (2 H, d, J = 6 Hz, CH_2), 5.70 (2 H, s, NH_2), 6.57 (1 H, broad t, J = 6 Hz, NH), 7.27 (5 H, s, Ph).

The yield of **phenylurea (24)** was 72%: mp 145–146 °C (lit.[33] mp 147–148 °C); ^1H NMR (Me_2SO-d_6) δ 5.90 (2 H, s, NH_2), 6.76–7.55 (5 H, m, Ph), 8.58 (1 H, s, NH).

Rearrangement of 1-Phenylethylurea (15a). To a stirred mixture of 1.64 g (0.010 mol) of **15a**, 20 ml of dry benzene, and 15 ml of dry *tert*-butyl alcohol kept at 0–5 °C (ice–salt bath) was added dropwise but rapidly 1.2 ml (1.09 g, 0.01 mol) of *tert*-butyl hypochlorite.[34] When the mixture became clear (1–2 min), the resultant solution (all of the urea had dissolved as it reacted) was added rapidly into a precooled (5 °C) solution of 5.6 g (0.05 mol) of potassium *tert*-butoxide in 30 ml of dry benzene and 30 ml of dry *tert*-butyl alcohol. The mixture was stirred for an additional 5–10 min and then poured with stirring into 300 ml of ice water. The aqueous layer was extracted with 1:1 methylene chloride–ether, and the combined organic layers were washed with water, dried ($MgSO_4$), and evaporated. The crude product (1.94 g, 82%) was a mixture of ***N*-(1-phenylethyl)-*N'*-carbo-*tert*-butoxyhydrazine (9a)** and a small amount of **8a.** The latter was relatively insoluble in *n*-pentane. Thus, recrystallization from *n*-pentane gave 1.78 g (75%) of **9a**: mp 72–73 °C; ^1H NMR δ ($CDCl_3$) 1.25 (3 H, d, J = 6.5 Hz, CH_3), 1.44 (9 H, s, *t*-Bu), 4.16 (1 H,

q, J = 6.5 Hz, CH), 4.00 (1 H, broad s, –NH), 6.16 (1 H, broad s, –NH), 7.32 (5 H, s, Ph). Alternatively, the crude product could be purified by chromatography on silica gel using 1:1 $CHCl_3$–*n*-pentane as eluent. Compound **9a** was eluted before **8a.**

Similar treatment of (*R*)-(+)-**15a,** $[\alpha]^{25}_{589}$ +45.11° (*c* 1.024, EtOH), gave 84% of (*R*)-(+)-**9a:** mp 70–74 °C; ^{1}H NMR δ ($CDCl_3$) 1.28 (3 H, d, J = 6.5 Hz, CH_3), 1.41 (9 H, s, *t*-Bu), 4.16 (1 H, q, J = 6.5 Hz, CH), 3.99 (H, broad s, –NH), 6.66 (H, broad s, –NH), 7.31 (5 H, s, Ph); $[\alpha]^{25}_{589}$ +97.44° (c 1.125, EtOH).

Rearrangement of *tert*-Butylurea (20). The procedure was essentially the same as that used for **15a** except that the unreacted **20** (52%) was recovered by evaporation of the aqueous layers. The yield of ***N*-*tert*-butyl-*N'*-carbo-*tert*-butoxyhydrazine (21)** was 40%: mp 66–68 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (9 H, s, *t*-Bu), 1.42 (9 H, s, *t*-Bu).

Anal. Calcd for $C_9H_{20}N_2O_2$: C, 57.42; H, 10.74; N, 14.87. Found: C, 57.15; H, 10.87; N, 14.92).

Chlorination of 20. To a solution of 0.387 g (0.0033 mol) of **20** in 12 ml of methanol, 0.36 g (0.4 ml, 0.0033 mol) of *tert*-butyl hypochlorite was added with stirring at 0 °C (ice–salt bath). After 3 min the methanol was removed under vacuum (<0.5 Torr) at −10 to 0 °C. The residue (a white solid) was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR: δ ($CDCl_3$) 1.28 (s, *t*-BuOH), 1.37 (s, **20**), 1.39 (s, *t*-BuNHCONHCl). The first two peaks were quite small. Addition of a small drop of *t*-BuOCl caused the area of the peaks at δ 1.28 and 1.39 to increase and that at δ 1.37 to decrease. Treatment of the crude *N*-chloro compound with potassium *tert*-butoxide in benzene–*tert*-butyl alcohol gave essentially the same mixture (based on its ^{1}H NMR spectrum) of **20** and **21** as that described for the rearrangement of **20.**

Similar treatment of *N,N'*-di-*tert*-butylurea[15] [δ (CCl_4) 1.27 (s, *t*-Bu)] gave a crude product with ^{1}H NMR (CCl_4) δ 1.32 (*t*-BuNH), 1.41 (*t*-BuNCl) [lit.[15] ^{1}H NMR (CCl_4) δ 1.33, 1.43].

Rearrangement of Benzylurea (15b). The procedure was essentially the same as that used for 1-phenylethylurea. ***N*-Benzyl-*N'*-carbo-*tert*-butoxyhydrazine (9b)** was extracted into pentane and purified by distillation to yield 82% of product: bp 100–105 °C (0.1 Torr); ^{1}H NMR ($CDCl_3$) δ 1.44 (9 H, s, *t*-Bu), 3.92 (2 H, s, CH_2), 4.25 (1 H, broad, NH), 6.83 (1 H, broad, NH), 7.27 (5 H, s, Ph).

Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.72; H, 7.99; N, 12.40.

A trace of benzaldehyde carbo-*tert*-butoxyhydrazone (**8b**) was left as the pentane-insoluble residue: mp 187–189 °C (lit.[35] mp 190–191 °C); ^{1}H NMR ($CDCl_3$) δ 1.52 (9 H, s, *t*-Bu), 7.25–7.80 (5 H, m, Ph), 7.85 (1 H, s, NH), 8.30 (1 H, s, –CH=).

Rearrangement of Phenylurea (24). A. The procedure used for the rearrangement of **15b** was followed. The methylene chloride–ether extracts were washed with water, dried ($MgSO_4$), and evaporated. The crude product was extracted with petroleum ether to give a 15% yield of *N*-phenyl-*N'*-carbo-*tert*-butoxyhydrazine (**3**): mp 91–92 °C (lit.[36] 91–93 °C); ^{1}H NMR ($CDCl_3$) δ 1.43 (9 H, s, *t*-Bu), 5.82 (1 H, broad, NH), 6.57 (1 H, broad, NH), 6.67–7.40 (5 H, m, Ph). The petroleum ether insoluble residue was essentially pure *p*-chlorophenylurea (**25**), yield 50%: mp 204–206 °C (lit.[37] mp 206 °C); ^{1}H NMR (Me_2SO-d_6) δ 5.94 (2 H, s, NH_2), 7.35 (5 H, m, Ar), 8.70 (1 H, s, NH).

B. To a stirred mixture of 1.36 g (0.0100 mol) of phenylurea, 40 ml of dry *tert*-butyl alcohol, and 1.6 g of Borax was added dropwise at room temperature 1.2 ml (1.09 g, 0.0100 mol) of *tert*-butyl hypochlorite. The temperature of the mixture rose to 30 °C. When the temperature fell to ambient, the resultant solution was added rapidly to a precooled (5 °C) solution of 5.6 g (0.050 mol) of potassium *tert*-butoxide in 30 ml of dry benzene and 30 ml of dry *tert*-butyl alcohol. The mixture was stirred for an additional 5–10 min and then poured with stirring into 300 ml of ice and water. The aqueous layer was extracted with 1:1 methylene chloride–ether, and the combined organic layers were washed with water, dried ($MgSO_4$), and evaporated. The crude product (1.20 g, 58%) was extracted with petroleum ether to give 0.65 g (31%) of **3.** The residue gave 0.50 g (39%) of *p*-chlorophenylurea.

Cleavage of N-Substituted *N'*-Carbo-*tert*-butoxyhydrazines. General Procedure. In general the carbo-*tert*-butoxyhydrazines **9** were cleaved by passing anhydrous HCl through solutions of **9** in absolute ethanol (ca. 20–30 ml/0.1 mol) with stirring at the ice bath temperature until the reaction mixture became milky in appearance. Passage of the HCl was continued for ca. 1 h; then the mixture was stirred for 1–2 h under nitrogen. Anhydrous ether was added to the mixture (in some instances) and he mixture was stored in the freezer overnight. The product was collected by suction filtration (under nitrogen) and (if desired) recrystallized from a limited amount of methanol (adding anhydrous ether as necessary), again with storage of the recrystallization mixture in the freezer overnight. Suction filtration (under nitrogen) and washing with anhydrous ether gave the crude hydrazine hydrochloride (**12**), which was stored under nitrogen in a drybox. Elemental analysis of several such hydrochlorides showed them to be mixtures of the mono- with relatively small amounts of the dihydrochlorides. Further purification of **12** was not particularly effective, and, since for our purposes the mixtures sufficed, little effort was expended in this direction. The following specific examples demonstrate what can be done where a more nearly pure sample of the hydrazine (**19**) is required.

Hydrogen chloride was passed into a solution of 4.93 g (0.209 mol) of the (*R*)-(+)-**9a** described above in 50 ml of absolute ethanol with stirring (magnetic) and cooling (ice–salt bath). The reaction temperature was kept under 30 °C. After a white precipitate began to form (about 0.5–1 h) the passage of HCl was continued for 1 h. The mixture was diluted with dry ether and stored in the freezer overnight. The solid that formed was filtered under nitrogen and washed with dry ether, yielding 3.55 g (98.6%) of crude (*R*)-(+)-1-phenylethylhydrazine hydrochloride (**12a**): mp 179–180 °C; ^{1}H NMR (D_2O) δ 1.27 (3 H, d, J = 7.0 Hz, CH_3), 4.08 (1 H, q, J = 7.0 Hz, CH), 7.17 (5 H, s, Ph).

To a solution of 1.72 g (0.01 mol) of (*R*)-(+)-**12a** in 30 ml of water a 1 N solution of sodium bicarbonate in water was added slowly with stirring until the solution was basic to litmus. The mixture was extracted quickly with three 50-ml portions of chloroform, and the chloroform solutions were dried ($MgSO_4$) and evaporated under a stream of nitrogen. Distillation of the residue gave 1.2 g (89%) of **(*R*)-(+)-1-phenylethylhydrazine (19a):** bp 74 °C (1 mm) [lit.[38] bp 75 °C (1.1 mm)]; ^{1}H NMR ($CDCl_3$) δ 1.26 (3 H, d, J = 6.5 Hz, CH_3), 3.06 (3 H, s, NH + NH_2), 3.68 (1 H, q, J = 6.5 Hz, CH), 7.30 (5 H, s, Ph); $[\alpha]^{25}_{589}$ +32.49° (*c* 1.010, benzene) [lit.[22,23] $[\alpha]^{25}_D$ −30.3° (*c* 0.784, benzene) for the *optically pure* (*S*)-(−) isomer].

Treatment of 0.648 g (0.00345 mol) of **21** in 30 ml of absolute ethanol with hydrogen chloride as described above gave 0.46 g (107%) of crude ***tert*-butylhydrazine hydrochloride (22).** The crude product was dissolved in hot 1:1 methanol–ethyl acetate, filtered, and diluted with ethyl acetate until the solvent composition was ca. 1:5. After storage in the freezer 0.409 g (95%) of product was obtained: mp 191–192 °C (lit.[39] mp 192–194 °C); ^{1}H NMR (D_2O) δ 1.27 (s, *t*-Bu).

Registry No.—**1,** 100-63-0; **2,** 1070-19-5; **3,** 42116-43-8; **4,** 60295-43-4; **5,** 579-45-3; **5** HCl, 13815-63-9; **8b,** 24469-50-9; (+)-**9a,** 60325-12-4; **9b,** 53370-84-6; **10ax,** 60295-44-5; **10ay,** 60295-45-6; **11ax,** 60295-46-7; **11ax** HCl, 60295-47-8; **11ay,** 60295-48-9; **11cy,** 60295-49-0; **11cy** HCl, 60295-50-3; (+)-**12a,** 60362-49-4; (±)-**13a,** 618-36-0; (+)-**13a,** 3886-69-9; **13b,** 100-46-9; (±)-**15a,** 60295-51-4; (+)-**15a,** 16849-91-5; **15b,** 538-32-9; (+)-**19a,** 60325-13-5; **20,** 1118-12-3; **20** *N*-chloro derivative, 25544-61-0; **21,** 60295-52-5; **22,** 7400-27-3; **24,** 64-10-8; **25,** 140-38-5; benzoyl chloride, 98-88-4; acetic anhydride, 108-24-7.

References and Notes

(1) Part 19: H. E. Baumgarten, D. G. McMahan, V. J. Elia, B. I. Gold, V. W. Day, and R. O. Day, *J. Org. Chem.*, preceding paper in this issue.
(2) This work was supported in part by Grant GP-28261 from the National Science Foundation and a traineeship to H.W.T. from the National Aeronautics and Space Administration.
(3) R. A. Moss and C. E. Powell, *J. Org. Chem.*, **40,** 1213 (1975).
(4) See ref 3–10 in ref 3.
(5) E. Müller in E. Müller, "Methoden der Organische Chemie" (Houben-Weyl), Vol. IX, Part 2, Georg Thieme Verlag, Stuttgart, 1967, pp 5–62.
(6) G. L. Lockemann, *Chem. Ber.*, **43,** 2223 (1910).
(7) E. G. Laws and N. N. Sidgwick, *J. Chem. Soc.*, 2085 (1911).
(8) L. A. Carpino, *Acc. Chem. Res.*, **6,** 191 (1973).
(9) H. E. Baumgarten, P. L. Creger, and R. L. Zey, *J. Am. Chem. Soc.*, **82,** 3977 (1960).
(10) M. C. Chaco, P. R. Stapp, J. A. Ross, and N. Rabjohn, *J. Org. Chem.*, **27,** 3371 (1962).
(11) M. C. Chaco and N. Rabjohn, *J. Org. Chem.*, **27,** 2765 (1962).
(12) In several earlier attempts we encountered some difficulty in selectively hydrolyzing the carboethoxy group in the carboethoxy analogue of **10.**
(13) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94,** 7159 (1972).
(14) H. E. Baumgarten, *J. Am. Chem. Soc.*, **84,** 4975 (1962).
(15) F. D. Greene, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.*, **34,** 2254 (1969).
(16) P. Schestakov, *Z. Angew. Chem.*, **16,** 1061 (1903); cf. J. S. Chalsty and S. S. Israelstam, *J. S. Afr. Chem. Inst.*, **9,** 37 (1956), for other references.
(17) D. W. Lum and I. L. Mador, U.S. Patent 2 917 545; *Chem. Abstr.*, **54,** 6549e (1960); cf. ref 5, p 34.
(18) A. Stempel, J. Zelauskas, and J. A. Aeschlimann, *J. Org. Chem.*, **20,** 412 (1955).
(19) H. Gustafsson and U. Ragnarsson, *Acta Pharm. Suec.*, **11,** 493 (1974); H. Gustafson, *Acta Chem. Scand., Ser. B,* **29,** 93 (1975).
(20) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Com-

pounds", Vol. I., W. A. Benjamin, New York, N.Y., 1965, p 274.
(21) I. Weil and J. C. Morris, *J. Am. Chem. Soc.*, **71**, 1664 (1949).
(22) K. R. Kopecky and T. Gillan, *Can. J. Chem.*, **47**, 2371 (1969).
(23) Reaction of 95.6% optically pure (*S*)-(−)-1-phenylethylamine with hydroxylamine-*O*-sulfonic acid gave 8% of pure (*S*)-(−)-1-phenylethylhydrazine, $[\alpha]^{25}D$ −29.0° (*c* 0.784, benzene).[22] From these data Moss and Powell[3] have calculated the specific rotation of the *optically pure* hydrazine to be $[\alpha]^{25}D$ −30.3° (c 0.784, benzene) and have used the result to estimate not only the optical purity of their own hydrazine but also the stereoselectivity of their method of preparation. We believe that an accurate value for the specific rotation of (+)-**19a** cannot be based on the earlier data[22] because the optical purity of the (−)-**19a** would depend upon the efficacy of the separation of a small amount of (−)-**19a** from a large amount of unreacted **13a** by vacuum distillation through a 6-in. Vigreux column.
(24) J. S. Chalsty and S. S. Israelstam, *J. S. Afr. Chem. Inst.*, **9**, 33 (1956).
(25) L. A. Carpino, *J. Am. Chem. Soc.*, **79**, 4427 (1957).
(26) Other examples may be found in the Ph.D. Theses of H. W. Taylor (1971) and D. R. Hwang (1974), University of Nebraska-Lincoln.
(27) In a few experiments 5% Pt/C for 10 g of substrate was substituted for Pd/C. In these instances the Pt/C catalyst was wet with about 3 ml of water before being added to the hydrogenation vessel.
(28) P. Adams, U.S. Patent 3 161 676 [*Chem. Abstr.*, **62**, 9023*h* (1965)].
(29) Calculations based on density and rotation values cited by A. Ault, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 932.
(30) A. P. Terent'ev, R. A. Gracheva, and V. T. Bezruchko, *J. Org. Chem. USSR* (*Engl. Transl.*), **5**, 1048 (1969).
(31) Available commercially or by preparation from *tert*-butyl alcohol (which gives a better product than that from KNCO): L. I. Smith and O. H. Emerson, "Organic Syntheses", Collect Vol. III, Wiley, New York, N.Y., 1955, p 15.
(32) M. Brander, *Recl. Trav. Chim. Pays-Bas*, **37**, 67 (1917).
(33) T. L. Davis and K. C. Blanchard, *J. Am. Chem. Soc.*, **45**, 1816 (1923); "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 453.
(34) M. J. Mintz and C. Walling, "Organic Syntheses", Collect Vol. V, Wiley, New York, N.Y., 1973, p 184.
(35) R. Ohme, East German Patent 64 463 (1968); *Chem. Abstr.*, **71**, 49335t (1968).
(36) L. A. Carpino, *J. Am. Chem. Soc.*, **79**, 4427 (1957).
(37) B. Singh, H. Krall, and R. Sahasrabudhey, *J. Indian Chem. Soc.*, **23**, 373 (1946).
(38) C. G. Overberger and A. V. Di Giulio, *J. Am. Chem. Soc.*, **80**, 6562 (1958).
(39) O. Westphal, *Chem. Ber.*, **74B**, 759 (1941).

Reactions of *N*-Sulfinylarylamines with Carbonyl Compounds and a Nitrile in the Presence of Copper

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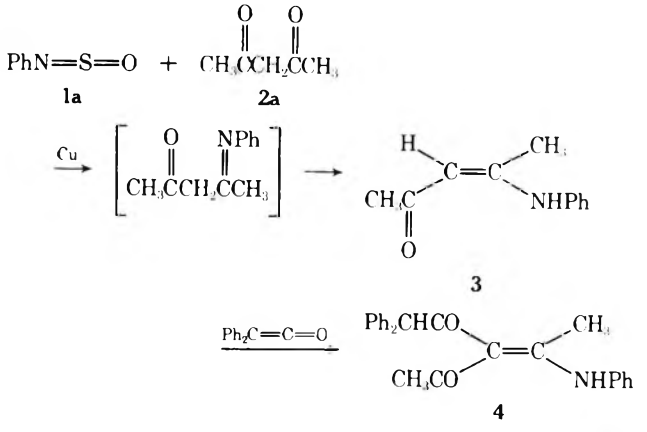
The copper-catalyzed reactions of *N*-sulfinylarylamines **1a,b** with activated carbonyl **2a–d,f** and nitrile compounds **12** were studied. Each carbonyl compound gave amino ketones **3, 5, 8, 9,** and **11** and sulfides **6** and **7.** Phenylacetonitrile (**12**) yielded *trans*-α,β-dicyanostilbene (**13**). The formation mechanism of these products was discussed.

Reactions of *N*-sulfinyl-*p*-toluenesulfonamides with various aldehydes and ketones can lead to *N*-sulfonylimines,[1,2] oxathioles,[3,4] and α-sulfonamido ketones.[5] In this paper we report on the reactions of the less reactive *N*-sulfinylanilines and the effect of copper[6] in these reactions.

A mixture of *N*-sulfinylaniline (**1a**), acetylacetone (**2a**), and copper shavings in mesitylene was refluxed for 6 h to give 4-anilino-3-penten-2-one (**3**)[10] in 46% yield; gas was evolved. Without copper, however, only starting **1a** and **2a** were recovered. Thus, copper catalyzes the formation of the enamino ketone **3** from **1a** and **2a.**

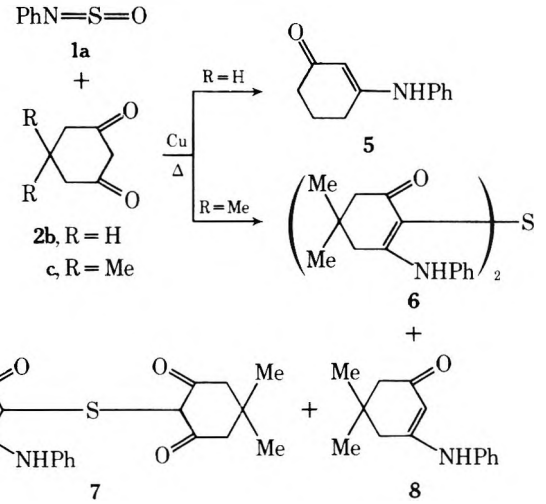
Scheme I



The reaction of **3** with diphenylketene gave **4,** analogous to the products from enamino ketones and isothiocyanates.[7]

The reaction between **1a** and 1,3-cyclohexanedione (**2b**) similarly took place to provide 3-anilino-2-cyclohexen-1-one (**5**) in quantitative yield.

Scheme II

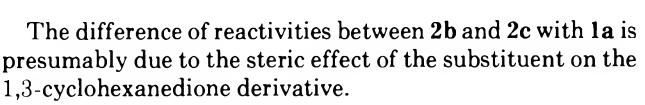


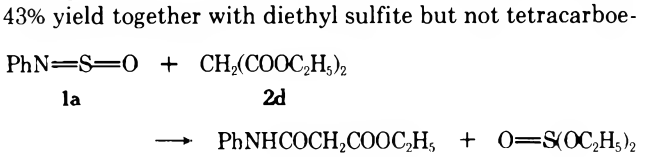
In contrast to **2b,** use of 5,5-dimethyl-1,3-cyclohexanedione (**2c**) gave rise to the formation of unexpected sulfide **6** in 67% yield along with two minor products, the sulfide **7** (16%) and the anilino ketone **8** (12%).

In a separate reaction, treatment of **8** with sulfur under the same conditions gave the sulfide **6** in good yield. Similar treatment of an equimolar mixture of **8** and **2c** with sulfur afforded a mixture of **6** (40%) and the unsymmetrical sulfide **7** (43%). These results suggest that the sulfides, **6** and **7,** were formed in the reaction by oxidative coupling between **8** and either a second molecule of **8** or **2c** in the presence of elemental sulfur. The latter could be produced by reduction of sulfur dioxide or sulfur monoxide on copper in the reaction system.

The difference of reactivities between **2b** and **2c** with **1a** is presumably due to the steric effect of the substituent on the 1,3-cyclohexanedione derivative.

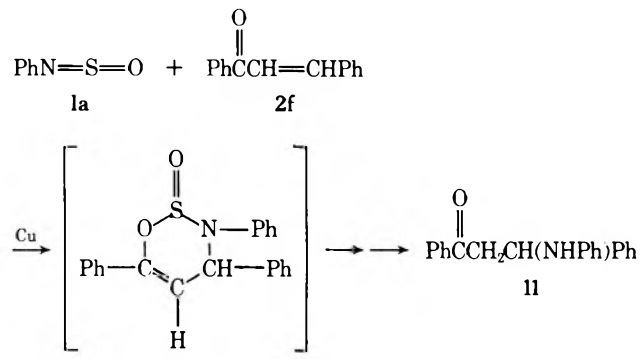
A similar reaction of diethyl malonate (**2d**) with **1a** in refluxing xylene for 6 h gave malonanilic acid ethyl ester (**9**) in 43% yield together with diethyl sulfite but not tetracarboethoxyethylene as reported in the reaction with *N*-sulfinyl-*p*-toluenesulfonamide.[3] A reaction of *N*-sulfinylaniline (**1a**) with 2,5-hexanedione (**2e**) under similar conditions produced only 1-phenyl-2,5-dimethylpyrrole (**10**) in 65% yield. The



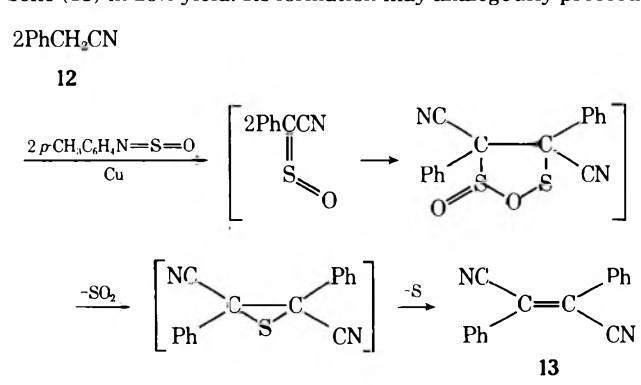


formation of **10** is explicable by intramolecular dehydration of intermediate 2-anilino-2-hexen-5-one corresponding to the enamino ketones as shown above.

With benzalacetophenone as the carbonyl reagent, (β-anilino-β-phenyl)ethyl phenyl ketone (**11**) was obtained in 58% yield. For the formation mechanism of the product **11**, reduction and hydrolysis of the 1,4 cycloadduct of **1a** to **2f** are conceivable, but attempts to isolate the cycloadduct were unsuccessful.



In the reaction using phenylacetonitrile (**12**), in place of 1,3-diketones, as the active methylene compound, copper metal also catalyzed the formation of *trans*-α,β-dicyanostilbene (**13**) in 26% yield. Its formation may analogously proceed via a sequence of sulfinylation of **12** to phenyl cyanosulfine, dimerization, decomposition to 2,3-dicyano-2,3-diphenylthiirane, and successively reductive desulfurization of the thiirane by copper metal or heat, as proposed by previous workers.[3,4,8,9]



However, copper salts such as cuprous or cupric chlorides showed no catalytic effect in any of the above reactions.

Experimental Section

All melting points were determined with a Yanagimoto micromelting apparatus and are uncorrected. The NMR spectra were obtained on a Joellmm 3H-60 spectrometer with tetramethylsilane as an internal standard. The ir spectra were recorded with a Jasco IR-E spectrometer. The mass spectra were taken with a Hitachi RMU-6E spectrometer.

Materials. *N*-Sulfinylaniline (**1a**) and *N*-sulfinyl-*p*-toluidine (**1b**) were prepared from the corresponding amines and thionyl chloride. Copper shavings (Wako Chemicals) were dried in vacuo before use.

General Procedure. In a dried, three-necked, 100-ml, round-bottomed flask, fitted with a reflux condenser and stirrer, were placed *N*-sulfinylamines (0.03 mol), ketones (0.03 mol), copper shavings (3 g) and mesitylene (or *m*-xylene, 30 ml). The reactions were carried out at refluxing temperature under dry N_2.

Reaction of *N*-Sulfinylaniline (1a) with Acetylacetone (2a). A solution containing **1a** (4.20 g, 0.03 mol), **2a** (3.0 g, 0.03 mol), and copper shavings (3 g) in 30 ml of dry mesitylene was allowed to stir under reflux for 6 h. The organic layer was separated and concentrated in vacuo. The residue was chromatographed on silica gel using hexane as eluent to give 2.40 g (46%) of **4-anilino-3-penten-2-one (3)**, which was recrystallized from benzene–hexane affording a pure sample: mp 49–51 °C (lit.[10] mp 47–48 °C); ir (Nujol) 1590 (C=O) and 1560 cm^{-1} (C=C); NMR (C_6D_6) δ 1.55 (s, 3 H, CH_3C=C), 2.05 (s, 3 H, $COCH_3$), 4.95 (s, 1 H, C=CH), 6.50–7.15 (m, 5 H, phenyl protons), and 12.90–13.10 [broad, 1 H, PhN**H**C=CCOCH$_3$ (cis)].

Reaction of 3 with Diphenylketene. Diphenylketene (0.58 g, 3 mmol) dissolved in 5 ml of dry benzene was added dropwise to a stirred solution of **3** (0.53 g, 3 mmol) in 10 ml of benzene. The reaction took place immediately to give 1.10 g of white crystals. The crude white crystals were recrystallized from methylene chloride–benzene to give pure **1,1-diphenyl-3-acetyl-4-anilino-3-penten-2-one (4)**: mp 174–176 °C; ir (Nujol) 1645 (C=O), 1580 (C=O), and 1545 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.70–2.05 [broad, 3 H, **CH**$_3$C=CCOCHPh$_2$ (cis)], 2.10 (s, 3 H, $COCH_3$), 5.50 (s, 1 H, methine proton), 6.95–7.55 (m, 15 H, phenyl protons), and 18.50–18.75 [broad, 1 H, PhN**H**C=CCOCH$_3$ (cis)]; mass spectrum (70 eV) *m/e* 369 (M^+) and 194 $(Ph_2CCO)^+$.

Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.26; H, 6.28; N, 3.79. Found: C, 81.25; H, 6.22; N, 3.58.

Reaction of *N*-Sulfinylaniline (1a) with 1,3-Cyclohexanedione (2b). The reaction was carried out as described above using **1a** (4.2 g, 0.03 mol), **2b** (3.4 g, 0.03 mol), and copper shavings (3 g). After similar treatment, **3-anilino-2-cyclohexen-1-one (5)** was obtained in a yield of 5.55 g (99%): mp 186–186.5 °C (from chloroform–benzene); ir (Nujol) 3240 (NH), 1590 (C=O), and 1570 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.65–2.65 [m, 6 H, $-(CH_2)_3-$], 5.50 (s, 1 H, HC=C), 6.90–7.45 (m, 5 H, phenyl protons), and 8.25–8.35 (broad, 1 H, NH); mass spectrum (70 eV) *m/e* 187 (M^+).

Anal. Calcd for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 77.18; H, 6.92; N, 7.36.

Reaction of *N*-Sulfinylaniline (1a) with 5,5-Dimethyl-1,3-cyclohexanedione (2c). The reaction of **1a** (4.2 g, 0.03 mol) with **2c** (4.2 g, 0.03 mol) in the presence of copper shavings (3 g) was carried out in a similar manner as described above. After similar treatment, the residue was chromatographed on silica gel using hexane–benzene and benzene as eluent. The first fraction gave a mixture of **bis(1-oxo-3-anilino-5,5-dimethyl-2-cyclohexen-2-yl) sulfide (6)** and **(1-oxo-3-anilino-5,5-dimethyl-2-cyclohexen-2-yl) (1,3-dioxo-5,5-dimethylcyclohexan-2-yl) sulfide (7)**. Pure samples of individual **6** (4.61 g, 67%) and **7** (0.90 g, 16%) were isolated by repeated recrystallization of the mixture from benzene–hexane.

6 had mp 265–266 °C; ir (Nujol) 1585 (C=O) and 1550 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.00 (s, 12 H, methyl protons), 2.38 (s, 4 H, C=C**CH**$_2$–) 2.50 (broad s, 4 H, $COCH_2$–), 7.20–7.40 (m, 10 H, phenyl protons), and 11.10–11.25 (broad, 2 H, NH); mass spectrum (70 eV) *m/e* 460 (M^+), 246, and 216.

Anal. Calcd for $C_{28}H_{32}N_2O_2S$: C, 73.02; H, 7.00; N, 6.08. Found: C, 72.85; H, 6.87; N, 6.05.

7 had mp 208–210 °C; ir (Nujol) 1620 (C=O), 1585 (C=O), and 1550 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.00 (s, 6 H, methyl protons), 1.06 (s, 6 H, methyl protons), 2.25–2.50 (broad, 8 H, methylene protons), 7.15–7.35 [m, 6 H, phenyl protons (5 H) and methine proton (1 H)],

and 10.50–10.65 (broad, 1 H, NH); mass spectrum (70 eV) *m/e* 385 (M^+), 246, 215, and 172.

Anal. Calcd for $C_{22}H_{27}NO_3S$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.58; H, 6.69; N, 3.52.

The second fraction afforded 0.82 g (12%) of **3-anilino-5,5-dimethyl-2-cyclohexen-1-one** (**8**), mp 184–185 °C (benzene–hexane), as yellowish needles: ir (Nujol) 3200 (NH), 1590 (C=O), and 1560 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.00 (s, 6 H, methyl protons), 2.05 (s, 2 H, $-CH_2C=C$), 2.35 (s, 2 H, $COCH_2-$), 5.30 (s, 1 H, CH=C<), 7.05–7.40 (m, 5 H, phenyl protons), and 8.70–8.80 (broad, 1 H, NH); mass spectrum (70 eV) *m/e* 215 (M^+).

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.76; H, 7.82; N, 6.28.

Reaction of 3-Anilino-5,5-dimethyl-2-cyclohexen-1-one (8) with Sulfur. A solution of 1.08 g (5 mmol) of **8** and 0.32 g (10 mmol) of sulfur in 15 ml of mesitylene containing copper shavings (1.0 g) was refluxed for 3 h. After the reaction mixture was allowed to stand at ambient temperature overnight, the resulting solid was filtered and recrystallized from benzene to give 0.85 g (74%) of **bis(1-oxo-3-anilino-5,5-dimethyl-2-cyclohexen-2-yl) sulfide,** mp 265–266 °C, which was consistent with **6** obtained in the above reaction.

Reaction of a Mixture of 3-Anilino-5,5-dimethyl-2-cyclohexen-1-one and 5,5-Dimethyl-1,3-cyclohexanedione with Sulfur. The reaction was similarly carried out as described above using **8** (1.08 g, 5 mmol), **2c** (0.70 g, 5 mmol), sulfur (0.64 g, 20 mmol), and copper shavings (1.0 g). After removal of the resulting 0.45 g (40%) of the sulfide **6**, the filtrate was concentrated in vacuo and the residue was chromatographed on silica gel to give 0.82 g (43%) of **(1-oxo-3-anilino-5,5-dimethyl-2-cyclohexen-2-yl)(1,3-dioxo-5,5-dimethylcyclohexan-2-yl) sulfide,** mp 208–210 °C, which was consistent with **7** obtained in the above reaction.

Reaction of *N*-Sulfinylaniline (1a) with Diethyl Malonate (2d). The reaction was carried out at 140 °C for 6 h using the procedure described above with **1a** (4.20 g, 0.03 mol), **2d** (4.80 g, 0.03 mol), and copper shavings (3 g) in *m*-xylene (30 ml). After removal of solvent containing formed diethyl sulfite, of which structure was determined by comparison of the retention time with that of an authentic sample, the residue was similarly treated to give 2.65 g (43%) of **malonanilic acid ethyl ester** (**9**): mp 38–40 °C (lit.[11] mp 38–39 °C); ir (Nujol) 3300 (NH), 1730 (C=O), and 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.85 (t, 3 H, CH_2CH_3), 3.20 (s, 2 H, $COCH_2CO$), 3.85 (q, 2 H, CH_2CH_3), 6.85–7.75 (m, 5 H, phenyl protons), and 9.10–9.30 (broad, 1 H, NH).

Reactions of *N*-Sulfinylaniline (1a) with Ketones 2e,f. The reactions were carried out in a similar manner. After similar workup, **1-phenyl-2,5-dimethylpyrrole** (**10**) and **(β-anilino-β-phenyl)ethyl phenyl ketone** (**11**) were obtained in 65 and 58% yields, respectively.

10 had mp 50–51 °C (lit.[12] mp 49–51 °C); white plates; ir (Nujol) 1590 cm^{-1} (C=C); NMR ($CDCl_3$) δ 2.05 (s, 6 H, methyl protons), 5.90 (s, 2 H, CH=C), and 7.00–7.50 (m, 5 H, phenyl protons); mass spectrum (70 eV) *m/e* 171 (M^+).

11 had mp 171–172 °C; pale yellow needles; ir (Nujol) 3350 (NH) and 1655 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.40 (d, J = 7 Hz, 2 H, $COCH_2-$), 3.85–4.15 (broad, 1 H, NH), 4.98 (t, J = 7 Hz, 1 H, CH_2-**CH**<), and 6.40–7.15 (m, 15 H, phenyl protons); mass spectrum (70 eV) *m/e* 301 (M^+) and 209 (M^+ − NHPh).

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.52; H, 6.14; N, 4.69.

Reaction of *N*-Sulfinyl-*p*-toluidine (1b) with Phenylacetonitrile (12). The reaction was carried out at 140 °C for 6 h using the procedure described above with **1b** (3.06 g, 0.02 ml), **12** (4.68 g, 0.04 mol), and copper shavings (2 g) in 20 ml of *m*-xylene. After similar treatment, the residue was chromatographed on silica gel to give 0.60 g (26%) of ***trans*-α,β-dicyanostilbene** (**13**): mp 161–162 °C (lit.[13] mp 161 °C); ir (Nujol) 2250 cm^{-1} (CN); NMR ($CDCl_3$) δ 7.10–7.95 (m, phenyl protons).

Registry No.—**1a**, 1122-83-4; **1b**, 15795-42-3; **2a**, 123-54-6; **2b**, 504-02-9; **2c**, 126-81-8; **2d**, 105-53-3; **2e**, 110-13-4; **2f**, 94-41-7; **3**, 26567-78-2; **4**, 60224-19-3; **5**, 24706-50-1; **6**, 60224-20-6; **7**, 60224-21-7; **8**, 18940-21-1; **9**, 53341-66-5; **10**, 83-24-9; **11**, 742-43-8; **12**, 140-29-4; **13**, 2450-55-7; copper, 7440-50-8; diphenylketene, 525-06-4.

References and Notes

(1) G. Kresze and R. Albrecht, *Angew. Chem.*, **74**, 781 (1962).
(2) G. Kresze, D. Sommerfeld, and R. Albrecht, *Chem. Ber.*, **98**, 601 (1965).
(3) G. Kresze and W. Wucherpfennig, *Angew. Chem.*, **79**, 109 (1967).
(4) U. Jacobson, T. Kempe, and T. Norin, *J. Org. Chem.*, **39**, 2722 (1974).
(5) T. Minami, Y. Tsumori, K. Yoshida, and T. Agawa, *J. Org. Chem.*, **39**, 3412 (1974).
(6) T. Minami and T. Agawa, *Tetrahedron Lett.*, 4109 (1968).
(7) (a) J. Goerdeler, A. Laqua, and C. Linder, *Chem. Ber.*, **107**, 3518 (1974); (b) Z. B. Behrend, F. C. Meyer, and J. Buchholz, *Justus Liebigs Ann. Chem.*, **314**, 224 (1901); (c) R. Behrend and P. Hesse, *ibid.*, **329**, 341 (1903).
(8) C. J. Ireland and J. S. Pizey, *J. Chem. Soc., Chem. Commun.*, 4 (1972).
(9) M. Ohka, T. Kojitani, S. Yanagida, M. Okahara, and S. Komori, *J. Org. Chem.*, **40**, 3540 (1975).
(10) G. O. Dudek and R. H. Holm, *J. Am. Chem. Soc.*, **83**, 2099 (1961).
(11) F. D. Chattaway and J. M. D. Olmsted, *J. Chem. Soc.*, **97**, 939 (1910).
(12) H. Kofod, L. E. Sutton, and J. Jackson, *J. Chem. Soc.*, 1467 (1952).
(13) D. G. Coe, M. M. Gale, R. P. Linstead, and C. J. Timmons, *J. Chem. Soc.*, 123 (1957).

Intramolecular Diels–Alder Reactions. 12. Competitive [4 + 2] and [2 + 2] Cycloadditions of *N*-(Phenylpropargyl)-*cis*-cinnamamide[1a]

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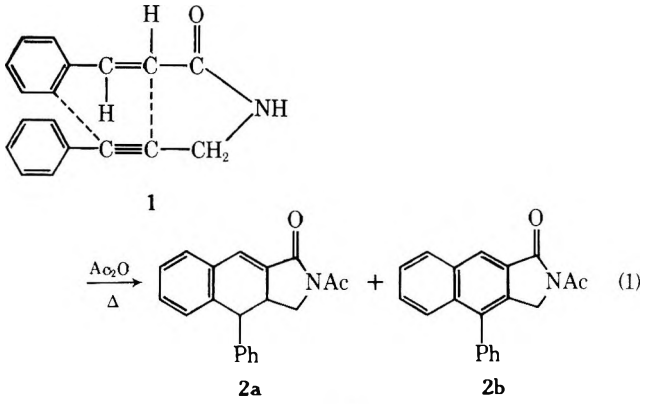
Refluxing *N*-(phenylpropargyl)-*cis*-cinnamamide in Ac_2O gave competitive [4 + 2] and [2 + 2] intramolecular cycloadditions in mode 2 to form (a) a mixture of benz[*f*]isoindole (**2b**) and its dihydro derivative **2a** and (b) substituted 3-pyrrolin-2-one **12** (following spontaneous cycloreversion), respectively. Structural studies on **12** and its bromo and dideuterio derivatives are reported. Modal selectivity in the cyclizations is interpreted in terms of relative frontier molecular orbital energy levels, while regiospecificity is interpreted in terms of stereochemical relationships. Action of the C≡C in an electron acceptor role in these cycloadditions is discussed.

In a preceding paper in this series[2] we described the syntheses of the nine possible unsaturated amides of the type $Ph(C_2)CH_2NHC(=O)(C_2)'Ph$, where (C_2) and $(C_2)'$ are variously *cis*-CH=CH–, *trans*-CH=CH–, and –C≡C– units. Six of these amides were investigated for possible intramolecular cyclization in refluxing acetic anhydride. Of these six, one [$(C_2) = (C_2)' =$ *trans*-CH=CH–] failed to undergo cyclization, while the other five underwent [4 + 2] cycloadditions either in mode 1 ("normal" Diels–Alder reaction) or mode 2 "abnormal" Diels–Alder reaction), or in a combination of both modes.[2] In particular, *N*-(phenylpropargyl)-*trans*-cinnamamide (**1**) cyclized in mode 2 to yield an unresolved mixture (**2**) (ca. 4:1) of *N*-acetyl lactams **2a** and **2b** in 75% yield (eq 1). The present paper concerns the cyclization of a seventh one of these am-

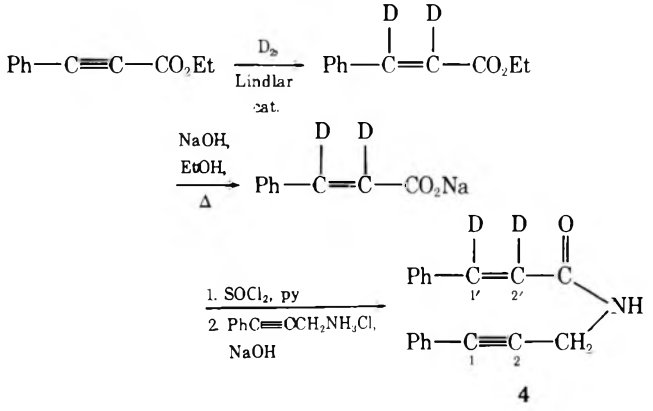


1

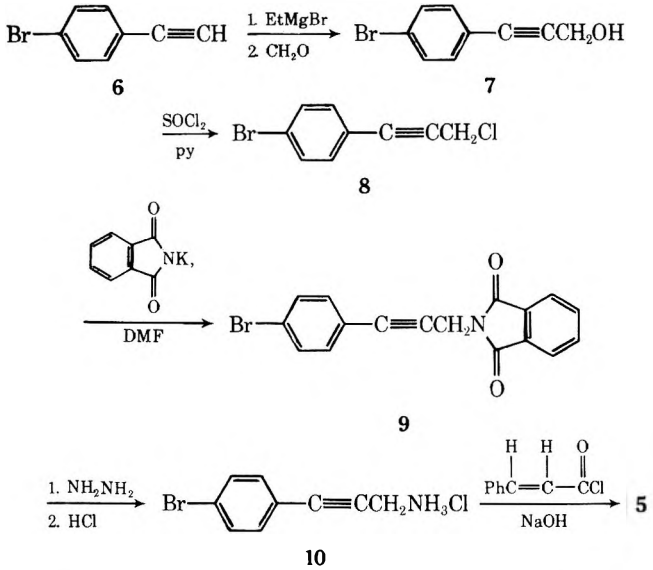
2a 2b

ides, vis., *N*-(phenylpropargyl)-*cis*-cinnamamide (**3**), as well as its dideuterio derivative **4** and its *p*-bromo derivative **5**. Synthetic routes to **4** and **5** are shown in Schemes I and II. The overall yield of intermediate amine hydrochloride **10** from *p*-bromophenylacetylene (**6**) is 45%.

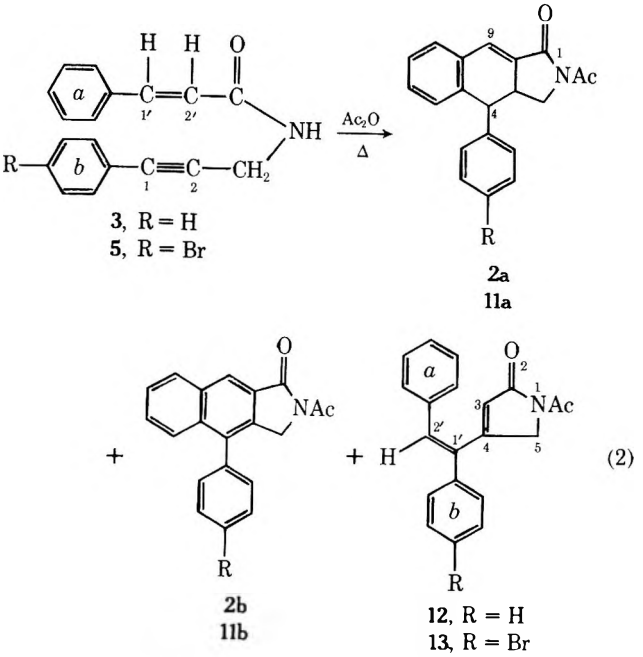
Scheme I



Scheme II



Cyclization of **3** or **5** in refluxing acetic anhydride yields two crystalline products (eq 2). For **3**, these are the same unresolved mixture **2** (mp 270 °C, 23%, isolated from concentrated solution) as formed from **1**, plus a new *N*-acetyl lactam **12** ($C_{20}H_{17}NO_2$, mp 132 °C, 37%, obtained on evaporation of the mother liquor from crystallization of **2**). For **5**, they are the mixture **11** (of **11a** and **11b**, mp 286 °C, 27%, isolated as for **2**) and the *N*-acetyl lactam **13** (mp 113 °C, 28%, isolated as for **12**). Compounds **12** and **13** were assigned the same carbon skeletal structures on the basis of closely similar ^{1}H NMR



3, R = H
5, R = Br

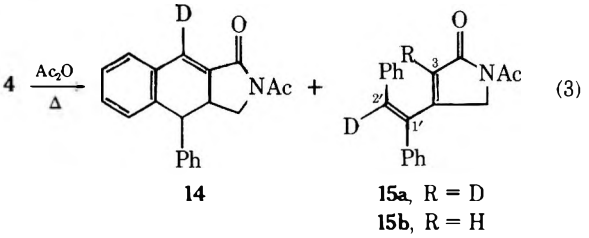
2a
11a

2b
11b

12, R = H
13, R = Br

spectra. The only significant difference between these spectra was the occurrence of a four-proton A_2B_2 multiplet centered at δ 7.38 for **13**, in place of a five-proton singlet for a phenyl group at δ 7.34 for **12**. Analogously, the ^{1}H NMR spectral patterns of **2** and **11** were very similar to one another, though markedly different from those of **12** and **13**. The composition of **11**, as a mixture of **11a** and **11b** (10–15% of the latter), was based on ^{1}H NMR integrations and the earlier structural studies on **2**.[2]

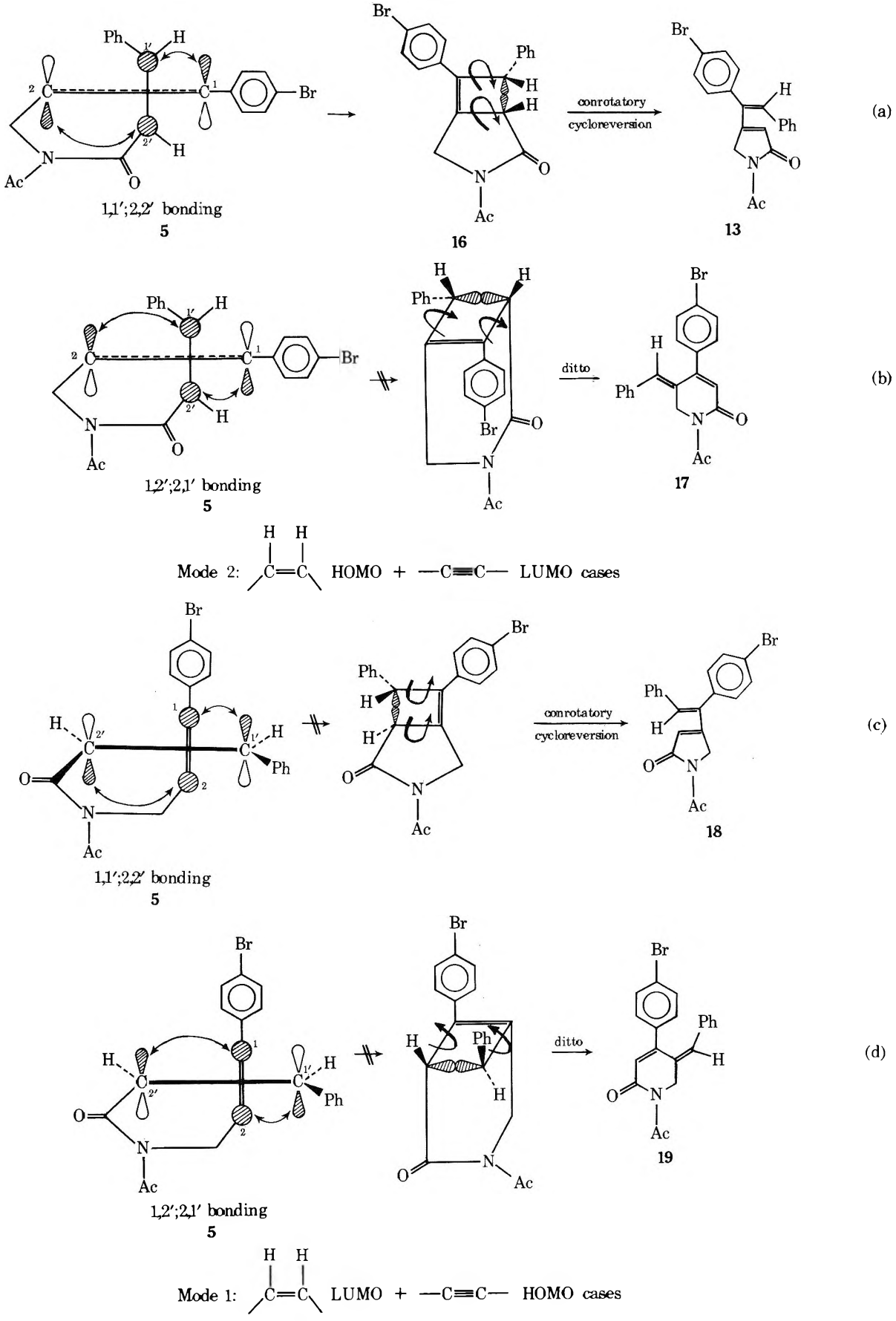
Assignment of the structure of (*Z*)-1-acetyl-4-(1,2-diphenyl)vinyl-3-pyrrolin-2-one to **12** is consistent with the following observations made on this substance. Ozonolysis produces benzaldehyde. The infrared spectrum in $CHCl_3$ shows imide bands at 1730 and 1700 cm^{-1}, while in KBr the spectrum has absorptions at 845 (trisubstituted alkene), 755, and 695 cm^{-1} (5 vicinal aromatic H).[3] The ^{1}H NMR spectrum consists of four singlets which correlate with the presence of two different phenyl groups, H-2′, and Ac, respectively, a triplet at δ 6.00 (J_{allyl} = 1.5 Hz) for H-3, and a doublet at δ 4.32 for two H at C-5. The mass spectrum contains prominent peaks at *m/e* 218 (100%) and 202 (29%) that correspond to the respective losses of AcN=C=O and [CH_2N(Ac)=C=O + 2 H] from the molecular ion. An ion fragment at *m/e* 178 for $C_{14}H_{10}^+$ implies that the phenyl groups are located on adjacent carbon atoms. Indicative of a more extensive conjugated system in **12** than in its open-chain precursor **3** is a bathochromic shift of the longest wavelength maximum ($\Delta\lambda$ = 60 nm) in the ultraviolet absorption spectrum after cyclization. Corroborating this change is an increase in the ease of polarographic reduction ($\Delta E_{1/2}$ = 0.45 V vs. SCE) after cyclization. A definitive structural assignment for **12**, however, was obtained only from an x-ray crystallographic study of **13**,[4] which established the locations of the double bonds, clarified the stereochemistries at C-1′ and C-2′, and correlated rings a and b in the open-chain amides **3** and **5** with those in cyclization products **12** and **13**.



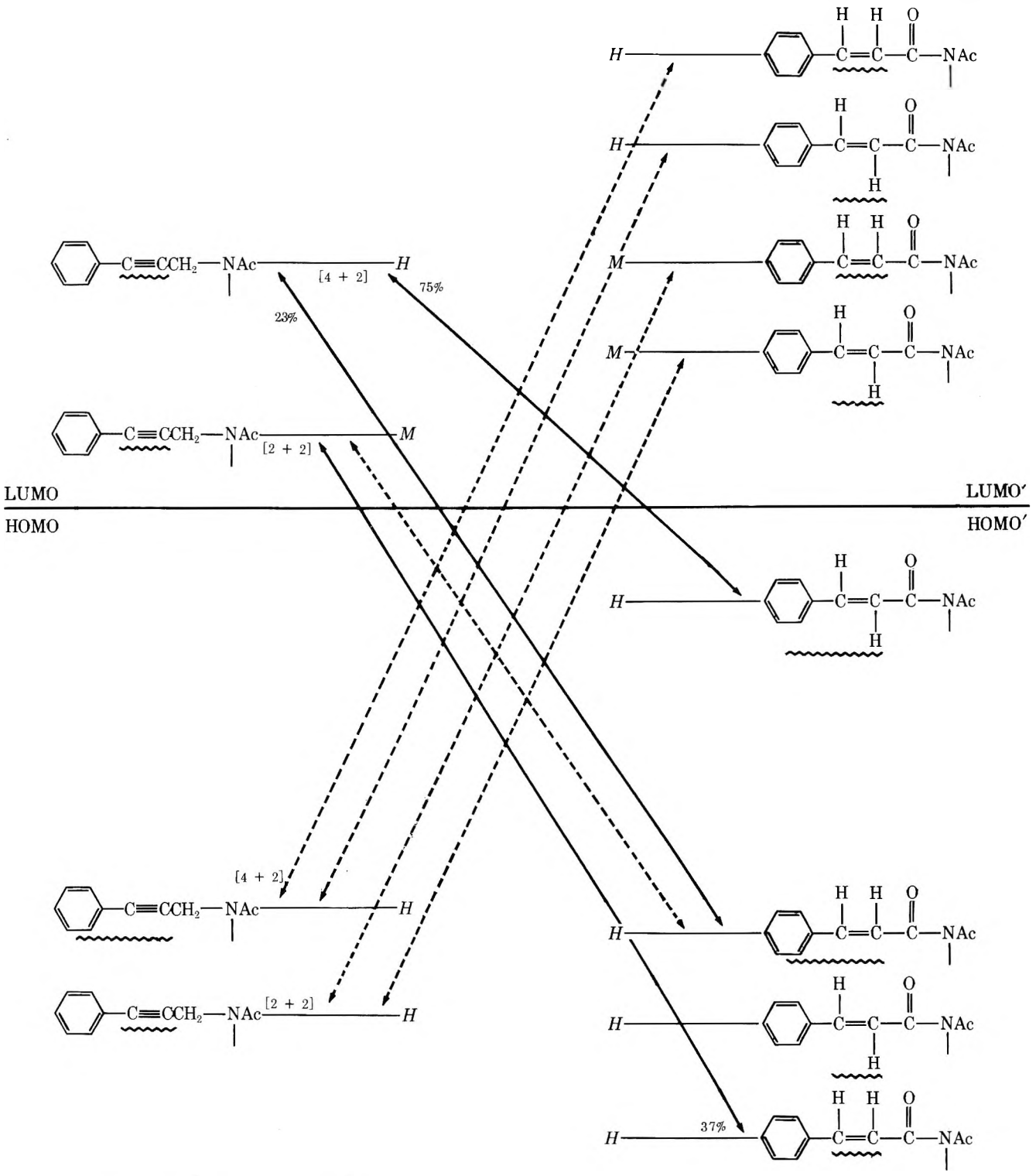
14 **15a**, R = D
15b, R = H

To help elucidate mechanistic details of the molecular rearrangement involved in the transformation **3** → **12**, deuterated compound **4** (96% isotopically pure) was refluxed in acetic anhydride in the previous manner to yield **14** (18%, mp 270 °C, ostensibly free of any aromatized component, as based on ^{1}H NMR and mass spectra), plus a mixture (32%) of dideuterio compound **15a** and monodeuterio compound **15b** (ratio of 1.22:1) (eq 3). On the basis of the cyclizations of **4** and **5** it is

Scheme III



Scheme IV. LUMO Control in Mode 2 [4 + 2] and [2 + 2] Cycloadditions of *N*-(Phenylpropargyl)cinnamamides[a]



[a] *H* and *M* denote Hückel-type and Möbius-type molecular orbital energy levels, respectively.[11]

apparent that in the transformation of **3** into **12** C-1 becomes C-1′, C-2 becomes C-4, C-1′ becomes C-2′, and C-2′ becomes C-3. Hence, during this transformation the bond between C-1′ and C-2′ is broken, while new bonds between C-1 and C-1′ and between C-2 and C-2′ are formed. As noted in the following paragraphs, these are the characteristics which are expected for an intramolecular, thermally induced, concerted [$_\pi 2_s + {}_\pi 2_a$] cycloaddition reaction to form a strained cyclobutene intermediate, plus the thermally induced, concerted conrotatory cycloreversion of the intermediate ([$_\sigma 2_a + {}_\pi 2_s$] or [$_\sigma 2_s + {}_\pi 2_a$]) to a butadiene structure.

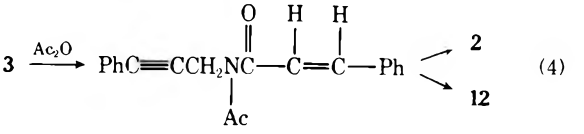
A priori, there are four distinguishable ways in which [$_\pi 2_s + {}_\pi 2_a$] cycloaddition of **3**, **4**, or **5** can be envisioned (see Scheme III). In the formality of Scheme III the (C_2) and $(C_2)'$ units of **5** are shown in the orthogonal conformation for which thermal cycloaddition is symmetry allowed.[5] In case a the plane of the vinylene unit is taken to be that of the paper and the (C_2) (i.e., C≡C) linear unit stretches across the double bond. This geometry allows the (C_2) and $(C_2)'$ units to approach closely in a sterically least hindered manner. Consistent with the studies on the deuterated amide **4**, new bonds form between the pair C-1 and C-1′ and the pair C-2 and C-2′. The process involves suprafacial addition to the cis double bond and antarafacial addition to the triple bond to form the hypothetical inter-

mediate **16** (a fused 4,5-bicyclic ring system with a bridgehead carbon–carbon double bond). Strained intermediate **16** then undergoes conrotatory cycloreversion of the four-membered ring to yield the observed product **13**. Suprafacial addition to the $(C_2)'$ unit and antarafacial addition to the (C_2) unit implies an interaction between HOMO′, the highest occupied molecular orbital energy level of the $(C_2)'$ unit, and LUMO, the lowest unoccupied molecular orbital energy level of the (C_2) unit. In other words, the $(C_2)'$ unit is serving as an electron donor and the (C_2) unit is serving as an electron acceptor. We shall designate this manner of [2 + 2] cycloaddition as mode 2, where mode 1 will involve interaction between LUMO′ and HOMO, i.e., with $(C_2)'$ in the role of electron acceptor and (C_2) in that of electron donor. It might be noted that **3** undergoes both [4 + 2] and [2 + 2] cycloadditions in mode 2, i.e., where the C≡C unit is an electron acceptor.[2,6]

Case b (Scheme III) illustrates an alternative possibility for cyclization in mode 2, but with a change in regiospecificity. Cases c and d represent mode 1 cyclization, with the same two alternatives for regiospecificity. In mode 1 the C=C would be oriented edgewise to the linear C≡C, with, perhaps, some increased steric crowding of substituents on these units in the transition state. Addition would occur suprafacially to (C_2) and antarafacially to $(C_2)'$.

No evidence for the formation of compounds **17–19** was found. Hence, it is clear that intramolecular [2 + 2] cycloaddition of **3** occurs with both modal selectivity and regiospecificity. As indicated previously,[2] the same considerations apply to the intramolecular [4 + 2] cycloadditions of **1** and **3**. Subsequent paragraphs will be concerned with the rationalizations of these observations.

Since conversion of *cis*-cinnamic acid (and its derivatives) into *trans*-cinnamic acid (and derivatives) is a well-known isomerization, one might anticipate that the [4 + 2] cycloaddition of **3** occurs by means of the pathway **3** → **1** (or *N*-acetyl-**1**) → **2**. Experimental evidence, however, indicates that isomerization of **3** prior to Diels–Alder cycloaddition is unlikely. As noted previously,[2] spectral examination of the reaction mixture of **3** in acetic anhydride showed no detectable concentration of a trans intermediate after 1 h of refluxing. Likewise, neither *cis*-cinnamylamine[2] nor phenylpropargyl *cis*-cinnamate[7] is isomerized on extended refluxing in acetic anhydride. Most likely the routes from **3** to **2** and to **12** involve competitive cyclizations of the acetylated intermediate **20**, as



(4)

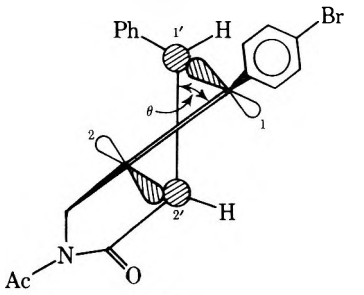
20

indicated in eq 4. We assume that this pathway is the correct one in the arguments which follow.

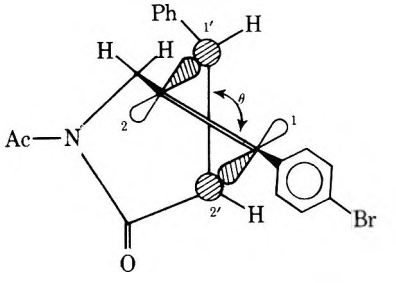
We ascribe the preference for mode 2 cyclization of both **1** and **3** (as their *N*-acetyl derivatives) primarily to a combination of the high electron affinity and the low electron-donating capacity of the C≡C bond.[2,8,9] This leads to LUMO control of the cyclizations as illustrated in the hypothetical MO energy level diagram (Scheme IV). In this scheme[10] cycloadditions which are observed experimentally are represented by solid double-headed arrows. Those which are theoretically possible, but are not observed experimentally, are represented by broken arrows. Yields observed are also shown. Scheme IV is constructed on the basis of the following postulated relationships. (1) Interaction between addendum units increases as the vertical separation of energy levels decreases, and vice versa. (2) For either end of the open-chain starting amide, a 4-π-electronic system is a better electron donor (higher MO energy level) than is the corresponding 2-π system. (3) Of $(C_2)'$ units the trans isomer is both a stronger electron donor and an electron acceptor than is its cis counterpart. (4) For [4 + 2] thermal cycloadditions, only Hückel-type MO energy levels are considered for the addenda. Contrariwise, for [2 + 2] thermal cycloadditions a Möbius-type unoccupied MO energy level (i.e., a lower energy level than corresponds to the Hückel one)[11] is used for the (C_2) or $(C_2)'$ unit which adds antarafacially.[12] (5) Mode 2 selectivity is shown by arrows which connect the LUMO quadrant to the HOMO′ quadrant (negative slope), while mode 1 selectivity connects LUMO′ and HOMO quadrants (positive slope).

Scheme V depicts a stereochemical rationale for the regioselectivity of [2 + 2] cycloaddition of **3** by means of 1,1′;2,2′

Scheme V



a
1,1′;2,2′ bonding

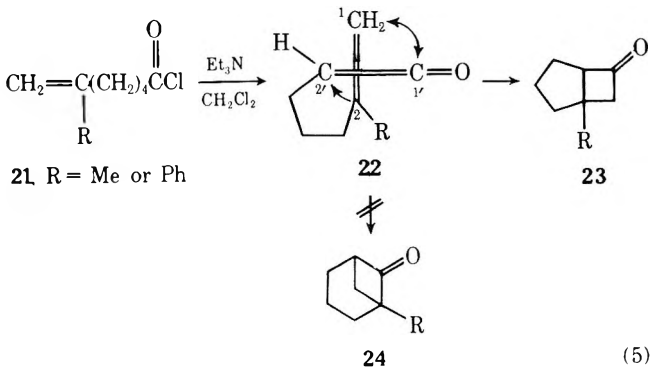


b
1,2′;2,1′ bonding

bonding, in preference to 1,2′;2,1′ bonding. In order to attain a crossed conformation of the C=C and C≡C bonds the molecule must coil with the aryl ends passing over one another. In the formal representations of Scheme III, the dihedral angle (θ) shown for the C_1–C_2 and $C_{1'}$–$C_{2'}$ bonds is 90°. However, as shown in Scheme V, maximum p-lobe overlap in the transition state will occur for $\theta \simeq 45°$ or 135°. The former conformation (case a) is easily attained without undue strain in bond angles elsewhere in the molecule. The latter conformation (case b), on the other hand, will be more difficult to attain because of the requisite stretching of bond lengths and/or alteration of bond angles in the –C–N–C– system. Only if this system contained a longer chain of atoms would one expect case b to offer energetic competition or preference to case a.

It might be noted that a precedent exists for the same regiospecificity in an analogous N-free system. Thus, Baldwin and Page[13] reported the conversion of 6-substituted 6-heptenoyl chlorides **21** into bicyclo[3.2.0]heptanones **23** (rather than into bicyclo[3.1.1]heptanones **24**), presumably via the intermediate unsaturated ketene **22** (eq 5). It is apparent that the symmetry relationships between the crossed C=C units in **22** are similar to those between the crossed C=C and C≡C units in **3**, but the mode of cyclization of **22** cannot be ascertained from the product formed.

Under simplistic conditions one would expect Scheme IV to reflect approximately the relative yields of products from competitive [4 + 2] and [2 + 2] cycloaddition processes. Ob-



(5)

servation of exclusive [4 + 2] cyclization from **1** is consistent with a higher HOMO′ for the $(C_2)'$–C=C_{Ar} unit than for the $(C_2)'$ unit in the substrate. Inclusion of the Möbius-type LUMO energy level for the yne (C_2) unit in the scheme permits a rationalization for the larger yield of **12** (via [2 + 2] cycloaddition) than of **2** ([4 + 2] adduct) from amide **3**.

Experimental Section[14]

***p*-Bromophenylpropargyl Alcohol (7).** To a stirred solution of ethylmagnesium bromide (prepared from 4.5 g of Mg and 15 ml of EtBr) in 120 ml of ether at room temperature in an atmosphere of nitrogen was added (all at once) a solution of 30 g of *p*-bromophenylacetylene[15] (**6**) [ir ($CHCl_3$) 3300, 2120, 830 cm^{-1}; NMR ($CDCl_3$) δ 7.32 (center of A_2B_2 m, J_{AB} = 8.5 Hz, 4 aromatic H) and 3.07 (s, 1 H, C≡CH)]. After evolution of ethane ceased (2.5 h), a stream of anhydrous formaldehyde (from thermal depolymerization of paraformaldehyde) in nitrogen carrier gas was introduced until a test for residual Grignard reagent[16] was negative. The mixture was treated with ice and then with excess 10% H_2SO_4 and extracted with ether. Evaporation of the dried (K_2CO_3) organic layer and sublimation of the residue at 70 °C (0.7 mm) gave 23.6 g (67%) of needles: mp 80.5–81.5 °C; ir ($CHCl_3$) 3630, 3430 (OH), 2240 cm^{-1} (w, C≡C); NMR ($CDCl_3$) δ 7.33 (center of A_2B_2 m, J_{AB} = 8.5 Hz, 4 aromatic H), 4.47 (s, 2 H, CH_2OH), 2.37 (broad, 1 H, OH).

Anal. Calcd for C_9H_7BrO: C, 51.21; H, 3.34; Br, 37.86. Found: C, 51.61; H, 3.02; Br, 37.89.

***p*-Bromophenylpropargyl Chloride (8).** The conversion of **7** into **8** followed the procedure used to prepare phenylpropargyl chloride.[17] The product was obtained as a crude solid (86%), converted to plates on evaporative distillation at 65 °C (0.7 mm): mp 41–42 °C; ir ($CHCl_3$) 2270, 2220 cm^{-1}; NMR ($CDCl_3$) δ 7.31 (center of A_2B_2 m, J_{AB} = 8.5 Hz, 4 aromatic H), 4.31 (s, 2 H, CH_2Cl); MS *m/e* (rel intensity)[18a] 232 (12), 230 (44), and 228 (36) (M^+), 195 (97) and 193 (100) (M − Cl), 144 (33, M − [Cl + Br]).

Anal. Calcd for C_9H_6BrCl: C, 47.09; H, 2.63; total halogen (as Cl), 30.90; relative isotopic abundances of molecular ions, 0.32/1.3/1.0. Found: C, 46.92; H, 2.51; total halogen (as Cl), 31.19; relative intensities of molecular ions, 0.33/1.2/1.0.

***N*-(*p*-Bromophenylpropargyl)phthalimide (9).** A mixture of 31.2 g (0.136 mol) of **8**, 28 g (0.15 mol) of potassium phthalimide, and 700 ml of dimethylformamide was stirred at 50 °C for 10 h, cooled, and poured into water. The precipitate was collected by filtration and combined with product from $CHCl_3$ extraction of the filtrate to give 41 g (89%) of **9** (mp 213–217 °C), purified by recrystallization from MeCN and sublimation (160 °C, 0.8 mm) to give prisms: mp 214–215.5 °C; MS *m/e* 339 (100, M^+).

Anal. Calcd for $C_{17}H_{10}BrNO_2$: N, 4.12. Found: N, 3.85.

***p*-Bromophenylpropargylammonium Chloride (10).** A mixture of 31.5 g of imide **9**, 3.14 g of hydrazine (97%), and 1.4 l. of methanol was stirred and refluxed for 2 h. Then 65 ml of concentrated hydrochloric acid was added and refluxing was continued for 30 min longer. The cooled mixture was filtered (to remove phthalhydrazide). The filtrate was concentrated to 30 ml and filtered to collect crude solid **10** (20 g, 87%), obtained as plates from absolute EtOH: mp 255–259 °C dec; NMR (Me_2SO-d_6) δ 7.61 (center of A_2B_2 m, J_{AB} = 8.5 Hz, 4 aromatic H), 4.72 (broad signal, 2 H, CH_2NH_2·HCl, exchanged in D_2O–DCl), 3.92 (broad signal, 2, CH_2N); MS *m/e* (rel intensity)[18b] 210 (97) and 208 (100) (M − [H + HCl]), 130 (58, M − [HCl + Br]).

***N*-(*p*-Bromophenylpropargyl)-*cis*-cinnamamide (5).** Schotten–Baumann reaction between **10** and *cis*-cinnamoyl chloride was conducted in a previously described manner[2] to give crude amide **5** (needles from benzene–petroleum ether, mp 108.5–109.5 °C, 70%), recrystallized fromthe same solvent: mp 110–111 °C; NMR ($CDCl_3$) δ 7.7–7.1 (m, 9 aromatic H), 6.80 (d, J = 12.5 Hz, 1 H, CH=CHCO), 5.98 (d, CH=CHCO) superimposed on 6.2–5.7 (broad signal, 2 H total, NH), 4.24 (d, J = 5.5 Hz, 2 H, CH_2NH); MS *m/e* (rel intensity)[18c] 341 (22) and 339 (24) (M^+), 131 (100, PhCH=CHCO$^+$), 103 (68, PhCH=CH$^+$) 102 (27), 77 (44, Ph^+).

Anal. Calcd for $C_{18}H_{14}BrNO$: C, 63.54; H, 4.15; Br, 23.49; N, 4.12. Found: C, 63.38; H, 4.11; Br, 23.77; N, 4.17.

***N*-(Phenylpropargyl)-α,β-dideuterio-*cis*-cinnamamide (4).** In the manner of Bloomfield and Fuchs[19] ethyl phenylpropiolate was reduced catalytically in the presence of D_2 gas. Hydrolysis of the deuterated ester[2] gave α,β-dideuterio-*cis*-cinnamic acid [NMR (neat) δ 7.7–6.9 (m, aromatic H), 12.32 (s, CO_2H)]. Schotten–Baumann reaction of the acid chloride plus phenylpropargylammonium chloride[2] gave needles of **4**: mp 97–98 °C (from benzene–petroleum ether); ir ($CHCl_3$) 3450 (w), 1660 cm^{-1} (s); NMR ($CDCl_3$) δ 7.8–7.1 (m, aromatic H), 6.1–5.5 (broad, NH), 4.27 (d, J = 5.5 Hz, CH_2NH); MS *m/e* (rel intensity)[18c] 263 (97, M^+), 262 (43), 158 (26, PhC≡CCH_2NHCO^+), 133 (100, PhCD=CDCO$^+$), 115 (25, PhC≡CCH_2^+), 105 (71, PhCD=CD$^+$), 78 (38), 77 (25).

Anal. Calcd for $C_{18}H_{13}D_2NO$: D, 13.33 atom % excess. Found: D, 12.80 atom % excess.

Cyclization of *N*-(Phenylpropargyl)-*cis*-cinnamamide (3). A solution of 0.5 g of amide **3**[2] in 300 ml of Ac_2O was refluxed for 6 h, concentrated (in vacuo) to 50 ml, cooled, and filtered to give 135 mg (23%) of platelets (mp 269–270 °C), identified as Diels–Alder mixture **2** by direct comparison with the product obtained from analogous cyclization of *N*-(phenylpropargyl)-*trans*-cinnamamide.[2]

Evaporation of the filtrate gave a red-brown gum, converted to faintly yellow prisms on crystallization from ethanol (yield 213 mg, 37%, mp 127–128 °C). Recrystallization gave purified **12**: mp 131–132 °C; ir ($CHCl_3$) 1730, 1700 cm^{-1}; ir (KBr) 1730, 1670, 845, 755, 695 cm^{-1}; uv (absolute EtOH) λ_{max} 237 nm (log ϵ 4.25), 310 (4.08); λ_{min} 222 (4.04), 287 (4.04); NMR ($CDCl_3$) δ 7.34 (s, 5 aromatic H), 7.28 (s, 5 aromatic H), 7.02 (s, 1 H, H at C-2′), 6.00 (t, J = 1.5 Hz, 1 H, H at C-3), 4.32 (d, J = 1.5 Hz, 2 H, methylene at C-5), 2.52 (s, 3 H, Ac); MS *m/e* (rel intensity)[18c] 303 (73, M^+), 261 (28, M − CH_2CO), 260 (38, M − Ac), 218 (100, $C_{17}H_{14}^+$ or M − AcNCO, checked by high resolution), 217 (58), 203 (21), 202 (29), 178 (9, $C_{14}H_{10}^+$, checked by high resolution), 43 (26, Ac^+), 188 (metastable, 217 → 202), 157–159 (metastable, 303 → 219, 303 → 218).

Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.07; H, 5.36; N, 4.42.

Refluxing a solution of either **2** or **12** in Ac_2O–AcOD gave no exchange, as based on the NMR spectra.

Cyclization of Bromoamide 5. A solution of 4 g of **5** in 2.4 l. of Ac_2O was refluxed in an atmosphere of N_2 for 6 h. Concentration of the solution to 35 ml gave 1.22 g (27%) of crystalline product **11**: mp 284–286 °C dec; NMR ($CDCl_3$) δ 8.1–6.5 (m, 9 H, aromatic H plus H-9), 4.0–3.0 (m, 4 aliphatic H), 2.55 (s, 3 H, Ac) for **11a**, which contains 10–15% of aromatized compound **11b** as based on singlets at δ 4.70 (methylene) and 2.67 (Ac).

Anal. Calcd for $C_{20}H_{16}BrNO_2$: C, 62.84; H, 4.22; N, 3.67. Found: C, 62.44; H, 4.22; N, 3.93.

Evaporation of the filtrate from **11** gave a black gum which was stirred with 30 ml of ethanol at room temperature. The resultant yellow solution was decanted from insoluble black oily residue and cooled to −10 °C to yield 1.25 g (28%) of yellow, crystalline **13**: mp 112–113 °C; NMR ($CDCl_3$) δ 7.31 (s, aromatic H in ring a) which is superimposed on 7.38 (center of A_2B_2 m, J_{AB} = 8.5 Hz, 9 H total, aromatic H in ring b), 7.05 (s, 1 H, H at C-2′), 6.01 (t, J = 1.8 Hz, 1 H, H at C-3), 4.31 (d, J = 1.8 Hz, 2 H, CH_2NAc), 2.53 (s, 3 H, Ac); MS *m/e* (rel intensity)[18d] 383 (48) and 381 (51) (M^+), 340 (31) and 338 (29) (M − Ac), 298 (36) and 296 (41) (M − AcNCO), 284 (50) and 282 (70) (M − CH_2NAcCO), 217 (100, M − [AcNCO + Br]), 216 (36), 215 (46), 203 (27), 202 (64), 86 ($AcNCOH^+$), 43 (97, Ac^+).

Anal. Calcd for $C_{20}H_{16}BrNO_2$: C, 62.84; H, 4.22; N, 3.67. Found: C, 62.55; H, 4.19; N, 3.27.

Cyclization of Deuterioamide 4. A solution of 2.35 g of **4** in 1.5 l. of Ac_2O was refluxed for 6 h, concentrated to 200 ml, and allowed to stand at room temperature to deposit 0.5 g (18%) of monodeuterolactim **14**: mp 271–272 °C; NMR ($CDCl_3$) δ 7.5–6.6 (m, 9 aromatic H), 4.1–3.0 (m, 4 aliphatic H), 2.60 (s, 3 H, Ac); MS *m/e* (rel intensity)[18d] 304 (100, M^+), 262 (70, M − CH_2CO), 205 (26, M − CH_2NAcCO), 204 (27), 203 (34), 179 (65), 43 (33, Ac^+). From these spectra one can estimate that **14** contains no more than 8% of aromatized product.

Evaporation of the mother liquor from **14** and cooling the residue to −10 °C gave a yellow solid, recrystallized from EtOH to produce 0.9 g (32%) of mixture **15**: mp 127.5–128.5 °C; ir (CS_2) 1730 (vs), 1700

(s), 840 (w), 780 (m), 750 (m), 690 cm^{-1} (s); NMR ($CDCl_3$) δ 7.33 (s, aromatic H), 7.27 (s, aromatic H), 4.30 (s, methylene), 2.52 (s, Ac) for **15a**, plus a weak triplet at 6.0 for the presence of some **15b**; MS *m/e* (rel intensity)[18d] 305 (60, M^+), 304 (29), 263 (26, M − CH_2CO), 262 (38, M − Ac), 220 (100, M − AcNCO), 219 (90), 218 (45), 217 (29), 205 (26, PhCD=CPhC=CH^+), 204 (39), 203 (29), 43 (53, Ac^+).

Anal. Calcd for $C_{20}H_{15}D_2NO_2$: D, 11.77 atom % excess. Found: D, 9.10 atom % excess (i.e., 55% **15a** and 45% **15b**).

Polarography. Polarographic reduction of **3** and **12** in the solvent–electrolyte CH_3CN–Et_4NBr was conducted by Dr. D. R. Olson in the manner previously described.[20] Half-wave reduction potentials found are presented in the following table.

Compd	$-E_{1/2}$[a] in anhydrous medium	$-E_{1/2}'$	$-E_{1/2}$ with 3.8% H_2O added	$-E_{1/2}'$
3	1.98[b]	Poor	1.88	2.43
	2.19[b]	wave		
12	1.53	2.38	1.47	2.44

[a] In volts vs. a saturated calomel electrode. [b] Two half-waves of equal heights.

Ozonolysis of 12. A solution of 0.74 g of **12** in 25 ml of dry CH_2Cl_2 (containing 1% pyridine) was treated with a stream of ozone until the reaction mixture became green. It was then stirred with a mixture of 1.3 g of powdered Zn and 2.5 ml of glacial HOAc for 2 h, filtered, and evaporated. Treatment of the viscous yellow residue with 5 ml of 2,4-dinitrophenylhydrazine reagent[21] gave 0.1 g (15%) of benzaldehyde 2,4-DNP derivative, mp 230–232 °C, identified (after recrystallization) by direct comparison with an authentic sample.

Registry No.—**2a**, 59015-42-8; **2b**, 59015-46-2; **3**, 59015-39-3; **4**, 60224-30-8; **5**, 60224-31-9; **6**, 766-96-1; **7**, 37614-58-7; **8**, 60224-32-0; **9**, 60224-33-1; **10**, 60224-34-2; **11a**, 60224-35-3; **11b**, 60224-36-4; **12**, 60224-37-5; **13**, 54153-66-1; **14**, 60224-38-6; **15a**, 60224-39-7; **15b**, 60224-40-0; potassium phthalimide, 1074-82-4.

References and Notes

(1) (a) This investigation was supported in part by research grant GM 12730 from the National Institutes of General Medical Sciences, U.S. Public Health Service. For part 11 in this series see ref 7. (b) Teaching and Research Assistant, 1969–1973. (c) Research Assistant, 1965–1968.

(2) L. H. Klemm, T. M. McGuire, and K. W. Gopinath, *J. Org. Chem.*, **41**, 2571 (1976). As defined in this paper, mode 1 involves action of the $(C_2)'$ unit of the acid moiety as a "dienophile" and of the $Ph(C_2)$ unit of the amine moiety as a "diene", whereby cyclization occurs into the phenyl ring of the amine moiety. Mode 2 involves action of the (C_2) unit of the amine moiety as a "dienophile" and of the $Ph(C_2)'$ unit of the acid moiety as a "diene" whereby cyclization occurs into the phenyl ring of the acid moiety. In mode 1 the diene system is electron rich and the dienophile is electron deficient, while in mode 2 the diene system is electron deficient and the dienophile is electron rich.

(3) L. H. Bellamy, "The Infra-red Spectra of Complex Molecules", 2d ed, Wiley, New York, N.Y., 1958.

(4) L. H. Weaver, Y. N. Hwang, and B. W. Matthews, *Acta Crystallogr., Sect. B*, **30**, 2775 (1974).

(5) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1971, p 69.

(6) L. H. Klemm and T. M. McGuire, *J. Heterocycl. Chem.*, **9**, 1215 (1972).

(7) L. H. Klemm, V. T. Tran, and D. R. Olson, *J. Heterocycl. Chem.*, **13**, 741 (1976).

(8) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry", McGraw-Hill, New York, N.Y., 1969, p 147.

(9) J. Dale in "Chemistry of Acetylenes", H. G. Viehe, Ed., Marcel Dekker, New York, N.Y., 1969, pp 79–81.

(10) Scheme IV is an extended composite of parts of Schemes II and III from ref 2.

(11) H. E. Zimmerman, *Acc. Chem. Res.*, **4**, 272 (1971).

(12) The frontier MO energy level exhibited by a specific structural unit, e.g., a –C≡C–, varies with the substituents attached to the unit and with the direction in space from whence the addendum unit, e.g., *cis*-CH=CH–, approaches in order to undergo cycloaddition (i.e., in the extent of orbital overlap which is experienced by the interacting addenda). The effect of substituents on frontier MO energy levels has been considered by many authors [e.g., see K. N. Houk, *J. Am. Chem. Soc.*, **95**, 4092 (1973); K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier, and J. K. George, *ibid.*, **95**, 7287 (1973); N. D. Epiotis, *ibid.*, **95**, 5625 (1973)] and was taken into account in the [4 + 2] cycloaddition processes reported in ref 2. The geometric sense associated with the Huckel MO energy levels in Scheme IV assumes an approach of the π systems in parallel planes with endwise overlap of the p orbitals on the terminal atoms of the two systems in the transition state [M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry", McGraw-Hill, New York, N.Y., 1969, pp 319–320]. The geometric sense associated with the Möbius MO energy levels in Scheme IV assumes an approach of the π systems in edge-to-face, perpendicular planes (crossed bonds) with perpendicular overlap of the p orbitals on the terminal atoms in the transition state (see Scheme V). For simplicity we have arbitrarily assigned the geometric variations in MO energy levels exclusively to the unoccupied orbitals, though one can rationalize that there will be geometric variations in both occupied and unoccupied levels. It might be noted that Huckel and Möbius MO energy levels correspond only to two extreme geometric types of transition states. Intermediate geometric types can be visualized, but they may be energetically unfavorable [K. Fukui, "Theory of Orientation and Stereoselection", Springer-Verlag New York, New York, N.Y., 1975, pp 22–33].

(13) S. W. Baldwin and E. H. Page, *J. Chem. Soc., Chem. Commun.*, 1337 (1972); R. H. Bisceglia and C. J. Cheer, *ibid.*, 165 (1973).

(14) Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill., M-H-W Laboratories, Garden City, Mich., and Dr. Susan Rottschaefer of this laboratory. Deuterium analyses were performed by Josef Nemeth, Urbana, Ill. Ultraviolet spectra were determined by means of a Cary Model 15 spectrophotometer; infrared spectra, by means of a Beckman IR-5 or IR-7 instrument; mass spectra, by means of a CEC Model 21-110 instrument at 70 eV; and ^1H NMR spectra, by means of a Varian A-60 or XL-100 instrument with tetramethylsilane as internal standard.

(15) T. L. Jacobs, *Org. React.*, **5**, 50 (1949).

(16) H. Gilman and W. E. Catlin, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 188.

(17) L. H. Klemm, R. A. Klemm, P. S. Santhanam, and D. V. White, *J. Org. Chem.*, **36**, 2169 (1971).

(18) Includes all peaks of relative intensity greater than (a) 10%, (b) 40%, (c) 20%, (d) 25%.

(19) J. J. Bloomfield and R. Fuchs, *J. Org. Chem.*, **26**, 2991 (1961).

(20) L. H. Klemm, D. R. Olson, and D. V. White, *J. Org. Chem.*, **36**, 3740 (1971).

(21) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", 4th ed, Wiley, New York, N.Y., 1960, p 111.

Solvolysis of the Carcinogen *N*-Acetoxy-*N*-(4-stilbenyl)acetamide. Solvent Addition to an Intermediate Quinone Imide Methide[1]

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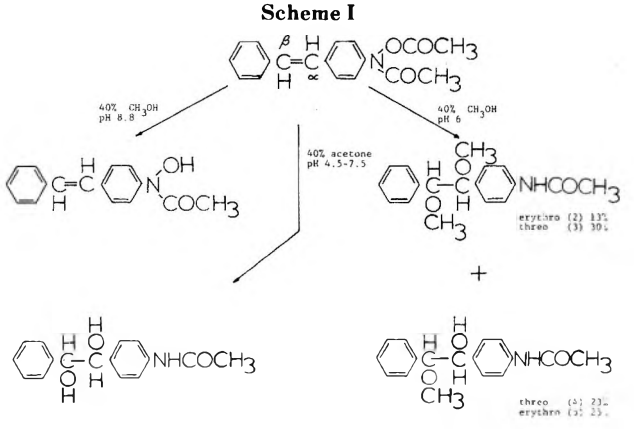
Decomposition of the carcinogen *N*-acetoxy-*N*-(4-stilbenyl)acetamide in 40% acetone yields 1,2-dihydroxy-1-phenyl-2-(4-acetamido)phenylethane as the only major product at pH values up to 7.5. Solvolysis in 40% methanol results in a mixture of isomeric 1,2-dimethoxy-1-phenyl-2-(4-acetamido)phenylethanes and 1-hydroxy-2-methoxy-1-(4-acetamido)phenyl-2-phenylethanes, plus a small amount of 1,2-dihydroxy-1-phenyl-2-(4-acetamido)phenylethane and minor amounts of other, unidentified substances. These products appear to result from nucleophilic attack on the β carbon of an intermediate delocalized nitrenium ion, followed by 1,6 addition of water or methanol to the quinone imide methide formed from the first step. In methanolic medium, increasing pH in the range 6.8–8.8 results in increasing replacement of bibenzyl derivatives by *N*-hydroxy-*N*-(4-stilbenyl)acetamide. These studies suggest a route by which related metabolites are formed in animals treated with *N*-(4-stilbenyl)acetamide, and offer clues to the structures of adducts between nucleic acid bases and *N*-acetoxy-*N*-(4-stilbenzyl)acetamide.

Studies in this laboratory are directed toward an understanding of the reactions of *N*-arylnitrenium ions with nucleic acid bases. Such ions are intermediates in the attack of nucleophiles on protonated *N*-arylhydroxylamines,[2] their esters,[3] or on esters of the corresponding hydroxamic acids.[4] Such molecules appear to be crucial intermediates in the metabolic activation of carcinogenic aromatic amines,[5] and adducts resulting from attack of nitrenium ions on nucleic acids in vivo have already been demonstrated.[6] We are making attempts to understand and predict the course of such reactions by the use of molecular orbital theory,[7] by a dialectical process of experimentally testing predictions from MO calculations, and modifying the calculations according to deviations from the original predictions. We are investigating the products of solvolysis of biologically relevant nitrenium ion precursors, in the expectation that the products obtained thereby will offer clues both to the success of our theoretical treatment and to the nature of complex adducts with nucleosides. In this paper is described the solvolysis of *N*-acetoxy-4-acetamidostilbene (**1**, a local carcinogen[5,8]), a model for active intermediates of the potent systemic carcinogen *N*-(4-stilbenyl)acetamide. Unique features of this particular compound are the facts that (1) it alone, of the four carcinogenic *N*-acetoxy-*N*-arylacetamides so far studied carefully, fails to react with the 8-carbon of guanine in the resulting adduct,[9] and (2) it is the only one of these four compounds which reacts significantly with cytidine.[5]

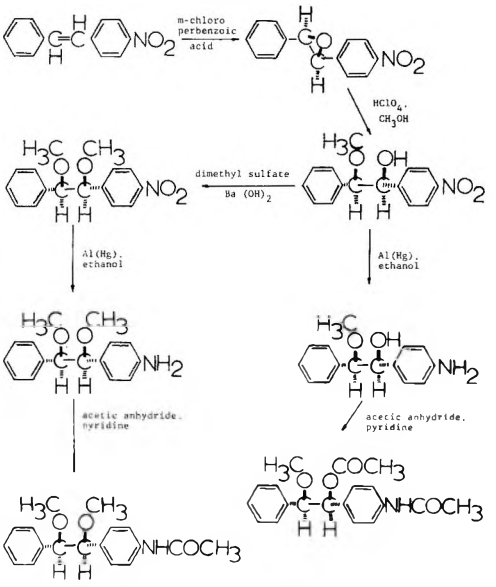
Results

A summary of the solvolysis products is presented in Scheme I. Structure proof and assignment of configuration were obtained by unambiguous synthesis of **2** from nitrostilbene oxide (Scheme II). Treatment of *trans*-4-nitrostilbene with *m*-chloroperbenzoic acid gave the trans epoxide in about

Scheme I



Scheme II



50% yield. Treatment of this epoxide with dilute methanolic perchloric acid gave a single product, as assayed by silica gel TLC. This compound was methylated, then reduced with aluminum amalgam and acetylated, to give a single product identical with **2**, which had already been characterized by NMR and mass spectrometry. The product of methanolysis of the epoxide was also reduced directly, then acetylated, to yield **15**, which was identical with the acetate of **5**. Mass spectral analysis established that the methoxy group was on the β carbon, so that the two syntheses established the stereochemistry of the products as well. Although four isomers could conceivably arise from acid-catalyzed solvolysis of **10** in methanol, ring opening at the α position is deactivated by the *p*-nitro substituent.[10] The structure of **15** confirms the predicted selectivity of ring opening of the epoxide. With the lack of a second product, we must also conclude not only that β-attack occurred, but that it resulted in total inversion of configuration, leading to the final stereochemistry shown. Further reactions did not involve the asymmetric centers.

A phenomenon noted by the Millers is the pH-dependent competitive formation of a β-substituted acetamidostilbene and α,β-disubstituted acetamidobibenzyl.[11] They found that β-methylmercapto-*N*-(4-stilbenylacetamide) was the major

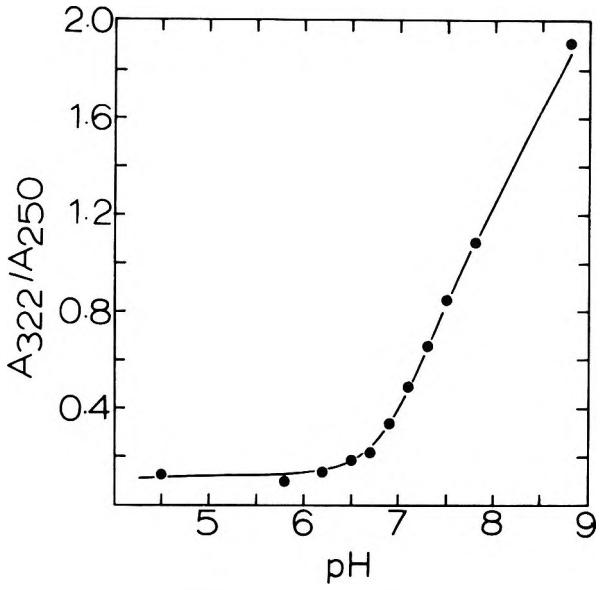


Figure 1. Effect of pH on ratio of stilbene to bibenzyl derivatives upon solvolysis of 1 in 40% methanol.

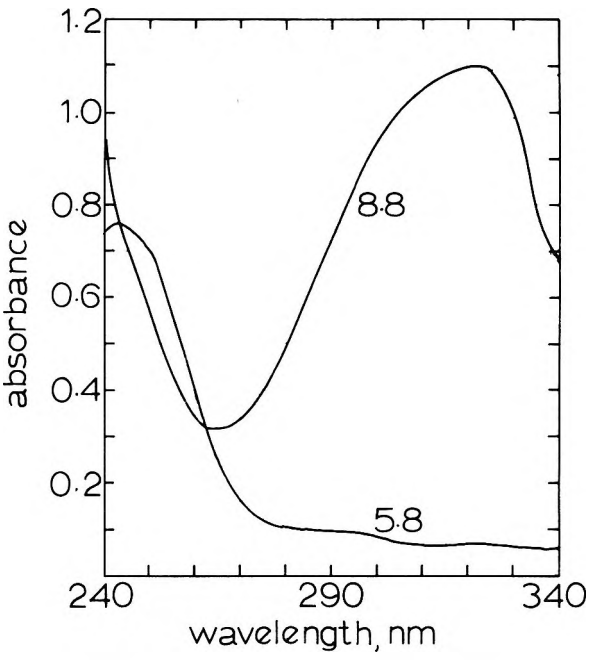


Figure 2. Ultraviolet spectra of product mixtures (after silica gel TLC) after solvolysis of 1 in 40% methanol at the pH values indicated.

product of reaction between 1 and methionine at pH 7.4, but noted a tenfold reduction in this compound at pH 6.5 concomitant with a corresponding increase in a hydrated methylmercaptoacetamidodibenzyl whose structure was not proven.[11] In the systems described here, however, a β-substituted acetamidostilbene was not observed. The yield of diols in 40% acetone does not change over a pH range of 4.5–7.5, nor is there any apparent change in the amount of the other minor products detectable by TLC. In 40% methanol, the mixture of **2–5** is increasingly replaced by 8 with increasing pH in the range 6.8–8.8 (Figure 1), as assayed by the change between the two spectra shown in Figure 2.

Discussion

The reactions of nitrenium ions derived from carcinogenic *N*-arylacetamides continue to provide useful insights into the chemistry of aromatic systems. In this case, the products obtained further confirm the previous prediction of the reactivity of the β carbon of the *N*-(4-stilbenyl)-*N*-acetylnitrenium ion. In fact, from these data, one can conclude that the delocalization is so extensive that the intermediate is better referred to as a highly stabilized carbonium ion. Hückel molecular orbital calculations predicted the β carbon to be by far the most reactive of the carbon atoms in this ion, based on frontier orbital coefficients. The same calculations, however, predicted that the nitrogen would be even more reactive. If this were so, one should expect that 1 would react with guanosine in the same manner as *N*-acetoxy-2-acetamidofluorene, *N*-acetoxy-4-acetamidobiphenyl, and *N*-acetoxy-2-acetamidophenanthrene. As mentioned briefly in the introduction, this is not the case, however.[9] Unlike what is found with the three compounds mentioned above, the reaction of 1 with [8-^{3}H]-guanosine yields a product mixture which retains tritium.[9] We have found that the major adduct from the reaction of 1 with guanosine lacks the stilbene chromophore (unpublished), which should not result from initial reaction at the nitrogen, but rather from reactions like those described in this paper. This same adduct does retain [8-^{3}H] from the starting guanosine. Furthermore, it shows no spectral change in the range pH 2–11, whereas 8-(*N*-2-fluorenylacetamido)guanosine[12] has a pK of 8.8. Finally, it is a highly polar product, as shown by its elution properties on Sephadex LH-20, suggesting minimization of the hydrophobic effect introduced by a large hydrocarbon group. These preliminary data thus suggest that the guanine adduct also results from reaction elsewhere than at the nitrogen of the intermediate nitrenium ion. More complete structural studies on the cytosine adduct (as the adduct with 1-methylcytosine) show that indeed substitution has taken place on the α and β carbons of the acetamidostilbene, yielding a hydroxy, (1-methyl)cytosylacetamidobibenzyl.

Thus, it appears that the simple HMO calculations carried out previously must be modified to recognize the large delocalization of charge into the aromatic system. The previous MO predictions in this series have been made on the basis of frontier orbital coefficients. If the calculated charge densities are instead used as the basis for predictions, the simple theory agrees entirely with our observations (Table I). From this table, it is clear that the "*N*-acetyl-*N*-4-stilbenylnitrenium ion" is no such thing, but is indeed a carbonium ion, with a small negative charge on the nitrogen. An apparent weakness with this approach is that it predicts greater reactivity at carbon in all of the ions presented. Whether this is in fact a weakness can only be determined by additional solvolysis studies on the other *N*-acetoxy-*N*-arylacetamides.

The ready formation of 8 in 40% methanol but not in aqueous acetone suggests that transesterification of 1 to an alcohol proceeds more readily than simply saponification. Comparable transacetylation of ribose in guanosine and of lysine in ribonuclease has been noted previously.[9,13]

The hydration of an intermediate quinone methide has been recognized previously,[14] but this may be the first instance of solvent addition to a quinone imide methide (Scheme III). It is surprising that no rearrangement of the type observed by the Millers was detected.[11] Although it is possible that *p*-phenacylacetanilide may have been a hidden product (its R_f on TLC was identical with that of 8), it was not noticeable in either solvolysis system. Similarly, in the methanolic system, there was no noticeable amount (pH 4.5–7.5) of any material which might have been characterized as β-methoxy-*N*-(4-stilbenyl)acetamide. Thus, solvent addition to the intermediate quinone imide methide appears to completely predominate over its rearrangement in this system. In the reaction with methionine, however, rearrangement is the major second step at pH 7.4.[11] A plausible explanation is that the

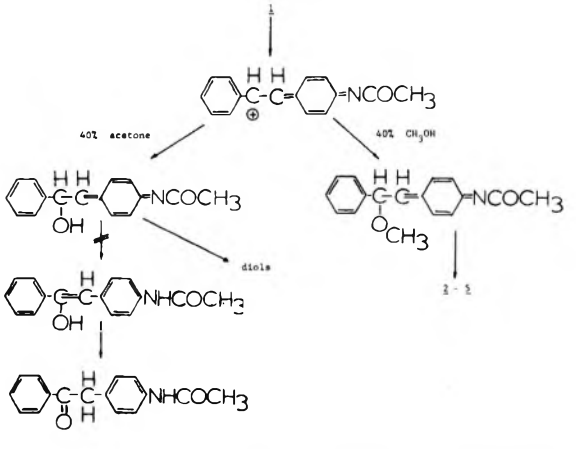
Table I. Charge Densities in *N*-Aryl-*N*-acetylnitrenium Ions[a]

Registry no.	Aryl substituent	Position[b]	Net charge
60239-50-1	4-Xenyl	2,6	0.017
		3,5	0.116
		8,12	0.084
		9,11	0.025
		10	0.079
		N	0.090
60239-51-2	2-Fluorenyl	1	0.097
		3	0.121
		4	0.042
		5	0.071
		6	−0.005
		7	0.094
		8	−0.017
		N	0.055
60239-52-3	2-Phenanthryl	1	0.277
		3	0.054
		4	0.056
		5	0.048
		6	0.003
		7	0.061
		8	0.002
		9	0.000
		10	0.048
		N	0.120
60239-53-4	4-Stilbenyl	2,6	0.087
		3,5	0.114
		8,12	0.038
		9,11	0.025
		10	0.078
		α	0.118
		β	0.254
		N	−0.058

[a] Calculation method given in ref 4. [b] Numbering as in ref 7.

intermediate sulfonium ion facilitates removal of the β proton to form a quinone imide methide ylide, which can then accept a proton on the nitrogen to re-form the stilbene electronic system and the sulfonium ion.

Scheme III



The nature of these reactions suggests that the reaction of **1** with nucleosides or nucleic acids will also differ markedly from the reactions of other *N*-acetoxy-*N*-arylacetamides. The compounds already studied all effect attachment of the imide nitrogen to C-8 of guanine,[6,12,15] or attachment of the aromatic ring to an extranuclear amino group.[7,16] It appears likely, however, that reaction of **1** with nucleic acids at pH 7.4 will result in true alkylation of the nucleic acid, by reaction of the β carbon with extranuclear amino groups, or with oxygen.[17]

A clear relationship between these findings and carcinogenicity cannot be established at this point. All of the amides mentioned herein produce mammary tumors in female rats, with roughly equal potency.[18-20] The *N*-acetoxy-*N*-arylacetamides vary widely in the ability to induce tumors locally, with no apparent relationship between reactivity (expressed as reaction rate, product yield, or product distribution) and carcinogenicity.[5,8,9] On the other hand, **1** stands out clearly from this group as being highly toxic toward human fibroblasts in culture, an observation which may indeed be related to reactions with nucleic acids suggested by our findings.[21] Finally, Neumann, et al. have found that a major urinary metabolite of dimethylaminostilbene in the rat is α,β-dihydroxyacetamidobibenzyl.[22] Whether this results from a hydroxamic acid ester or epoxidation of the double bond is a question requiring further studies of other, similar metabolites.

Experimental Section

Unless noted otherwise, all reagents were obtained from J. T. Baker Chemical Co., and were used as received. Melting points were taken on a Fisher-Johns apparatus, and are corrected to standards. Infrared spectra were determined in KBR pellets on a Perkin-Elmer 257 instrument. Ultraviolet spectra were obtained with a Beckman ACTA III instrument. High-resolution mass spectra and 270-MHz NMR spectra were determined by Mr. F.-T. Liu at the University of Chicago.

Solvolysis of *N*-Acetoxy-*N*-(4-stilbenyl)acetamide (1). An acetone solution (80 ml) of **1** (400 mg, prepared in this laboratory[15,23]) was mixed with 120 ml of water. The mixture was heated until a clear solution was obtained, then maintained at 40 °C for another 3 h. The acetone was removed on a rotary evaporator, and the aqueous solution extracted with five 100-ml portions of ether. Chromatography of the product on a silica gel column in 5% CH_3OH in CH_2Cl_2 yielded a light brown resin which was homogeneous on silica gel TLC in the same system and in ethyl acetate–benzene (7:3). The ir spectrum of this material (neat, between NaCl plates) showed a broad, intense band with maximum at 3300 cm^{-1}. A 1% solution in CH_2Cl_2 gave two sharp bands at 3600 and 3430 cm^{-1}, corresponding to a free O–H and a free secondary amide N–H, respectively. The uv spectrum of the material gave λ_{max} 248 nm (log ϵ 4.28), which is representative of all of the bibenzyl derivatives reported here. This material could be resolved into two fractions by chromatography on Sephadex LH-20 in water. The two substances yielded acetates which melted sharply (162–163, 146–148 °C), had largely identical ir spectra, and yielded the same major fragments on low-resolution mass spectroscopy. Elementary analysis for the major acetate (mp 163 °C) was as follows. Anal. Calcd for 1,2-bis(acetoxy)-1-phenyl-2-(4-acetamido)phenylethane: C, 67.61; H, 5.92; N, 3.94. Found: C, 67.92, H, 5.99; N, 4.08. Ir maxima of major product: 3290, 3190, 3120, 3060, 3050, 3040, 2965, 2940, 1740, 1660, 1602, 1530, 1498, 1458, 1416, 1375, 1345, 1320, 1286, 1235, 1185, 1163, 1128, 1108, 1080, 1035, 980, 940, 868, 840, 772, 740, 710, 690, 672, 660, 640 cm^{-1}.

An acetone solution (5 ml) of **1** (400 mg) was mixed with 80 ml of CH_3OH, then with 120 ml of water. This was heated as described above, the methanol removed on a rotary evaporator, and the products extracted with ether. The product mixture was chromatographed on a silica gel column, 1.5 × 100 cm, packed in CH_2Cl_2, and eluted with 500 ml each of 1, 2, and 5% CH_3OH in CH_2Cl_2. The first major products to emerge were **2** and **3**, which were mostly resolved from each other. A minor amount of an oil emerged, followed by the mixture of **4** and **5**. These were resolved by repeated rechromatography on a column of silica gel, 0.9 × 90 cm in 2% CH_3OH in CH_2Cl_2, and could be resolved, as well as **2** and **3**, by HPLC on a 1-m column of ODS Permaphase (Du Pont Instruments) eluted with water. The only remaining major band obtained from this column was the mixture of diols.

The above solvolysis was repeated using 0.1 M K_2HPO_4 instead of water. After heating as above and removal of methanol, a heavy precipitate was formed and was collected. TLC showed this to consist of mostly one substance. Recrystallization from methanol, column chromatography on silica gel, and recrystallization from ethyl acetate failed to remove a brown contaminant. Elementary analysis and comparison of the ir spectrum with that of authentic material showed this substance to be *N*-hydroxy-*N*-(4-stilbenyl)acetamide (**8**).

4-Nitrostilbene Oxide (10). 4-Nitrostilbene (**9**, 1.07 g, prepared in this laboratory[24]) and *m*-chloroperbenzoic acid (Aldrich, 85%, 1.00 g) were dissolved in 250 ml of CH_2Cl_2 at room temperature. After 6

days, TLC on silica gel (10% CH_2Cl_2 in petroleum ether) showed product in about 50% yield. After the solvent was removed, the mixture was chromatographed on 60 g of silica gel in 10–30% CH_2Cl_2 in petroleum ether. **9** emerged first, followed by **10**. Recrystallization of the epoxide from petroleum ether and benzene gave a first crop of 356 mg (mp 128–129.5 °C, lit. 125 °C)[25] and a second crop of 64 mg (mp 127–128 °C). Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.71; H, 4.56; N, 5.81. Found: C, 69.51; H, 4.65; N, 5.53. Uv maxima (95% ethanol) 281, 218 nm (log ε 3.14, 3.24); ir maxima at 3110, 3080, 3040, 2980, 2850, 1605, 1515, 1462, 1430, 1390, 1350, 1290, 1250, 1222, 1180, 1165, 1115, 1095, 1077, 1037, 977, 898, 871, 850, 837, 812, 768, 755, 715, 705 cm^{-1}.

1-Acetoxy-1-(4-acetamido)phenyl-2-methoxy-2-phenylethane (15). **10** (64 mg) was mixed with 10 ml of CH_3OH and 0.5 ml of concentrated $HClO_4$. Upon heating to 40 °C, all of the material dissolved. After 90 min, 0.8 g of $NaOCOCH_3 \cdot 3H_2O$ was added, and the solvent evaporated under reduced pressure. The residue was washed with five 2-ml portions of ether, and the combined ether extracts dried with Na_2SO_4 and evaporated. Acetic acid was removed with a stream of nitrogen, leaving 52 mg of an oil which crystallized on scraping, ir peaks at 3460, 2820 cm^{-1}. This material (50 mg, homogeneous on TLC on SiO_2 in CH_2Cl_2, and on HPLC on ODS Permaphase in H_2O) was dissolved in 3 ml of 95% ethanol and heated in a hot water bath (80–90 °C) with aluminum amalgam prepared from 2 cm^2 of minced Reynolds heavy duty aluminum foil,[26] with occasional replenishment of ethanol. After 45 min, 5 ml of ether was added, the mixture filtered, and the residue washed twice more with ether. The combined filtrate was evaporated under reduced pressure. Ir showed loss of $-NO_2$ with retention of $-OH$, $-OCH_3$. The crude product was treated overnight with 0.5 ml of pyridine and 0.3 ml of acetic anhydride, then diluted with 5 ml of water. The suspension was extracted with two 5-ml portions of ether, and the combined ether extracts washed with 10 ml of 0.5 M HCl, 10 ml of saturated $NaHCO_3$, and 10 ml of water, and dried over Na_2SO_4. Evaporation of the ether yielded a solid, mp 163–165 °C (petroleum ether/benzene). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.72; H, 6.42; N, 4.28. Found: C, 69.69; H, 6.51; N, 4.13. Ir maxima at 3320, 3200, 3130, 3060, 3040, 2980, 2930, 2870, 2825, 1740, 1675, 1606, 1550, 1520, 1460, 1420, 1375, 1325, 1245, 1190, 1130, 1112, 1097, 1075, 1040, 975, 915, 885, 862, 842, 822, 766, 710, 637 cm^{-1}. Major peaks of mass spectrum: 327.1474 (calcd for molecular ion, 327.1470), 207.0850, 206.0814 (calcd for $CH_3CONHC_6H_4CHOCOCH_3^+$, 206.0817), 165.0731, 164.0690, 122.0649, 121.0621 (base peak; calcd for $C_6H_5CHOCH_3^+$, 121.0653), 120.0455, 105.0334.

***erythro*-1,2-Dimethoxy-1-(4-acetamido)phenyl-2-phenylethane (2).** After solvolysis of **10** in acidic methanol, 258 mg of *erythro*-1-hydroxy-1-(4-nitro)phenyl-2-methoxy-2-phenylethane was dissolved in 5 ml of dimethyl sulfoxide and 5 ml of dimethylformamide.[27] The flask was cooled in ice and 1.5 g of $Ba(OH)_2 \cdot 8H_2O$ was added with magnetic stirring. Dimethyl sulfate (Eastman, 2 ml) was added dropwise under nitrogen. After 3 h, the nitrogen was removed and stirring continued overnight at room temperature. Concentrated ammonia (2 ml) was then added slowly and stirring continued for 30 min. The solution was extracted with two 30-ml portions of $CHCl_3$, and the extract dried over Na_2SO_4, evaporated under reduced pressure, redissolved in $CHCl_3$, washed with water, dried, and evaporated. The product was reduced with aluminum amalgam from 6 cm^2 of minced foil, and the product acetylated. After the usual workup and recrystallization from methanol, a product was obtained identical with **2** (HPLC on Permaphase/H_2O, ir), mp 182–183 °C. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.24; H, 7.02; N, 4.68. Found: C, 72.10; H, 7.15; N, 4.79.

Spectral Data for *erythro*- and *threo*-1,2-Dimethoxy-1-(4-acetamido)phenyl-2-phenylethane (2 and 3). Ir (**2**) 3300, 3260, 3190, 3120, 3060, 3030, 3000, 2930, 2900, 2880, 2820, 1670, 1610, 1555, 1530, 1515, 1457, 1450, 1415, 1375, 1320, 1270, 1245, 1235, 1210, 1190, 1108, 1040, 1020, 975, 945, 885, 862, 847, 837, 815, 780, 770, 740, 720, 690, 638 cm^{-1}; NMR (**2**, $CDCl_3$, Me_4Si reference) δ 2.21 (singlet, 3 H), 3.19 (singlet, 3 H), 3.20 (singlet, 3 H), 4.33 (quartet, 2 H), 7.17 (multiplet, 4 H), 7.30 (multiplet, 3+ H), 7.46 (doublet, 2+ H); mass spectrum (**2**) 268.1306 (calcd for M − OCH_3, 268.1337), 179.0916, 178.0866 (base peak; calcd for $CH_3CONHC_6H_4CHOCH_3^+$, 178.0868), 137.0676, 136.0750, 121.0612 (calcd for $C_6H_5CHOCH_3^+$, 121.0653), 120.0456.

Ir (**3**) 3310, 3190, 3110, 3060, 3030, 2970, 2930, 2900, 2825, 1690, 1602, 1530, 1517, 1495, 1470, 1457, 1410, 1370, 1312, 1280, 1253, 1220, 1188, 1160, 1115, 1090, 1080, 1055, 1012, 987, 970, 960, 868, 843, 775, 742, 716, 675, 641 cm^{-1}; NMR (**3**, $CDCl_3$, Me_4Si reference) δ 2.17 (singlet, 3 H), 3.28 (singlet, 3 H), 3.29 (singlet, 3 H), 4.32 (singlet, 2 H), 7.00 (multiplet, 4 H), 7.18 (multiplet, 3 H), 7.36 (doublet, 2 H), 7.56 (singlet, 1 H); mass spectrum (**3**) 268.1409 (calcd for M − OCH_3, 268.1337), 179.0893, 178.0842 (base peak; calcd for $CH_3CONHC_6H_4CHOCH_3^+$, 178.0868), 137.0698, 136.0777, 121.0614 (calcd for $C_6H_5CHOCH_3^+$, 121.0653), 120.0456.

Effect of pH on Solvolysis of 1. Stock solutions of 0.1 M K_2HPO_4 and 0.1 M KH_2PO_4 were mixed in the series 0:10, 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1, and 10:0 to give the pH values indicated in Figure 1. **1** was dissolved in acetone or methanol at a concentration of 150 μg/ml. Two milliliters of either stock solution of **1** was mixed with 3 ml of each buffer mixture. All samples were incubated at 37 °C for 24 h. Acetone was then removed by evaporation at reduced pressure, and the aqueous residue extracted with two 5-ml portions of ether. The methanol-containing samples were extracted directly with three 5-ml portions of ether. The ether was evaporated under nitrogen in a 10-ml test tube. Ethyl acetate (100 μl) was then added to each sample in an ice bath. The tubes were stoppered, the sides washed with the solvent, and 20-μl samples applied to a silica gel TLC plate. The plates were developed in 5% CH_3OH in CH_2Cl_2. Visual inspection under a uv hand lamp indicated no variation in the major spots between pH 4.5 and pH 7.8. The diol spots (from the acetone reaction mixtures) for pH values 4.5, 6.7, and 7.5 were scraped and eluted with 1 ml of 95% ethanol. Less than a 10% reduction in material was seen over this range. The combined spots for **2–5** were similarly assayed, and a major increase in stilbene compound detected. All spots from the methanol mixture assay plate were assayed (in 2 ml of 95% ethanol), and the results shown in Figures 1 and 2.

Acknowledgment. I thank Ms. Norma Naimy for repeated preparations of *N*-acetoxy-*N*-(4-stilbenyl)acetamide, and Ms. Becky Woodworth for performing the methylations. I am especially indebted to Professor N. C. Yang for offering the facilities available to him at the University of Chicago, and to Mr. F.-T. Liu for obtaining the NMR and mass spectra.

Registry No.—**1**, 26488-34-6; **2**, 60239-54-5; **3**, 60239-55-6; **9**, 1694-20-8; **10**, 14985-26-3; **15**, 60239-56-7; *erythro*-1,2-dihydroxy-1-phenyl-2-(4-acetamido)phenylethane, 60239-57-8; *threo*-1,2-dihydroxy-1-phenyl-2-(4-acetamido)phenylethane, 60239-58-9; *erythro*-1,2-bis(acetoxy)-1-phenyl-2-(4-acetamido)phenylethane, 60239-59-0; *threo*-1,2-bis(acetoxy)-1-phenyl-2-(4-acetamido)phenylethane, 60253-79-4; 1-hydroxy-1-(4-nitro)phenyl-2-methoxy-2-phenylethane, 60239-60-3; 1-hydroxy-1-(4-amino)phenyl-2-methoxy-2-phenylethane, 60239-61-4; 1,2-bis(methoxy)-1-phenyl-2-(4-nitro)phenylethane, 60239-62-5; 1,2-bis(methoxy)-1-phenyl-2-(4-amino)phenylethane, 60239-63-6.

References and Notes

(1) This is part 4 in the series "*N*-Aryl-*N*-acetylnitrenium Ions in Aromatic Amine Carcinogenesis". Reference 7 is the previous paper in this series. Supported by Grants CA-13155 and CA-18632 from the National Cancer Institute.
(2) (a) H. E. Heller, E. D. Hughes, and C. K. Ingold, *Nature (London)*, **168**, 909 (1951); (b) E. Kriek, *Biochem. Biophys. Res. Commun.*, **20**, 793 (1965); (c) C. M. King and B. Phillips, *J. Biol. Chem.*, **244**, 6209 (1969).
(3) H. Bartsch, C. Dworkin, E. C. Miller, and J. A. Miller, *Biochim. Biophys. Acta*, **304**, 42 (1973).
(4) J. D. Scribner, J. A. Miller, and E. C. Miller, *Cancer Res.*, **30**, 1570 (1970).
(5) E. C. Miller and J. A. Miller, *Ann. N.Y. Acad. Sci.*, **163**, 731 (1969).
(6) (a) E. Kriek, *Chem.-Biol. Interact.*, **3**, 19 (1971); (b) E. Kriek, *Cancer Res.*, **32**, 2042 (1972).
(7) J. D. Scribner and N. K. Naimy, *Cancer Res.*, **35**, 1416 (1975).
(8) J. D. Scribner and T. J. Slaga, *J. Natl. Cancer Inst.*, **54**, 491 (1975).
(9) J. A. Miller and E. C. Miller, *Prog. Exp. Tumor Res.*, **11**, 273 (1969).
(10) T. M. Santosusso and D. Swern, *J. Org. Chem.*, **40**, 2764 (1975).
(11) E. C. Miller, B. W. Butler, T. L. Fletcher, and J. A. Miller, *Cancer Res.*, **34**, 2232 (1974).
(12) E. Kriek, J. A. Miller, U. Juhl, and E. C. Miller, *Biochemistry*, **6**, 177 (1967).
(13) (a) E. J. Barry and H. R. Gutmann, *J. Biol. Chem.*, **248**, 2730 (1973); (b) E. J. Barry and H. R. Gutmann, *Chem.-Biol. Interact.*, **13**, 47 (1976).
(14) G. M. Buchan, J. W. A. Findlay, and A. B. Turner, *J. Chem. Soc., Chem. Commun.*, 126 (1975).
(15) J. D. Scribner and N. K. Naimy, *Cancer Res.*, **33**, 1159 (1973).
(16) E. Kriek and J. Westra, *Abstr Eur. Assoc. Cancer Res.*, 240 (1973).
(17) A. Dipple, P. Brookes, M. P. Rayman, and D. S. Mackintosh, *Biochemistry*, **10**, 4323 (1971).
(18) J. A. Miller, R. B. Sandin, E. C. Miller, and H. P. Rusch, *Cancer Res.*, **15**, 188 (1955).
(19) E. C. Miller, R. B. Sandin, J. A. Miller, and H. P. Rusch, *Cancer Res.*, **16**, 525 (1956).
(20) R. A. Andersen, M. Enomoto, E. C. Miller, and J. A. Miller, *Cancer Res.*, **24**, 128 (1964).
(21) V. M. Maher, N. Birch, J. R. Otto, and J. J. McCormick, *J. Natl. Cancer Inst.*, **54**, 1287 (1975).

(22) H.-G. Neumann, M. Metzler, and W. Topner, *Abstr. 2nd Eur. Assoc. Cancer Res.*, 159 (1973).
(23) P. D. Lotlikar, J. D. Scribner, J. A. Miller, and E. C. Miller, *Life Sci.*, **5**, 1263 (1966).
(24) M. Calvin and R. E. Buckles, *J. Am. Chem. Soc.*, **62**, 3324 (1940).
(25) B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955).
(26) H. Wislicenus and L. Kaufmann, *Ber.*, **28**, 1323 (1895), cited by L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 20.
(27) R. Kuhn and H. Trischmann, *Chem. Ber.*, **96**, 284 (1963).

The Iodomethylation of Nicotine. An Unusual Example of Competitive Nitrogen Alkylation[1]

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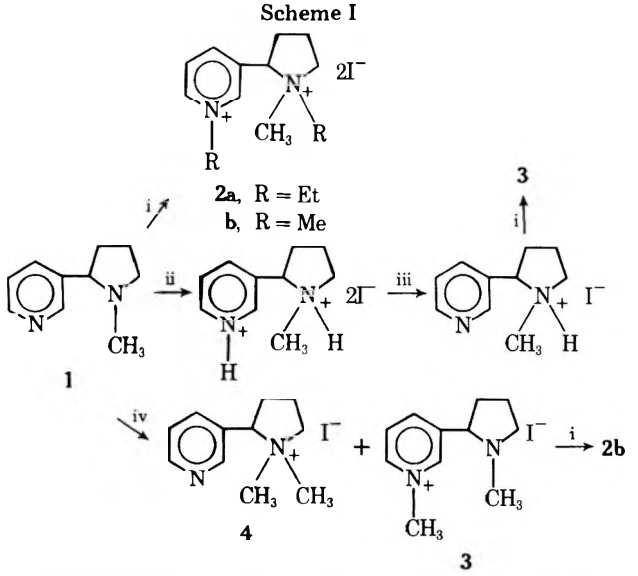
Alkylation of nicotine with 1 equiv of iodomethane in either methanol or acetonitrile leads to ca. 2.5:1 mixtures of *N'*-methylnicotinium iodide (**4**) and *N*-methylnicotinium iodide (**3**), and not to only **4** as previously indicated in the literature. The alkylation results reflect kinetic control of product. Control experiments indicate that the products are formed irreversibly under the reaction conditions. Alkylation of the nicotine analogue *N,N*-dimethyl-3-aminomethylpyridine with 1 equiv of iodomethane led only to trimethyl-3-picolylammonium iodide. Competitive alkylation experiments between nicotine and pyridine and *N*-methylpyrrolidine indicate that alkylation on nicotine's pyrrolidine nitrogen is decelerated, and the causes for this anomalous example of competitive nitrogen alkylation are discussed.

Nicotine (**1**) and its nitrogen alkylated products (e.g., **2–4**) have been of considerable biological and chemical interest for many years.[2-4] The earliest reported work on the alkylation of nicotine was published in 1853 by Kekule[5a] and in 1854 by Stahlschmidt[5b] who treated the alkaloid with iodoethane and iodomethane and obtained nicotine diethiodide (**2a**) and dimethiodide (**2b**), respectively. In 1897, Pictet and Genequand[6] reported their preparation of the two monomethiodides of nicotine, *N*-methylnicotinium iodide (**3**) and *N'*-methylnicotinium iodide (**4**), as shown in Scheme I. It is of interest to

Scheme I



Reagents: i, excess CH_3I; ii, HI; iii, 1 equiv of nicotine; iv, 1 equiv of CH_3I.

note that recent investigators[7] have reported the preparation of these compounds, in some cases with much difficulty, following the old literature procedures.

As a part of our interest in nicotine structure[8] and reactivity,[9] we now report that alkylation of this alkaloid with 1 equiv of iodomethane in either methanol or acetonitrile, following the literature procedures,[6,7c] leads to ca. 2.5:1 mixtures of **4**:**3** and not to only **4** as previously reported[6,7] (see Figures 1–3).[10] However, we have isolated **4** (68%) uncontaminated with either nicotine or **3** by continuous extraction of the aqueous solution of the **3** + **4** mixture with chloroform followed by removal of water from the aqueous phase. Rotary evaporation of the chloroform phase followed by ether trituration led to the isolation of **3** (28%). Alternatively, treatment of an acetic acid solution[11] of nicotine with 2 equiv of iodomethane at room temperature for 3 days followed by removal of the acetic acid and trituration with ether yields (58%) pure **3**.

The identity of these compounds is evident from their ^1H NMR spectra (see Figures 1–3 and data cited in the Experimental Section), elemental analyses, and mode of synthesis. In addition, treatment of either **3** or **4** with iodomethane leads quantitatively to *N,N'*-dimethylnicotinium diiodide (**2b**). Thus, simple high-yield procedures for the preparation of the two nicotine monomethiodides, uncontaminated with each other, are now available.

The Menschutkin reaction has been shown to be reversible in some cases, generally under forcing conditions.[13] Treatment of pure **3** or a **4**:1 mixture of **4**:**3** at 120 °C in acetonitrile in a sealed, degassed NMR tube resulted in no discernible chemical change after 36 h as judged by ^1H NMR of the total reaction mixture. Thus, the reaction product ratios in the nicotine alkylations are not complicated by the potential equilibration of products and starting material following selective quaternization; i.e., the alkylation results reflect kinetic rather than thermodynamic product control.

The iodomethylation of nicotine at pH >6 is an unusual example of competitive nitrogen quaternization,[13,14] especially since the pyrrolidine nitrogen of nicotine is almost three orders of magnitude more basic than nicotine's pyridine nitrogen (see Table I). While many factors other than basicity have a kinetic influence on the Menschutkin reaction, e.g., steric hindrance and solvation,[15] two limiting conditions could explain the nicotine alkylation results: (1) a rate decrease in pyrrolidine alkylation caused by the pyridine ring; and (2) a pyridine nitrogen alkylation rate enhancement due to the presence of the pyrrolidine ring. In an effort to distinguish between these two possibilities, two competitive alkylation experiments were performed. Treatment of a 1:1 mixture of nicotine and *N*-methylpyrrolidine with 1 equiv of iodomethane in methanol resulted in the formation of only *N,N*-dimethylpyrrolidinium

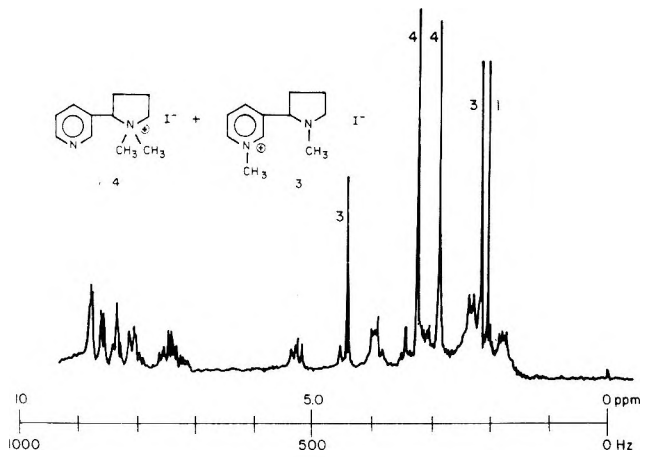


Figure 1. NMR spectra of total crude reaction product of nicotine and 0.75 equiv of iodomethane in acetonitrile in the presence of sodium carbonate at 100 MHz. The singlets are the *N*-methyl groups of nicotine, **3**, and **4**.

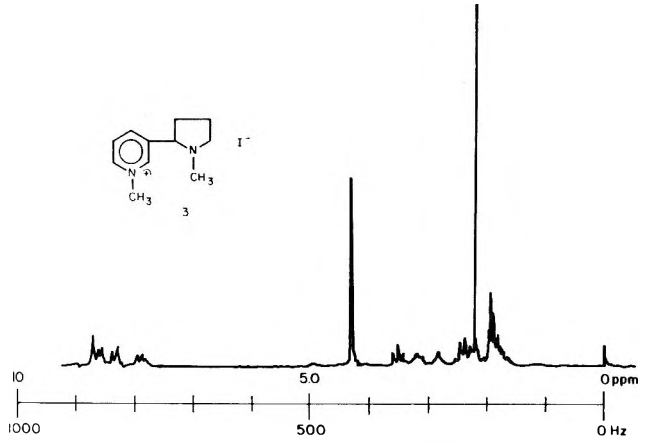
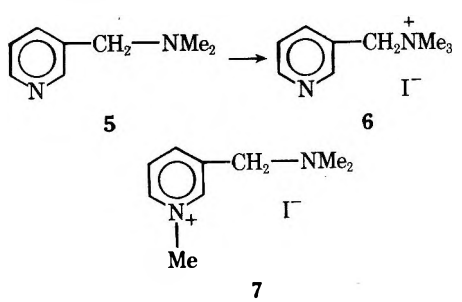


Figure 2. NMR spectra of *N*-methylnicotinium iodide (**3**) in acetonitrile-d_3 at 100 MHz.

iodide; no nicotine methiodides were observed (<1%) in the ^{1}H NMR spectra of the crude reaction product. Similarly, treatment of a 1:1 mixture of nicotine and pyridine with 1 equiv of iodomethane in acetonitrile led to a mixture of pyridine methiodide:**3**:**4** (ca. 1:1:2.5). It appears that for nicotine, alternative 1 above is operative and 2 above is not.

The pK_{a_1} value of nicotine (pK_{a_1} = 7.84, pK_{a_2} = 3.04)[9,16a] is 2.34 pH units less than the pK_a of *N*-methylpyrrolidine (pK_a = 10.18)[16b] and 1,2-dimethylpyrrolidine (pK_a = 10.2)[9] and 1.43 pH units less than that of 1-methyl-2-phenylpyrrolidine (pK_a = 9.27).[9,16] It is likely that this decrease in basicity of nicotine's pyrrolidine nitrogen will manifest itself in a decrease in this nitrogen's nucleophilicity. However, the pK_a values of nicotine compare extremely well with those of the nicotine analogue *N,N*-dimethyl-3-aminomethylpyridine (**5**) (pK_{a_1} = 7.8, pK_{a_2} = 3.1).[9] Alkylation of **5** with 1 equiv of iodomethane in acetonitrile results only in the formation of **6**;



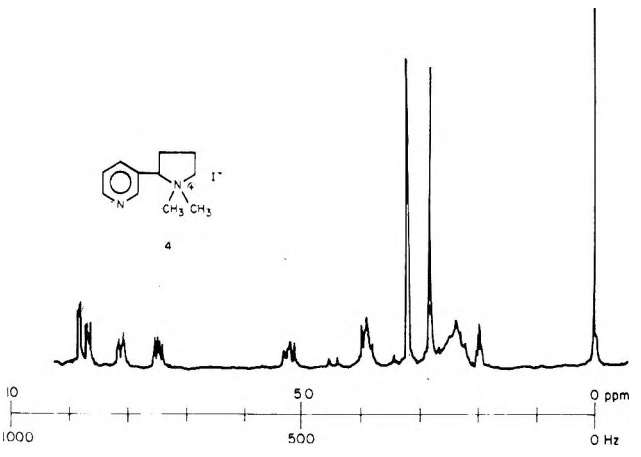


Figure 3. NMR spectra of *N'*-methylnicotinium iodide (**4**) in acetonitrile-d_3 at 100 MHz.

Table I. pK_a Values of Nicotine and Selected Nicotine Analogues

Compd	pK_{a_1}	pK_{a_2}	Ref
Nicotine (**1**)	7.84	3.04	*a, b*
1-Methyl-2-phenylpyrrolidine	9.27		*a, b*
N-Methylpyrrolidine	10.18		*c*
1,2-Dimethylpyrrolidine	10.2		*a*
N,N-Dimethyl-3-aminomethylpyridine (**5**)	7.8	3.1	*a*
Pyridine	5.19		*b*

[a] Reference 9. [b] Reference 16a. [c] Reference 16b.

no **7** was detected by evaluation of the ^{1}H NMR of the crude reaction mixture. Thus, a correlation between basicity and nucleophilicity alone does not account for the entire deceleration observed for nicotine. See Table I.

There are numerous examples of steric control in the Menschutkin reaction,[18] and the presence of the pyridine ring appears to act by destabilizing the N'-iodomethylation transition state for nicotine. Additional electronic or stereoelectronic factors can also be cited as important controlling factors. Experiments in progress may serve to elucidate the importance of these features.

Finally, it is interesting to note that the difficulty reported by many investigators in crystallizing **4** from the reaction of nicotine with iodomethane[7] stems from contamination with the now established major impurity, coalkylation product *N*-methylnicotinium iodide (**3**). In addition, the purity of the "*N'*-methylnicotinium iodide" obtained by the old literature methods[6] is open to question.

Experimental Section

The ^{1}H NMR spectra were obtained on a Varian XL-100 NMR spectrometer equipped with a Digilab NMR-3 FT accessory. The ir spectra were obtained on a Perkin-Elmer 621 spectrophotometer using Nujol mulls. Uv spectra were obtained on a Beckman spectrophotometer Acta-CV.

Iodomethylation of Nicotine in Acetonitrile. *N'*-Methylnicotinium Iodide (4) and *N*-Methylnicotinium Iodide (3). To a solution of 20.0 g of freshly distilled nicotine (0.123 mol) in 150 ml of acetonitrile was added sodium carbonate (9.75 g, 0.092 mol).[10] To this rapidly stirred mixture was added iodomethane (13.1 g, 0.0192 mol) (*Caution*: Cancer suspect agent!) in 150 ml of acetonitrile. The reaction mixture was stirred at room temperature for 3 days and filtered, and the precipitate washed with additional acetonitrile. The precipitate was tested for iodide by the standard silver nitrate–nitric acid method and no iodide was indicated. The filtrate and the washes were combined and rotary evaporated, yielding a thick, tan oil. NMR analysis of this oil showed it to be a mixture of nicotine:**4**:**3** (see Figures

1–3). This mixture was dissolved in 60 ml of water and continuously extracted with chloroform for 3 days. The combined chloroform portions were dried ($MgSO_4$) and rotary evaporated yielding an oily solid which was triturated with anhydrous ether. The resulting tan solid was vacuum dried, yielding 7.9 g (28% yield based on iodomethane used) of *N*-methylnicotinium iodide (**3**) identical with that prepared as described below.

The aqueous phase from the continuous extraction was rotary evaporated yielding a thick, yellow oil which was extremely hygroscopic. This material was subjected to high vacuum pumping for 1 week and spontaneously crystallized, giving 19.2 g (68% yield based on iodomethane used) of *N'*-methylnicotinium iodide (**4**): mp 135–137 °C; NMR (CD_3CN) δ 2.78 (s, 3), 3.16 (s, 3), 3.88 (m, 2), 5.10 (dd, 2, J = 8.1, 6.2 Hz), 7.52 (dd, 1, J = 8, 2 Hz), 8.10 (dt, 1, J = 8, 2, 2 Hz), 8.76 (dd, 1, J = 5, 2 Hz), and 8.86 (d, 1, J = 2 Hz); ir (Nujol mull) 3445 (m), 3000 (m), 1594 (m), 1579 (m), 1432 (vs), 1418 (m), 1333 (m), 1254 (m), 1027 (m), 1008 (m), 957 (m), 880 (m), 813 (s), and 718 cm^{-1} (vs); uv[19] max (H_2O) 264.5 nm (ϵ 2320), 258 (3140), 252 (2990), 226.0 (15 370).

Anal. Calcd for $C_{11}H_{17}N_2I$: C, 43.43; H, 5.63; N, 9.21; I, 41.72. Found: C, 43.35, 43.27; H, 5.50, 5.49; N, 9.12, 9.18; I, 42.13, 42.20.

N'-Methylnicotinium iodide was treated with 2 equiv of picric acid in absolute EtOH. The precipitate was crystallized from the reaction medium, yielding bright yellow crystals: mp 159–162 °C; NMR (Me_2SO-d_6) δ 2.78 (s, 3), 3.09 (s, 3), 3.77 (m, 2), 4.99 (m, 1), 7.99 (dd, 1, J = 8, 3.6 Hz), 8.56 (s, 4, picrate), 8.97 (dd, 1, J = 8, 1.6 Hz), and 9.03 (d, 1, J = 1.6 Hz).

Anal. Calcd for $C_{23}H_{22}N_8O_{14}$: C, 43.54; H, 3.50; N, 17.66. Found: C, 43.58, 43.53; H, 3.69, 3.71; N, 17.45, 17.50.

***N*-Methylnicotinium Iodide (3).** Freshly distilled nicotine (20.0 g, 0.123 mol) was added cautiously to 130 ml of glacial acetic acid. The mixture was allowed to cool to room temperature, and iodomethane (35.0 g, 0.246 mol) (*Caution*: Cancer suspect agent!) was added all at once. The resulting solution was allowed to stand at room temperature for 3 days. Most of the acetic acid was removed by rotary evaporation with mild heating. Trituration with ether (vigorous shaking) led to the formation of a nicely crystalline mass which was filtered and washed with ether to remove residual acetic acid and unreacted nicotine. The precipitate (25.7 g) was treated with concentrated aqueous sodium carbonate until the resulting solution reached a pH $\simeq$7. This solution was rotary evaporated under mild heating to a dryness and heated under reflux with 400 ml of chloroform for 2 h. The mixture was allowed to cool to room temperature and filtered. The residue was reextracted with chloroform under reflux, following the procedure above, and the combined chloroform layers were dried ($MgSO_4$), filtered, rotary evaporated, and crystallized from acetone yielding 21.3 g (58%) of analytically pure **3**: mp 165–165.5 °C (lit.[6] 165 °C); NMR (CD_3CN) δ 2.26 (s, 3), 2.92 (m, 1), 3.28 (m, 1), 3.59 (m, 1), 4.42 (s, 3), 8.02 (br m, 1), 8.5 (br d, 1, J = 8 Hz), 8.76 (br d, 1, J = 6 Hz), and 8.88 (br s, 1); ir (Nujol mull) 3027 (m), 2775 (vs), 1635 (m), 1503 (s), 1290 (m), 1190 (m), 1162 (s), 1153 (m), 1049 (s), 906 (m), 899 (m), 811 (s), and 671 cm^{-1} (vs); uv[19] max (H_2O) 264 nm (ϵ 4620), 224 (14 500).

Anal. Calcd for $C_{11}H_{17}N_2I$: c, 43.43; H, 5.64; N, 9.21; I, 41.72. Found: C, 43.62; H, 5.66; N, 9.15; I, 41.97.

The filtrate from the above reaction could be re-treated with additional quantities of iodomethane, thereby increasing the yield of **3**.

Competitive Alkylation Experiments. To a solution of nicotine (32.4 mg, 0.2 mmol) in ca. 200 μl of acetonitrile-d_3 in a 5-mm NMR tube was added pyridine (15.8 mg, 0.2 mmol) followed by iodomethane (28.4 mg, 12.5 μl, 0.2 mmol). The resulting solution was allowed to stand at room temperature in the presence of ca. 5 mg of sodium carbonate overnight. NMR analysis of the solution indicated that the NMR resonance of the *N*-methyl group of pyridine methiodide overlapped the resonance of the *N*-methyl group of *N*-methylnicotinium iodide (**3**). This equivalency was destroyed by addition of a small volume of trifluoroacetic acid, protonating **3** and shifting its *N*-methyl group downfield by ca. 2.5 Hz. The ratio of **3**:4:pyridine methiodide was ca. 1:2.5:1.

To a solution of nicotine (30.8 mg, 0.19 mmol) in ca. 200 μl of methanol-d_4 in a 5-mm NMR tube was added *N*-methylpyrrolidine (16.4 mg, 0.19 mmol) followed by iodomethane (27.2 mg, 11.9 μl, 0.19 mmol). The solution was allowed to stand at room temperature overnight in the presence of ca. 5 mg of sodium carbonate. NMR analysis of the resulting solution indicated only the formation of *N,N*-dimethylpyrrolidinium iodide: NMR (methanol-d_4) δ 3.12 (s, 6), 3.50 (m, 4), and 2.30 (m, 4). Neither **3** nor **4** (<2%) was observed in the reaction mixture.

Alkylation of *N,N*-Dimethyl-3-aminomethylpyridine (5). To a solution of *N,N*-dimethyl-3-aminomethylpyridine (139 mg, 0.98 mmol) in ca. 5 ml of acetonitrile was added iodomethane (62.3 μl, 0.98 mmol). The resulting solution was allowed to stand at room temperature overnight. NMR analysis indicated only the formation of the trimethylammonium iodide **6**: mp 128–130 °C (lit.[17] 135 °C); NMR (acetonitrile-d_3) δ 3.28 (s, 9), 4.94 (s, 2), 7.56 (dd, 1, J = 8, 4.5 Hz), 8.16 (dt, 1, J = 8, 2, 2 Hz), 8.72 (dd, 1, J = 4.5, 2 Hz), and 8.92 (d, 1, J = 2 Hz).

Anal. Calcd for $C_9H_{15}N_2I$: C, 38.86; H, 5.44; N, 10.07; I, 45.63. Found: C, 38.73; H, 5.54; N, 9.92; I, 45.84.

Acknowledgment. The authors thank Dr. E. B. Sanders for helpful discussions and Dr. W. R. Johnson for stimulating our interest in nicotine chemistry.

Registry No.—**1**, 54-11-5; **3**, 21446-46-8; **4**, 5959-86-4; 4 picrate, 60282-17-9; **5**, 2055-21-2; **6**, 60306-32-3; iodomethane, 74-88-4; *N,N*-dimethylpyrrolidinium iodide, 872-44-6.

References and Notes

(1) Presented at the American Chemical Society Centennial Meeting, San Francisco, Calif., Sept 3, 1976, Abstracts, No. ORGN-224.
(2) P. S. Larson and H. Silvette, "Tobacco, Experimental and Clinical Studies", Supplement I, Williams & Wilkins Co., Baltimore, Md., 1968, pp 39, 45, 56–59, 90, and 158, and references cited therein.
(3) U. S. Von Euler, Ed., "Tobacco Alkaloids and Related Compounds", Macmillan, New York, N.Y., 1965.
(4) K. E. Jackson, *Chem. Rev.*, **29**, 123 (1941); for numerous leading references to nicotine quaternary salts, involving synthesis and biological studies of many types, see *Chemical Abstracts*.
(5) (a) A. v. Planta and A. Kekule, *Ann. Chem. Pharm.*, **87**, 1 (1853); (b) see also C. von Stahlschmidt, *ibid.*, **90**, 218 (1854).
(6) A. Pictet and P. Genequand, *Ber. Dtsch. Chem. Ges.*, **30**, 2117 (1897).
(7) For example, see (a) J. H. Thompson, M. Angulo, L. Choi, M. Roch, and D. J. Jenden, *Experientia*, **28**, 1176 (1972); (b) Y. Soeda and I. Yamamoto, *Agric. Biol. Chem.*, **32**, 568 (1968); (c) R. B. Barlow and N. A. Dobson, *J. Pharm. Pharmacol.*, **7**, 27 (1955), with correction, *ibid.*, **7**, 296 (1955).
(8) J. F. Whidby and J. I. Seeman, *J. Org. Chem.*, **41**, 1585 (1976).
(9) J. F. Whidby, L. W. Morgan, and J. I. Seeman, in preparation.
(10) (a) The alkylation of nicotine with iodomethane in acetonitrile was performed in the presence of sodium carbonate to exclude the possibility of the formation of small amounts of HI which would protonate the more basic pyrrolidine nitrogen of nicotine, thereby causing pyridine alkylation (cf. nicotine alkylation in acetic acid). Identical results were observed, however, in the absence of sodium carbonate. (b) The reaction of **5** with iodomethane in acetonitrile led only to **6** in spite of the *absence* of sodium carbonate.
(11) Alkylation of nicotine in acetic acid was patterned after Jarboe.[12] We have examined the Menschutkin reactions of nicotine under a wide variety of conditions and these results will be published in due course.
(12) C. H. Jarboe and C. M. Schmidt, *J. Med. Chem.*, **13**, 333 (1970); (b) J. A. Schaeffer and C. H. Jarboe, *ibid.*, **13**, 1026 (1970).
(13) D. L. Garmaise and G. Y. Paris, *Chem. Ind. (London)*, 1645 (1967).
(14) (a) K. Oyama and R. Stewart, *J. Chem. Soc., Perkin Trans. 1*, 673 (1973); (b) R. Frampton, C. D. Johnson, and A. R. Katritzky, *Justus Liebigs Ann. Chem.*, **749**, 12 (1971); (c) J. W. Bunting and W. G. Meathrel, *Can. J. Chem.*, **48**, 3449 (1970).
(15) (a) D. C. Wigfield and B. Lem, *Tetrahedron*, **31**, 9 (1975), and references cited therein. (b) For an interesting discussion of these points, see W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, Chapter 2.
(16) (a) P. G. Stecher, Ed., "The Merck Index", Merck and Co., Rahway, N.J.; (b) J. A. Dean, Ed., "Lange's Handbook of Chemistry", 11th ed, McGraw-Hill, New York, N.Y., 1973, Tables 5–8.
(17) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 2134 (1968).
(18) See, for example, J. McKenna, *Top. Stereochem.*, **5**, 275 (1970), and references cited therein.
(19) The uv spectra of **3** and **4** are reported in ref 7c (note correction cited) but purity criteria for the preparations in this reference are either not cited (for **4**) or in question (for **3**, note melting point difference).

Studies on the Sodium Borohydride Reduction of Unsaturated Keto Nucleosides. Novel Route to Deoxy Nucleosides

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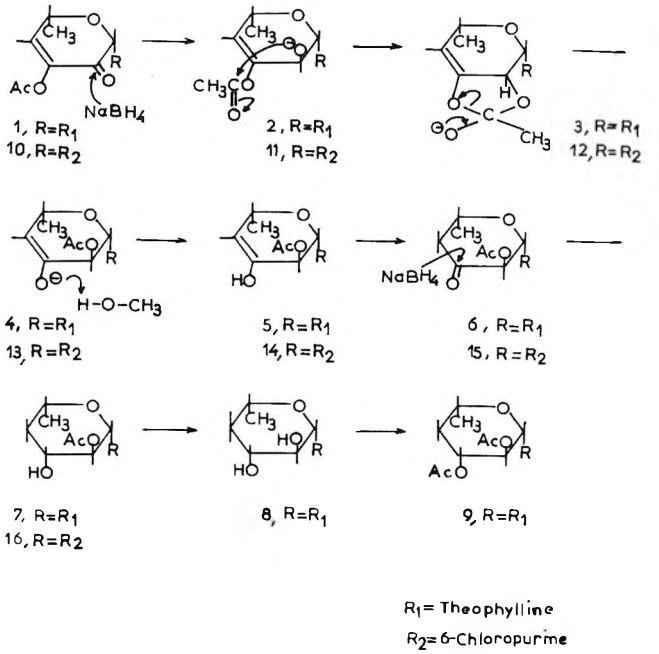
Received March 5, 1976

Reduction of α,β-unsaturated (ketohexosyl)purines, which constitute the first examples of unsaturated keto nucleosides, with sodium borohydride gave the corresponding deoxy nucleosides. Contrary to the recently reported (4′,6′-dideoxy-β-L-*glycero*-hex-3′-enopyranosulosyl)purines, which were obtained by acetylation of the corresponding keto nucleosides, the α anomer, subsequently described, was prepared by oxidation of the partially protected deoxyhexosylpurine. The mechanisms of these reductions were established by a study of the NMR spectra of the deoxy nucleosides using $NaBH_4$ in deuterated solvents and sodium borodeuteride in light solvents. 1,2 addition of the hydride was shown to be the mode of reduction of all the studied α- and β-unsaturated keto nucleosides. The ready availability of these unsaturated keto nucleosides provides extremely useful synthetic intermediate nucleosides especially for the preparation of nucleosides containing rare deoxy sugars.

The recent synthesis of the first unsaturated keto nucleosides[1,2,4] permitted the demonstration that these new nucleosides not only exhibit growth inhibitory activity against KB cells[3] but that they may constitute important synthetic intermediates in the nucleoside field owing to their stability in various media.[1-5]

We now report a study of the reduction of the recently synthesized unsaturated β-keto nucleosides **1**[4] and **10**[2] and that of the α isomer (**17**) subsequently described. These metal hydride reductions constitute in addition a new and facile route to deoxyhexosylpurines from (ketohexosyl)purines. It

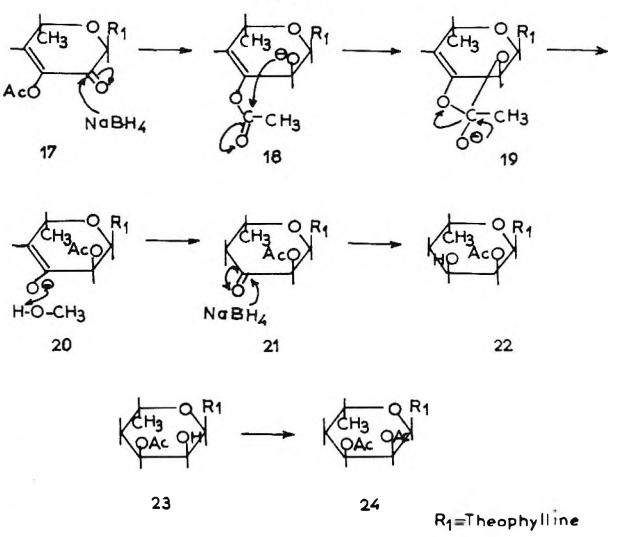
Scheme I



is also important to note that the study of the mechanisms could permit us to establish novel approaches to the synthesis of branched chain sugar nucleosides by nucleophilic addition.

As will be seen, the configuration of the molecule appears to have a real effect upon the direction of the attack of the carbonyl group. Thus, it was shown that reduction of both 7-(3′-*O*-acetyl-4′,6′-dideoxy-L-*glycero*-hex-3′-enopyranosulosyl)theophylline (**1**)[4] and its 6-chloropurine derivative (**10**) in methanol led to the saturated dideoxy nucleosides **7** and **16** having an equatorial OH-2′ whereas reduction of the α isomer (**17**) afforded the dideoxy derivative possessing an axial OH-2′ (**23**).

Scheme II



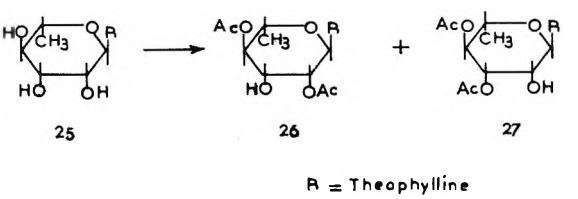
In the NMR spectra the anomeric protons of both **7** and **16** exhibited large coupling constants $J_{1',2'} = J_{2',3'} = 9$ Hz (the H-1′ proton of the starting compounds **1** and **10** exhibited only a singlet) indicating that H-1′, H-2′, and H-3′ are trans diaxial and OH-2′ equatorial. Considering that the bases are in equatorial position to the hexopyranose these correlations are possible only for the β-L-xylo configuration in the 1C conformation.

In the case of **23** the small coupling constant $J_{1',2'} = 1.5$ Hz indicated that OH-2′ was axial. In addition the H-3′ proton was also axial ($J_{3',4'ax} = 11$ Hz) and trans to the equatorial nitrogenous base. These relationships indicated that **23** has the α-L-ribo configuration in the C1 conformation.

Contrary to **1** and **10** which have been obtained by acetylation of the parent 2′-keto nucleosides,[2,6] the α isomer (**17**) was synthesized, as will be seen, by oxidation of the corresponding 3′,4′-diacetate (**27**).

This diacetate could be prepared by acid-catalyzed selective acetylation of 7-(6′-deoxy-α-L-mannohexopyranosyl)theophylline (**25**)[7] using acetic anhydride in the presence of the

Scheme III



etherate complex of boron trifluoride.[8] The reaction was carried out at 50 °C for 30 min and stopped by high vacuum distillation. Under these conditions a mixture of two diacetates (2′,4′- and 3′,4′-diacetate) was formed, but it contains mainly the desired 7-(3′,4′-di-*O*-acetyl-6′-deoxy-α-L-*manno*-hexopyranosyl)theophylline (**27**), as could be established from the nmr spectrum. Purification of the mixture was performed by oxidizing the mixture with the Pfitzner–Moffatt reagent.[14] This procedure gave only one compound which was characterized as 7-(3′-*O*-acetyl-4′,6′-dideoxy-α-L-*glycero*-hex-3′-enopyranosulosyl)theophylline (**17**). The NMR spectrum clearly indicated the conjugated structure of **17.** The H-1′ proton shifted downfield as expected (6.9 ppm instead of 6.4 ppm in the diacetate), also the H-4′ proton resonated at lower field (7.2 ppm) indicating a vinylic proton in β position to the carbonyl. The H-5′ proton was shifted to 4.95 ppm (from 4.2 ppm in **27**) indicating that this proton is vinylogous to a proton in α position to the carbonyl.

All these keto nucleosides are soluble in aqueous methanol. The reaction was carried out at room temperature for compound **1** and at above −50 °C for **10** and **17,** less stable comparatively than **1.**

The reductions appeared to be more stereospecific than those of steroidal enol acetates[9] since no other isomers were detected. The difference in the mode of reduction may be explained by invoking the influence of the base.

1,2 addition to the unsaturated keto nucleosides **1, 10,** and **17** should lead to the alcoholates **2, 11,** and **18** which undergo acetyl group migration to give the enolates **4, 13,** and **20.** These enols tautomerize to the corresponding 3′-keto nucleosides **6, 15,** and **21** which are further reduced to the deoxy nucleosides **7, 16,** and **22.** The α-deoxy nucleoside **22** undergoes another acetyl migration to give the 3′-acetyl nucleoside **23.**

These mechanisms have been established by a study of the NMR spectra of the deoxy nucleosides obtained by the reduction of **1, 10,** and **17** with $NaBH_4$ in deuterated solvents and of the NMR spectra of the same deoxy nucleosides prepared by using sodium borodeuteride in aqueous methanol.

There are two possible mechanisms to reduce α,β-unsaturated keto nucleosides by sodium borohydride: 1,2- or 1,4-hydride addition. The use of $NaBD_4$ led to deuterio analogues of the deoxy nucleosides. In the case of 1,2 addition only the 2′ and 3′ positions should be labeled whereas labeling of the 2′ and 4′ positions should indicate a 1,4 addition.

Since the NMR signals of compound **8** were not well separated, except for the H-1′, we synthesized the diacetate **9** in whose spectrum all the sugar protons were resolved. The acetylation of **8** was performed with acetic anhydride in pyridine. The disappearance of the H-2′ and H-3′ protons in the spectrum of **9** indicated 1,2-nucleophilic addition to 7-(3′-*O*-acetyl-4′,6′-dideoxy-β-L-*glycero*-hex-3′-enopyranos-2′-ulosyl)theophylline (**1**).[4]

In the NMR spectrum of the compound **16** (Table I, line 4) we also observed the disappearence of the H-2′ signal. Integration showed that two protons resonated at 3.6 ppm. In order to identify these protons we performed the reduction of **10** with $NaBD_4$. The NMR spectrum of the deuterio analogue of **16** indicated disappearance of one of the signals and appearance of a new signal as a ten-peak multiplet corresponding to H-5′. The multiplicity of this signal indicated that both H-4′$_{axial}$ and H-4′$_{equatorial}$ protons are coupled with H-5′. The signal at 3.6 ppm, absent in the spectrum of the deuterio analogue, could then be attributed to the H-3′ proton of **16.** Consequently, as the sodium borodeuteride labeled specifically the 2′ and 3′ positions of 6-chloro-(3′-*O*-acetyl-4′,6′-dideoxy-β-L-*arabino*-hexopyranosyl)purine (**16**) we can deduce that **10** is also reduced by the 1,2-addition mechanism.

The presence of an acetyl group in the 3′ position makes a

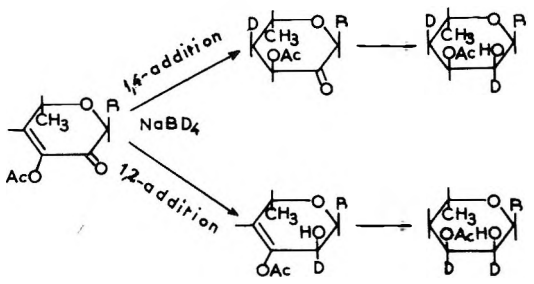
Table I

Line no.	Compd	Hydride	Redn solvent	Deuterio analogue	Chemical shifts, δ[a] H_1'	H_2'	H_3'	H_5'	H_6'	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'ax}$	$J_{3',4'eq}$	$J_{4'ax,5'}$	$J_{4'eq,5'}$	$J_{5',6'}$
1	**9**[b]	$NaBH_4$	CH_3OH/H_2O		6 d	5.7 t	5.1 se		1 d	9	9	10	5			6
2	**9**[b]	$NaBH_4$	CD_3OD/D_2O	Mono-deuterated	6 d	5.7 t	5.1 q		1 d	9	9		5			6
3	**9**[b]	$NaBD_4$	CH_3OH/H_2O	Di-deuterated	6 s				1 d							6
4	**16**[c]	$NaBH_4$	CH_3OH/H_2O		5.7 d	5.1 t	3.6	3.6	1.1 d	9	9					7
5	**16**[c]	$NaBH_4$	CD_3OD/D_2O	Mono-deuterated	5.7 d	5.1 t	3.6	3.6	1.1 d	9	9					7
6	**16**[c]	$NaBD_4$	CH_3OH/H_2O	Di-deuterated	5.7 s			3.6 m	1.1 d					7	2	7
7	**24**[b]	$NaBH_4$	CH_3OH/H_2O		6.7 d	5.9 q	5.5 o	4.2 m	1 d	1.5	3.2	11.5	5			7
8	**24**[b]	$NaBH_4$	CD_3OD/D_2O	Mono-deuterated	6.7 d	5.9 q	5.5 q	4.2 m	1 d	1.5	3.2	11.5				7
9	**24**[b]	$NaBD_4$	CH_3OH/H_2O	Di-deuterated	6.7 s			4.2 m	1 d							7

[a] s, singlet; d, doublet; t, triplet; q, quartet; se, sextet; o, octet; m, multiplet. [b] Solvent C_5D_5N. [c] CD_3OD.

1,4-addition mechanism possible (Scheme IV). As the NMR parameters of **23** did not permit us to ascertain the mode of

Scheme IV

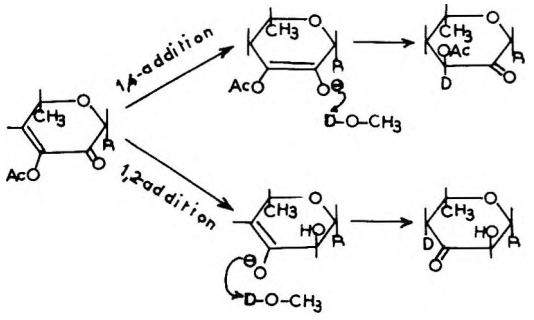


this hydride reduction, we synthesized the diacetate **24.** In the NMR spectrum of this molecule (**24**) we observed the disappearance of H-2′ and H-3′ signals. Consequently, as the 2′ and 3′ positions are labeled, 1,2 addition of the hydride should be also the mode of reduction of 7-(3′-*O*-acetyl-4′,6′-dideoxy-α-L-*glycero*-hex-3′-enopyranosyl-2′-ulosyl)theophylline (**17**).

All these results have been confirmed by a study of the reduction of the unsaturated 2′-keto nucleosides with $NaBH_4$ in deuterated solvents.

1,2 as well as 1,4 additions of hydride would lead to formation of the corresponding enols which react with deuterium from the solvent to form the saturated deuterio analogues (see Scheme V). In the case of 1,4 addition (2′,3′ double bond in the

Scheme V



enolate) the deuterium enters at C-3′ whereas for 1,2 addition (3′,4′ double bond) the reduction yields the 4′-deuterio product.

When **24** was deuterated no change in the multiplicity of H-2′ in the monodeuterated analogue was observed whereas the H-3′ signal (see Table I, lines 7 and 8) was reduced to a quartet indicating the disappearance of the coupling between H-3′ and $H\text{-}4'_{equatorial}$. This implies that C-4′ is labeled by deuterium and consequently that the unsaturated keto nucleoside (**17**) has undergone 1,2 addition.

Reduction of the unsaturated keto nucleoside (**1**) occurs by 1,2 addition. The NMR spectrum of the deuterio analogue of **9** showed (see Table I, line 2) disappearance of the H-3′, $H\text{-}4'_{axial}$ coupling. The H-3′ signal resonated as a quartet indicating that the C-4′ position is labeled by deuterium.

Concerning the monoacetate **23,** the presence of an acetyl group in the 3′ position seems inconsistent with a complete reduction of the unsaturated ketone (successive addition of two hydride ions). It is indeed established that the first attack leads to the enol acetate **18.** In these conditions the mode of reduction of this molecule should be a 1,4-addition mechanism. But this 1,4 addition is inconsistent with the evidence inferred from the isotopic labeling of the molecule.

The presence of the acetyl in the 3′ position could be explained by a migration of this group from the 2′-axial (**22**) to the more stable 3′-equatorial position (**23**).

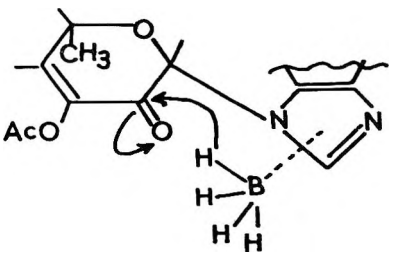


Figure 1.

Concerning the nucleophilic additions to the 3′-keto nucleosides **6, 15,** and **21,** it is well known that in the case of the α-substituted cyclohexanones the axial attack on the carbonyl group is generally favored and $NaBH_4$ reduction gives mainly the equatorial alcohol.[12] This is in accordance with the results of the hydride addition on the intermediate keto nucleosides **6, 15,** and **21,** which gave exclusively the equatorial alcohol as was clearly shown by the coupling constants of their NMR spectra.

The stereospecific axial attack could be explained in the case of **6** and **15,** which possess an equatorial 2′-acetyl, by the proximity of the nitrogeneous base. In the case of **21** the cis-axial 2′-acetyl group and the 4′-axial proton prevent the equatorial attack.

The unusual attack of hydride ion exclusively from the most hindered side in the case of the unsaturated β-keto nucleosides **1** and **10** may consequently be explained by invoking intramolecular participation of a neighboring group. Thus, as in the case of methyl hexopyranosuloses,[13] this group controls the direction of the reduction. Preference of the hydride for an approach cis to the base support the view that either the base or one of its functional groups participates in the formation of the complex with $NaBH_4$ which reduces the carbonyl stereospecifically (Figure 1).

The study of the NMR spectrum of the α-keto nucleoside **17** shows that, contrary to the reduction of **1** and **10,** the hydride attacks from the side trans to the nitrogeneous base. This could signify the nonparticipation of the purine in the reduction of **17.** So, as we have previously mentioned, the hydride approaches cis to the aglycon when the base controls the direction of the reduction.

Considering the stability and the facile preparation of the unsaturated ketohexose nucleosides[5] this novel approach to the synthesis of deoxy nucleosides, especially those containing rare deoxy sugars, provides a direct route to a variety of compounds possessing considerable biological interest.

Experimental Section

Solutions were evaporated at 40 °C under diminished pressure. Uv spectra were measured with a Varian-Techtron Model 635 spectrophotometer. Ir spectra were determined for potassium bromide pellets by use of a Perkin-Elmer Model 137 spectrometer. NMR spectra were recorded with a Varian T-60 instrument using tetramethylsilane as internal standard, and decoupling was effected with a Varian T-6059 spin decoupler, using the frequency-sweep mode. Optical rotations were determined with a Roussel-Jouan "Quick" polarimeter.

The gas–liquid chromatography of acetylated nucleosides was carried out using a Perkin-Elmer Model 990 instrument, with hydrogen flame ionization. Columns were packed with 100–200 mesh Gas-Chrom Z (Applied Sciences Laboratories Inc.) coated with 10% SE-30.

Reactions were monitored by TLC on Schleicher and Schull plastic sheets using (A) ethyl acetate and (B) chloroform–acetone (80/20). Nucleoside spots were detected by visual examination under uv light and by spraying with 30% sulfuric acid and heating at 105 °C. PLC was carried out on plates (20 × 40 cm) coated to a depth of 5 mm with Keiselgel GF_{254} (Merck) admixed with 15% of $CaSO_4$, using ethyl acetate.

Melting points were uncorrected. Elemental analysis were obtained from the Laboratoire de Microanalyse du CNRS.

7-(3′-*O*-acetyl-4′,6′-dideoxy-α-L-*glycero*-hex-3′-enopyranosulosyl)theophylline (17). A solution of 7-(6′-deoxy-α-L-*manno*-hexopyranosyl)theophylline (**27**,[7] 1.5 g, 4.5 mmol) in methanol (30 ml) was evaporated to dryness in vacuo. The semicrystalline material was then dissolved in acetic anhydride (60 ml, 588 mmol) and boron trifluoride etherate (36 μl, 2.65 mmol) was added. The solution was heated for 30 min at 50 °C and the solvents removed by high vacuum distillation. The obtained dark yellow oil containing a mixture of di- and triacetyl nucleosides was dissolved in ethyl acetate and purified by preparative TLC using ethyl acetate. Two faster moving major bands were detected by ultraviolet absorption. The slower moving of these bands was eluted with acetone to give a semicrystalline material which was dissolved in benzene (16 ml) and Me_2SO (16 ml). Dicyclohexylcarbodiimide (DCC, 2.8 g, 13.5 mmol) and dichloroacetic acid (0.3 ml, 3.75 mmol) were added[14] and the mixture was kept for 10 min at room temperature. Ethyl acetate (100 ml) and oxalic acid (1.2 g) dissolved in methanol were added and the mixture was stirred for 20 min.

Dicyclohexylurea was filtered off and the filtrate was washed with water (3 × 50 ml) and evaporated to a syrup. The crude material was dissolved in ethyl acetate and chromatographed on a silica gel (Merck 0.05–0.2 mm) column eluted with ethyl acetate (500 ml). Evaporation gave a syrup which crystallized at 0 °C from chloroform–methanol (1:5) to give **17** (0.391 g). The purity of the keto nucleoside was ascertained by GLC at 270 °C (retention time 1.5 min): mp 162–165 °C; $[\alpha]^{20}D$ −170° (*c* 0.1, $CHCl_3$); uv λ_{max} (MeOH) 273 nm (ε 10 000); R_f 0.7 (ethyl acetate); ν_{max} (KBr) 1740 cm^{-1} (acetyl); δ (CD_3COCD_3) 7.2 (d, $J_{4',5'}$ = 2 Hz), 6.9 (s), 4.9 (o, $J_{5',6'}$ = 7 Hz).

Anal. Calcd for $C_{15}H_{16}N_4O_6$: C, 51.73; H, 4.59; N, 16.09. Found: C, 51.73; H, 4.68; N, 16.45.

7-(3′-*O*-Acetyl-4′,6′-dideoxy-α-L-*ribo*-hexopyranosyl)theophylline (23). To a solution of **17** (348 mg, 1 mmol) in chloroform (2 ml), methanol (7.5 ml) and water (0.5 ml) were added. The mixture was cooled to −50 °C and sodium borohydride (300 mg, 7.85 mmol) was added. After storage at −50 °C for 4 min, chloroform (20 ml) was added and the mixture was washed with water (10 ml). Evaporation of the solvents gave a syrup which was purified by preparative TLC using ethyl acetate The major band at R_f 0.4 was eluted with acetone to give a syrup which crystallized from ethanol–pentane and recrystallized from ethanol (150 mg): mp 172–174 °C (sublimed at 164 °C), $[\alpha]^{20}D$ +70° (c 0.1, MeOH); R_f 0.4 (ethyl acetate); λ_{max} 274 nm (ε 7400); NMR δ (CD_3COOD) 6.4 (d, $J_{1',2'}$ = 1.5 Hz), 5.3 (o, $J_{2',3'}$ = 3, $J_{3',4'ax}$ = 11 Hz), 1.5 (d, $J_{5',6'}$ = 7 Hz).

Anal. Calcd for $C_{15}H_{20}N_4O_6$: C, 51.13; H, 5.68; N, 15.9. Found: C, 51.15; H, 5.57; N, 16.4.

The acetylation of **23** with acetic anhydride in pyridine gave 7-(2′,3′-di-*O*-acetyl-4′,6′-dideoxy-α-L-*ribo*-hexopyranosyl)theophylline (**24**) as a syrup: $[\alpha]^{20}D$ = +92 (c 0.1, ethanol); λ_{max} 274 nm (ε 7900); NMR (C_6D_6) acetyl δ 1.56, 1.62.

7-(4′,6′-Dideoxy-β-L-*xylo*-hexopyranosyl)theophylline (8). Sodium borohydride (210 mg, 6.3 mmol) was added to a stirred solution of 7-(3′-*O*-acetyl-4′,6′-dideoxy-β-L-*glycero*-hex-3′-enopyranosulosyl)theophylline (**1**,[4] 310 mg, 1 mmol) in methanol (10 ml). After 2 min water was added (10 ml) and the mixture was extracted with ethyl acetate (3 × 20 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. 7-(4′,6′-Dideoxy-β-L-*xylo*-hexopyranosyl)-theophylline (**8**, 180 mg) was crystallized from ethanol: mp 213–214 °C; $[\alpha]^{20}D$ +5° (*c* 0.1, acetone); R_f 0.55 (*t*-BuOH–H_2O); λ_{max} 275 nm (ε 7300).

Anal. Calcd for $C_{13}H_{18}N_4O_5$: C, 50.25; H, 5.81; N, 18.05. Found: C, 50.14; H, 5.80; N, 18.05.

7-(2′,3′-Di-*O*-acetyl-4′,6′-dideoxy-β-L-*xylo*-hexopyranosyl)theophylline (9). Compound **8** (1,0 g, 3.22 mmol) was dissolved in a mixture of acetic anhydride (5 ml) and pyridine (10 ml). After 45 min at room temperature, the mixture was evaporated in vacuo, and toluene was distilled from the syrupy residue which then crystallized from ethanol to give **9** (1.2 g, 95%): mp 210–211 °C; $[\alpha]^{20}D$ +25° (c 0.1, acetone); λ_{max} 274 nm (ε 7510); ir C=O (acetyl) 1740 cm^{-1}; R_f 0.54 (ethyl acetate).

Anal. Calcd for $C_{17}H_{22}N_4O_7$: C, 51.77; H, 5.58; N, 14.4. Found: C, 51.96; H, 5.61; N, 14.68.

6-Chloro-9-(2′-*O*-acetyl-4′,6′-dideoxy-β-L-*xylo*-hexopyranosyl)purine (16). The same procedure was used as for compound **21** except that 150 mg (0.46 mmol) of **10** was used and the solution was stirred for 20 min at −50 °C. After evaporation of the solvents the crude material crystallized from chloroform to give pure **16** (90 mg): mp 186 °C; $[\alpha]^{20}D$ 0 (*c* 0.1, MeOH); λ_{max} 264 nm (ε 6500).

Anal. Calcd for $C_{13}ClH_{15}N_4O_4$: C, 47.8; H, 4.6; N, 17.15. Found: C, 48.28; H, 4.76; N, 17.19.

The deuterio analogue was crystallized from chloroform, mp 190 °C, λ_{max} 264 nm (ε 8000).

Anal. Calcd for $C_{13}ClH_{13}D_2N_4O_4$: C, 47.5; H, 5.17; N, 17.04. Found: C, 47.02; H, 4.61; N, 16.62.

The acetylation of this deuterio nucleoside with acetic anhydride in pyridine gave 6-chloro-9-(2′,3′-di-O-acetyl-2′,3′-dideuterio-4′,6′-dideoxy-β-L-*xylo*-hexopyranosyl)purine, which crystallized from ethanol, mp 153°C.

Anal. Calcd for $C_{15}ClH_{15}D_2N_4O_5$: C, 48.58; H, 4.58; N, 15.11. Found: C, 48.63; H, 4.59; N, 15.43.

Preparation of Deuterio Analogues. These analogues were prepared by using deuterated or light solvents either with sodium borohydride or with sodium borodeuteride. The procedure applied was identical with that used for compounds **23**, **8**, and **16**.

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Registry No.—**1**, 39848-20-9; **8**, 60195-84-8; **9**, 60195-85-9; **10**, 50615-83-3; **16**, 60195-86-0; **16**-d_2, 60195-87-1; **16**-d_2Ac, 60195-88-2; **17**, 60251-49-2; **23**, 60195-89-3; **24**, 60195-90-6; **27**, 60209-47-4.

References and Notes

(1) K. Antonakis, *C. R. Acad. Sci., Ser. C*, **275**, 1101 (1972).
(2) K. Antonakis and M. Bessodes, *Carbohydr. Res.*, **30**, 192 (1973).
(3) K. Antonakis and I. Chouroulinkov, *Biochem. Pharmacol.*, **23**, 2095 (1974).
(4) K. Antonakis and M. J. Arvor-Egron, *Carbohydr. Res.*, **27**, 468 (1973).
(5) K. Antonakis, *Chimia*, **29**, 59 (1975).
(6) K. Antonakis and M. J. Arvor, *C. R. Acad. Sci., Ser. C*, **272**, 1982 (1971).
(7) K. Antonakis and J. Herscovici, *C. R. Acad. Sci., Ser. C*, **273**, 2099 (1972); J. Herscovici and K. Antonakis, *J. Chem. Soc., Perkin Trans. 1*, 979 (1974).
(8) T. Nakagawa and T. Takamoto, *Bull. Chem. Soc. Jpn.*, **44**, 192 (1971).
(9) B. Bellau and T. F. Callagher, *J. Am. Chem. Soc.*, **73**, 4458 (1951).
(10) C. Djerassi, E. Battres, M. Valesco, and G. Rosenkranz, *J. Am. Chem. Soc.*, **74**, 1712 (1952).
(11) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962).
(12) D. C. Wigfield and D. J. Phelps, *J. Am. Chem. Soc.*, **96**, 543 (1974); D. C. Wigfield, S. Feiner, and D. J. Phelps, *J. Org. Chem.*, **40**, 2533 (1975).
(13) G. J. F. Chittenden and R. Guthrie, *J. Chem. Soc.*, 1508 (1966).
(14) U. Brodbeck and J. G. Moffatt, *J. Org. Chem.*, **35**, 3552 (1970).

An Alternative Synthesis of Anomeric Methyl 2-Deoxy-4-thio-D-*erythro*-pentofuranosides

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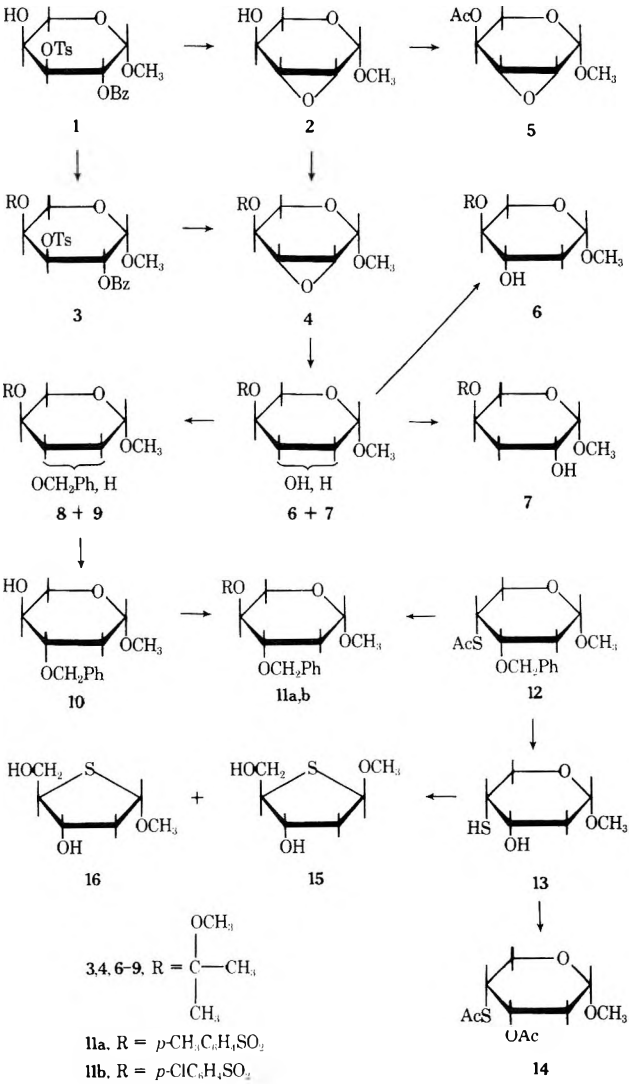
The anomeric methyl 2-deoxy-4-thio-D-*erythro*-pentofuranosides (**15, 16**), which are useful precursors for the synthesis of 2′-deoxy-4′-thionucleosides, were prepared from the readily available methyl 2-*O*-benzyl-3-*O*-tosyl-β-L-arabinopyranoside (**1**). Successive treatment of **1** with sodium methoxide and 2-methoxypropene–HCl gave methyl 2,3-anhydro-4-*O*-(2-methoxyisopropyl)-β-L-lyxopyranoside (**4**). Opening the anhydro ring in **4** with $LiAlH_4$ furnished, in high yield, a 12:1 mixture of the 2-deoxy (**6**) and 3-deoxy (**7**) acetals. Benzylation of **6** with benzyl bromide–sodium hydride and acetic acid hydrolysis gave methyl 3-*O*-benzyl-2-deoxy-β-L-*threo*-pentopyranoside (**10**). Tosylation or *p*-chlorobenzenesulfonylation of **10**, followed by nucleophili displacement of the tosyloxy or *p*-chlorobenzensulfonyloxy groups with potassium thioacetate, afforded methyl 3-*O*-benzyl-4-*S*-acetyl-4-thio-2-deoxy-α-D-*erythro*-pentopyranoside (**12**). Treatment of **12** with sodium–NH_3 gave methyl 4-thio-2-deoxy-α-D-*erythro*-pentopyranoside (**13**), which was converted to a mixture of α and β anomers (**15, 16**) of methyl 2-deoxy-4-thio-D-*erythro*-pentofuranoside by acid methanolysis.

The preparation of anomeric methyl 2-deoxy-4-thio-D-*erythro*-pentofuranosides (**15, 16**) has been described by Nayak and Whistler.[1,2] The synthesis, which starts from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and comprises 15 steps, does not readily lend itself to the preparation of the relatively large amounts of the sugar intermediate needed for the synthesis of nucleosides. We have, therefore, developed a shorter route to the synthesis of **15** and **16**.

The readily available starting material, methyl 2-*O*-benzoyl-3-*O*-*p*-toluenesulfonyl-β-L-arabinopyranoside (**1**), was prepared from methyl 2-*O*-benzoyl-β-L-arabinopyranoside by a slight modification of the procedure of Reist et al.[3] It has been reported that compound **1** when treated with 2 mol of sodium methoxide in methanol at room temperature for 18 h gives an 80% yield of semicrystalline methyl 2,3-anhydro-β-L-lyxopyranoside[3] (**2**). In addition, Buchanan and Fletcher[4] showed that treatment of the 4-*O*-acetyl derivative of **1** with 3 mol of sodium methoxide in methanol at room temperature for 6 h gave a 1:5.6 mixture of methyl 3,4-anhydro-β-L-arabinopyranoside and **2** in 61% yield; formation of the second epoxide derivative is thought to be due to migration of the epoxide. By modifying the reaction conditions, we were able to obtain a nearly quantitative yield of **2**. Acetylation of **2**, using acetic anhydride in pyridine, produced crystalline methyl 2,3-anhydro-4-*O*-acetyl-β-L-lyxopyranoside (**5**) in quantitative yield. Treatment of compound **2** in a chloroform–benzene solution with 2-methoxypropene,[5] in the presence of a catalytic amount of hydrogen chloride, gave methyl 2,3-anhydro-4-*O*-(2-methoxyisopropyl)-β-L-lyxopyranoside (**4**) in 94% yield. For large-scale preparations of **4**, it was more advantageous to introduce the acetal protecting group into **1**, and subsequent treatment with sodium methoxide produced compound **4** in almost a quantitative yield. The NMR spectrum of **4** showed a singlet corresponding to two *C*-methyl groups and two singlets for two *O*-methyl groups. The signal for the anomeric proton appeared in the spectrum as a doublet at δ 4.93.

Anhydro-ring opening of **4** with lithium aluminum hydride in ether gave a 94% yield of a 12:1 mixture of 2-deoxy and 3-deoxy acetals **6** and **7** which were separated by silica gel chromaography. The structures of **6** and **7** were established on the basis of their NMR spectra which gave signals for two *C*-methyl and two *O*-mthyl groups, and signals for the anomeric protons of **6** (d of d, $J_{1-2,2'}$ = 2.7 and 7.4 Hz) and **7** (d, $J_{1,2}$ = 3 Hz). It is interesting to note that compound **4** underwent $LiAlH_4$ reduction predominantly at C-2, possibly due to steric hindrance of the large vicinal trans acetal group. For large-scale preparation, separation of **6** and **7** can be omitted. Benzylation of the crude mixture of **6** and **7** with benzyl bromide–sodium hydride in dioxane, or benzyl bromide–sodium hydride in Me_2SO, followed by mild acetic acid hydrolysis of the protecting acetal group, gave a mixture of methyl 3-*O*-benzyl-2-deoxy-β-L-*threo*-pentopyranoside (**10**) and methyl 2-*O*-benzyl-3-deoxy-β-L-*threo*-pentopyranoside, from which **10** was separated by fractional crystallization in 63 and 72% overall yield, respectively. No attempt was made to increase the yield of **10** by separation of mother liquors because of the



close similarity of R_f of **10** and its 3-deoxy isomer. Treatment of **10** with *p*-toluenesulfonyl or *p*-chlorobenzenesulfonyl chloride in a chloroform–pyridine solution afforded methyl 2-deoxy-3-*O*-benzyl-4-*O*-(*p*-toluenesulfonyl)-β-L-*threo*-pentopyranoside (**11a**) or methyl 2-deoxy-3-*O*-benzyl-4-*O*-(*p*-chlorobenzenesulfonyl)-β-L-*threo*-pentopyranoside (**11b**), respectively, in almost quantitative yields.

Nucleophilic displacement of the secondary *p*-toluenesulfonyloxy group with thioacetate[1,2,6,7] has been widely used for the introduction of the thio groups into sugars. When polar and steric effects in the reacting systems are unfavorable, the reaction requires relatively high temperatures to proceed and may be accompanied by undesirable side reactions. Because the leaving capability of the arenesulfonyloxy group in nucleophilic displacement reactions increases with increasing electron-withdrawing power of the substituents on the phenyl ring,[8-10] the readily available *p*-chlorobenzenesulfonate should have a rate advantage over the corresponding tosylate. Displacement of *p*-bromobenzenesulfonate or *p*-nitrobenzenesulfonate, which are also better leaving groups than is the tosylate, with thioacetate may be complicated by aromatic ring substitution; these groups have been shown to undergo aromatic ring substitution in displacement reactions with sodium azide[10] and dimethylamine.[11] Comparison of **11a** to **11b** in the reaction with potassium thioacetate showed that while the tosyloxy group required 110–117 °C and 24 h for its displacement, the *p*-chlorobenzenesulfonyl group could be displaced at 75–80 °C in 16 h. The yield of methyl 3-*O*-benzyl-4-*S*-acetyl-4-thio-2-deoxy-α-D-*erythro*-pentofuranoside (**12**) from **11b** was 66% as compared with a 45% yield of **12** obtained from **11a** where the tosyl group was used. Deblocking of the benzyl protecting group with concurrent removal of the acetyl group in **12**, using sodium in liquid NH_3, gave a syrupy methyl 4-thio-2-deoxy-α-D-*erythro*-pentopyranoside (**13**). The ir spectrum of **13** showed no absorption bands corresponding to the benzyl and thio acetyl groups. The presence of the mercapto group was indicated by a positive nitroprusside reaction[12,13] and the absorption band at 2570 cm^{-1} in the ir spectrum of **13**. Proof that **13** was not a "dimer" was further substantiated by preparation of its di-*O*-acetyl derivative **14**. The NMR spectrum of **14** gave signals for the *O*-acetyl and *S*-acetyl groups. The presence of the *S*-acetyl group was also shown by a characteristic absorption band at 1695 cm^{-1} in the ir spectrum of **14**. Acid methanolysis of **13** at a reflux temperature afforded a mixture of α and β anomers of methyl 2-deoxy-4-thio-D-*erythro*-pentofuranosides (**15** and **16**) in 96% yield.

Experimental Section

Melting points were determined on a Thermolyne, No. MP-126000 melting point apparatus and are not corrected. The NMR spectra were recorded on a Varian A-60 or XL-100 spectrometer using Me_4Si as the internal standard. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer. Optical rotation data were determined on a Perkin-Elmer 141 polarimeter. Solvents were removed under reduced pressure on a Buchler rotary evaporator. Thin layer chromatography was performed on precoated plastic sheets (silica gel N-HR/UV_{254}, Brinkman Instruments, Inc.), in the following solvent systems: (A) benzene–acetone (9:1); and (B) chloroform–methanol (10:1). The spots were detected by uv absorbance or by spraying the sheets with 10% (v/v) sulfuric acid–ethanol and heating. Column chromatography was run on silica gel (J.T. Baker No. 3405). Elemental analyses were performed by Robertson Laboratory, Florham Park, N.J.

Methyl 2-*O*-Benzoyl-3-*O*-(*p*-toluenesulfonyl)-β-L-arabinopyranoside (1). The following procedure was a modification of the method reported by Reist et al.[3] Methyl 2-*O*-benzoyl-β-L-arabinopyranoside (60 g, 0.224 mol) in pyridine (200 ml) was cooled below −10 °C. To this solution was added dropwise with stirring and continued cooling a solution of *p*-toluenesulfonyl chloride (45.2 g, 0.236 mol) in anhydrous pyridine (200 ml), precooled to 0 °C. The reaction mixture was stirred at 0 °C for 16 h and then at room temperature for 7 h. TLC (solvent A) showed four spots corresponding to starting material, 3,4-di-*O*-tosyl derivative, 3-*O*-tosyl derivative **1**, and presumably the 4-*O*-tosyl derivative of methyl 2-*O*-benzoyl-β-L-arabinopyranoside. The reaction was stopped by the dropwise addition of ice–water (800 ml) with stirring. The mixture was then stirred at room temperature for 16 h. The precipitate, which contained largely the ditosyl byproduct and some **1** was filtered and the filtrate was extracted with chloroform (4 × 200 ml). The chloroform extract was washed with dilute hydrochloric acid, water, saturated sodium bicarbonate solution, and water. After drying (Na_2SO_4), it was evaporated to a syrup. Crystallization twice from methanol gave 48 g of **1**, mp 112.5–112.7 °C (lit.[3] 111–113 °C).

Fractional crystallization of the precipitate portion from ethanol gave an additional 6 g of **1**, the total yield of **1** being 54 g (57.5%).

Methyl 2,3-Anhydro-β-L-lyxopyranoside (2). A chloroform (50 ml) solution of methyl 2-*O*-benzoyl-3-*O*-(*p*-toluenesulfonyl)-β-L-arabinopyranoside (**1**, 21 g, 49.8 mmol) was diluted with benzene (200 ml) and the solution was then cooled to 0 °C. To this solution was added with stirring a precooled (0 °C) solution of sodium methoxide in methanol (50 ml containing 1.2 g, 52 mmol of sodium). The reaction mixture was kept at room temperature and the progress of the reaction was followed by TLC (solvent A). After completion of the reaction (4 h), the white precipitate (sodium *p*-toluenesulfonate) was filtered and washed with benzene and ether. The combined filtrate and washings were concentrated to a syrup. Methyl benzoate was removed at 40 °C (10^{-2} mmHg). Methyl 2,3-anhydro-β-L-lyxopyranoside (**2**) crystallized readily from ethyl acetate–petroleum ether as long needles (7.15 g, 98%): mp 71–72 °C (lit. 65–66,[4] 70–70.5 °C[3]); NMR (acetone-d_6) δ 3.37 (s, 3 H, OCH_3), 4.85 (d, 1 H, $J_{1,2}$ = 3 Hz, H-1).

Methyl 4-*O*-Acetyl-2,3-anhydro-β-L-lyxopyranoside (5). Compound **2** (2.54 g) was acetylated overnight at room temperature using pyridine (50 ml) and acetic anhydride (10 ml). The excess acetic anhydride was decomposed by addition of methanol. The reaction mixture was poured into ice water and extracted with benzene (3 × 50 ml). The benzene solution was washed successively with cold dilute hydrochloric acid, water, sodium bicarbonate solution, and water. It was dried (Na_2SO_4) and concentrated to a syrup which crystallized slowly on storing in a desiccator over P_2O_5: mp 30–31 °C; $[\alpha]^{25}D$ +92.8° (*c* 1.0, $CHCl_3$) lit.[4] $[\alpha]D$ +81.7°); NMR ($CDCl_3$) δ 2.14 (s, 3 H, $CH_3C{=}O$), 3.46 (s, 3 H, OCH_3), 3.37–4.00 (4 H, H-2, H-3, and H-5), 4.95 (d, 1 H, $J_{1,2}$ = 3.0 Hz, H-1), 5.08 (br s, 1 H, H-4).

Methyl 2-*O*-Benzoyl-3-*O*-*p*-toluenesulfonyl-4-*O*-(2-methoxyisopropyl)-β-L-arabinopyranoside (3). Compound **1** (41 g) was dissolved in a mixture of alcohol-free chloroform (100 ml) and anhydrous benzene (100 ml) with stirring. To this solution was added 2-methoxypropene (50 g) followed by 5 drops of chloroform saturated with gaseous hydrogen chloride. After 1 h at room temperature, the reaction was completed as shown by TLC (solvent A). The reaction mixture was neutralized by the addition of triethylamine (1 ml) and concentrated to a syrup. On addition of absolute ethanol, **3** crystallized readily, mp 118–119 °C. The yield was quantitative: $[\alpha]^{25}D$ +198.3° (*c* 2.9, $CHCl_3$); NMR ($CDCl_3$) δ 1.41 (s, 6 H, 2 CCH_3), 2.29 (s, 3 H, tosyl CH_3), 3.30 and 3.33 (two s, 6 H, 2 OCH_3), 3.77 (m, 2 H, H-5), 4.35 (m, 1 H, H-4), 4.88–5.63 (m, 3 H, H-1, H-2, and H-3), 6.98–7.88 (m, 9 H, aromatic). Anal. Calcd for $C_{24}H_{30}O_9S$: C, 58.3; H, 6.11; S, 6.48. Found: C, 58.1; H, 6.1; S, 6.6.

Methyl 2,3-Anhydro-4-*O*-(2-methoxyisopropyl)-β-L-lyxopyranoside (4). A. From 3. Compound **3** (51 g, 0.103 mol) was dissolved in anhydrous benzene (500 ml) and the solution was cooled to 0 °C. To this solution was added with stirring a methanolic sodium methoxide solution (2.5 g, 0.109 mol of sodium in 125 ml of anhydrous methanol) which was precooled to 0 °C. The reaction mixture was kept at room temperature for 5 h. The precipitate (sodium tosylate) was filtered and washed with anhydrous benzene. The combined filtrate and washings were evaporated to a syrup, redissolved in benzene (1 l.), washed with a small amount of water (50 ml) saturated with sodium chloride, and evaporated to a syrup. Methyl benzoate was removed at 40 °C (10^{-2} mmHg). The product crystallized as white needles during the evaporation: mp 48.5–49 °C; yield 21.7 g (96.5%); $[\alpha]^{25}D$ +56.5° (c 3.3, $CHCl_3$); NMR ($CDCl_3$) δ 1.42 (s, 6 H, 2 CCH_3), 3.26 and 3.45 (two s, 6 H, 2 OCH_3), 4.93 (d, 1 H, $J_{1,2}$ = 2.2 Hz, H-1). Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.0; H, 8.31. Found: C, 54.8; H, 8.4.

B. From 2. Compound **2** (7.3 g, 0.05 mmol) was dissolved in alcohol-free chloroform (20 ml) and anhydrous benzene (10 ml). To this solution was added 2-methoxypropene (10 g) and a drop of chloroform saturated with hydrogen chloride gas. After 1 h at room temperature, triethylamine (1 ml) was added and the solution was evaporated to a syrup at a bath temperature below 25 °C. The syrup was dissolved in absolute alcohol and cooled to 0 °C to give **4** as long needles (10.3 g, 94%), mp 47–48 °C.

Methyl 2-Deoxy-4-*O*-(2-methoxyisopropyl)-β-L-*threo*-pentopyranoside (6) and Methyl 3-Deoxy-4-*O*-(2-methoxyisopropyl)-β-L-*threo*-pentopyranoside (7). Lithium aluminum hydride (9 g) was suspended in anhydrous ether (500 ml) in a 2-l. three-necked round-bottomed flask which was equipped with a stirrer, a dropping funnel, and a reflux condenser. To the stirred suspension was added dropwise a solution of **4** (21.8 g, 0.1 mol) in anhydrous ether (500 ml) in such a way as to produce gentle refluxing. After 3 h, TLC (solvent A) showed that the starting material disappeared. The excess hydride was decomposed by the dropwise addition of ethyl acetate followed by water. The white precipitate was filtered and washed thoroughly with ethyl ether. To the combined filtrates was added solid sodium chloride (20 g) and the mixture was extracted with benzene (4 × 100 ml). The benzene extract was evaporated to give a crude syrupy mixture of **6** and **7** (20.8 g, 94.4%). A portion (2 g) of this mixture was separated by chromatography on a dry silica gel column, eluted with a benzene–ethyl acetate–triethylamine (10:1:1) mixture to give syrupy products **6** (1.8 g) and **7** (0.15 g). For **6**: NMR (acetone-d_6) δ 1.35 (s, 6 H, 2 CCH_3), 3.21 and 3.35 (two s, 6 H, 2 OCH_3), 4.48 (d of d, 1 H, $J_{1\text{-}2,2'}$ = 2.7 and 7.4 Hz, H-1). Anal. Calcd for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found: C, 55.9; H, 9.1. For **7**: NMR (acetone-d_6) δ 1.30 (s, 6 H, 2 CCH_3), 3.2 and 3.35 (two s, 6 H, 2 OCH_3), 4.52 (d, 1 H, $J_{1,2}$ = 3 Hz, H-1). Anal. Calcd for $C_{10}H_{20}O_5 \cdot {}^1/_4C_6H_6$: C, 57.60; H, 9.03. Found: C, 57.7; H, 8.9.

Methyl 2-Deoxy-3-*O*-benzyl-β-L-*threo*-pentopyranoside (10). A. By Benzylation of 6 and 7 with Benzyl Bromide–Sodium Hydride in Dioxane. To a crude mixture of **6** and **7** (20.75 g), dissolved in freshly distilled dioxane (250 ml), was added sodium hydride (20 g of 50% oil dispersion, washed with anhydrous ethyl ether and dried under reduced pressure) and the reaction mixture was stirred at room temperature under nitrogen overnight. To this cooled (5 °C) reaction mixture was added dropwise benzyl bromide (10 ml) with stirring and cooling. The reaction mixture was kept at room temperature for 24 h and cooled to 5 °C, and more prewashed sodium hydride (10 g) followed by benzyl bromide (10 ml) was added. This procedure was repeated two more times at 24-h intervals. After 7 days, when the reaction was completed as shown by TLC (solvent A), triethylamine (30 ml) was added to the reaction mixture to convert the excess benzyl bromide into quaternary amine salt and the excess sodium hydride was decomposed by addition of water while the reaction mixture was kept cool by an ice–water bath. The mixture was saturated with solid sodium chloride and extracted with benzene (4 × 300 ml). The benzene solution was dried (Na_2SO_4) and concentrated at a bath temperature of 30 °C to a syrup. The syrup was dissolved in 80% acetic acid (50 ml) and stirred at room temperature for 10 min. The reaction mixture was evaporated to a syrup which was coevaporated with toluene to remove residual acetic acid. Fractional crystallization of the residue from benzene–cyclohexane gave 14.2 g (63.3%) of **10** as white needles, mp 73–73.5 °C, $[\alpha]^{25}D$ +95.9° (*c* 1.0, $CHCl_3$).

B. By Benzylation of 6 and 7 with Benzyl Bromide–Sodium Hydride in Me_2SO. Sodium hydride (12 g, obtained from 25 g of a 50% oil dispersion) was added in small portions to a solution of a crude mixture of **6** and **7** in freshly distilled Me_2SO (200 ml) under nitrogen with stirring and cooling in an ice bath. After 4 h, benzyl bromide (10 ml) was added dropwise to the cooled mixture which was then stirred at room temperature for 6–8 h. Sodium hydride (12 g) followed by benzyl bromide (15 ml) were added to the reaction mixture, cooled in an ice bath and the mixture then was stirred at room temperature for 6–8 h. This procedure was repeated two more times. Triethylamine (30 ml) and water were added to the reaction mixture followed by saturation with solid sodium chloride. Extractions of the mixture with chloroform (4 × 300 ml) and evaporation of the chloroform solution under reduced pressure (10^{-2} mmHg) and at a bath temperature of 70 °C gave a syrupy residue which was treated with 80% acetic acid (50 ml) at room temperature for 10 min. The reaction mixture was worked up as described under A benzylation to give 20.7 g (72%) of crystalline **10**: mp 73–74 °C; NMR ($CDCl_3$) δ 1.65 and 2.24 (two m, 2 H, H-2), 3.48 (s, 3 H, OCH_3), 4.39 (d of d, 1 H, $J_{1\text{-}2,2'}$ = 2.8 and 8.2 Hz, H-1), 4.62 (d of d, 2 H, *J* = 12 Hz, benzylic H), 7.34 (br s, 5 H, aromatic H). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.52; H, 7.61. Found: C, 65.8; H, 7.5.

Methyl 2-Deoxy-3-*O*-benzyl-4-*O*-(*p*-toluenesulfonyl)-β-L-*threo*-pentopyranoside (11a). To a solution of compound **10** (3.87 g, 16.2 mmol) in alcohol-free chloroform (3 ml) and dry pyridine (50 ml) was added a solution of *p*-toluenesulfonyl chloride (15 g, 78.6 mmol) in alcohol-free chloroform (10 ml) and dry pyridine (100 ml), and the reaction mixture was stirred for 24 h, when TLC (solvent A) showed that the reaction was completed. The reaction mixture was cooled and poured into 500 ml of ice and water and the mixture was stirred at room temperature for 16 h. The mixture was then extracted with chloroform (4 × 100 ml) and the combined chloroform extracts were washed with cold hydrochloric acid, water, dilute sodium bicarbonate solution, and finally with water until neutral. The solution was dried (Na_2SO_4) and evaporated to yield a syrup which crystallized from 95% ethanol: yield 6.26 g (98.5%) of **11a** as small needles; mp 75–76 °C; $[\alpha]^{25}D$ +48° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$) δ 1.66 and 2.27 (two m, 2 H, H-2), 2.40 (s, 3 H, tosyl CH_3), 3.40 (s, 3 H, OCH_3), 3.61 (m, 1 H, H-3), 4.36–4.56 (3 H, benzylic and H-1, overlap), 7.20–7.80 (m, 9 H, aromatic H). Anal. Calcd for $C_{20}H_{24}O_6S$: C, 61.2; H, 6.16; S, 8.17. Found: C, 61.0; H, 6.2; S, 8.0.

Methyl 2-Deoxy-3-*O*-benzyl-4-*O*-(*p*-chlorobenzenesulfonyl)-β-L-*threo*-pentopyranoside (11b). **11b** was prepared from **10** (6 g, 0.025 mol) and *p*-chlorobenzenesulfonyl chloride (30 g, 0.142 mol) by the procedure used for the preparation of **11a**: yield 11.2 g (98%); mp 126–127 °C; $[\alpha]^{25}D$ +56.7° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$) δ 1.68 and 2.22 (two m, 2 H, H-2), 3.44 (s, 3 H, OCH_3), 3.59 (m, 1 H, H-3), 4.34–4.62 (3 H, benzylic and H-1, overlap), 7.12–7.88 (m, 9 H, aromatic H). Anal. Calcd for $C_{19}H_{21}O_6SCl$: C, 55.3; H, 5.13; S, 7.77; Cl, 8.59. Found: C, 55.3; H, 5.2; S, 8.0; Cl, 8.8.

Methyl 2-Deoxy-3-*O*-benzyl-4-*S*-acetyl-4-thio-α-D-*erythro*-pentopyranoside (12). From 11a. Compound **11a** (2.5 g, 25.6 mmol) and freshly recrystallized potassium thioacetate (2.92 g, 25, 6 mmol) were stirred in freshly distilled DMF (50 ml) at an oil bath temperature of 117 °C under a current of dry nitrogen for 24 h. The reaction mixture was cooled to 0 °C and poured with stirring into dry xylene (150 ml). After 16 h at room temperature, the precipitated salts were filtered and washed with dry xylene. The combined filtrates were evaporated to a syrupy residue at a bath temperature of 40 °C. Extraction of the residue with *n*-heptane (4 × 50 ml) and evaporation of the heptane solution gave a syrup, which was dissolved in dry pyridine (20 ml) and cooled to 0 °C. Acetic anhydride (5 ml) was added to this solution, and the reaction mixture was stirred at room temperature for 16 h. The mixture was then poured with stirring into ice–water (50 ml) and stirring was continued at room temperature for 16 h. The mixture was extracted with chloroform and the extract was washed with water (2 × 10 ml), dried (Na_2SO_4), and evaporated to a syrup. Crystallization of this syrup from 95% ethanol gave compound **12** (0.85 g, 45%) as long needles: mp 69.5–79 °C; $[\alpha]^{25}D$ +13.4° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$) δ 1.86 (m, 2 H, H-2), 2.38 (s, 3 H, thioacetyl H), 3.46 (s, 3 H, OCH_3), 4.42 (d of d, 1 H, $J_{1\text{-}2,2'}$ = 7.0 and 3.5 Hz, H-1), 4.58 (s, 2 H, benzylic H), 7.36 (br s, 5 H, aromatic H). Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.8; H, 6.80; S, 10.8. Found: C, 60.7; H, 6.9; S, 10.8.

B. From 11b. Compound **11b** (20 g, 48.4 mmol) was stirred with potassium thioacetate (20 g, 175 mmol) in dry DMF (200 ml) at 75–80 °C in an oil bath under a current of dry nitrogen for 16 h. The reaction mixture was worked up as described above. The yield of **12** was 9.5 g (66.2%), mp 69–70 °C.

Methyl 2-Deoxy-4-thio-α-D-*erythro*-pentopyranoside (13) and Methyl 2-Deoxy-3-*O*-acetyl-4-*S*-acetyl-4-thio-α-D-*erythro*-pentopyranoside (14). Ammonia (200 ml), distilled from sodium, was added to a solution of **12** (3.25 g, 11 mmol) in 1,2 dimethoxyethane (20 ml) under nitrogen with stirring at a temperature of −78 °C (acetone–dry ice bath). Freshly cut sodium was added in small pieces (70–150 mg) to the stirred solution until the blue color of the solution persisted for 30 min. The excess sodium was decomposed by the addition of solid ammonium chloride, and ammonia was allowed to evaporate in a current of dry nitrogen. The mixture was extracted with chloroform (4 × 50 ml) and filtered and the solid washed with chloroform (2 × 10 ml). The combined filtrates were evaporated to a syrup (1.3 g). The ir spectrum of **13** showed no benzyl and thioacetyl absorption bands. whil it gave mercapto and hydroxy group absorption bands at 2570 and 3500 cm^{-1}, respectively. Compound **13** gave also a positive nitroprusside reaction.

Syrupy **13** (1.3 g) was acetylated with acetic anhydride (5 ml) in pyridine (15 ml) at room temperature overnight. Workup of the reaction gave **14** as syrup in quantitative yield: ir (film) 1695 (–SAc), 1740 cm^{-1} (–OAc); $[\alpha]^{25}D$ +114.4° (*c* 1.03, $CHCl_3$); NMR (acetone-d_6) δ 1.93 (s, 3 H, acetyl), 2.33 (s, 3 H, thioacetyl), 3.37 (s, 3 H, OCH_3), 4.57 (d of d, 1 H, $J_{1\text{-}2,2'}$ = 5.6 and 3.4 Hz, H-1). Anal. Calcd for $C_{10}H_{16}O_5S$: C, 48.37; H, 6.50; S, 12.9. Found: C, 48.4; H, 6.7; S, 13.1.

Methyl 2-Deoxy-4-thio-β- and α-D-*erythro*-pentofuranosides (15 and 16). Methyl 2-deoxy-4-thio-α-D-*erythro*-pentopyranoside (**13**, 6.5 g) was dissolved in 0.1% methanolic HCl solution (500 ml) and the solution was refluxed under nitrogen for 90 min, when TLC (solvent B) showed that the reaction was completed. The solution was cooled to room temperature and neutralized with solid lead carbonate. The precipitate was filtered and washed thoroughly with methanol. Evaporation of combined filtrates gave a syrupy mixture of **15** and **16** which was separated by dry silica gel column chromatography using solvent B as the eluent to give methyl 2-deoxy-4-thio-α-D-*erythro*-

pentofuranoside (16, 2.39 g, 37%), $[\alpha]^{25}D$ +315.6° (c 1.08, $CHCl_3$) [lit.[2] $[\alpha]^{25}D$ +314° (c 1, $CHCl_3$)], and methyl 2-deoxy-4-thio-β-D-*erythro*-pentofuranoside (15, 3.86 g, 59.5%), $[\alpha]^{25}D$ −278° (c 1.02, $CHCl_3$) (lit.[2] $[\alpha]^{25}D$ −277.6°).

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References and Notes

(1) U. G. Nayak and R. L. Whistler, *J. Org. Chem.*, **34**, 3819 (1969).
(2) U. G. Nayak and R. L. Whistler, *Justus Liebigs Ann. Chem.*, **741**, 131 (1970).
(3) E. J. Reist, L. V. Fisher, and D. E. Gueffroy, *J. Org. Chem.*, **31**, 226 (1966).
(4) J. G. Buchanan and R. Fletcher, *J. Chem. Soc. C*, 1926 (1966).
(5) M. S. Newman and M.C.V. Zwan, *J. Org. Chem.*, **38**, 2910 (1973).
(6) M. Bobek and R. L. Whistler in "Methods in Carbohydrate Chemistry", Vol. VI, R. L. Whistler and J. N. BeMiller, Ed., Academic Press, New York, N.Y., 1972, p 292.
(7) M. Chmielewski and R. L. Whistler, *J. Org. Chem.*, **40**, 639 (1975).
(8) R. E. Robertson, *Prog. Phys. Org. Chem.*, **4**, 213 (1967).
(9) C. M. Paleos, R. S. Varveri, and G. A. Gregoriou, *J. Org. Chem.* **39**, 3594 (1974).
(10) M. C. Wu, L. Anderson, C. W. Slife, and L. J. Jensen, *J. Org. Chem.*, **39**, 3014 (1974).
(11) D. Horton, J. S. Jewell, and H. S. Prihar, *Can. J. Chem.*, **46**, 1580 (1968).
(12) K. A. H. Morner, *Hoppe-Seyler's Z. Physiol. Chem.*, **28**, 594 (1889).
(13) W. I. Patterson, W. B. Geiger, C. R. Mizell, and M. Harris, *J. Res. Natl. Bur. Stand.*, **27**, 89 (1941).

Reduction of Ketones with Incorporation of Deuterium at the α Position. Anomalous Reduction of Keto Sugar Derivatives[1,2]

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Reduction of the 3-keto sugar methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (1) with sodium borohydride in moist methanol proceeded stereospecifically to the allose derivative (2) having the 3-hydroxyl group axially oriented. Use of sodium borodeuteride under similar conditions gave the corresponding labeled analogue (characterized as its diacetate 11) deuterated completely and exclusively at C-3, indicating equatorial attack on 1 by the reductant. In contrast, when the reduction was performed in dry 2-propanol, there resulted a 1:1 mixture of the axial 3 alcohol (allo derivative 2) nd the equatorial 3 alcohol (gluco derivative 3). When the latter reduction was repeated with sodium borodeuteride in dry 2-propanol, the allo product was again found to be labeled completely and exclusively at C-3 (as shown by the NMR spectrum of its diacetate 11), but the gluco product 3 (studied as its diacetate 12) was found to be fully protiated at C-3 and fully deuterated at C-2. The labeling experiments thus show that the gluco product 3 arises not by axial attack of the reductant at the ketonic (C-3) position of the precursor (1), but by stereospecific attack at the α position (C-2) of a presumed enediolic intermediate derived from 1. The ready generation of a 2,3-enediol from 1 is demonstrated by preparation of the enediol diacetate 4. Lithium aluminum hydride in tetrahydrofuran and sodium borohydride in *N,N*-dimethylformamide both reduce 1 exclusively to the axial 3 alcohol 2. Zinc borohydride in 1,2-dimethoxyethane reduced 1 without cleavage of the 2-*O*-acetyl group to give mainly the allo product (8), together with a small proportion of gluco derivative (9). These results indicate the need for caution in interpreting results of label incorporation through reduction as a means of locating carbonyl groups in sugar derivatives, at least when dry alcoholic media are used. The results also suggest useful possibilities for synthesis of specifically labeled sugars.

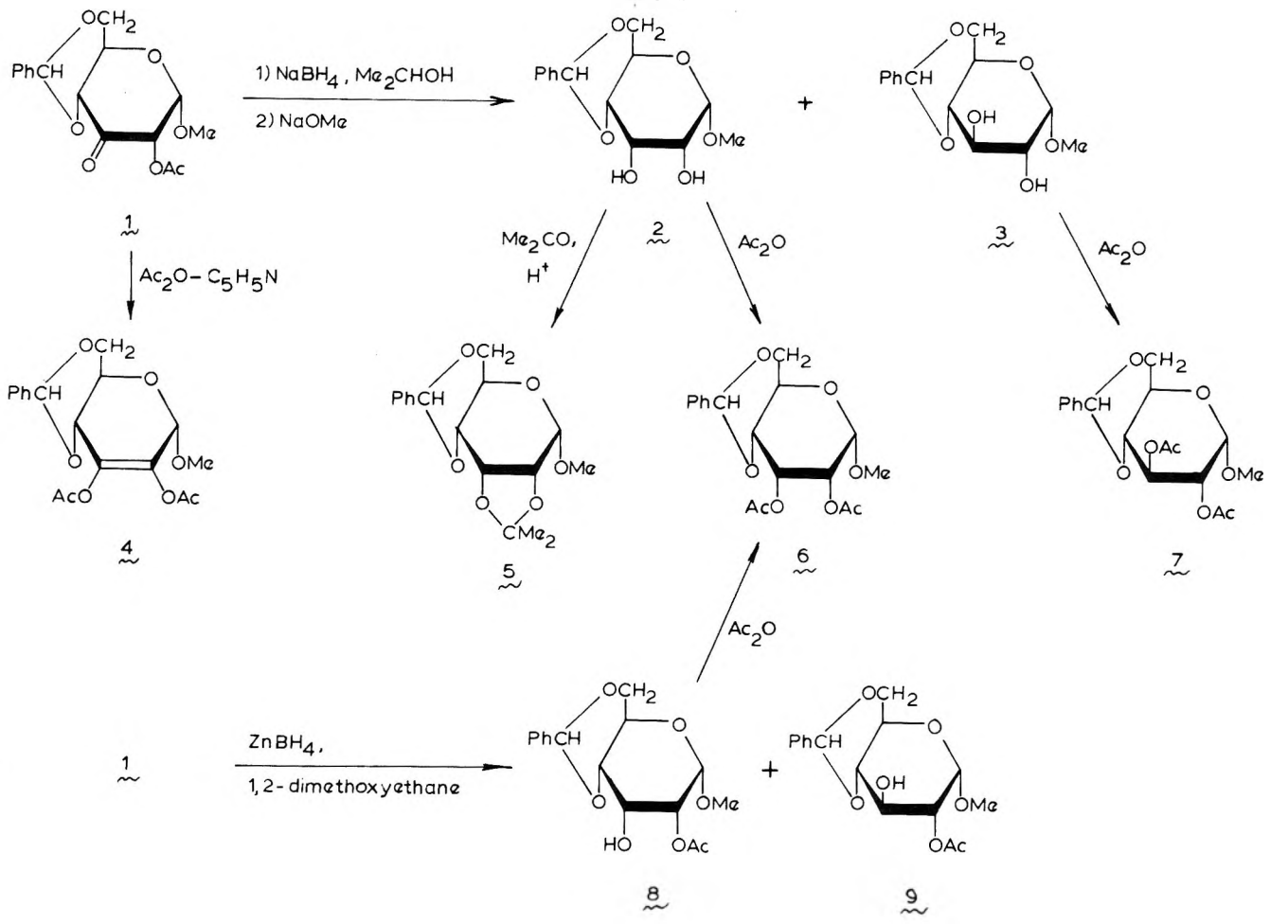
The reduction of sugar derivatives having one free ketonic group gives mixtures of two secondary alcohols, isomeric at the original carbonyl position, in relative proportions strongly controlled by steric factors. The sequence of oxidation–reduction is commonly used[3] to prepare alcohols of inverted stereochemistry from the precursor and for "marking" the site of oxidation with deuterium or tritium by use of appropriately labeled reductants.[4,5] The present report developed on the one hand from a program[6,7] designed to furnish specifically labeled sugars of use as biochemical probes and for interpretation of complex NMR and mass spectral patterns, and on the other from studies[8-10] concerning the mechanism whereby metal salts protect cellulose from oxidative degradation during bleaching.

This study describes the use of a model ketone, methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose[10,11] (1), and related derivatives for evaluation of the regio- and stereoselectivity of its reduction with deuterated hydride reductants. It is shown that, according to the nature of the solvent used, reduction may take place exclusively (as is usually supposed) at the carbonyl group, or alternatively by attack at the position α to the carbonyl group, to give concurrently the corresponding α-labeled derivative.

Results and Discussion

Reduction of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (1) with sodium borohydride in aqueous methanol gave methyl 4,6-*O*-benzylidene-α-D-allopyranoside (2), iolated in near-quantitative yield, as a chromatographically homogeneous dihydrate. The product was further characterized as the anhydrous compound by recrystallization from benzene. Conversion of 2 under essentially nonacidic conditions into methyl 4,6-*O*-benzylidene-2,3-*O*-isopropylidene-α-D-allopyranoside (5) served to establish the 2,3-cis geometry of the reduced product. Furthermore, hydrolysis of 2 led exclusively to D-allose, detected chromatographically on paper and clearly differentiated from either glucose, mannose, or galactose. The free sugar obtained by

Scheme I



hydrolysis was also firmly characterized as the crystalline phenylosazone. The syrupy 2,3-diacetate (**6**) of **2** gave an NMR spectrum in benzene-d_6 (see Tables I and II) consistent with the allo configuration; in particular the characteristic chemical shifts and spin couplings of H-1, H-2, and H-3 stand in clear contrast to values for the corresponding D-gluco product (**7**). It may be noted that **2** was quite difficult to acetylate to completion; conventional acetylation conditions gave mainly a monoacetate.

Similarly, when **1** was reduced with lithium aluminum hydride in tetrahydrofuran or with sodium borohydride in methanol–*N,N*-dimethylformamide,[11] the product was that (**2**) having the D-allo configuration. As would be expected, the sole product of these hydride reductions is that isomer which arises via quasi-equatorial attack of the hydride species from the apparent less hindered side of the carbonyl group. Sodium borohydride in either methanol or methanol–*N,N*-dimethylformamide[11] evidently exerts sufficient base strength to remove the 2-*O*-acetyl group.

In sharp contrast to the foregoing results, reduction of the ketone **1** in dry 2-propanol, a solvent frequently used in kinetic studies[12] of reductions by borohydride, gave (after removal of the acetyl groups) an approximately 1:1 mixture of two products that were found to be the D-allo derivative **2** and its 3 epimer, namely, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**3**). Each product was isolated and characterized on a crystalline basis. Conversion of these into their respective diacetates **6** and **7** permitted a first-order NMR spectral analysis of the ring-proton signals. The spectrum of **7** at 250 MHz in benzene-d_6 was identical with that of the product obtained upon acetylation of the reduction products described in the preceding paragraphs.

The use of zinc borohydride in dry 1,2-dimethoxyethane gave 64% of crystalline methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-allopyranoside (**8**), identified by NMR spectroscopy (see Tables I and II) and by conversion into the diacetate **6**, together with 14% of the known[14,15] methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**9**). Interestingly, this reduction procedure affords products in which the 2-*O*-acetyl group is retained. Thus it might be supposed at this point that the formation of both **2** (or **8**) and **3** (or **9**) could arise from attack of the hydride species on **1** from the equatorial and axial directions, respectively.

However, examination of the diacetates of the products from the reduction of **1** with sodium borodeuteride in dry 2-propanol revealed that, whereas the D-allo isomer **11** was labeled (as expected) exclusively at C-3, the D-gluco isomer **12** was monodeuterated in the 2 position, and not (as might be expected) at C-3. The crystalline diacetate **12** was identified by comparison of its melting point and optical rotation with those of the known[13] unlabeled compound **7**. The NMR spectrum of **12** in deuterated benzene (see Table I) was identical with that[13] of compound **7**, except that no H-2 resonance was observed, and the H-1 signal had become a singlet (loss of $J_{1,2}$ proton–proton coupling) and the H-3 signal was evident as a doublet (loss of $J_{2,3}$ proton–proton coupling), thus pinpointing the substitution by deuterium at C-2. A similar NMR analysis was conducted on the D-allo diacetate, where

Table I. NMR Chemical Shift Data[a]

Registry no.	Compd	Solvent	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	PhCH	OAc	OMe	Aryl	Other
42400-52-2	1[b]	$CDCl_3$[c]	5.21 d	5.41 dd	*d*		3.80–4.48 m			5.56 s	2.20 s	3.44 s	7.38 m	
4153-17-7	2	C_6D_6[e]	4.47 d	3.41 t	4.08 t	2.93 dd	3.98 sx	4.16 m	3.44 m	5.29 s	*d*	2.91 s	6.18–6.64 m	
3162-96-7	3[f]	$(CD_3)_2SO$[c]	4.99 d	3.75	*g*	*g*	4.53	*g*	*g*	5.92 s	*d*	3.68 s	6.92 m	
59830-63-6	4	$CDCl_3$[e]	5.10 s	*d*	*d*	4.74 d	4.12 sx	4.32 dd	3.86 t	5.55 s	2.16 s, 2.21 s	3.49 s	7.36 m, 7.45 m	
59830-64-7	5	$CDCl_3$[e]	4.70 d	4.35 dd	4.58 dd	3.79 dd	4.20 sx	4.37 sx	3.69 t	5.56 s	*d*	3.42 s	7.32, 7.5 m	1.42, 1.62 s CMe_2
56687-82-2	6	C_6D_6[c]	4.61 d	4.94 dd	5.83 t	3.07 dd	4.12–4.49 m		3.51–3.59 m	5.29 s	1.76 s	3.05 s	7.58, 7.19 m	
57564-28-0	11	C_6D_6[h]	4.61 d	4.94 d	*d*	3.07 d	4.12–4.49 m		3.31–3.59 m	5.29 s	1.76 s	3.05 s	7.58, 7.19 m	
4141-45-1	7[f]	C_6D_6[e]	4.91 d	5.11 dd	6.02 t	3.48 t	3.85 sx	4.00 dd	3.47 dd	5.23 s	1.69, 1.72 s	2.95 s	7.16, 7.55 m	
57538-71-3	12	C_6D_6[e]	4.91 s	*d*	6.02 d	3.48 t	3.85 sx	4.00 dd	3.47 dd	5.23 s	1.69, 1.72 s	2.95 s	7.16, 7.55 m	
57538-70-2	8	$CDCl_3$[c]	4.83 d	4.89 dd	*i*	3.59 dd	4.16 m	4.39 dd	3.76 t	5.58 s	2.17 s	3.45 s	7.34 m	
59830-65-8	8-*d*	$CDCl_3$[h]	4.83 d	4.89 d	*i*	3.59 d	4.16 m	4.39 dd	3.76 t	5.58 s	2.17 s	3.45 s	7.34 m	
25577-40-6	9	$CDCl_3$[e]	4.95 d	4.79 dd	4.15 t	3.52 t	3.84 sx	4.40 dd	3.74 t	5.53 s	2.13 s	3.39 s	7.40 m	
28642-65-1	10	$CDCl_3$[h]	5.32 d	5.62 d	*d*		3.88–4.53 m			5.59 s	*d*	3.50 s	7.42, 8.12 m	
55338-59-5	13	$CDCl_3$[e]	4.78 s	*d*	5.74 d	3.90 dd	4.31 sx	4.41 dd	3.82 dd	5.52 s	2.18 s	3.51 s	7.35–7.50 m	

[a] Chemical shifts are on the δ (ppm) scale: d, doublet; t, triplet; m, multiplet; dd, doublet of doublets; sx, sextet. [b] See ref 10. [c] At 100 MHz. [d] No signal. [e] At 250 MHz. [f] See ref 13. [g] Not determined because of second-order effects. [h] At 90 MHz. [i] Exact chemical shift not determined; obscured by other resonances.

no H-3 signal was observed, and H-2 resonated as a doublet (with loss of $J_{2,3}$ proton–proton coupling); the H-4 signal was not distinct because of overlap with other signals. The mass spectra of both **11** and **12** showed molecular ions at *m/e* 367, one unit higher than for their nondeuterated analogues.

In a further extension to a related example, the 2-*O*-benzoyl analogue of **1**, namely, methyl 2-*O*-benzoyl-α-D-*ribo*-hexopyranosid-3-ulose (**10**), was reduced under conditions identical with those used for the reduction of **1**. After O-debenzoylation and subsequent acetylation of the products, there was obtained an approximately 1:8 mixture of the D-allo (**11**) and D-gluco (**12**) diacetates. These were separated by column chromatography and identified by NMR spectroscopy. Apparently, relative to the acetoxy group, the benzoyloxy group at C-2 facilitates deuterium incorporation at that carbon atom.

Such anomalous incorporations of deuterium α to the ketone group appear to be novel. Related precedent is evident in at least two publications that have documented epimerizations, α to a ketone group, occurring during reduction with borohydride. One example[16] cites the epimerization, with sodium borohydride in methanol, of a bicyclic ketone having a very acidic α-hydrogen atom. A later publication[17] describes the epimerization of menthone, 3-thujone, and 3-isothujone at the α position as each is reduced by sodium borohydride in anhydrous solvents. Moreover, it was found[17] in the latter studies that the addition of at least 5% of water to the solvent was sufficient to inhibit the epimerization, an observation that led the investigators to conclude that a very strongly basic species exists in anhydrous alcoholic or ethereal solutions of sodium borohydride.

Prompted by the latter findings, both compounds **1** and **10** were reduced with sodium borodeuteride in 19:1 2-propanol–water. The product, isolated as its diacetate, was found to be entirely the D-allo derivative **11**, having deuterium incorporation exclusively at C-3. No D-gluco isomer (**12**) was evident, despite careful examination of the products by TLC and NMR spectroscopy.

The classical reduction mechanism readily accounts for the formation of **11**, but the D-gluco-2-*d* product **12** must arise via attack of the reductant at C-2. Possibly, in the dry solvent containing a base (such as BD_4^-), an enol A might become the substrate, with attack of the hydride from the upper face of the molecule to give, under product-development control, the D-gluco-2-*d* isomer B. Such a process would be favored in terms of release of steric strain in the species A, and may help to account for the fact that the 2-benzoate **10**, having a more bulky 2 substituent, gives rise to ~80% of the D-gluco-2-*d* product, compared with only ~50% with the 2-acetate **1**. That no D-manno product is found may be explained on steric grounds; the axial methoxyl group presumably offers sufficient hindrance to prevent approach of the hydride species from the underside of the molecule. The foregoing mechanism invokes a nucleophilic attack on an enediol intermediate, normally considered to be an unfavorable process, and other possible mechanisms should also be considered. Anchimeric participation by the 2-*O*-acyl group is one such possibility, but such a mechanism by way of a 2,3-ortho ester type of intermediate is difficult to reconcile with the observed D-gluco (and not D-allo) stereochemistry of the 2-deuterated product **12**. Further experimental work will be necessary to test the various possible mechanistic hypotheses.

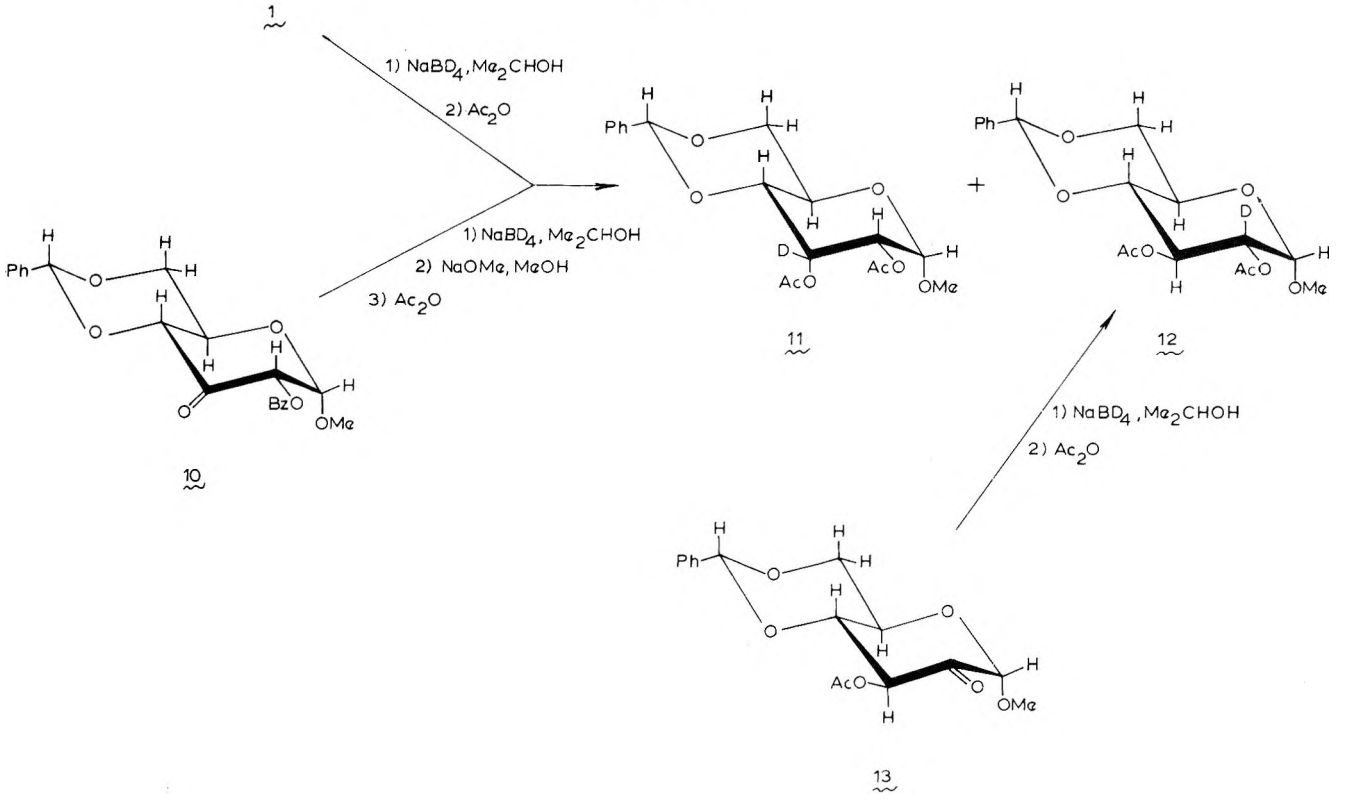
No enolization between C-3 and C-4 was evident in these reactions. Steric factors would probably exert some impedance to development of sp^2 hybridization at the ring-fusion position (C-4), but inductive stabilization by the 2-acyloxy group is probably the most important factor influencing formation of the 2,3-enol. The 2-benzoyloxy group would be the more effective intermediate of the two 2-acyloxy groups for such

Table II. First-Order Proton–Proton Coupling Constants[a]

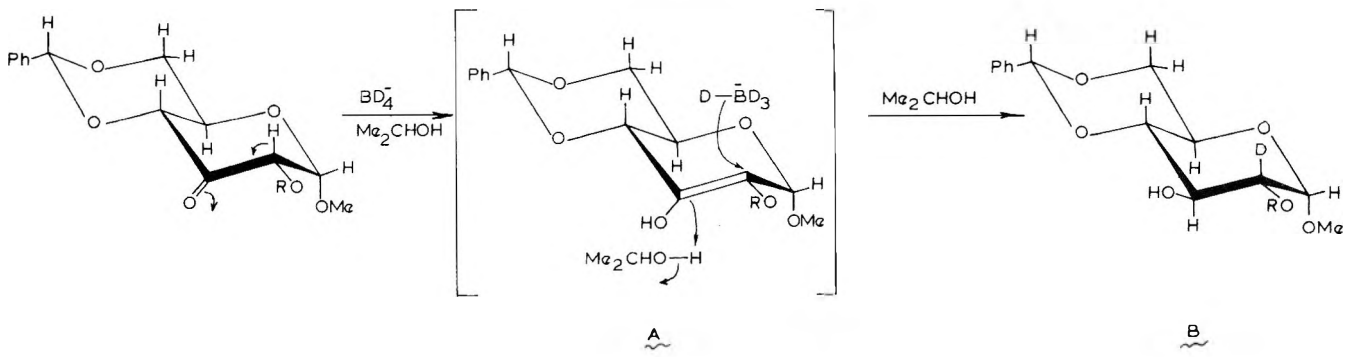
Compd	Solvent	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
1[b]	$CDCl_3$[c]	4.25	*d*	*d*	*e*	*e*	*e*	*e*
2	C_6D_6[f]	4	3.8	3.8	10	5	10	10
3	$(CD_3)_2SO$[c]	3.8	*e*	*e*	*e*	*e*	*e*	*e*
4	$CDCl_3$[f]				9.1	4.6	10.0	10.3
5	$CDCl_3$[c]	4.7	5.8	3.7	10.0	5.0	10.5	10.5
6	C_6D_6[c]	4.1	3.5	3.5	9.5	*e*	*e*	*e*
11	C_6D_6[h]	4.1	*d*	*d*	9.5	5.0	10.0	10.0
7[g]	C_6D_6[c]	4.0	10.0	10.0	10.0	5.0	10.0	11.2
12	C_6D_6[f]	*d*	*d*	10.0	10.0	5.0	10.0	11.2
8	$CDCl_3$[c]	4.0	4.5	2.6	9.5	5.0	9.4	9.4
8 (3-deut)	$CDCl_3$[h]	4.0	*d*	*d*	9.5	5.0	9.4	9.4
9	$CDCl_3$[c]	4.5	4.5	*e*	*e*	*e*	*e*	*e*
10	$CDCl_3$[h]	4.4	*d*	*d*	*e*	*e*	*e*	*e*
13	$CDCl_3$[f]	*d*	*d*	10.9	9.1	5.0	10.0	10.0

[a] Coupling constants are given in hertz. [b] Shows $J_{2,4} = 1.25$ Hz. [c] At 100 MHz. [d] Nonexistent proton for coupling. [e] Not measured because of second-order effects. [f] At 250 MHz. [g] See ref 13. [h] At 90 MHz.

Scheme II



Scheme III



1 R = $MeC(=O)-$

10 R = $PhC(=O)-$

stabilization. Acetylation of **1** under vigorous conditions (hot acetic anhydride–pyridine) gave 74% of the crystalline enediol diacetate **4**, whose NMR spectrum clearly indicated that the site of unsaturation was C-2–C-3 and not C-3–C-4.

In a further study related to the reduction of the glycos-3-uloses **1** and **10**, the borodeuteride reduction of methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose (**13**), prepared by oxidation of its alcohol precursor[15] with acetic anhydride–methyl sulfoxide, was examined. In both aqueous methanol and dry 2-propanol, only the D-gluco-2-*d* product was detected. Similar results have been observed[18] on reducing the ketone **13** with sodium borohydride in methanol–*N,N*-dimethylformamide. In this instance, the failure to detect any significant proportion of C-3-labeled product may arise from steric hindrance by the axial methoxyl group at C-1, which would be expected to inhibit axial attack by the reagent at C-3 of an enolic intermediate. Vigorous acetylation of **13** converted it into the enediol diacetate **4**.

The foregoing results point out the need for caution in assigning structures to products arising from the reduction of carbohydrate ketonic intermediates when dry solvents are employed. The use of solvents that contain at least 5% of water appears to be necessary to ensure labeling exclusively at the carbonyl carbon atom. On the other hand, the use of dry solvents may provide some new procedures for the synthesis of specifically labeled sugars heretofore accessible only with difficulty.

Experimental Section

General Methods. Evaporations were performed on a rotary evaporator at 45 ± 5 °C. Melting points were measured either on a microscope hotstage (Leitz) or in a capillary melting point apparatus (Hoover) and are not corrected. Optical rotations were determined either with a Quick-Polarimeter (Roussel and Jouan) or a Perkin-Elmer Model 141 spectropolarimeter. NMR spectra were recorded at either 90, 100, or 250 MHz with respectively Brüker WH-90, Varian HA-100, or Cameca-250 instruments; chemical shifts are reported on the δ scale (ppm) downfield from the internal standard of tetramethylsilane. Mass spectra (70 eV ionizing voltage) were determined with an AEI-MS9 instrument. Thin layer chromatography was performed with silica gel G (Merck), and column chromatography with silica gel 60 (Merck), 70–230 mesh (gravity flow) or <200 mesh (medium pressure in 316 stainless-steel columns at 6–10 atm). Solvents used were A, 3:1 dichloromethane–ether; B, 9:1 ether–hexane; C, 1:1 ether–hexane; or D, 7:3 chloroform–acetone.

General Procedure for Acetylation. To a solution of the alcohol in pyridine was added acetic anhydride with stirring. The mixture was stirred at room temperature, with protection from moisture, for the indicated time, after which the reaction was terminated by the addition of ice, with further stirring for 0.5–1 h. Volatile materials were evaporated off, and small portions of toluene were evaporated two to five times from the residue to remove traces of pyridine. The product was then dissolved in a small volume of chloroform or dichloromethane, washed sequentially with equal volumes of water, saturated aqueous sodium hydrogen carbonate, and water, and then dried (magnesium sulfate or sodium sulfate), to give, after evaporation of the solvent, a product that was processed, either by chromatography or crystallization, to give the pure acetate.

General Procedure for Processing Borohydride Reduction Reactions. After the reduction procedure indicated and decomposition of the excess reagent, the solvent was evaporated off, and methanol was repeatedly evaporated from the residue to remove boric acid as the volatile methyl borate. The product was thendissolved in chloroform or dichloromethane, washed with water, and the organic extract was dried (magnesium sulfate or sodium sulfate). The solvent was then evaporated and the product was either chromatographed or crystallized to give the pure compound.

Reduction of Methyl 2-*O*-Acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (1). A. With Sodium Borohydride in Aqueous Methanol. To a stirred solution of 800 mg (2.48 mmol) of the hexulose **1** in 90 ml of methanol was added 150 mg (3.58 mmol) of a solution of sodium borohydride in water. After 3 h, the solution was neutralized with a stream of carbon dioxide, and the methanol was evaporated off. Processing by the general method described gave 680 mg (97%) of an oil, homogeneous by TLC (R_f 0.31, solvent A). Crystallization from dichloromethane–hexane gave 934 mg (62%) of pure **2**: mp 58–60, 167–168 °C (anhydrous, from benzene); $[\alpha]^{21}D$ +128° (*c* 1, chloroform) [lit.[11] mp 60 °C, for the dihydrate, mp 148–149, mp[19] 175–177 °C, $[\alpha]D$ +126° (*N,N*-dimethylformamide[11])]; for NMR data see Tables I and II.

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.53; H, 6.29.

B. With Lithium Aluminum Hydride. A solution of 500 mg (13.5 mmol) of lithium aluminum hydride in 30 ml of tetrahydrofuran was added dropwise to a cold (0 °C), stirred solution of 1.03 g (3.10 mmol) of the hexulose **1** in 25 ml of the same solvent. After 2 h at 0 °C, the solution was heated under reflux for 1 h and cooled, and the excess reductant was decomposed with ethyl acetate. The resultant suspension was filtered through a bed of Celite, and the filtrate was evaporated to dryness. The residue was triturated in chloroform, and the remaining salts, which were precipitated upon addition of a few drops of saturated aqueous sodium hydrogen carbonate, were filtered off. The organic extract, after conventional processing, gave 700 mg (78%) of **2** as an oil that was homogeneous by TLC. Crystallization as in the preceding experiment gave product **2** (mp 58–59 °C) that was identical by $[\alpha]D$ and NMR spectrum with that from the preceding borohydride reduction of **1**.

C. With Sodium Borohydride in 2-Propanol. To a solution of 644 mg (2.00 mmol) of the glycos-3-ulose **1** in 250 ml of dry 2-propanol (reagent grade) was added 76 mg (4 equiv) of sodium borohydride, portionwise, with stirring and protection from moisture. After 0.5 h, the excess of reagent was decomposed by addition of a few drops of acetic acid. Processing by the general method described gave an oil that was dried and dissolved in 50 ml of dry methanol to which a 10-mg pellet of sodium had been added. After 1 h the solution was neutralized with carbon dioxide, and the solvent was evaporated off. The crude, deacetylated product was applied to a column of silica gel (45 g) and eluted successively with chloroform and then 9:1, 8:2, and 7:3 chloroform–methano (250 ml each) to give 186 mg (33%) of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**3**), mp 164–165 °C, $[\alpha]D$ +112° (*c* 1, chloroform) [lit.[20] mp 163–164 °C, $[\alpha]D$ +110° (c 2, chloroform)], and 198 mg (35%) of methyl 4,6-*O*-benzylidene-α-D-allopyranoside dihydrate, identical by melting point and $[\alpha]D$ with the products from the foregoing reductions A and B. An additional 43 mg (8.5%) of **2** and **3** was obtained as a mixture.

D. With Zinc Borohydride. To a solution of 363 mg (1.12 mmol) of **1** in 8 ml of dry 1,2-dimethoxyethane was added 4 ml (~2 mmol) of a solution of zinc borohydride[21] in the same solvent. After 0.5 h, TLC indicated complete reduction of **1**, and the excess of borohydride was decomposed by the addition of a 1 M solution of sodium hydrogen tartrate. The solvent was evaporated, and the residue was processed to give 290 mg of an oil that by TLC (solvent A) revealed two components (R_f 0.70 and 0.56). Chromatography on a column (1.4 × 60 cm) of silica gel (solvent A, 250 ml) gave 232 mg (64%) of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-allopyranoside (**8**) that was crystallized from ethyl acetate–hexane: mp 69–71 °C; $[\alpha]^{25}D$ +59.5° (*c* 0.8, chloroform); for NMR data see Tables I and II.

Anal. Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.28; H, 6.08.

With an additional 120 ml of solvent, 51 mg (14%) of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**9**) was obtained: mp 133–134 °C; $[\alpha]^{25}D$ +112° (*c* 1.2, chloroform) [lit.[22] mp 133–134 °C, $[\alpha]^{29}D$ +112° (*c* 0.9, chloroform)].

Methyl 2,3-Di-*O*-acetyl-4,6-*O*-benzylidene-α-D-allopyranoside (6). By the general procedure described, 200 mg (0.71 mmol) of **2** in 2 ml of pyridine was acetylated for 3 days with 2 ml (2.16 g, 21 mmol) of acetic anhydride. The oily product was applied to a column of silica gel (15 g) which was eluted with 65 ml of solvent A to give 256 mg (99%) of pure **6** as a syrup, $[\alpha]^{23}D$ +54° (c 1, chloroform), *m/e* 366 [$M^{\cdot+}$]. For NMR data see Tables I and II.

Anal. Calcd for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found: C, 59.02; H, 5.95.

Acetylation of Methyl 2-*O*-Acetyl-4,6-*O*-benzylidene-α-D-allopyranoside (8). A solution of 100 mg (0.31 mmol) of **8** in 5 ml of pyridine was acetylated during 20 h with 1 ml (an excess) of acetic anhydride. TLC (solvent B) of the oily product showed two zones (R_f 0.58, identical with **6**) and unreacted **2** (R_f 0.28). Column chromatography (solvent C, 100–200 psi, 1 × 50 cm) resolved the mixture to give 71 mg (68%) of **6**, $[\alpha]^{23}D$ +54° (*c* 1, chloroform), identical with authentic **6** by NMR spectroscopy; also obtained was 21 mg (19%) of unreacted **8**, mp 69–70 °C.

Methyl 4,6-*O*-Benzylidene-2,3-*O*-isopropylidene-α-D-allopyranoside (5). To a solution of 1.33 g (4.71 mmol) of **2** in 15 ml of dry acetone was added 1.5 g of anhydrous copper(II) sulfate. After stirring for 50 h at 20 °C, the suspension was filtered, and the filtrate

was evaporated to dryness to give an oil that by TLC (solvent A) was shown to be a mixture of starting material **2** (R_f 0.31) and a new product (R_f 0.94). Chromatography over a column (1.4 × 60 cm) of silica gel with solvent A gave 256 mg (19%) of an oil that eluted in 65 ml of solvent. Crystallization from dichloromethane–hexane gave 124 mg (8%) of pure **5**, mp 119–121 °C, $[\alpha]^{25}$D +131° (*c* 1.4, chloroform).

Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.33; H, 6.89.

Nonreacted **2** was recovered by eluting the column with an additional 235 ml of the solvent, yield 930 mg (69.9%), mp 59 °C.

Hydrolysis of Methyl 4,6-*O*-Benzylidene α-D-allopyranoside (2) and Identification of the Product as D-Allose. A. Hydrolysis. A solution of 50 mg (0.18 mmol) of **2**, obtained from either of the proceeding experiments (A or B), in 10 ml of 0.1 M hydrochloric acid was heated for 1 h under reflux. After cooling, the acid was neutralized by passing the solution through a small column of Amberlite MB-3 resin. Concentration of the aqueous eluate gave 19 mg of a crystalline product that was indistinguishable on paper chromatography (R_f 0.29, 1:4:1 pyridine–ethyl acetate–water, detection with aniline phthalate and sodium metaperiodate–benzidine) from allose and clearly distinguishable from glucose (R_f 0.26), mannose (R_f 0.32), and galactose (R_f 0.20).

B. Conversion into the Phenylosazone. To a solution of 400 mg of crude hydrolysate from **2** in 60 ml of water was added a solution of phenylhydrazine (0.5 ml) in acetic acid (0.5 ml), and the mixture was heated for 2 h at 100 °C. Cooling to 5 °C produced 359 mg of a yellow, semicrystalline product which, after nine crystallizations from 1:1 ethanol–water, gave yellow needles, mp 166–169 °C (lit.[23] mp 167–168 °C), $[\alpha]^{25}$D −38° (*c* 0.44, 2:3 pyridine–ethanol) [lit.[23] $[\alpha]$D −36.7° → (3 h) −48.4° (*c* 0.4, pyridine–ethanol)].

Reduction of Methyl 2-*O*-Acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (1) with Sodium Borodeuteride. A. In Dry 2-Propanol. To a solution of 533 mg (1.65 mmol) of **1** in 90 ml of anhydrous 2-propanol [dried over 3A molecular sieves (Linde)] was added portionwise 60 mg (3.46 equiv) of sodium borodeuteride with stirring and protection from moisture. After 0.5 h, 2–3 drops of acetic acid were added to decompose the excess of hydride, and the solution was evaporated to dryness. Analysis by TLC (solvent D) of the product obtained by the general processing procedure described revealed that the starting ketone **1** was absent, and that two closely migrating zones (R_f 0.70–0.75) were present. Acetylation of the crude product with 2 ml (an excess) of acetic anhydride and 10 ml of pyridine for 8 h at 25 °C gave a product containing three components (R_f 0.74, 0.58, and 0.28, solvent B). Subsequent pressure-column chromatography as in the preceding experiment gave sequentially as follows: (a) 195 mg (32%) of methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside-2-*d* (**12**), mp 106.5–107 °C (lit.[24] for the nondeuterated product mp 108–109 °C), $[\alpha]^{23}$D +74° (*c* 1, chloroform) (lit.[23] $[\alpha]$D +75.5° in chloroform), *m/e* 367 [M·+], R_f 0.74; (b) 139 mg (23%) of methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-allopyranoside-3-*d* (**11**), $[\alpha]$D +54° (c 1, chloroform), *m/e* 367 [M·+], R_f 0.58, and (c) 148 mg (28%) of unreacted monoacetate (as the 3-*d* analogue of **8**), mp 69–70 °C, R_f 0.29. In addition 62 mg (10%) of a mixture of **11** and **12** was obtained.

B. In 19:1 2-Propanol–Water. The foregoing reduction was repeated using 250 mg (0.78 mmol) of **1**, 30 mg (3.6 equiv) of sodium borodeuteride, and 60 ml of 19:1 2-propanol–water. Processing and acetylation as in procedure A revealed a product that showed two zones by TLC analysis (solvent B), R_f 0.58 and 0.29, corresponding to the allo diacetate **6** (**11**, 3-deuterated isomer) and the allo monoacetate **8** (as the 3-deuterated analogue), respectively. Column chromatography as in A gave 231 mg (81%) of **11**, $[\alpha]$D +54° (c 1, chloroform), identical with **11** from A by NMR spectroscopy, together with 24 mg (8%) of the 3-deuterated monoacetate identical with **8** by melting point.

Reduction of Methyl 2-*O*-Benzoyl-4,6-O-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (10) with Sodium Borodeuteride. A. In Dry 2-Propanol. As in the reduction of **1**, 384 mg (1 mmol) of **10**[25] was reduced with 42 mg (4 equiv) of sodium borodeuteride with 100 ml of anhydrous 2-propanol as solvent. The product obtained by the general procedure described was dissolved in 50 ml of anhydrous methanol. A 20-mg pellet of sodium was added, and the solution was stirred for 1 h, at which time the solution was neutralized with acetic acid, and the solvent was evaporated off. The crude product was acetylated with 2 ml (an excess) of acetic anhydride in 10 ml of pyridine for 8 h at 25 °C to give a product that by TLC (solvent B) showed three carbohydrate components (R_f 0.74, 0.58, and 0.29) identical with those from reduction of **1**. Chromatography as in the foregoing example resolved the mixture as follows: (1) 302 mg (83%) of the D-gluco derivative **12**, mp 106–107 °C, $[\alpha]$D +74° (*c* 1, chloroform); (2) 38 mg (10%) of the D-allo derivative **11**, $[\alpha]^{23}$D +4° (c 1, chloroform), R_f 0.58; (3) a trace of the D-allo monoacetate **8** (as its 3-deuterated analogue), R_f 0.29.

B. In 19:1 2-Propanol–Water. As in the preceding reduction, 77 mg (0.2 mmol) of **10** in 30 ml of 19:1 2-propanol–water was reduced with 10 mg (5.8 equiv) of sodium borodeuteride. The products, after acetylation (30 h), were examined by TLC (solvent B). Only the zones having R_f 0.58 (major) and 0.29 (trace) were present. Column chromatography as in part A gave 56 mg (75%) of the allo diacetate-3-*d* (**11**), $[\alpha]$D +54° (*c* 1, chloroform), identical with the product from the identical reduction of **1** by NMR spectroscopy. No gluco product (**12**) was detected.

Methyl 3-*O*-Acetyl-4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose (13). To a solution of 8 ml of acetic anhydride and 16 ml of methyl sulfoxide was added 1.63 g (5.06 mmol) of methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside,[15] and the mixture was stirred for 24 h, with protection from moisture. The mixture was evaporated to an oil that was applied to a column of silica gel (45 g) which was eluted with solvent A to afford 1.12 g (61%) of **13** that crystallized from chloroform–hexane, mp 104–106 °C, $[\alpha]^{25}$D +74° (*c* 0.9 chloroform), R_f 0.78 (solvent A).

Anal. Calcd for $C_{16}H_{18}O_4 \cdot H_2O$: C, 56.48; H, 5.92. Found: C, 56.62; H, 6.18.

For the anhydrous compound, Kondo et al.[18] reported mp 103–104 °C, $[\alpha]^{14}$D +36° (*c* 0.6, chloroform).

Reduction of Methyl 3-*O*-Acetyl-4,6-*O*-benzylidene-α-D-*xylo*-hexopyranosid-2-ulose (13). A. With Sodium Borodeuteride in Aqueous Methanol. To a solution of 200 mg (0.59 mmol) of the glycosulose **13** in 20 ml of 1:1 water–methanol was added portionwise, with stirring, 200 mg (5.28 mmol) of sodium borodeuteride. After ~30 min, carbon dioxide was added and the solvents were evaporated off. The residue was processed by the general procedure described to give a product (R_f 0.23, solvent A) that was acetylated in 2 ml of pyridine with 2 ml of acetic anhydride for 48 h to yield 210 mg of an oil (R_f 0.91, solvent A) that crystallized from chloroform–hexane to give 133 mg (55%) of **12**, identical with authentic 2-deuterated **12** by NMR spectroscopy, mp 106 °C, $[\alpha]^{25}$D +70° (*c* 1, chloroform).

B. With Sodium Borodeuteride in Dry 2-Propanol. To a solution of 302 mg (0.89 mmol) of the 2-ulose **13** in 5 ml of dry 2-propanol was added portionwise 110 mg (2.60 mmol) of sodium borodeuteride. The reaction was processed exactly as in A, to give, after column chromatography (15 g of silica gel, solvent A) of the acetylated product, 227 mg (70%) of pure **12**, identical with 2-deuterated **12** by NMR spectroscopy, mp 105 °C, $[\alpha]^{25}$D +70° (*c* 1, chloroform).

Methyl 2,3-i-*O*-acetyl-4,6-*O*-benzylidene-α-D-*erythro*-hex-2-enopyranoside (4). To a solution of 500 mg (1.55 mmol) of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (**1**) in 10 ml of dry pyridine was added 2.5 ml of acetic anhydride, and the mixture was heated with stirring for 3 days at 70 °C, at which time TLC revealed a new zone having R_f 0.85 (solvent A, R_f 0.78 for **1**). The solution was evaporated, and toluene (5 × 10 ml) was evaporated from the residue, which was finally dissolved in benzene (30 ml) and decolorized (animal charcoal). The oil (717 mg) obtained upon solvent evaporation was chromatographed on a column of silica gel (35 g) with solvent A to give, in 45 ml of eluent, 415 mg (74%) of the product having R_f 0.85. Crystallization from dichloromethane–heptane gave **4**: mp 187–190 °C; $[\alpha]^{25}$D +117° (*c* 1.34, chloroform); NMR data, see Tables I and II.

Anal. Calcd for $C_{18}H_{20}O_8$: C, 59.33; H, 5.53. Found: C, 59.56; H, 5.78.

Further elution of the column gave 168 mg of unreacted **1**.

The same product was obtained by similar acetylation of methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose (**13**).

Acknowledgments. The authors thank Mr. C. Boeder for preliminary experimental work on the reduction of compound **1**.

Registry No.—2-Phenylosazone, 59830-66-9; phenylhydrazine, 100-63-0; methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside, 18031-57-7.

References and Notes

(1) This work was supported by NIH Grant GM-11976 (OSURF Project 1820) and by a research grant from the Société L'Air Liquide, Paris.
(2) For a preliminary account see D. C. Baker, C. Boeder, J. Defaye, A. Gadelle, and D. Horton, *Carbohydr. Res.*, **40**, C6 (1975).
(3) See, for example, D. C. Baker, D. Horton, and C. G. Tindall, Jr., *Carbohydr.*

Res., 24, 192 (1972); Methods Carbohydr. Chem., 7, 3 (1976); J. Defaye and A. Gadelle, Carbohydr. Res., 42, 373 (1975).
(4) J. E. G. Barnett and D. L. Corina, Adv. Carbohydr. Chem. Biochem., 27, 127 (1972).
(5) D. M. Clode and D. Horton, Carbohydr. Res., 12, 477 (1970); 17, 365 (1971); 19, 329 (1971); D. C. Baker and D. Horton, ibid., 21, 269 (1972); D. C. Baker and T. H. Haskell, J. Med. Chem., 18, 1041 (1975).
(6) D. Horton and J. S. Jewell, Carbohydr. Res., 3, 255 (1966); D. Horton, J. S. Jewell, E. K. Just, and J. D. Wander, ibid., 18, 49 (1971).
(7) D. Horton, J. S. Jewell, E. K. Just, J. D. Wander, and R. L. Foltz, Biomed. Mass Spectrom., 1, 145 (1974).
(8) J. Defaye and A. Gadelle, Pulp Pap. Mag. Can., 75, 50 (1974).
(9) J. Defaye, H. Driguez, and A. Gadelle, Carbohydr. Res., 38, C4 (1974).
(10) J. Defaye and A. Gadelle, Carbohydr. Res., 35, 264 (1974).
(11) Y. Kondo, Carbohydr. Res., 30, 386 (1973).
(12) H. C. Brown and K. Ichikawa, J. Am. Chem. Soc., 84, 373 (1962).
(13) D. Horton and J. H. Lauterbach, J. Org. Chem., 34, 86 (1969).
(14) E. J. Bourne, M. Stacey, C. E. M. Tatlow, and J. C. Tatlow, J. Chem. Soc., 826 (1951).
(15) R. W. Jeanloz and D. A. Jeanloz, J. Am. Chem. Soc., 79, 2579 (1957).
(16) W. F. Erman and T. J. Flautt, J. Org. Chem., 27, 1526 (1962).
(17) V. Hach, E. C. Fryberg, and E. MacDonald, Tetrahedron Lett., 2629 (1971).
(18) Y. Kondo, N. Kashimura, and K. Onodera, Agric. Biol. Chem., 38, 2553 (1974).
(19) B. R. Baker and D. H. Buss, J. Org. Chem., 30, 2304 (1965).
(20) N. K. Richtmyer, Methods Carbohydr. Chem., 1, 108 (1962).
(21) P. Crabbé, G. A. Garcia, and C. Rius, J. Chem. Soc., Perkin Trans. 1, 810 (1973).
(22) E. J. Bourne, M. Stacey, C. E. M. Tatlow, and J. C. Tatlow, J. Chem. Soc., 826 (1951).
(23) G. J. F. Chittenden and R. D. Guthrie, J. Chem. Soc. C, 695 (1966).
(24) D. S. Mathews and G. T. Robertson, J. Chem. Soc., 696 (1933).
(25) F. A. Carey and K. O. Hodgson, Carbohydr. Res., 12, 463 (1970).

Synthesis of the ABC Ring System of Batrachotoxin and Several Related Highly Functionalized Cholane Derivatives[1]

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The objective of this work is the synthesis of the ABC ring system of the powerful neuropoison batrachotoxin (1) from cholic acid (2), utilizing intermediates which permit subsequent elaboration to the entire toxin molecule. Thus, stereoselective routes to a series of highly functionalized cholane derivatives are described, culminating with an efficient synthesis of **58** as follows: **2** → **5** → **38** → **51** → **53** → **58**. It was also shown that earlier established side-chain degradation procedures are applicable in this series, **7** → **22** and **40** → **45**, as potential entries to the D,E ring system of **1**. Unsuccessful approaches to the ABC ring system of **1** included the synthesis from **2** of epoxides **8** and **9**. Whereas earlier the oxidative cyclization of **18** → **20** had been described, epoxides **8** and **9** afforded ketones **12** and **13** under the cyclization conditions without formation of the desired **21**. In another approach, rather than 3α,9α-oxide **24**, dione **23** was obtained in high yield by treatment of epoxide **17** with methoxide ion. While **23** was convertible into ketone **25**, this last substance afforded neither hydrazone **28** nor epoxide **34**, two key intermediates required for a fragmentation approach to the ABC ring system. In another attempt **25** was reduced to an epimeric mixture **29** of C-7 alcohols. Mild MeOH–acid treatment of **29** led to a mixture of unsaturated keto steroids rather than to the desired 3α,9α-oxido ketal **33**.

Batrachotoxin (**1**) is one of four rare, powerfully toxic steroid alkaloids found in the skin of a small, brightly colored Colombian frog of the genus *Phyllobates*.[3] The molecule has proven important as a tool for the study of ion movements in electrogenic membranes.[4] Following the elegant structural elucidation studies of Witkop,[3] batrachotoxin has been the target of synthetic studies, those of Wehrli culminating in the formal total synthesis of the molecule from other steroids.[5] We have already described in preliminary form the synthesis of the ABC ring system of **1** from the readily available cholic acid (**2**).[1] We now present the details of this work together with the stereoselective synthesis and some reactions of several highly functionalized cholane derivatives which have proven useful in our initial evaluation of practical synthetic routes to the ABC ring system of batrachotoxin.

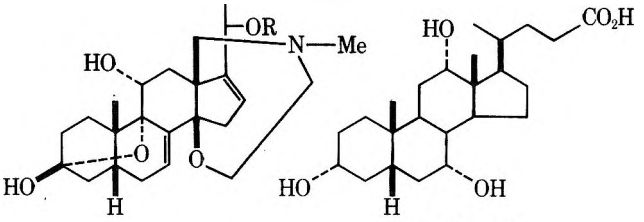
Our initial plan called for the synthesis of an intermediate possessing functional groups in the ABC portion of the molecule which would be relatively inert toward reagents required for the elaboration of the DE portion of the molecule, yet be readily convertible into the ABC system after the DE synthetic operations were completed. Methyl 3α,7α-diacetoxy-9α,11α-oxidocholanate (**6**) seemed ideal in view of the remarkable chemical stability exhibited by the 9α,11α-oxido grouping in several AB-cis steroids.[6] Moreover, Fieser[7] showed that the closely related alcohol **18** could be converted directly into the 11-oxo-3β-hydroxy 3α,9α-oxide **20** by oxidation with CrO_3.

Accordingly, epoxide **6** was synthesized from cholic acid as follows. Cholic acid (**2**) was converted into enone **3** by the method of Fieser.[8] Desulfurization of the corresponding dithioketal **4** afforded olefin **5**, epoxidation of which with *m*-chloroperoxybenzoic acid (MCPA) led to the desired epoxide **6**. The oxide ring was assigned the α orientation in accordance with the rule of rear attack,[9] the distinctive NMR splitting pattern of the C_{11} axial proton,[10] and the chemical shifts of the protons attached to C-18 and 19.[11] The overall process afforded 50 g of **6** starting with 200 g of cholic acid.

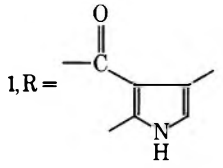
As a first step toward construction of the DE ring system of batrachotoxin, the acid **7** was prepared from epoxide **6** by selective hydrolysis of **6** with aqueous K_2CO_3–MeOH, affording acid alcohol **8** in 96% yield. Acetylation of **8** produced **7**. Treatment of **7** with $Pb(OAc)_4$[12] gave olefin **22** in high yield. Δ^{22}-Steroids have been employed by others[13] for efficient production of either bisnor acids or C-20 ketones.

Before proceeding further with the DE ring elaboration it seemed prudent to demonstrate the synthesis of the ABC system from epoxide **6** using Fieser's[7] oxidative cyclization procedure (**18** → **20**). Unfortunately, all attempts to oxidize acid **8** or its methyl ester **9** employing variations of Fieser's method uniformly led in near-quantitative yield to keto epoxides **12** and **13** with no hint of the desired oxide **21**. At the time it seemed likely that in **8** the 7α (axial) acetoxy group sterically prevented formation of the 3α,9α-oxide linkage present in **20**. In the light of our synthesis of ester **54** by an-

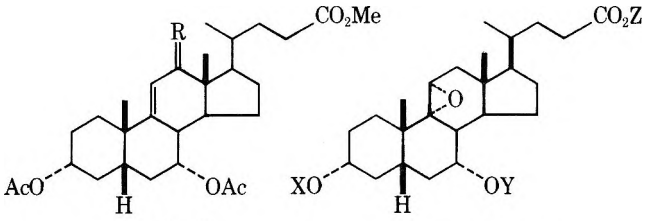
Chart I



2 (cholic acid)



1, R =

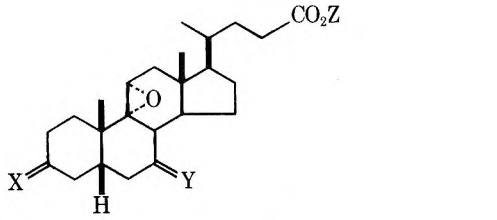


3, R = O

4, R =

5, R = H, H

6, X = Y = Ac; Z = Me
7, X = Y = Ac; Z = H
8, X = H; Y = Ac; Z = H
9, X = H; Y = Ac; Z = Me
10, X = Y = H; Z = Me
11, X = Ac; Y = H; Z = Me



12, X = O; Y = ; Z = H

13, X = O; Y = ; Z = Me

14, X = O; Y = ; Z = Me

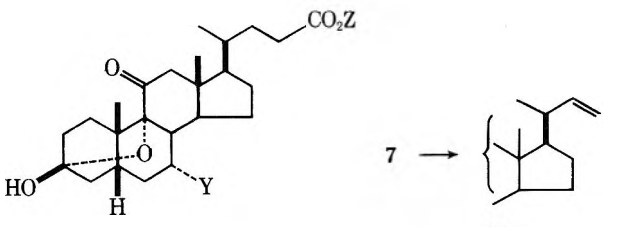
15, X = ; Y = O; Z = Me

16, X = ; Y = O; Z = Me

17, X = Y = O; Z = Me

18, X = ; Y = H, H; Z = Me

19, X = ; Y = O; Z = Me



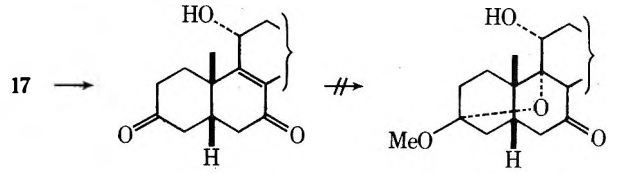
20, Y = H; Z = Me
21, Y = OAc; Z = H

22

other route (see below) this explanation seems tenuous. Epoxide **12** was characterized as its ester **13**, which on treatment with methoxide ion in methanol gave alcohol **14**.

These results required that the ABC ring system be assembled in a multistep manner from one of the above intermediates. The following exploratory chemistry was carried out. Treatment of diacetate **6** with methoxide ion afforded diol **10** in 93% yield. Reacetylation of **10** led to alcohol **11**, oxidation of which gave the 7-ketone **15**. Earlier,[14] a compound provisionally assigned the structure **15** was obtained as a by-product from the oxidation of a $\Delta^{7,9(11)}$-steroid. Its properties differed somewhat from those we have observed for **15** and are inconsistent with that structure (see Experimental Section).

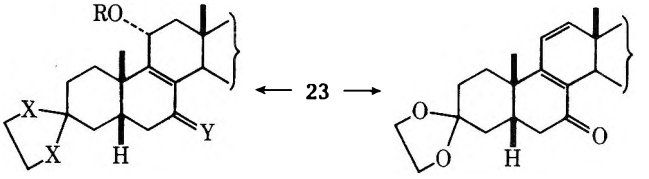
Gentle methoxide treatment of **15** afforded alcohol **16**. Finally, dichromate oxidation of diol **10** produced diketone **17**. With this latter substance in hand we had hoped to go directly to 3α,9α-oxide **24** by reaction with methoxide ion in methanol. Instead, dione **23** was obtained in greater than 90% yield. This substance could not be made to undergo cyclization to **24** under a variety of either acidic or basic conditions.



23 **24**

A second attempt to produce the 3α,9α-oxide linkage also proceeded from epoxide **17**. Thus, while Fieser[7] was able to effect a near-quantitative conversion of 3-oxo-9α,11α-oxido-5β-steroids into 11β-chloro-3α,9α-hemiacetals using HCl, our 3,7-dioxo-α-epoxide **17** failed to react with HCl under Fieser's conditions.

At this point we formulated a new plan toward the ABC ring system of batrachotoxin (see Scheme I) which required the synthesis of intermediates selectively ketalized at C-3. Exchange ketalization of dione **23** with TsOH and 2-methyl-2-



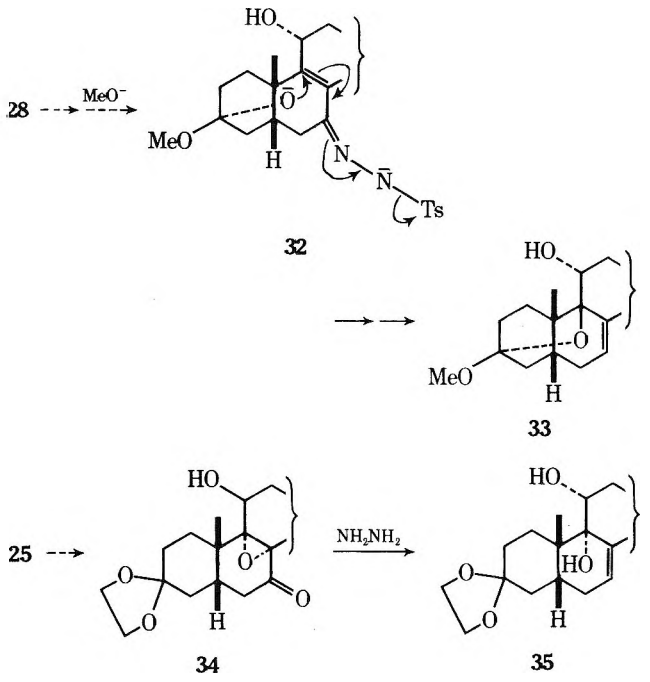
31

25, R = H; X = Y = O
26, R = Ac; X = Y = O
27, R = Ac; X = S; Y = O
28, R = H; X = O; Y = N—NTS
29, R = H; X = O; Y = H, OH
30, R = Ac; X = O; Y = H, OH

ethyldioxolane led to a complex mixture from which ketal **25** could be isolated in only 7% yield. Moreover, the highly selective[15,16] reagent, DMF ethylene acetal, and **23** under mild conditions led to dienone **31** (tentative assignment) in 30% yield. Formation of **31** is remarkable since the hydroxy group in **23** is a vinylogous α-hydroxy ketone.

An alternative synthesis of ketal **25** in good overall yield resulted from the selective ketalization of dione epoxide **17** with DMF ethylene acetal to produce ketal **19**, followed by treatment with methoxide ion. Efforts to execute the plan of Scheme I which envisaged a novel methoxide ion induced fragmentation (**32** → **33**) of the tosylhydrazone **28** were thwarted by our inability to prepare **28** in acceptable yield from ketone **25**. Similarly, an intended use of the Wharton reaction[17] in the conversion of epoxy ketone **34** to olefin **35** was prevented by the extreme resistance of the double bond of **25** toward a variety of epoxidizing agents, including MCPA and alkaline H_2O_2. With the aim of removing the C-7 ketone

Scheme I



function of **25** for another series of experiments, this substance was converted into acetate **26** and then treated with ethanedithiol. Rather than formation of the C-7 thioketal, we observed complete exchange at C-3, producing dithioketal **27**.

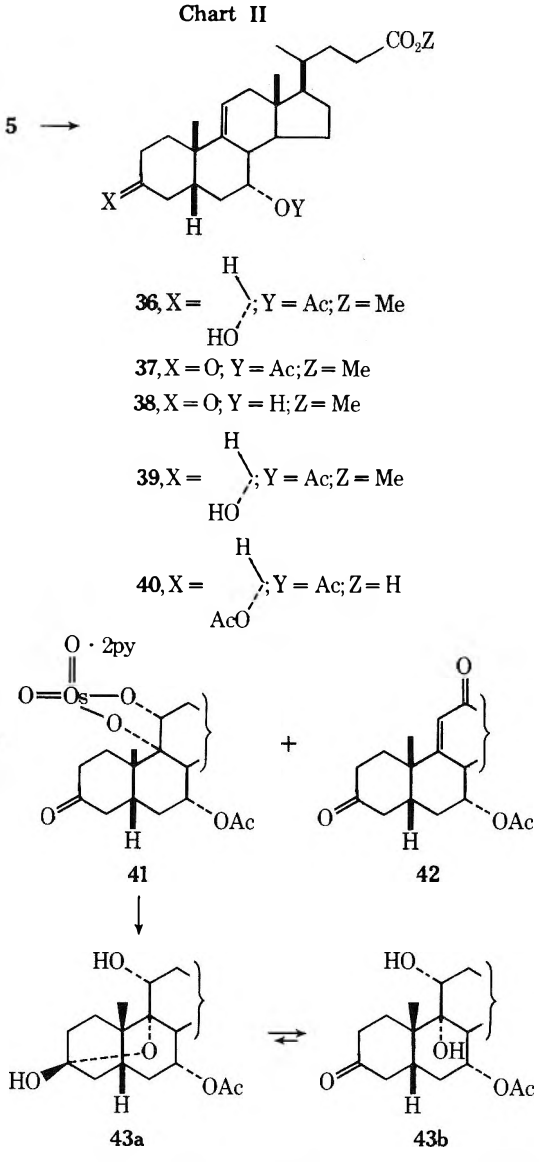
Our final efforts toward utilization of these substances for batrachotoxin-oriented synthetic work involved $NaBH_4$ reduction of ketone **25** to a crystalline epimeric mixture **29** of alcohols at C-7. Witkop[3] indicated that the ring system produced by $NaBH_4$ reduction of batrachotoxinin A underwent facile acid-catalyzed rearrangements to a mixture of enediols involving C-7, 8, 9, and 11. We therefore treated intermediate enediol **29** with very dilute HCl in MeOH with the hope of trapping the correct isomer as the $3\alpha,9\alpha$-oxide **33**. Even under very mild conditions we observed a clean conversion to what appeared to be a mixture of Δ^8-3,7-dione and Δ^8-3,11-dione steroids. Similarly, acetate **30**, prepared by $NaBH_4$ reduction of **26**, failed to afford the desired ring system present in **33**.

During the course of the above experiments there appeared a report from the Wehrli laboratory[18] of a successful osmylation of a 3-oxo-$\Delta^{9(11)}$-5β-steroid. Whereas in Fieser's[6] account of the inertness of the 5β-$\Delta^{9(11)}$-steroids toward OsO_4 reaction conditions were not given, Wehrli[18] achieved osmylation in pyridine at 25 °C over 7 days. An ideal candidate for the osmylation and subsequent introduction of the ring B double bond in our series was keto acetate **37**. This substance was obtained in high overall yield from diacetate **5** via selective hydrolysis to alcohol **36** followed by esterification to **39** and subsequent oxidation.

In keto acetate **37** the axial 7α-acetate group was expected to retard still further reaction with the bulky osmium reagent. In the event the reaction required 8 days (followed by TLC). Chromatography afforded crystalline osmate ester **41** in 50% yield together with starting **37** (34%) and a crystalline byproduct, enone **42**, in 15% yield. Formation of this latter product is interesting in that to our knowledge, allylic oxidation during osmylation is without precedent, although Cross[19] observed the oxidation of secondary alcohols during osmylation. Cleavage of osmate **41** proceeded well with H_2S–NH_4Cl, producing hemiacetal **43** (see below for a discussion of hemiacetal vs. ring open equilibria) in 93% yield.

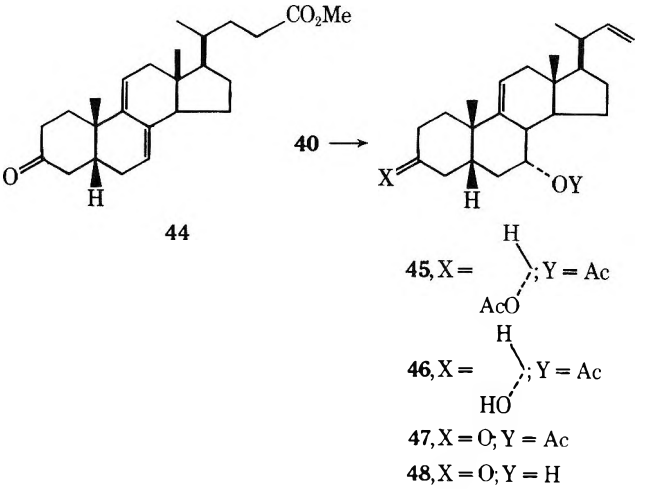
Our synthetic series at this point was linked to earlier work through the conversion of acetate **37** into alcohol **38** followed

Chart II



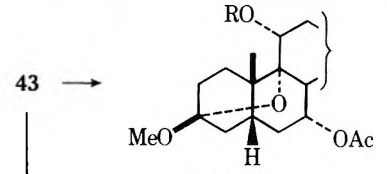
by dehydration with $POCl_3$ in pyridine to the known[14] $\Delta^{7,9(11)}$-ketone **44**.

A series of $\Delta^{9(11),22}$-dienes were also prepared at this stage as potential candidates for osmylation studies. Thus, acetylation of **36** gave acid **40**, oxidative decarboxylation of which with $Pb(OAc)_4$ afforded crystalline diene **45** in 90% yield. Ketones **47** and **48** were then prepared from intermediate alcohol **46** by oxidation followed by deacetylation as in the previous preparations of the corresponding C-24 esters **37** and **38**. Preliminary studies indicated that the presence of an

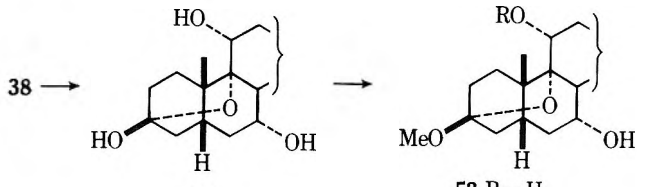


unprotected hydroxyl group in the 7α position greatly facilitated the reaction of the 9(11) double bond with OsO_4. We were thus led to the discovery of the facile reaction of alcohol ester **38** with OsO_4 in which hemiacetal **51** was obtained after 1 day reaction in 98% yield.

Originally we had prepared **51** by deacetylation of **43**. Acetate **43** was at first converted into acetal **49** by treatment with acidic MeOH and thence to diacetate **50** by acetylation. To our surprise, prolonged reflux of **49** with methoxide ion in



49, R = H
50, R = Ac

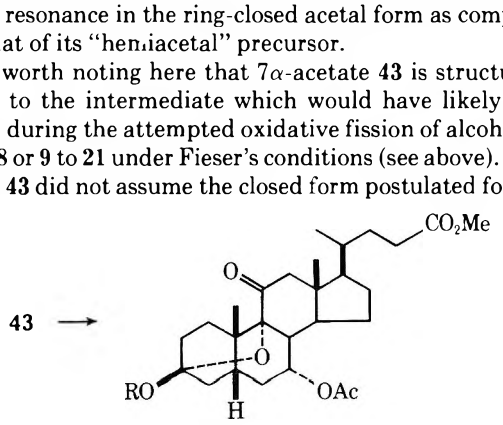


51 **52**, R = H
53, R = Ac

MeOH did not effect deacetylation at C-7 to give diol **52**. This suggested that, once formed, diol acetal **52** might undergo selective acetylation at C-11, producing 11α-acetate acetal **53**. Accordingly, diol hemiacetate **51** was converted into acetal **52** and treated with acetic anhydride–pyridine, affording **53** in near-quantitative yield.

Thus far we have indicated the structure of steroids **43** and **51** as hemiacetals although equilibrium with the ring-opened isomer is possible. Indeed, inspection of the NMR spectra (see Experimental Section) of the well-characterized crystalline steroids **43** and **51** shows quite clearly that 7α-acetate **43** exists (at 25 °C in $CDCl_3$) primarily in the ring-opened 3-keto 9α-alcohol form **43b**, whereas **51** appears to be a slowly (NMR time scale) equilibrating mixture of closed and open forms. These conclusions follow by noting the position of the C-19 methyl resonance in the ring-closed acetal form as compared with that of its "hemiacetal" precursor.

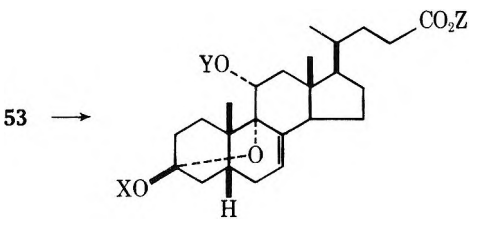
It is worth noting here that 7α-acetate **43** is structurally similar to the intermediate which would have likely been formed during the attempted oxidative fission of alcohol epoxides **8** or **9** to **21** under Fieser's conditions (see above). Since acetate **43** did not assume the closed form postulated for that



54, R = H
55, R = Me

intermediate, some support is lent to the steric argument advanced above to explain the failure of 3α,9α-oxide formation from **8** or **9**. We further examined this process by oxidizing **43** to the 11-keto hemiacetal **54**, purified as the acetal **55**. Interestingly, however, the angular methyl resonances of keto acetate **54**, when compared with those for acetal **55**, indicated that when a C-11 keto group was present, the ring closed form is dominant at equilibrium (cf. **43** above).

Returning to the completion of the synthesis of the toxin's ABC ring system, dehydration of 11α-acetate **53** with $POCl_3$



56, X = Me, Y = Ac; Z = Me
57, X = H; Y = Ac; Z = Me
58, X = Y = Z = H
59, X = Y = H; Z = Me

in pyridine afforded Δ^7-acetal **56** as a colorless oil. The protective methyl acetal of **56** was then hydrolyzed with dilute perchloric acid, giving crystalline Δ^7-hemiacetal **57**. Finally, alkaline hydrolysis of **57** afforded the ABC ring system of batrachotoxin as contained in 3β,11α-dihydroxy-3α,9α-oxido-5β-chol-7-enic acid (**58**), mp 172–174 °C, and its methyl ester **59**.

Experimental Section[20]

Methyl 3α,7α-Diacetoxy-5β-chol-9(11)-enate (5). To a solution of methyl 3α,7α-diacetoxy-12-oxo-5β-chol-9(11)-enate (**3**,[8] 50.2 g, 0.10 mol, mp 154–156 °C) in $CHCl_3$ (50 ml) was added 1,2-ethanedithiol (42 ml) and the solution was cooled to −15 °C. (N_2). Anhydrous HCl (ca. 2 l.) was then passed through the solution after which the temperature was raised and maintained at 0 °C for 20 h. The usual workup gave 50.5 g of crude **4** (87%) suitable for further reaction, *m/e* 578 (M^+). To a solution of crude **4** (10.0 g) in absolute EtOH (200 ml) was added Raney nickel (ca. 65 g) and the mixture was refluxed (N_2) for 8 h. The usual workup afforded 8.10 g of foam. Crystallization from hexane gave **5** (7.16 g, 85%, mp 104–108 °C) as colorless needles suitable for further reaction. Two additional crystallizations from hexane gave the analytical sample as colorless needles: mp 114–115 °C; NMR δ 0.62 (s, 3, C-18 H), 1.10 (s, 3, C-19 H), 2.04 (s, 6, $COCH_3$), 3.72 (s, 3, CO_2CH_3), 4.62 (m, 1, C-3 H), 5.12 (m, 1, C-7 H), 5.51 (m, 1, C-11 H); *m/e* 428 (M − AcOH), 413, 368, 353. Anal. Calcd. for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08. Found: C, 71.63; H, 9.26.

Methyl 3α,7α-Diacetoxy-9α,11α-oxido-5β-cholanate (6). To a solution of **5** (15.0 g, 30.7 mmol) in $CHCl_3$ (80 ml) was added MCPA (6.0 g). The mixture was stirred at 45 °C overnight. The usual workup followed by crystallization from hexane and then MeOH gave **6** (12.0 g, 77%, mp 123–126 °C) as colorless prisms. Preparative TLC afforded the analytical sample: mp 125.5–127 °C; NMR δ 0.67 (s, 3, C-18 H), 1.16 (s, 3, C-19 H), 2.05 (s, 3, C-7 $COCH_3$), 2.11 (s, 3, C-3 $COCH_3$), 3.15 (m, 1, C-11 H), 3.73 (s, 3, CO_2CH_3), 4.70 (m, 1, C-3 H), 5.21 (m, 1, C-7 H); *m/e* 504 (M^+), 462, 444, 402, 384. Anal. Calcd for $C_{29}H_{44}O_7$: C, 69.02; H, 8.79. Found: C, 69.25; H, 8.88.

3α-Hydroxy-7α-acetoxy-9α,11α-oxido-5β-cholanic Acid (8). A mixture of **6** (500 mg), K_2CO_3 (700 mg), MeOH (10 ml), and water (4 ml) was heated briefly on the steam bath until a clear solution was obtained. The temperature of the solution was then maintained at 40–45 °C for 6 h. The usual workup produced a colorless oil which was crystallized from MeOH–water, affording pure **8** (430 mg, 96%) as long, colorless needles: mp 177–179 °C; *m/e* 448 (M^+), 446, 416, 388, 294, 280. Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.83; H, 9.12.

3α,7α-Diacetoxy-9α,11α-oxido-5β-cholanic Acid (7). A solution of **8** (225 mg), pyridine (0.75 ml), and Ac_2O (0.4 ml) was heated (N_2) at 100 °C for 0.5 h. The usual workup gave a light yellow oil which was crystallized from acetone–hexane to yield **7** (218 mg, 89%, mp 175–180 °C) suitable for further reaction. Recrystallization from acetone–hexane gave the analytical sample: mp 182–183 °C; *m/e* 490 (M^+), 448, 430, 388, 370. Anal. Calcd for $C_{28}H_{42}O_7$: C, 68.55; H, 8.63. Found: C, 68.47; H, 8.74.

3α,7α-Diacetoxy-9α,11α-oxido-5β-24-norchol-22-ene (22). To **7** (188 mg) was added benzene (2.75 ml), $Pb(OAc)_4$ (330 mg), $Cu(OAc)_2$ (16 mg), and pyridine (0.15 ml). This mixture was heated (N_2) on the steam bath for 0.5 h. Filtration and removal of the solvent gave a green oil (246 mg). Chromatography over silica gel (4 g) gave **22** (54 mg) as a colorless oil. Yields approaching 90% have been obtained with longer reaction periods (4–6 h). Crystallization occurred on slow evaporation of a hexane solution giving **22** as small, colorless needles: mp (liquid transition at 80 °C) 103–106 °C; *m/e* 444 (M^+),

402, 384, 368, 342. Anal. Calcd for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found: C, 72.85; H, 9.24.

Methyl 3α-Hydroxy-7α-acetoxy-9α,11α-oxido-5β-cholanate (9). An ethereal solution of 8 (50 mg) was treated with excess CH_2N_2. The ether was then removed to afford **9** as an oil which crystallized from hexane as long, colorless needles (49 mg, 95%): mp 114–114.5 °C; *m/e* 462 (M^+). Anal. Calcd for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 70.31; H, 9.37.

3-Oxo-7α-acetoxy-9α,11α-oxido-5β-cholanic Acid (12) and Methyl 3-Oxo-7α-acetoxy-9α,11α-oxido-5β-cholanate (13). Following the method of Fieser,[8] alcohol 8 (33 mg) was dissolved in HOAc (0.75 ml) and cooled to 9 °C at which point a solution of chromic acid (35 mg) in water (0.06 ml) was added. After the solution had stood at 4 °C for 16 h, the usual workup gave **12** (30 mg, 91%) as a waxy, white solid: NMR δ 0.71 (s, 3, C-18 H), 1.28 (s, 3, C-19 H), 2.06 (s, 3, $COCH_3$), 3.17 (m, 1, C-11 H), 5.21 (m, 1, C-7 H), 9.67 (1, CO_2H). Crude **12** (28 mg) was taken up in MeOH (1 ml) and a trace of 48% HBr added. The mixture was allowed to stand overnight. Removal of the solvent gave **13** (28 mg, 97%) as a colorless oil. Two recrystallizations from hexane gave the analytical sample: mp 132–133 °C; *m/e* 460 (M^+), 418, 400. Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.41; H, 8.75. Found: C, 70.39; H, 9.17. The keto acid **12** was also obtained when this chromate oxidation procedure was carried out at 25 °C. At 40 °C a complex mixture of products was produced. Methyl ester **9** also afforded ketone **13** when oxidized with chromic acid at 9 °C or with sodium dichromate in acetic acid at 25 °C.

Methyl 3-Oxo-7α-hydroxy-9α,11α-oxido-5β-cholanate (14). To **13** (20 mg) was added excess NaOMe–MeOH solution. After a 2-h reflux (N_2), the usual workup afforded **14** (16 mg, 88%) (acetone–hexane) as long, colorless needles: mp 137–138 °C; *m/e* 418 (M^+), 400, 385, 382. Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.78; H, 9.47.

Methyl 3α,7α-Dihydroxy-9α,11α-oxido-5β-cholanate (10). To **6** (9.80 g) was added a solution formed from Na (1.2 g) added to MeOH (80 ml) and the reaction mixture was refluxed (N_2) for 2 h. The usual workup afforded **10** as white needle clusters (7.6 g, 93%, mp 114–120 °C) (aqueous EtOH) suitable for further reaction. Chromatography and then recrystallization from methylcyclohexane afforded the analytical sample of **10** as long, colorless needles: mp 126–126.5 °C; *m/e* 420 (M^+), 402, 384. Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.42; H, 9.67.

Methyl 3α-Acetoxy-7α-hydroxy-9α,11α-oxido-5β-cholanate (11). To **10** (50 mg) was added (N_2) at 0 °C a solution of Ac_2O in pyridine (16:1, 2 ml). The resulting solution was stirred at 25 °C for 5 h. The usual workup yielded 59 mg of crude, partly crystalline material. Chromatography over silica gel (2 g) gave pure **11** (44 mg, 80%) as small, colorless needles: mp 129–130 °C; *m/e* 462 (M^+), 444, 402, 384. Anal. Calcd for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 70.04; H, 9.22.

Methyl 3α-Acetoxy-7-oxo-9α,11α-oxido-5β-cholanate (15). To **11** (26 mg) in HOAc (0.5 ml) was added a solution of sodium dichromate dihydrate (9 mg) in HOAc (0.1 ml) and the dark solution was left at 25 °C for 3 h. Pouring the solution over ice and dilution with water gave a precipitate which was filtered to yield 25.0 mg of a white powder. Recrystallization from hexane afforded pure **15** (20.0 mg, 76%) as colorless needles: mp 147–147.5 °C; NMR δ 0.69 (s, 3, C-18 H), 1.38 (s, 3, C-19 H), 2.00 (s, 3, $COCH_3$), 3.12 (m, 1, C-11 H), 3.68 (s, 3, CO_2CH_3), 4.80 (m, 1, C-3 H); *m/e* 460 (M^+), 432, 416, 400, 189. Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.41; H, 8.75. Found: C, 70.29; H, 8.75.

Fieser[14] had provisionally assigned the same structure **15** to a by-product isolated after perbenzoic acid oxidation of methyl 3α-acetoxychola-7,9(11)-dienate. He found for **15** mp 152–153.5 °C. Found: C, 70.81; H, 8.91. His material crystallized from cold $CHCl_3$–MeOH, a solvent system too polar for recrystallization of **15**.

Methyl 3α-Hydroxy-7-oxo-9α,11α-oxido-5β-cholanate (16). To **15** (15 mg) was added excess NaOMe–MeOH solution. The resulting solution was refluxed for 0.5 h (N_2). The usual workup followed by chromatography over silica gel (0.5 g) afforded **16** (8 mg, 50%) as small needles. Recrystallization from acetone–hexane gave the analytical sample, mp 145–145.5 °C. Anal. Calcd for $C_{25}H_{38}O_5$; *m/e* 418.272. Found: *m/e* 418.271.

Methyl 3,7-Dioxo-9α,11α-oxido-5β-cholanate (17). To **10** (6.00 g) dissolved in HOAc (80 ml) was added a solution of sodium dichromate dihydrate (3.4 g) in HOAc (30 ml). The resulting dark solution was stirred overnight at 25 °C and then poured into water (3.5 l.). The usual workup followed by crystallization from acetone–hexane gave slightly dark **17** (4.50 g, 76%, mp 165–170 °C). An analytical sample was prepared by chromatography over silica gel: mp 171–173 °C; *m/e* 416 (M^+), 401, 398, 388, 372; ORD Φ_{302}^{22} −133°, Φ_{266}^{22} +3100°. Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71; *m/e* 416.256. Found: C, 71.67; H, 8.53; *m/e* 416.253. Treatment of **17** with a saturated solution of HCl in $CHCl_3$ after the method of Fieser[15] gave after workup complete recovery of **17**.

Methyl 3,7-Dioxo-11α-hydroxy-5β-chol-8-enate (23) and 3,7-Dioxo-11α-hydroxy-5β-chol-8-enic Acid. To **17** (1.00 g) was added a solution of NaOMe prepared from MeOH (25 ml) and Na (0.1 g). The reaction mixture was then heated briefly on a steam bath to give a clear solution which was cooled and stirred at 25 °C for 0.5 h. White needles of enone **23** began to separate out during this period. The mixture was cooled to 0 °C and neutralized with HOAc, and the product was precipitated with water (800 ml). Filtration gave crude **23** (890 mg, 89%, mp 195–198 °C). Recrystallization from MeOH afforded long, colorless needles (765 mg, 76.5%): mp 200–201 °C; NMR δ 0.65 (s, 3, C-18 H), 1.64 (s, 3, C-19 H), 3.66 (s, 3, CO_2CH_3), 4.82 (m, 1, C-11 H); ir 3595 (w), 3450 (w), 2945 (s), 1710 (s), 1668 cm^{-1} (s, enone); *m/e* 416 (M^+), 414, 412, 398, 383; uv max EtOH) 252 nm (log ε 3.95). Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.77; H, 8.69.

The corresponding C-24 acid of **23** was obtained as colorless needles by treatment of **17** with KOH in MeOH. This acid, which readily gave **23** on reaction with diazomethane, analyzed as the monohydrate (mp 189–191 °C). Anal. Calcd for $C_{24}H_{34}O_5 \cdot H_2O$: C, 68.55; H, 8.63. Found: C, 68.43; H, 8.36.

Methyl 3-Ethylenedioxy-7-oxo-5β-chola-8,11-dienate (31). To a solution of **23** (700 mg) in CH_2Cl_2 (25 ml) were added dimethylformamide ethylene acetal (2.5 ml) and HOAc (2.5 ml). This solution was refluxed (N_2) for 3 h. The usual workup followed by chromatography over silica gel (10 g) afforded **31** (213 mg, 30%) as light yellow needles. Recrystallization from hexane gave the analytical sample: mp 144–146 °C; NMR δ 0.67 (s, 3, C-18 H), 1.27 (s, 3, C-19 H), 3.67 (s, 3, CO_2CH_3), 3.90 (s, 4, OCH_2–), 6.03 (d, J = 10 Hz, 1, C-11 H), 6.78 (d, J = 10 Hz, 1, C-12 H); ir 2950 (s), 1726 (s), 1644 cm^{-1} (s, dienone); *m/e* 442 (M^+), 427, 411, 397, 327, 300; uv max (EtOH) 310 nm (log ε 3.88). Anal. Calcd for $C_{27}H_{38}O_5$: C, 73.27; H, 8.65. Found: C, 73.23; H, 8.77.

Methyl 3-Ethylenedioxy-7-oxo-9α,11α-oxido-5β-cholanate (19) and 3-Ethylenedioxy-7-oxo-9α,11α-oxido-5β-cholanic Acid. To a solution of **17** (2.00 g) in CH_2Cl_2 (55 ml) were added dimethylformamide ethylene acetal (6 ml) and HOAc (6 ml). The resulting light yellow solution was refluxed (N_2) for 3 h. The usual workup afforded 3.5 g of a yellow solid wet with high-boiling liquids. Extraction of this material into hot heptane (4 × 50 ml) left a dark yellow residue (350 mg). On cooling to 0 °C the heptane solution yielded **19** (529 mg, mp 162–166 °C) as hard white crystals. Chromatography of the mother liquor over silica gel (30 g) (benzene) afforded an additional 889 mg of **19**. The combined portions of **19** (1.42 g, 64%, mp 162–166 °C) were suitable for further reaction. The analytical sample was obtained by recrystallization from heptane: mp 169–171 °C; *m/e* 460 (M^+), 445, 442, 432, 416. Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.41; H, 8.75. Found: C, 70.55; H, 8.75.

Several attempts were made to prepare epoxide **34** by treatment of **19** in *t*-BuOH/water/NaOH, with 30% H_2O_2.[21] In all cases saponified **19** was isolated in near-quantitative yield as small, colorless needles: mp 189–190 °C; *m/e* 446 (M^+), 444, 428, 413; uv max (EtOH) 250 nm (log ε 3.93). The elemental analysis showed fractional retention of water. Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.54; H, 8.99.

Methyl 3-Ethylenedioxy-7-oxo-11α-hydroxy-5β-chol-8-enate (25). To **19** (200 mg) was added a solution of NaOMe prepared from MeOH (20 ml) and Na (100 mg). The mixture was briefly heated (N_2), forming a light yellow solution which was cooled to 25 °C and stirred for 0.5 h. The usual workup followed by crystallization from acetone–hexane afforded **25** as colorless plates (174 mg, 87%): mp 140–141 °C; NMR δ 0.58 (s, 3, C-18 H), 1.35 (s, 3, C-19 H), 3.63 (s, 3, CO_2CH_3), 3.87 (s, 4, OCH_2–), 4.58 (m, 1, C-11 H); ir 2487 (w), 2947 (s), 1727 (s), 1666 cm^{-1} (s, enone); *m/e* 460 (m^+), 442, 427, 411, 328; uv max (EtOH) 250 nm (log ε 3.93). Anal. Calcd. for $C_{27}H_{40}O_6$: C, 70.41; H, 8.75; *m/e* 460.282. Found: C, 70.41; H, 9.21; *m/e* 460.280.

Methyl 3-Ethylenedioxy-7-oxo-11α-acetoxy-5β-chol-8-enate (26) and Methyl 3-Ethylenedithio-7-oxo-11α-acetoxy-5β-chol-8-enate (27). To **25** (100 mg) was added pyridine (3 ml) and Ac_2O (0.5 ml) and the solution was heated (N_2) at reflux for 3 h. The usual workup followed by chromatography over silica gel (2 g) afforded acetate **26** (110 mg) as a colorless oil which would not crystallize: NMR δ 0.62 (s, 3, C-18 H), 1.32 (s, 3, C-19 H), 2.02 (s, 3, $COCH_3$), 3.63 (s, 3, CO_2CH_3), 3.88 (s, 4, OCH_2–), 5.63 (dd, J = 7, 4.5 Hz, 1, C-11 H).

To a solution of crude **26** (130 mg) in $CHCl_3$ (2 ml) was added 1,2-ethanedithiol (0.025 ml). After cooling to −15 °C (N_2), dry HCl was bubbled through the solution for 1 min. After 20 h at 5 °C, the bright red solution was basified with solid Na_2CO_3, diluted with ether,

and filtered. The ether solution was washed successively with cold 5 N NaOH, water, 2 N HCl, water, and brine. After drying (Na_2SO_4) the solvent was removed, affording 101 mg of a yellow oil. Chromatography over silica gel gave **27** as a light yellow oil. Dissolving this oil in methanol and allowing the solvent to evaporate overnight provided long, thin, yellow needles of **27** (89.5 mg, 65%): mp 105 °C dec; NMR δ 0.58 (s, 3, C-18 H), 1.33 (s, 3, C-19 H). 2.03 (s, 3, $COCH_3$), 3.28 (s, 4, SCH_2–), 3.67 (s, 3, CO_2CH_3), 5.60 (m, 1, C-11 H); ir 2960 (m), 1729 (s), 1676 cm^{-1} (m, enone); *m/e* 534 (M^+), 492, 474, 459, 443, 416, 414, 359, 328, 305; uv max (EtOH) 248 nm (log ϵ **4**). Anal. Calcd for $C_{29}H_{42}O_5S_2$: C, 65.13; H, 7.92. Found: C, 65.17; H, 8.03.

Isomerization of Intermediates 30 and 29. To a solution of crude **26** (148 mg) in MeOH (2 ml) was added $NaBH_4$ (100 mg). The mixture was stirred (N_2) for 3 h at 25 °C. The usual workup afforded 142 mg of a white powder. Extraction into hot hexane and removal of the solvent gave **30** (130 mg, 88%) as a white powder (mixture of C-7 epimers): NMR δ 0.60 (s, 3, C-18 H), 1.67 (s, 3, C-19 H), 2.01 (s, 3, $COCH_3$), 3.67 (s, 3, CO_2CH_3), 3.92 (s, 4, OCH_2–), 4.13 (m, 1, C-7 H), 5.63 (m, 1, C-11 H); *m/e* 444 (M − AcOH), 442, 426, 411, 395, 364, 312. Attempts to isomerize **30** to the Δ^7-9-ol with aqueous oxalic acid/dioxane, HCl/MeOH/water, or THF/water/$HClO_4$ led to products spectrally identified as diones and enones. Alcohol **29** (prepared as above from **25** and $NaBH_4$) gave mixtures of enones [uv max (EtOH) 253 nm] upon treatment with aqueous acid.

3α-Hydroxy-7α-acetoxy-5β-chol-9(11)-enic Acid (36). A mixture of 5 (8.10 g), K_2CO_3 (11.5 g), MeOH (160 ml), and water (65 ml) was heated briefly on the steam bath and then maintained at 40–45 °C for 6 h. Concentration under vacuum, dilution with water, and addition of HOAc (9 ml) gave a flocculent white precipitate. Filtration and drying gave crude **36** (7.15 g, 99%) as a white powder: NMR δ 0.58 (s, 3, C-18 H), 1.05 (s, 3, C-19 H), 2.00 (s, 3, $COCH_3$), 3.50 (m, 1, C-3 H), 5.00 (m, 1, C-7 H), 5.43 (m, 1, C-11 H), 7.10 (CO_2H); *m/e* 432 (M^+), 417, 372, 357, 354, 339. 300. The crude product resisted all attempts at crystallization and was used without further purification. Anal. Calcd for $C_{26}H_{40}O_5$: *m/e* 432.288. Found: *m/e* 432.290.

Methyl 3α-Hydroxy-7α-acetoxy-5β-chol-9(11)-enate (39) and Methyl 3-Oxo-7α-acetoxy-5β-chol-9(11)-enate (37). To the crude acid **36** (6.94 g) dissolved in dioxane (50 ml) was added to solution of diazomethane in ether until the yellow color persisted. Removal of the volatiles under vacuum gave **39** (7.00 G, 98%) as an essentially pure colorless oil: *m/e* 446 (M^+), 386, 371. 368, 353. Anal. Calcd for $C_{27}H_{42}O_5$: *m/e* 446.303. Found: *m/e* 446.307.

To crude ester alcohol **39** (6.90 g) in HOAc (65 ml) was added a solution of sodium dichromate dihydrate (1.95 g) in HOAc (20 ml). After 10 h at 25 °C, the usual workup followed by chromatography over silica gel (20 g) gave pure **37** (6.34 g, 92%) as a colorless oil: NMR δ 0.64 (s, 3, C-18 H), 0.96 (d, J = 5.0 Hz, 3, C-21 H), 1.18 (s, 3, C-19 H), 2.10 (s, 3, $COCH_3$), 3.68 (s, 3, CO_2CH_3), 5.15 (m, 1, C-7 H), 5.66 (m, 1, C-11 H); *m/e* 444 (M^+), 412, 384, 369, 353. Anal. Calcd for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found: C, 72.51; H, 9.15.

Methyl 3-Oxo-7α-acetoxy-9α,11α-dihydroxy-5β-cholanate Osmate Ester (41) and Methyl 3,12-Dioxo-7α-acetoxy-5β-chol-9(11)-enate (42). To a solution of **37** (1.00 g) in pyridine (7 ml) was added osmium tetroxide (0.5 g) and the solution kept in the dark (N_2) for 8 days. The reaction was monitored by TLC and exhibited maximum formation of **41** between 5 and 7 days and a slow, steady increase of by-product **42**. The pyridine was removed under vacuum and the dark brown residue was extracted with benzene.

The benzene-soluble portion was chromatographed over silica gel (10 g) giving recovered **37** (340 mg, 34%), crystalline **42** (160 mg, 15%), and the crude dark crystalline osmate ester **41** (960 mg, 50%). Crude **41** could be recrystallized from ether as small, white needles of the dipyridine adduct, mp 168 °C dec. Enone **42** was recrystallized from hexane as long, colorless needles: mp 150–150.5 °C; NMR δ 0.99 (s, 3, C-18 H), 1.03 (d, J = 6 Hz, 3, C-21 H), 1.34 (s, 3, C-19 H), 2.00 (s, 3, $COCH_3$), 3.68 (s, 3, CO_2CH_3), 5.26 (m, 1, C-7 H), 5.97 (d, J = 2.4 Hz, 1, C-11 H); ir 2946 (m), 1722 (s), 1679 cm^{-1} (s, enone); *m/e* 458 (M^+), 427, 398, 328, 257, 243; uv max (EtOH) 236 nm (log ϵ 4.03). Anal. Calcd for $C_{27}H_{38}O_6$: C, 70.72; H, 8.35. Found: C, 70.84; H, 8.46.

Methyl 3β,11α-Dihydroxy-3α,9α-oxido-7α-acetoxy-5β-cholanate (43). To the crude osmate **41** (869 mg) were added dioxane (20 ml) and saturated aqueous NH_4Cl (20 ml). H_2S was bubbled through this mixture for 1 h after which it was heated to 65 °C for 1 h. The cooled mixture was filtered through Celite with EtOAc washings. The solvents were removed and the crude product crystallized from acetone–hexane to provide **43** (450 mg, 93%, mp 112–116 °C) as light yellow crystals which contained a trace amount of osmate **41**. The analytical sample was obtained by chromatography over silica gel: mp 117–119 °C; NMR δ 0.72 (s, 3, C-18 H), 0.95 (d, J = 6 Hz, 3, C-21 H), 1.20 (s, 3, C-19 H), 2.10 (s, 3, $COCH_3$), 3.68 (s, 3, CO_2CH_3), 3.94 (m, 1, C-11 H), 5.08 (m, 1, C-7 H); ir 3491 (w), 2956 (s), 1726 cm^{-1} (s); *m/e* 478 (M^+), 460, 418, 400, 147. Anal. Calcd for $C_{27}H_{42}O_7$: C, 67.76; H, 8.84. Found: C, 67.87; H, 8.97.

Methyl 3-Oxo-7α-hydroxy-5β-chol-9(11)-enate (38). To **37** (436 mg) dissolved in MeOH (3 ml) was added a solution of MeONa prepared from MeOH (2 ml) and Na (ca. 100 mg) and the resulting solution was refluxed for 3 h. The usual workup gave a colorless oil which afforded **38** (364 mg, 88%, mp 123–126 °C) as white needles on crystallization from hexane. Chromatography over silica gel (6 g) gave the analytical sample: mp 127–128 °C; NMR δ 0.66 (s, 3, C-18 H), 0.95 (d, J = 5 Hz, 3, C-21 H), 1.16 (s, 3, C-19 H), 3.68 (3, s, CO_2CH_3), 4.07 (m, 1, C-7 H), 5.65 (m, 1, C-11 H); ir 3605 (w), 2945 (s), 1710 cm^{-1} (s); *m/e* 402 (M^+), 400, 384, 369, 332, 314. Anal. Calcd for $C_{25}H_{38}O_4$: *m/e* 402.277. Found: *m/e* 402.276.

Methyl 3-Oxo-5β-chola-7,9(11)-dienate (44). To **38** (100 mg) dissolved in pyridine (5 ml) was added $POCl_3$ (0.5 ml) and the resulting solution was stirred (N_2) at 25 °C overnight. The usual workup followed by crystallization from acetone–hexane gave **44** (88 mg, 92%) as small, white needles, mp 140–142 °C (lit.[14] 143.5–144 °C).

3α,7α-Diacetoxy-5β-chol-9(11)-enic Acid (40). To **36** (1.00 g) were added pyridine (4 ml) and Ac_2O (2 ml) and the resulting solution was heated at 100 °C (N_2) for 0.5 h. The usual workup gave a colorless oil which formed long needles of **40** (920 mg, 84%, mp 198 °C) on crystallization from acetone–hexane. Recrystallization from acetone–hexane gave the analytical sample: mp 205 °C; *m/e* 474 (M^+), 414, 399, 354. 339. Anal. Calcd for $C_{28}H_{42}O_6$: C, 70.86; H, 8.92. Found: C, 70.94; H, 8.80.

3α,7α-Diacetoxy-24-nor-5β-chola-9(11),22-diene (45). To **40** (500 mg) were added benzene (7.5 ml), $Pb(OAc)_4$ (900 mg), $Cu(OAc)_2$ (44 mg), and pyridine (0.4 ml). This mixture was heated at 100 °C (N_2) for 2.5 h. After cooling, the mixture was filtered and the filtrate was evaporated, giving a green oil which was chromatographed on silica gel (5 g) to give pure **45** (405 mg, 90%, mp 101–103 °C) as small, white needle clusters: *m/e* 428 (M^+), 413, 368, 353, 308. Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41; *m/e* 428.293. Found: C, 75.26; H, 9.56; *m/e* 428.288.

3α-Hydroxy-7α-acetoxy-24-nor-5β-chol-9(11),22-diene (46) and 3-Oxo-7α-acetoxy-24-nor-5β-chola-9(11),22-diene (47). A mixture of **45** (200 mg), K_2CO_3 (280 mg), MeOH (4 ml), and water (1.6 ml) was heated briefly at 100 °C to form a clear solution and then stirred at 45 °C for 6 h. Removal of most of the methanol under vacuum, dilution with water, and extraction with $CHCl_3$ gave crude **46** as a light yellow oil (180 mg): NMR δ 0.62 (s, 3, C-18 H), 1.07 (s, 3, C-19 H), 2.00 (s, 3, $COCH_3$), 3.48 (m, 1, C-3 H), 4.80 and 4.96 (m. 2, C-23 H), 5.00 (m, 1, C-7 H), 5.48 (m, 1, C-11 H), 5.60 (m, 1, C-22 H). Alcohol **46** (180 mg) was oxidized without further purification by dissolving in HOAc (2 ml), adding solid sodium dichromate dihydrate (50 mg), and allowing the solution to stand at 25 °C for 12 h. Dilution with water and extraction with $CHCl_3$ gave crude **47** which was chromatorgaphed over silica gel (4 g) to afford pure **47** (131 mg, 73% from **45**) as a colorless oil: NMR δ 0.68 (s, 3, C-18 H), 1.06 (d, J = 6 Hz, 3, C-21 H), 1.18 (s, 3, C-19 H), 2.00 (s, 3, $COCH_3$), 4.84 (dd, J = 2 and 5 Hz, 1, C-23 H), 4.96 (dd, J = 12 and 2 Hz, 1, C-23 H), 5.17 (m, 1, C-7 H), 5.70 (m, 2, C-11 H and C-22 H); *m/e* 384 (M^+), 340, 324, 309. Anal. Calcd for $C_{25}H_{36}O_3$: *m/e* 384.266. Found: *m/e* 384.268.

3-Oxo-7α-hydroxy-24-nor-5β-chola-9(11),22-diene (48). To **47** (100 mg) was added excess MeONa solution. The resulting solution was refluxed (N_2) for 2 h. The usual workup followed by crystallization from hexane afforded pure **48** (74 mg, 83%): mp 109–110 °C; *m/e* 324 (M^+), 327, 324, 314, 313. Anal. Calcd for $C_{23}H_{34}O_2$: *m/e* 342.256. Found: *m/e* 342.256.

Methyl 3β,7α,11α-Trihydroxy-3α,9α-oxido-5β-cholanate (51).

A. From 43. To **43** (120 mg, mp 112–116 °C) was added a MeONa solution prepared from MeOH (5 ml) and Na (ca. 100 mg). The resulting solution was refluxed (N_2) for 2 h. The usual workup followed by two recrystallizations from methylcyclohexane gave pure **51** (79 mg, 82%) as long, colorless needles: mp 185–185.5 °C; NMR δ 0.71 (s, 3, C-18 H), 0.96 (d, J = 5 Hz, 3, C-21 H), 1.18 (s, temperature sensitive, C19 H), 3.67 (s, 3, CO_2CH_3), 4.04 (m, 2, C-7 H and C-11 H), 4.16–4.34 (1, variable, OH); ir 3940 (very broad), 2945 (s), 1705 cm^{-1} (s, sh); *m/e* 436 (M^+), 418, 400. Anal. Calcd for $C_{25}H_{40}O_6$: C, 68.78; H, 9.23. Found: C, 68.45; H, 9.42.

B. From 38. To **38** (71 mg) was added pyridine (1.5 ml) containing 75 mg of OsO_4. After 1 h the reaction was complete. Chromatography yielded the osmate ester dipyridine adduct (145 mg, 100%) as a brown solid which gave on osmate cleavage (see **43**) crude diol hemiacetal **51** (76 mg, 98%) identified by its NMR spectrum and melting point.

Methyl 3β-Methoxy-3α,9α-oxido-7α-acetoxy-11α-hydroxy-5β-cholanate (49). To a solution of **43** (50 mg) in MeOH (5 ml) was

added a drop of 48% HBr. After 0.5 h at 25 °C, the solution was neutralized by addition of solid $NaHCO_3$. The usual workup gave crude **49** as a colorless oil which was chromatographed over silica gel (1 g), affording **49** (41 mg, 79%) as a pure oil which would not crystallize: NMR δ 0.70 (s, 3, C-18 H), 0.96 (d, J = 5 Hz, 3, C-21 H), 1.00 (s, 3, C-19 H), 2.07 (s, 3, $COCH_3$), 3.47 (s, 3, OCH_3), 3.67 (m, 1, C-11 H), 4.98 (m, 1, C-7 H); ir 3578 (w), 2950 (s), 1725 cm^{-1} (s); *m/e* 492 (M^+), 432, 400, 390, 279. Anal. Calcd for $C_{28}H_{44}O_7$: C, 68.26; H, 9.00; *m/e* 492.309. Found: C, 67.81; H, 8.96; *m/e* 492.305.

Methyl 3β-Methoxy-3α,9α-oxido-7α,11α-diacetoxy-5β-cholanate (50). A solution of **49** (20 mg) in pyridine (1.5 ml) and Ac_2O (0.25 ml) was heated at 40 °C for 6 h (N_2). Evaporation of the solvent gave an oily residue which was dissolved in EtOAc and filtered through alumina. Removal of the solvent gave a colorless oil which crystallized from hexane at −10 °C, affording white crystals of **50** (15 mg, 71%) which liquefied to a pure oil: NMR δ 0.78 (s, 3, C-18 H), 0.95 (s, 3, C-19 H), 2.08 (s, 6, $COCH_3$), 3.50 (s, 3, OCH_3), 3.67 (s, 3, CO_2CH_3), 5.00 (m, 2, C-7 and C-11 H); ir 2956 (m), 1727 cm^{-1} (s); *m/e* 534, 492, 432, 414. Anal. Calcd for $C_{30}H_{46}O_8$: *m/e* 534.319. Found: *m/e* 534.319.

Methyl 3β-Methoxy-3α,9α-oxido-7α,11α-dihydroxy-5β-cholanate (52). To a solution of **51** (22 mg) in MeOH (2 ml) was added a trace of 48% HBr. After 0.5 h, the usual workup followed by chromatography over silica gel gave pure **52** (19 mg, 85%) which crystallized from hexane as long, colorless needles: mp 155–156 °C; NMR δ 0.70 (s, 3, C-18 H), 0.96 (d, J = 5 Hz, 3, C21 H), 1.00 (s, 3, C-19 H), 3.30 (s, 3, OCH_3), 3.67 (s, 3, CO_2CH_3), 3.5–4.0 (m, 2, C-7 H and C-11 H); ir 3580 (w), 3500 (s), 2945 (s), 1726 cm^{-1} (s); *m/e* 450 (M^+), 432, 364, 302, 293. Anal. Calcd for $C_{26}H_{42}O_6$: C, 69.30; H, 9.39; *m/e* 450.298. Found: C, 69.31; H, 9.86; *m/e* 450.296.

Methyl 3β-Methoxy-3α,9α-oxido-7α-hydroxy-11α-acetoxy-5β-cholanate (53). A solution of **52** (50 mg) in pyridine (1.5 ml) and Ac_2O (0.25 ml) was heated to 40 °C for 6 h (N_2). The usual workup gave **53** (55 mg, 100%) as a pure, colorless oil which would not crystallize: NMR δ 0.80 (s, 3, C-18 H), 0.95)d, J = 5 Hz, 3, C-21 H), 0.96 (s, 3, C-19 H), 3.40 (s, 3, OCH_3), 3.68 (s, 3, CO_2CH_3), 3.74 (m, 1, C-7 H), 5.10 (dd, J = 11 and 5 Hz, 1, C-11 H); ir 3505 (w), 2945 (s), 1676 cm^{-1} (s); *m/e* 492 (M^+), 461, 432, 346, 302. Anal. Calcd for $C_{28}H_{44}O_7$: *m/e* 492.309. Found: *m/e* 492.308.

Methyl 3β-Hydroxy-3α,9α-oxido-7α-acetoxy-11-oxo-5β-cholanate (54) and Methyl 3β-Methoxy-3α,9α-oxido-7α-acetoxy-11-oxo-5β-cholanate (55). To a solution of 43 (45 mg) in CH_2Cl_2 (1 ml) was added 6 equiv of a 5% CH_2Cl_2 solution of CrO_3–pyridine complex[22] at 10 °C. After 0.5 h the solvent was removed under vacuum and the organic material was taken up in benzene and chromatographed over silica gel to afford hemiacetal **54** (27 mg, 60%) as a tacky, colorless oil: NMR δ 0.61 (s, 3, C-18 H), 1.10 (s, 3, C-19 H), 2.13 (s, 3, $COCH_3$), 3.67 (s, 3, CO_2CH_3), 5.06 (m, 1, C-7 H), Acetal **55** was immediately prepared from **54** (27 mg) by treatment with HBr in methanol (1 ml) (see **49**). Chromatography over silica gel gave pure **55** (18 mg, 64%) as a clear oil: NMR δ 0.62 (s, 3, C-18 H), 1.10 (s, 3, C-19 H), 2.10 (s, 3, $COCH_3$), 3.42 (s, 3, OCH_3), 3.67 (s, 3, CO_2CH_3), 5.09 (m, 1, C-7 H); ir 2960 (s), 1712 cm^{-1} (s); *m/e* 490 (M^+), 472, 420, 402. Anal. Calcd for $C_{28}H_{42}O_7$: *m/e* 490.293. Found: *m/e* 490.293.

Methyl 3β-Methoxy-3α,9α-oxido-11α-acetoxy-5β-chol-7-enate (56). To a solution of **53** (50 mg) in pyridine (2.5 ml) was added $POCl_3$ (0.25 ml) and the solution was stirred overnight (N_2) at 25 °C. The usual workup gave **56** (47 mg, 100%) as a pure, colorless oil which would not crystallize. Chromatography over silica gel provided the analytical sample: NMR δ 0.66 (s, 3, C-18 H), 0.88 (s, 3, C-19 H), 0.91 (d, J = 5 Hz, 3, C-21 H), 2.09 (s, 3, $COCH_3$), 3.32 (s, 3, OCH_3), 3.67 (s, 3, OCH_3), 3.67 (s, 3, CO_2CH_3), 5.09 (dd, J = 11 and 5 Hz, 1, C-11 H), 5.21 (m, 1, C-7 H); ir 2946 (s), 1725 cm^{-1} (s); *m/e* 474 (M^+), 432, 414, 399, 367, 328, 299, 149. Anal. Calcd for $C_{28}H_{42}O_6$: *m/e* 474.298. Found: *m/e* 474.295.

Methyl 3β-Hydroxy-3α,9α-oxido-11α-acetoxy-5β-chol-7-enate (57). To a solution of **56** (40 mg) in HOAc (0.5 ml) and water (0.5 ml) was added 60% $HClO_4$ (0.02 ml). After 12 h at 25 °C, the usual workup gave crude **57** (33 mg) which contained some of the corresponding acid. Treatment with CH_2N_2 and then chromatography over silica gel gave pure **57** (30 mg, 77%) which crystallized from acetone–hexane as small needles: mp 100–103 °C; NMR δ 0.66 (s, 3, C-18 H), 0.88 (s, 3, C-19 H), 0.92 (d, J = 5 Hz, 3, C-21 H), 2.10 (s, 3, $COCH_3$), 3.68)s, 3, CO_2CH_3), 5.09 (dd, J = 11 and 5 Hz, 1 C-11 H), 5.21 (m, 1, C-7 H); ir 3576 (w), 2946 (s), 1732 cm^{-1} (s); *m/e* 460 (M^+), 419, 412, 400, 385, 382, 371, 327. Anal. Calcd for $C_{27}H_{40}O_6$: *m/e* 460.282. Found: *m/e* 460.281.

3β,11α-Dihydroxy-3α,9α-oxido-5β-chol-7-enic Acid (58) and Methyl 3β,11α-Dihydroxy-3α,9α-oxido-5β-chol-7-enate (59). To a solution of **57** (24 mg) in EtOH (2 ml) was added 0.2 N NaOH (2 ml) and the mixture was boiled for 1 h. The EtOH was removed under vacuum and the mixture was poured into dilute HOAc. The white precipitate was crystallized twice from acetone–hexane to give **58** (14.7 mg, 70%, mp 170–173 °C). Recrystallization from CH_3CN gave the analytical example: mp 172–174 °C; NMR δ 0.56 (s, 3, C-18 H), 0.94 (s, 3, C-19 H), 0.96 (d, J = 5 Hz, 3, C-21 H), 3.84 (dd, J = 12 and 5 Hz, 1, C-11 H), 5.26 (m, 1, C-7 H); ir 3571 (w), 2942 (s), 1710 mm^{-1} (s); *m/e* 404 (M^+), 386, 371, 368, 353, 316. Anal. Calcd for $C_{24}H_{36}O_5 \cdot \frac{1}{3}H_2O$: C, 70.22; H, 9.00; *m/e* 460.256. Found: C, 70.21; H, 8.98; *m/e* 460.256.

The methyl ester **59** was prepared by treating **58** (8 mg) with excess CH_2N_2 in ether. Chromatography of the crude product over silica gel gave **33** (6 mg, 72%) as an amorphous white solid which formed gels on attempted crystallization from acetone–hexane or methylcyclohexane: NMR δ 0.56 (s, 3, C-18 H), 0.94 (s, 3, C-19 H), 3.68 (s, 3, CO_2CH_3), 3.84 (m, 1, C-11 H), 5.26 (m, 1, C-7 H); ir 3586 (w), 2945 (s), 1731 cm^{-1} (s); *m/e* 418 (M^+), 400, 385, 382, 367, 346, 313, 285. Anal. Calcd for $C_{25}H_{38}O_5$: *m/e* 418.272. Found: *m/e* 418.268.

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References and Notes

(1) A preliminary account of this work has been published: R. R. Schumaker and J. F. W. Keana, *J. Chem. Soc., Chem. Commun.*, 622 (1972).
(2) Alfred P. Sloan Foundation Fellow, Recipient of a Research Career Development Award from the National Institutes of Health.
(3) T. Takuyama, J. Daly, and B. Witkop, *J. Am. Chem. Soc.*, **91**, 3931 (1969).
(4) E. X. Albuquerque, J. W. Daly, and B. Witkop, *Science*, **172**, 995 (1971); T. Narahashi, E. X. Albuquerque, and T. Deguchi, *J. Gen. Physiol.*, **58**, 54 (1971).
(5) R. Imhof, E. Gössinger, W. Graf, L. Berner-Fenz, H. Berner, R. Schaufelberger, and H. Wehrli, *Helv. Chim. Acta*, **56**, 139 (1973).
(6) L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **73**, 118 (1951).
(7) H. Heymann and L. F. Fieser, *J. Am. Chem. Soc.*, **73**, 5252 (1951); **74**, 5938 (1952).
(8) L. F. Fieser, S. Rajagopalan, E. Wilson, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 4133 (1951).
(9) T. F. Gallager and T. H. Kritchevsky, *J. Am. Chem. Soc.*, **72**, 882 (1950).
(10) K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1964).
(11) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963). The calculated δ values for the α-epoxide are 1.15 (C-19 H) and 0.65 ppm (C-18 H), while the observed values are 1.16 and 0.67 ppm. The calculated values for the β-epoxide are 1.07 and 0.83 ppm.
(12) A. S. Vaidya, S. M. Dixit, and A. S. Rao, *Tetrahedron Lett.*, 5173 (1968).
(13) A. S. Narula and S. Dev, *Tetrahedron*, **27**, 119 (1971).
(14) L. F. Fieser, W.-Y. Huang, and J. C. Babcock, *J. Am. Chem. Soc.*, **75**, 116 (1953).
(15) H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Justus Liebigs Ann. Chem.*, **641**, 1 (1961).
(16) H. Vorbrueggen, *Steroids*, **1**, 45 (1963).
(17) P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961).
(18) W. Graf, H. Berner, L. Berner-Fenz, E. Gössinger, R. Imhof, and H. Wehrli, *Helv. Chim. Acta*, **53**, 2267 (1970).
(19) B. E. Cross, *J. Chem. Soc. C*, 501 (1966).
(20) The preamble to the Experimental Section of P. N. Strong and J. F. W. Keana, *J. Org. Chem.*, **40**, 956 (1975), applies here. NMR spectra were determined in $CDCl_3$ solution. Optical rotations were run in $CHCl_3$ on a Perkin-Elmer Model 141 polarimeter.
(21) H. O. House and R. S. Ro, *J. Am. Chem. Soc.*, **80**, 2428 (1958).
(22) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

Photooxygenation of 1,3-Cholestadiene and Related Compounds[1]

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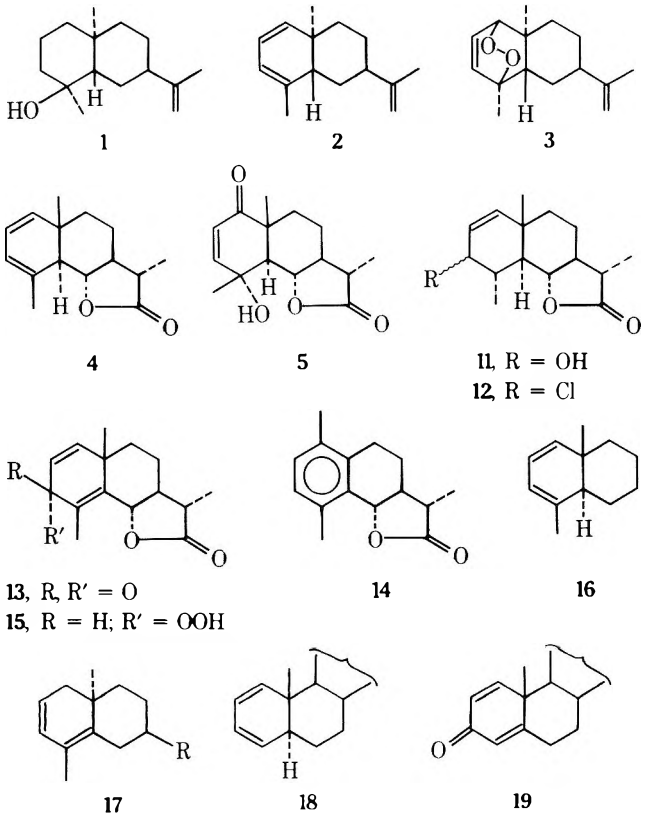
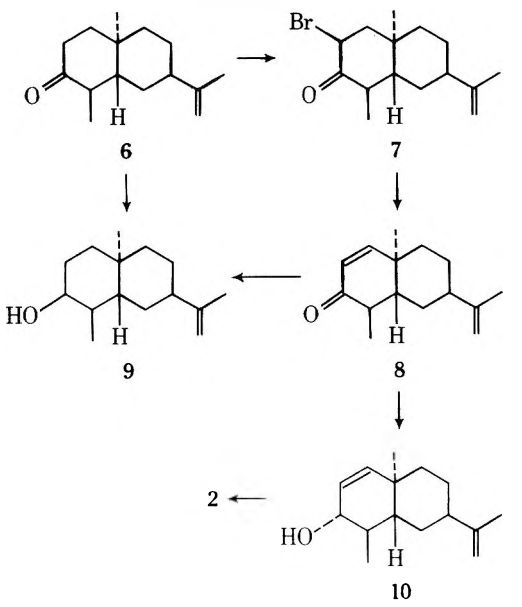
In an effort to effect stereoselective and regioselective total syntheses of the sesquiterpenes intermedeol (1) and tauresmisin (5), homoannular dienes (2) (5-epi-10-epieudesma-1,3,11-triene) and 4 (6, 11βH-eudesma-1,3-dien-6,13-olide) were subjected to photochemical oxygenation. Diene 2 gave a complex mixture of products, while 4 gave mixtures of santonin and hyposantonin, the result of a photochemical ene reaction. The expected endoperoxides could not be detected. 1,3-Cholestadiene (18) was also subjected to photochemical oxygenation and gave 1,4-cholestadien-3-one (19) as the only isolable product derived from 18. These results are discussed in terms of the steric requirements for endoperoxide formation. The syntheses of compounds 2 and 4 are described, and methods of preparation of 1,3-cholestadiene are discussed.

In the course of a general synthetic program in the sesquiterpene field, a variet of approaches to the 10-epieudesmane group of these natural products have been explored.[2] A major goal of this program was a convenient total synthesis of intermedeol[3] (5-epi-10-epieudesma-11-en-4β-ol, 1), a presumed biosynthetic precursor of the valencene–nookatone group of sesquiterpenes. An attractive regioselective and stereoselective synthetic approach to 1 involved the photooxygenation of 5-epi-10-epieudesma-1,3,11-triene (2), to give endoperoxide 3 which could be converted to intermedeol in a relatively few steps. In addition, the photooxygenation product of the related diene (4) derived from santonin[4] could serve as a precursor for another sesquiterpene, tauremisin (5).[5]



Triene 2 was prepared from 4-epi-5-epi-10-epieudesm-11-en-3-one (6)[6] as outlined in Scheme I. Utilizing a modification of a procedure employed in a total synthesis of occidentalol,[7] ketone 6 was condensed with ethyl formate and the resulting formyl compound brominated to give α-bromo ketone 7, which was smoothly dehydrohalogenated to enone 8. Reduction of 8 with potassium tri-*sec*-butylborohydride[8] quite unexpectedly gave 4-epi-5-epi-10-epieudesm-11-en-3β-ol (9), the result of conjugate reduction, as the only isolable product.[9] The structure and stereochemistry of 9 were confirmed by its preparation from ketone 6 by reduction with potassium tri-*sec*-butylborohydride. In contrast, lithium aluminum hydride reduction of enone 8 gave a crystalline alcohol which, on the basis of its spectral properties (see Experimental Section), was assigned structure 10 in which the hydroxyl group is quasi-equatorial. Attempted dehydration of 10 by means of toluenesulfonic acid at room temperature[7] gave complex mixtures, while von Rudloff's procedure[10] afforded recovered alcohol. The dehydration of 10 was finally accomplished by use of the procedure utilized by a Syntex group for preparation of steroidal 1,3-dienes.[11] Reaction of alcohol 10 with thionyl chloride gave an unstable allylic chloride which on heating in dimethylformamide–pyridine afforded triene 2. Photooxygenation of 2, followed by treatment with basic alumina to convert the endoperoxide to the corresponding hydroxy enone,[12] gave a mixture of at least seven compounds, which on the basis of spectral data contained little if any of the desired product. In view of simultaneous experiments with diene 4 (see below) this reaction was not investigated further.

Scheme I



Base treatment of the endoperoxide derived from diene 4 would be expected to lead to a convenient synthesis of tauremisin (5), a sesquiterpene isolated simultaneously some years ago by two groups.[5] Although one total synthesis of this compound has been reported,[13] the final stages of the synthesis were carried out without the isolation or purification of intermediates and in very poor overall yield. Diene 4 has

been prepared by Corey in five steps from santonin and used in the synthesis of dihydrocostunolide.[4] In this synthesis of **4** the mixture of epimeric precursor alcohols (**11**) was dehydrated directly; however, in this work compound **4** was prepared from the mixture of epimeric allylic chlorides in the same manner used for the preparation of triene **1**. Photooxygenation of **4**, followed by treatment with basic alumina, gave no trace of tauremisin (**5**), but afforded instead mixtures of santonin (**13**) and hyposantonin (**14**). These products undoubtedly both arise from hydroperoxide **15**, santonin by the normal mode of decomposition of hydroperoxides, and hyposantonin by a variation of the dienol–benzene rearrangement. Hydroperoxide **15** is in turn derived from **4** by way of a photochemical ene reaction.[14] Although the photochemical ene reaction of singlet oxygen with homoannular dienes has been observed as a competing reaction with endoperoxide formation in a few cases,[14] at the time this work was completed the only other apparent example of the exclusive occurrence of the ene reaction of a cisoid conjugated diene was in the case of a highly hindered triterpene derivative.[15] The failure of the normal 1,4-cycloaddition reaction of singlet oxygen in that case was attributed to "steric hindrance". Following the completion of this work, however, Sasson and Labovitz reported that photooxygenation of diene **16** afforded only products from a photochemical ene reaction, while a similar diene lacking the angular methyl group reacted normally, giving the endoperoxide as a major product.[16] These authors attribute the failure of diene **16** to form an endoperoxide to "a strong 1,3-diaxial interaction between the angular methyl group and an ethylenic bridge". This explanation cannot, however, be correct, because the diaxial interactions in the endoperoxides derived from dienes **16**, **4**, and **2** are no worse than those in the endoperoxides derived from 2,4-cholestadiene[17] or two dienes (**17**, R = isopropyl[18] or isopropenyl[19]) closely related to **2** and **16**, which readily form endoperoxides.

In order to gain additional insight into the steric affects in the reactions of homoannular dienes, 1,3-cholestadiene (**18**)[20] was subjected to photooxygenation. When diene **18** which had been prepared from 3β-chlorocholest-1-ene by heating in dimethylformamide[11,20c] was subjected to photooxygenation, two crystalline compounds were obtained. The major product was 1,4-cholestadien-3-one (**19**), the result of the ene reaction, while the minor product (ca. 10%) was identified as the endoperoxide derived from 2,4-cholestadiene.[17] Since there is no reasonable mechanism for the formation of this endoperoxide from diene **18**, this product was assumed to be an artifact derived from 2.4-cholestadiene present as a contaminant in diene **18**. To confirm this conclusion, 1,3-cholestadiene was also prepared from the tosylhydrazone of 1-cholesten-3-one.[20b] Photooxygenation of **18** prepared in this manner gave a product which contained no endoperoxide, but which did contain a small amount of 2-cholestene, which was undoubtedly an impurity in the starting diene. The 2,4-cholestadiene present in the 1,3-diene prepared by Dauben's method probably arises from the pyridine hydrochloride catalyzed isomerization of **18** (see Experimental Section). The 2-cholestene present in **18** prepared by Herz's method may originate from some 3-cholestanone present in the 1-cholesten-3-one precursor of **18**, or it may arise during the reaction of the tosylhydrazone with methyllithium.

It is quite apparent that the photooxygenation of dienes structurally similar to 1,3-cholestadiene leads exclusively, or nearly exclusively, to products arising from photochemical ene reactions. This can be explained neither in terms of diaxial interactions (see above) nor in terms of "steric hindrance", since 1,3-cholestadiene is a relatively unhindered diene. Examination of Dreiding models of the endoperoxides derived from 1,3-cholestadiene and 2,4-cholestadiene indicates that there is considerable strain inflicted in the endoperoxide derived from the 1,3-diene as a result of fusing a second ring in a trans relationship to a full boat 2-cyclohexene system. Although there is also appreciable strain of the same type present in the endoperoxide derived from the 2,4-diene, qualitatively the strain appears to be less. Since a diene similar to **16** without the angular methyl group gives a endoperoxide in reasonable yield,[16] it is apparent that diaxial interactions must also play a role in determining the course of these reactions.[21]

Experimental Section[22]

2β-Bromo-4-epi-5-epi-10-epieudesm-11-en-3-one (7). A solution of 6.45 g of 4-epi-5-epi-10-epieudesm-11-ene-3-one (**6**)[6] in 100 ml of dry ether was added slowly to a cold (ice bath), stirred mixture of 4.50 g of sodium hydride (50% dispersion), 50 ml of ethyl formate, 8 drops of methanol, and 200 ml of dry ether. The reaction mixture was then allowed to warm to room temperature and stirred for 18 h under nitrogen. Sufficient water was added to decompose the excess hydride and the reaction mixture extracted with three portions of iced 10% aqueous sodium hydroxide. The combined aqueous extracts were washed with ether, acidified with cold dilute hydrochloric acid, and extracted with ether. The ethereal extracts were washed with water and dried and the solvent removed at reduced pressure to give 5.83 g of formyl compound as a brown oil which was brominated without further purification.

To a stirred solution of 6.23 g of the above formyl compound in 150 ml of ethanol containing 30 g of barium hydroxide was added slowly 8.05 g of pyridimium bromide perbromide in 150 ml of ethanol. The reaction mixture was stirred at room temperature for 0.75 h, poured into water, and extracted with three portions of ether. The extracts were combined, washed with water, and dried and the solvent removed to give a yellow oil which slowly crystallized. Recrystallization from hexane gave 6.09 g (69%) of material, mp 53–63 °C, which was sufficiently pure for subsequent reactions. The analytical sample, mp 77–78 °C, was prepared by repeated recrystallizations from hexane: ir 5.76 μ; NMR δ 1.10 (d, J = 7 Hz, C**H**$_3$CH), 1.20 (s, 3 H, CH$_3$), 1.69 (s, 3 H, CH$_3$C=), 4.75 (m, 2 H, CH$_2$=C).

Anal. Calcd for $C_{15}H_{23}BrO$: C, 60.20; H, 7.75; Br, 26.71. Found: C, 60.23; H, 7.90; Br, 27.02.

4-Epi-5-epi-10-epieudesma-1,11-dien-3-one (8). To a solution of 5.76 g of bromo ketone **7** in 200 ml of dry dimethylformamide was added 6.0 g of lithium bromide and 8.0 g of lithium carbonate. The mixture was heated, with stirring, at 125 °C under nitrogen for 18 h, cooled, and poured cautiously into dilute aqueous acetic acid and the resulting suspension extracted with three portions of ether. The ethereal extracts were combined, washed well with water, and dried and the solvent removed to give a pale yellow oil. Distillation (150–170 °C, bath temperature, 0.04 mm) gave 3.44 g (83%) of ketone **8** as a colorless liquid: ir 5.99, 6.01 μ; NMR δ 1.08 (s, 3 H, CH$_3$), 1.09 (d, 3 H, C**H**$_3$CH), 1.65 (d, J = 1 Hz, CH$_3$C=), 4.69 (m, 2 H, CH$_2$=C), 5.48 (1 H d, J = 9 Hz, CH=CHC=O), 6.25 (d, 1 H, J = 9 Hz, C**H**=CHC=O).

For analysis the compound was converted to the 2,4-dinitrophenylhydrazone, mp 129–131 °C, from ethanol–ethyl acetate.

Anal. Calcd for $C_{21}H_{26}N_4O_4$: C, 63.30; H, 6.58; N, 14.06. Found: C, 63.20; H, 6.45; N, 14.01.

4-Epi-5-epi-10-epieudesm-11-en-3β-ol (9). A. A solution of 0.714 g of 4-epi-5-epi-10-epieudesma-1,11-dien-3-one (**8**) in 20 ml of dry tetrahydrofuran was added to 60 ml of a cooled (0 °C) 0.5 M solution of K-Selectride in tetrahydrofuran. The reaction mixture was stirred under nitrogen at 0 °C for 2 h and the excess hydride destroyed by the cautious addition of water. To the stirred reaction mixture was then added 50 ml of 2 N sodium hydroxide, followed by the cautious addition of 35 ml of 30% hydrogen peroxide. The reaction mixture was stirred at ambient temperature for 18 h, and the aqueous layer separated and washed with two portions of ether. The ethereal washings were combined with the original orgainc layer, washed with water and brine, and dried and the solvent removed at reduced pressure to give 0.504 (70%) of alcohol as a colorless oil. This material was identical with that prepared in part B below.

B. Reduction of 0.183 g of 4-epi-5-epi-10-epieudesm-11-en-3-one (**6**) using 20 ml of K-Selectride following the procedure described in part A gave 0.145 g (79%) of alcohol **9** as a colorless oil. Distillation (bp

140–150 °C, bath, 0.12 mm) gave the analytical sample as a viscous, water-white liquid: ir 2.91, 6.13, 11.33 μ; NMR δ 0.88 (s, 3 H, CH_3), 0.88 (d, 3 H, J = 6 Hz, CH_3CH), 1.71 (s, 3 H, CH_3C=), 3.78 (m, 1 H, CHOH), 4.82 (m, 2 H, CH_2=).

Anal. calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.70. Found: C, 81.14; H, 11.65.

4-Epi-5-epi-10-epieudesma-1,11-dien-3β-ol (10). To a cooled (0 °C) solution of 2.76 g of unsaturated ketone **8** in 200 ml of dry ether was added 1.00 g of lithium aluminim hydride. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Crushed ice was added cautiously to decompose the excess hydride and the ethereal solution decanted from the precipitated solids. The inorganic salts were washed with ether, the ethereal solutions combined and dried, and the solvent removed to give 2.48 g (90%) of oil which crystallized on standing. This material was essentially homogeneous to TLC and was used without purification for subsequent transformation. For analysis a small quantity of the alcohol was recrystallized from methanol-water to give white needles: mp 87–88 °C; ir 3.02, 6.18, 11.30 μ; NMR δ 0.99 (s, 3 H, CH_3), 0.99 (d, J = 5 Hz, 3 H, CH_3CH), 1.72 (s, 3 H, CH_3C=C), 3.77 (br d, J = 8 Hz, 1 H, CHOH), 4.88 (m, 2 H, C_3H_2=C), 5.45 (s, 2 H, CH=CH).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.86, H, 11.00.

5-Epi-10-epieudesma-1,3,11-triene (2). To a cooled (0 °C) solution of 0.280 g of allylic alcohol **10** in 25 ml of dry benzene was added, with stirring, 1 ml of thionyl chloride. The reaction mixture was stirred at 0 °C for 0.5 h, allowed to warm to ambient temperature, and stirred for an additional 1 h. The solvent was removed at reduced pressure with gentle warming, and the residue taken up in ether. The ethereal solution was washed with 5% aqueous sodium carbonate and water and dried and the solvent removed to give the 3-chloro compound as an unstable, pale yellow oil. This material was taken up in 20 ml of dimethylformamide, 1 ml of pyridine was added, and the mixture was heated at reflux under nitrogen for 18 h. After cooling, the reaction mixture was poured into water and extracted with three portions of hexane. The hexane extracts were washed with successive portions of water, iced 5% hydrochloric acid, 5% sodium carbonate, and water and dried and the solvent removed at reduced pressure to give a yellow oil. This oil was taken up in hexane and chromatographed on 10 g of Merck alumina. Elution with hexane gave 0.170 g (53%) of hydrocarbon **2** as a colorless liquid which slowly decomposed on standing: ir 6.10, 11.21 μ; NMR δ 0.82 (s, 3 H, CH_3), 1.78 (br s, 6 H, CH_3C=), 4.85 (br s, 2 H, CH_2=), 5.60 (m, 3 H, CH=CHCH=C–); uv max (CH_3OH) 267 nm (ε 3600); mass spectrum *m/e* (rel intensity) 202 (100), 187 (58), 159 (100), 157 54), 145 (92).

6,11β*H*-Eudesma-1,3-dien-6,13-olide (4). Allylic alcohol **11** was converted to diene **4** by the method described above for the preparation of 5-epi-10-epieudesma-1,3,11-triene. From 0.50 g of alcohol there was obtained, after recrystallization from hexane, 0.21 g (46%) of material, mp 83–86 °C (lit. mp 95–97 °C[4]). The spectral properties were in agreement with those reported by Corey, and the material was homogeneous to TLC (silica gel G, hexane–benzene, 1:1).

Photooxygenation of 6,11β*H*-Eudesma-1,3-dien-6,13-olide. A solution of 0.340 g of **4** in 170 ml of 95% ethanol containing 0.025 g of eosin and 1.5 ml of pyridine was irradiated at 0 °C with a 275-W Westinghouse sun lamp for 18 h while oxygen was bubbled through the solution. The solvents were removed at reduced pressure, and the residue was taken up in benzene–ether (1:1) and absorbed on 8 g of Merck alumina. After standing for 3 h, the column was eluted with benzene–ether (1:1) to give 0.154 g of semisolid which TLC (silica gel G, benzene–ethyl acetate, 6:1) showed was a mixture of five compounds, two of which accounted for the bulk of the material. The R_f value of the principal component of this mixture corresponded to that of santonin, while the R_f value of the other major component corresponded to that of hyposantonin. Trituration of the crude mixture with ether afforded 0.063 g of santonin (**13**), mp and mmp 169–171 °C. In another run, 0.138 g of crude material was dissolved in benzene and chromatographed on 10 g of Woelm silica gel. The first benzene–ethyl acetate (5:1) fractions gave 0.021 g of hyposantonin (**14**), which was identical with a sample prepared earlier,[23] while the final fractions eluted with the same solvents gave 0.026 g of santonin. The intermediate fractions afforded 0.021 g of mixtures of santonin, hyposantonin, and two minor constituents of the reaction mixture.

1,3-Cholestadiene (18). This compound was prepared either by the method of Dauben[20b] or that of Herz.[20c] Using Dauben's procedure, 9.96 g of crude 1-cholesten-3β-ol gave 2.74 g (29%) of diene: mp 59–60 °C; $[\alpha]^{21}D$ +84° (*c* 0.57) (lit. mp 60–61 °C, $[\alpha]^{23}D$ +78° [20b]). Neither the yield nor quality of the product could be improved by purification of alcohol or the intermediate allylic chloride. From 2.00 g of the tosylhydrazone of 1-cholesten-3-one, mp 166–168 °C dec (lit. mp 168–170 °C dec[20c]), using Herz's procedure there was obtained 0.390 g of diene, mp 55–58 °C, $[\alpha]^{20}D$ +66° (c 0.96) (lit. mp 67–68 °C, $[\alpha]^{20}D$ + 73° [20c]), plus a quantity of unreacted hydrazone. The spectral properties of material obtained by both methods were in agreement with those reported by Dauben.[20c]

When a sample of 0.121 g of diene **18** was heated at reflux in 25 ml of dimethylformamide for 24 h, it was recovered unchanged; however, the addition of 1 ml of pyridine and 3 drops of concentrated hydrochloric acid (conditions which duplicate Dauben's dehydrohalogenation) gave a gummy mixture of hydrocarbons. 1,3-Cholestadiene as originally prepared by Tamm and Albrecht[20a] was reported to have mp 67–68 °C, $[\alpha]D$ +73°.

Photooxygenation of 1,3-Cholestadiene. Diene **18** prepared by Dauben's method was photooxygenated in the manner described above for photooxygenation of **4**. From 1.160 g of diene in 200 ml of 1:1 benzene–ethanol containing 4 ml of pyridine and 0.030 g of eosin, there was obtained, after treatment with basic alumina, 1.107 g of crude material which was dissolved in hexane–benzene (4:1) and chromatographed on 100 g of Merck alumina. Elution with hexane–benzene (3:1) gave 0.103 g of the endoperoxide derived from 2,4-cholestadiene, mp 107–109 °C, which was identical with a sample prepared by photooxygenation of the diene.[17] Elution with hexane–benzene (1:1) gave 0.528 g of 1,4-cholestadien-3-one (**19**), mp and mmp 108–111 °C. The spectral properties were identical with those of a sample prepared by an alternate route. Elution with benzene gave 0.049 g of a mixture containing dienone **19** and small quantities of two other unidentified compounds.

Photooxygenation of 0.311 g of diene **18** prepared by Herz's procedure gave 0.083 g of dienone **19** and 0.063 g of 2-cholestene as needles from acetone, mp 67–69 °C. This material has an infrared spectrum identical with that of a sample, mp 67–68 °C, prepared by the method of Mauthner,[24] mmp 67–69°C.

Registry No.—**2**, 60184-24-9; **4**, 4678-04-0; **6**, 28290-27-9; **7**, 60184-25-0; **8**, 60184-26-1; 8 2,4-DNPH, 60184-27-2; **9**, 60209-18-9; **10**, 60184-28-3; **11**, 4678-03-9; **18**, 4117-49-1.

References and Notes

(1) Presented at the Southeastern–Southwestern Regional Meeting of the American Chemical Society, Oct 29–31, 1975.
(2) J. W. Huffman, C. A. Miller, and A. R. Pinder, *J. Org. Chem.*, in press.
(3) (a) G. L. Chetty, V. B. Zalkow, and L. H. Zalkow, *Tetrahedron Lett.*, 3223 (1968); (b) L. H. Zalkow, V. B. Zalkow, and D. R. Brannon, *Chem. Ind. (London)*, 38 (1963); (c) J. W. Huffman and L. H. Zalkow, *Tetrahedron Lett.*, 751 (1973); (d) the total synthesis of intermedeol has been described (ref 2 and L. H. Zalkow, M. Smith, G. L. Chetty, A. M. Shaligram, and P. Ingwalson, *J. Org. Chem.*, in press).
(4) E. J. Corey and A. G. Hortmann, *J. Am. Chem. Soc.*, **87**, 5736 (1965).
(5) (a) T. A. Geissman and G. A. Ellestad, *J. Org. Chem.*, **27**, 1855 (1962); (b) K. S. Rybalko and L. Dolejs, *Collect. Czech. Chem. Commun.*, **26**, 803 (1961).
(6) R. Howe and J. F. McQuillin, *J. Chem. Soc.*, 2670 (1955).
(7) M. Sergent, M. Mongrain, and P. Deslongchamps, *Can. J. Chem.*, **50**, 336 (1972).
(8) C. A. Brown, *J. Am. Chem. Soc.*, **95**, 4100 (1973).
(9) B. Ganem, *J. Org. Chem.*, **40**, 146 (1975), reported several examples of conjugate reduction by this reagent subsequent to the completion of this phase of the synthesis of triene **2**.
(10) E. von Rudloff, *Can. J. Chem.*, **39**, 1860 (1961).
(11) B. Berkoz, A. P. Cross, M. E. Adame, H. Carpio, and A. Bowers, *J. Org. Chem.*, **28**, 1976 (1963).
(12) M. Mousseron-Canet, J.-P. Dalle, and J.-C. Mani, *Bull. Soc. Chim. Fr.*, 1561 (1968).
(13) V. K. Honwad, E. Siscovic, and A. S. Rao, *Tetrahedron*, **23**, 1273 (1967).
(14) R. W. Denny and A. Nickon, *Org. React.*, **20**, 133 (1973).
(15) M. Mousseron-Canet and J.-P. Chaband, *Bull. Soc. Chim. Fr.*, 245 (1969).
(16) I. Sasson and J. Labovitz, *J. Org. Chem.*, **40**, 3670 (1975).
(17) E. L. Skau and W. J. Bergman, *J. Org. Chem.*, **3**, 166 (1938).
(18) J. W. Huffman, *J. Org. Chem.*, **37**, 2736 (1972).
(19) H. C. Barrett and G. Büchi, *J. Am. Chem. Soc.*, **89**, 5665 (1967).
(20) (a) C. Tamm and R. Albrecht, *Helv. Chim. Acta*, **42**, 2177 (1959); (b) J. E. Herz, E. Gonzalez, and B. Mandel, *Aust. J. Chem.*, **23**, 857 (1970); (c) W. G. Dauben, R. G. Williams, and R. D. McKelvey, *J. Am. Chem. Soc.*, 95, 3932 (1973).
(21) It should be noted that in the reaction of diene **16** lacking the angular methyl group, approximately 10% of the product arises from the ene reaction as it does with dienes **17** (ref 17 and 18). The differences in energy of activation for the ene reaction and endoperoxide formation are apparently rather small, and a slight increase in the energy of activation for the endoperoxide reaction in dienes structurally similar to 1,3-cholestadiene apparently decreases its rate relative to that of the ene reaction to the point where the ene reaction predominates.
(22) Melting points were determined on a Kofler hot stage apparatus and are

uncorrected. Infrared spectra were taken as liquid films on sodium chloride plates or as KBr disks using a Perkin-Elmer Model 137 spectrophotometer and are reported in microns. Nuclear magnetic resonance spectra were obtained using a Perkin-Elmer Hitachi R-24 spectrometer with deuteriochloroform as solvent. All spectra are reported in parts per million relative to tetramethylsilane (δ). Mass spectra were determined using a Du Pont 21-490 mass spectrometer at 70 eV ionization potential. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(23) J. W. Huffman, *J. Org. Chem.*, **28**, 601 (1963).
(24) J. Mauthner, *Monatsh. Chem.*, **20**, 643 (1909).

Isolation and Structural Elucidation of New Potent Antileukemic Diterpenoid Esters from *Gnidia* Species[1,2]

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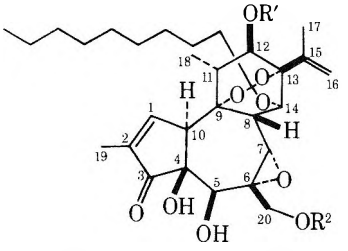
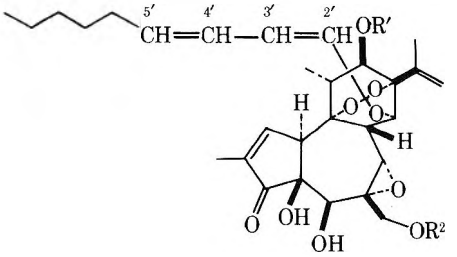
The isolation and structural elucidation of the new potent antileukemic principles, gnidilatin 20-palmitate (**1**), gnidilatidin 20-palmitate (**2**), and gnidilatin (**3**), and the new toxic diterpenoids, gnidilatidin (**4**) and gnidiglaucin (**5**), are reported. Esters **1** and **2** were proven to be C-20 palmitate esters of gnidilatin (**3**) and gnidilatidin (**4**), respectively, by acylation of **3** and **4** with palmitoyl chloride. Methanolysis of **1**, **3**, and **5** afforded the tetrol **6** as a common parent diterpenoid ortho ester. The tetrol **7** was obtained from **2** and **4**. Catalytic hydrogenation of **3** and **4** gave dihydrognidilatin (**8**).

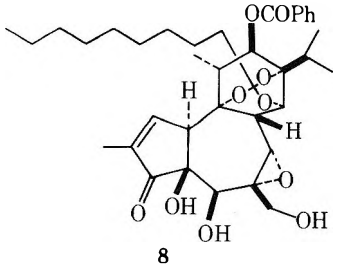
In the course of a continuing search for tumor inhibitors from plant sources, we found that alcoholic extracts of *Gnidia latifolia* Gilg.[3] and *Gnidia glaucus* Fres.[4] (Thymelaeaceae) showed significant activity in vivo against P-388 leukemia in mice.[5] We report herein the isolation and structural elucidation of the potent antileukemic principles, gnidilatin 20-palmitate (**1**), gnidilatidin 20-palmitate (**2**), and gnidilatin (**3**), and the companion toxic principles gnidilatidin (**4**) and gnidiglaucin (**5**).



1, R′ = COPh; R² = $COC_{15}H_{31}$
3, R′ = COPh; R² = H
5, R′ = $COCH_3$; R² = H
6, R′ = H; R² = H



2, R′ = COPh; R² = $COC_{15}H_{31}$
4, R′ = COPh; R² = H
7, R′ = H; R² = H



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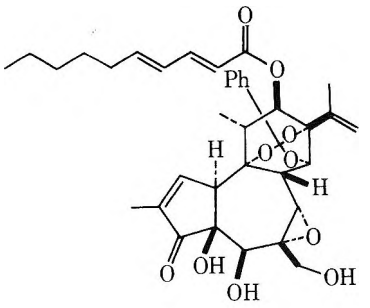

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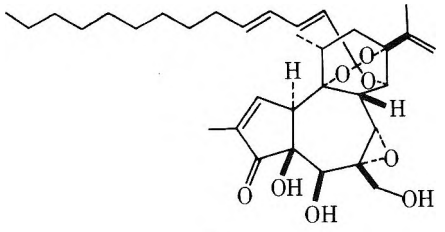

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Fractionation of the ethanol extract of *G. latifolia*, guided by a combination of an in vivo assay for antileukemic activity (P-388) and a goldfish toxicity test,[6] revealed that both the antileukemic and piscicidal activity were concentrated in the chloroform layer of a chloroform–water partition. Column chromatography on SilicAR yielded two active fractions (A and B) upon elution with ethyl acetate–benzene (1:9 and 3:7, respectively). Column chromatography of fraction A on silica gel and subsequent preparative layer chromatography on silica gel gave two closely related compounds, gnidilatin 20-palmitate (**1**), $C_{53}H_{78}O_{11}$, and gnidilatidin 20-palmitate (**2**), $C_{53}H_{74}O_{11}$. Successive column chromatography of fraction B on silica gel, then Celite, followed by preparative TLC on silica gel gave two closely related compounds, gnidilatin (**3**), $C_{37}H_{48}O_{10}$, and gnidilatidin (**4**), $C_{37}H_{44}O_{10}$.

The initial spectral data (ir, NMR) of these compounds indicated that they were structurally related to gnididin (**9**)[7] and huratoxin (**10**),[8] previously isolated from *Gnidia lamprantha* Gilg. (Thymelaeaceae) and *Hura crepitans* L. (Euphorbiaceae), respectively. The NMR spectrum of gnidilatidin (**4**) was almost identical with that of gnididin (**9**) except for the signals for the diene vinyl protons (at C-2′, 3′, 4′, and 5′),

which were identical with those of huratoxin (10). These data indicated that the only difference between 4 and 9 was the position of the benzoate and decadienoate esters, a conclusion supported by the uv spectra. While gnididin (9) showed absorption at 260 nm (characteristic of dienoate esters), gnidilatidin (4) showed absorption at 232 nm (characteristic of conjugated dienes). Methanolysis of 9 gave methyl decadienoate,[7] while 4 gave methyl benzoate and the tetrol 7, $C_{30}H_{40}O_9$. Although C-5 and C-12 proton absorptions each appear as a singlet, the site of benzoate attachment in 4 can be assigned on the basis of chemical shift. In the NMR spectrum of 4 the methine resonance (τ 4.88, s, 1 H), which was shifted to τ 6.09 in the spectrum of 7, was consistent with esterification at the C-12 position. Moreover, the C-5 methine resonance of 4 remains essentially unchanged from that of 7 and occurs downfield from the absorption which would be expected if the hydroxyl at C-12 were free. Hence gnidilatidin was assigned the structure 4. The stereochemistry of the double bonds in the 2,4-decadienoate group remains to be established.

A comparison of the molecular formulas and spectral data of gnidilatidin 20-palmitate (2) and gnidilatidin (4) indicated that gnidilatidin 20-palmitate (2) was the palmitate ester of gnidilatidin (4). Proof was obtained by direct transformation; thus upon treatment with palmitoyl chloride in pyridine, gnidilatidin (4) was converted to gnidilatidin 20-palmitate (2). In addition, methanolysis of 2 afforded tetrol 7. The structural problem which remained at this point was the determination of the site of attachment of the palmitate group to gnidilatidin (4). The NMR signals for the C-20 protons of 2 appeared at lower magnetic field by ~0.4 ppm than the corresponding signals of gnidilatidin (4) (see Table I), which indicated that C-20 was the point of attachment of the palmitate ester. Thus gnidilatidin 20-palmitate was shown to have the structure 2.

The molecular formula of gnidilatin (3) indicated that it was a tetrahydro derivative of gnidilatidin (4), and, as expected, the NMR spectrum of 3 did not have signals corresponding to decadienoate vinyl protons. Catalytic hydrogenation of gnidilatin (3) and gnidilatidin (4) over 10% palladium–carbon gave dihydro and hexahydro derivatives, respectively. Spectral data and TLC comparisons indicated the identity of these compounds.

Gnidilatin 20-palmitate (1) was shown to be the 20-palmitate of gnidilatin (3) by the same method as that used for the structural elucidation of gnidilatidin 20-palmitate (2).

By an isolation procedure very similar to that described above, gnidiglaucin (5) was isolated from an alcoholic extract of *Gnidia glaucus* Fres.

The molecular formula $C_{32}H_{46}O_{10}$ was advanced for gnidiglaucin (5) on the basis of high-resolution mass spectrometry. The presence of an acetate ester was indicated by the loss of 42 and 43 amu in the mass spectrum. Furthermore, there appeared in the NMR spectrum a signal for the acetate group at τ 8.16 (3 H, s). The other signals of gnidiglaucin (5) were very similar to that of gnidilatin (3) except for the absence of signals corresponding to a benzoate group, which indicated that gnidiglaucin (5) was the 12-acetate of the tetrol 6. Methanolysis of gnidiglaucin (5) gave a deacetyl derivative which was identical with the tetrol 6 obtained from gnidilatin (3). A comparison of the NMR spectrum of gnidiglaucin (5) with that of tetrol 6 led to the conclusion that the position of the acetate group was at C-12.

Gnidilatin 20-palmitate (1) and gnidilatidin 20-palmitate (2) exhibited substantial inhibitory activity at optimal doses of 0.5–2 mg/kg of body weight against the P-388 leukemia in mice, and gnidilatin (3) showed moderate inhibitory activity at about 80 μg/kg. On the other hand, gnidilatidin (4) and

Table I. NMR Spectra of Diterpenoid Esters and Derivatives[a]

	1	5	7	8	10	11	12	14	16	17	18	19	20
Gnidilatin 20-palmitate (1)	2.54 br s	5.88 s	6.60 s	6.49 d J = 2	6.30 br s	7.53 q J = 7	4.90 s	5.29 d J = 2	5.10 s	8.22 s	8.69 d J = 7	8.30 br s	5.27, 6.23 AB q J = 12
Gnidilatidin 20-palmitate (2)	2.41 br s	5.76 s	6.36 s	6.29 d J = 2	6.07 br s	7.50 q J = 7	4.77 s	5.10 d J = 2	4.99 s	8.12 s	8.68 d J = 7	8.23 br s	5.28, 6.13 AB q J = 12
Gnidilatin (3)	2.54 br s	5.89 s	6.47 s	6.47 d J = 2	6.22 br s	7.52 q J = 7	4.90 s	5.26 d J = 2	5.10 br s	8.20 s	8.67 d J = 7	8.28 br s	6.27, 6.45 AB q J = 11
Gnidilatidin (4)	2.50 br s	5.87 s	6.44 s	6.44 d J = 2	6.20[b]	7.50 q J = 7	4.88 s	5.20 d J = 2	5.08 br s	8.18 s	8.66 d J = 7	8.28 br s	6.20[b]
Gnidiglaucin (5)	2.53 br s	5.83 s	6.53 s	6.61 d J = 2	6.30 br s	7.72 q J = 7	5.15 s	5.39 d J = 2	5.11 br s	8.23 br s	8.77 d J = 7	8.23 br s	6.16, 6.30 AB q J = 12
(6)	2.45 br s	5.75 s	6.50 s	6.30 d J = 2.5	6.25 br s	7.52 q J = 7	6.16 s	5.37 d J = 2.5	4.95, 4.90 each s	8.14 s	8.78 d J = 7	8.17 br s	6.11, 6.29 AB q J = 12
(7)	2.41 br s	5.76 s	6.47 s	6.25 d J = 2	5.93 ~6.16[b]	7.51 q J = 7	6.09 s	5.28 d J = 2	4.90 s	8.12 s	8.77 d J = 7	8.19 br s	5.93 ~6.16[b]
Gnididin (9)		5.73 s	6.37[b]	6.37[b]	6.08[b]	7.50 q J = 7	4.89 s		4.98 s	8.12 s	8.62 d J = 7	8.21 br s	6.08[b]
Huratoxin (10)	2.39	5.77	6.54	7.06 d J = 2.5				5.55 d J = 2.5	5.08, 4.96 s	8.20 s		8.20 br s	6.16

[a] Spectra were measured as $CDCl_3$ solutions at 100 MHz. Coupling constants are in hertz and shift values are in units of τ. Multiplicity: d, doublet; q, quartet; s, singlet; br s, broadened singlet; AB q, AB quartet. [b] Inclusive of the other indicated protons.

gnidiglaucin (**5**) showed no inhibitory activity. These data indicate that the 12-benzoate and 20-palmitate esters may act as important carrier moieties (e.g., in processes concerned with cell penetration or selective molecular complex formation).[9] Investigations are in progress to determine the significance of the epoxide, the cyclopentenone, the ortho esters, and of the other structural features which may be important for the antileukemic activity of these diterpenoid esters.

Experimental Section

General. Uv spectra were measured on a Beckman Model DK-2A recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer Model 257 recording spectrophotometer. NMR spectra were determined on a Varian HA-100 spectrometer or a JEOL PS-100 pulsed FT NMR spectrometer interfaced to a Texas Instrument JEOL 980 A computer, and chemical shifts are reported using the τ scale. Mass spectra were determined on Hitachi Perkin-Elmer Model RMU-6E or AEI Model MS-902 spectrometers. Values of $[\alpha]$D were determined on a Perkin-Elmer Model 141 automatic polarimeter. All thin layer chromatography was carried out on commercially prepared plates; silica gel refers to silica gel 60 F-254 (E. Merck) and ChromAR to ChromAR 7GF (Mallinckrodt). For column chromatography silica gel refers to silica gel 60 (E. Merck), SilicAR to SilicAR CC-7 (Mallinkrodt), and Celite to Celite 545 (distributed by Sargent-Welch). Visualization of TLC was effected with vanillin spray (2.5 g vanillin–10 ml ethanol–50 ml concentrated sulfuric acid).

Extraction and Preliminary Fractionation of *Gnidia latifolia*. The dried ground wood of stems and stem bark (30 kg) was extracted at room temperature by stirring with 95% ethanol (216 l.) for 24 h. The extraction mixture was filtered and concentrated below 30 °C in vacuo to a syrupy residue (~900 ml). The residue was partitioned between chloroform (3 × 8 l.) and water (10 l.) and the combined chloroform layers were concentrated to give a brown tar (440 g), which was chromatographed on a SilicAR CC-7 column (5 kg) by eluting with benzene followed by benzene containing increasing amounts of ethyl acetate. Elution with 10% ethyl acetate in benzene gave fraction A (35 g), which was found to be active against P-388 lymphocytic leukemia in the mouse (PS). Elution with 30% ethyl acetate in benzene gave fraction B (58 g), which showed activity against PS and toxicity against goldfish.

Isolation of Gnidilatin 20-Palmitate (1) and Gnidilatidin 20-Palmitate (2). Careful column chromatography of fraction A on silica gel (600 g) with hexane containing increasing amounts of acetone gave a fraction which was shown to contain two closely related compounds. Preparative thin layer chromatography of this fraction on silica gel gave gnidilatin 20-palmitate (**1**, 62 mg, 0.0002%) [$[\alpha]^{23}$D +45° (*c* 0.58, $CHCl_3$); uv (MeOH) λ_{max} 231 nm (ϵ 18 000); ir ($CHCl_3$) 2.83, 3.41, 3.50, 5.79, 6.12, 6.24, 6.29, 7.90 μ; mass spectrum *m/e* 890.5539 (M^+, calcd for $C_{53}H_{78}O_{11}$ 890.5544)], and gnidilatidin 20-palmitate (**2**, 45 mg, 0.00015%) [$[\alpha]^{23}$D +27° (*c* 0.15, $CHCl_3$); uv (MeOH) λ_{max} 232 nm (ϵ 41 000); ir ($CHCl_3$) 2.85, 3.42, 3.52, 5.80, 5.91, 6.04, 6.13, 6.24, 6.30, 7.90 μ; mass spectrum *m/e* 886.5237 (M^+, calcd for $C_{53}H_{74}O_{11}$, 886.5231)].

Isolation of Gnidilatin (3) and Gnidilatidin (4). Column chromatography of fraction B on SilicAR (700 g) with chloroform containing increasing amounts of methanol gave an active fraction (7 g). Partition chromatography on Celite (10% $CHCl_3$–heptane:17% aqueous methanol) followed by preparative TLC on silica gel gave gnidilatin (**3**, 37 mg, 0.00012%) [$[\alpha]^{23}$D +52° (c 0.24, $CHCl_3$); uv (MeOH) λ_{max} 231 nm (ϵ 15 000); ir ($CHCl_3$) 2.83, 3.41, 3.49, 5.79, 5.89, 6.12, 6.24, 6.28, 7.89 μ; mass spectrum *m/e* 652.3240 (M^+ calcd for $C_{37}H_{48}O_{10}$, 652.3248)] and gnidilatidin (**4**, 33 mg, 0.00011%) [$[\alpha]^{23}$D +28° (*c* 0.16, $CHCl_3$); uv (MeOH) λ_{max} 232 nm (ϵ 36 000); ir ($CHCl_3$) 2.84, 3.42, 3.50, 5.85, 5.90, 6.14, 6.25, 6.28, 7.87 μ; mass spectrum *m/e* 648.2927 (M^+, calcd for $C_{37}H_{44}O_{10}$, 648.2935)].

Methanolysis of Gnidilatidin (4). To 0.5 ml of 0.1 N sodium methoxide in methanol was added gnidilatidin (**4**, 3 mg). The mixture was stirred at room temperature for 18 h. The reaction mixture was dried with a stream of nitrogen, and separated by preparative TLC on ChromAR to give methyl benzoate and the tetrol **7** (2.3 mg): uv (MeOH) λ_{max} 231 nm (ϵ 30 000); ir ($CHCl_3$) 2.90, 5.89, 6.05, 6.14, 6.24 μ; mass spectrum *m/e* 544.2672 (M^+, calcd for $C_{30}H_{40}O_9$, 544.2672).

Acylation of Gnidilatidin (4) with Palmitoyl Chloride. To a solution of gnidilatidin (**4**, 5 mg) in 0.5 ml of pyridine was added palmitoyl chloride (50 μl) and the reaction mixture was kept at room temperature for 2 h. The reaction mixture was evaporated to dryness with a stream of nitrogen and separated by preparative TLC on ChromAR to give a palmitate (5.1 mg), which was found to be identical with gnidilatidin 20-palmitate (**2**) by comparison of spectral data.

Methanolysis of Gnidilatidin 20-Palmitate (2). Methanolysis of gnidilatidin 20-palmitate (**2**, 15 mg), as described above for gnidilatidin (**4**), gave the tetrol **7** (2.5 mg), methyl benzoate, and methyl palmitate, identified by comparison with authentic samples.

Catalytic Hydrogenation of Gnidilatin (3). Gnidilatin (**3**, 5 mg) was subjected to atmospheric pressure hydrogenation in absolute ethanol (5 ml) using 10% palladium on charcoal (5 mg) as catalyst. After 2 h the catalyst was removed by filtration and the solvent was evaporated to afford a colorless glass (5 mg). Preparative TLC on ChromAR with 3% methanol in chloroform gave dihydrognidilatin (**8**, 4.2 mg): uv (MeOH) λ_{max} 231 nm (ϵ 17 000); ir ($CHCl_3$) 2.83, 5.80, 5.83, 6.13, 6.25, 6.29, 7.89 μ; NMR ($CDCl_3$) τ 9.16–9.04 (9 H, m, 16-, 17-, and 10′-H), 8.78 (~16 H), 8.73 (3 H, d, J = 7 Hz, 18-H), 8.29 (3 H, br s, 19-H), 7.57 (1 H, q, J = 7 Hz, 11-H), 6.60 (1 H, d, J = 2 Hz, 8-H), 6.50 (1 H, s, 7-H), 6.32 (1 H, br s, 10-H), 6.31, 6.15 (2 H, AB q, J = 12 Hz, 20-H), 5.90 (1 H, s, 5-H), 5.50 (1 H, d, J = 2 Hz, 14-H), 4.90 (1 H, s, 12-H), 2.56 (1 H, br s, 1-H), 2.64–2.07 (5 H, PhCOO); mass spectrum *m/e* 654.3408 (M^+, calcd for $C_{37}H_{50}O_{10}$, 654.3405).

Catalytic Hydrogenation of Gnidilatidin (4). Gnidilatidin (**4**, 5 mg) was hydrogenated as described above for gnidilatin (**3**) to give hexahydrognidilatidin (4.3 mg), which was characterized by direct spectral comparison with 8 described above.

Acylation of Gnidilatin (3) with Palmitoyl Chloride. Acylation of gnidilatin (**3**, 5 mg) with palmitoyl chloride, as described above for gnidilatidin (**4**), gave the palmitate (4.8 mg), characterized as gnidilatin 20-palmitate (**1**) by direct spectral comparison with the authentic sample.

Methanolysis of Gnidilatin (3). Methanolysis of gnidilatin (**3**, 3 mg), as described above for gnidilatidin (**4**), gave the tetrol **6** (2.2 mg): uv (MeOH) λ_{max} 241 nm (ϵ 6000); ir ($CHCl_3$) 2.90, 5.89, 6.12 μ; mass spectrum *m/e* 548.2980 (M^+, calcd for $C_{30}H_{44}O_9$, 548.2985).

Methanolysis of Gnidilatin 20-Palmitate (1). Methanolysis of gnidilatin 20-palmitate (**1**, 5 mg) by the same method used for gnidilatidin (**4**) afforded methyl benzoate, methyl palmitate, and the tetrol **6** (2.8 mg), which was identified by spectral comparison with **6** described above.

Isolation of Gnidiglaucin (5). The dried ground roots (30 kg) of *Gnidia glaucus* Fres. were extracted by the same method described for *G. latifolia* to give a brown tar (1.45 kg), which was partitioned between chloroform (4 + 2 + 2 l.) and water (4 l.). The combined chloroform layers were concentrated to give a brown tar (335 g), which was further partitioned between 10% aqueous methanol (2 l.) and petroleum ether (2 + 1 l.). The combined petroleum ether layers were concentrated to give a brown oil (135 g), which was chromatographed on a SilicAR column (1.5 kg) by eluting with chloroform containing increasing amounts of methanol. Elution with 2% methanol in chloroform gave a fish-toxic fraction (2.5 g), preparative TLC of which on silica gel yielded gnidiglaucin (**5**, 30 mg, 0.0001%): $[\alpha]^{24}$D +36° (c 0.50, $CHCl_3$); uv (MeOH) λ_{max} 241 nm (ϵ 7600); ir ($CHCl_3$) 2.82, 5.72, 5.90, 6.14, 8.00 μ; mass spectrum (chemical ionization: methane reagent gas) *m/e* 591.3140 (M^+ + H, calcd for $C_{32}H_{47}O_{10}$, 591.3166).

Methanolysis of Gnidiglaucin (5). Methanolysis of gnidiglaucin (**5**, 5 mg), as described above for gnidilatidin (**4**), gave the tetrol **6** (3.8 mg), identified by spectral comparison with **6** obtained from gnidilatin (**3**).

Registry No.—**1**, 60195-67-7; **2**, 60195-68-8; **3**, 60195-69-9; **4**, 60195-70-2; **5**, 60209-66-7; **6**, 60209-62-3; **7**, 60195-71-3; **8**, 60195-72-4; **9**, 55306-11-1; **10**, 33465-16-6; palmitoyl chloride, 112-67-4.

References and Notes

(1) Tumor Inhibitors. 117. Part 116: S. M. Kupchan, Y. Shizuri, T. Murae, J. G. Sweeny, H. R. Haynes, M.-S. Shen, J. C. Barrick, R. F. Bryan, D. van der Helm, and K. K. Wu, submitted for publication.

(2) This investigation was supported by grants from the National Cancer Institute (CA-11718) and the American Cancer Society (CI-102K), and by contracts with the Division of Cancer Treatment, National Cancer Institute (NO1-CM-12099 and NO1-CM-67002).

(3) The wood of stems and stem bark were collected in Kenya in Nov 1972.

(4) The roots were collected in Tanzania in Oct 1973. The authors acknowledge with thanks receipt of both dried plant materials from Dr. Robert E. Perdue, Jr., U.S. Department of Agriculture, in accordance with the program developed by the National Cancer Institute.

(5) Antileukemic activity was assayed under the auspices of the National Cancer Institute, by the procedures described by R. I. Geran, N. H. Greenberg, M. M. McDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, **3**, 1 (1972). Gnidilatin 20-palmitate and gnidilatidin 20-palmitate showed T/C ca. 170 at dosage levels between 2 and 0.5 mg/kg. In addition, these compounds showed significant inhibitory activity (i.e., T/C > 125) at doses down to 20 μg/kg. Gnidilatin showed T/C 140–130 in the 80–20 μg/kg

dosage range.
(6) Piscicidal activity was assayed using a procedure similar to that described by W. A. Gersdorff, *J. Am. Chem. Soc.*, **52**, 3440 (1930). Gnidilatin, gnidilatidin, and gnidiglaucin showed toxicity at concentrations of 50 μg/l.
(7) S. M. Kupchan, J. G. Sweeny, R. L. Baxter, T. Murae, V. A. Zimmerly, and B. R. Sickles, *J. Am. Chem. Soc.*, **97**, 672 (1975).
(8) K. Sakata, K. Kawazu, and T. Mitsui, *Agric. Biol. Chem.*, **35**, 2113 (1971).
(9) A similar proposal has been advanced for the role of the long aliphatic chain in the piscicidal activity of huratoxin; cf. ref 8.

Synthesis of α-Dehydrobiotin[1]

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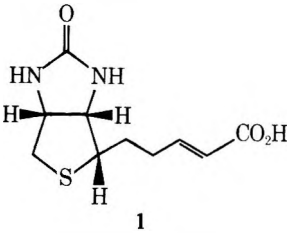
α-Dehydrobiotin has been synthesized from the bicyclic sulfonium salt **7**. The five-carbon acid side chain was elaborated by cleavage of the sulfonium ring with acetate ion, hydrolysis to a hydroxypropyl side chain, oxidation to a propionaldehyde side chain, and coupling with triethyl phosphonoacetate. A new reagent, orthophosphoric acid, was used to effect debenzylation of the urea moiety.

α-Dehydrobiotin (**1**) is an extremely effective antagonist of biotin that has been isolated from a natural source as a



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consequence of its antibiotic activity against a variety of bacteria and fungi.[2] Subsequently, it was reported that α-dehydrobiotin is accompanied by two other biotin antagonists[3] and that it is a product of the catabolism of biotin.[4]

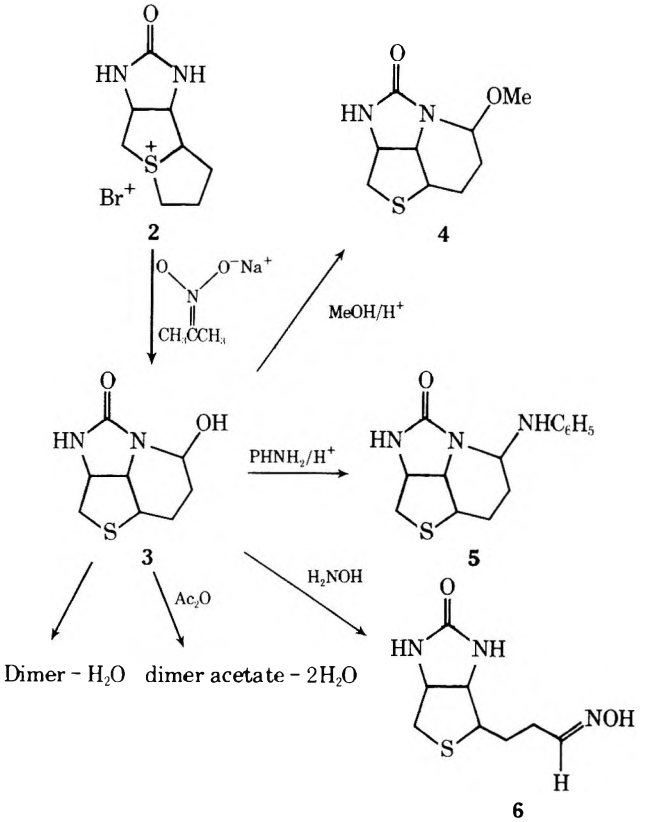
We undertook synthesis of this biologically interesting molecule since we had available experience and intermediates derivingfrom the synthesis of biotin itself.[5] The approach we followed was to divert the biotin synthesis cited above at a stage in which the difficult stereochemical problems have been solved and in which a reactive center is present where the double bond is to be formed.

Debenzylated Series. The intermediate which was expected to be the most useful in this kind of approach is the cyclic sulfonium salt **2**;[5c] however, as will be seen, an unexpected difficulty developed. The first step is oxidation of the terminal carbon atom of the latent side chain in **2** to the oxidation level of an aldehyde. Analogy from the biotin synthesis[5] suggests that sulfonium salt **2** can react as if it were a covalent bromide with the appropriate side chain. Accordingly **2c**[6] was reacted with the sodium salt of 2-nitropropane,[7] to give a compound assigned structure **3c**, a hemiacetal form of desired aldehyde. Since a priori sulfonium salt **2** has two other points where attack of the nitronate anion could have occurred, hemiacetal **3c** was submitted to x-ray crystallographic analysis for confirmation of its structure. Two stereoscopic views of the result are shown in Figure 1. Additional confirmation was obtained by reaction of **3c** with methanol or aniline under acidic conditions to give **4c** or **5c**, respectively. Reaction with hydroxylamine gave oxime **6c**, the only compound of the series with an actual rather than a latent side chain.

The next operation to be carried out is addition of the remaining two carbon atoms of the side chain. Reaction of **3c** with triethyl phosphonoacetate[8] should have been feasible, but we could obtain no product. Perhaps the hemiacetal ring is so stable that there is no appreciable concentration of the aldehyde form. Reaction of **3c** with malonic acid and piperidine gave a product whose elemental analysis and mass spectrum are consistent with a dimer of a dehydration product of **3c**. This propensity of **3c** to self-condense was also evident when treatment of **3c** with acetic anhydride gave a similar "dimer" acetate. Since these products did not appear to have any synthetic utility, their structures were not investigated further. The NMR spectrum of the "dimer" is not readily interpretable, but is clearly not consistent with any symmetrical dimer.

Racemic Series (a). These unproductive results forced a retreat to the precursor of **3**, the dibenzyl derivative **7** (X = Br). Here we chose a lengthier reaction sequence. The ring was cleaved with acetate ion to give **8a** whose basic hydrolysis gave alcohol **9a**. The next operation was to specifically oxidize the alcohol function to an aldehyde without affecting the thioether function. This was achieved with dimethyl sulfoxide/dicy-

Scheme I



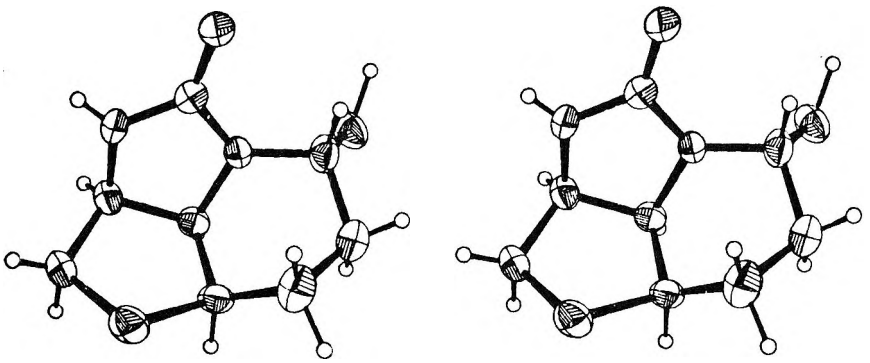
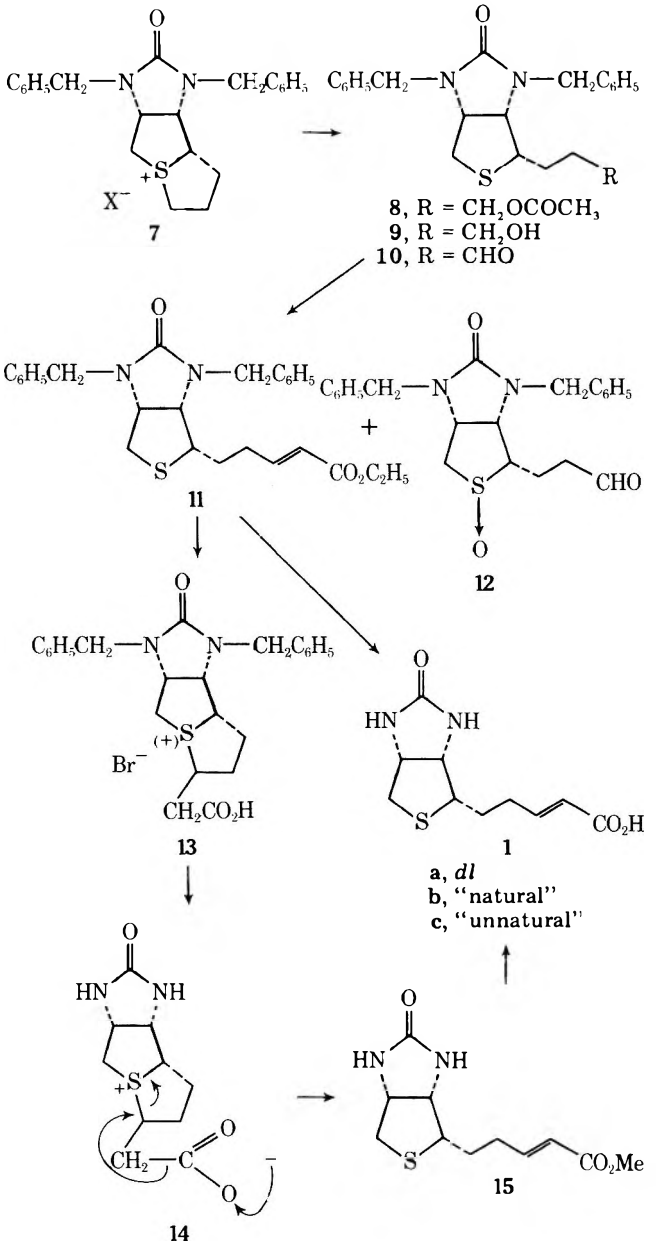


Figure 1.

clohexylcarbodiimide combination[9] in 60% yield. The two-carbon fragment was added with the sodium salt of triethyl phosphonoacetate[8] to give **11a** in 50% crude yield. There remained only removal of the benzyl protecting groups to complete the synthesis.

Two reagents for debenzylation of the cyclic urea moiety are known. Neither one proved very satisfactory owing to the reactivity of the α,β-unsaturated ester functionality. Using one, sodium in liquid ammonia,[5a] on **11a** we obtained a reaction mixture whose NMR spectrum contained peaks for the vinyl hydrogens at only about half the expected intensity. Presumably the conjugated double bond was partially reduced and consequently this method was not investigated further. Using the other, concentrated hydrobromic acid, we obtained, after brief heating, a product in 67% yield to which structure **13a** was assigned on the basis of its NMR spectrum (no vinyl protons). Prolonged heating under reflux gave a poor yield of material presumed to be the hydrobromide of the debenzylated zwitterion **14**. Since we feared a fragmentation reaction[10] as indicated by the arrows on **14**, this crude reaction product was treated directly with methanolic hydrogen chloride to esterify the carboxyl group. Treatment of this reaction mixture with sodium bicarbonate then gave a low yield of methyl ester **15** which on alkaline hydrolysis gave *dl*-α-dehydrobiotin (**1a**).

Scheme II



Optically Active Series. Synthesis of *d*-dehydrobiotin (**1b**) followed along the same lines; that is, the sulfonium salt **7b** (X = *d*-camphorsulfonate) was converted to aldehyde **10b**, the side chain was lengthened with triethyl phosphonoacetate, and then the benzyl groups were removed. However, some experimental modifications could be incorporated with profit. Since we had available large quantities of the optical antipode **7c** (X^- = *d*-camphorsulfonate) a good many model experiments were made with material derived from this substance.

Optically active aldehyde **10b** could not be obtained crystalline. On the suspicion that impurities associated with the dimethyl sulfoxide/carbodiimide method were preventing crystallization and easy purification, other methods of oxidation were examined. Both the Collins reagent[11] and pyridinium chlorochromate[12] gave **10b** in approximately 40% yield accompanied by some sulfoxide **7b**. Thus both of these methods possess a good degree of specificity for oxidation of an alcohol group in the presence of a sulfide. Even though the aldehyde still remained an oil, at least it was demonstrated that these three methods are about equivalent in this case.

The problem of removing the benzyl groups of **11b** was solved in a much more efficient manner than previously by using orthophosphoric acid containing phenol as a benzyl acceptor. The yield of **1b** from **11b** was 53% without any indication of cyclized products such as **13** and **14** which had been obtained using hydrobromic acid. A possible explanation for these differing results might be that the sulfonium salts are formed only by displacement of bromide ion from an intermediary β-bromo acid derived by addition of hydrogen bromide to the double bond.

It does not appear that orthophsphoric acid has been recognized previously as a useful reagent for removing benzyl groups. However, polyphosphoric acid has been used for the removal of α-methylbenzyl groups from amides.[13] Here it was

ineffective. Thus the use of orthophosphoric acid allowed completion of a short synthesis of the antibiotic *d*-α-dehydrobiotin (**1**) from the sulfonium salt **7b** with all steps going in reasonable yield.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on Varian T-60 and HA-100 instruments and are reported in parts per million from internal tetramethylsilane. Infrared and mass spectra were recorded on Perkin-Elmer 137 and CEC-110B instruments, respectively. Elemental analyses were conducted under the supervision of Dr. F. Scheidl of our microanalytical laboratory.

3-Hydroxy-1,2,3,6,6aα,7,8aα,8bα-octahydro-5*H*-pyrido[1,-2,3-*cd*]thieno[3,4-*d*]imidazol-5-one (3). A mixture of 18 ml of 2-nitropropane and 65 ml of 3 N sodium hydroxide was heated on the steam bath until the pH was about 7–8. Then 13.2 g of **2c** was added and the mixture was heated under reflux for 3.5 h. It was then cooled in an ice bath and the solid collected to give 7.7 g (75%) of product, mp 184–185 °C dec. Recrystallization from water gave colorless bars, 50% recovery: mp 168–178 °C dec; NMR (Me_2SO) δ 6.65 (s, 1, NH), 5.52 (d, 1, J = 4 Hz, OH), and 5.20 ppm (m, 1, NCHO); ir (KBr) 1590 and 1640 cm^{-1}.

Anal. Calcd for $C_8H_{12}N_2O_2S$: C, 47.97; H, 6.04; N, 13.99. Found: C, 47.63; H, 6.04; N, 14.14.

Crystallography. Crystals of **3** are monoclinic, space group $P2_1$, with a = 6.44 (1), b = 8.39 (1), c = 8.38 (1) Å, β = 103.67 (5)°, and Z = 2. The intensity data were measured on an automated diffractometer by a peak-top scan technique (narrow θ–2θ scans). Nickel-filtered Cu Kα radiation and pulse height discrimination were used. An empirical correction was applied to convert the peak top data to integrated scan data; no absorption correction was made (μ = 29.3 cm^{-1}). The crystal used for data collection was approximately 0.05 × 0.15 × 0.20 mm in size. A total of 643 independent reflections were recorded for θ <57°, of which 582 were considered observed. The structure was solved by standard Patterson and Fourier methods and was refined by full matrix least squares. The hydrogen atoms were located on a difference map calculated after anisotropic refinement of the heavier atoms. In the final cycles of refinement, anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atom parameters were refined. The final unweighted and weighted discrepancy indices are R = 0.036 and wR = 0.049 for the 582 observed reflections. There are no features greater than ±0.3 eA^{-3} on the final difference map.

3-Methoxy-1,2,3,6,6aα,7,8aα,8bα-octahydro-5*H*-pyrido[1,2,-3-*cd*]thieno[3,4-*d*]imidazol-5-one (4). A mixture of 2 g of **3**, 0.2 g of *p*-toluenesulfonic acid, and 100 ml of methanol was heated under reflux for 50 min and then cooled to room temperature. Solid sodium bicarbonate was added until the mixture was neutral. The mixture was then filtered, and the filtrate was concentrated in vacuo to dryness. The residue was crystallized from methanol to give 2.2 g of **4**, mp 155–160 °C. Recrystallization from methanol gave colorless prisms: mp 160–163 °C; ir (KBr) 1720 and 1670 cm^{-1}; NMR (Me_2SO-d_6) δ 1.4–2.4 (m, 4, $-CH_2CH_2-$), 2.63 (d, 1, J_{AB} gem = 12 Hz, CH_AH_BS), 2.94 (dd, 1, J_{AB} gem = 12 Hz, J_{BX} vic = 4 Hz, CH_AH_BS), 3.12 (s, 3, $-OCH_3$), 3.47 (m, 1, –CHS), 4.19 (m, 2, NCHCHN), 4.79 (m, 1, NCHO), 6.75 ppm (s, 1, NH).

Anal. Calcd for $C_9H_{14}N_2O_2S$: C, 50.45; H, 6.58; N, 13.07. Found: C, 50.43; H, 6.86; N, 12.83.

Preparation of 5. A mixture of 3 g of **3**, 1.5 ml of aniline, 5 ml of benzene, and a trace of *p*-toluenesulfonic acid was heated on the steam bath for 10 min. The solid was collected from the cooled mixture and washed with benzene to give 3.5 g of crude product. This was dissolved in 50 ml of methylene chloride and washed with 50 ml of saturated sodium bicarbonate solution. The methylene chloride phase was dried over sodium sulfate and evaporated in vacuo to give 3.3 g of foam which was crystallized from ethyl acetate to give 2.5 g of **5**, mp 167–170 °C. Recrystallization from ethyl acetate/ethanol gave colorless needles: mp 181–184 °C (sinter 177 °C); uv max 290 nm (ε 1800) and 243 (13 550); ir ($CHCl_3$) 3450, 3440 (NH), and 1700 cm^{-1}; NMR (Me_2SO-d_6) δ 1.35–2.50 (m, 4, $-CH_2CH_2-$), 2.78 (m, 2, J gem = 13 Hz, CH_2S), 3.41 (m, 1, CHS), 4.14 (m, 2, NCHCHN), 5.17 (m, 1, NCHN), 5.90 (d, 1, J = 6 Hz, NHPh), 6.54 (s, 1, NHCO), and 6.40–7.2 ppm (m, 5, Ph).

Anal. Calcd for $C_{14}H_{17}N_3OS$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.08; H, 6.15; N, 15.23.

4-(3-Hydroxyiminopropyl)perhydro-2*H*-thieno[3,4-*d*]imidazol-2-one (6). A mixture of 1 g of **3**, 0.5 g of hydroxylamine hydrochloride, 0.6 g of sodium acetate, 5 ml of ethanol, and 5 ml of water was heated under reflux for 1 h. The reaction mixture was cooled and concentrated in vacuo. The residue was triturated with water and recrystallized from ethanol/hexane to give 0.5 g of **6**, mp 202–205 °C dec. Recrystallization from ethanol/hexane gave colorless prisms: mp 202–204 °C dec; NMR (Me_2SO) δ 6.65 (m, 1, –CH=N).

Anal. Calcd for $C_8H_{13}N_3O_2S$: C, 44.64; H, 6.09; N, 19.52. Found: C, 44.42; H, 6.02; N, 19.25.

Dehydration of 3. A mixture of 1 g of **3**, 1 ml of piperidine, 10 ml of methanol, 10 ml of water, and 1 g ofmalonic acid was allowed to stand at room temperature for 24 h and then warmed on the steam bath for 0.5 h. It was then concentrated in vacuo. The residue was crystallized from water to give an amorphous white solid. Recrystallization from ca. 40 ml of water gave 0.7 g. Recrystallization from methanol/ether gave white needles: mp 200–210 °C dec; MS m/e 364.

Anal. Calcd for $C_{16}H_{20}N_4O_2S_2$: C, 52.72; H, 5.53; N, 15.37. Found: C, 52.96; H, 5.41; N, 14.55.

Treatment of 3 with Acetic Anhydride. A mixture of 1 g of **3** and 10 ml of acetic anhydride was heated under reflux for 4 h. The reaction mixture was filtered to remove a small amount of white insoluble material and the filtrate was concentrated in vacuo. The residue was crystallized from ether to give 0.8 g of product, mp 220–230 °C. Recrystallization from 2-propanol gave fine white needles: mp 258–263 °C dec; MS m/e 448.

Anal. Calcd for $C_{20}H_{24}N_4O_4S_2$: C, 53.55; H, 5.40; N, 12.50. Found: C, 53.34; H, 5.59; N, 12.34.

***l*-1,3-Dibenzyl-2-oxohexahydrothieno[3,4-*d*]imidazole-4-propanol Acetate (8b).** A solution of 47.6 g (80 mmol) of *l*-3,4-(1′,3′-dibenzyl-2′-ketoimidazolido)-1,2-trimethylenethiophanium *d*-camphorsulfonate (**7b**) and 16 g (0.2 mol) of anhydrous sodium acetate in 1 l. of ethanol was stirred and heated under reflux for 2.5 h, and then cooled and concentrated in vacuo. The residue was diluted with 1 l. of water to give 30.8 g (90%) of **8b**, mp 95–98 °C. A pure sample was obtained as colorless prisms on two recrystallizations from 2-propanol: mp 98–100 °C; ir ($CHCl_3$) 1730 and 1692 cm^{-1}; $[\alpha]^{25}D$ −50.3° (c 1, $CHCl_3$).

Anal. Calcd for $C_{24}H_{28}N_2O_3S$: C, 67.89; H, 6.65; N, 6.60; S, 7.55. Found: C, 68.24; H, 6.51; N, 6.68; S, 7.62.

Preparation of 8a. An analogous reaction of **7a** bromide gave **8a** as colorless prisms from 2-propanol, mp 100–103 °C.

Anal. Found: C, 67.89; H, 6.56; N, 6.63.

***l*-1,3-Dibenzyl-2-oxohexahydrothieno[3,4-*d*]imidazole-4-propanol (9b).** A solution of 25.4 g (60 mmol) of **8b** in 500 ml of ethanol and 60 ml of 1 N sodium hydroxide was heated under reflux for 3 h and allowed to stand overnight at room temperature. After the solution had been diluted with water and brine, it was extracted with methylene chloride in three portions. The residue obtained after the methylene chloride extracts had been dried over sodium sulfate and concentrated in vacuo was crystallized from methylene chloride/petroleum ether to give 18.8 g (82%) of **9b**, mp 75–77 °C. Recrystallization from methylene chloride/petroleum ether gave colorless needles: mp 85–87 °C; ir ($CHCl_3$) 3650 and 1690 cm^{-1}; $[\alpha]^{25}D$ −54° (c 1, $CHCl_3$).

Anal. Calcd for $C_{22}H_{26}N_2O_2S$: C, 69.09; H, 6.85. Found: C, 69.09; H, 6.89.

Preparation of 9a. This compound was obtained similarly from **8a** as colorless prisms from methylene chloride/petroleum ether, mp 105–107 °C. Anal. Found: C, 69.33; H, 6.66.

***dl*-1,3-Dibenzyl-2-oxohexahydrothieno[3,4-*d*]imidazole-4-propionaldehyde (10a).** To 10 ml of dry dimethyl sulfoxide were added in this order 3.5 g of **9a**, 5.6 g of *N,N′*-dicyclohexylcarbodiimide, 0.7 ml of pyridine, and 0.5 ml of trifluroacetic acid. This mixture was stirred for 4 h, and excess carbodiimide was decomposed by addition of 5 g of oxalic acid in 25 ml of methanol and some ether. After having been stirred for 1 h, the mixture was filtered and the precipitate washed with ether. The filtrate was diluted with water and extracted with four portions of ether. The ethereal extracts after drying and concentrating gave 3.8 g of an oil. This oil was dissolved in benzene and adsorbed on 90 g of silica gel which was then eluted with 250 ml of benzene, 300 ml of methylene chloride, and 250 ml of methylene chloride/ethyl acetate (4:1). Crystallization of the residue left on concentrating of the last eluate from hexane gave 2.5 g (62%) of crude **10a**, mp 95–106 °C. Recrystallization from methylene chloride/hexane gave off-white prisms: mp 110–113 °C; ir ($CHCl_3$) 1720 and 1690 cm^{-1}; NMR ($CDCl_3$) 9.74 ppm (–CHO).

Anal. Calcd for $C_{22}H_{24}N_2O_2S$: C, 69.45; H, 6.36; N, 7.36; S, 8.41. Found: C, 69.39; H, 6.48; N, 7.10; S, 8.32.

Oxidation of 9b with Pyridinium Chlorochromate. A mixture of 50 g (0.13 mol) of **9b**, 298 g of pyridinium chlorochromate, and 3 l.

of methylene chloride was stirred at room temperature for 1.5 h. The methylene chloride solution was then decanted from the black tars, washed with 2 × 1 l. of 3 N hydrochloric acid, and dried over sodium sulfate. It was then filtered through 500 g of Florisil in a sintered glass funnel. The Florisil was washed with 4 l. of methylene chloride. The eluates were combined and concentrated in vacuo to give 19.9 g of crude **10b** as an oil. Next, the Florisil was eluted with 3 l. of tetrahydrofuran. The eluate was concentrated in vacuo and the residue was crystallized from ether to give 4.7 g of crude **12b**, mp 80–84 °C. Recrystallization from benzene/ether gave colorless prisms, mp 85–90 °C.

Anal. Calcd for $C_{22}H_{24}N_2O_3S$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.94; H, 6.02; N, 7.31.

Oxidation of 9c with Dipyridinechromium Oxide. To a mixture of 200 g of dipyridinechromium oxide, 5 g of phosphorus pentoxide, and 2 l. of methylene chloride was added a solution of 50 g of **4c** in 200 ml of methylene chloride with good stirring. A dark tar began to separate immediately and stirring was stopped. After 20 min the methylene chloride solution was filtered through Celite and the residual tar washed with methylene chloride. The combined methylene chloride filtrates were concentrated in vacuo to 500 ml, washed with 2 × 250 ml of N hydrochloric acid, 250 ml of water, and 250 ml of brine, and dried over sodium sulfate. This solution was filtered through 200 ml of Florisil. The Florisil was washed with methylene chloride. Concentration of the first 500 ml of eluate in vacuo left 27.2 g of brownish oil. A further 14.9 g of less pure product was obtained on concentration of the second 500 ml of eluate (TLC 1:1 ether/benzene; silica gel G plates).

***dl*-1,3-Dibenzyl-2-oxohexahydrothieno[3,4-*d*]imidazole-4-α-penta-Δ$^{\alpha}$-enoic Acid Ethyl Ester (11a).** To a suspension of 0.25 g (50% oil dispersion, 5 mmol) of sodium hydride in 30 ml of dry tetrahydrofuran was added dropwise a solution of 1.2 g (5 mmol) of triethyl phosphonoacetate in 20 ml of dry tetrahydrofuran at 10 °C. The solution was stirred for 1 h at room temperature, and then cooled to 10 °C. A solution of 1.9 g (5 mmol) of **10a** in 25 ml of tetrahydrofuran was added dropwise at 5–8 °C. The reaction mixture was then stirred for 1 h in the ice bath, diluted with water, and extracted with three portions of ether. The residue from the dried ether extracts (sodium sulfate) was crystallized from ethyl acetate/hexane to give 1.4 g (60%) of crude **11a**, mp 79–85 °C. Recrystallization from ethyl acetate/petroleum ether and from aqueous ethanol gave colorless prisms: mp 96–100 °C; NMR ($CDCl_3$) δ 5.80 (d, 1, J = 15.5 Hz) and 6.8 ppm (m, 1, –CH=CH–).

Anal. Calcd for $C_{26}H_{30}N_2O_3S$: C, 69.30; H, 6.71; N, 6.22; S, 7.12. Found: C, 69.27; H, 6.78; N, 6.57; S, 6.97.

Preparation of 11b. Treatment of **10b** in an analogous fashion gave a 50% yield of crude **11b** from hexane/petroleum ether, mp 70–75 °C. Recrystallization from petroleum ether/hexane gave colorless plates, mp 90–92 °C. Anal. Found: C, 69.40; H, 6.90; N, 6.10; S, 7.21.

***dl*-1,3-Dibenzyl-2-oxo-6-carboxymethyldecahydroimidazo-[4,5-*c*]thieno[1,2-*a*]thiolium Bromide (13a).** A mixture of 2.2 g (5 mmol) of **11a** and 22 ml of 48% hydrobromic acid was heated under reflux for 0.5 h, cooled, washed with benzene, and concentrated in vacuo. The residue crystallized from water to give 1.7 g (67%) of **13a**, mp 203–208 °C. Recrystallization from methanol gave colorless prisms, mp 214–216 °C.

Anal. Calcd for $C_{24}H_{27}BrN_2O_3S$: C, 57.25; H, 5.41; N, 5.56; S, 6.37. Found: C, 57.39; H, 5.44; N, 5.47; S, 6.50.

Preparation of 13c. Treatment of 5 g of **11c** in a similar manner gave 2 g of **13c** from 2-propanol, mp 182–188 °C. For characterization this material was dissolved in 20 ml of warm water to give a cloudy solution which was filtered and then neutralized with solid sodium bicarbonate. The inner salt which precipitated was collected and recrystallized from chloroform to give colorless needles: mp 113–115 °C dec; ir ($CHCl_3$) 1700 and 1600 cm^{-1}.

Anal. Calcd for $C_{24}H_{26}N_2O_3S$: C, 68.22; H, 6.20; N, 6.63. Found: C, 67.90; H, 6.32; N, 6.45.

6-Carboxymethyl-2-oxodecahydroimidazo[4,5-*c*]thieno-[1,2-*a*]thiolium Inner Salt (14c). A mixture of 5 g of **11c**, 10 ml of xylene, and 100 ml of 48% hydrobromic acid was heated under reflux for 5.5 h with an apparatus such that the heavier of the two phases was returned to the flask. The reaction mixture was cooled, treated with charcoal, and concentrated in vacuo. The residue was dissolved in water, and the solution passed through a column of 125 ml of Amberlite IRA-400 ion exchange resin in the hydroxide form using water to elute. Concentration of the first 100 ml of eluate in vacuo left 1.25 g of crude **14c**, mp 140–150 °C (with foaming). Recrystallization from ethanol/water gave colorless needles: mp 217–221 °C; ir (KBr) 1680, 1650, and 1560 cm^{-1}; uv max none above 200 nm; NMR (D_2O) no band in the vinyl region.

Anal. Calcd for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56. Found: C, 49.81; H, 5.91; N, 11.60.

***d*-α-Dehydrobiotin (1b). A. Via Hydrobromic Acid Debenzylation.** A mixture of 2 g of **11b** and 50 ml of 48% hydrobromic acid was stirred for 1 h at room temperature. During this time most of the ester dissolves. The solution was then slowly heated to reflux and slow distillation maintained for 1 h. During this time 10 ml of hydrobromic acid and 0.8 ml of immiscible material distilled out. The solution was heated under reflux without distillation for 1 h, and then the distillate was collected for 0.5 h to give a further 15 ml of hydrobromic acid and 1 ml of immiscible material. The solution was washed with benzene and concentrated in vacuo to 1 g of residue. This residue was diluted with 1 ml of 48% hydrobromic acid and 100 ml of anhydrous methanol and the solution stored at room temperature for 2 days. The solution was stirred with excess sodium bicarbonate for 5 h at 25 °C, filtered, and concentrated in vacuo. The residue was dissolved in methylene chloride. The solution was filtered, washed with saturated sodium bicarbonate, dried, and concentrated in vacuo. The residue was crystallized from acetone/ether to give 0.3 g (25%) of crude methyl ester **15b**, mp 133–140 °C. This ester was warmed on the steam bath for 5 min with 1.2 ml of 1 N sodium hydroxide; the solution was filtered and kept for 0.5 h at room temperature. The acid **1b** was precipitated by addition of 1.7 ml of 1 N hydrochloric acid to give 0.2 g, mp 235–242 °C. This material was combined with that from three similar reactions and recrystallized from water with addition of chloroform to dissolve any monobenzyl derivative which might be present. Two more recrystallizations from water with charcoal and one from methanol gave white prisms: mp 256–257.5 °C; ir (KBr) 3420, 1710, 1675 cm^{-1}; $[\alpha]^{25}D$ + 105.7° (c 1.2, 0.1 N NaOH) [reported[2] mp 238–240 °C; $[\alpha]^{25}D$ +92° (0.1 N NaOH)].

Anal. Calcd for $C_1H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.50. Found: C, 49.29; H, 5.62; N, 11.38.

B. Via Phosphoric Acid Debenzylation. A mixture of 12 g of **11b**, 2.8 g of phenol, and 120 g of orthophosphoric acid[14] was heated in an oil bath at 150 °C for 3 h. The reaction mixture was cooled, diluted with ice to 1 l., and extracted with 2 × 500 ml of ether. The ether was washed with 200 ml of water. The aqueous layers were combined, neutralized with solid potassium carbonate, and made strongly basic with solid sodium hydroxide. The alkaline solution was heated on a steam bath for 1 h, cooled, and extracted with 800 ml of ethyl acetate. It was then acidified with concentrated sulfuric acid. The precipitate was collected, dissolved in 1 N sodium hydroxide, and reprecipitated with sulfuric acid to give 3.4 g of α-dehydrobiotin (**1b**), mp 255–258 °C.

***dl*-α-Dehydrobiotin Methyl Ester (15a).** Treatment of **11a** according to procedure A above and treatment of the residue of the neutralized esterification solution with saturated aqueous sodium bicarbonate solution which had been adjusted to pH 8 with 3 N sodium hydroxide gave crude **15a**, mp 160–170 °C. Recrystallization from methanol/ether gave colorless plates, mp 169.5–172 °C.

Anal. Calcd for $C_{11}H_{16}N_2O_3S$: C, 51.54; H, 6.29; N, 10.93. Found: C, 51.84; H, 6.63; N, 11.01.

***dl*-α-Dehydrobiotin (1a).** Alkaline hydrolysis of **15a** and recrystallization from ethanol gave **1a** as colorless needles, mp 238–240 °C.

Anal. Calcd for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56. Found: C, 49.36; H, 5.78; N, 11.38.

Registry No.—**1a**, 27368-91-8; **1b**, 10118-85-1; **2c**, 60209-09-8; **3c**, 60184-13-6; **4c**, 60184-14-7; **5c**, 60184-15-8; **6c**, 60184-16-9; **7a** (X = Br), 60209-10-1; **7b** (X = *d*-camphorsulfonate), 68-91-7; **8a**, 27368-86-1; **8b**, 27368-82-7; **9a**, 27368-87-2; **9b**, 27368-83-8; **10a**, 27512-85-2; **10b**, 29455-31-0; **11a**, 27368-88-3; **11b**, 27368-84-9; **11c**, 60209-11-2; **12b**, 60184-17-0; **13**, 27368-89-4; **14**, 60184-18-1; **15a**, 27368-90-7; **15b**, 60209-12-3; 2-nitropropane, 79-46-9; methanol, 67-56-1; aniline, 62-53-3; hydroxylamine hydrochloride, 5470-11-1.

Supplementary Material Available. Tables of positional and thermal parameters for the structure of **3** (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) A portion of this work was reported in preliminary form: *J. Am. Chem. Soc.*, **92**, 3520 (1970).
(2) L. J. Hanka, M. B. Bergy, and R. B. Kelly, *Science*, **154**, 1667 (1967).
(3) D. G. Martin, L. J. Hanka, and L. M. Reineke, *Tetrahedron Lett.*, 3791 (1971).
(4) L. J. Hanka, L. M. Reineke, and D. G. Martin, *J. Bacteriol.*, **100**, 42 (1969).
(5) M. W. Goldberg and L. H. Sternbach, U.S. Patents (a) 2 489 23; (b) 2 489 235; (c) 2 489 238 (1949). This work is outlined by L. H. Sternbach in "Comprehensive Biochemistry", Vol. 11, M. Florkin and E. H. Stotz, Ed.,

Elsevier, Amsterdam, 1963, Chapter 6.
(6) Since the absolute configuration has little effect on the chemistry, a convention will be used in which a behind the numeral refers to racemic compounds, b refers to compounds with absolute configuration of *d*-biotin, and c refers to compounds with absolute configuration opposite to that of *d*-biotin.
(7) H. B. Hass and M. L. Bender, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 932.
(8) W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).
(9) K. E. Pfitzner and S. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661 (1965).
(10) See C. A. Grob and P. W. Schiess, *Angew. Chem.*, **79**, 1, (1967).
(11) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968); H. H. Sisler, J. D. Buch, and O. E. Accountius, *J. Am. Chem. Soc.*, **70**, 3827 (1948); R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(12) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975). We used this reagent independently under the mistaken assumption that it was pyridine dichromate, whose use as an oxidizing agent was described by W. M. Coats and J. R. Corrigan, *Chem. Ind. (London)*, 1594 (1969). Consequently, we did not use the excellent conditions of Corey and Suggs.
(13) A. G. Mohan and R. T. Conley, *J. Org. Chem.*, **34**, 3259 (1969).
(14) We first heated **11** with polyphosphoric acid from an old bottle with a cracked cap and did obtain debenzylation. However, when a fresh bottle was used, no product was obtained. This result suggested that the material in the old bottle had become hydrated and that effective reagent had been orthophosphoric acid.

An Improved Synthesis of Octaethylporphyrin

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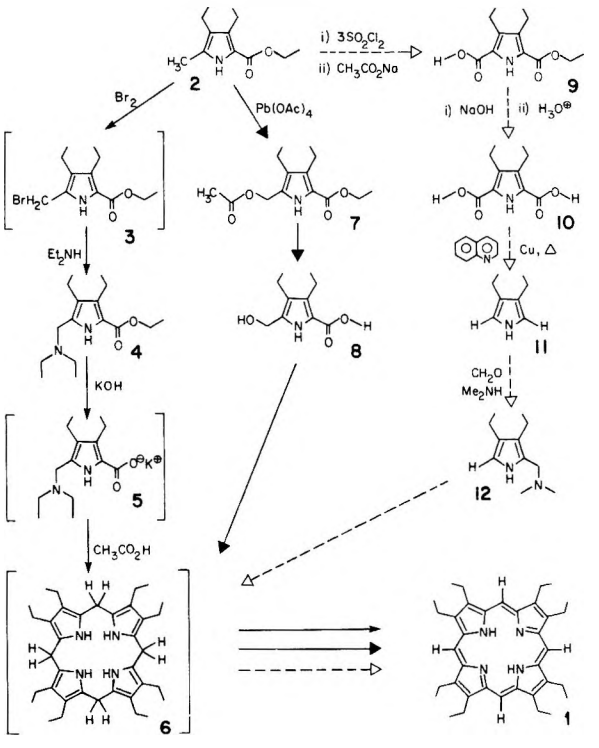
A convenient and economical synthesis of octaethylporphyrin, which proceeds via 2-*N*,*N*-diethylaminomethyl-5-ethoxycarbonyl-3,4-diethylpyrrole, is reported.

Octaethylporphyrin (OEP, **1**) is, by reason of its symmetry, high solubility, and stability, one of the more important and widely used models for the study of porphyrin chemistry. In the past, its synthesis has been tedious and erratic, particularly whenever more than a few grams were required. The usual syntheses, those of Inoffen et al.[1] and of Whitlock and Hanauer[2] (based on earlier work of Eisner, Lichtarowicz, and Linstead),[3] are summarized by Scheme I.

Scheme I



We report here an improved means of converting the common intermediate, 2-ethoxycarbonyl-3,4-diethyl-5-methylpyrrole (**2**), to OEP by procedures that are both facile and expeditious, which avoid the need to isolate overly sensitive intermediates such as **8**, **10**, **11**, or **12**, and which give improved overall yields. We also report procedures of improved convenience and reliability for the synthesis of the pyrrole **2** in especially high purity, using unpurified ethyl propionylacetate.

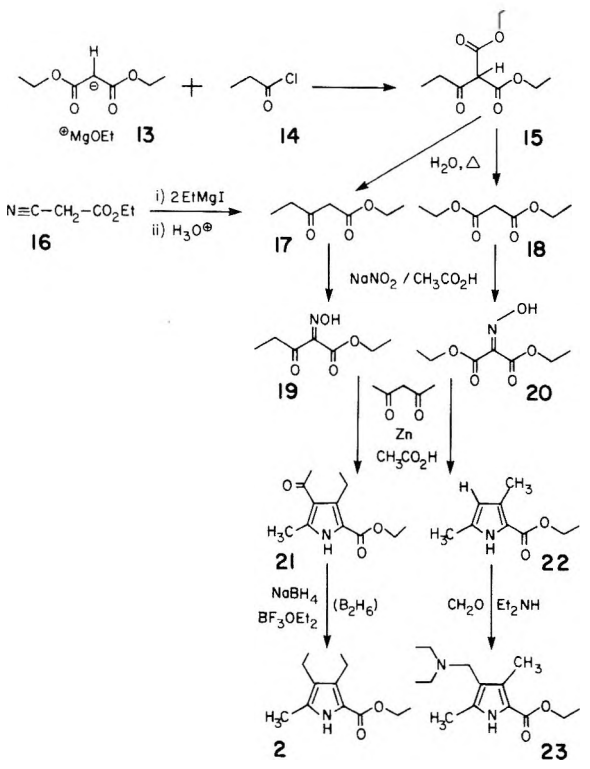
The Grignard synthesis of ethyl propionylacetate from ethyl cyanoacetate[4] requires a large excess of expensive ethyl iodide, some of which is wasted in formation of the cyanoacetate ester anion. The ethyl propionylacetate formed, however, is of high purity. An alternative synthesis has been devised by Kenner[5] and MacDonald:[6] Ethoxymagnesium diethyl malonate and propionyl chloride give diethyl propionylmalonate, which, after isolation in pure form by vacuum distillation, was hydrolyzed in boiling water. The hydrolysis gave ethyl propionylacetate, in moderately good yield, contaminated, however, by regenerated diethyl malonate, which was difficult to separate by distillation without an especillly efficient column. MacDonald,[6] unlike Kenner,[5] took note of this impurity and purified his ethyl propionylacetate via the bisulfite complex, not, however, without loss of yield.

We prefer to carry this impurity into the Knorr reaction with 2,4-pentanedione, and thereby maximize use of the ethyl propionylacetate. Nitrosation converts part of the diethyl malonate impurity to diethyl oximinomalonate which under the Knorr conditions with 2,4-pentanedione gives the otherwise useful 2-ethoxycarbonyl-3,5-dimethylpyrrole[7] (**22**).

Even when pure ethyl propionylacetate was used, pyrrole **22** was still generated via the Fischer–Fink[8] side reaction. As this impurity requires removal at a later stage in any case, purification of ethyl propionylacetate made from diethyl malonate was clearly superfluous for our purposes.

Although 2-ethoxycarbonyl-3,5-dimethylpyrrole (**22**) can be removed from the β-acetyl pyrrole (**21**) by several recrystallizations, considerable loss of product ensues, and so we have found it desirable to carry this impurity through the subsequent diborane reduction, which it survived intact. Treatment of the crude reduction product at reflux with ex-

cess diethylamine and formaldehyde effected quantitative conversion of the impurity (22) to the Mannich base[9] (23), which was then removed by acid extraction.



It should be noted in passing that the direct nitrosation of diethyl propionylmalonate (15) in the hope of obtaining ethyl oximinopropionylacetate (19), instead led exclusively to diethyl oximinomalonate (20).

Our synthesis of OEP, like Inhoffen's,[1] makes use of the α-methyl substituent of 2 to provide the porphyrin meso carbons, unlike Whitlock and Hanauer,[2] who amputated both pyrrolic α carbons only to replace one by a delicate Mannich reaction. Bromination of 2 generated the sensitive α-bromomethylpyrrole (3) which was not isolated, but instead immediately quenched with an excess of diethylamine. The pyrrylmethylamine (4) was then purified by extraction into ice-cold acid followed by prompt regeneration by basification with ammonia.

Conversions of α-methylpyrrole (2) to the amine 4 as high as 90% have been obtained. However, we have so far been unable to devise conditions which guarantee such high yields reproducibly, and hence this reaction should never be attempted on too large a scale. The pyrrylmethylamine (4) is an oil, indefinitely stable at room temperature, and a convenient and reliable precursor to OEP, into which it can be converted in 1 day, in 50+% yield. Saponification of the ester function with ethanolic potash gave the labile, aminomethylpyrrole carboxylate salt, which was treated in situ with excess acetic acid and warmed to reflux in a stream of air. The porphyrin crystallized as the reaction proceeded, occasionally contaminated by the crystalline intermediate octaethylporphyrinogen (6). Refluxing the crude product in toluene under air effected completion of the oxidation of this intermediate to OEP.

It has been claimed[10] that transition-metal halides could convert propionaldazine to 3,4-dimethylpyrrole at reflux temperatures. All attempts to repeat the synthesis, or to effect the analogous conversion of butyraldazine to 3,4-diethylpyrrole, proved fruitless. Instead, pyrazoles [3(5)-ethyl-4-methyl- and 3(5)-*n*-propyl-4-ethyl-] were obtained. These had undoubtedly arisen from the well-known[11] internal aldolization of the azine, followed by oxidation of the intermediary pyrazolines. No pyrroles were ever detected, either in the crude reaction mixture or after workup. The conversion of azines to pyrazolines is well documented,[11-13] and these have afforded the corresponding pyrazoles upon oxidation. Had the synthesis in fact succeeded, the resulting 3,4-diethylpyrrole would have greatly facilitated the large-scale production of OEP via the Whitlock–Hanauer route.[2]

Experimental Section

Diethyl Propionylmalonate.[5] Magnesium turnings (300 g, 12.34 mol) were placed in a 12-l. round-bottom flask equipped with a stirrer, addition funnel, gas inlet, and efficient condenser. A solution of diethyl malonate (1920 g, 12 mol) in absolute ethanol (960 ml) was prepared. Absolute ethanol (300 ml), followed by a portion of this solution (~300 ml), was added to the magnesium and with a slow stream of nitrogen passing through the apparatus, carbon tetrachloride (5 ml) was added to initiate the reaction. Stirring was begun as soon as the vigorously exothermic reaction set in. The remaining diethyl malonate solution was added cautiously so that the reaction proceeded vigorously, but not violently. If the malonate addition should be interrupted, even briefly, and then resumed the reaction may not immediately restart. Instead, after an initial induction period the reaction may suddenly boil up and foam. To ensure that a buildup of unreacted diethylmalonate does not occur the mixture should be heated on a steam bath to maintain reflux temperature. As the reaction proceeded solid appeared and the reaction mixture became too thick to stir.

When the addition was complete the mixture was allowed to cool and absolute ether (3200 ml, 5 lb) was added. The mixture was then refluxed until only traces of metal remained. Freshly distilled propionyl chloride (1110 g, 12 mol) was slowly added to the stirred mixture, which was then allowed to stand overnight at room temperature.

Sulfuric acid (588 g, 6 mol) was poured onto excess crushed ice and diluted to 3500 ml with additional water. The cold acid was added dropwise to the stirred ethereal solution. The mixture was separated and the organic layer thoroughly washed with water. The solvent was removed and the remaining oil distilled under vacuum. The fraction boiling at 123–140 °C (20 mm) was collected. Yields varied in this reaction from 1800 to 2200 g.

^{1}H NMR δ_{Me_4Si} (CCl_4) (K = keto and E = enol tautomers) 1.04 (E, t, J = 7 Hz, CH_3CH_2CO), 1.26 (E + K, t, J = 7 Hz, CH_3CH_2O), 1.29 (K, t, J = 7.3 Hz, CH_3CH_2CO), 2.44 (E, q, J = 7.3 Hz, CH_3CH_2CO), 2.60 (K, q, J = 7.3 Hz, CH_3CH_2CO), 4.16 (E, q, J = 7 Hz, CH_3CH_2O), 4.19 (K, q, J = 7.5 Hz, CH_3CH_2O), 4.23 (E, q, J = 7.5 Hz, CH_3CH_2O), 4.42 (K, s, methine H), 13.35 (E, bs, OH). In CCl_4 the sample contains almost equal amount of the enol and keto tautomers.

Ethyl Propionylacetate.[5] A stirred mixture of diethyl propionylmalonate and water (2 ml/g) was slowly distilled at atmospheric pressure for 4.5 h. Additional water was occasionally added to replace that which had distilled over. After cooling, the distillate was combined with the still-pot residue. The mixture was separated and the aqueous phase extracted twice with ether. The organic layers were combined and the solvent removed. The remaining oil was then distilled at 26 mm. The fraction boiling at 90–115 °C was collected. NMR spectroscopy showed this material to contain approximately 75% ethyl propionylacetate and 25% diethyl malonate. Diethyl propionylmalonate (1 kg) was hydrolyzed in two equal lots, and the product collected as fractions boiling at 23.5–24 mm: bp 81–90 °C, 33.23 g; bp 90.5–96.5 °C, 339.88 g (by NMR consisting of 83% ethyl propionylacetate and 17% diethyl malonate); bp 96.5–110 °C, 162.03 g (by NMR 75% ethyl propionylacetate and 25% diethyl malonate). Total yield of crude distillate 535.14 g.

^{1}H NMR δ_{Me_4Si} (CCl_4) 1.01 (K + E, t, J = 7 Hz, CH_3CH_2CO), 1.23 (K + E + malonate, t, J = 7.5 Hz, CH_3CH_2O), 2.21 (E, q, J = 7.5 Hz, CH_3CH_2CO), 2.54 (K, q, J = 7.5 Hz, CH_3CH_2CO), 3.28 (malonate, s, $OCOCH_2COO$), 3.38 (K, s, $OCOCH_2CO$), 4.12 (K, q J = 7.5 Hz, OCH_2CH_3), 4.15 (E or malonate, q, J = 7.5 Hz, OCH_2CH_3), 4.94 [E, s, OCOCH=C(OH)-], 12.08 (E, br, OH). Keto–enol ratio approximately 9:1; malonate content variable.

4-Acetyl-2-ethoxycarbonyl-3-ethyl-5-methylpyrrole[17] (21). The quantities given below are for a reaction on the molar scale. The reaction may be conveniently carried out on a 4–6-mol scale. The reaction vessel for the Knorr reaction requires 1.5–2 l./mol.

Into an ice-cooled Erlenmeyer flask equipped with a magnetic stirrer were placed crude ethyl propionylacetate (148 g) and glacial acetic acid (200 ml). A solution of sodium nitrite (69 g) in water (110 ml) was added dropwise to the stirred solution at such a rate as to

maintain the temperature below 45 °C. The solution was ready for the Knorr reaction as soon as the nitrite addition was complete.

Into a 200-ml three-necked round bottom flask, equipped with a mechanical stirrer and addition funnel, were placed 2,4-pentanedione (150 ml, 1.5 mol) and glacial acetic acid (200 ml). The ethyl oximinopropionyl acetate solution was added dropwise and zinc dust (260 g, 4 mol) was added in portions so as to maintain the temperature close to reflux. The zinc dust is best added as a thick aqueous slurry, which avoids much of the clumping the zinc otherwise suffers. Halfway through the addition additional 2,4-pentanedione (50 ml) and acetic acid (200 ml) were added. When the addition was complete the reaction was essentially over, and before the temperature fell below 100 °C the solution was decanted from the residual zinc which was washed with acetic acid. The combined supernatant and washings were diluted to four times their volume with water. The product oiled out and then crystallized.

When solid, the product was collected by filtration and thoroughly washed with water. The solid was dissolved in methylene dichloride, which caused the water present to separate. The two phases were filtered to remove any residual zinc. The organic phase was separated and washed with water. The methylene dichloride was removed on a steam bath and toward the end was replaced by hot hexane. Boiling was continued until all the methylene dichloride had been removed and the remaining hexane barely covered the crystallized solid. After cooling the product was collected by filtration, washed with hexane, and air dried to give the product (**21**) contaminated with 2-ethoxycarbonyl-3,5-dimethylpyrrole (**22**). The yield of **21** based upon the ethyl propionylacetate was 55%: ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 1.20 (t, 3 H, J = 7.5 Hz), 1.38 (t, 3 H, J = 7.5 Hz), 2.48 (s, 3 H), 2.58 (s, 3 H), 3.11 (q, 2 H, J = 7.5 Hz), 4.36 (q, 2 H, J = 7.5 Hz), 10.58 (bs, 1 H).

The impurity 2-ethoxycarbonyl-3,5-dimethylpyrrole (**22**) had the following ^{1}H NMR spectrum in $CDCl_3$: δ 1.36 (t, 3 H, J = 7.5 Hz), 2.26 (s, 3 H), 2.31 (s, 3 H), 4.32 (q, 2 H, J = 7.5 Hz), 5.78 (d, 1 H, J = 3 Hz), 9.98 (br, 1 H).

2-Ethoxycarbonyl-3,4-diethyl-5-methylpyrrole. The reduction procedure of Whitlock and Hanauer[2] was used with a few modifications. For large-scale reactions less solvent was required, but the reaction mixture became viscous, and care had to be exercised while quenching the excess diborane with glacial acetic acid. The use of glacial acetic acid is superior to quenching with water since the volume of hydrogen liberated is reduced by two-thirds, and the final mixture is far less viscous.

Into an ice-cooled 12-l. round-bottom flask equipped with a mechanical stirrer, additional funnel, gas inlet, and condenser was placed, under nitrogen, crude 4-acetyl-2-ethoxycarbonyl-3-ethyl-5-methylpyrrole (1000 g). Tetrahydrofuran (5500 ml) was added, and the mixture stirred until the solid dissolved. Sodium borohydride (312 g, 8 mol) was added to the chilled solution, followed by the dropwise addition of boron trifluoride etherate (1600 g) so as to maintain the temperature at 10 °C. When the addition was complete the mixture was stirred for a further 1 h. An excess of glacial acetic acid was then cautiously added until gas evolution ceased, after which excess water was added. The aqueous phase was separated, and the organic layer filtered to remove boric acid, which was washed with ether. The combined THF/ether solution was taken down to dryness and the residue was dissolved in 95% ethanol (2000 ml).

Diethylamine (250 ml) and 37% aqueous formaldehyde (250 ml) were added, followed by concentrated HCl (5 ml). The mixture was refluxed overnight, the solution taken down to dryness, and the residue dissolved in ether. The ethereal solution was extracted with water, and then with 5% hydrochloric acid until the washings remained acid. Virtually all of the brown color passed into the acidic solution, from which the Mannich base, 2-ethoxycarbonyl-4-*N*,*N*-diethylaminomethyl-3,5-dimethylpyrrole, may be recovered by the addition of aqueous ammonia. The ethereal solution was given a final wash with water and the volume reduced to 1500 ml. On cooling the product crystallized. To this mixture was then added 70% aqueous methanol (2000 ml). The resulting slurry was filtered, and the product washed with 70% aqueous methanol and air dried: yield 740 g [85% based on the β-acetylpyrrole (**21**) in the starting material]; mp 75.5–76.5 °C (lit.[18] 75 °C); ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 1.04 (t, 3 H, J = 7.5 Hz), 1.13 (t, 3 H, J = 7.5 Hz), 1.33 (t, 3 H, J = 7.5 Hz), 2.20 (s, 3 H), 2.35 (q, 2 H, J = 7.5 Hz), 2.67 (q, 2 H, J = 7.5 Hz), 4.28 (q, 2 H, J = 7.5 Hz), 10.29 (br, 1 H).

5-*N*,*N*-Diethylaminomethyl-2-ethoxycarbonyl-3,4-diethylpyrrole. To an uncooled stirred solution of *dry* 2-ethoxycarbonyl-3,4-diethyl-5-methylpyrrole (104.5 g, 0.5 mol) in anhydrous ether (1500 ml), under dry nitrogen, was added, dropwise and rapidly, a solution of bromine (83 g, 0.52 mol) in dichloromethane (270 ml). The reaction was exothermic and the mixture refluxed. After 20 min the addition was complete and the mixture was stirred for a further 20 min. Diethylamine (175 ml, 1.69 mol) in absolute ether (500 ml) was added to the rapidly stirred solution over a period of 5 min causing the mixture to reflux and change from deep red to pale yellow. The mixture was stirred for a further 30 min. Water (1000 ml) was added and the mixture separated. The organic phase was washed with water, and then excess crushed ice added. The water was separated, and 37% hydrochloric acid (100 ml) was diluted to 1000 ml with ice and water and used to wash the organic phase. The aqueous layer was then quickly washed with ether and added to 30% ammonium hydroxide (100 ml) in water (100 ml). The product, which immediately oiled out, was extracted from the aqueous phase with petroleum ether (300 ml, bp 20–40 °C). The organic layer was washed with water, dried over sodium sulfate, and filtered, and the solvent removed under vacuum, yield 135 g (90%). Note, however, that yields of about 60% are obtained until the operator becomes familiar with the reaction! Prolonged contact of the product with aqueous solution of amine hydrochloride greatly reduces the yield by conversion to the dipyrromethane.

Anal. Calcd for $C_{16}H_{28}N_2O_2$: C, 68.52; H, 10.08; N, 10.00. Found: C, 68.47; H, 10.24; N, 10.32.

^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 1.00 (t, 6 H, J = 7 Hz), 1.05 (t, 3 H, J = 7 Hz), 1.12 (t, 3 H, J = 7 Hz), 1.32 (t, 3 H, J = 7 Hz), 2.38 (q, 2 H, J = 7 Hz), 2.48 (q, 4 H, J = 7 Hz), 2.70 (q, 2 H, J = 7 Hz), 3.48 (s, 2 H), 4.26 (q, 2 H, J = 7 Hz), 9.43 (bs, 1 H).

Octaethylporphyrin. 5-*N*,*N*-Diethylaminomethyl-2-ethoxycarbonyl-3,4-diethylpyrrole (28.0 g, 0.1 mol) in 95% ethanol (100 ml) was treated with a solution of potassium hydroxide (13.2 g, ~0.2 mol) in water (20 ml). The mixture was heated on a steam bath for 3 h and then diluted to 200 ml with water. The mixture was cooled in an ice bath and acetic acid (200 ml) was added. The mixture was then boiled with magnetic stirring. When the solution had become very dark, air was passed through it. After boiling for 1 h, by which time the solution was reduced to half its original volume, the solution was diluted with an equal volume of methanol; after cooling to room temperature, the product was collected by filtration, and washed with methanol to give 7.0 g (52%) of OEP.

Occasionally the product was a mixture of octaethylporphyrinogen and octaethylporphyrin. This mixture when heated under reflux in toluene (20 ml/g) was oxidized to the porphyrin and on cooling gives a high recovery of the pure product. The porphyrin itself can be recrystallized from toluene, with the aid of a Soxhlet extractor.

3(5)-Ethyl-4-methylpyrazole. Propionaldazine was prepared by dropwise addition of freshly redistilled propionaldehyde to ice-cooled hydrazine hydrate in stoichiometric amount, dried by extraction into toluene, and distilled at atmospheric pressure, bp 140–141.5 °C. The azine (50 g) and anhydrous nickel chloride (0.69 g, Alpha Inorganics, used without further purification) were refluxed under argon (heating mantle) for 24 h, and (after no pyrroles could be found) then refluxed in air for another 24 h. The crude reation mixture was then distilled at atmospheric pressure, mostly in the range of 202–232 °C. Main cut, bp 212–222 °C, 15.49 g, was slightly impure 3(5)-ethyl-4-methylpyrazole:[14] ^{1}H NMR[16] δ 1.21 (t, 3 H, J = 7.5 Hz), 1.98 (s, 3 H), 2.60 (q, J = 7.5 Hz, 2 H), 7.17 (5, 1 H), 13.13 (br, H). This spectrum agrees with the previously published spectrum, as does the infrared spectrum.[15]

3(5)-Propyl-4-ethylpyrazole. Butyraldazine, prepared similarly, bp 179–187 °C, led to 3(5)-propyl-4-ethylpyrazole, characterized by NMR: δ 0.94 (t, J = 7.5 Hz, 3 H), 1.18 (t, J = 7.5 Hz, 3 H), 1.66 (sextet, J = 7 Hz, 2 H), 2.42 (q, J = 7.5 Hz, 2 H), 2.59 (t, J = 7.5 Hz, 2 H), 7.26 (s, H), 12.22 (br, H).

This product was obtained by overnight reflux of the azine in *p*-xylene in the presence of such diverse catalysts as anhydrous cobalt iodide or ammonium chloride, and air.

Acknowledgments. We wish to thank the National Institutes of Health (AM 17989), the National Research Council of Canada, The National Science Foundation (GP-33515), and Strem Chemical Co. for generous financial support. One of us (J.B.P.) thanks the National Science Foundation for a predoctoral fellowship (1968–1972).

Registry No.—**2,** 16200-50-3; **4,** 60223-98-5; **14,** 79-03-8; **15** keto form, 21633-77-2; **15** enol form, 31575-85-6; **17** keto form, 4949-44-4; **17** enol form, 60223-99-6; **18,** 105-53-3; **19,** 35011-25-7; **21,** 37013-86-8; **22,** 2199-44-2; 2,4-pentanedione, 123-54-6; 3(5)-ethyl-4-methylpyrazole, 7231-33-6; propionaldazine, 15601-98-6; propionaldehyde, 123-38-6; 3(5)-propyl-4-ethylpyrazole, 60224-00-2; butyraldazine, 30020-59-8; butyraldehyde, 123-72-8; octaethylporphyrin, 2683-82-1.

References and Notes

(1) H. H. Inhoffen, J. H. Fuhrhop, H. Voigt, and H. Brockmann, Jr., *Justus Liebigs Ann. Chem.*, **695**, 133 (1966).
(2) H. W. Whitlock and R. Hanauer, *J. Org. Chem.*, **33**, 2169 (1968).
(3) U. Eisner, A. Lichtarowicz, and R. P. Linstead, *J. Chem. Soc.*, 733 (1957).
(4) G. W. Anderson, I. F. Halverstadt, W. H. Miller, and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, **67**, 2197 (1945).
(5) J. Ellis, A. H. Jackson, A. C. Jain, and G. W. Kenner, *J. Chem. Soc.*, 1935 (1964).
(6) J. L. Archibald, D. M. Walker, K. B. Shaw, A. Markovac, and S. F. MacDonald, *Can. J. Chem.*, **44**, 345 (1966).
(7) G. G. Kleinspehn, *J. Am. Chem. Soc.*, **77**, 1546 (1955).
(8) H. Fischer and E. Fink, *Hoppe-Seyler's Z. Physiol. Chem.*, **280**, 123 (1944).
(9) A. Treibs and R. Zinsmeister, *Chem. Ber.*, **90**, 87 (1957).
(10) C. H. Stapfer and R. W. D'Andrea, *J. Heterocycl. Chem.*, **7**, 651 (1970).
(11) A. N. Kost and I. I. Grandberg, *Zh. Obshch. Khim.*, **26**, 2319–2322 (1956); *Chem. Abstr.*, **51**, 5054*d* (1957).
(12) I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.*, **28**, 3071–3075 (1958); *Chem. Abstr.*, **53**, 10188*f* (1959).
(13) I. I. Grandberg, W.-P. Ting, A. N. Kost, and V. I. Kozlova, *Zh. Obshch. Khim.*, **31**, 544–548 (1961); *Chem. Abstr.*, **55**, 23496*h* (1961).
(14) C. Alberti and G. Zerbi, *Farmaco, Ed. Sci.*, **7**, 527–539 (196); *Chem. Abstr.*, **58**, 5660*e* (1963).
(15) G. Zerbi and C. Alberti, *Spectrochim. Acta*, **19**, 1261–1273 (1963); *Chem. Abstr.*, **59**, 5937*d* (1963).
(16) M. Cola and A. Perotti, *Gazz. Chim. Ital.*, **94**, 1268–1277 (1964).
(17) H. Fischer and R. Bäumler, *Justus Liebigs Ann. Chem.*, **468**, 70 (1929).
(18) H. Fischer and R. Bäumler, *Justus Liebigs Ann. Chem.*, **468**, 93 (1929).

Characterization of Spiro-Bislactonic Phenolic Metabolites of Proteaceae by ^{13}C Nuclear Magnetic Resonance

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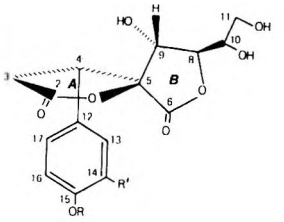
The ^{13}C NMR characteristics of a group of spiro-bislactonic phenolic metabolites of *Leucadendron* and *Leucospermum* species of the Proteaceae have been studied. The structure of a new member of this group, leudrin, has been established.

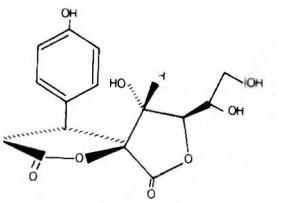
The great promise which ^{13}C NMR spectra have held for the characterization of natural products[2] has been richly fulfilled by the many studies now appearing. This tool has been used to establish the nature of alkyl chains unambiguously,[3] to demonstrate functional groups in puzzling circumstances,[4] to confirm or correct empirical formulas, and, in happy circumstances, to establish, together with ^1H NMR, the structures of surprisingly complex molecules without degradative or x-ray crystal studies.[5] However, in general, fruitful study of complex natural products has been possible only within the context of a series of closely related materials,[6] for knowledge of the factors which determine the chemical shifts of carbons in alicyclic and heterocyclic systems is still growing.[7] We describe here ^{13}C NMR studies of a group of plant phenolics not previously so studied which exemplify these problems, and which, with the support of the data of ^1H spectra taken at the field of a superconducting magnet, have led to the structure of a novel compound.

Previous studies on the phenolic constituents of the family Proteaceae have elucidated the structures and the stereochemistry[8] of leucodrin (**1**),[9] conocarpin (**4**),[10] conocarpic acid (**8**), and its methyl ester reflexin (**9**).[11] The structure and stereochemistry of leucodrin have been confirmed by an x-ray crystallographic study,[12] but those of the other compounds are based on interconversion and degradative studies, and on the spectral properties of the products. The configurations of C-4 in **1** and **4** have been established as *R* and *S*, respectively, by degradation of each to the corresponding *p*-methoxyphenylsuccinic acid, while that of C-10 is *S* in each case, as the chain of atoms C-8, C-10, and C-11 can be excised from both molecules in the form of L-glyceraldehyde. A key transformation in these studies is the conversion of conocarpin by bromine water to the spiroquinomethide ether (**5**), possible only for the configurations of C-4, C-5, and C-9 shown. The dienone–phenol rearrangement of **5** to a chroman such as **6** is attended by an upfield shift of H-8 in that compound,[10] which seems best accommodated by the configuration shown. Thus the configurations of all centers of the conocarpin series are firmly established with the exception of that at C-8. This paper particularly examines the ^{13}C NMR characteristics of this series of compounds.

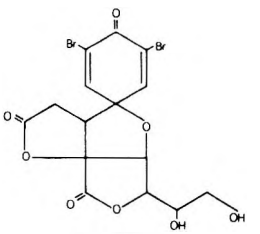
^{13}C Characteristics. The ^{13}C resonances observed in the ^1H noise-decoupled spectra are readily divided into several functional group categories[2] and methine and methylene carbons are readily recognized by off-resonance decoupled spectra. Within the aromatic group, C-15 is readily differen-



1, leucodrin, R = R′ = H
2, leucodrin methyl ether, R = CH_3, R′ = H
3, dimethylleudrin, R = CH_3, R′ = OCH_3



4, conocarpin



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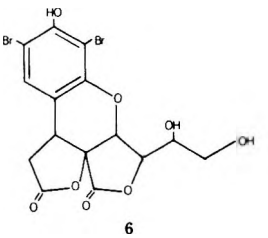

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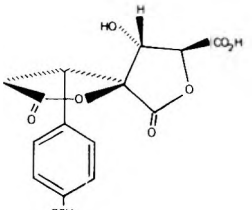
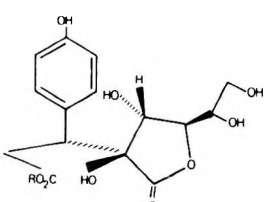


7, norleucodrinic acid methyl ether



8, conocarpic acid, R = H
9, reflexin, R = CH_3

Table I. Chemical Shifts in Dimethyl Sulfoxide Solution (ppm from Me_4Si)

Compd	Carbon atoms															
	2	3	4	5	6	8	9	10	11	12	13	14	15	16		17
Leucodrin (1)	175.0	33.6	41.3	90.3	172.3	80.2	69.5	68.4	61.6	123.7	130.3	115.8	157.4	115.8		130.3
Leucodrin methyl ether (2)	174.9	33.5	41.3	90.2	172.2	80.3	69.6	68.4	61.7	125.6	130.4	114.4	159.4	114.4		130.4
															OCH_3	55.4
Norleucodrinic acid methyl ether (7)	174.6	33.3	41.3	89.3	171.2	77.4	72.4	168.7		125.2	130.4	114.5	159.6	114.5		130.4
															OCH_3	55.4
Dimethyl-leudrin (3)	174.9	33.4	41.5	90.2	172.2	80.3	69.5	68.4	61.5	125.9	111.9	148.9[a]	148.7[a]	112.8		121.4
															OCH_3	55.6
Conocarpin (4)	174.7	32.7	47.6	88.0	172.7	79.4	73.4	67.8	61.8	122.8	130.5	115.3	157.2	115.3		130.5
Reflexin (9)	177.7	34.0	46.8	79.7	173.2	80.3	75.9	69.1	62.3	127.8	131.4	115.0	156.6	115.0		131.4
															OCH_3	51.5
Conocarpic acid (8)	169.5	31.2	44.8	74.9	173.9	82.7	79.0	69.4	61.4	126.6	129.6	115.6	157.1	115.6	129.6	

[a] These values can be interchanged.

tiated from C-12 and C-14/16 from C-13/17 by established hydroxyl substitution values.[2] The corresponding peaks of the phenol ethers, 2 and 7, show the anticipated downfield shifts for C-15 and upfield shifts for C-14 and C-16. Of the methylene carbons recognized in the off-resonance spectra, that at high field is readily assigned to C-3, and that in midfield to C-11; the latter is, of course, absent in the spectrum of 7. The two carbonyl peaks present in all of the spectra are differentiated by the observation that the one near 172 ppm (C-6) remains fairly constant throughout the series, while that at 175 ppm in the dilactones (C-2) is shifted in the compounds with ring A open. The remaining singlet at midfield is the signal of C-5. Four methine carbons are recognized by off-resonance spectra; that at high field clearly corresponds to C-4, but the distinction of C-8, C-9, and C-10 poses a more difficult problem. Because H-9 in the ^1H NMR spectra of this series of compounds is a doublet well separated from the signals of the other ^1H nuclei, it is possible to demonstrate by single frequency decoupling at the H-9 ^1H frequency that the signal near 70 ppm in the ^{13}C NMR spectra corresponds to C-9; the ^1H resonances of H-8 and H-10 are, however, closely coupled. Assignment of the resonances of carbon atoms C-8 and C-10 is based on the observation that the resonance at lower field shows more variation with stereochemical and structural changes; it is therefore C-8. The resonance at higher field is more nearly constant throughout the series, and is more suitable for C-10, distant from the site of these changes. The choice is consistent with the effects anticipated from the larger number of heavy atoms separated by two bonds from C-8.

The spectra of these compounds in dimethyl sulfoxide show the intriguing characteristic of broadened lines for the unsubstituted aromatic carbon atoms, C-13/17 and C-14/16, reflected to a lesser extent by other peaks. That this broadening results from an exchange of chemical shifts is supported by the spectra at higher temperatures in which the peaks are sharpened to widths characteristic of the resolution of the spectrometer. The phenomenon is dependent on the solvent, for the spectra of leucodrin (1) in methanol are sharp at room temperature, but broaden on chilling to −40 °C. Although the effect may result only from viscosity effects and more effective relaxation, earlier findings[11] indicated unusual steric crowding between the aromatic ring and the 9-hydroxyl of conocarpin. Inspection of Dreiding molecular models of this series of compounds clearly shows further strong steric interactions of the aromatic atoms C-13/17 and H-13/17 with the atoms at position 9 and, in the ring A opened compounds, at position 5. It was therefore interesting to compare the spectrum of conocarpin with that of leucodrin in a mobile solvent. Methanol is unsatisfactory for this purpose, however, as the more strained lactone system of conocarpin readily opens in methanol.[11] This difficulty was obviated by conversion of conocarpin to its tetrakistrimethylsilyl ether by reaction with trimethylsilylimidazole. A chloroform solution of this derivative shows aromatic peaks of normal half-width for all carbon atoms. The broadening of the peaks for C-13/17 and C-14/16 thus may be ascribed to the solvation of the oxygen-containing groups in the parent compounds.

Discussion

It is clear from the evolving knowledge of the relation of ^{13}C chemical shifts to the structures of cyclic systems that the effects of substituents and stereochemistry are subtle and complex.[7] Apparently, beyond the carbon directly substituted, the stereochemistry of a substituent is more important than its electronegativity.[7f] The effect of ring size may depend primarily on the dihedral angles of the ring atoms and the attached ^1H.[7g] In any event, the steric compression of attached ^1H can give rise to either shielding or deshielding.[7c,f]

In the series studied here, such effects produce chemical shift differences which cannot be completely explained. Gross structural changes do indeed produce anticipated major changes in the spectra. Thus, the opening of the lactone ring (4 vs. 8) results in an upfield shift of the carbinyl carbon, C-5, of 13.5 ppm and an upfield shift of 5.2 ppm in the carboxyl carbonyl. However, C-8, C-9, and C-12 are shifted substantially downfield, 3.3, 5.6, and 3.8 ppm. Of these, C-9 is two bonds away from the site of change, and might be expected to show a downfield shift. (The chemical shift of C-2 of butyl acetate is 31.2, while that of 1-butanol is 35.3.) However, the more distant C-8 and C-12 clearly show effects not paralleled in acyclic compounds. Comparison of leucodrin (1) to conocarpin (4) allows an evaluation of the effect of the steric compression noted in the chemistry of these compounds.[11] Two of the carbon atoms at the site of compression, C-4 and C-9, show downfield shifts (6.3 and 3.9 ppm) in conocarpin, while two show upfield shifts (C-5, 2.3, and C-12, 0.9 ppm). The remaining carbon atoms of the two diastereomers show essentially the same chemical shifts. It is perhaps even more surprising that the simple conversion of conocarpic acid (8) to its ester, reflexin (9), is accompanied by substantial alteration of the shifts in the unaffected lactone ring and aromatic system: C-5 and C-12 are shifted downfield 4.8 and 1.2 ppm, while C-8, C-9, and C-13/17 are shifted upfield, 2.4, 3.1, and 1.8 ppm.

If the changes produced by minor modifications of these structures are not readily intelligible, however, it is indeed clear that the chemical shifts very sensitively reflect the exact structural arrangement and shape of these molecules, and can be used as a fingerprint of the structural moieties involved.

An opportunity to utilize this empirical observation arose

Table II. ^{1}H Characteristics (in $CDCl_3$ Solution) of the Trimethylsilyl Ether Derivatives

	^{1}H chemical shifts												Trimethylsilyl ethers		
Compd	3a	3b	4	8	9	10	11a	11b	13	14	16	17	C-9	C-15	C-10,11
Leucodrin (1)	2.88	3.34	4.19	3.65	4.87	3.81	3.54	3.38	7.30	6.83	6.83	7.30	0.33	0.32	0.17, −0.04
Dimethylleudrin (3)	2.83	3.30	4.14	3.66	4.86	3.76	3.51	3.35	6.95		6.85	6.90	0.27	0.12	−0.03
Conocarpin (4)	2.83	3.33	3.88	4.02	4.69	3.88	3.51	3.68	7.25	6.90	6.90	7.25	0.26	0.13	−0.06, 0.11
Norleucodrinic acid methyl ether (7)	2.72	3.15	4.12	3.78	4.73				7.33	6.90	6.90	7.33	0.25		
Conocarpic acid (8)	2.85	3.31	3.78	3.78	5.05	3.56	3.36	3.46	7.11	6.76	6.76	7.11	0.22	0.20	−0.06, 0.09

	^{1}H coupling constants, Hz								
Compd	3a,3b	3a,4	3b,4	8,9	8,10	10,11a	10,11b	11a,11b	13,14
Leucodrin (1)	−17.1[a]	8.9[a]	13.4[a]	8.4[a]	1.7[a]	6.8	7.5	−10.0	8.7
Dimethylleudrin (3)	−17.5	8.7	13.2	8.2[a]	1.4[a]	6.8	8.0	−10.0	2.0 (13,17) 9.0 (16,17)
Conocarpin (4)	−17.1	5.8	8.3	3.5[a]	5.9[a]	6.5	4.5	−10.8	
Norleucodrinic acid methyl ether (7)	−17.1[a]	8.6[a]	13.0[a]	8.2[a]					
Conocarpic acid (8)	−17.5	2.0	5.9	8.5	2.0	8.2	6.3	−9.4	8.8 (J(4,9) = 1.5)

[a] Verified by INDOR.

in the study of a phenolic dilactone leudrin.[13] Preliminary characterization of this compound suggests that it shares many structural characteristics common to the dilactones of the leucodrin series and that its structure could be that of leucodrin carrying a further hydroxy substituent at position 14. In particular, the ^{1}H NMR spectrum at 220 MHz allows the determination of the chemical shifts and coupling constants of the alicyclic system, which correspond closely to those earlier observed for leucodrin. To allow a close comparison of such values, and an evaluation of their significance, the ^{1}H spectra of a group of compounds within the series were studied as their trimethylsilyl ether derivatives, and the results are collected in Table II. However, the close correlation of the ^{13}C chemical shifts of Table I, in the context of the strong dependence of these values demonstrated above, not only supports the proposed structure of dimethylleudrin but also indicates its stereochemistry.

Experimental Section

^{13}C spectra were determined on a Varian XL-100 NMR spectrometer equipped with a Digi-Lab Fourier transform accessory. Exciting pulses at approximately 300 Hz below the frequency of tetramethysilane were used, the free induction decay being sampled at 12 kHz, to fill an 8K data table, giving an effective resolution of 1.5 Hz. Typically, 70 000 FID's were collected overnight. Homonuclear INDOR experiments were conducted on the XL-100 at 100 MHz. High-field spectra were obtained on a Varian HR-220 spectrometer.[14]

Trimethylsilyl ethers were formed by mixing the phenols with approximately threefold (by weight) quantities of trimethylsilylimidazole at room temperature. Mass spectra were determined after a few hours on an LKB-2000 mass spectrometer. Solutions so prepared were stable for several days.

Leucodrin (1): m/e (rel intensity) 614 (1), 613 (3), 612 (5, $C_{27}H_{48}Si_4O_8$), 597 (1), 540 (1), 525 (1), 509 (2), 480 (4), 465 (1), 464 (2), 463 (7), 451 (1), 423 (5), 408 (1), 391 (2), 219 (16), 218 (8), 217 (35), 205 (9), 192 (20), 177 (11), 147 (15), 133 (4), 124 (3), 120 (5), 117 (10), 103 (12), 75 (11), 74 (10), 73 (100), 45 (8).

Norleucodrinic acid methyl ether (7): m/e (rel intensity) 466 ($C_{21}H_{38}O_8Si_2$, 1), 451 (1), 361 (1), 291 (1), 149 (2), 148 (3), 147 (25), 134 (4), 125 (11), 98 (15), 89 (3), 88 (6), 86 (39), 85 (4), 84 (57), 83 (6), 75 (3), 74 (3), 73 (37), 70 (4), 69 (7), 68 (100), 67 (10), 59 (5), 49 (13), 47 (19), 45 (9), 43 (11), 41 (70), 40 (37), 39 (12), 38 (9), 35 (8), 28 (25)

Conocarpin (4): m/e (rel intensity) 614 (1), 613 (3), 612 ($C_{27}H_{48}Si_4O_8$, 5), 597 (2), 509 (2), 480 (4), 463 (3), 451 (3), 423 (6), 292 (2), 293 (2), 219 (20), 217 (28), 205 (12), 193 (4), 192 (18), 177 (8), 147 (16), 133 (4), 129 (2), 120 (5), 117 (11), 103 (11), 75 (12), 74 (9), 73 (100), 68 (5), 59 (3), 45 (6), 41 (3), 28 (6).

Dimethylleudrin (3): m/e (rel intensity) 585 (2), 584 ($C_{26}H_{44}O_9Si_3$, 5), 217 (5), 191 (2), 164 (5), 149 (3), 148 (3), 147 (18), 141 (2), 140 (17), 125 (12), 103 (2), 98 (16), 88 (2), 86 (50), 84 (70), 75 (4), 74 (4), 73 (46), 70 (3), 69 (7), 68 (100), 67 (11), 59 (2), 51 (2), 49 (14), 47 (20), 45 (7), 43 (8), 42 (5), 41 (64), 40 (34), 39 (7), 38 (5), 35 (5), 28 (24).

Registry No.—1, 14225-07-1; 1 trimethylsilyl derivative, 59873-48-2; 2, 59873-49-3; 3, 59873-50-6; 3 trimethylsilyl derivative, 59873-51-7; 4, 30358-74-8; 4 trimethylsilyl derivative, 59905-86-1; 7, 13565-22-5; 7 trimethylsilyl derivative, 59873-52-8; 8, 39236-59-4; 8 trimethylsilyl derivative, 59873-53-9; 9, 40036-19-9.

References and Notes

(1) (a) National Heart and Lung Institute. (b) The University of the Witwatersrand.
(2) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972; (b) G. C. Levy and G. N. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972.
(3) R. D. Plattner, G. F. Spencer, D. Weisleder, and R. Kleiman, *Phytochemistry*, **13**, 2597 (1974).
(4) P. Yates, F. N. MacLachlan, I. D. Rae, M. Rosenberger, A. G. Szabo, C. R. Willis, M. P. Cava, M. Behforouz, M. V. Lakshmikantham, and W. Zeiger, *J. Am. Chem. Soc.* **95**, 7842 (1973).
(5) R. B. Bates and D. J. Eckert, *J. Am. Chem. Soc.*, **94**, 8258 (1972).
(6) Examples abound; inter alia, (a) E. W. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Schell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, *J. Am. Chem. Soc.*, **95**, 4990 (1973); (b) C. R. Smith, R. V. Madrigal, D. Weisleder, K. L. Mikolajszak, and R. J. Highet, *J. Org. Chem.*, **41**, 593 (1973); (c) S. Omura, A. Nakagawa, A. Neszmelyi, S. D. Gero, A. M. Sepulchre, F. Piriou, and G. Lukacs, *J. Am. Chem. Soc.*, **97**, 4001 (1975).
(7) E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.*, **97**, 322 (1975); (b) H. Ziffer, J. I. Seeman, R. J. Highet, and E. A. Sokoloski, *J. Org. Chem.*, **39**, 3698 (1974); (c) S. H. Grover, J. B. Stothers, J. R. Swenson, and C. T. Tan, *Can. J. Chem.*, **53**, 581 (1975); (e) S. H. Grover and J. B. Stothers, *ibid.*, **53**, 589 (1975); (f) H. Beierbeck and J. K. Saunders, *ibid.*, **53**, 1307 (1975); (g) S. H. Grover, D. H. Marr, J. B. Stothers, and C. T. Tan, *ibid.*, **53**, 1351 (1975).
(8) G. W. Perold, A. J. Hodgkinson, A. S. Howard, and P. E. J. Kruger, *J. Chem. Soc., Perkin Trans. 1*, 2457 (1972).
(9) G. W. Perold and K. G. R. Pachler, *J. Chem. Soc. C*, 1918 (1966).
(10) P. E. J. Kruger and G. W. Perold, *J. Chem. Soc. C*, 2127 (1970).
(11) G. W. Perold, A. J. Hodgkinson, and A. S. Howard, *J. Chem. Soc., Perkin Trans. 1*, 2450 (1972).
(12) R. D. Diamand and D. Rogers, *Proc. Chem. Soc., London*, 63 (1964).
(13) Leudrin has been found (G.W.P.) to occur in a number of *Leucadendron* species which also produce leucodrin, but not in *Leucospermum* species which produce the diastereomer, conocarpin. The chemical degradation of leudrin and a synthetic route for leucodrin to leudrin are being published elsewhere. Its 14,15-dimethyl ether, mp 222 °C, is the stable and highly crystalline derivative (3) discussed in this paper.
(14) We are indebted to Mr. R. B. Bradley of the National Institute of Arthritis, Metabolism and Digestive Diseases and Professor J. M. Edwards of the University of Connecticut for these spectra.

Survey of ^{13}C–H Splittings in Alkenes

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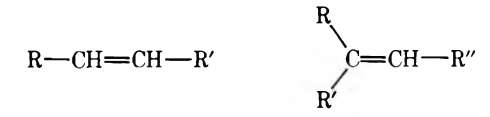
Line separations due to splitting of the natural abundance ^{13}C signal by neighboring hydrogens are reported for a variety of di- and trisubstituted alkenes. For the trisubstituted alkenes, these line separations should be very close to true coupling constants. Qualitatively, the splittings conform to the prediction that carbon should show decreasing three-bond coupling constants in the order $sp^1 > sp^2 > sp^3$ with regard to the hybridization of the coupling carbon nucleus. However, the ranges of the coupling constants are not well separated for cis nuclei and also overlap for trans nuclei. The splittings are sufficiently regular in incidence that they are of use in assigning *E* or *Z* character to trisubstituted alkenes.

A number of papers have emphasized the parallelism between H–H NMR coupling constants and ^{13}C–H coupling constants.[1-4] Since proton coupling constants in alkenes such as **1** have been used for years to distinguish between *E* and *Z* isomers, the question arises whether ^{13}C–H coupling constants might not be of equal use with more highly substituted alkenes such as **2**. DeHaan and Van de Ven and Roberts et al. have



1 **2**

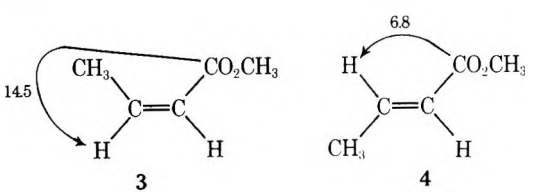
advanced a useful method of determining alkene configuration based on ^{13}C chemical shifts.[5] However, this method seems best applied in cases where both the *E* and the *Z* isomers are available for comparison purposes. If only a single isomer is available the assignment of configuration would be difficult if unusual steric or electronic effects were present.[6,7]

The use of additivity relationships, based on substituent effects on ^1H chemical shifts, seems to be an even more powerful method for determining alkene configuration.[6] However, deviations from additivity predictions for carbonyl and other alkene substituents have been noted.

It was hoped that ^{13}C–H coupling constants would show sufficient regularity so that these data also could be used to identify *E* or *Z* isomers. Studies of chemical shifts and of coupling constants would complement one another, and provide the researcher with a battery of techniques for configuration assignment.[8]

Marshall and Seiwell have reported that a very large $^3J_{CH}$ value (14.5 Hz) is found between carbonyl and trans hydrogen in **3**, and a smaller value (6.8 Hz) is found for cis nuclei in **4**, rather similar to the variation in H–H coupling constants with geometry in other molecules.[9,10] The coupling constant for trans ^{13}C–H nuclei was substantially higher than for certain α,β-unsaturated ketones briefly investigated in our laboratory.[11] A secondary objective of the present study was to observe the range in coupling constants as structure was varied.

In other studies, Karabatsos and Orzech suggested that bond angle variations imposed by steric constraints gave rise to sizable variations in ^{13}C–H coupling constants,[1] but electronegativity effects were not considered to be very important.[1c] Perlin's data, however, could be interpreted in terms of a sizable electronegativity effect.[12] Lemieux and co-workers



3 **4**

also emphasized the importance of stereoelectronic factors on variations in $^3J_{CH}$.[13,14]

In earlier studies, H–H coupling constants in alkenes were shown to vary over a twofold range for trans nuclei and over a fivefold range for cis nuclei, depending upon the type of alkene substitution.[15] The effects of electronegativity, as determined by Banwell and Sheppard and by Schaefer, are given in eq 1 and 2, where E_X is an electronegativity parameter for the substituent X.[16]

$$J_{cis} = 11.71\,(1 - 0.34E_X) \quad (1)$$

$$J_{trans} = 19.0\,(1 - 0.17E_X) \quad (2)$$

If ^{13}C–H coupling constants indeed parallel H–H coupling constants, similar electronegativity effects would be expected.[17]

In considering the various factors that may affect the magnitude of $^3J_{CH}$, the hybridization of carbon deserves special mention. This factor, of course, is not present in H–H coupling constants. Karabatsos pointed out that $^3J_{CH}$ should decrease in the order $sp^1 > sp^2 > sp^3$ if the Fermi contact mechanism of spin coupling were dominant.[16,18,19] A third objective of this study was to observe the effect of hybridization on $^3J_{CH}$, although these effects are hard to differentiate from electronegativity effects in certain cases.

Table I lists the ^{13}C NMR data for over 40 alkenes. The data quoted in Table I are line separation(s) (LS) measured directly from the spectra rather than true coupling constants ($^3J_{CH}$), which must be derived from the LS by computer simulation. The LS values should be of more use to the practicing chemist. In Table I, the data for trisubstituted alkenes are of foremost interest. In such alkenes, couplings between cyanide or carbonyl and hydrogen represent an AX spin system, and thus, LS and $^3J_{CH}$ are identical. For methyl substituted alkenes, an AM_3X spin system is present, where M are the methyl protons; LS should again be very close to $^3J_{CH}$.

The deviation of LS from $^3J_{CH}$ should be most serious for disubstituted alkenes. These alkenes were investigated in order to observe the variation of LS with structure in compounds whose configuration has been firmly established by other means. For disubstituted alkenes such as (*E*)-cinnamic acid (**28**), the carbonyl ^{13}C nucleus represents X of an ABX spin system, where the alkene hydrogens are A and B. Owing to the large difference in chemical shift of A and B, among other factors, the deviation of LS from $^3J_{CH}$ is small (−0.2 Hz). For propenylbenzene, the methyl ^{13}C represents X of an ABM_3X spin system. For the *Z* isomer **8**, computer simulation shows that LS is again very similar to $^3J_{CH}$, within the error in data acquisition, ±0.25 Hz. However, for the *E* isomer, LS does not correspond to $^3J_{CH}$ because of the small chemical shift difference between A and B, and large J_{AB} and $|J_{AX} - J_{BX}|$ terms.[15b] For simplicity, all splittings will be termed LS whether or not they also correspond to true coupling constants.

Table I. Line Separations Due to Coupling of the ^{13}C Nucleus with the ^{1}H Nucleus Indicated

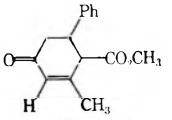
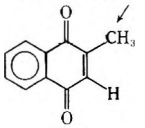
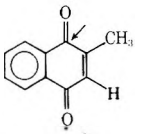
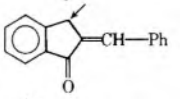
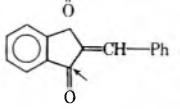
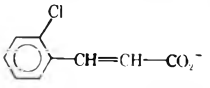
Registry no.	Compd	Isomer	Structure	Orientation of coupled nuclei	LS, Hz
674-76-0	5	*E*	i-$C_3H_7CH{=}CH{-}CH_3$	Cis	~6
690-08-4	6	*E*	t-$C_4H_9{-}CH{=}CH{-}CH_3$	Cis	6.9
4894-61-5	7	*E*	$Cl{-}CH_2{-}CH{=}CH{-}CH_3$	Cis	6.0
		E	$Cl{-}CH_2{-}CH{=}CH{-}CH_3$	Cis	~7
766-90-5	8	*Z*	$Ph{-}CH{=}CH{-}CH_3$	Trans	10.0
873-66-5	9	*E*	$Ph{-}CH{=}CH{-}CH_3$	Cis	6.6
104-54-1	10	*E*	$Ph{-}CH{=}CH{-}CH_2OH$	Cis	6.8
21087-29-6	11	*E*	$Ph{-}CH{=}CH{-}CH_2Cl$	Cis	8.0
833-81-8	12	*E*	$Ph{-}CH{=}C(CH_3)Ph$	Trans	8.3
98-83-9	13		$H_2C{=}C(CH_3)Ph$	Cis	6.6
				Trans	11.1
541-47-9	14		$HO_2C{-}CH{=}C(CH_3)_2$	Cis	7.1
				Trans	8.4
141-79-7	15		$CH_3{-}CO{-}CH{=}C(CH_3)_2$	Cis	7.0
				Trans	8.0
54435-79-9	16	*Z*	$Ph{-}CO{-}CH{=}C(CH_3)Ph$	Cis	6.7
22573-24-6	17	*E*	$PhCO{-}CH{=}C(CH_3)Ph$	Trans	7.8
23652-86-0	18	*Z*	$CH_3CO{-}CH{=}C(CH_3)NHCH_2Ph$	Cis	6.1
60135-00-4	19			Cis	6.2
58-27-5	20			Cis	5.7
				Trans	~10
17434-21-8	21	*E*		Trans	8.5
		E		Cis	~6
14182-01-5	22	*E*	$Ph{-}CH{=}C(CH_3){-}CO{-}Ph$	Trans	8.5
		E	$Ph{-}CH{=}C(CH_3){-}CO{-}Ph$	Cis	6.4
123-73-9	23	*E*	$CH_3{-}CH{=}CH{-}CHO$	Cis	6.0
		E	$CH_3{-}CH{=}CH{-}CHO$	Cis	8.8
104-55-2	24	*E*	$Ph{-}CH{=}CH{-}CHO$	Cis	8.8
33603-90-6	25	*Z*	$Ph{-}CH{=}C(Br){-}CHO$	Cis	7.8
584-45-2	26		$Ph{-}CH{=}C(CO_2^-)_2$	Cis	7.3
			$Ph{-}CH{=}C(CO_2^-)_2$	Trans	10.8
17041-60-0	27		$CH_3{-}CH{=}C(CO_2CH_3)_2$	Cis	7.0
			$CH_3{-}CH{=}C(CO_2CH_3)_2$	Trans	12.2
140-10-3	28	*E*	$Ph{-}CH{=}CH{-}CO_2^-$ (D_2O)	Cis	6.3
		E	$Ph{-}CH{=}CH{-}CO_2H$ ($CDCl_3$)	Cis	7.0
704-96-1	29	*Z*		Trans	12.0
705-54-4	30	*Z*	$Ph{-}CH{=}C(Cl)CO_2^-$	Cis	5.0
557-24-4	31	*Z*	$^-O_2C{-}CH{=}CH{-}CONH_2$	Trans	11.5
		Z	$^-O_2C{-}CH{=}CH{-}CONH_2$	Trans	12.2
498-23-7	32	*Z*	$^-O_2C{-}C(CH_3){=}CH{-}CO_2^-$	Trans	10.8
		Z	$^-O_2C{-}C(CH_3){=}CH{-}CO_2^-$	Cis	7.3
498-24-8	33	*E*	$^-O_2C{-}C(CH_3){=}CH{-}CO_2^-$	Cis	6.7
		E	$^-O_2C{-}C(CH_3){=}CH{-}CO_2^-$	Trans	8.3
584-99-6	34	*E*	$^-O_2C{-}C(Br){=}CH{-}CO_2^-$	Trans	9.5
644-80-4	35	*Z*	$^-O_2C{-}C(Br){=}CH{-}CO_2^-$	Cis	4.3
80-62-6	36		$CH_3O_2C{-}C(CH_3){=}CH_2$	Cis	~6.5
			$CH_3O_2C{-}C(CH_3){=}CH_2$	Trans	~12
60135-01-5	37	*E*	$CH_3O_2C{-}C(CN){=}CH{-}CH(CH_3)_2$	Cis	~6
		E	$CH_3O_2C{-}C(CN){=}CH{-}CH(CH_3)_2$	Trans	13.8
14533-86-9	38	*E*	$CH_3O_2C{-}C(CN){=}CH{-}Ph$	Cis	~7
		E	$CH_3O_2C{-}C(CN){=}CH{-}Ph$	Trans	14.0
1885-38-7	39	*E*	$NC{-}CH{=}CH{-}Ph$	Cis	8.7
2700-22-3	40		$(NC)_2{-}C{=}CH{-}Ph$	Cis	8.4
			$(NC)_2{-}C{=}CH{-}Ph$	Trans	14.4
53587-72-7	41	*E*	$NC{-}C(CH_3){=}CH{-}Ph$	Cis	8.8
		E	$NC{-}C(CH_3){=}CH{-}Ph$	Trans	8.2
13343-78-7	42	*Z*	$Ph{-}C{\equiv}C{-}CH{=}CH{-}Ph$	Trans	15.0
13343-79-8	43	*E*	$Ph{-}C{\equiv}C{-}CH{=}CH{-}Ph$	Cis	8.2

Table II

Hybridization of carbon	Ranges of LS values, Hz (common values)	
	Cis nuclei	Trans nuclei
sp^1 (CN, C≡C)	8.2–8.7 (~8)	14–15 (~14)
sp^2 (CO)	4.3–10	9.5–16.9
sp^3 (CH_2X)	5.7–8.0 (~6)	7.7–11.0 (~8)

In Table I, the compounds are loosely grouped in the order sp^3, sp^2, sp^1 with regard to the hybridization of the carbon coupled to the alkene proton. Table II shows a summary of these results. For cis nuclei, the range of LS between nuclei of different hybridization is not large. For trans nuclei, the LS roughly follow the predicted order sp^1, sp^2, sp^3, although considerable overlapping of ranges occurs.[19b]

Table III illustrates the effect of varying the type of ^{13}C nucleus coupled to H in an otherwise constant hydrocarbon skeleton. The acid chloride and aldehyde groups show the largest LS values for carbonyl groups. In Table I, the aldehydes **23, 24,** and **65** exhibit similarly large values. Carboxylic acid, ester, and amide groups are not well differentiated (compare also **26–33, 36–38,** and **57–59**). Ketones consistently have the smallest LS values (cf. Scheme I). The presence of a conjugating group such as phenyl substituted at carbonyl (e.g., **55**) has little effect compared to alkyl groups (e.g., **56;** also Scheme I). It is noteworthy that rigid (**21**) and nonrigid (**22**) ketone groups have similar LS values.[20] Except for the aldehyde group and oxime, the LS values are arranged such that ^{13}C nuclei that have large LS values lie upfield in chemical shift and vice versa.[21,22] The LS values parallel $^1J_{CH}$ values for H–CO–X, again except for X = H.[23]

As with H–H couplings, the effects of electronegative groups appears to be quite large. Comparison of bromomaleic acid (**34**) with citraconic acid (**32**) shows that the former has the lower LS (9.5 vs. 10.8 Hz). The difference between **35** and **33** is even greater (4.3 vs. 6.7 Hz), similar to the case in H–H couplings where the electronegative substituent is trans to one proton (cf. eq 2 vs. eq 1). This series involves substituents of similar size, and thus differential steric effects are not likely to be important. The bromo aldehyde **25** shows a lower LS than **24** or **53.** Chlorocinnamic acid (**30**) has a lower LS than phenylcinnamic acid (**49**), although steric effects are variable in these compounds.

Scheme I

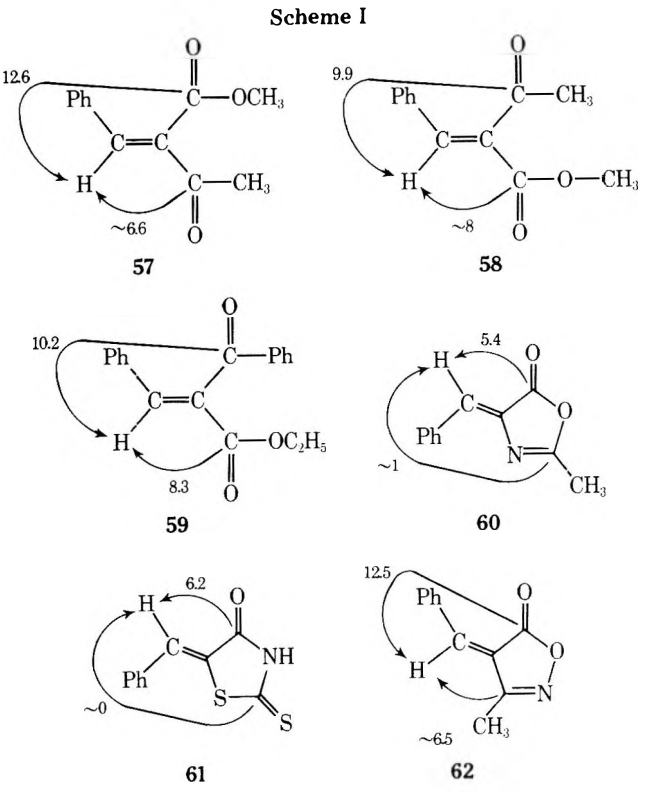
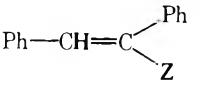
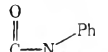


Table III. LS of Substituted Stilbenes



Z[a]	Compd[b]	LS (trans)	Registry no.	Compd[b]	LS (cis)	Registry no.
CN	**44** (*Z*)	14.2	6114-57-4	**45** (*E*)	9.0	16610-80-3
	**46** (*Z*)	16.9	60135-02-6	**47** (*E*)	9.9	51388-67-1
	**48** (*Z*)	12.5	91-47-4	**49** (*E*)	7.3	91-48-5
		*c*		**50** (*E*)	7.4	36854-27-0
	**51** (*Z*)	11.5	60135-03-7	**52** (*E*)	6.8	60135-04-8
				**53** (*E*)	10.0	1755-47-1
				**54** (*E*)	9.2	60135-05-9
				**55** (*E*)	6.0	7474-65-9
				**56** (*E*)	~6	38661-88-0

[a] Stilbene substituent. [b] The letter in parentheses refers to the configuration of the compound. [c] Data for a slightly impure compound are 12.5 Hz.

Electronegative substituents substituted on the carbon coupled to hydrogen appear to increase LS values. The series **9**, **10**, and **11** shows an increasing LS as the electronegativity of the substituent increases from H (LS 6.6 Hz), OH (6.8 Hz), to Cl (8.0 Hz). In **7**, the chloromethyl group has an apparent larger LS than methyl.[19b,24] Moving from 2-methyl-1,3-diphenyl-2-propen-1-one (**22**) to its bromomethyl analogue results in an increase in LS from 8.5 to 10 Hz. However, comparison of **39** and **43** indicates only a slightly larger LS for cyanide than alkyne.[25]

With regard to the effect of substitution on the C=C double bond, disubstituted alkenes appear to have larger LS than trisubstituted alkenes for trans CH_3–H couplings (the difference would be still larger if $^3J_{CH}$ values were calculated as $^3J_{CH}$ > LS). Thus **8** and **13** show LS of 10–11 Hz, whereas **12**, **14**, **15**, and **17** show LS of ca. 8 Hz. However, for CO–H couplings, disubstituted alkenes have larger LS in some cases but not in others.

The LS values discussed above show significant variation with structure, but these variations are by no means worse than variations in $^3J_{HH}$ previously used to assign configuration in compounds of general structure **1**.[15] Using the data of Table I, certain molecules were investigated whose state of isomerism could not be assigned in any other way.[26] These compounds are shown in Scheme I. Compounds **57** and **58** were obtained as an inseparable mixture upon condensation of methyl acetoacetate with benzaldehyde. The major component, **57**, showed a large LS for the ester carbonyl and a small LS for the ketone; **57** is thus the *Z* isomer. Compound **58** shows the reverse LS characteristics, and it is therefore the *E* isomer. Compound **59** (mp 89 °C) was obtained by condensation of ethyl benzoylacetate with benzaldehyde and it is clearly the *E* isomer.

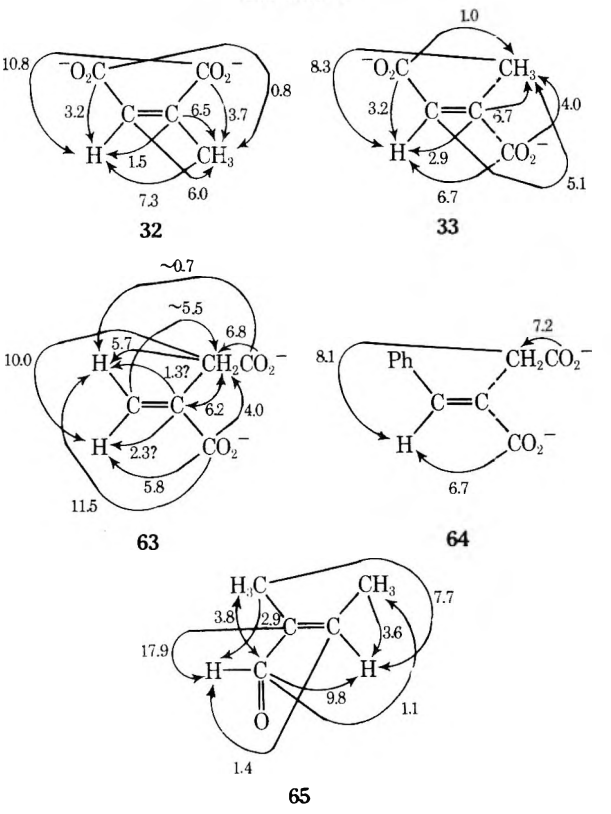
The configuration of the azlactone and rhodanine derivatives (**60** and **61**, Scheme I) was predictable on the basis that the maximum path for resonance between CO and Ph should be present.[27] In both cases, the CO and alkene proton are cis, as indicated by the low LS value, and CO and Ph are therefore trans as predicted. However, for the isoxazolinone **62**, the CO and Ph are cis as shown by the large LS, thus confirming previous assignments.[28] In this case a steric effect between the ring methyl and phenyl probably destabilizes the *E* isomer.[27c,29]

In citraconic, mesaconic, and itaconic acids (Scheme II), a relatively complete survey of all LS values was obtained. The two-bond coupling constants (i.e., line separations, strictly speaking) were not characterized by a particularly large variation in absolute magnitude, unlike a number of literature examples.[30a,b]

For phenylitaconic acid (**64**), the LS values confirm the earlier assignment of configuration based on chemical transformations.[31] In tigaldehyde (**65**) some uncertainty exists in the assignment of splittings, but generally the aldehyde group is seen to have large LS values not only to the alkene proton, but to other protons in the molecule. LS values for couplings to CHO are also sizable.

Certain experimental difficulties reduce the effectiveness of this technique for configurational assignment. The data acquisition is fairly time consuming, often requiring an overnight run. A sizable concentration of sample must be used (in our hands, a 10% w/v solution was near the minimum, in $CDCl_3$ or about 5% in D_2O). Alkyl groups other than methyl groups were difficult to study even using block acquisition due to extensively split signals. The disc data systems now coming into use may eliminate this difficulty, however. From the data in Table I, it is seen that the LS values for methyl groups cis or trans to an alkene proton are not sufficiently differentiated in some cases to warrant a firm assignment of configuration.

Scheme II



Experimental Section

Compounds **5**, **6**, **7**, **10**, **11**, **13**, **14**, **23**, **24**, **28**, **31**, **32**, **33**, **36**, **39**, **63**, and **65** were commercial products, mostly from Aldrich Chemical Co.; these were used without additional purification. Their ^{13}C NMR spectra indicated a reasonable level of purity. Compound **20** was an undergraduate laboratory preparation, that was recrystallized several times, mp 104.5–106.0 °C (lit.[32] 105–106 °C). Compound **21** was obtained from Dr. Henry Baumgarten. The remaining chemicals were synthesized by the method given in the literature reference given with the physical properties, except as noted.

(*E*)- and (*Z*)-Propenylbenzenes (8 and 9) were available from a previous study.[33a] These were prepared by a Witting reaction using the method of Shemyakin.[33b]

(*E*)-1,2-Diphenyl-1-propene (12), mp 81–82 °C (lit.[34] 80–82 °C).

Mesityl oxide (15), bp 126–130 °C (lit.[35] 126–131 °C).

Dypnone (16 and 17), bp 155 °C (1 mm) [lit.[36] 155 °C (1 mm)]; the product obtained was a mixture of about 85% the *E* isomer and about 15% *Z*. Despite the low concentration of the *Z* isomer, accurate NMR data could be obtained in this particular case.

Methyl 3-(*N*-benzylamino)-2-butenoate (18) was prepared in situ by adding molar equivalent quantities of benzylamine and methyl acetoacetate,[37a] followed by rapid NMR determination. Although ^1H NMR gave evidence for both isomers, the longer time period necessary for ^{13}C NMR gave the mixture time to isomerize, and ^{13}C NMR data for only the *Z* isomer could be obtained.[37b]

4-Carbomethoxy-3-methyl-5-phenyl-2-cyclohexenone (19), mp 85 °C, was available from an earlier study.[38] The NMR for a related compound, 3,5-dimethyl-2-cyclohexenone, was very similar to that given for **19**.

(*E*)-2-Methyl-1,3-diphenyl-2-propenone (22), bp 167 °C (0.6 mm) [lit.[39] 190 °C (28 mm)].

(*Z*)-2-Bromo-3-phenyl-2-propenal (25), mp 68–69 °C (lit.[40] 70.5 °C).

Benzylidenepropanedioic acid (26) was prepared by condensation of malonic acid with benzaldehyde, mp 196.5 °C dec (lit.[41a] 195–196 °C). Compound **27** was similarly prepared, bp 110–112 °C (15 mm) [lit.[41b] 110–112 °C (15 mm)].

(*Z*)-*o*-Chlorocinnamic acid (29) was prepared by irradiating the *E* isomer in a quartz flask with a 100-W Hanovia lamp for 1 week, and fractionally recrystallizing the resulting mixture of isomers. The higher melting isomer was sacrificially eliminated, plus any *Z* isomer carried along in the precipitation. The resulting product had mp 133–135.5 °C (lit.[42] 136 °C).

(*Z*)-2-Chloro-3-phenyl-2-propenoic acid (30), mp 136–137 °C (lit.[43] 138–139 °C).

(*E*)-Bromobutenedioic acid (34), mp 146–147 °C (preheated oil bath, rapid heating) (lit.[44] 140–141 °C).

(*Z*)-Bromobutenedioic acid (35), mp 180–181 °C (lit.[45] 180–183 °C).

(*E*)-Methyl 2-Cyano-4-methyl-3-pentenoate, (37). A center cut of a large distillation was taken, bp 110 °C (20 mm). The compound was prepared as in ref 46: NMR (5% $CDCl_3$ δ 1.15 [d, 6, $CH(CH_3)_2$], ~3 [m, 1, $CH(CH_3)_2$], 3.88 (s, 3, CH_3O_2C), and 7.47 (d, 1, J = 10.2 Hz, CH=C); mass spectrum (70 eV) m/e (rel intensity) 153.06 (M^+, 21.9), 138 (82.8), 125 (20.8), 121 (100), 110 (67.9), 106 (78.9), 94 (86.4), 67 (34), and 43 (25).

(*E*)-Methyl 2-cyano-3-phenyl-2-propenoate (38), mp 88–89 °C (lit.[46] 89 °C).

Benzylidenepropanedinitrile (40), mp 83–84 °C (lit.[47] 87 °C).

(*E*)-2-Methyl-3-phenyl-2-propenenitrile (41), bp 108–110 °C (4 mm) [lit.[48] 120 °C (14 mm)].

(*E*) and (*Z*)-1,4-Diphenyl-1-buten-3-ynes (42 and 43) were prepared by the general procedure of Brandsma,[49a] whereby phenylacetylide was added to styrene oxide, and the resulting alcohol was converted to the tosylate, and thence to the alkene using potassium *tert*-butoxide; from the resulting mixture of products, the *E* isomer could be obtained by crystallization, mp 94–96 °C (lit.[49b] 97 °C). The remaining oil appeared to be roughly an equimolar mixture of *E* and *Z* isomers by NMR. In our hands, either isomerization or decomposition occurred on attempted distillation. The ^{13}C resonances of the two isomers were well separated and did not interfere with one another.

Z isomer: ^1H NMR (60 MHz, $CDCl_3$) δ 5.88 (d, 1, J = 12.0 Hz, PHC≡C–CH), 6.63 (d, 1, J = 12.0 Hz, PhC**H**), and 7.2 (m, 10, Ph).

E isomer: ^1H NMR (60 MHz, $CDCl_3$) δ 6.35 (d, 1, J = 16.5 Hz, PhC≡C–C**H**), 7.01 (d, 1, J = 16.5 Hz, PhC**H**), and 7.2 (m, 10, Ph).

(*Z*)-2,3-Diphenylpropenitrile (44), mp 86–87 °C (lit.[50] 88 °C).

(*E*)-2,3-Diphenylpropenitrile (45). This material was prepared by dehydrating the corresponding oxime. The literature[51] preparation was a solid, mp 49–51 °C, but we were unable to crystallize this compound. The compound was purified by column chromatography on silica gel (eluted with a 1:9 mixture of ether and Skellysolve B). Thin layer chromatography showed only a single spot in eight solvent systems: NMR (5% $CDCl_3$) δ 7.0–7.4 (m, 11, Ph, and C**H**=C); mass spectrum (70 eV) m/e (rel intensity) 205.0893 (M^+, 100), 204 (93.7), 203 (21.5), 202 (13.9), 191 (14.7), 190 (36.1), 178 (27.8), 177 (35.6), and 176 (27.53).

(*Z*)-2,3-Diphenyl-2-propenoic acid (48), mp 138–139 °C (lit.[32] 136–137 °C). The *Z* acid chloride **46** was prepared from this acid using PCl_5 or $SOCl_2$. Considerable difficulty was encountered upon attempts to purify and crystalline the acid chloride (isomerization and/or hydrolysis), and so in later runs, the crude acid chloride was run (NMR) immediately after synthesis: NMR (5%, $CDCl_3$) δ 6.87 (s, 1, CH=C) and 7.1–7.5 (m, 10, Ph).

(*E*)-2,3-Diphenyl-2-propenoic acid (49), mp 172–173 °C (lit.[32] 173–174 °C). The acid chloride **47** was prepared similarly to **46.** The ester **50** was prepared by Fischer esterification of **49,** mp 75–76 °C (lit.[32] 75–76 °C).

(*E*)-*N*-Methyl-*N*,2,3,-triphenylpropenamide (52). PCl_5 (3.0 g, 14.4 mmol) and **49** (3.0 g, 13.4 mmol) were added to 100 ml of CH_2Cl_2 and stirred overnight. The solvent and the $POCl_3$ side product were distilled off under reduced pressure. Pyridine (10 ml) and *N*-methylaniline (5 ml) were added and allowed to stand for several hours. The product was taken up with ether, and extracted with several portions of 1 M HCl until the aqueous layer was acidic. The ether was extracted with water and then with 5% $NaHCO_3$, dried ($MgSO_4$), and evaporated, yielding a yellow solid, which was recrystallized from 95% ethanol giving 2.0 g (44% yield) of **52:** mp 109–110 °C; ^1H NMR (5% $CDCl_3$) δ 3.32 (s, 3, NCH_3), 6.8–7.2 (m, 16, aryl and alkene protons); mass spectrum (70 eV) m/e (rel intensity) 313.1465 (M^+, 58.5), 207 (65.1), 180 (25.2), 179 (100), 178 (48) and 77 (13).

The *Z* amide **51** was prepared by adding a large excess of *N*-methylaniline to 1.1 g (4.4 mmol) of the *Z* acid chloride, followed by stirring for 1 h. Ether was added, and the mixture was extracted with 3 M HCl until the wash was acidic, followed by extractions with water and dilute $NaHCO_3$ and saturated NH_4Cl. The solution was dried ($MgSO_4$) and ether was evaporated. The resulting solid was recrystallized from ether–pentane, giving 0.6 g of product (48% yield): mp 132–133 °C; NMR (5%, $CDCl_3$) δ 3.33 (s, 3, NCH_3), 6.62 (5, 1, CH=C), and 7.3–7.4 (m, 15, Ph); mass spectrum (70 eV) m/e (rel intensity) 313.1453 (M^+, 45), 207 (59), 179 (100), 178 (45), and 77 (4).

(*E*)-2,3-Diphenyl-2-propenal (53), mp 92–94 °C (lit.[52] 94 °C). The 3-(4-tolyl) analogue of **53** gave very similar NMR results.

(*E*)-2,3-Diphenyl-4-propenal oxime (54), mp 164–166 °C (lit.[53] 165 °C).

(*E*)-1,2,3-Triphenyl-2-propen-1-one (55) was obtained in some runs as an oil, bp 144–146 °C (1.5 mm) [lit.[54] 136° (0.2 mm)]. In other runs, a solid was obtained, which was recrystallized to purity, mp 54–56 °C). The solid was used for the NMR run.

(*E*)- and (*Z*)-Methyl 2-aceto-3-phenyl-2-propenoates (57 and 58) were obtained as an inseparable mixture by condensing methyl acetoacetate with benzaldehyde, bp 110–115 °C (1.5 mm) [lit.[56] 158–162 °C (12 mm)].

(*E*)-Ethyl 2-benzoyl-3-phenyl-2-propenoate (59) was prepared similarly to **57** and **58,** except that the isomer indicated could be obtained in a crystalline state, mp 98.5–99.5 °C (lit.[57] 95.0–96.5 °C).

4-Benzylidene-2-methyl-2-oxazolin-5-one (60) was prepared by condensation of the parent azlactone with benzaldehyde, mp 149–150 °C (lit.[58] 146–147 °C).

Benzylidenerhodanine (61) was similarly prepared, mp 197–200 °C (lit.[59] 200 °C).

4-Benzylidene-3-methyl-2-isoxazolin-5-one (62), mp 140–141 °C (lit.[60] 142 °C).

Phenylitaconic acid (64) was prepared by the Stobbe condensation, mp 191–192 °C (lit.[61] 192 °C dec).

^{13}C NMR Spectra. Spectra were run on a Varian XL-100 instrument at normal probe temperature. The concentration of the samples was 0.3–1.0 g/3.0 ml of solvent. The higher concentration was used whenever possible to improve data acquisition statistics. Both coupled and decoupled spectra were run; the latter utilized 5K spectral width, and the former utilized a 1K spectral width or very infrequently a 2K spectral width. In runs using a 1K width, the error in LS indicated by the computer was 0.25 Hz. For runs in D_2O (mostly carboxylic acids in the form of their potassium salt), the level of base added (potassium carbonate) was just adequate to ensure solubility (pH usually 6–8). The gated mode of decoupler operation was used for coupled spectra.[62]

In a typical run (for **30**), 0.3 g of substrate was dissolved in 3 ml of $CDCl_3$ (plus 0.5 ml of Me_2SO-d_6 to improve solubility); a 1K spectral width was used with acquisition time of 4 s, pulse delay of 1.5 s, and a pulse width of 20 μs (ca. 30° tipping angle); 5K of transients were collected, and a 500-Hz filter was used.

In this particular study, the attempted use of $Cr(acac)_3$ to enhance relaxation rates and reduce the time for data acquisition was unsuccessful, probably owing to the interaction of $Cr(acac)_3$ with the protons of the molecule. However, in other studies, this reagent was successfully used to improve observations of ^{31}P–^{13}C coupling constants.

Acknowledgments. Partial funds for purchase of the Varian XL-100 instrument were provided by NSF Grant GP-10293, which is gratefully acknowledged.

Registry No.—Benzylamine, 100-46-9; methyl acetoacetate, 105-45-3; (*E*)-*o*-chlorocinnamic acid, 939-58-2; *N*-methylaniline, 103-67-3.

References and Notes

(1) (a) G. J. Karabatsos and C. E. Orzech, Jr., *J. Am. Chem. Soc.*, **87,** 560 (1965); (b) G. J. Karabatsos, C. E. Orzech, Jr., and N. Hsi, *ibid.*, **88,** 1817 (1966), and related papers; (c) see, however, G. J. Karabatsos and C. E. Orzech, Jr., *ibid.*, **86,** 3574 (1964).

(2) (a) F. J. Weigert, and J. D. Roberts, *J. Am. Chem. Soc.*, **91,** 4940 (1969); (b) F. J. Weigert, M. Winokur, and J. D. Roberts, *ibid.*, **90,** 1566 (1968).

(3) J. L. Marshall, D. Miller, S. Conn, R. Seiwell, and A. Ihrig, *Acc. Chem. Res.*, **7,** 333 (1974).

(4) For other studies see (a) G. Barbieri and F. Taddei, *J. Chem. Soc. B,* 1903 (1971); *J. Chem. Soc., Perkin Trans. 2,* 262 (1972); (b) D. M. McKinnon and T. Schaefer, *Can. J. Chem.*, **49,** 89 (1971); (c) K. R. Harris, *Spec. Period. Rep.*, **3,** 85 (1973), and references cited therein.

(5) (a) J. Dehaan and L. Van de Ven, *Org. Magn. Reson.*, **5,** 147 (1973); (b) J. D. Roberts, D. E. Dorman, and M. Jautelat, *J. Org. Chem.*, **36,** 2757 (1971).

(6) (a) U. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron,* **25,** 691 (1969); **25,** 2023 (1969), and related papers; (b) G. Decotes, Y. Bahurel, G. Pingeon, and R. Rostaing, *Bull. Soc. Chim. Fr.,* 282 (1970); (c) S. W. Tobey, *J. Org. Chem.*, **34,** 1281 (1969); (d) D. F. Ewing and K. Parry, *J. Chem. Soc. B,* 970 (1970).

(7) (a) W. Beckenbaugh, S. Wilson, and P. Leffler, *Tetrahedron Lett.*, 4281 (1972); (b) G. Ambruscato, P. D. Ellis, and T. T. Tidwell, *J. Chem. Soc., Chem. Commun.*, 988 (1972); (c) G. E. Maciel, P. D. Ellis, J. J. Natterstad, and G. B. Savitsky, *J. Magn. Reson.*, **1,** 589 (1969).

(8) Other methods used to identify configuration include the following. (1) Infrared spectroscopy: P. Duke and D. Boykin, Jr., *J. Org. Chem.*, **37,** 1436 (1972); J. Cason and M. Kalm, *ibid.*, **19,** 1947 (1954); Fr. Gasanov, *Opt. Spektrosk. (Akad. Nauk SSSR, Otd. Fiz.-Mat. Nauk),* **3,** 76 (1967); *Chem. Abstr.*, **68,** 7788a (1968); J. Clark, *Appl. Spectrosc.*, **22,** 204 (1968); F.

Geise, F. Mijlhoff, G. Renes, and F. Rummens, *J. Mol. Strukt.*, **17,** 37 (1973). (2) Long-range NMR coupling constants: R. R. Fraser, *Can. J. Chem.*, **38,** 549 (1960); R. R. Fraser and P. McGreer, *ibid.*, **39,** 505 (1961). (3) Ultraviolet spectroscopy (and NMR): K. Nilsson and S. Sternhell, *Acta Chem. Scand.*, **19,** 2441 (1966). (4) NMR chemical shifts: (a) V. Watts and J. H. Goldstein, *Chem. Alkenes*, **2,** 1 (1970); (b) A. Bahl and W. Kemp, *J. Chem. Soc. C*, 1583 (1971); (c) J. Elguero and C. Marzin, *Bull. Soc. Chim. Fr.*, 3401 (1973); (d) D. Kevill, E. Weiler, and N. H. Cromwell, *J. Org. Chem.*, **29,** 1276 (1964). (5) Shift reagents: M. Zinic, M. Stromar, and D. Kolbach, *Hem. Ind.*, **28,** 15 (1974); C. Beaute, Z. Walkowski, Z. Merda, and J. Lelandais, *Tetrahedron Lett.*, 2473 (1971). (6) Truly unique methods include clathrate inclusion: W. Schlenk, Jr., *Justus Liebigs Ann. Chem.*, **7,** 1179 (1973); M. Nicolaides and F. Laves, *J. Am. Chem. Soc.*, **76,** 2596 (1954). (7) A general discussion of NMR methods: F. A. L. Anet, *Determination Org. Struct. Phys. Methods*, **3,** 343 (1971).

(9) J. A. Marshall and R. Seiwell, *J. Magn. Reson.*, **15,** 150 (1974).

(10) K. Crecely, R. Crecely, and J. H. Goldstein, *J. Mol. Spectrosc.*, **37,** 251 (1971), reported greater ^{13}C coupling constants for trans nuclei than for cis nuclei in molecules such as acrolein.

(11) Our determination for (*E*)-crotonic acid, however, agrees well with that of Marshall and Seiwell[9] for **4.**

(12) A. S. Perlin and J. Schwarcz, *Can. J. Chem.*, **50,** 3667 (1972).

(13) R. U. Lemieux, T. Nagabhushan, and B. Paul, *Can. J. Chem.*, **50,** 773 (1972), and later papers.

(14) In studies of proton coupling constants in alkenes, several other factors have been shown to affect the magnitude of the coupling constant. Thus, Rummens and DeHaan, *Org. Magn. Reson.*, **2,** 351 (1970), discussed certain J_{HH} variations in terms of rehybridization of the sp^2 carbon atoms. Schiebe, Seiffert, Hohlneicher, Jutz, and Springer, *Tetrahedron Lett.*, 5053 (1966), showed that increasing sp^2–sp^2 single bond length in butadienes gave smaller values of ^3J. Yalymova and Samitov, *Zh. Org. Khim.*, **6,** 1945 (1970), also considered electronegativity effects. M. Cooper and S. L. Manatt, *Org. Magn. Reson.*, **2,** 511 (1970), considered the effect of bond angle variations on $^3J_{HH}$.

(15) (a) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, N.Y., 1969, p 358.

(16) (a) C. Banwell and N. Sheppard, *Discuss. Faraday Soc.*, **34,** 115 (1962); (b) T. Schaefer, *Can. J. Chem.*, **40,** 1 (1962).

(17) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, pp 348–362, presents a general discussion of the topic.

(18) G. J. Karabatsos, J. Graham, and F. Vane, *J. Phys. Chem.*, **65,** 1657 (1962); (b) see also F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.*, **89,** 2967 (1967); (c) G. Binsch, J. Lambert, B. Roberts, and J. D. Roberts, *ibid.*, **86,** 5564 (1964); (d) G. Miyazima, T. Utsumi, and K. Takahashi, *J. Phys. Chem.*, **73,** 1370 (1969).

(19) (a) The combination of π and σ pathways for spin coupling in alkenes, in comparison to only the σ pathway in Karabatsos' cases,[18] represents an unknown factor. J. Murrell and R. Ditchfield, *Mol. Phys.*, **15,** 533 (1968), suggested that π contributions to $^3J_{HH}$ are small. See also G. Gray, P. Ellis, D. Traficante, and G. Maciel, *J. Magn. Reson.*, **1,** 41 (1969). (b) W. von Philipsborn and R. Hollenstein, *Helv. Chim. Acta*, **55,** 2030 (1972); **56,** 847 (1973); report LS values of 9–10 Hz for trans C=**C**–C=**CH** couplings.

(20) The s-cis conformer is preferred in simple (nonrigid) chalcones: B. Arbuzov, Y. Yuldasheva, I. Anonimova, R. Shagidullin, A. Chernova, and D. Fazliev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1258 (1969); *Chem. Abstr.*, **71,** 80535 (1970); however in α-substituted chalcones, a mixture of s-cis and s-trans forms seems more likely.

(21) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p 110.

(22) R. L. Lichter and J. D. Roberts, *J. Am. Chem. Soc.*, **93,** 5218 (1971), and references cited therein, have emphasized the possible importance of changes in excitation energy on coupling constants. Parallel changes occurred in *J* and chemical shift in the system studied. See also ref 17, p 104, for a general discussion.

(23) Reference 17, p 353.

(24) A. M. Ihrig and J. L. Marshall, *J. Am. Chem. Soc.*, **94,** 1756 (1972).

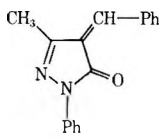
(25) For previous configuration studies on alkenyl cyanides, see R. Heilmann and J. Bonnier, *C. R. Acad. Sci.*, **248,** 2442 (1959).

(26) The difference in ketone carbonyl chemical shift was −7.5 ppm ($\delta_{57} - \delta_{58}$), whereas the difference in ester carbonyl chemical shift was +3.3 ppm. Thus, the carbonyl cis to phenyl was the most "deshielded". A steric shift such as discussed by DeHaan and Van de Ven[5] for alkyl groups cannot explain the chemical shift data. Matter et al. noted a fairly large difference in ^1H chemical shift for protons cis to *ester* compared to protons cis to a *ketone* function, but in other cases irregularities involving carbonyl groups were noted.[6] Thus, the ^1H chemical shift method for isomer identification should be applied with caution to **57** and **58.**

(27) (a) G. Stewart and H. Eyring, *J. Chem. Educ.*, **35,** 550 (1958), state that electrons do not like to go "around corners"; (b) R. C. Bingham, *J. Am. Chem. Soc.*, **98,** 535 (1976); (c) H. Zimmerman and L. Ahramjian, *ibid.*, **81,** 2086 (1959).

(28) H. Price, K. Williamson, and K. Brocklehurst, *Chem. Commun.*, 884 (1968).

(29) Determination of configuration in the pyrazolone derivative



was hampered by insolubility (TFA was added to improve solubility). The LS between CO and alkene H is ca. 8.5 Hz, whereas for **C**=N–**H,** the LS is ca. 6 Hz, which suggests the *Z* configuration. G. Desimoni, A. Gamba, P. Righetti, and G. Tacconi, *Gazz. Chim. Ital.*, **102,** 491 (1972) also assigned configuration as *Z*.

(30) (a) F. J. Weigert and J. D. Roberts, *J. Phys. Chem.*, **73,** 449 (1969); (b) K. L. Servis, J. Casanova, Jr., and M. Geisel, *Org. Magn. Reson.*, **1,** 209 (1969); (c) O. Yamamoto, W. Watanabe, and K. Kikuchi, *Mol. Phys.*, **17,** 249 (1969).

(31) H. Stobbe and O. Horn, *Chem. Ber.*, **41,** 3983 (1908).

(32) L. F. Fieser and K. L. Williamson, "Organic Experiments", D. C. Heath, Boston, Mass., 1975, pp 335, 278. See also C. Koelsch and P. Johnson, *J. Am. Chem. Soc.*, **65,** 565 (1943).

(33) (a) G. M. Underwood, A. Chan, T. Green, and C. A. Kingsbury, *J. Org. Chem.*, **38,** 2735 (1973); (b) L. Bergelson and M. Shemyakin, *Tetrahedron*, **19,** 149 (1963).

(34) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74,** 5828 (1952).

(35) A. I. Vogel, "Practical Organic Chemistry", 3d ed, Longmans, Green and Co., New York, N.Y., 1956, p 353.

(36) "Organic Syntheses", Collect. Vol III, E. Horning, Ed., Wiley, New York, N.Y., 1955, p 367.

(37) (a) M. Conrad and L. Limpach, *Chem. Ber.*, **21,** 525 (1888); (b) A. Sanchez, T. Aldave, and U. Scheidegger, *J. Chem. Soc. C*, 2570 (1968).

(38) C. Kingsbury, R. Egan, and T. Perun, *J. Org. Chem.*, **35,** 2913 (1970).

(39) E. P. Kohler, *Am. Chem. J.*, **31,** 642 (1904).

(40) T. Zincke and D. von Hagen, *Chem. Ber.*, **26,** 651 (1884). Beilstein (Drittes Erganzungswerke) lists the configuration as *E*, but recent *Chemical Abstracts* show apparently the same isomer as *Z*. See also A. Robert, J. Pommeret, and A. Foucaud, *Tetrahedron*, **28,** 2085 (1972).

(41) (a) W. Rodionow, *J. Am. Chem. Soc.*, **51,** 847 (1929); (b) F. Goss, J. Thorpe, and C. K. Ingold, *J. Chem. Soc.*, **123,** 3342 (1923).

(42) R. Stoermer, *Chem. Ber.*, **44,** 637 (1911).

(43) R. Stoermer and P. Heymann, *Chem. Ber.*, **46,** 1249 (1913).

(44) R. Fittig and C. Petri, *Justus Liebigs Ann. Chem.*, **195,** 56 (1879).

(45) A. Michael, *J. Prakt. Chem.*, **52,** 289 (1895).

(46) J. Sudborough and L. Lloyd, *J. Chem. Soc.*, **73,** 81 (1898).

(47) R. Heuck, *Chem. Ber.*, **28,** 2251 (1895).

(48) P. Pfeiffer, J. Engelhardt, and W. Alfuss, *Justus Liebigs Ann. Chem.*, **467,** 158 (1928).

(49) (a) L. Brandsma, "Preparative Acetylenic Chemistry", Elsevier, Amsterdam, 1971, p 60; (b) F. Straus, *Justus Liebigs Ann. Chem.*, **342** 190 (1905).

(50) C. Kingsbury, *J. Org. Chem.*, **33,** 1128 (1967).

(51) P. Pfeiffer, I. Engelhardt, and W. Alfuss, *Justus Liebigs Ann. Chem.*, **467,** 158 (1928).

(52) G. Payne and P. Williams, *J. Org. Chem.*, **26,** 651 (1961).

(53) H. Meerwein and H. Dott, *J. Prakt. Chem.*, **97,** 225 (1918).

(54) Reference 36, p 156.

(55) H. Zimmermann, L. Singer, and B. Thyagarajan, *J. Am. Chem. Soc.*, **81,** 108 (1959).

(56) J. Erickson, *J. Am. Chem. Soc.*, **67,** 1382 (1945).

(57) J. Postma and J. Arens, *Recl. Trav. Chim. Pays-Bas*, **75,** 1385 (1956).

(58) E. Erlenmeyer, Jr., *Justus Liebigs Ann. Chem.*, **337,** 265 (1904).

(59) M. Nencki, *Chem. Ber.*, **17,** 2277 (1884).

(60) E. Gilbert, *J. Am. Chem. Soc.*, **59,** 1074 (1937).

(61) H. Stobbe, *Chem. Ber.*, **41,** 4350 (1908).

(62) O. A. Gansow and W. Schittenhelm, *J. Am. Chem. Soc.*, **93,** 4294 (1971).

Bromination of Ethylenic Compounds. 38.[1a] Isoreactivity of Trisubstituted Geometrical Isomers

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The bromination rate constants of 30 trisubstituted alkenes (A_3) with various small or bulky alkyl substituents, measured in methanol, are high—between 48 and 1.26×10^5 M^{-1} s^{-1}. Comparisons with the reactivities of mono- and disubstituted alkenes show that in the A_3 series, the steric decelerating effect of an alkyl group becomes more important than its polar effect. This steric effect is observed in A_3 for small groups whereas in less substituted olefins it arises only when substituents are bulky. We conclude that the overall congestion of the molecule rather than the individual bulk of each substituent is the principal rate-determining factor in bromination of alkenes. Isoreactivity of *Z*-*E* isomeric pairs is also observed and is attributed to the preservation of ground state interactions in the bromonium-ion-like transition states. The increasing importance of steric effects with increase in the number of substituents is understood in terms of predominant bromine–substituent interactions in the rate-determining step.

The systematic study of the bromination of ethylenic compounds carried out in this laboratory has enabled us to account for the influence of several parameters on this reaction—structure, solvent, salts,[1] and reactant concentration[3]—and to deepen our knowledge of the mechanism by the discovery of a π complex as the first unstable intermediate whose ionization leads to the σ complex, the intermediate formed in the rate-determining step.[4]

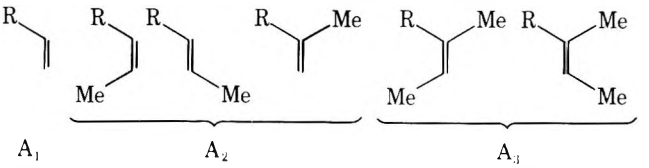
However, it is not easy to set up general and informative structure–reactivity relationships for alkene bromination, for essentially two reasons.[1a,b] Firstly, owing to the fact that the starting substrate is an olefin, there are two carbon atoms concerned by the ionization processes, whereas the empirical substituent parameters are generally defined by reactions involving one carbon atom. Secondly, bromination is influenced by both polar and steric substituent effects. Thus, the reactivity of only a limited number of compounds can be expressed in terms of classical free-energy relationships. Moreover, such relationships can account neither for the reactivity differences of cis and trans alkenes nor for the cumulative but not strictly additive effects of substituents, even when there are only two substituents to the carbon–carbon double bond.

We have therefore studied the reactivity of trisubstituted alkenes in order to determine whether the conclusions based on less substituted alkenes could be transposed to alkenes which are more crowded in the vicinity of the double bond.

Kinetic Results. To extend the data previously obtained[1b] for nine trisubstituted alkenes (A_3), we measured the bromination rate constants of 30 other A_3 in the same conditions—MeOH, 0.2 M NaBr, 25 °C—by the previously described couloamperometric method.[5] The results are given in Table I.

In methanol, in the presence of bromide ions, two brominating agents, Br_2 and Br_3^-, are in equilibrium, $Br_2 + Br^- \rightleftharpoons Br_3^-$, so that the measured rate constants k_{exp} are composite.[6] Elementary rate constants, k_{Br_2} and $k_{Br_3^-}$, were obtained by varying the bromide ion concentration for trimethyl-[7] and dimethyl-*tert*-butylethylenes.[6b] The rate constant[6c] ratios, $Q = 39.4$ and 18, respectively, for these compounds are higher than the limit, $Q = 16$, established for methanol[6b] and below which k_{exp} does not parallel k_{Br_2}. Moreover, the previously determined equation,[6a] $\log k_{Br_2} = \log k_{exp} + 1.13$, by which k_{Br_2} can be estimated from k_{exp} remains valid here. Consequently, the variations of the overall rate constants in Table I can be used to measure the variations of the elementary rate constants k_{Br_2}.

Attenuation of the Polar Contribution of the Substituents and Enhancement of Their Steric Effects in A_3 Relative to A_2 and A_1 Alkenes. *The contribution of an alkyl group R* to the reactivity of the A_3 population can be compared to that of the same group R in the corresponding mono- and disubstituted alkenes: CH_2=CHR, MeCH=CHR, and MeCH=CMeR with R = Me, Et, *n*-Pr, *i*-Pr, *sec*-Bu, and *t*-Bu.



The reactivity ratios, $I = k_{exp}(R)/k_{exp}(Me)$, which represent the effect of R relative to the methyl, depend markedly on the number of substituents. These ratios shown in Figure 1 reveal an attenuation of the accelerating polar effect of a substituent and a considerable enhancement of its decelerating steric effect when the number of substituents increases from two to three. Thus, the replacement of a methyl by an ethyl group increases the reactivity by a factor of 1.58 for A_1 alkenes, 1.60 for *cis*-A_2, and by only 1.19 for *Z*-A_3. In the same way, the introduction of a *tert*-butyl in the place of a methyl decreases the reactivity by a factor of 2.3 for A_1, 2.0 for *cis*-A_2, and 18.4 for *Z*- or *E*-A_3.

Similar analysis of the reactivity of the *gem-trisubstituted alkenes*, $(R_1)_2C$=CHR, reveals a comparable variation of the contribution of an alkyl group. Data on A_1 and A_2 showed that the replacement of a methyl group by an ethyl enhances the reactivity by a factor of approximately 1.5. This factor can legitimately be attributed[1b] to the enhancement of polar effects on passing from methyl to ethyl. This increase in reactivity does not remain valid for the trisubstituted alkenes. For example, the replacement of the two *gem*-methyl groups in 2-methyl-2-pentene by two ethyls diminishes the reactivity. If we calculate the expected increase in reactivity by enhancement of polar effects, the decrease which can be attributed to enhancement of steric effects is a factor of 3.25.

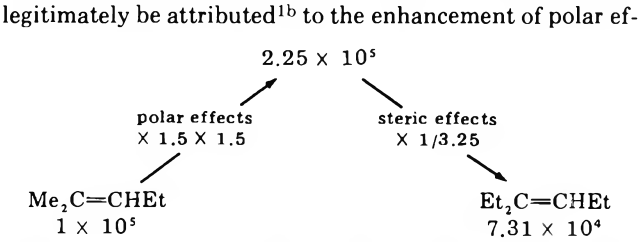


Table I. Bromination Rate Constants of Trisubstituted Alkenes

Registry no.	No.	Alkene	k_{exp}, M^{-1} s^{-1} [a]
627-97-4	1	Me_2C=CH-*n*-Bu	7.23×10^4
16993-86-5	2	Me_2C=CH-*n*-Pe	7.16×10^4
16789-51-8	3	Et_2C=CH-Et	7.31×10^4
19781-31-8	4	Et_2C=CH-*n*-Bu	5.76×10^4
4485-13-6	5	*n*-Pr_2C=CH-Et	2.83×10^4
59643-66-2	6	*t*-Bu_2C=CH-Et	4.80×10
10574-36-4	7	*Z*-Me-*n*-PrC=CH-Me	4.85×10^4
20710-38-7	8	*E*-Me-*n*-PrC=CH-Me	4.73×10^4
4914-89-0	9	*Z*-Et-MeC=CH-Et	1.26×10^5
3899-36-3	10	*E*-Et-MeC=CH-Et	1.10×10^5
4914-91-4	11	*Z*-*i*-Pr-MeC=CH-Me	2.16×10^4
4914-92-5	12	*E*-*i*-Pr-MeC=CH-Me	2.03×10^4
19550-81-3	13	*Z*-*sec*-Bu-MeC=CH-Me	1.05×10^4
19550-82-4	14	*E*-*sec*-Bu-MeC=CH-Me	1.05×10^4
39761-64-3	15	*Z*-*t*-Bu-MeC=CH-Me	3.63×10^3
39761-57-4	16	*E*-*t*-Bu-MeC=CH-Me	3.60×10^3
42067-48-1	17	*Z*-*i*-Pr-EtC=CH-Me	3.88×10^4
42067-49-2	18	*E*-*i*-Pr-EtC=CH-Me	9.50×10^3
14255-24-4	19	*Z*-*n*-Pr-MeC=CH-Et	5.98×10^4
13714-85-7	20	*E*-*n*-Pr-MeC=CH-Et	5.95×10^4
59643-67-3	21	*Z*-Me-EtC=CH-*sec*-Bu	8.06×10^3
59643-68-4	22	*E*-Me-EtC=CH-*sec*-Bu	8.06×10^3
59643-69-5	23	*Z*-Et_2CH-EtC=CH-Me	5.36×10^2
59643-70-8	24	*E*-Et_2CH-EtC=CH-Me	5.36×10^2
59643-71-9	25	*Z*-Et-MeC=CH-*t*-Bu	1.90×10^4
59643-72-0	26	*E*-Et-MeC=CH-*t*-Bu	1.90×10^4
59643-73-1	27	*Z*-*i*-Pr-MeC=CH-*n*-Pr	1.98×10^4
59643-74-2	28	*E*-*i*-Pr-MeC=CH-*n*-Pr	1.98×10^4
59643-75-3	29	*Z*-*i*-Pr-MeC=CH-Et	3.03×10^4
27656-50-4 [b]	30	*Z*- + *E*-*neo*-Pe-MeC=CH-*t*-Bu	1.80×10^2
27656-49-1 [c]			

[a] k_{exp} measured in methanol, 0.2 M NaBr at 25 °C. Standard deviation: ±4–7% from five to six runs. [b] *Z*. [c] *E*.

Analogous decreases are observed for the two other trisubstituted alkene pairs for which the reactivity of the *gem*-diethylalkene is always less than that of the *gem*-dimethyl. The observed steric decelerating factors in Et_2C=CHR relative to Me_2C=CHR, calculated after taking into account the polar factor of 1.5 × 1.5, are 2.73 and 2.82 for R = Me and *n*-Bu, respectively. Thus, with the introduction of two ethyl groups, and although the individual steric contribution of ethyl groups is generally considered to be small, the enhancement of the steric effects compensates the increase in the inductive effects and the *gem*-diethyl trisubstituted alkenes are less reactive than the corresponding *gem*-dimethyl alkenes. When this comparison is carried out for two bulky groups in geminate position, the relative decrease in reactivity is still higher (Table II). The decrease observed in A_2 series for bulky groups only appears in A_3 even when the geminate substituents are ethyl groups.

In conclusion, although the reactivity of the trisubstituted ethylenes is higher than that of mono- and disubstituted ethylenes, the reactivity enhancement caused by increasing the degree of substitution is substantially lower than that expected from polar substituent effects estimated in less substituted olefins.[8] The accumulation of alkyl substituents on the double bond results in an increasingly important contribution from total steric effects.

Isoreactivity of the *Z* and *E* Isomers. From Table I, it appears that the *Z* and *E* isomers have very similar reactivities with bromine, excluding only the isolated case[10] of the couple 17–18. The position of the R_3 substituent, relative to R_1 or R_2, the geminate substituents, is unimportant whatever the size of R_3. This can be understood in part by considering the differences in reactivity between disubstituted cis and trans alkenes. The higher reactivity of the cis isomer has been attributed[1b,11] to easier approach of the bromine in the cis isomer, whose substituents are in the same part of the olefinic plane, steric repulsions between bromine and substituents can be avoided if the bromine attacks off the perpendicular and approaches from the side opposite the substituents. For the trans isomer, bromine approach must be perpendicular without possible minimization of repulsions. In *Z* and *E* isomers, there are always two substituents in the trans configuration so that minimization of repulsions by off perpendicular attack is impossible. Thus, it is not surprising that these A_3 isomers exhibit similar reactivities. However, the reactivity differences between cis and trans isomers depend on the size of the substituents and similar differences might be expected for A_3 when one bulky group is cis or trans to another small one. In particular, for compounds where R_2 is bulky and R_1, R_3 are small, the *Z* compound could react slightly more rapidly

than the *E* isomer. This is not, however, confirmed by the isomeric couples 15–16, 23–24, or 27–28.

Furthermore, complementary thermodynamic and con-

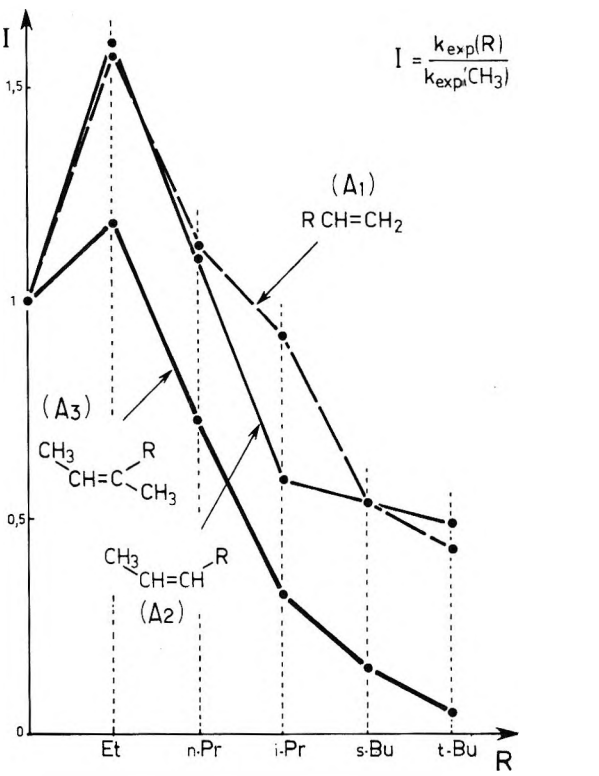


Figure 1. Increase of the decelerating effect of an alkyl group R from A_1 to A_3 alkenes.

Table II. Decelerating Steric Effects of Two *gem*-Alkyl Groups on the Reactivity of Di- and Trisubstituted Alkenes

R_1	k_{rel}, $(R_1)_2C$=CH_2	Registry no.	k_{rel}, $(R_1)_2C$=CHEt	Registry no.
Me	1.00	115-11-7	1.00	625-27-4
Et	1.65	760-21-4	0.73	16789-51-8
t-Bu	4.65×10^{-3}	5857-68-1	0.48×10^{-3}	

formational reasons can be advanced to explain the similar reactivities of the Z and E isomers.

No conformational studies of trisubstituted alkenes are at present available. However these A_3 alkenes have pairs of substituents in geminate, cis, and trans configurations at the same time. Recent calculations and experimental data[12] indicate that, in cis olefins, repulsions between nonbonded atoms are minimized by opening of the C–C=C angle[13] rather than by twisting the molecule or deformation of the double bond. For the simplest *gem*-disubstituted olefin, isobutene,[14] this angle is not significantly deformed but for more bulky substituents one would expect it to be somewhat closed. With three alkyl groups on the double bond, supplementary steric constraints must exist. Therefore, in addition to the C–C=C angle deformation, the occurrence of some twist about the sp^2–sp^2 bond, apparently absent in A_2 alkenes, is not impossible. Isoreactivity of Z–E isomers suggests a similar crowding of the two sides of the double bond. Until detailed structural data on these crowded olefins are available, it is difficult to state with certainty how the Z and E isomers become sterically equivalent toward bromine attack.

Thermodynamic data on A_3 alkenes[15,16] show that the enthalpies of formation of Z and E isomers differ very little, whereas between cis and trans alkenes[15–19] these differences can amount to several kcal M^{-1} (Table III). In bromination, it has been shown[19] that the reactivity differences of A_2 alkenes are very small compared to the large stability differences between their ground states, which means that these differences are retained in the transition states. It is, therefore, reasonable to expect an even smaller difference in reactivity for the Z–E isomers whose ground states are energetically very similar.

Interactions in the Bromonium-Ion-Like Transition States. The overall crowding of the olefin influences the reactivity more than the steric effects of individual alkyl groups, so that steric effects of substituents increase and become more important than their polar effects, as the number of substituents increases. Moreover, the fact that steric tensions in the ground state are preserved in the transition state might suggest that the latter are bromonium-ion-like. It was thought that steric repulsions between nonbonded atoms increase on passing from the alkene to the bromonium ion,[20] whereas in an α-bromocarbonium ion these interactions can be minimized since the hybridization of one carbon atom changes from sp^2 to sp^3.[21] In fact, this hypothesis is not valid: Yates et al.[19] have shown that transition state tensions are similar to those of ground states, regardless of the carbonium or bromonium nature of the intermediates.

To determine the nature of the intermediate of A_3 bromination we measured the stereoselectivity of the reaction in chloroform of the Z and E 3-methyl-2-pentene.[23] The dibromides obtained result from an anti addition with a stereospecificity of at least 99%, as observed for disubstituted alkenes. Moreover, detailed analysis of reactivity–structure correlations,[24] including the least crowded A_3 alkenes, shows that bromonium ion intermediates account for the substituent effects better than carbonium ions. Thus, there is at present no evidence for carbonium ion intermediates in A_3 bromination and it is reasonable to assume that the intermediate remains a bromonium ion, even for the most heavily substituted olefins.

The type of interaction which controls the rate-determining step is that between bromine and substituents[26] and not the modifications of the interactions between nonbonded substituents as was advanced for nitration.[25]

This is clearly evidenced by the retention of the ground state tensions in the transition states.[19] Thus, the interactions controlling the rate can only be those between bromine and substituents. The high sensitivity of the reactivity of alkenes to total steric crowding, which determines the ease of approach of the bromine toward the olefinic carbon atoms, is consistent with this view.

Table III. Differences of Enthalpies of Formation between Isomeric Alkenes

Registry no. Cis	Registry no. Trans	Alkene pair	$\Delta\Delta H_f°$[a]	Ref
624-64-6	590-18-1	*cis–trans*-MeCH=CH-Me	1.0	15
627-20-3	646-04-8	*cis–trans*-MeCH=CH-Et	0.88	15
7688-21-3	4050-45-7	*cis–trans*-MeCH=CH-*n*-Pr	0.37	15
691-38-3	674-76-0	*cis–trans*-MeCH=CH-*i*-Pr	0.96	15
762-63-0	690-08-4	*cis–trans*-MeCH=CH-*t*-Bu	4.90	18
15840-60-5	692-24-0	*cis–trans*-EtCH=CH-*i*-Pr	1.0	15
690-92-6	690-93-7	*cis–trans*-EtCH=CH-*t*-Bu	5.12	19
10557-44-5	692-70-6	*cis–trans*-*i*-PrCH=CH-*i*-Pr	1.96	19
692-47-7	692-48-8	*cis–trans*-*t*-BuCH=CH-*t*-Bu	10.5	16
922-62-3 (*Z*)	616-12-6 (*E*)	*Z–E*-Me-EtC=CH-Me	0.22	15
		Z–E-Me-*n*-PrC=CH-Me	0	15
		Z–E-Me-*i*-PrC=CH-Me	0	15
		Z–E-Et-MeC=CH-Et	0.62	16

[a] $\Delta\Delta H_f° = \Delta H_f°$ (cis) $- \Delta H_f°$ (trans) or $\Delta H_f°$ (Z) $- \Delta H_f°$ (E) in kcal M^{-1}.

Experimental Section

Starting Materials. The alkenes are commercial products (Chemical Samples) with the exception of 2,2-dimethyl-3-*tert*-butyl-3-hexene, which was synthesized in the laboratory.[27] All the compounds were purified by GLC. The structures and geometries (Z and E) of all alkenes were checked by NMR, ir, and mass spectroscopy. NaBr (Prolabo RP) was used after drying for 24 h at 120 °C. Absolute methanol was freed of impurities likely to be brominated by two distillations over bromine and its water content was less than 0.03% (w/w).

Kinetic measurements were performed by the method of coulamperometry developed in this laboratory.[4] The concentration–time data (second-order kinetics) were handled by a computer. In the particular case of a Z–E mixture where the alkenes 30 (mixture ca. 50/50) could not be separated by GLC, the measurements were performed on the purified GLC mixture. The logarithmic plot obtained from the kinetic data is a straight line up to 95% of the reaction. If there is any reactivity difference between the Z and E isomers, it is less than the experimental error (5%) and we have therefore attributed to the two isomers the same reactivity.

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References and Notes

(1) (a) Preceding paper: E. Bienvenue-Goëtz and J. E. Dubois, *J. Org. Chem.*, **40**, 221 (1975). (b) J. E. Dubois and G. Mouvier, *Bull. Soc. Chim. Fr.*, 1426 (1968). (c) M. F. Ruasse and J. E. Dubois, *J. Am. Chem. Soc.*, **97**, 1977 (1975). (d) X. Q. Huynh and J. E. Dubois, *J. Chim. Phys.*, 1482, 1488 (1972).
(2) Address to which correspondence should be sent.
(3) D. Grosjean, G. Mouvier, and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 1735 (1973).
(4) F. Garnier and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 3797 (1968).
(5) J. E. Dubois, P. Alcais, and G. Barbier, *J. Electroanal. Chem.*, **8**, 359 (1964).

(6) (a) E. Bienvenue-Goetz and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 2086 (1968). (b) J. E. Dubois and X. Q. Huynh, *ibid.*, 1436 (1968). (c) For trimethyl- and dimethyl-*tert*-butylethylenes, the rate constants k_{Br_2} experimentally measured are 1.29×10^6 and 1.67×10^5 M^{-1} s^{-1}, respectively.
(7) M. Marie de Ficquelmont, Doctoral Thesis, CNRS AO 8355, Paris, 1973.
(8) A referee has pointed out that the values for the k_{Br_2} process could be close to the diffusion controlled limit for bimolecular reactions. The bromination rate constants for enols limited by reagent diffusion has been evaluated as 10^9 M^{-1} s^{-1}.[9] The rate constants measured for the trialkyl- and tetraalkylethylenes are below this limit by at least two powers of ten. It seems unlikely that the structural effects of alkenes could lower the diffusion controlled limit to such an extent. Therefore we can reasonably assume that the measured substituent effects are the effects on the bromination reaction.
(9) J. E. Dubois and J. Toullec, *Tetrahedron*, **29**, 2859 (1973).
(10) The exception of this couple to the general isoreactivity of the *Z*–*E* isomers is not easily understood. The presence of an *i*-Pr group could explain this deviation: Figure 1 shows that this group has an abnormal effect on the relative reactivities in the A_2 series. However, this interpretation is not satisfactory since the couples 11–12 and 27–28 do not exhibit the same deviation.
(11) C. L. Dean, D. G. Garratt, T. T. Tidwell, and G. H. Schmidt, *J. Am. Chem. Soc.*, **96**, 4958 (1974).
(12) N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.*, **94**, 5734 (1972); E. W. Garbisch, Jr., S. M. Schildcrout, D. P. Patterson, and C. M. Sprecher, *ibid.*, **87**, 2932 (1965).
(13) O. Ermer and S. Lifson, *J. Am. Chem. Soc.*, **95**, 4121 (1973).
(14) V. W. Laurie, *J. Chem. Phys.*, **34**, 1516 (1961); L. H. Scharpen and V. W. Laurie, *ibid.*, **39**, 1732 (1963).
(15) D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds", Wiley, New York, N.Y., 1969, Chapter 14.
(16) (a) J. D. Rockenfeiler and F. D. Rossini, *J. Phys. Chem.*, **65**, 267 (1961); (b) H. F. Bartolo and F. D. Rossini, *ibid.*, **64**, 1685 (1960).
(17) K. W. Egger, *J. Am. Chem. Soc.*, **89**, 504 (1967).
(18) R. B. Turner, D. E. Nettelton, Jr., and M. Perelman, *J. Am. Chem. Soc.*, **80**, 1430 (1958); R. B. Turner, A. D. Jarrett, P. Goebel, and B. J. Mallon, *ibid.*, **95**, 790 (1973).
(19) (a) K. Yates and R. S. MacDonald, *J. Am. Chem. Soc.*, **93** 6297 (1971); (b) *J. Org. Chem.*, **38**, 2465 (1973).
(20) (a) P. B. D. De La Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems", American Elsevier, New York, N.Y., 1966; (b) T. G. Taylor, *Acc. Chem. Res.*, **2**, 152 (1969); (c) I. Roberts and G. E. Kimball, *J. Am. Chem. Soc.*, **59**, 947 (1937).
(21) Bach et al.[22] attribute a bond index ρC-Br of 0.34 to the symmetrical bromonium ion, close to that of the covalent bond in CH_3Br (ρ = 0.57). This index would be only 0.068 in an α-bromocarbonium ion whose stability is about 25 kcal M^{-1} less than that of the bromonium ion.
(22) R. D. Bach and H. F. Henneike, *J. Am. Chem. Soc.*, **92**, 5589 (1970).
(23) J. E. Dubois and J. Chretien, to be published.
(24) E. Bienvenue-Goetz and J. E. Dubois, to be published.
(25) E. G. Bordwell and J. B. Biranowsky, *J. Org. Chem.*, **32**, 629 (1967).
(26) J. E. Dubois and G. Mouvier, *Tetrahedron Lett.*, 1629 (1965).
(27) J. S. Lomas, D. S. Sagatys, and J. E. Dubois, *Tetrahedron Lett.*, 1349 (1971); 165 (1972).

Bromination of Ethylenic Compounds. 39. Predominance of Steric Effects on the Reactivity of Tetrasubstituted Alkenes[1]

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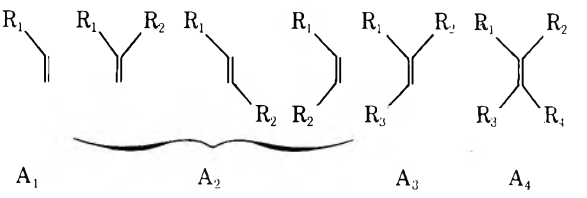
The bromination rate constants of 15 tetrasubstituted A_4 alkenes have been measured in methanol. Comparison of the effect of R in the trimethylalkylethylenes $Me_2C{=}CMeR$ with that of the same R in less substituted alkenes, $RCH{=}CH_2$, $RCH{=}CHMe$, or $Me_2C{=}CHR$, shows that the rate-diminishing steric effect is enhanced as the number of methyl on the double bond increases. Furthermore, the reactivity diminishes progressively when the methyls of tetramethylethylene are successively replaced by ethyl groups. Thus, substituent steric effects become more important than polar ones for the tetrasubstituted alkenes. Whereas for less substituted alkenes reactivity–structure correlations in terms of σ^* are obtained, a correlation with ΣE_s^c only accounts for the reactivity of tetrasubstituted alkenes. The importance of steric effects is further underlined by the absence of any relationship between the reactivity and the ionization potentials in the A_4 series and by the similarity of the substituent effects on bromination and on the addition reactions of bulky electrophiles whose rates are controlled by steric effects.

The systematic study of the bromination of ethylenic compounds has focused on several olefin populations: alkenes,[1,2] arylalkenes (styrenes and diphenylethylenes),[3] and cycloalkenes.[4] In order to complete previous studies on mono-, di-, and trisubstituted alkenes, we measured the reactivity of tetrasubstituted alkenes for which only the simplest structures, tetramethyl- and trimethylethylethylenes, have so far been studied.[2,9]

On the basis of early data of Dubois and Mouvier, the kinetic effect of different alkyl groups, their number, and their relative positions were evaluated.[2] Polar and steric effects, expressed in terms of linear free energy relationship, are additive for only a limited number of alkenes. The polar reaction constant has been determined from monoalkenes where it has been shown that steric effects are weak and negligible. The study of tetraalkylethylenes should allow us to determine the role of steric effects on their reactivity.

Results

We shall use the abbreviation A_4 for the tetrasubstituted alkenes and A_1, A_2, and A_3 for the mono-, di-, and trisubstituted ones, respectively.



For our study of the A_4 series, we have chosen 15 alkenes, either commercial or synthetized in the laboratory,[5] with substituents ranging from methyl to neopentyl. The rate constants, measured competitively[6] or directly[7] in our usual medium (methanol with 0.2 M NaBr at 25 °C), are given in Table I. In addition, we measured under the same conditions the rate constants of two *gem*-A_2 alkenes whose values were useful in the discussion which follows:

$$n\text{-Bu-MeC}{=}CH_2 \quad k_{exp} = 2.27 \times 10^3 \ M^{-1} \ s^{-1}$$

$$n\text{-Pe-MeC}{=}CH_2 \quad k_{exp} = 1.98 \times 10^3 \ M^{-1} \ s^{-1}$$

Table I shows distinct series in the A_4 population. The first group contains the trimethylalkylethylenes, $Me_2C{=}CMeR$, with variable R (compounds no. 1–8). The second one contains

Table I. Bromination Rate Constants of Tetrasubstituted Alkenes

Registry no.	No.	Alkene	k_{exp}[a]	Ref	Precision, %
563-79-1	1	$Me_2C{=}CMe_2$	9.16×10^5	*b*	4
10574-37-5	2	$Me_2C{=}CMe\text{-}Et$	6.5×10^5	*c*	9
7145-20-2	3	$Me_2C{=}CMe\text{-}n\text{-}Pr$	3.32×10^5	*d*	1
3074-64-4	4	$Me_2C{=}CMe\text{-}n\text{-}Bu$	3.55×10^5	*d*	1.5
19781-18-1	5	$Me_2C{=}CMe\text{-}n\text{-}Pe$	3.38×10^5	*d*	1
565-77-5	6	$Me_2C{=}CMe\text{-}i\text{-}Pr$	1.03×10^5	*d*	1
32540-07-1	7	$Me_2C{=}CMe\text{-}i\text{-}Bu$	3.76×10^4	*d*	1
33175-59-6	8	$Me_2C{=}CMe\text{-}neo\text{-}Pe$	1.78×10^3	*d*	1
10557-44-5	9	*cis*-Me-EtC=CEt-Me	3.83×10^5	*c*	8
19550-88-0	10	*trans*-Me-EtC=CEt-Me	3.66×10^5	*c*	8
19780-67-7	11	$Me_2C{=}CEt_2$	1.56×10^5	*c*	4
50787-13-8	12	$Et_2C{=}CMe\text{-}Et$	1.08×10^5	*c*	3
868-46-2	13	$Et_2C{=}CEt_2$	2.56×10^4	*c*	3
19780-61-1	14	$Me_2C{=}CEt\text{-}n\text{-}Bu$	8.83×10^4	*c*	6.5
50787-14-9	15	$Et_2C{=}CEt\text{-}n\text{-}Pr$	1.43×10^4	*c*	6

[a] Rate constants in M^{-1} s^{-1} measured at 25 °C in methanol, 0.2 M NaBr. [b] Reference 2. [c] Couloamperometrically measured, ref 7. [d] Measured by competitive method described in Experimental Section and in ref 6.

only those A_4 alkenes with methyl and ethyl substituents (no. 1, 2, and 9–13).

The elementary rate constant[8] for the free bromine addition, k_{Br_2}, and Q ratio, $k_{Br_2}/k_{Br_3^-}$, have been measured elsewhere[9] for trimethylethylethylene. The Q value, 21.6, is higher than the limit of 16 established previously[10] and the rate constant k_{Br_2}, calculated by the relationship[8] $\log k_{r_2} = \log k_{exp} + 1.13$, is in satisfactory agreement with the experimental k_{Br_2} value, 1.23×10^7 M^{-1} s^{-1}.[9]

Consequently, it can be assumed that the variations of k_{exp} parallel those of k_{Br_2} and that the structural effects measured on k_{exp} are representative of those on k_{Br_2}.

Specific Effect of a Variable Alkyl Group R on the Reactivity. In Figure 1 are shown the effects of a group R on the reactivity of the trimethylalkylethylenes (A_4) compared to the effect of the same R in ethylene- (series A_1) or methyl- (A_2) and dimethyl- (A_3) alkenes.[1,2]

The balance between the accelerating polar and retarding steric contributions is revealed when R is methyl and ethyl (left-hand side of Figure 1). The progressive introduction of methyl groups on ethylene increases the reactivity nonadditively, the last methyl giving the smallest acceleration. The replacement of methyl by ethyl enhances the reactivity by a factor of 1.5 for A_1 and A_2, of only 1.15 for A_3, and finally 0.60 for A_4. Thus, the replacement of methyl by ethyl in A_4 diminishes the reactivity: the steric contribution becomes more important than the polar one, even with a group as small as ethyl.

When R is a bulky group, the steric contribution is the most important factor (right-hand side of Figure 1). The greater the number of methyl substitutents, the greater the reactivity decreases. Thus, the neopentyl diminishes the reactivity by a factor of 5.3 for A_1, 32.7 for A_2, and 514 for A_4.

Therefore whereas steric effects exceed the polar ones in A_1, A_2, and A_3 only when R is bulky, they are preponderant in the A_4 series even when the methyl group is replaced by the small ethyl group: consequently, tetramethylethylene is the most reactive acyclic alkene.[11]

Predominant Steric Contribution of an Ethyl Group in A_4 Alkenes. Inspection of Table I shows a continuous decrease in reactivity of tetramethylethylene by progressive replacement of methyl by ethyl groups. If the increase in the electron-donating polar effect on passing from methyl to ethyl results in an acceleration of 1.5, as shown by uncrowded mono- and disubstituted alkenes,[2] we can calculate that reactivity

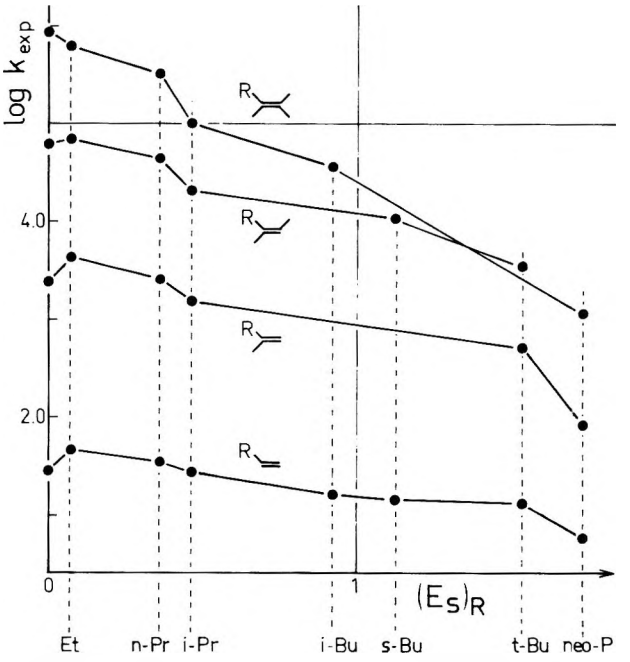


Figure 1. Increase in the steric deceleration by R of alkene bromination with the number of methyl groups on the double bond.

of tetraethylethylene is reduced by a factor of 180 owing to the intervention of steric effects.

Analogous introduction of one or several ethyl groups in less substituted alkenes did not lead to similar attenuations in reactivity.[2] In Figure 2, we compare the effect of the replacement of the methyl groups by ethyl in the A_4 series with the effect of progressive replacement of the hydrogens of ethylene by ethyl groups. We observe a large increase in reactivity on passing from mono- to di- and triethylethylenes, the diminution being evident only with the introduction of the fourth ethyl, whereas in A_4 the decelerating effect is observed upon the first replacement of methyl by ethyl.

We observed generally[2,9] for disubstituted alkenes the reactivity sequence trans < cis < gem. However, if we compare compounds 9, 10, and 11, we obtain, considering only the relative positions of the ethyl groups, the sequence cis $\simeq$ trans $\gg$ gem: the reactivity of the *gem*-dimethyldiethylethylene is 3.4 times smaller than would be expected from the k_{gem}/k_{cis}

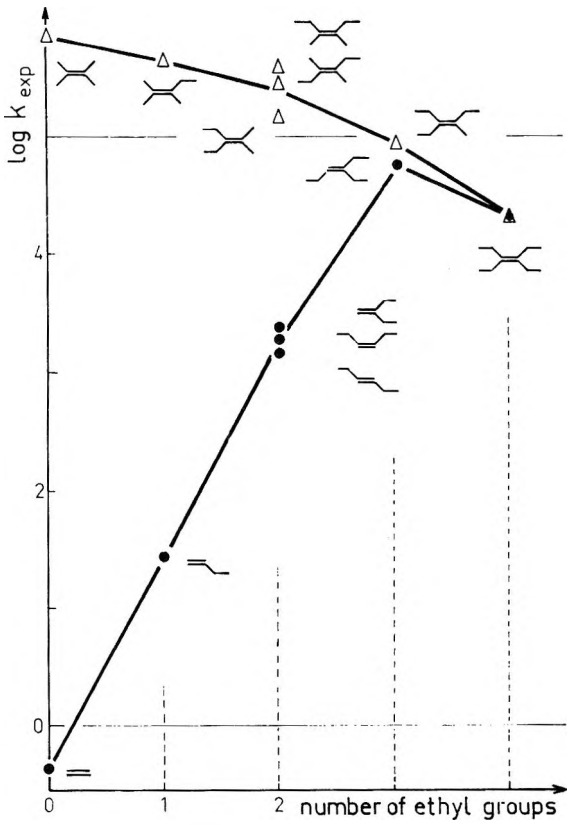


Figure 2. Effects of ethyl substituents on alkene reactivity: accelerating polar contribution in mono-, di-, or triethylethylenes; decelerating steric contribution in tetrasubstituted ethylenes.

ratio of the corresponding diethylethylenes. Thus, the accumulation of substituents affects not only the overall reactivity of the alkenes but also the relative reactivities of the geometric isomers.

The inversion of the reactivity sequence of geometric isomers could also result from the enhancement of substituent steric effects in the geminate position. The same effect was previously observed in disubstituted alkenes when the alkyl substituents are particularly bulky. For example for the di-*tert*-butylethylenes, the sequence is trans ≃ cis ≫ gem.[2,9]

Criteria for the Participation of Steric Effects. It can be confirmed by several criteria that the influence of steric effects on the reactivity of A_4 alkenes toward bromine is important. We examine successively a physicochemical criterion, the ionization potential, which is related to the substituent inductive effect, and two kinetic criteria based on the comparison of the bromination rate constants of A_4 with those of other addition reactions where steric effects have been identified as the rate-determining factor.

A. Ionization Potentials. Our recent photoelectron spectroscopic study of numerous alkenes allowed us to show that the electronic effects of substituents on the ionization potential (IP) are the most important, their steric effects having only a secondary effect.[13]

The increasing electron-donating effect of alkyl groups leads to a diminution of the IP and to an increase in electrophilic reactivity. Consequently, if there were an IP/log k_{exp} correlation, it should have a *negative slope*. Such correlation has been observed for the bromination of the less crowded methylalkenes.[14] For A_4 alkene bromination, there does not exist any linear relationship between IP and log k; at best, a tendency toward a positive correlation can be observed. This confirms our preceding conclusion that polar effects play only a minor role in bromination of A_4.

Table II. Steric Effects on Reactivity of Alkenes as a Function of the Electrophile

	Relative reactivities		
A_4	Br_2 this work	NO[17]	O_2[18]
$Me_2C{=}CMe_2$	1.0	1.0	1.0
$Me_2C{=}CMe$-Et	0.58	0.88	0.69
$Me_2C{=}CMe$-*n*-Pr	0.36	0.57	0.66

B. Kinetic Data on Various Additions to A_4. The addition of O_3 to very crowded olefins is very sensitive to steric effects of alkyl substituents[15] but the only study on A_4 is concerned with the reaction products alone[16] for compounds no. 1, 2, 9, 10, and 11. The only kinetic data on A_4 are the rates of photooxidation of NO in the presence of alkenes[17] and the deactivation of singlet oxygen O_2 ($^1\Delta_g$).[18] The *same reactivity decrease* is observed for the only three structures studied in the three reactions (Table II).

The steric effects of alkene substituents are less marked in NO addition and singlet oxygen deactivation because these electrophilic reagents are probably less voluminous than bromine. Therefore these data could signify that the electrophile–substituent interactions are an important rate-determining factor.

We have also compared the kinetic effect of an alkyl group R on the bromination of A_4 alkenes with the effect of the same R in the addition of two bulky reagents to less crowded R-substituted alkenes, since other data are not available. In these latter reactions, additions of bis-3-methyl-2-butylborane[19] and 2-4-dinitrobenzenesulfenyl chloride,[20] the steric effect very clearly predominates over the inductive one[21] because of the very large steric requirements of the electrophile. Between the A_4 bromination and these additions, we obtain (Figure 3) four satisfactory linear correlations of the form

$$\log k(\mathrm{R}) = a \log k_{exp}(\mathrm{R}) + b$$

where R = Me, Et, *n*-Pr, *n*-Bu, *i*-Pr, *i*-Bu, *t*-Bu, and *neo*-Pe; k_{exp}(R) is the rate constant for the bromination of RMeC=CMe_2; and k(R) are the rate constants obtained by Pritzkow[20] and Brown[19] for 1-alkenes $RCH{=}CH_2$ and for the cis and trans 2-alkenes, RCH=CHMe.

This comparison of the kinetic data confirms that the contribution of steric effects to the reactivity of A_4 toward bromine is important.

Linear Free Energy Relationships, Log $k_{exp} = f(\Sigma E_s)$. For the bromination of alkenes mono-, di-, or trisubstituted by small linear groups, we have obtained[2] a linear free energy relationship with polar constants, σ^*, and thus determined the sensitivity of bromination to polar effects of substituents: $\rho = -3.10$. As expected from our qualitative observations on the substituent effects by crowding of the alkenes, we obtain no relationship between log k_{exp} and σ^* for the A_4 alkenes, even for *n*-alkyl substituents.

Since from the previous analysis of substituent effects, we established that steric effects are of considerable importance, we now attempt to correlate the reactivity of A_4 alkenes by means of the empirical E_s parameters. We have used two scales of steric constants, those of Taft,[22] E_s, and those of Hancock, E_s^c, calculated from the former so as to correct for hyperconjugation.[23] With Taft's E_s, we observe an almost correct linear relationship only for the trimethylalkylethylenes:

$$\log k_{exp} = 1.55\ (\pm 0.10)\ E_s + 5.98\ (\pm 0.08)$$

$$(r = 0.986 \text{ and } \Psi = 0.13)$$

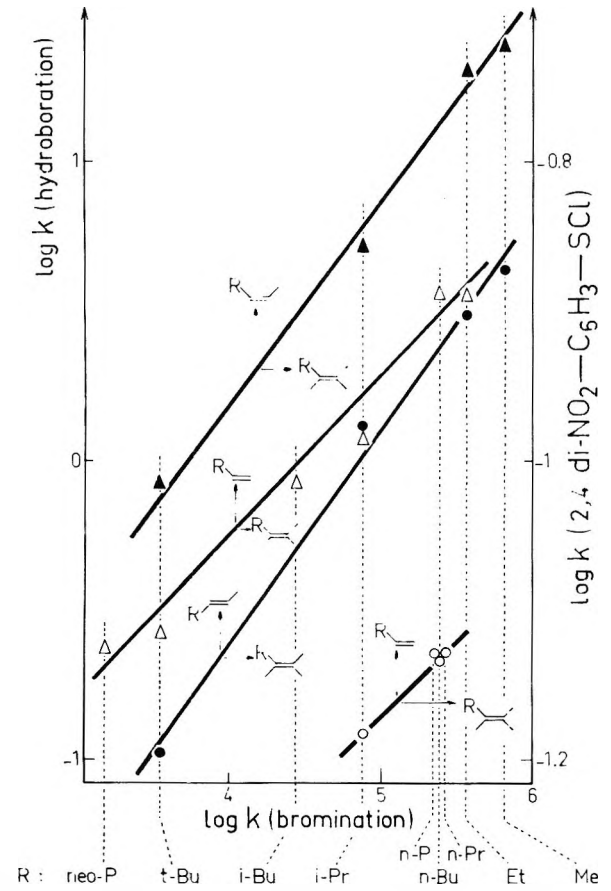


Figure 3. Effects of alkyl substituents on additions controlled by steric effects: hydroboration[18] of mono- (○), cis (▲), and trans (●) dialkylethylenes vs. bromination; addition of 2,4-dinitrobenzene sulfenyl chloride[19] to monoalkylethylenes (△) vs. bromination of tetraalkylethylenes. For trimethyl-*tert*-butylethylene, the bromination rate constant has been extrapolated from Figure 4.

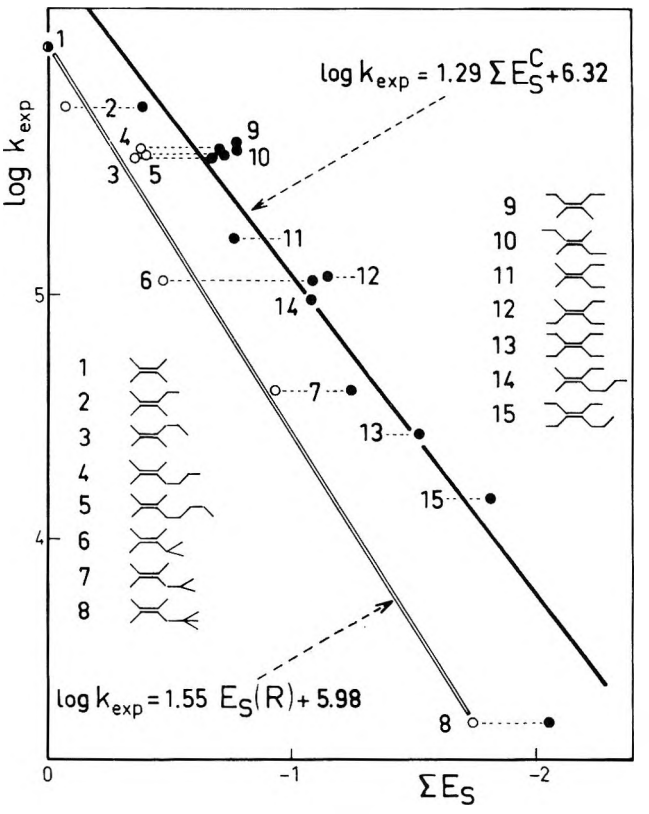


Figure 4. Correlation of the bromination rate constants for tetraalkylethylenes with steric parameters E_s.

The use of Hancock's constants allows us to include all the A_4 alkenes in a unique correlation:[24]

$$\log k_{exp} = 1.29\ (\pm 0.11)\ \Sigma E_s^c + 6.32\ (\pm 0.12)$$

$$(r = 0.962 \text{ and } \Psi = 0.29)$$

These relationships are shown in Figure 4.

Considering present and earlier data for the bromination of the various alkene sets, we obtain[2] very different free energy relationships: $\log k = f(\Sigma\sigma^*)$ for alkenes with a very few simple substituents, then $\log k = f(\Sigma\sigma^*, \Sigma E_s)$ for alkenes with bulkier substituents, and finally $\log k = f(\Sigma E_s)$ for the A_4.

The diversity of the structure–reactivity correlations in bromination exhibits clearly the increasing weight of steric effects as the degree of substitution of the alkene increases. Assuming, in the absence of contradictory data, that the mechanism of bromine addition is the same for all the alkenes, the absence of a general relationship shows that the classical structural parameters and the notions of independence and additivity of substituent effects, applied successfully to numerous reactions,[25] *cannot be transposed to a much more complex reaction center such as the ethylenic double bond.*

The initial hypothesis that the E_s values are additive, contested in particular by Miller[26] and by Shorter,[25] for polysubstituted compounds, fails to account adequately for all the observed reactivities of alkenes. On a very crowded reaction center, the interactions between the nonbonded alkyl groups are large[27] and the enhancement of the steric effects results from mutual hindrance to the free rotation of the alkyl groups. The calculation of these supplementary steric restrictions, for example, in the forms of increments

$$\Sigma E_s = \sum_{i=1}^{4} E_s(R_i) + \Delta E_s(R_1 - R_2) + \Delta E_s(R_2 - R_3) + \ldots$$

for a given reaction and a restricted set of compounds is possible but we think that it is only of limited interest.

Conclusion

The absence of stereochemical and thermodynamic data on A_4 prevents us discussing the reaction mechanism as we did for A_3.[1] It is nevertheless likely that for the A_4 as for the A_3, the importance of steric effects indicates a clear predominance of bromine-substituent interactions in the rate-determining step.

The synthesis and the kinetic, thermodynamic, and stereochemical studies of new A_4 are worthwhile in order to confirm these conclusions on the remarkable evolution of the balance between polar and steric effects.

Another important result of our study on crowded olefins is the demonstration that the steric effects of a given alkyl group depend markedly on the other substituents on the alkene, i.e. *on its environment.* Therefore, it is not possible to attribute a value to a steric parameter without defining its environment. This notion has already been advanced in the acid-catalyzed migration of alkyl groups in ketones.[23] If the environment influences the steric effect, it becomes impossible to obtain quantitative structure–reactivity relationships and it is, then, necessary to develop new approaches where these steric effects will be defined by taking into account the overall topology of the molecule. Developments of reactivity–topology treatment[29] might be more fruitful than the classical approach based on empirical parameters of individual alkyl groups.

Experimental Section

Starting Materials. The alkenes were either commercial samples (Chemical Samples) or were synthesized in the laboratory[5] (com-

pounds no. 7, 8, 12, 13, and 15 of Table I). All the alkenes were purified by GLC (Intersmat IGC 12M apparatus) on the following columns: (a) 40% $AgNO_3$, saturated solution in ethylene glycol on Firebrick FBC 22 (length 1.50 m, diameter 6 mm); (b) 20% DEGS on FBC 22 (3 m × 6 mm).

The purity of the reactants as checked by GLC was always better than 99%. The retention times were determined on column b under the following conditions: H_2 20 ml/min; air 300 ml/min; He (carrier gas) 10 ml/min; oven temperature 25 °C; injector 150–200 °C. The structure of all the alkenes was checked by NMR, ir, and mass spectroscopy. The ir spectrum is not very useful, the C=C band at 1620–1670 cm^{-1} being always very weak and disappearing completely for the two symmetrical alkenes. Nevertheless, the absence of bands associated with vinylic protons is a good criterion of purity of the A_4. The NMR spectra (JEOL, solvent CCl_4, Me_4Si internal standard, 60 MHz) were always sufficient for the unambiguous verification of the structures of the alkenes. The mass spectra were used in support of the NMR spectra.

NaBr and MeOH were purified as described previously.[2,7]

Kinetic Measurements. Direct measurements were performed by couloamperometry.[7] For all the alkenes studied, the reaction is overall second order and the appropriate log plot is a straight line to at least 90% reaction. We have checked particularly the rate constant of tetramethylethylene, which was determined by another method, coulometric concentrostat,[2] and was substantially corrected after improvement of the method. The two values are in agreement: $k_{exp} = 9.16 \times 10^5\ M^{-1}\ s^{-1}$ (by couloamperometry, $\pm 3.6 \times 10^4$, that is, the standard deviation on 12 runs is 4%).

Competitive measurements were performed by GLC as described previously.[6] The partial order relative to the alkene is unity in all cases. The reactivities relative to tetramethylethylene (k_{TME}) are determined with an error always less than 2%. To improve the precision, alkenes 7 and 8 of Table I, of low reactivity, were studied in competition with two alkenes of known rate constant.

Precision. The time–concentration data (direct method) and concentration data (competitive method) were handled by a computer. The agreement between the values determined by the two methods is excellent and is in accord with the idea that there is a single mechanism for direct and competitive bromination of alkenes.[6] For these very rapid reactions, the competitive method is more precise than couloamperometry.

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References and Notes

(1) D. Grosjean, G. Mouvier, and J. E. Dubois, *J. Org. Chem.*, preceding paper in this issue.
(2) J. E. Dubois and G. Mouvier, *Bull. Soc. Chim. Fr.*, 1426, 1441 (1968); J. E. Dubois and E. Bienvenue-Goëtz, *ibid.*, 2094 (1968); E. Bienvenue-Goetz and J. E. Dubois, *J. Org. Chem.*, **40**, 221 (1975).
(3) J. E. Dubois and A. Schwarcz, *Tetrahedron Lett.*, 2167 (1964); A. F. Hegarty, J. S. Lomas, W. V. Wright, E. D. Bergmann, and J. E. Dubois, *J. Org. Chem.*, **37**, 2218, 2222 (1972); M. F. Ruasse and J. E. Dubois, *ibid.*, **38**, 493 (1973).
(4) J. E. Dubois and P. Fresnet, *Tetrahedron*, **29**, 3407 (1973).
(5) J. S. Lomas, D. S. Sagatys, and J. E. Dubois, *Tetrahedron Lett.*, 599, 1349 (1971); 165 (1972).
(6) G. Mouvier, D. Grosjean, and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 1729 (1973).
(7) J. E. Dubois, P. Alcais, and G. Barbier, *J. Electroanal. Chem.*, **8**, 359 (1964).
(8) J. E. Dubois and E. Bienvenue-Goëtz, *Bull. Soc. Chim. Fr.*, 2089 (1968); J. E. Dubois and X. Q. Huynh, *Tetrahedron Lett.*, 3369 (1971).
(9) M. Marie de Ficquelmont, Doctoral Thesis, CRNS AO 8355, Paris, 1973.
(10) J. E. Dubois and X. Q. Huynh, *Bull. Soc. Chim. Fr.*, 1436 (1968).
(11) Slightly higher reactivities are found in the cycloalkene series.[12] Actually, the identified highest bromination rate constant is that of 1,2-dimethylcyclopentene, $k_{Br_2} = 2.8 \times 10^7\ M^{-1}\ s^{-1}$ in methanol at 25 °C; that calculated[8] for tetramethylethylene is only $1.2 \times 10^7\ M^{-1}\ s^{-1}$. These reactivity differences are likely due to the additional nonbonded interactions involved in cycloalkene bromination. In contradiction with results on other additions,[20] the *cis*-cyclooctene is in bromination less reactive than other cycloalkenes. This has been interpreted by a change in the transition state structure.[12]
(12) J. E. Dubois and P. Fresnet, *Tetrahedron Lett.*, 2195 (1974).
(13) P. Masclet, D. Grosjean, G. Mouvier, and J. E. Dubois, *J. Electron Spectrosc. Relat. Phenom.*, **2**, 225 (1973).
(14) D. Grosjean, P. Masclet, and G. Mouvier, *Bull. Soc. Chim. Fr.*, 573 (1974).
(15) W. A. Mosher in "Ozone Chemistry and Technology", *Adv. Chem. Ser.*, **No. 21**, 140 (1956).
(16) R. W. Murray, J. W. P. Lin, and D. A. Grunke in "Ozone Reactions with Organic Compounds", *Adv. Chem. Ser.*, **No. 112**, 9 (1972).
(17) G. A. Glasson and C. S. Tuesday, *Environ. Sci. Technol.*, **4**, 916 (1970).
(18) R. E. Huie and J. T. Herron, *Int. J. Chem. Kinet.*, **5**, 197 (1973).
(19) H. C. Brown and A. W. Moerikofer, *J. Am. Chem. Soc.*, **85**, 2063 (1963).
(20) W. Pritzkow, G. Just, G. Lorenz, U. Jahnke, G. Collin, M. Röllig, L. Winguth, P. Dietrich, C. E. Döring, H. G. Hauthal, and A. Wiedenhöft, *J. Prakt. Chem.*, **311**, 238 (1969).
(21) J. E. Dubois and G. Mouvier, *Tetrahedron Lett.*, 1629 (1965).
(22) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, Chapter 13.
(23) C. K. Hancock, E. A. Meyers, and B. J. Yager, *J. Am. Chem. Soc.*, **83**, 4211 (1961); T. Fujita, C. Takayama, and M. Nakajima, *J. Org. Chem.*, **38**, 1623 (1973).
(24) The E_s^c of Hancock are generally more satisfactory, with the exception of tetramethylethylene, which deviates significantly owing to the way in which E_s^c is calculated; it is not surprising that the correlations log $k_{exp} = f(\Sigma E_s)$ with E_s^c are slightly less good than those with E_s for the eight trimethylalkylethylenes but slightly better for all 15 A_4 because of the decrease, in the second case, of the statistical weight of tetramethylethylene.
(25) J. Shorter in "Advances in Linear Free Energy Relationships", N. B. Chapman and J. Shorter, Ed., Plenum Press, New York, N.Y., 1972, Chapter 2.
(26) S. Miller, *J. Am. Chem. Soc.*, **81**, 101 (1959); O. Exner, *Collect. Czech. Chem. Commun.*, **25**, 1044 (1960).
(27) J. Metzger, D. Roussel, and M. Chanon, *Tetrahedron Lett.*, 1861 (1971).
(28) J. E. Dubois and P. Bauer, *J. Am. Chem. Soc.*, **90**, 4511 (1968); P. Bauer and J. E. Dubois, *ibid.*, in press.
(29) J. E. Dubois, A. Massat, and P. Guillaume, *J. Mol. Struct.*, **4**, 385, 403 (1969); J. E. Dubois and H. Herzog, *J. Chem. Soc., Chem. Commun.*, 932 (1972).

Bromination and Lithiation: Two Important Steps in the Functionalization of Polystyrene Resins

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Reactions used for the bromination and lithiation of cross-linked polystyrene resins have been explored. In the presence of bromine and catalytic amounts of a thallium(III) salt, polystyrene resins are smoothly brominated and give homogeneous reactive resins with a highly reproducible degree of functionalization. These resins can be lithiated easily by reaction with an excess of *n*-butyllithium in benzene. Other swelling agents such as tetrahydrofuran gave incomplete removal of the bromine. The direct lithiation of polystyrene with *n*-butyllithium and tetramethylethylenediamine gave lithiated polymers containing approximately 2 mequiv of functional group per gram, while direct lithiation in the presence of triethylenediamine gave lower degrees of functionalization. The lithiated resins were used to prepare polymers containing carboxylic acid, thiol, sulfide, boronic acid, amide, silyl chloride, phosphine, alkl bromide, aldehyde, alcohol, or trityl functional groups for applications in polymer-assisted syntheses.

Functionalized resins have found numerous applications[1,2] recently as supports in solid-phase synthesis,[3] reagents[4] or protecting groups[5,6] in organic synthesis, and supports for chromatography or catalysis.[2,7] The reactions which are used in the functionalization of insoluble resins are similar to those carried out on soluble materials, but are usually more difficult to control and evaluate owing to the insolubility of the resins, which makes the reaction heterogeneous and often prevents the simple characterization of the products by the usual methods of analysis.

A large number of the functional resins which have been prepared to date were synthesized by chemical modification of cross-linked polystyrene. When functional groups are to be introduced by modification of a preformed polymer, the purity of the starting material must be ascertained[8] since minute amounts of surface impurities remaining from the emulsion polymerization reaction may prevent the introduction of certain types of functional groups. This is particularly true with solvent-swellable cross-linked polystyrene beads which are much more sensitive to surface impurities than highly cross-linked macroreticular resins since the latter contain pores of well-defined size and accessibility. It should be emphasized, however, that the washed solvent-swellable resins are usually more reactive and often give better yields than their macroreticular counterparts.[5,9] In addition, since the degree of functionalization of a resin prepared via several successive reactions is usually wholly dependent on the control of the first functionalization reaction, it is important to design these reactions in such a way that they are easily reproducible and yield reactive polymers with easily replaceable functional groups.

A review of the literature shows that two versatile types of functional resins are those in which some of the aromatic rings are halogenated or metalated, yet the procedures commonly used in the halogenation or metalation of polystyrene resins are often described incompletely or are impractical, difficult to control, and sometimes even yield unreactive resins. In other cases, the metalation reactions are incomplete and leave behind other functional groups which may prove troublesome in further reactions or in the characterization of the polymers.

Halogenation of Polystyrene Resins. The method used most often in the bromination of insoluble polystyrene resins was developed by Heitz and Michels[10] and involves the reaction of polystyrene with bromine in the presence of ferric chloride as catalyst. This procedure gave resins containing from 2.2 to 3.9 mequiv of bromine per gram. The reaction has, however, been reported to give unreproducible results[11] and often yields a colored resin of low quality and lacking homogeneity.[12] In addition, we have observed that in a number of cases the polymer is less reactive than that prepared by other methods. A second procedure, first described by Camps et al.,[11] uses the reaction of a stoichiometric amount of thallium acetate with the resin followed by bromination to produce a polymer containing about 1 mequiv of bromine per gram. This procedure was also used by Weinshenker et al.[12,13] to prepare polymers containing up to 4 mequiv of bromine per gram. The major drawbacks of this procedure are that a large amount of costly thallic acetate is used in the reaction (e.g., 100 g of thallic acetate sesquihydrate for 50 g of cross-linked polystyrene[13]) and that an extensive washing procedure is required to remove the considerable amount of sparingly soluble thallium salts generated by the reaction. However, this method affords a polymer which is visually cleaner than that obtained in the ferric chloride catalyzed bromination, and the reaction is presumed to occur at the para position of the aromatic rings of the polystyrene.

We have reinvestigated the bromination of cross-linked polystyrene with the aim of obtaining a reliable procedure for the preparation of a clean and homogeneous polymer with a predictable degree of substitution of the aromatic rings.

A number of catalysts, solvents, and reaction conditions were studied for the bromination of cross-linked polystyrene. As can be seen in Table I, the ferric chloride catalyzed bromination of polystyrene gave reasonably consistent results when the reaction was carried out in refluxing carbon tetrachloride for short periods of time in the dark. The degree of substitution could be controlled by varying the amount of bromine used in the reaction. High degrees of functionalization were obtained by using a slight excess of bromine, but under the reaction conditions, polybromination was not observed. We also studied the bromination of 1% cross-linked polystyrene in the presence of thallic acetate. Our results indicate that the thallic acetate is not required in stoichiometric amount but that very small amounts of the reagent are sufficient to catalyze the reaction. Once again the reactions were carried out in carbon tetrachloride with a short refluxing period in the dark. The polymers obtained were almost colorless and had a cleaner appearance than those obtained by the ferric chloride method; in addition, the reaction seemed to proceed more easily than with ferric chloride as a smooth disappearance of the bromide was observed to occur rapidly at reflux temperature. As can be seen in Table I, the degree of functionalization obtained in each reaction was found to be independent of the amount of thallic acetate used and was only a function of the amount of bromide. Thus the reaction was easily performed

Table I. Bromination of 1% Cross-Linked Polystyrene[a]

Expt	Catalyst	Molar ratio catalyst/PS	Molar ratio bromine/PS	mequiv bromine per gram	Degree of functionalization
1	$FeCl_3$	1:77	1.12:1	4.97	0.85
2	$FeCl_3$	1:61	1.12:1	5.32	0.96
3	$FeCl_3$	1:37.5	0.39:1	2.87	0.39
4	$Tl(OAc)_3$	1:9.6	0.42:1	2.89	0.39
5	$Tl(OAc)_3$	1:50	0.41:1	2.66	0.35
6	$Tl(OAc)_3$	1:105	0.21:1	1.76	0.21
7	$Tl(OAc)_3$	1:62	0.44:1	3.10	0.43
8	$TlCl_3$	1:58	1.25:1	6.05[b]	>1
9	$TlCl_3$	1:68	1.16:1	5.16	0.91
10	$TlCl_3$	1:78	0.4:1	2.95	0.40
11	$TlCl_3$	1:61	0.43:1	3.15	0.43
12	Tl salt[c]		0.48:1	3.19	0.44

[a] Typical reaction conditions were as follows: reaction in CCl_4 1 h at room temperature followed by 1.75 h at reflux. [b] Reaction at reflux temperature for 24 h. [c] Thallium salt recovered from expt 4.

Table II. Carboxylation of Lithiated Polystyrene

Starting resin Br, mequiv/g	Molar ratio BuLi/Br	Solvent	Product COOH, mequiv/g	Product Br, mequiv/g
2.89	4:1	THF	1.4	1.53
2.89	3:1	Cyclohexane	1.3	1.45
2.89	3:1	Benzene	2.9	0
2.78	2.4:1	Toluene	2.7	0

with small amounts of thallic acetate and yielded polymers with desirable physical aspect and easily controlled degree of substitution.

To ascertain whether other thallium(III) salts were also useful catalysts in this bromination, the reaction was attempted using catalytic amounts of thallic chloride, and, in every case, the reaction gave results comprable to those obtained for thallic acetate. In one instance we observed the introduction of more than one bromine atom per aromatic ring, but this result was only obtained in a reaction involving an excess of bromine and a 24-h reaction period at reflux temperature.

Excellent results were also obtained when a small amount of an unknown thallium salt recovered after a previous bromination with thallium acetate was used as catalyst in a new bromination reaction. Other catalysts such as zinc chloride in tetrahydrofuran or stannic chloride in carbon tetrachloride gave polymers with very low degrees of functionalization and would therefore only be suitable for applications involving the introduction of small numbers of functional groups. An interesting result was obtained when the bromination reaction was carried out in acetic acid: the reaction mixture containing the cross-linked polymer became gradually homogeneous as the polymer dissolved. Cleavage of the polymer chains was extensive as evidenced by the low viscosity ($[\eta] = 0.115$, 30 °C, toluene) of the brominated polymer after 1 day of reaction. This depolymerization was, however, only observed when acetic acid was used in conjunction with the catalyst.

The iodination of cross-linked polystyrene proved to be more difficult and we observed that the degree of functionalization depended on the amount of thallic trifluoroacetate used. Thus, unlike the bromination reaction in which the thallium salt acted as a catalyst, a stoichiometric amount of thallic trifluoroacetate was required to effect the iodination.

Lithiation of Cross-Linked Polystyrene. Two main reaction routes have been studied for the lithiation of soluble polystyrene. The first one, developed by Braun,[14] involved the reaction of a solution of halogenated polystyrene with an excess of *n*-butyllithium. The reaction was usually carried out on substrates obtained by polymerization of *p*-iodostyrene. The second route, developed by Chalk,[15] involved the direct lithiation of a solution of polystyrene by reaction with a 1:1 complex of *n*-butyllithium and *N,N,N′,N′*-tetramethylethylenediamine. This reaction was studied further by Evans et al.,[16] who showed that both meta and para lithiation occurred with a meta–para ratio of 2:1.

A number of workers have used the first route and prepared cross-linked polystyryllithium intermediates by the two-step bromination–lithiation procedure.[11-13] We have also used this reaction route in a number of preparations and have found that the outcome of the reaction varied considerably depending on the type of polymer used, its degree of bromination, and the solvent used for the lithiation. Thus, brominated macroreticular resins were found to react completely with *n*-butyllithium in tetrahydrofuran,[17] even when the starting resin contained a large proportion of brominated aromatic rings. In contrast, the lithiation of 1% cross-linked resins in THF gave varying results depending on the degree of functionalization. In the case of brominated polymers containing approximately 1–1.5 mequiv of bromine per gram, we obtained almost complete removal of the bromine in one reaction with *n*-butyllithium, while more highly substituted polymers required several successive treatments with this reagent. For example, a polymer containing 3 mequiv of bromine per gram, when allowed to react with excess *n*-butyllithium in THF and quenched with methanol, yielded a product which still contained 1.9 mequiv Br/g. A second treatment under the same reaction conditions reduced the bromine content to 0.6 mequiv/g, and a third treatment resulted in complete removal of the bromine from the polymer. In contrast to this behavior, a single treatment with *n*-butyllithium in benzene was sufficient to effect complete removal of the bromine from a 1% cross-linked polymer containing 3 mequiv of bromine per gram. These results were confirmed by a second study in which the 1% cross-linked polymer was brominated, then allowed to react with an excess of *n*-butyllithium, and the resulting product quenched by addition of a slurry of dry ice in tetrahydrofuran. The results of this study, shown in Table II, indicate clearly that the lithiation reaction is incomplete in tetrahydrofuran or cyclohexane but occurs quantitatively in benzene or toluene. The difference in behavior for the lithiation in cyclohexane vs. benzene or toluene can be explained easily if one considers the swelling properties of these solvents. In benzene or toluene, the 1% cross-linked resin is fully swollen and allows easy penetration of the reagent while in cyclohexane the resin is only partially swollen and therefore a number of reactive sites are located in pores which are inaccessible to the reagent.

Table III. Direct Lithiation of Cross-Linked Polystyrene[a]

Solvent	Polystyrene, mequiv	Amine used (mmol)	n-BuLi mmol	Reaction conditions	Ⓟ-COOH, mequiv/g
Cyclohexane	27	TMEDA (25)	34	65°C, 4.5 h	2.0
Cyclohexane	25	TMEDA (25)	27	70°C, 1.5 h	1.4
Cyclohexane	25	TMEDA (56)	30	67°C, 4 h	2.0
Heptane	26	TMEDA (25)	27	68°C, 3 h	1.52
Benzene	26	TMEDA (25)	27	70°C, 3.5 h	0.15
Tetrahydrofuran	24	TMEDA (25)	35	75°C, 3 h	0
Cyclohexane	30	TEDA (24)	25	65°C, 3 h	0.4
Cyclohexane	19	TEDA (18)	18	70°C, 4 h	0.6
Cyclohexane	24	TEDA (22)	32	70°C, 24 h	1.1

[a] TMEDA = tetramethylethylenediamine; TEDA = triethylenediamine.

This explanation does not hold true for a comparison of the lithiation reaction in tetrahydrofuran vs. benzene or toluene since all three solvents have excellent swelling properties. It is more likely that in the more polar solvent, tetrahydrofuran, ionic repulsions limit the accessibility of the reagent thus causing the reaction to stop once a fraction of the functional groups have reacted with *n*-butyllithium.

The direct lithiation of 2% cross-linked polystyrene by reaction with a 1:1 complex of *n*-butyllithium and *N,N,N′,N′*-tetramethylethylenediamine was recently reported by Fyles and Leznoff.[19] The resulting lithiated polymer, after quenching with carbon dioxide, yielded a carboxylated resin containing 0.6–0.9 mequiv of functional group per gram.[19] Better results were obtained with a macroreticular polymer, which after lithiation and quenching with carbon dioxide, gave resins containing from 1.1 to 1.5 mequiv of functional group per gram. This one-step lithiation reaction is advantageous for applications in which the position of the functional group on the aromatic ring is unimportant since, as was mentioned earlier, the lithiation occurs on both meta and para positions.[16] We have investigated the direct lithiation with the aim of improving the degree of functionalization since, in a number of applications, it might be desirable to obtain more highly functionalized resins. Our procedure involved the reaction of an amine–*n*-butyllithium complex with the resin at 65–70 °C in a nonpolar solvent. The minimum degree of functionalization of the lithiated resins was estimated by acid–base titration of the carboxylic acid resin obtained by rapid quenching of the lithiated resin with carbon dioxide. As can be seen in Table III, best results were obtained with tetramethylethylenediamine (TMEDA) in a nonpolar hydrocarbon solvent such as cyclohexane or heptane.

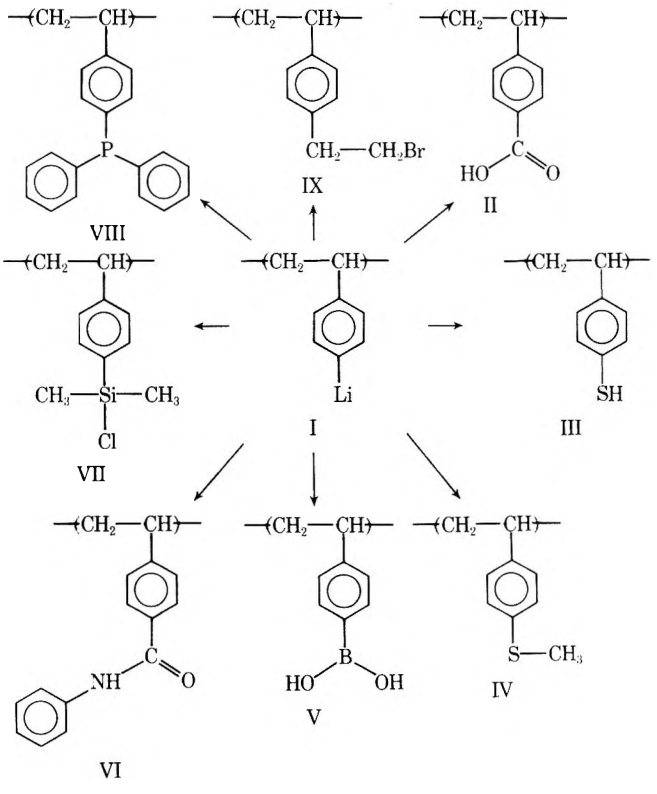
An increase in the molar ratio TMEDA–*n*-BuLi from 0.7:1 to 1.9:1 did not change the degree of functionalization while shorter reaction times decreased it noticeably. Other solvents such as benzene or tetrahydrofuran were unsuitable for the reaction. In another series of experiments, triethylenediamine was used instead of TMEDA but the reaction was more sluggish and longer reaction times were required to achieve a degree of functionalization greater than 1 mequiv per gram.

In our experiments with TMEDA–*n*-butyllithium we observed that the degree of functionalization of 2 mequiv per gram, which is obtained readily under the conditions shown in Table III, seemed to be the maximum which could be obtained after carboxylation. This functionalization corresponds to the introduction of carboxyl groups on 23% of the aromatic rings of the polystyrene resins. Presumably this is due to the fact that the solvents chosen for the reaction are unable to swell the resin and thus the penetration of the relatively bulky TMEDA–butyllithium complex in the pores of the resin is severely limited and only the most accessible sites can be functionalized. It must be remembered, however, that the actual percentage of aromatic rings which are lithiated is probably higher than 23% since the carboxylation reaction which is used for the measurement of the degree of functionalization is not quantitative.

A comparison of the bromination–lithiation vs. direct lithiation procedure would therefore indicate that the two-step lithiation is probably the method of choice if control of the position of lithiation and of the degree of functionalization is desired, since predictable results can be obtained in the bromination over a very broad range of degrees of functionalization; in addition, since the resin is fully swollen during the bromination, a more even distribution of the functional groups can be expected.

To test the reactivity of the polystyryllithium resin and explore its application to the preparation of polystyrene resins containing various functional groups, a number of reactions were studied (Schemes I and II). In all cases the lithiated

Scheme I



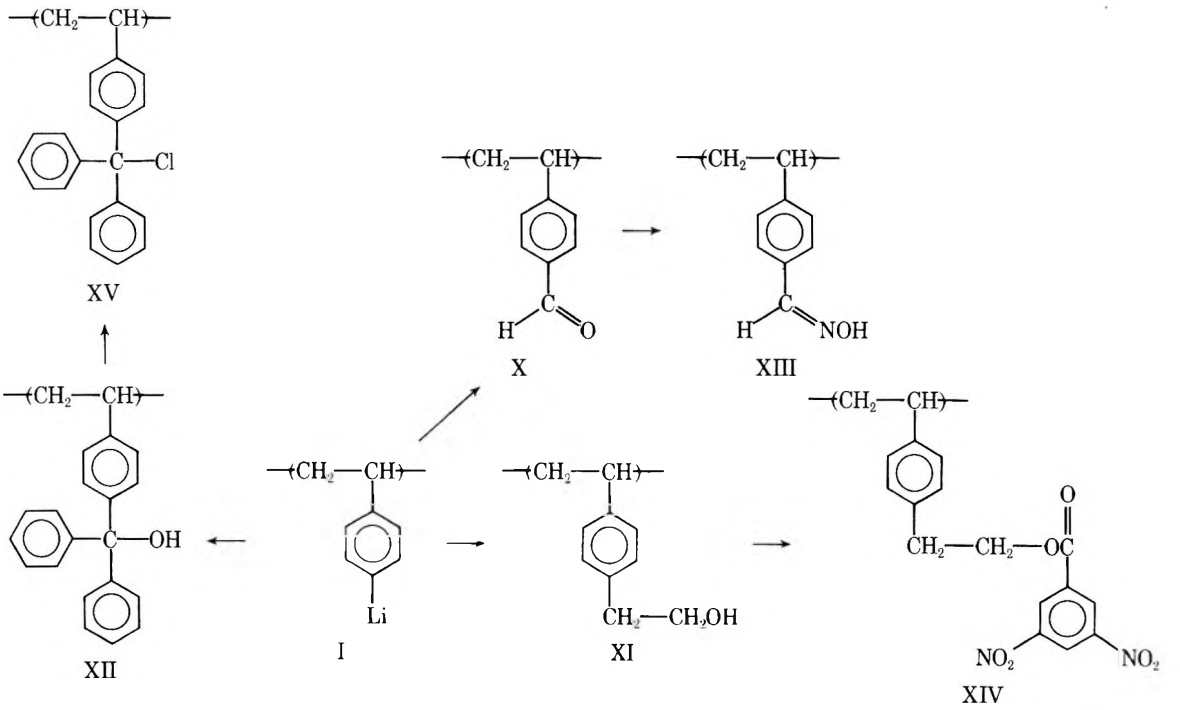
resins were prepared in situ from their brominated precursor since this procedure allowed the calculation of a functional group yield for every reaction. The results of these reactions are shown in Table IV. In most cases the functional yield could be estimated either by direct titration[18] for resin II, or by elemental analysis for sulfur, boron, nitrogen, silicon, phosphorus, or bromine for resins III–IX. As can be seen in Scheme

Table IV. Reactions of Lithiated Resin I[a]

Precursor Ⓟ-Br			Product			
mequiv/g	Degree of functionalization	Reagent	Structure	mequiv/g	Degree of functionalization	Functional yield, %
2.89	0.39	CO_2	II Ⓟ-COOH	2.9	0.35	90
2.8	0.37	S_8	III Ⓟ-SH	3.9[b]	*d*	*d*
3.1	0.43	CH_3SSCH_3	IV Ⓟ-SCH_3	2.6	0.31	72
2.89	0.39	$B(OCH_3)_3$	V Ⓟ-$B(OH)_2$	3.15	0.38	97
2.89	0.39	$C_6H_5N{=}C{=}O$	VI Ⓟ-$CONHC_6H_5$	2.2	0.31	80
3.1	0.43	$Si(CH_3)_2Cl_2$	VII Ⓟ-$Si(CH_3)_2Cl$	2.2	0.28	65
2.8	0.37	$ClP(C_6H_5)_2$	VIII Ⓟ-$P(C_6H_5)_2$	1.92	0.31	84
1.76	0.21	$BrCH_2CH_2Br$	IX Ⓟ-CH_2CH_2Br	1.13	0.14	67
2.8	0.37	$(CH_3)_2NCHO$	X Ⓟ-CHO	2.3[c]	0.26	70
2.89	0.39		XI Ⓟ-CH_2CH_2OH	2.8[c]	0.33	85
2.8	0.37	$C_6H_5COC_6H_5$	XII Ⓟ-$C(C_6H_5)_2OH$	1.4[c]	0.20	54

[a] Reactions performed using 1% cross-linked brominated polystyrene using *n*-butyllithium in benzene for the lithiation. [b] 3.9 mequiv of S per gram. The resin contains S–S bonds in addition to S–H bonds. [c] Calculated from the elemental analysis of a derivative; see Scheme II. [d] See ref 20.

Scheme II



II, the estimation of the yields for resins X, XI, XII was done by the preparation of derivatives XIII, XIV, and XV for which reliable elemental analyses for nitrogen or chlorine could be carried out. The yields quoted for X–XII should be taken as minimum yields since an additional step was required for the analysis. In all cases no attempts were made to optimize the yields.

We are presently studying polymeric reagents and protecting groups derived from resins III–VII.

Experimental Section

The resins used in this research were a solvent-swellable 1% divinylbenzene–styrene copolymer, Bio-Beads SX 1, purchased from Bio-Rad Laboratories, and a macroreticular resin, Amberlite XE-305, purchased from British Drug House. Tetrahydrofuran (THF) used in the experiments below was purified by distillation from lithium aluminum hydride. Benzene, cyclohexane, and toluene were dried over calcium hydride. All other chemicals were reagent grade and used without further purification unless specified. All the lithiation reactions and the reactions involving lithiated resin intermediates were carried out under inert atmosphere in a specially designed flask fitted with a coarse porosity fritted glass filter. This one-piece reaction vessel allowed the addition or removal of solvents and excess reagents or by-products, the washing of the resin, etc., without transfer or exposure to the atmosphere. Infrared spectra were recorded on Perkin-Elmer 457 or Beckman IR-20 A spectrophotometers using potassium bromide pellets. Elemental analyses were performed by Chemalytics Inc., Galbraith Laboratories, or in this laboratory (halogen analyses only) using a Parr peroxide bomb with 200–300-mg samples of the halogenated resins.

Washing of Cross-Linked Polystyrene Resins. The resins used

were washed routinely to remove surface impurities.[8] The following solutions were used at 60–80 °C with, in each case, a contact time of 30–60 min with the resin: 1 N NaOH, 1 N HCl, 2 N NaOH–dioxane (1:2), 2 N HCl–dioxane (1:2), H_2O, dimethylformamide. The resins were then washed at room temperature with the following: 2 N HCl in methanol, H_2O, methanol, methanol–dichloromethane (1:3), methanol–dichloromethane (1:10). The resins were then dried under reduced pressure at 50–70 °C. In general the washing was accompanied by a loss of weight of up to 10%.

Bromination of Cross-Linked Polystyrene Resins. A. Partial Bromination of 1% Cross-Linked Polystyrene Beads. To a suspension of 20 g of washed resin in 300 ml of carbon tetrachloride was added 1.18 g of thallic acetate. The reaction mixture was stirred in the dark for 30 min, then 13.6 g of bromine in 20 ml of carbon tetrachloride was added slowly. After stirring for 1 h at room temperature in the dark, the mixture was heated to reflux for 1.5 h. The reaction mixture, which had lost all the coloration due to free bromine, was collected on filter and washed with carbon tetrachloride, acetone, acetone–water (2:1), acetone, benzene, and methanol. After drying under vacuum, 26.3 g of resin containing 3.10 mequiv of bromine per gram was obtained (24.8% Br). Thus the resin obtained in this preparation had functional groups on 43% of the aromatic rings (theory 44%). Similar reaction conditions were used in bromination reactions with thallic chloride or ferric chloride as catalysts. The results of the bromination reactions are shown in Table I. In one instance (expt 4, Table I), the spent thallium salt was recovered after the reaction and used as catalyst (0.1 g for 2 g of resin) in the bromination of a fresh sample of polystyrene (expt 12, Table I). The reaction carried out as described above gave a very homogeneous, almost colorless, brominated resin containing 3.19 mequiv Br/g. In all cases the resins obtained from the thallium salt catalyzed reaction were visually cleaner than those obtained from the ferric chloride catalyzed reactions.

B. Bromination of a Macroreticular Resin with an Excess of Bromine. One hundred grams of dry Amberlite XE-305 resin was suspended in 1 l. of dry carbon tetrachloride and 1 g of anhydrous ferric chloride was added. The reaction mixture was stirred in the dark while a solution of 60 ml of bromine in 250 ml of carbon tetrachloride was added slowly. The reaction mixture was then stirred overnight at room temperature. The resulting mixture, which still contained free bromine, was filtered and the resin washed repeatedly with acetone until all the bromine coloration had disappeared. Further washings were made with dioxane–water (2:1) and butanone. After drying in vacuo at 60 °C the cream-colored polymer weighed 145.1 g and contained 3.93 mequiv of bromine per gram. The resin obtained by this procedure was, however, not very homogeneous.

A duplicate experiment carried out under the same reaction conditions yielded a colored product containing 3.3 mequiv of bromine per gram.

Lithiation of 1% Cross-Linked Brominated Resin. A. In Tetrahydrofuran Followed by Methanol Quenching. A brominated resin (2.45 g) (3 mequiv Br/g) was swollen in 30 ml of dry THF and 4 ml of 2.5 M *n*-BuLi in hexane was added. After 1.5 h at room temperature the liquid phase was removed and 30 ml of dry THF was added followed by 4.5 ml of 2.5 M *n*-BuLi in hexane. The reaction mixture was stirred and heated to 65–70 °C for 1.5 h. After removal of the liquid phase, a new 30-ml portion of dry THF was added followed by 3 ml of methanol. The brown coloration of the polymer disappeared instantly. After filtration, the polymer was washed with THF, methanol, THF–water (2:1), water, THF–water (2:1), THF, and finally methanol. After drying, 2.23 g of polymer was obtained. Elemental analysis for bromine revealed that the polymer still contained 1.95 mequiv of Br/g. The above reaction sequence was repeated using 1.81 g of the polymer recovered above (1.95 mequiv Br/g) and two successive additions of 2.5 M *n*-BuLi (3 ml at room temperature, and 3.5 ml at 65–70 °C). After quenching with methanol and washing as above, 1.61 g of a resin containing 0.68 mequiv Br/g was obtained. After a third treatment with two successive portions of *n*-BuLi (2 ml at room temperature, then 3 ml at 65–70 °C) followed by quenching with methanol and washing, the resin was found to have lost all its bromine.

B. In Tetrahydrofuran Followed by Quenching with Carbon Dioxide. A stirred suspension of 1.73 g of brominated resin (2.89 mequiv/g) in 20 ml of dry THF was treated with 5 ml of 1.6 M *n*-BuLi in hexane for 1.5 h at room temperature. The liquid phase was removed and 20 ml of dry THF was added followed by 3 ml of 1.6 M *n*-BuLi; after 1 h of stirring at room temperature the liquid phase was again removed and a third portion of 20 ml of dry THF and 4 ml of 1.4 M *t*-BuLi were added. After 1 h of stirring at room temperature, the liquid phase was removed, the resin was washed twice with dry THF, and a slurry of powdered dry ice in dry THF was added. After washing twice with THF–2 N HCl (3:1) the resin was washed further as described above in A, then dried to yield 1.59 g of a resin which still contained 1.53 mequiv of Br/g. In addition, acid–base titration of the resin[18] showed that it contained 1.4 mequiv of –COOH group per gram.

C. In Cyclohexane Followed by Quenching with Carbon Dioxide. The lithiation was carried out by heating a suspension of 2.04 g of brominated resin (2.89 mequiv/g) in 20 ml of cyclohexane with 10 ml of 1.6 M *n*-BuLi in hexane at 68 °C for 3 h. After quenching with solid carbon dioxide in THF, washing and drying, 1.92 g of a resin containing 1.45 mequiv Br/g and 1.3 mequiv –COOH/g was obtained.

D. In Benzene or Toluene Followed by Quenching with Carbon Dioxide. The lithiation was carried out using 2.04 g of brominated resin (2.89 mequiv/g) swollen in 30 ml of dry benzene by adding 10 ml of 1.6 M *n*-BuLi and stirring the suspension at 60 °C for 3 h. After quenching with powdered carbon dioxide in THF, washing, and drying, 1.86 g of a polymer containing 2.9 mequiv of –COOH per gram was obtained. The infrared spectrum of the polymer included very broad hydroxyl and carbonyl absorptions. Similar results were obtained using toluene as solvent (see Table II).

Direct Lithiation of Cross-Linked Polystyrene Resin. Washed polystyrene (2.8 g, 27 mequiv) was suspended in 20 ml of dry cyclohexane containing 4 ml (25 mmol) of tetramethylethylenediamine (TMEDA) and 13.5 ml of 2.5 M *n*-BuLi were added to the stirred mixture. The reaction mixture turned red gradually during 4.5 h of heating at 65 °C. After the liquid phase was removed, the resin was rinsed twice with dry cyclohexane to yield the desired lithiated resin.

The lithiated resin prepared above was quenched by addition of a slurry of dry ice in tetrahydrofuran. After washing as described above and drying, the resin contained 1.99 mequiv of –COOH per gram.

Similar reactions were carried out under different reaction conditions with TMEDA or triethylenediamine. The reaction conditions and results of these experiments are summarized in Table III.

Applications of Lithiated Resin I to the Preparation of Selected Functional Polymers. All the reactions shown in Schemes I and II were carried out on a lithiated resin prepared by reaction of a 1% cross-linked solvent-swellable brominated resin using an excess of *n*-BuLi in benzene (65 °C, 2.5 h). After cooling and removal of the liquid phase, the lithiated resin was washed two or three times with dry benzene. After addition of enough dry THF or benzene to fully swell the resin, an excess of the required reagent was added as described below.

Preparation of Polymeric Thiol III Ⓟ-SH. Resin I was prepared from 3.14 g of brominated polystyrene (2.8 mequiv/g). The resin was suspended in 35 ml of dry THF and 3.31 g of sulfur was added. The reaction mixture turned dark red instantly, then became brown as heat was evolved. After 1 h at room temperature, 30 ml of 3 N HCl was added and the stirring was continued for 30 min. After filtration, the resin was washed repeatedly with THF–water (3:1), THF, CCl_4, CS_2, ether, ethanol, water, THF–water (2:1), THF, and finally methanol. After drying, 3.0 g of resin III were obtained.

The infrared spectrum of the resin included a –SH absorption at 2560 cm^{-1}.

Anal. S, 12.6 (3.9 mequiv/g); Br, none. This result indicates that S–S bonds as well as SH bonds must be present in the polymer.[20]

Preparation of Polymeric Sulfide IV Ⓟ-SCH_3. The lithiated resin was prepared from 10 g of brominated polystyrene (3.1 mequiv/g). The resin was suspended in 100 ml of dry THF and 11 ml of methyl disulfide was added with stirring. After 15 min at room temperature and 30 min at 65 °C, the resin was collected on a filter and washed successively with THF, ether, THF–water (2:1), water, THF, benzene, and finally methanol. After drying 8.64 g of resin IV was obtained.

Anal. S, 8.33 (2.6 mequiv/g); Br, none.

A similar resin has been prepared on macrocreticular Amberlite XE-305 by other workers.[13]

Preparation of Polymeric Boronic Acid V Ⓟ-$B(OH)_2$. Resin I was prepared from 15 g of brominated polystyrene (2.78 mequiv/g). The resin was suspended in 150 ml of dry THF and 18 ml of trimethyl borate was added. After stirring at room temperature overnight, the liquid phase was removed and the resin washed with THF. After addition of 140 ml of dioxane, 12 ml of water, and 36 ml of HCl, the mixture was heated to 60 °C with stirring for 1.5 h. The resin was then collected on a filter and washed repeatedly with dioxane–water (3:1), dioxane, acetone, and finally methanol. The dry resin weighed 12.96 g and its infrared spectrum included a large hydroxyl absorption.

Anal. B, 3.4 (3.15 mequiv/g).

A similar resin has been prepared in our laboratory[6] using Amberlite XE-305.

Preparation of Polymeric Amide VI Ⓟ-$CONHC_6H_5$. The lithiated resin was prepared from 1.91 g of brominated polystyrene (2.89 mequiv/g). The resin was swollen in 20 ml of dry benzene and 3 ml of phenyl isocyanate was added. After 15 min of stirring at room temperature, the mixture was stirred at 65 °C for 30 min. The resin was collected on a filter and washed successively with ethanol, THF, water, THF–water (2:1), THF, ether, and finally methanol. After drying, 2.13 g of VI was obtained. The infrared spectrum of VI showed a large carbonyl absorption at 1650 cm^{-1} and NH peaks at 3380 and 3300 cm^{-1}.

Anal. N, 3.04 (2.2 mequiv/g); Br, none.

Preparation of Silylated Polymer VII Ⓟ-$Si(CH_3)_2Cl$. Resin I was prepared from 2.46 g of brominated polystyrene (3.1 mequiv/g). The resin was suspended in 35 ml of dry benzene and 4 ml of dichlorodimethylsilane was added. After 45 min at room temperature, the polymer was collected on a filter and washed repeatedly with dry benzene to yield VII. Resin VII could be used directly without further purification (removal of lithium chloride). For analytical purposes the chloride was hydrolyzed to the corresponding silanol by addition of water in pyridine. After washing with pyridine, THF, THF–water (3:1), water, THF, benzene, and finally ether, the resin was dried under vacuum to yield 2.45 g of a resin which exhibited large hydroxyl absorptions at 3600 and 3380 cm^{-1}, and bands at 1250 (Si–C), 820 (Si–OH), 770 cm^{-1} (Si–C).

Anal. Si, 6.16 (2.2 mequiv/g).

Preparation of Polymeric Phosphine VIII Ⓟ-$P(C_6H_5)_2$. The lithiated resin was prepared from 2.49 g of brominated polystyrene (2.8 mequiv/g). The resin was suspended in 30 ml of dry THF and 5 ml of chlorodiphenylphosphine was added. After 1.75 h at room temperature the resin was collected on a filter and washed as above for IV. After drying the resin weighed 2.87 g.

Anal. P, 5.96 (1.92 mequiv/g); Br, none.

A polymer prepared by other workers[11] via a similar reaction sequence contained 0.7 mequiv P/g.

Preparation of Polymeric Bromide IX Ⓟ-CH_2CH_2Br. Resin I was prepared from 2.30 g of brominated polystyrene (1.76 mequiv/g). Resin I was added to a solution of 7 ml of 1,2-dibromoethane in 40 ml of dry benzene and the mixture was stirred at room temperature for 2.5 h. After filtration the resin was washed as described above for IV. After drying, 2.19 g of IX was obtained.

Anal. Br, 9.04 (1.13 mequiv/g).

Preparation of Polymeric Aldehyde X Ⓟ-CHO and Its Oxime XIII. Resin I was prepared from 2.6 g of brominated polystyrene (2.8 mequiv/g). The resin was suspended in 35 ml of dry THF and 5 ml of *N,N*-dimethylformamide was added with stirring. After 1.75 h at room temperature, the resin was collected on a filter and washed with THF–water (2:1), THF–water–HCl (8:2:1), water, THF–water (2:1), THF, and finally methanol. After drying, the resin weighed 2.25 g. The ir spectrum of X included absorptions at 2720 ad 1690 cm^{-1}.

For analytical purposes, the oxime XIII was prepared by reaction of 0.79 g of X with 1 g of hydroxylamine hydrochloride in 10 ml of pyridine. After 4 h at 90 °C, the resin was washed successively with pyridine, water, THF–water (2:1), THF, benzene, dichloromethane, and methanol. After drying, 0.8 g of resin XIII was obtained. The ir spectrum of XIII showed a large hydroxyl absorption at 3350 cm^{-1} and no residual carbonyl absorption.

Anal. N, 3.1 (2.2 mequiv/g).

The minimum degree of functionalization of X could be calculated from this analysis and corresponds to 2.3 mequiv of aldehyde functional group per gram.

Preparation of Polymeric Alcohol XI Ⓟ-CH_2CH_2OH and Its 3,5-Dinitrobenzoate XIV. Resin I was prepared from 1.73 g of brominated polystyrene (2.89 mequiv/g). The resin was suspended in 25 ml of dry THF at −50 °C and 8 ml of condensed ethylene oxide was added. The mixture was allowed to reach room temperature gradually (1 h) and the resin was collected on a filter, then washed successively with THF–water (3:1) THF–water–HCl (8:2:1), water, THF, methanol, and finally ether. After drying, the resin weighed 1.49 g and exhibited a large hydroxyl absorption in the ir spectrum.

For analytical purposes the 3,5-dinitrobenzoate XIV was prepared by reaction of 0.46 g of XI with 0.63 g of 3,5-dinitrobenzoyl chloride in 10 ml of dry pyridine. After 1.5 h at 85 °C, the resin was filtered and washed as described above to yield 0.66 g of XIV. The ir spectrum XIV included a large carbonyl absorption at 1730 cm^{-1}.

Anal. N, 5.07 (3.62 mequiv N/g). The minimum degree of functionalization of XI could be calculated from this analysis and corresponds to 2.80 mequiv of $-CH_2CH_2OH$ functional group per gram.

Preparation of Polymeric Alcohol XII Ⓟ-$C(C_6H_5)_2OH$ and Its Chloride XV. Resin I was prepared from 13 g of brominated polystyrene (2.8 mequiv/g). The lithiated resin was suspended in 100 ml of dry THF and 11 g of benzophenone in 40 ml of THF was added. An exothermic reaction occurred immediately. After 2 h at room temperature the resin was collected on a filter and washed as described above for IV. After drying under vacuum 14.24 g of XII was obtained. The ir of XII included large hydroxyl absorptions at 3430 and 3580 cm^{-1}. The degree of functionalization calculated from the gain in weight of the resin corresponds to 1.6 mequiv of functional group per gram. This is confirmed by the analysis of chloride XV which contains 1.4 mequiv of chlorine per gram. The preparation of chloride XV has been described previously.[5]

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Registry No.—Divinylbenzenestyrene copolymer, 9003-70-7; thallic acetate, 15843-14-8.

References and Notes

(1) A volume containing reprints of 62 important papers in this field has been published recently: E. C Blossey and D. C. Neckers, Ed., "Solid Phase Synthesis", Halsted Press, New York, N.Y., 1975.
(2) D. C. Neckers, *J. Chem. Educ.*, **52**, 695 (1975).
(3) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963).
(4) C. C. Leznoff, *Chem. Soc. Rev.*, **3**, 65 (1974).
(5) J. M. J. Fréchet and L. J. Nuyens, *Can. J. Chem.*, **54**, 926 (1976).
(6) E. Seymour and J. M. J. Fréchet, *Tetrahedron. Lett.*, 1149 (1976).
(7) C. U. Pittman, *Chem. Technol.*, 560 (1973).
(8) H. M. Relles and R. W. Schluenz, *J. Am. Chem. Soc.*, **96**, 6469 (1974).
(9) J. M. J. Fréchet and K. E. Haque, *Macromolecules*, **8**, 130 (1975).
(10) W. Heitz and R. Michels, *Makromol. Chem.*, **148**, 9 (1971).
(11) F. Camps, J. Castells, M. J. Fernando, and J. Font, *Tetrahedron Lett.*, 1713 (1971); J. Moreto, J. Albaiges, and F. Camps, *An. Quim.*, **70**, 638 (1974).
(12) N. M. Weinshenker, G. A. Crosby, and J. Y. Wong, *J. Org. Chem.*, **40**, 1966 (1975).
(13) G. A. Crosby, N. M. Weinshenker, and H. S. Uh, *J. Am. Chem. Soc.*, **97**, 2232 (1975).
(14) D. Braun, *Makromol. Chem.*, **30**, 85 (1959).
(15) A. J. Chalk, *J. Polym. Sci., Part B*, **6**, 649 (1968).
(16) D. C. Evans, L. Phillips, J. A. Barrie, and M. H. George, *J. Polym. Sci., Polym. Chem. Ed.*, **12**, 199 (1974).
(17) To effect complete removal of all the bromine from the macroreticular resin in tetrahydrofuran, two or three additions of an excess of butyllithium were required with removal of the liquid phase before addition of a new portion of solvent and reagent.
(18) J. M. J. Fréchet and C. Schuerch, *J. Am. Chem. Soc.*, **93**, 492 (1971).
(19) T. M. Fyles and C. C. Leznoff, *Can. J. Chem.*, **54**, 935 (1976).
(20) **Note Added in Proof.** The S–S bonds were removed by reduction with $LiAlH_4$ in THF to yield the polymeric thiol (2.9 mequiv of sulfur per gram) with a degree of functionalization of 0.34 (91% yield).

Competitive Sigmatropic Hydrogen Shifts in Bicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehydes[1]

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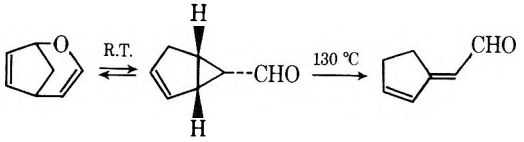
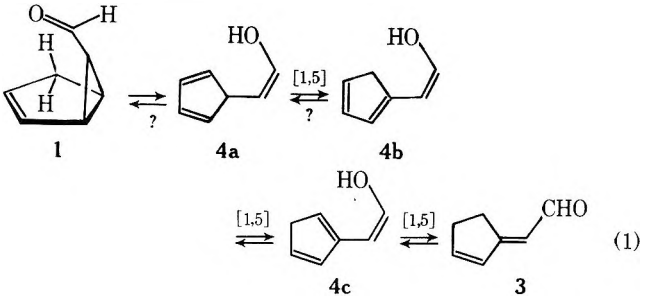
4-*exo*-Methyl- and 2-methylbicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (**1b** and **12**, respectively) each rearrange thermally to a mixture of (*E*)-2-methyl- and (*E*)-3-methyl-2-cyclopenten-1-ylideneacetaldehyde (**23** and **24**, respectively). The ratio of **24**:**23** obtained from **1b** is ~10, whereas that from **12** is ~0.2. Mechanistic evidence is presented that supports the conclusion that the formation of the mixture of aldehydes is a consequence of competition between concerted homodienyl [1,5] and homotrienyl [1,7] hydrogen migrations that initiate the reaction. The kinetic preference for the latter mode of rearrangement is rationalized on the basis of the relative energies of the molecular orbitals involved in the two different sigmatropic processes.

In 1968, Bickelhaupt et al.[2] reported that bicyclo[3.1.0]-hex-2-ene-6-*endo*-carboxaldehyde (**1**), which at ambient temperatures is in equilibrium with 2-oxabicyclo[3.2.1]octa-3,6-diene (**2**),[3] rearranged at elevated temperatures to (*E*)-2-cyclopenten-1-ylideneacetaldehyde (**3**). They provided



2 **1** **3**

evidence that the reaction proceeded by way of the sequence shown in eq 1 by trapping isomers **4b** and **4c** with dimethyl acetylenedicarboxylate. Furthermore, **4b** and **4c** could also

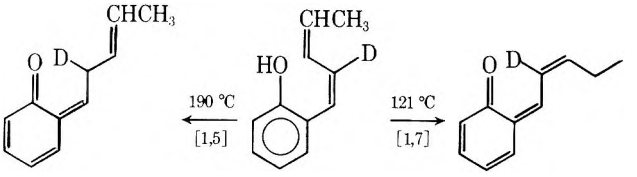


1 **4a** **4b** **4c** **3** (1)

be generated from **3**, demonstrating thereby the reversibility of the last two 1,5-hydrogen shifts.

At the time of their report, there existed ample precedent that suggested that the first step in the scheme, viz., conversion of **1** to **4a**, reasonably could occur via a homodienyl [1,5] hydrogen shift;[4] homotrienyl [1,7] hydrogen migrations were then unknown. However, it appeared to us that **1** might well be rearranging by competing homodienyl [1,5] and homotrienyl [1,7] sigmatropic pathways, even though orbital orientations (vide infra) might suppress the importance of the latter process.

There is a paucity of data in the literature that bears on the possible relationship between the rates of competing sigmatropic reactions of a specific type, e.g., hydrogen migration, and the respective orders of these reactions, although there is some evidence suggesting that the higher order pathway is kinetically favored.[5] Thus, the diene **5** appears to undergo [1,7] hydrogen migrations at 121 °C to produce **6**, but it is only after being heated to 190 °C that **5** can be induced to undergo a [1,5] hydrogen shift to produce **7**.[5a] Certainly to the extent that the transition state for a sigmatropic hydrogen migration can be characterized as a hydrogen atom interacting with the termini of the π system over which the transfer is occurring, and if other factors such as strain and steric effects are neglected,

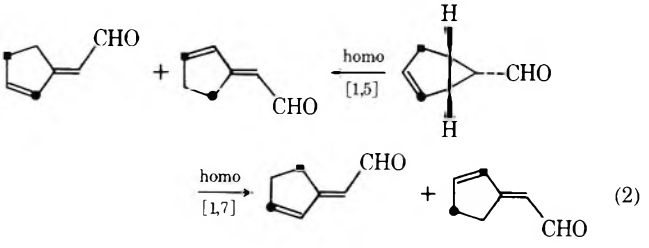


7 **5** **6**

molecular orbital theory would predict greater stability for the transition state affording the more delocalized π system. The obvious consequence of this is that for two competing processes of different order, the higher order pathway would be kinetically preferred.

There clearly are conformational factors as well as significant differences in product stabilities that hamper definitive interpretation of the meaning of the greater rate in **5** of the [1,7] hydrogen shift as compared to the [1,5] process. In this context, the possibility of the two analogous pathways operating in the rearrangement of **1** appeared all the more interesting because their existence would provide an excellent opportunity to evaluate the relative rates of competing sigmatropic reactions in a substrate in which gross steric and conformational factors, as far as can be evaluated from molecular models, were equivalent and in which differences in stabilities of initially formed products could be minimized. Thus an investigation was undertaken to test for the possible existence of competing modes of rearrangement of bicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehydes.

The conceptalization of derivatives of **1** appropriate for a differentiation of a homodienyl [1,5] from a homotrienyl [1,7] hydrogen migration in the ring-opening reaction described above is uncomplicated. Clearly, a label at either C-2 or C-4 (or at C-1 or C-5) would introduce the molecular asymmetry necessary to make the products of the two pathways distinct (eq 2). A methyl group was chosen as the label in this work



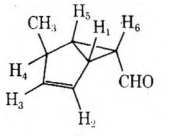
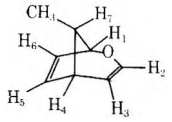
(2)

both to facilitate the synthesis of the desired substrates and to minimize perturbations in the basic bicyclic system.

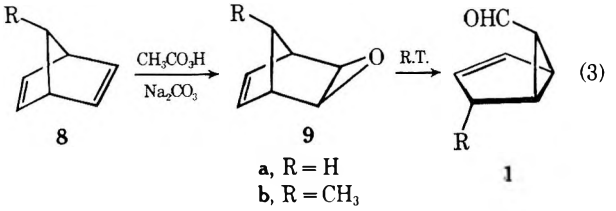
Results

Synthesis of Bicyclic Aldehydes. A facile entry into the bicyclo[3.1.0]hex-2-ene ring system has been reported by

Table I. ^{1}H NMR Data for 1b and 10

Compd	Chemical shift (δ), multiplicity [coupling constant, Hz]								
 1b	CH_3 1.10 d [7.0]	H_1 1.64–2.65 m	H_5	H_6	H_2 5.91 t [2.0]	H_3	H_4 2.85 dq [7.0, 2.0]	H_7 —	CHO 9.12 d [6.5]
 10	0.87 d [7.0]	4.42 bs	6.26 m	5.16 m	5.67 m	4.95 t [6.0]	2.0–2.65 m		

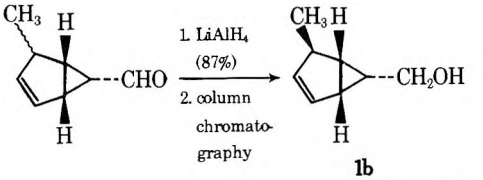
Meinwald et al.[6] These workers found that reaction of bicyclo[2.2.1]hepta-2,5-diene (**8a**) with buffered peroxyacetic acid afforded bicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (**1a**), and provided evidence that implicated the epoxide **9a** as the precursor to **1a** (eq 3).[7] It was felt that application of this reaction to 7-methylbicyclo[2.2.1]hepta-2,5-diene (**8b**) might initially provide **9b** which, in turn, would isomerize to a bicyclic aldehyde, viz., 4-*exo*-methylbicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (**1b**), suited to our purposes. Of course, such an outcome required that peroxidation occur not only stereoselectively exo but also regioselectively anti to the 7-methyl substitutent. The former requirement has ample precedent in Meinwald's work[6] as well as in that of others,[8] whereas the latter is supported by the observation that introduction of a *syn*-7-methyl group in the bicyclo[2.2.1]-hept-2-ene system retards the rate of epoxidation by a factor of ca. 100 relative to the unsubstituted compound.[9] Consequently, a synthetic approach to **1b** via **8b** appeared highly attractive.[10,12]



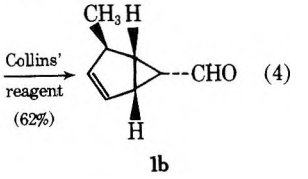
(3)

8 9 1

a, R = H
b, R = CH_3



1b

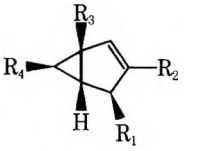


(4)

1b

In fact, peroxidation of **8b** afforded, in 62% yield, a 3:1 mixture of an aldehyde and two contaminants; we did not characterize the latter compounds, but they have been identified by Padwa and Koehn as the two endo epoxides that can be formed from **1b**.[11] Attempts at achieving separation of the crude reaction mixture by either GLC or column chromatography were unsuccessful owing to the extensive polymerization and/or decomposition that attended these techniques. Consequently, a chemical approach to purification was first developed, although it ultimately was discovered that the desired aldehyde could be isolated by low-temperature (−78 °C) fractional crystallization. The chemical sequence involved reduction of the reaction mixture with lithium aluminum hydride, column chromatographic isolation of the desired alcohol, and regeneration of the aldehyde function by oxidation with Collins' reagent (eq 4).[14] That structural rearrangement had not attended the purification sequence outlined in eq 4 was demonstrated by the identity of the ^{1}H NMR spectrum of the aldehyde isolated in this manner with that of the aldehyde obtained by low-temperature fractional crystalization.

The assignment of structure **1b** to the aldehyde is based on the method of synthesis and spectroscopic analyses. Although the complete data for the assignment are contained in the Experimental Section, a summary of the arguments will be presented here. The ^{1}H NMR spectrum of **1b** is consistent with that expected for bicyclo[3.1.0]hex-3-ene-6-*endo*-carboxaldehyde as resonances assignable both to it and to the homo-oxy Cope rearrangement product, **10**, expected[3,15] to be in equilibrium with it are present (Table I). Integration of the methyl resonances revealed a ratio of **1b**:**10** of 3. The endo configuration of the aldehyde moiety is assigned by analogy to the observations of Meinwald et al.[6] and of Klumpp et al.[3,15] by the shift upfield of the formyl proton of **1b** by 0.3 ppm relative to cyclopropanecarboxaldehydes,[16] as a result of the shielding effect of the double bond, and by the existence of the equilibrium between **1b** and **10**. Finally, the all-important assignment of the C-4 methyl group as exo is based on the following considerations: (1) Aldehyde **1b**, the major product of peracid oxidation of 7-methylbicyclo[2.2.1]hepta-2,5-diene (**8b**), is expected on stereochemical grounds to result from epoxidation anti to the 7-methyl group, the ultimate consequence of which is exo stereochemistry for the methyl group of **1b**. (2) The coupling constant, J_{H4-H5}, is 0–2 Hz, a magnitude in accord with that predicted from the Karplus equation[17] for vicinal coupling between hydrogens at a dihedral angle of ca. 90°, and a value observed in the closely analogous compounds, **11a**[18] and **11b**.[19] (3) The chemical shift of the methyl group is insensitive to the transformation of the functionality at C-6 from the alcohol (δ 1.0 ppm) to the aldehyde (δ 1.1 ppm) or the acetate (δ 1.0 ppm). (4) The propensity for thermal rearrangement (vide infra). All these data are in accord with structure **1b**.[20]

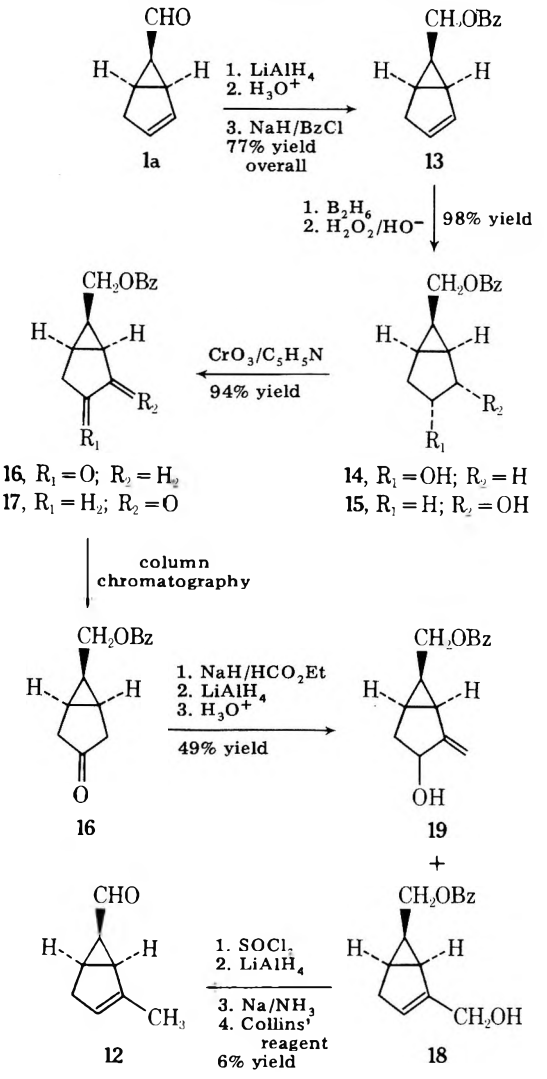


11

a, $R_1 = CH_3$; $R_3 = R_4 = H$; $R_2 = i$-Pr
b, $R_1 = R_2 = R_4 = Ph$; $R_3 = H$

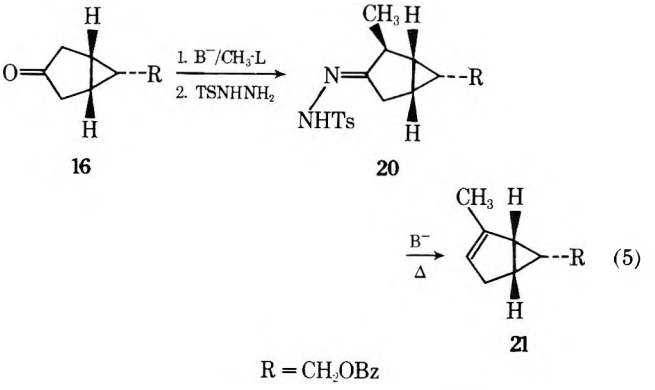
The considerably more complex scheme employed for synthesis of 2-methylbicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (**12**) is outlined in Chart I. The evidence sup-

Chart I. Synthesis of 2-Methylbicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (12)



porting the structural assignments is contained in the Experimental Section, and only some of the more salient features of the synthesis will be described here. The aldehyde moiety of **1a** was protected as the benzyl ether since attempts at acetal formation under either protic or aprotic conditions led, in our hands, to a variety of uncharacterized products. The hydroboration of **13** to produce a mixture of alcohols **14** and **15**[21] was, as anticipated,[22] somewhat regioselective as judged by ir and ^{1}H NMR spectra of the ketones **16** and **17** obtained from the alcohols by Sarett oxidation.[23] Thus, the major product had $\nu_{C=O}$ 1739 cm^{-1}, a value consistent with a nonconjugated cyclopentanone,[24] and possessed high molecular symmetry as adjudged from its ^{1}H NMR spectrum: the exo and endo protons at C-2 and C-4 were revealed as an AB quartet, J_{gem} = 19.5 Hz, and the low-field half of this quartet, which represents the exo protons, was split into a pair of doublets, J_{vic} = 5 Hz, by coupling with the protons on C-1 and C-5; furthermore, the C-7 protons showed magnetic equivalence, appearing as a sharp doublet. In contrast, the minor product had $\nu_{C=O}$ 1723 cm^{-1}, a frequency consonant with the presence of a five-membered ring ketone conjugated with a cyclopropane ring,[24] and provided a ^{1}H NMR spectrum devoid of evidence of molecular symmetry; e.g., the aliphatic protons at C-1, C-3, C-4, and C-5 appeared as a broad multiplet, and the diastereotopic protons at C-7 were now a broad, rather than sharp, doublet. Consequently, these data support the contention that the major product, present in a 2:1 ratio relative to **17**, was the desired ketone **16**. The ketones could be separated by either fractional distillation or column chromatography.

It had originally been envisioned that **16** could be transformed to a precursor, **21**, of **12** by alkylation followed by base-induced decomposition of the tosylhydrazone, **20** (eq 5).[25] However, our initial lack of success at monoalkylating

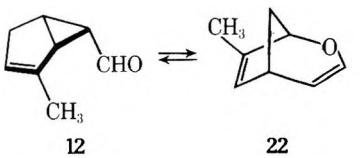


(5)

16 [*t*-BuO$^-$/MeOTs/DMF (polyalkylation) and Stork–Dowd imine alkylation[26] (lack of deprotonation of the imine suspected)] encouraged us to pursue the route shown in Chart I.[27] The ratio of allylic alcohols, **18** and **19**, formed by reduction of the α-hydroxymethylene ketone obtained from **16**, was ca. 9:1 as shown by integration of the vinylic and aromatic regions of the ^{1}H NMR spectrum of the crude mixture. Treatment of the mixture of alcohols with thionyl chloride followed by reduction with lithium aluminum hydride afforded **21** (eq 5) in 41% yield. In accord with the structure assignment, the ^{1}H NMR spectrum of **21** revealed an allylic methyl group at δ 1.75 as a broad singlet and a single vinyl proton at δ 4.4–5.2 ppm as a broad multiplet.

The deprotection of **21** was accomplished in 44% yield by reduction with sodium in liquid ammonia, and the resulting alcohol, without purification, was oxidized to the desired bicyclic aldehyde, **12**, with Collins' reagent.[14] The isolated **12** proved to be contaminated with ca. 20% of two other aldehydes as shown by ^{1}H NMR analysis, and owing to the sensitivity of **12** to mild acids, bases, and oxygen, further purification could not be achieved.

Evidence for the assignment of the aldehyde as 2-methylbicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (**12**) rests on spectral analysis and on the fact that **12** thermally rearranges to a mixture of the same two products as are obtained from the isomeric aldehyde **1b** (vide infra). In analogy with **1b** the ^{1}H NMR spectrum of **12** supports the existence of an equilibrium between the bicyclic aldehyde and its homo-oxy Cope isomer (**22**, eq 6) although the presence of impurities make an

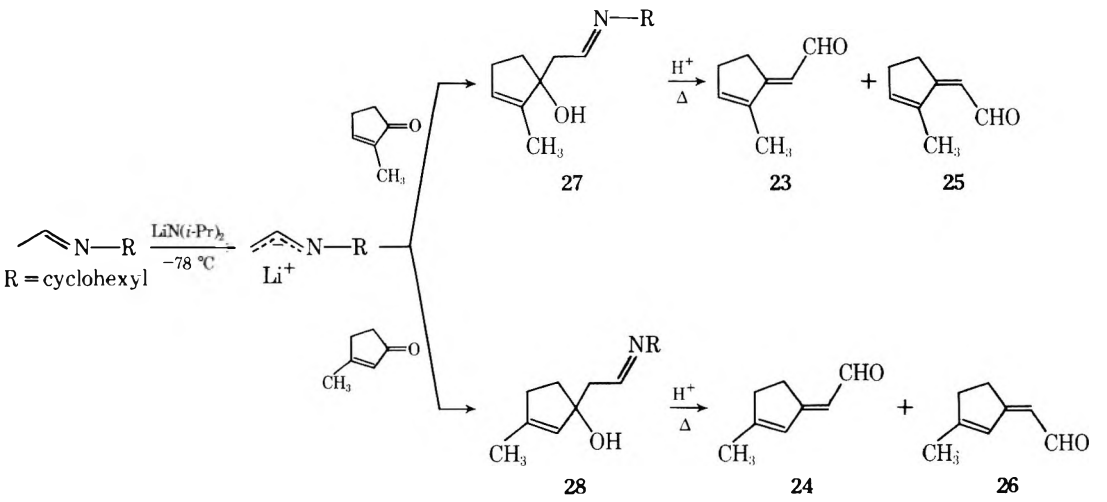


(6)

accurate assessment of the equilibrium impossible in this case. Thus, **12** is characterized by a doublet (J = 6.5 Hz) at δ 9.1 (CHO), narrow multiplets at δ 5.4 (vinyl) and 1.8 (methyl), and a broad, unresolved multiplet at δ 0.8–2.8 ppm, whereas **22** is revealed by multiplets at δ 4.6 (H_1), 5.0 (H_4), 5.7 (H_2), 6.0 (H_5); the H-4 and H-7 protons are buried in the broad multiplet centered at ca. δ 2 ppm.

Synthesis of Rearrangement Products. By analogy to the report of Bickelhaupt et al.,[2] the major products of the thermal rearrangement of aldehydes **1b** and **12** were anticipated to be (*E*)-2-methyl-2-cyclopenten-1-ylideneacetaldehyde (**23**) and (*E*)-3-methyl-2-cyclopenten-1-ylideneace-

Chart II. Synthesis of Expected Rearrangement Products



taldehyde (**24**), respectively. Authentic specimens of these two products were readily prepared by application of the "directed aldol condensation", developed by Wittig and Frommeld,[28] to 2- and 3-methylcyclopent-2-enone, respectively (Chart II). Thus treatment of these ketones with the anion of *N*-cyclohexylacetaldehydeimine afforded the corresponding β-hydroxy imines **27** and **28** in 70% yield. Hydrolysis and dehydration of these hydroxy imines and isolation of the resulting unsaturated aldehydes were accomplished in one step by steam distillation in the presence of oxalic acid.

Treatment of **27** in this manner afforded, in 55% yield, a mixture of two aldehydes in a ratio of ca. 90:10. The structure of the major component was tentatively assigned as the *E* isomer **23** on the expectation that the method of synthesis would provide the thermodynamically more stable isomer. ^{1}H NMR analysis of the reaction mixture supported this conclusion and provided evidence over and above the method of synthesis for the gross structure of **23**. Thus, the aldehydic proton appeared as a doublet at δ 9.78 (J = 7.5 Hz), the ring vinylic proton as a broad singlet at δ 6.00, the exocyclic vinylic proton as a doublet of triplets with fine splitting at δ 5.76 (J = 7.5, 2 Hz), and the remaining protons as multiplets at δ 2.70 (H_5), 3.20 (H_4), and 1.57 ppm (CH_3). The assignments were supported by decoupling experiments in the following way: saturation of the aldehydic resonance at δ 9.78 collapsed the resonance at δ 5.76 to a triplet; irradiation at this latter frequency converted the six-line multiplet at δ 3.20 to a lopsided triplet; and, finally, decoupling of the resonance at δ 3.20 considerably sharpened the broad singlet at δ 6.00 ppm. Furthermore, the resonance for the aldehydic proton of the minor isomer was deshielded by 0.06 ppm relative to the major component of the mixture. Such deshielding suggests that this aldehydic proton is in the deshielding cone of the double bond of the cyclopentyl ring, as would be expected if the minor isomer were assigned the *Z* configuration.

The analogous hydrolysis and dehydration of hydroxy imine **28** also yielded a mixture of two aldehydes in a ratio of ca. 60:40. The major isomer was again assigned the *E* configuration, i.e., structure **24**, on the basis that the aldehydic and vinylic protons were deshielded by 0.06 and 0.8 ppm, respectively, relative to the major isomer. Additionally, examinations of models suggested that there is less steric compression between the aldehyde moiety and the C-5 hydrogens of the ring than between the vinyl hydrogen of the ring and the aldehyde group.[29]

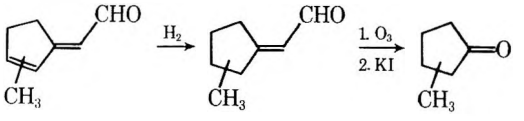
Thermal Rearrangements. A dilute solution of **1b** in a 9:1 mixture of hexane and tetrahydrofuran was first degassed and then heated in an evacuated, sealed Pyrex ampule at 160 °C for 12 h. Under these conditions, a 90% yield of rearranged aldehydes was obtained. That the product mixture was constituted of the α,β,γ,δ-unsaturated aldehydes **23** and **24** was shown by GLC and ^{1}H NMR analysis. Furthermore, integration of the areas of the respective GLC peaks showed that **23** predominated over **24** by a factor of ca. 9:1, a fact that was consonant with the observation that the ^{1}H NMR spectrum of the mixture was essentially superimposable with that of **23**.[30,31]

Table II. Analyses of Thermolysis Mixtures

Run	Substrate	Temp, °C[a]	Time, h	23, %	24, %
1[b]	**1b**	130	48	91	9
2[c]	**1b**	130	48	92	8
3[c]	**1b**	130	48	91	9
4[c]	**1b**	160	12	88	12
5[c]	**1b**	160	12	89	11
6[c]	**12**	130	48	18	82
7[b]	**24**	135	12	0	100[d]

[a] Temperature fluctuation during an individual run was ca. ±4 °C. [b] Analysis via hydrogenation–ozonolysis sequence with quantitation by GLC; maximum error is estimated to be ±1%. [c] Analysis via GLC; maximum error is estimated to be ±2%. [d] A small amount of polymerization was the only observable reaction.

Because the GLC peaks of **23** and **24** were broad and resolution of them was not complete, a second method of analysis of the thermolysis mixture was developed. This method involved catalytic hydrogenation of the more labile γ,δ π bond of the cyclopentene ring followed by reductive ozonolysis of the remaining double bond (eq 7). The mixture of 2- and 3-



(7)

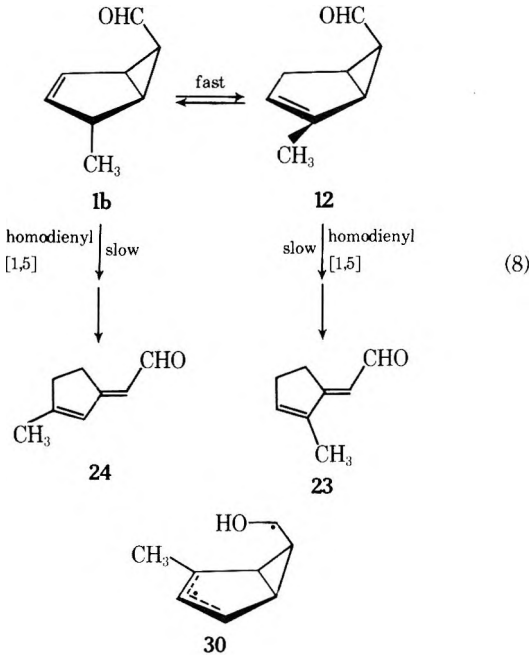
methylcyclopentanones (**29**) that resulted was then readily analyzed by GLC techniques. The results of this method of analysis as well as of the direct GLC analysis of the unsaturated aldehydes **23** and **24** are collected in Table II.

Runs 1–3 clearly illustrate the reproducibility of the analytical techniques, and runs 6 and 7 demonstrate that the rearrangement is under kinetic rather than thermodynamic control, i.e., equilibria of the type **1b** ⇄ **12** and **1** ⇄ **4a** (eq 1) are not established under the reaction conditions. The slight dependence of the product ratio on temperature is shown by runs 4 and 5.

Owing to the limited quantities of the isomeric starting aldehydes **1b** and **12**, an extensive investigation of the homogeneity of their thermal rearrangements was not possible. However, such studies were carried out on a model system, the unmethylated aldehyde **1a**. Thermolysis of **1a** under conditions identical with those used for rearrangement of **1b** and **12** except for addition of catalysts showed that both acidic (protic and aprotic) and basic (pyridine) catalysts promoted polymerization and rearrangement reactions that were not observed in the uncatalyzed thermal process. These observations, combined with the previously reported kinetic study of the rearrangement of **1a**,[1] support our belief that the thermal isomerizations of **1b** and **12** are homogeneous, unimolecular pocesses.

Discussion

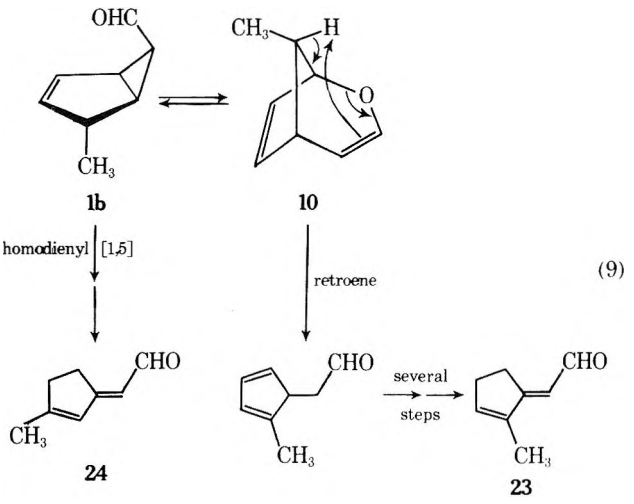
The observation of a mixture of aldehydes **23** and **24** upon thermolysis of **1b** (runs 1–5, Table II) can be rationalized mechanistically in several ways, as the following discussion illustrates; fortunately, our results appear consistent with only a single mechanistic concept. One possible mechanism invokes a rapid preequilibrium between **1b** and **12**, possibly via participation of the carbonyl oxygen, followed by rate-determining homodienyl [1,5] hydrogen shifts (eq 8). This pathway



(8)

to products is rendered untenable by comparison of the product ratios from runs 1–3 with that from run 6. Obviously, the proposal of this rapid preequilibrium would prompt the prediction that the ratio of **23** and **24** be essentially independent of whether **1b** or **12** was the starting aldehyde. This prediction is dramatically refuted by the results.

A second mechanism that accounts for formation of **23** and **24** from **1b** involves competition between a homodienyl [1,5] shift and an intramolecular retroene reaction from **10** (eq 9). However, examination of molecular models suggests that there is little, if any, overlap between the C-8 hydrogen atom of **10** and the π bond syn to it, whereas the C-4 hydrogen atom of **1b** can lie within the van der Waals radius of the carbonyl π bond. Yet the observed product radio would require the former process to dominate kinetically over the latter were this mechanism to be operating. Another factor that appears to militate against such a combination of processes is the considerable difference between the known energy of activation (42–45 kcal/mol)[32,33] of the retroene reaction that converts vinyl isopropyl ether to propane and acetaldehyde, and the



(9)

energy of activation of 29.3 kcal/mol reported for the conversion of **1a** to **3**.[1] The observed difference of some 13–17 kcal/mol in energies of activation cannot easily be accounted for by favorable strain or geometrical factors present in the bicyclic system relative to the acyclic model. Thus, although this more complex mechanism rationalizes the formation of the two aldehydes **23** and **24**, it appears to account neither for the ratio of the two products nor for the energy of activation for rearrangement of a substrate, **1a**, that is extremely analogous to **1b** and **12**.

The thermolysis results recorded in Table II, therefore, seem most appropriately interpreted as being the consequence of kinetically competitive homodienyl [1,5] and homotrienyl [1,7] hydrogen migrations. That the mode of opening of the cyclopropyl ring is kinetically controlled is shown by the fact that **1b** and **12** produce such markedly different ratios of products under identical reaction conditions and by the observation that one of the rearrangement products, **24**, is stable to the reaction conditions. It is possible, therefore, to exclude establishment of an equilibrium that interconverts **1** and **4a** (eq 1), a possibility that previously had been untested, and the intervention of which would make the reaction subject to thermodynamic control. Furthermore, the strong dependence of product ratio upon whether **1b** or **12** is the substrate for the thermolysis conclusively excludes the generation of common intermediates, e.g., **30**, that might be anticipated were the rearrangement to be stepwise in nature and supports the contention that the reaction is initiated by transfer of the endocyclic allylic proton to the carbonyl oxygen *in concert* with irreversible cyclopropyl ring opening.

Our data show the homotrienyl [1,7] hydrogen migration to be kinetically favored over the homodienyl [1,5] process by a factor of 8–10. If it is assumed that the preexponential factors for the two processes are identical, a reasonable assumption since the same geometry (see below) appears to be required for each reaction, then the [1,7] process is seen to be favored energetically by ca. 1.8 kcal/mol.

Evaluation of the basis for the energetic difference between the two pathways requires examination of the geometric and electronic features of their respective transition states. From consideration of molecular models as well as the overall course of the first step of the rearrangement (eq 1), the optimum ground state conformation for reaction is that depicted in Figure 1. As shown in Figure 1, the aldehyde moiety essentially bisects the [3.1.0] skeleton so that the aldehydic and C-6 hydrogen atoms are eclipsed, an orientation most conducive to double bond formation between their respective carbon atoms. This geometry also affords maximum overlap between the carbon–carbon bonds of the cyclopropane ring and the p orbital of the aldehydic carbon atom. An obvious consequence of this molecular geometry is that the endo hydrogen atom at

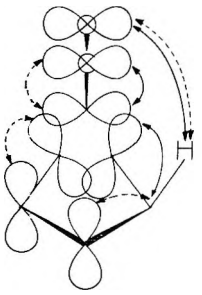


Figure 1. Reactive conformer of bicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde; orbital interactions shown for homo [1,5] (—) and homo [1,7] (- - -) hydrogen shifts (see text).

C-3 is transferred to the same lobe of the p orbital on oxygen independent of whether a homodienyl [1,5] or a homotrienyl [1,7] hydrogen shift is occurring. The same basic conformation, therefore, appears ideal for both modes of rearrangement observed in the bicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde system. According to this analysis, geometric factors do not account for the observed regioselectivity.

From the electronic standpoint, both modes of isomerization are "allowed" pericyclic transformations. As depicted with arrows in Figure 1, the homodienyl reaction can be characterized as $[_\sigma 4_s + _\pi 2_s]$ and the homotrienyl process as $[_\sigma 4_s + _\pi 2_s + _\pi 2_a]$.[34] The two isomerizations alternatively could be classified as having transition states corresponding to a Hückel ($4n + 2$) and a Möbius ($4n$) π-electron array, respectively, thereby fulfilling the requirement that thermally allowed reactions controlled by orbital symmetry possess aromatic transition states.[35,36]

Unfortunately, use of an argument based upon the relative delocalization energies of Hückel benzene and Möbius cyclooctatetraene to explain the preference for the homotrienyl process in our system is precluded by the absence of both theoretical and experimental data on the Möbius system. However, an alternate approach yields a clue to the origin of the differences in the energies of the transition states for the two competing modes of rearrangement.

This approach views the two transition states as possessing characteristics of the corresponding homodienyl or homotrienyl radicals. Although there are no experimental data available on the delocalization energies (DE) of such radicals, the estimated difference in DE between a dienyl and a trienyl radical is ca. 5 kcal/mol in favor of the latter species,[37] and some portion of this difference should apply to the corresponding homo species. Even if the full 5 kcal/mol difference applied, attenuation of this value to the 1.8 kcal/mol necessary to rationalize our results is consistent with the expectation that the transition state for hydrogen transfer with concomitant ring opening is anticipated to be more reactant- than productlike.[40]

The attenuation of the energy difference between trienyl and dienyl radicals, as measured by the ratios of products formed by homo [1,7] vs. homo [1,5] sigmatropic rearrangements in our bicyclic aldehydes, may also be partly a consequence of geometrical factors. As noted by Schakel and Klumpp,[41] the dihedral angle between the endo hydrogen atom at C-4 and the bent cyclopropyl bond between C-5 and C-6 is near 0° in the bicyclo[3.1.0] system (cf. Figure 1); this orientation of orbitals would appear to be stereoelectronically ideal for the simultaneous cleavage of these bonds, the process we believe to be occurring in the homodienyl [1,5] hydrogen shift. A similar analysis of the dihedral angle between the p orbital at C-2 and the C-1–C-6 cyclopropyl bond shows this angle as well as that between the endo hydrogen at C-4 and the p orbital at C-3 to be nonzero and leads to the conclusion that the geometries of bonds associated with the homotrienyl [1,7] process are less than ideal from a stereoelectronic standpoint. The consequence, then, is a narrowing of the energy gap between the two competing processes.[42]

It can be noted in passing that the data of Table II also suggest a slightly greater preference for the homotrienyl pathway in **1b** as compared to **12**. A potential rationale for this preference may lie in the fact that the 1,5-disubstituted cyclopentadiene initially arising from the homotrienyl rearrangement of **1b** is probably more stable than the 2,5-disubstituted cyclopentadiene resulting from the corresponding process in **12**.[43] The relative energies of the transition states for the homotrienyl rearrangement from **1b** and **12** may reflect this anticipated difference in stabilities of the products formed initially.

In conclusion, the thermal isomerization of 2-methyl- and of 4-*exo*-methylbicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (**1b** and **12**, respectively) leads to a mixture of (*E*)-2-methyl- and (*E*)-3-methyl-2-cyclopenten-1-ylideneacetaldehyde (**23** and **24**, respectively). A mechanistic analysis of these rearrangements supports the conclusion that there is a direct correlation between orbital energies and relative rates of closely analogous concerted reactions occurring via transition states having essentially identical geometries.

Experimental Section

Infrared spectra (ir) were obtained with a Beckman IR-5A spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were recorded with either a Varian Associates A-60 or HA-100 spectrometer; all spin decoupling was performed on the HA-100. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane at 0.00 ppm. Unless otherwise noted, ^{1}H NMR data are reported in the following manner: ppm downfield from Me_4Si, number of protons, multiplicity, absolute number of the coupling constant (if measurable), and the carbon atom(s) to which the hydrogen(s) are attached (if known). The solvents for ^{1}H NMR samples were carbon tetrachloride and deuteriochloroform.

All melting points and boiling points are uncorrected with the former being taken in open capillaries with Mel-Temp apparatus.

Gas–liquid phase chromatography (GLC) analyses were performed with a Varian Aerograph A-90-P3. Helium was used as the carrier gas at a flow rate of ca. 60 ml/min unless otherwise noted, and retention times were recorded with respect to air. The following columns were used: column A, 4 m × 0.25 in., 10% Carbowax 20M on 60/80 mesh Firebrick; column B, 4 m × 0.25 in., 30% SE-30 on 60/80 mesh Firebrick; column C, 1 m × 0.25 in., 15% FFAP on 60/80 mesh Chromosorb P (acid washed); column D, 4 m × 0.25 in., 15% FFAP on 60/80 mesh Chromosorb P (acid washed); column E, 6 ft × 0.25 in., 3% SE-30 on Aeropak 30.

Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz., and Galbraith Laboratories, Inc., Knoxville, Tenn.

4-*exo*-Methylbicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (1b). Oxidation of 7-Methylbicyclo[2.2.1]hepta-2,5-diene (8b).[45] A mixture of anhydrous sodium carbonate (24.3 g, 0.23 mol), dry methylene chloride (105 ml), and 7-methylbicyclo[2.2.1]hepta-2,5-diene (**8b**, 12.8 g, 0.12 mol) in benzene (approximately 12 ml) was cooled to ca. 5 °C, and peroxyacetic acid (40%, 14.5 ml, 0.09 mol), which contained anhydrous sodium acetate (0.5 g), was added at such a rate as to maintain the temperature below 15 °C. The reaction mixture was stirred for 2–3 h at room temperature (negative peroxide test) and filtered. After the filter cake was washed with methylene chloride, the filtrates were combined, dried, and concentrated in vacuo. The residue was fractionally distilled to give 6.8 g (62%) of a mixture of *exo*-methyl aldehyde, **1b**, bp 74–77 °C (30 mm), and two endo epoxides.[11]

Spectral data: ^{1}H NMR of mixture, four methyl doublets centered at δ 1.1 and 0.9 (exo aldehyde) and 1.0 and 0.83 (endo epoxides); ir 1692 cm^{-1}.

4-*exo*-Methyl-6-*endo*-hydroxymethylbicyclo[3.1.0]hex-2-ene. To a stirred slurry of lithium aluminum hydride (0.53 g, 14 mmol) in anhydrous ether (50 ml) was added the mixture from (6.8 g, 56 mmol) in anhydrous ether (25 ml). Hydrolysis was accomplished by the successive addition of water (1.6 ml), 15% sodium hydroxide (0.5 ml), and water (0.5 ml). The reaction mixture was filtered, and the filter cake was stirred with hot ethyl acetate and refiltered. The filtrates were combined and concentrated in vacuo. The light-colored residue was distilled to give 5.7 g (84%) of product alcohols, bp 68–88 °C (10

mm). The desired 4-*exo*-methyl alcohol was isolated by column chromatography with silica gel. Elution (100-ml fractions) was accomplished in the following manner.

Fractions 1–8, benzene, discard; 9–17, benzene–ether, 95:5, presumed endo epoxides (0.33 g); 18–20, benzene–ether, 95:5, 0.15 g of product. At this point the column was dismounted and its contents were extracted with ethyl acetate. The extracts were combined and concentrated in vacuo to give 4.3 g of the pure alcohol as established by GLC analysis (column A, 100 °C; column C, 100 °C; column E, 90 °C).

Spectral data: ^{1}H NMR δ 5.70 (2 H), bs [vinylic H]; 4.31 (1 H), bs [OH]; 3.30 (2 H), d, J = 7 Hz [$-CH_2O$]; 2.6–1.9 (2 H), bm [C_1–C_4 H]; 1.56–1.12 (2 H), m [C_5–C_6 H]; 1.0 (3 H), d, J = 7.0 Hz [CH_3]; ir 3400 cm^{-1} [OH].

Anal. Molecular ion, *m/e* 124.0889 (calcd for $C_8H_{12}O$, 124.0888). Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.60; H, 9.66.

Conversion of the 4-*exo*-methyl alcohol to its acetate was accomplished by addition of the alcohol (0.1 g, 8 mmol) to a solution of acetic anhydride (4 g, 40 mmol) in anhydrous pyridine (4 ml). After workup, the acetate was purified by vacuum line transfer (0.001 mm, 25 °C) and was found to be homogeneous by GLC analysis (column A, 100 °C; column C, 90 °C; column E, 90 °C).

Spectral data: ^{1}H NMR δ 5.6 (2 H), bs [vinylic H]; 3.81 (2 H), d, wfs, J = 7.5 Hz [$-CH_2O$]: 2.6–1.9 (2 H), bm [C_1–C_4 H]; 1.6–1.2 (2 H), m [C_5–C_6 H]; 1.92 (3 H), s [$CH_3C{=}O$]; 1.03 (3 H), d, J = 7.0 Hz [CH_3C_4].

4-*exo*-Methylbicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (1b). The 4-*exo*-methyl alcohol (0.62 g, 5 mmol), dissolved in methylene chloride, was added dropwise (10–15 min) to a suspension of Collins' reagent[14] (10 g, 36 mmol) in anhydrous methylene chloride (200 ml). The reaction mixture was allowed to stir for an additional 30 min and was filtered. The dark filtrate was washed successively with water, 0.3 N hydrochloric acid, and saturated brine solution and concentrated in vacuo. The light brown residue was purified by vacuum line transfer to yield 0.38 g (62%) of aldehyde which was found to be subject to polymerization at room temperature.

Spectral data: ^{1}H NMR for **1b** δ 9.12 (1 H), $J \simeq$ 6.5 Hz, d [HC=O]; 5.91 (2 H), unresolved t [vinylic H]; 2.86 (1 H), dq, wfs, $J_{H_6CH_3}$ = 7.0, $J_{4,5}$ = 0–2.5 Hz [C_4 H]; 1.45–2.7 (3 H), m [C_1, C_5, C_6 H]; 1.1 (3 H), d, J = 7.0 Hz [CH_3]. Ir 1692 cm^{-1} [C=O]. ^{1}H NMR for **7** δ 6.26 (1 H), m [C_6 H]; 5.67 (1 H), m [C_3 H]; 5.16 (1 H), m [C_7 H]; 4.95 (1 H), t, J = 6 Hz [C_4 H]; 4.42 (1 H), bs [C_1 H]; 2.0–2.65 (2 H), m [C_5, C_8 H]; 0.87 (3 H), d, J = 7 Hz [CH_3].

At ambient temperatures, the ratio of **1b** to **7** was found to be 3:1 by integration of the respective methyl doublets.

2-Methylbicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (12). 6-*endo*-Hydroxymethylbicyclo[3.1.0]hex-2-ene. Bicyclo-[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (**1a**,[6] 12.6 g, 117 mmol) was reduced with lithium aluminum hydride (1.11 g, 29.2 mmol) according to the procedure described above. Distillation provided 8.1 g (87%) of the alcohol, bp 83–85 °C (13 mm).

Spectral data: ^{1}H NMR δ 5.58 (2 H), tt [vinylic H]; 3.83 (1 H), bs ν [OH]; 3.32 (2 H), d, $J_{6,7}$ = 7.5 Hz [C_7 H]; 2.8–0.9 (5 H), m [C_1, C_4, C_5, C_6 H]; ir 3450 cm^{-1} [OH].

6-*endo*-Benzyloxymethylbicyclo[3.1.0]hex-2-ene (13). Benzylation was accomplished by a modification of the procedure of Tate and Bishop.[46] The alcohol **10** (8.1 g, 81 mmol) was added dropwise over ca. 10 min to a slurry of sodium hydride (5.6 g, 260 mmol) and anhydrous benzyl chloride (130 ml). After the addition was complete, the reaction mixture was heated to 120 °C and stirred for 3 h. After filtration of the reaction mixture and extraction of the filter cake with hexane, the combined filtrates were concentrated under reduced pressure. Fractional distillation of the residue afforded the product (89%), bp 88–90 °C (0.5 mm), which was contaminated with a small amount of benzyl chloride (GLC analysis, column E, 150 °C).

Spectral data: ^{1}H NMR δ 7.2 (5H), s [ArH]; 5.7–5.32 (2 H), m [vinylic H]; 4.36 (2 H), s [$-CH_2Ar$]; 3.21 (2 H), d, $J \simeq$ 7 Hz [CH_2O]; 2.43–0.9 (5 H), bm [remaining H].

6-*endo*-Benzyloxymethylbicyclo[3.1.0]hexan-3-ol (14) and 6-*endo*-Benzyloxymethylbicyclo[3.1.0]hexan-2-ol (15). Diborane was produced by the dropwise addition of sodium borohydride (9.7 g, 256 mmol) in diglyme (270 ml) to a solution of boron trifluoride etherate (65.5 ml, 512 mmol) in diglyme (60 ml).[47] The diborane generated was carried via a stream of nitrogen into an ice-cold solution of the alkene (113.5 g, 567 mmol) in anhydrous THF (250 ml).

The reaction mixture was stirred for 10 h at room temperature and then was hydrolyzed by successive addition of water (55 ml), 3 N sodium hydroxide (88 ml), and 30% hydrogen peroxide (88 ml), while the temperature was maintained at 30–50 °C. Ether (200 ml) was added, and the reaction mixture was stirred for an additional 1 hr. The ethereal layer was decanted, and the aqueous layer was extracted with ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated (aspirator) to yield 121.3 g (98%) of an oily residue which was not further purified: ^{1}H NMR, no vinylic protons.

6-*endo*-Benzyloxymethylbicyclo[3.1.0]hex-3-one (16) and 6-*endo*-Benzyloxymethylbicyclo[3.1.0]hex-2-one (17). The alcohols **14** and **15** (121.3 g, 567 mmol), dissolved in anhydrous pyridine (114 ml), were added in one portion to a mixture of chromic anhydride (114 g, 1.14 mol) and pyridine (1200 ml)[23] contained in a 2-l. Erlenmeyer, and the reaction mixture was stirred for 12 h. Ethyl acetate (500 ml) was added to precipitate the chromium salts. After an additional 0.5 h of stirring, the reaction mixture was filtered through a bed of Celite, and the filtrate was concentrated in vacuo to a volume of ca. 150 ml. The concentrate was dissolved in ether and washed successively with 3 N hydrochloric acid, 5% sodium bicarbonate, and brine solution. The ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The light-colored residue was distilled through a 10-cm Vigreux and the fraction with bp 102–130 °C (0.01 mm) was collected, 113 g (94%). However, this fraction was contaminated with some low-boiling components and contained approximately a 2:1 mixture of **16** (3-one) to **17** (2-one) as shown by GLC analysis (colunm E, 175 °C).

By repeated fractional distillation, the major product (**16**) was obtained in greater than 90% purity, 20 g, bp 130–131 °C (0.01 mm); the boiling point of **17** was higher, 132–137 °C (0.01 mm).

Separation of the two ketones was also effected by column chromatography on silica gel (50 g per gram of crude ketone) when the column was eluted in the following manner (100-ml fractions).

Fractions 1–6, benzene, discard; 7–9, benzene–ether (90:10), discard; 10–11.5, benzene–ether (85:15), 3-one (1.2 g); 11.5–12.5, benzene–ether (75:25), mixture of 3-one and 2-one (0.2 g) (2:1); 12.5–14, benzene–ether (75:25), 2-one (0.26 g).

Spectral data: ^{1}H NMR of **16** δ 7.2 (5 H), s [ArH]; 4.35 (2 H), s [benzylic H]; 3.21 (2 H), d, $J \simeq$ 7.5 Hz [CH_2O]; 2.41 (2 H), dd, wfs, $J_{gem} \simeq$ 22.4, $\Delta\nu_{gem} \simeq$ 22.4, $J_{vic} \simeq$ 5 Hz [exo C_2, C_4 H); 2.03 (2 H), d, J_{gem} = 19.5, $J_{vic} \simeq$ O Hz [endo C_2, C_4 H]; 1.9–0.9 (3 H), m [cyclopropyl H].

Anal. Molecular ion, *m/e* 216.1146 (calcd for $C_{14}H_{16}O_2$, 216.1150). Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.59; H, 7.75.

Spectral data: ^{1}H NMR of **17** δ 7.21 (5 H), s [ArH]; 4.43 (2 H), s [benzylic H]; 3.47 (2 H), bd, $J \simeq$ 7.5 Hz [CH_2O]; 2.4–1.2 (7 H), bm [remaining H]; ir (mixture) 1739 [3-one], 1723 cm^{-1} [2-one].

2-Hydroxymethylene-6-*endo*-benzyloxymethylbicyclo-[3.1.0]hex-3-one. A modification of the procedure of Weisenborn, Remy, and Jacobs was used for hydroxymethylation,[48] Anhydrous benzene (500 ml), purified ethyl formate (33 g, 45 mmol), and sodium hydride (4.35 g, 180 mmol) were combined, and the ketone **16** (19.2 g, 89 mmol), dissolved in benzene (100 ml), was added dropwise. The resulting reaction mixture was allowed to stir under a static nitrogen atmosphere for 2 days. Excess sodium hydride was destroyed by addition of methanol (20 ml) in ether (100 ml). Water was added until all suspended solids were in solution, and the organic layer was decanted. Following extraction of the aqueous layer with ether, it was neutralized (pH 5) with 6 N hydrochloric acid and extracted with ether. The ethereal layer was washed with saturated brine, dried (Na_2SO_4), and concentrated to give an oily residue (21.7 g, 98%) that was used without further purification.

Spectral data: ir 3560–2500 and 1725–1640 cm^{-1} [hydroxymethylene ketone].

2-Hydroxymethyl-6-*endo*-benzyloxymethylbicyclo[3.1.0]-hex-2-ene (18) and 2-Methylene-6-*endo*-benzyloxymethylbicyclo[3.1.0]hexan-3-ol (19). The hydroxymethylene ketone (21.8 g, 89 mmol) in anhydrous ether (100 ml) was added dropwise to a slurry of lithium aluminum hydride (8.64 g, 220 mmol) in anhydrous ether (1 l.). After the addition was complete, the reaction mixture was stirred and heated at reflux for 8 h. Hydrolysis and workup yielded 10 g (49%) of an oily mixture of the alcohols **18** and **19** which resisted further purification.

Spectral data: ^{1}H NMR δ 5.1 [1 H], m [vinylic H]; ir 3420 [OH], 1653 and 1625 cm^{-1} [C=C].

2-Chloromethyl-6-*endo*-benzyloxymethylbicyclo[3.1.0]-hex-2-ene. The crude alcohols **18** and **19** (10 g, 43 mmol) in ether (25 ml) were added dropwise to a stirred solution of purified thionyl chloride (6.62 g, 55.6 mmol) and anhydrous ether (25 ml). After stirring the solution for 1 h, the ether was removed under reduced pressure, and the residue was subjected to a vacuum of 0.01 mm to remove trace amounts of volatile impurities. The crude product was used immediately in the next step: ir, disappearance of OH stretch.

2-Methyl-6-*endo*-benzyloxymethylbicyclo[3.1.0]hex-2-ene. The procedure of White and Gupta[27] was modified by the use of tet-

rahydrofuran rather than diisopropyl ether as solvent. The chloride(s) from above (0.043 mmol) was reduced with lithium aluminum hydride to yield, after short-path distillation, 3.8 g (41%) of products, bp 89–130 °C (0.08 mm), which was used directly in the next step.

Spectral data: ^{1}H NMR δ 7.21 (5 H), s [ArH]; 5.2–4.9 (1 H), bm [vinylic H]; 4.38 (2 H), s [OCH_2]; 1.75 (3 H), bs [allylic methyl].

2-Methyl-6-*endo*-hydroxymethylbicyclo[3.1.0]hex-2-ene. The benzyl ether (3.8 g, 14.8 mmol) in anhydrous ether (10 ml) was added to 300 ml of liquid ammonia. Sodium (1.2 g, 50 mg-atoms) was added, and the reaction mixture was stirred for ca. 30 min. The deep blue color was discharged by the dropwise addition of methanol, and the ammonia was allowed to evaporate.

Pentane (50 ml) and water (100 ml) were added to the residue, and the layers were separated. The aqueous layer was extracted with ether, and the organic extracts were combined, washed with saturated brine solution, dried (sodium sulfate), and concentrated. The residue was distilled to give 1.7 g of a colorless liquid, bp 65–99 °C (10 mm). The liquid was purified by GLC (column C, 100 °C) to give 420 mg of product (44%).

Spectral data: ^{1}H NMR δ 5.33–5.00 (1 H), m [vinylic H]; 3.81 (1 H), bs [OH]; 3.31 (2 H), m [CH_2O]; 1.8–1.6 (3 H), m [allylic methyl]; 0.8–2.7 (5 H), m [remaining H].

2-Methylbicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (12). 2-Methyl-6-*endo*-hydroxymethylbicyclo[3.1.0]hex-2-ene (0.21 g, 2 mmol) was oxidized with Collins' reagent[14] (3.3 g) in methylene chloride according to the procedure described previously. The aldehyde **12** was purified by vacuum transfer (0.001 mm) at room temperature to give 65 mg of crude product, estimated to be ca. 80% pure by ^{1}H NMR analysis.

Spectral data: ^{1}H NMR δ 9.2 (1 H), d, $J \simeq 6.5$ Hz [CHO]; 5.4 (1 H), m [vinylic proton]; 1.8 (3 H), m [allylic methyl]; 2.8–0.8 (5 H), bm [remaining H].

^{1}H NMR for 7-methyl-2-oxabicyclo[3.2.1]octa-3,6-diene (**22**): δ 5.95 (1 H), m [C_6H]; 5.71 (1 H), m [C_3 H]; 5.0 (1 H), m [C_4H]; 4.6 (1 H), m [C_1 H]; 1.9 (3 H), m [allylic methyl]; 2.8–0.8 (2 H), m [C_5, C_8 H].

(*E*)- and (*Z*)-2-Methyl-2-cyclopenten-1-ylideneacetaldehyde (23 and 25). Diisopropylamine (2.0 g, 0.02 mol) in ether (10 ml) was slowly added to an ice-cold solution of anhydrous ether (40 ml) and methyllithium (11.8 ml of 1.7 M in ether, 0.02 mol). Acetaldehyde cyclohexylimine[28] (2.5 g, 20 mmol) in ether (5 ml) was added, the resulting solution was cooled to −78 °C, and 2-methyl-2-cyclopenten-1-one[49] (1.9 g, 20 mmol) in ether (10 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 12 h. Hydrolysis of the reaction mixture, followed by concentration of the organic layer provided 3.3 (75%) of the hydroxy imine **27** as a viscous oil.

A portion of this oil (1.0 g, 4.5 mmol) was dissolved in ether (50 ml), and the ethereal solution was added to oxalic acid (10 g) and water (50 ml); the mixture was rapidly steam distilled. The distillate was saturated with salt and extracted with ether. The extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Low temperature crystallization (approximately −78 °C) from ten volumes of ether provided 0.3 g (55%) of the desired aldehydes. GLC analysis (column C, 135 °C) revealed the presence of a two-component mixture with overlapping peaks with the minor isomer 25 being eluted first. The ratio of **23** to **25** was approximately 92:8.

Spectral data: ^{1}H NMR (HA-100) δ 9.78 (1 H), d: J = 7.5 Hz [CHO]; 6.00 (1 H), bs [vinylic H of cyclopentene ring]; 5.76 (1 H), dt wfs, J = 7.5, 2 Hz [vinylic H of *exo*-methylene]; 2.70 (2 H), 6-line m [H at C-5 of cyclopentene ring]; 3.20 (2 H), 6-line m [H at C-4 of cyclopentene ring]; 1.57 (3 H), 6-line m [CH_3].

(*E*)- and (*Z*)-3-Methyl-2-cyclopenten-1-ylideneacetaldehyde (24 and 26). A mixture of the aldehydes **24** and **26** was prepared from 3-methyl-2-cyclopenten-1-one[50] (20 mmol) in an overall yield of 57% by the procedure previously described for the preparation of **20** and **22**. Low temperature crystallization at ca. −78 °C from ten volumes of ether provided the two aldehydes as a low-melting (ca. 25 °C) solid which polymerized readily upon exposure to air. GLC analysis (column C, 132 °C) indicated that the ratio of **24** to **26** was approximately 60:40.

Spectral data: ^{1}H NMR of **24** δ 9.75 (1 H), d, $J \simeq 7.0$ Hz [aldehydic H]; 6.16–6.02 (1 H), m [vinylic H of cyclopentene ring]; 5.92–5.68 (1 H), m [vinylic H of *exo*-methylene]; 3.18–2.38 (4 H), m [CH_2 of cyclopentene ring]; 2.05 (3 H), bs [CH_3]. ^{1}H NMR of **26** δ 9.81 (1 H), d, $J \simeq 7.0$ Hz [aldehydic H]; 7.00–6.80 (1 H), m [vinylic H of cyclopentene ring]; 5.68–5.50 (1 H), m [vinylic H of *exo*-methylene]; 3.18–2.38 (4 H), m [CH_2 of cyclopentene ring]; 2.05 (3 H), bs [CH_3].

Thermal Rearrangements and Product Analyses. Thermolyses of **1b**, **12**, and **23** were conducted on degassed samples contained in sealed Pyrex glass ampules which were heated in an aluminum-tube oven controlled by a variable transformer. The temperature of the oven fluctuated by no more than 3–4 °C during the course of thermolysis once equilibrium temperature had been established.

Thermolysis of 4-*exo*-Methylbicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (1b). The thermolyses were conducted on dilute, degassed solutions of **1b** (0.5%) in hexane–tetrahydrofuran (10:1). The thermal rearrangements were conducted at 130 ± 3 and 160 ± 4 °C for 48 and 12 h, respectively.

After opening of the ampules and removal of solvent, the oily residue was purified by vacuum line transfer at room temperature (0.001 mm) to provide **23** and **24** in a yield of 90%. Analysis of the purified products was accomplished by GLC (column C, 140 °C). The products were shown to be identical with authentic samples by comparison of relative GLC retention times. Furthermore, the ^{1}H NMR spectrum of the mixture resulting from the thermolysis of **1b** at 130 °C was found to be virtually superimposable with the spectrum of an authentic sample of the 2-methyl aldehyde **23**.

Degradation of the Thermal Rearrangement Products 23 and 24. The mixture of rearranged aldehydes **23** and **24** (325 mg, 2.66 mmol) in 5 ml of ethyl acetate was hydrogenated over 10% palladium on charcoal (30 mg). After 1 equiv of hydrogen had been consumed, the solution was filtered and the filtrate was concentrated to give the α,β-unsaturated aldehydes (324 mg) in a yield of 98%.

A solution of these aldehydes (324 mg, 2.61 mmol) in chloroform–methanol was ozonized at −10 °C. The ozonolysis mixture was acidified with glacial acetic acid and reduced with excess potassium iodide solution. After reduction of liberated iodine with sodium thiosulfate, and extraction of the aqueous layer with pentane, the organic extracts were combined, dried ($MgSO_4$), and concentrated at −10 °C under aspirator vacuum to yield a mixture of 2- and 3-methylcyclopentanone (**29**). Preparative GLC (column D at 100 °C) provided pure samples of the ketones. The ir spectra of these products were superimposable with the ir spectra of authentic samples.[51] GLC retention times of these products were identical with those of authentic samples.

Thermolysis of 2-Methylbicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (12). A degassed solution of **12** in hexane–tetrahydrofuran (10:1) was heated at 130 °C for 48 h. Removal of the solvent and purification of the residue by vacuum line transfer provided the two rearrangement aldehydes **23** and **24** which were quantitated by GLC (column C, 140 °C).

Thermolysis of 3-Methyl-2-cyclopenten-1-ylideneacetaldehyde (24). A degassed solution of **24** (0.5%) in hexane–tetrahydrofuran was heated at 135 °C for 12 h. This resulted in the formation of a small amount of polymer, but in no isomerization to **23** as evidenced by GLC analysis (column C, 140 °C).

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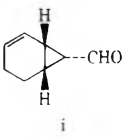
Registry No.—**1a**, 4729-05-9; **1b**, 35391-55-0; **7**, 60153-50-6; **8b**, 13437-93-9; **10**, 60153-51-7; **12**, 35391-56-1; **13**, 60153-52-8; **14**, 60153-53-9; **15**, 60153-54-0; **16**, 60153-55-1; **17**, 60153-56-2; **18**, 60153-57-3; **19**, 60153-58-4; **22**, 60153-59-5; **23**, 41828-82-4; **24**, 60153-60-8; **25**, 60153-61-9; **26**, 60153-62-0; **27**, 60153-63-1; 4-*exo*-methyl-6-*endo*-hydroxymethylbicyclo[3.1.0]hex-2-ene, 60153-64-2; 4-*exo*-methyl-6-*endo*-hydroxymethylbicyclo[3.1.0]hex-2-ene acetate, 60153-65-3; 2-hydroxymethylene-6-*endo*-benzyloxymethylbicyclo[3.1.0]hex-3-one, 60153-66-4; 2-chloromethyl-6-*endo*-benzyloxymethylbicyclo[3.1.0]hex-2-ene, 60153-67-5; 2-methyl-6-*endo*-benzyloxymethylbicyclo[3.1.0]hex-2-ene, 60153-68-6; 2-methyl-6-*endo*-hydroxymethylbicyclo[3.1.0]hex-2-ene, 60153-69-7; acetaldehyde cyclohexylimine, 1193-93-7; 2-methyl-2-cyclopenten-1-one, 1120-73-6; 3-methyl-2-cyclopenten-1-one, 2758-18-1.

References and Notes

(1) A preliminary account of this work has appeared: J. C. Gilbert, K. R. Smith, G. W. Klumpp, and M. Schakel, *Tetrahedron Lett.*, 125 (1972).
(2) F. Bickelhaupt, W. L. deGraaf, and G. W. Klumpp, *Chem. Commun.*, 53 (1968).
(3) M. Rey and A. S. Dreiding, *Helv. Chim. Acta*, **48**, 1985 (1965).
(4) H. M. Frey and R. Walsh, *Chem. Rev.*, **69**, 103 (1969), and references cited therein.
(5) (a) H. Heimgartner, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **53**, 173 (1970); (b) C. J. Gaasbeek, H. Hogeveen, and H. C. Volger, *Recl. Trav. Chim. Pays-Bas*, **91**, 821 (1972).
(6) J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Am. Chem. Soc.*, **85**, 582 (1963).
(7) J. Meinwald, S. S. Labana, and G. H. Wahl, *Tetrahedron Lett.*, 1789 (1965).
(8) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, and references cited therein.

(9) H. C. Brown, J. H. Kawakami, and S. Ikegami, *J. Am. Chem. Soc.*, **92,** 6914 (1970).
(10) These same considerations for predicting the regioselectivity of peroxidation of **8b** have been noted by Padwa et al.[11]
(11) A. Padwa and W. Koehn, *J. Org. Chem.*, **23,** 4007 (1973).
(12) Epoxidation of 7-*tert*-butoxybicyclo[2.2.1]hepta-2,5-diene (**8,** R = *t*-BuO) apparently occurs regioselectively syn to the 7 substituent, as evidenced by the formation of 3-*endo*-*tert*-butoxybicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde (**1,** R = *endo*-*t*-BuO);[13] however, the selectivity is undoubtedly a consequence of complexation of the peracid by the ethereal oxygen prior to expoxidation.
(13) G. W. Klumpp, A. H. Veefkind, W. L. de Graaf, and F. Bickelhaupt, *Justus Liebigs Ann. Chem.*, **706,** 47 (1967).
(14) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).
(15) G. W. Klumpp, J. W. F. K. Barnick, A. H. Veefkind, and F. Bickelhaupt, *Recl. Trav. Chim. Pays-Bas,* **88,** 766 (1969).
(16) J. Wiemann, N. Thoai, and F. Weisbuch, *Bull. Soc. Chim. Fr.* 2187 (1964).
(17) M. Karplus, *J. Chem. Phys.*, **30,** 11 (1969).
(18) W. von E. Doering and E. K. G. Schmidt, *Tetrahedron*, **27,** 2005 (1971).
(19) A. Padwa and S. Clough, *J. Am. Chem. Soc.*, **92,** 5308 (1970).
(20) Padwa and Koehn have also assigned structure **1b** to the aldehyde arising from peroxidation of **8b**;[11] however, the spectral data they report do not allow an unambiguous assignment of stereochemistry of the C-4 methyl group.
(21) The exo stereochemistry of the hydroxyl function was not rigorously demonstrated but is assigned by analogy.[19]
(22) H. E. Zimmerman, D. S. Crumrine, D. Dopp, and P. A. Huyffer, *J. Am. Chem. Soc.*, **91,** 434 (1969).
(23) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75,** 422 (1953).
(24) K. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, San Francisco, Calif., 1962.
(25) See ref 18 for examples of tosylhydrazone decomposition in the bicyclo[3.1.0]hexan-3-one system.
(26) G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85,** 2178 (1963).
(27) This sequence is based on the procedure devised by White and Gupta for the conversion of α-hydroxymethylene ketones to methyl-substituted alkenes J. D. White and D. N. Gupta, *J. Am. Chem. Soc.*, **90,** 6171 (1968).
(28) G. Wittig and F. Frommeld, *Chem. Ber.*, **97,** 3548 (1964).
(29) Some further support for the configurational assignment is the report that in $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes the trans,cis isomer is thermodynamically more stable than the cis,cis isomer: A. Viola and J. H. MacMillan, *J. Am. Chem. Soc.*, **92,** 2404 (1970).
(30) Aldehyde **23** was also reported by Padwa and Koehn as the major thermolysis product from **1b.**[11]
(31) In addition to **23** and **24,** six other cyclopentenylideneacetaldehydes potentially could be formed in the thermolysis of **1b.** These other isomers appear from analysis of the ^{1}H NMR spectrum of the thermolysis mixture to be present in trace amounts, if at all. For example, the only evidence that the 4- and 5-methyl-2-cyclopentenylidenyl isomers, the two most likely additional products, were present lies in a low intensity multiplet at δ 0.9–1.2 ppm in the ^{1}H NMR spectrum.
(32) T. O. Bamkole and E. U. Emovan, *J. Chem. Soc. B,* 332 (1968).
(33) A. T. Blades, *Can. J. Chem.*, **31,** 418 (1953).
(34) R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1970.
(35) H. E. Zimmerman, *Acc. Chem. Res.*, **4,** 272 (1971).
(36) M. J. S. Dewar, *Angew. Chem., Int. Ed. Engl.*, **10,** 761 (1971).
(37) No experimental value is available for the delocalization energy (DE) in a heptatrienyl radical. However, a rough estimate of this DE can be made if the trend noted in DE for allyl (12 ± 2 kcal/mol)[38a] and for pentadienyl (20 ± 2 kcal/mol)[38b,c] extends to heptatrienyl. A value for some 25 ± 2 kcal/mol would result.[39]
(38) (a) W. von E. Doering and G. H. Beasley, *Tetrahedron,* **29,** 2231 (1973), and references cited therein; (b) K. W. Egger and M. Jola, *Int. J. Chem. Kinet.,* **2,** 265 (1970); (c) H. M. Frey and A. Krantz, *J. Chem. Soc. A,* 1159 (1969).
(39) Reference to theoretical estimations of the DE of the various radicals is of little predictive value. Thus, to the extent that the difference in enthalpy of the reaction, RH → R· + H·, is a measure of DE, heptatrienyl is *more* stable than pentadienyl by 0.1–0.5 kcal/mol according to one calculation [N. C. Baird, *Can. J. Chem.*, **49,** 338 (1971)], and less stable by 2.6 kcal/mol by another [S. Kirschner (MINDO/3, private communication with permission to cite].
(40) G. S. Hammond, *J. Am. Chem. Soc.*, **77,** 334 (1955).
(41) M. Schakel and G. W. Klumpp, *Recl. Trav. Chim. Pays-Bas,* **92,** 605 (1973).
(42) The somewhat greater kinetic preference has been noted in i for the homotrienyl [1,7] hydrogen shift as compared to the homodienyl [1,5] pro-



i

cess, viz. 24:1; in this case, however, the geometries of the transition states required for transfer of either the C-4 or the C-5 hydrogen atom to the carbonyl oxygen are clearly different for the two competing processes. Consequently, this increased ratio does not necessarily reflect more accurately the relative energies of the molecular orbitals involved in the two reactions.
(43) The methylation of methylcyclopentadienide produces a 3.5:1 ratio of "ortho" to "meta" disubstituted cyclopentadienes.[44] To the extent that the transition state for alkylation reflects differences in thermodynamic stabilities of products, the observed ratio suggests the "ortho" osomer to be at least 0.7 kcal/mol more stable than the "meta".
(44) J. McLean and P. Haynes, *Tetrahedron,* **21,** 2313 (1965).
(45) P. R. Story and S. R. Fahrenholtz, *J. Org. Chem.*, **28,** 1716 (1963).
(46) M. E. Tate and C. T. Bishop, *Can. J. Chem.*, **41,** 1801 (1963).
(47) G. Zweifel and H. C. Brown, *Org. React.*, **13,** 31 (1963).
(48) F. L. Weisenborn, D. C. Remy, and T. L. Jacobs, *J. Am. Chem. Soc.*, **76,** 552 (1954).
(49) H. N. A. Al-Jallo and E. S. Wright, *J. Chem. Soc. B,* 73 (1966).
(50) R. M. Acheson and R. Robinson, *J. Chem. Soc.*, 1127 (1952).
(51) 2-Methylcyclopentanone was purchased from Chemical Samples Co. 3-Methylcyclopentanone was obtained by catalytic hydrogenation of 3-methylcyclopent-2-en-1-one.

Meisenheimer Complexes. 1,1 and 1,3 Adducts from 2,6-Dinitro-4-trifluoromethylsulfonyl- and 4-Methylsulfonylanisoles. Kinetics in Methanolic Dimethyl Sulfoxide

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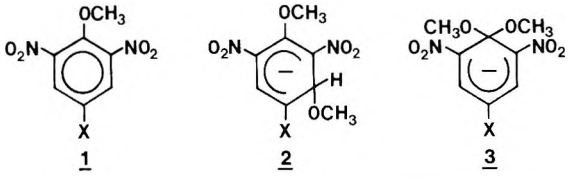
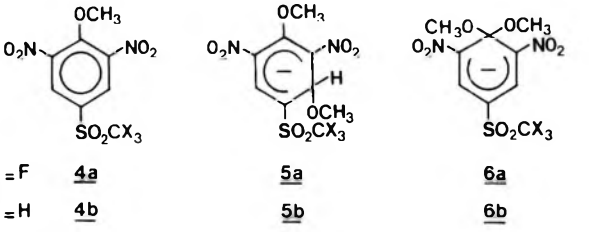
In methanolic solution, 2,6-dinitro-4-trifluoromethylsulfonylanisole (**4a**) gives a Meisenheimer 1,1-dimethoxy adduct **6a** which is completely formed in a solution with methoxide ion concentration as low as 5×10^{-4} M. The kinetics of formation and decomposition of **6a** have been studied between pH 4 and 13.5 by using buffer solutions. Whereas the reaction **4a** + CH_3O^- → **6a** is the only one observed above pH 12, the formation of **6a** arises partly from the attack of a methanol molecule on the parent ether **4a** between pH 10 and 11. Ths is apparently the first report of this kind in the field of benzenic Meisenheimer complexes. At pH >14.2, i.e., in methanolic solutions of potassium methoxide 3×10^{-3} – 0.2 M, the formation of the transient 1,3-dimethoxy adduct **5a** precedes that of **6a**. The kinetic and thermodynamic parameters for formation and decomposition of **5a** and **6a** are compared with data obtained in this work for the analogous 1,3 and 1,1 adducts **5b** and **6b** derived from 2,6-dinitro-4-methylsulfonylanisole **4b** as well as with data previously reported for the trinitro 1,3 and 1,1 adducts **9** and **8**. The results emphasize the much greater stabilizing effect exerted by the SO_2CF_3 group on the Meisenheimer adducts as compared with that of the nitro and methylsulfonyl groups. The adducts **5a** and **6a** are in fact the most stable benzenic 1,3 and 1,1 adducts yet observed in methanol. The dimethyl sulfoxide influence on the reactions is also discussed.

NMR studies have shown that the reaction of various substituted 4-X-2,6-dinitroanisoles **1** with methoxide ion in Me_2SO initially yields the 1,3 complex **2** which is subsequently



converted into the thermodynamically more stable 1,1 complex **3**.[2-5] Kinetic studies of this interaction in methanol–Me_2SO mixtures allowed a better understanding of its mechanism.[6,7] Decreasing the Me_2SO content in the mixtures results in a dramatic decrease in the stability and the lifetime of 1,3 complexes which are thus less easily observed in mixtures rich in methanol.[6-8] As could be expected, the minimum Me_2SO amount necessary to their detection is, however, dependent to a large extent on the electron-withdrawing power of the X substituent. Whereas 1,3 complexes formed from 4-fluoro- and 4-chloro-2,6-dinitroanisoles[6a] are only observable in mixtures with >70% Me_2SO by weight, those formed from 2,4,6-trinitroanisole[7] and 3,5-dinitro-4-methoxypyridine[6c] (considered to be a 4-aza-2,6-dinitroanisole) can be seen in pure methanol despite very short half-lives of about 0.10 and 0.40 s, respectively, at 25 °C.

The Hammett σ parameters determined for the SO_2CF_3 group from pK_a measurements on anilines, phenols, and benzoic acids containing this substituent indicate that it is the strongest neutral electron-withdrawing group which has ever been studied.[9] This is clearly reflected in nucleophilic aromatic substitution reactions. Both 1-chloro-2-nitro-4-trifluoromethylsulfonyl- and 1-chloro-4-nitro-2-trifluoromethylsulfonylbenzenes react faster than does 1-chloro-2,4-dinitrobenzene with nucleophiles such as methoxide ion or amines.[10] In view of these findings, we could reasonably expect the reaction of methoxide ion with 2,6-dinitro-4-trifluoromethylsulfonylanisole to give a 1,3 complex as well as a 1,1 complex which are more stable than the respective complexes of less activated substrates. This is, of course, of interest with respect to general implications of the formaton of such species in nucleophilic aromatic substitution reactions.[11] As a continuation of our work in this area, we have therefore carried out a comprehensive kinetic and thermodynamic analysis of the formation and decomposition of **5a** and **6a** in methanol and methanol–Me_2SO mixtures. Following a preliminary communication,[12] we now report detailed results and additional data for this study. For the purpose of comparison, we report also rate and equilibrium data for the reaction of methoxide ion with 2,6-dinitro-4-methylsulfonylanisole (**4b**) in the same mixtures.



Results

2,6-Dinitro-4-trifluoromethylsulfonylanisole (4a). A. 1,1-Complex Formation in Methanol. The reaction of methoxide ion with **4a** in methanol results in the immediate formation of the yellow-colored 1,1 adduct **6a**, the absorption spectrum of which is shown in Figure 1 (λ_{max} 465 nm, ϵ 15 300 M^{-1} cm^{-1}). At this wavelength, the parent molecule has negligible absorption. The formation of **6a**, which was identified by NMR spectroscopy,[5] appears, in fact, to be complete in a solution with methoxide ion concentration as low as 5×10^{-4} M. We had, therefore, to use buffer solutions in the range pH 4–13.5 to carry out a comprehensive study of the formation and decomposition of **6a**. The buffer solutions were prepared from various carboxylic acids and phenols AH and made up so as to give a total ionic strength of 0.01 M from the buffer species A^- alone without any added neutral salt. As we have shown previously,[13] the mean activity coefficient $\gamma_\pm$ could then be calculated by using a simplified Debye–Hückel type equation ($\log \gamma_\pm = -Bz^2\sqrt{\mu}$), thus allowing the hydrogen ion concentration $[H^+]$ of the methanolic solutions to be deduced from the measured activity a_{H^+} of the solvated proton ($[H^+] = a_{H^+}/\gamma_\pm$). The pH values are relative to the standard state in methanol.

A plot (not shown) of the variations at 465 nm of the optical density obtained at equilibrium as a function of pH shows that

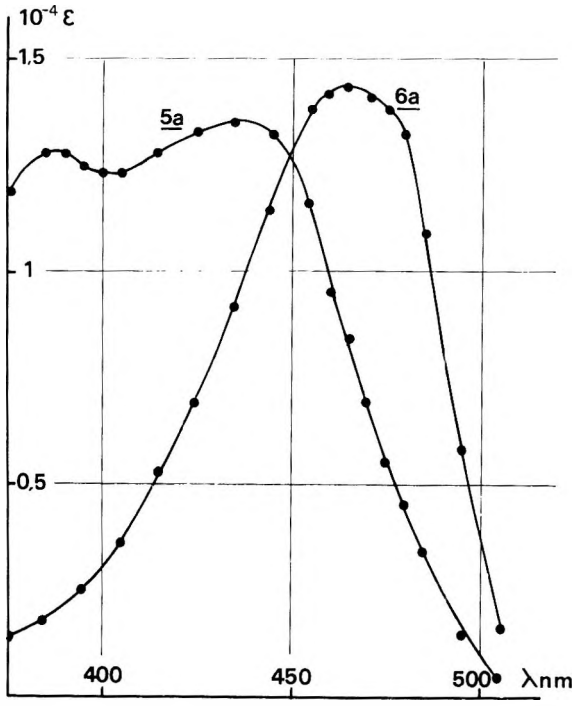


Figure 1. Absorption spectra of complexes **5a** and **6a** in methanol.

the 1,1 complex **6a** is half formed at pH 10.68. In view of the relatively high value of the coefficient B in methanol[13] (B = 1.80), this $pH_{1/2}$ value corresponds to the pK_a value for the formation of **6a** (eq 1) at μ = 0.01 M. Assuming $\gamma_{4a} \simeq 1$ in eq 2, which is here a reasonable assumption, the thermodynamic pK_a value at zero ionic strength was determined by a Debye–Hückel extrapolation from similar $pH_{1/2}$ measurements at μ = 2.5 × 10^{-3}, 5 × 10^{-3}, and 2 × 10^{-2} M: pK_a^{4a} = 10.90 ± 0.03.

$$\mathbf{4a} + CH_3OH \rightleftarrows \mathbf{6a} + H^+ \qquad K_a = \frac{a_{6a}a_{H^+}}{a_{4a}} \tag{1}$$

$$pK_a = pH_{1/2} - \log \frac{\gamma_{6a}}{\gamma_{4a}} \tag{2}$$

Employing the stopped-flow method as well as conventional methods, we have investigated the kinetics of the formation and decomposition of **6a** at 465 nm. In all cases, the appearance or disappearance of **6a** was a clear first-order process. The pH dependence of the observed first-order rate constant k_{obsd} for the combined formation and decomposition of **6a** is shown in Figure 2. Variation of buffer concentration at constant pH did not significantly change the value of k_{obsd} with experimental error, indicating the absence of catalysis by buffer, at least at the low concentrations used. In addition, a smooth pH–rate profile was obtained despite the fact that buffers of varying chemical types were used, showing as expected in methanol that buffer species (particularly phenoxide anions) do not react with **4a.** We have observed essentially similar behavior in the case of 2,4,6-trinitroanisole (**7**),[14] and 2,4-dinitro-5-methoxythiophene and -selenophene (**10** and **12**)[15] (see structures in discussion).

The rate constant k_{obsd} reflects the rate of approach to equilibrium between **4a** and **6a** and is the sum of the individual pseudo-first-order rate constants k_f and k_d, respectively, for the formation and decomposition of **6a.** As shown previously,[15,16] k_f and k_d for such a system may be calculated from eq 3 and 4 where $a_{H^+_{1/2}} = 10^{-pH_{1/2}}$.

$$k_f = \frac{k_{obsd}}{1 + \dfrac{a_{H^+}}{a_{H^+_{1/2}}}} \tag{3}$$

$$k_d = \frac{k_{obsd}}{1 + \dfrac{a_{H^+_{1/2}}}{a_{H^+}}} \tag{4}$$

Complete data are graphically represented in Figure 3, which shows the pH dependence of k_f and k_d.

As those observed for **7**, **10**, and **12**[14,15] as well as for 4,6-dinitro-7-methoxybenzofurazan (**14**)[1c] (see structure in discussion), these pH–rate profiles fit very well to equations of the form

$$k_f = k_1^{CH_3OH} + k_2[CH_3O^-] = k_1^{CH_3OH} + \frac{k_2K_s}{a_{H^+}\gamma_\pm} \tag{5}$$

$$k_d = k_{-1}[H^+] + k_{-2} = \frac{k_{-1}a_{H^+}}{\gamma_\pm} + k_{-2} \tag{6}$$

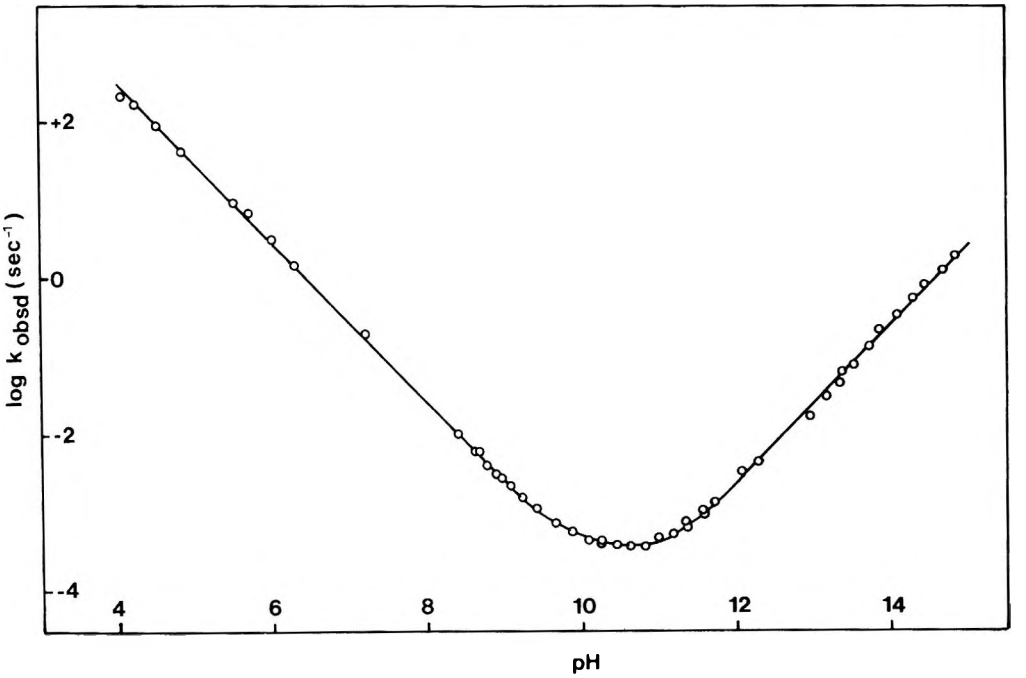


Figure 2. The pH dependence of k_{obsd} (s^{-1}) for the formation and decomposition of the adduct **6a** in methanol: 20 °C, μ = 0.01 M.

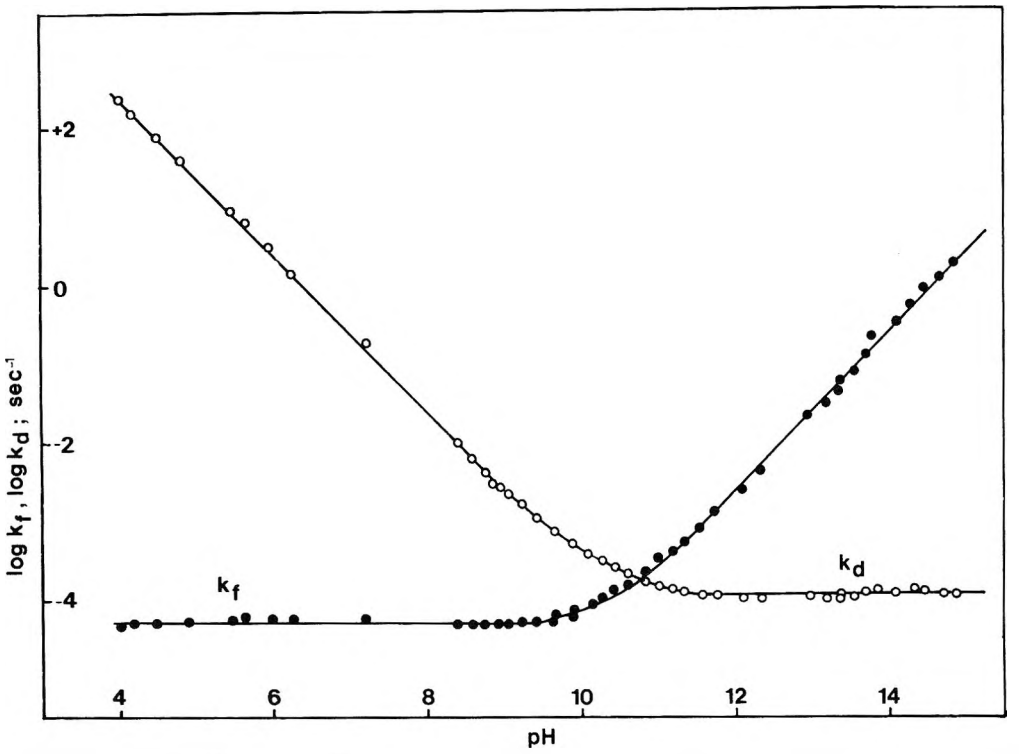


Figure 3. The pH dependence of k_f (s^{-1}) and k_d (s^{-1}) for the formation and decomposition of the adduct **6a** in methanol: 20 °C, μ = 0.01 M.

Scheme A shows the reactions to which the various constants refer, viz., $k_1^{CH_3OH}$ and k_2 represent attack of **4a** by methanol and methoxide ion, respectively, while k_{-1} and k_{-2} refer to H^+-catalyzed and spontaneous decomposition of **6a**, respectively. The various rate coefficients have been easily

Scheme A

$$\mathbf{4a} + CH_3OH \underset{k_{-1}}{\overset{k_1^{CH_3OH}}{\rightleftharpoons}} \mathbf{6a} + H^+ \quad (7)$$

$$\mathbf{4a} + CH_3O^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathbf{6a} \quad (8)$$

determined from the two linear portions of each of k_f and k_d pH–rate profiles (high and low pH regions of each, respectively). We thus obtain $k_1^{CH_3OH} = 5 \times 10^{-5}\ s^{-1}$, $k_{-1} = 1.66 \times 10^6\ M^{-1}\ s^{-1}$, $k_2 = 141\ M^{-1}\ s^{-1}$, $k_{-2} = 1.17 \times 10^{-4}\ s^{-1}$ ($K_s = 10^{-16.86}$ at 20 °C[13]).

Inserting these values into the expression given by eq 9 for k_{obsd}, we see that at low pH (pH <9), $k_{obsd} = k_d$, i.e., only the reverse reaction **6a** + H^+ → **4a** + CH_3OH is important while above pH 12 $k_{obsd} = k_f$, i.e., only the reaction **4a** + CH_3O^- → **6a** is important. This is in agreement with our experimental results. In the intermediate pH range, values of the terms $k_2K_s/a_{H^+}\gamma_\pm$ and/or $k_{-1}a_{H^+}/\gamma_\pm$ cannot be neglected relative to the sum $k_{-2} + k_1^{CH_3OH}$ so that no plateau appears in the experimental pH profile (see Figure 2).

$$k_{obsd} = \frac{k_{-1}a_{H^+}}{\gamma_\pm} + k_{-2} + k_1^{CH_3OH} + \frac{k_2K_s}{a_{H^+}\gamma_\pm} \quad (9)$$

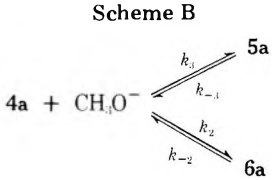
The formation of the adduct **6a** has also been studied in dilute solutions of potassium methoxide 5×10^{-4}–3×10^{-3} M, keeping the ionic strength μ constant at 0.01 M by adding NaBr as necessary. In this case, only the reaction 8 occurs and the observed first-order rate constant k_{obsd} is given by the reduced equation

$$k_{obsd} = k_{-2} + k_2[CH_3O^-] \quad (10)$$

A plot of k_{obsd} against the methoxide ion concentration afforded a good straight line with a slope equal to k_2 and an intercept equal to k_{-2}. As expected from the data obtained in buffer solutions, the intercept was, in fact, not distinguishable from zero and did not allow a new estimation of k_{-2}. In contrast, a nice agreement was observed between the value of 150 $M^{-1}\ s^{-1}$ so obtained for k_2 and that determined (141 $M^{-1}\ s^{-1}$) from the pH profile of Figure 3 (see Table I).

B. 1,3-Complex Formation in Methanol. When the methoxide ion concentration was greater than 3×10^{-3} M, the oscilloscope pictures revealed that the appearance of **6a** is preceded by the much faster formation of a thermodynamically less stable species which is completely formed in a solution of potassium methoxide 0.20 M. In view of previous results in analogous systems,[2-4] there was little doubt that this species, which shows an absorption band at 430 nm (ϵ 14 000 $M^{-1}\ cm^{-1}$), was the 1,3 adduct **5a** (Figure 1). We have, in fact, recently confirmed the structure of this transient 1,3 adduct by NMR spectroscopy in Me_2SO-d_6.[5]

Scheme B



Scheme B describes the interaction which consists of two separated steps. The first step is the fast equilibration between **4a** and **5a**. Assuring pseudo-first-order conditions with an excess of the methoxide reagent (concentration range of 5×10^{-3}–0.2 M) the observed first-order rate constant k'_{obsd} for this process is given by eq 11.

$$k'_{obsd} = k_{-3} + k_3[CH_3O^-] \quad (11)$$

Values of k_3 and k_{-3} were easily obtained from a plot of k'_{obsd} vs. $[CH_3O^-]$, which is linear: $k_3 = 750\ M^{-1}\ s^{-1}$, $k_{-3} = 25\ s^{-1}$. We calculated the equilibrium constant $K_3 = 30\ M^{-1}$ from $K_3 = k_3/k_{-3}$.

Table I. Rate and Equilibrium Constants for the Formation and Decomposition of Benzenic or Heterocyclic *gem*-Dimethoxyl Complexes 6a, 6b, 8, 11, 13, and 15 in Methanol at 20 °C

	6a[a]	6b[a]	8	11[d]	13[d]	15[e]
k_2, M^{-1} s^{-1}	141	1.75	11.8[b]	28.2	71	2.52×10^5
k_{-2}, s^{-1}	1.17×10^{-4}	1.68×10^{-2}	6.05×10^{-4} [b]	7.8×10^{-5}	1.04×10^{-5}	4.9×10^{-6}
$k_1^{CH_3OH}$, s^{-1}	5×10^{-5}	1.50×10^{-7}	1.80×10^{-6} [c]	10^{-7}	5.75×10^{-7}	4.46×10^{-3}
$k_{-1}^{H^+}$, M^{-1} s^{-1}	1.66×10^6	4.7×10^7	2.9×10^6 [c]	1.05×10^4	2.65×10^3	1.7×10^3
pK_a	10.68	14.86	12.58[b]	11.16	9.86	5.93

[a] This work. [b] Calculated at 20 °C from data in ref 4b. [c] Reference 14. [d] Reference 15. [e] Reference 16.

The second step is the slow equilibrium formation of the stable 1,1 adduct **6a** from the molecule which is considered to be in instantaneous equilibrium with **5a**. As previously shown,[6,7] the pertinent expression for the corresponding observed first-order rate constant k''_{obsd} is given by

$$k''_{obsd} = k_{-2} + \frac{k_2[CH_3O^-]}{1 + K_3[CH_3O^-]} \quad (12)$$

Neglecting k_{-2}, which is small compared with the second term at these base concentrations, eq 12 reduces to

$$k''_{obsd} = \frac{k_2[CH_3O^-]}{1 + K_3[CH_3O^-]} \quad (13)$$

Whereas a plot of k''_{obsd} vs. $[CH_3O^-]$ is curved (Figure 4), an inversion plot according to

$$\frac{1}{k''_{obsd}} = \frac{1}{k_2[CH_3O^-]} + \frac{K_3}{k_2} \quad (14)$$

is linear. The intercept and the reciprocal of the slope provide $K_3/k_2 = 0.182$ s and $k_2 = 174$ M^{-1} s^{-1}, respectively, leading to a value of 31.7 M^{-1} for K_3. In view of the differences in the ionic strength of the solutions, the results compare well with our earlier determinations. On the other hand, and as expected, k''_{obsd} reaches a plateau at the highest base concentrations where we have a complete initial formation of **5a** (Figure 4). Since this latter complex undergoes a complete conversion into **6a**, the maximum value of k''_{obsd}, which is given by

$$k''_{obsd}{}^{max} = \frac{k_2}{K_3} = k_{-2}\frac{K_2}{K_3} \quad (15)$$

can be used as a reference for its lifetime. A half-life of about 0.14 s is thus calculated for **5a** in pure methanol ($t_{1/2} = 0.693/k''_{obsd}{}^{max}$).

C. 1,1- and 1,3-Complex Formation in Solutions of Potassium Methoxide in Methanol–Me_2SO Mixtures. In methanol–Me_2SO mixtures with a Me_2SO content equal to or greater than 13.35% Me_2SO by weight, the formation of **5a** was found always to precede that of **6a**, even at the lowest methoxide ion concentrations used. Scheme B was therefore analyzed as just described in methanol. In mixtures containing 13.35 and 25.3% Me_2SO by weight, both k_3 and k_{-3} could be determined from the linear plots of k'_{obsd} vs. $[CH_3O^-]$ and consequently K_3 from the ratio k_3/k_{-3}. Measuring k''_{obsd} for the appearance of **6a** also allowed the determination of k_2 and K_3. At higher Me_2SO concentrations, k_{-3} was too small for an accurate determination and plots of k'_{obsd} vs. $[CH_3O^-]$ afforded only k_3 values. On the other hand, the plots of k''_{obsd} vs. $[CH_3O^-]$ are limited to the plateau corresponding to the maximum value of k''_{obsd}, preventing also a determination of k_2 and K_3 from eq 14.

The rate and equilibrium parameters for the formation and decomposition of **6a** in methanol are compared in Table I with analogous data reported for the most stable *gem*-dimethoxyl complexes **8**, **11**, **13**, and **15** previously studied. Table II summarizes the various kinetic and equilibrium parameters

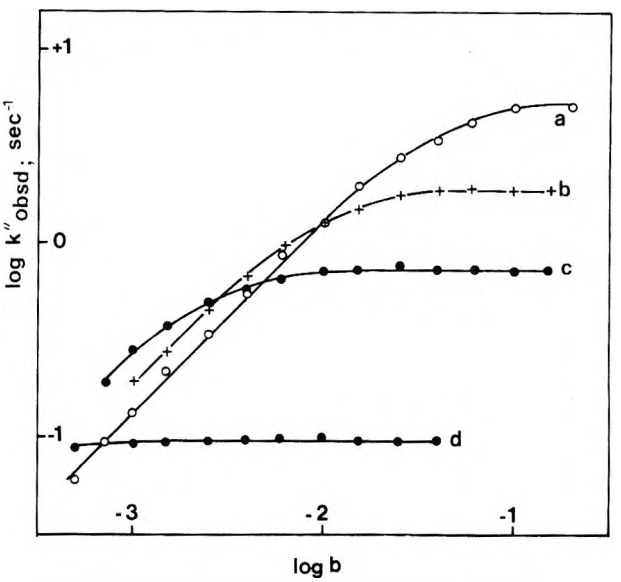


Figure 4. Plots of k''_{obsd} against methoxide ion concentration b for the appearance of **6a** in methanol (a), 13.35% (b), 25.3% (c), and 47.5% (d) Me_2SO.

associated with the formation and decomposition of **5a** and **6a** in the methanol–Me_2SO mixtures.

2,6-Dinitro-4-methylsulfonylanisole (4b). In the concentration range of 5×10^{-4}–10^{-1} M, the reaction of methoxide ion with **4b** in methanol and methanol–Me_2SO mixtures with less than about 35% Me_2SO by weight gives directly the pink-colored 1,1 complex **6b** [λ_{max} (CH_3OH) 512 nm (ϵ 19 000 M^{-1} cm^{-1})]. The observed first-order rate constant k_{obsd} for the equilibrium attainment of **4b** is therefore given by eq 10. Plotting k_{obsd} vs. $[CH_3O^-]$ easily yields values of k_2 and k_{-2} for formation and decomposition of **6b**. The equilibrium constant K_2 was calculated from $K_2 = k_2/k_{-2}$.

In the mixtures with higher Me_2SO concentrations, the formation of the 1,3 adduct **5b** [λ_{max} 455 nm (ϵ 20 600 M^{-1} cm^{-1})] occurs first followed by the much slower appearance of **6b**. A kinetic analysis of the interaction according to scheme B leads to the rate and equilibrium parameters for the formation and decomposition of **5b** and **6b** which are listed in Table III.

Discussion

General Features. As can be seen in Tables I and IV, the stability of the trifluoromethylsulfonyl 1,1 and 1,3 complexes **6a** and **5a** is respectively 70- and 12-fold higher than that of the trinitro analogues **8** and **9** which are usually considered to be the references for this type of complex. Replacing the 4-SO_2CF_3 group of **4a** by a 4-SO_2CH_3 group still causes a more dramatic decrease in the K values for complex formation. Whereas the 1,1 complex **6b** is about 10^4-fold less stable than **6a**, the 1,3 complex **5b** is not observable in pure methanol as opposed to **5a**. Using an estimated value of 0.08 for $K_3{}^{5b}$ in

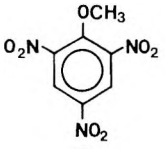
Table II. Kinetic and Equilibrium Parameters for the Reaction of Methoxide Ion with 4a in Methanol and Various Methanol–Me_2SO Mixtures at 20 °C

Solvent composition % Me_2SO by weight	1,3 complex 5a			1,1 complex 6a				
	k_3, $M^{-1}\,s^{-1}$	k_{-3}, s^{-1}	K_3, M^{-1}	k_2, $M^{-1}\,s^{-1}$	k_{-2}, s^{-1}	K_2, M^{-1}	k_{obsd}^{max}, s^{-1}	$t_{1/2}$, s
0	750	25	30	141, 150	1.17×10^{-4}	1.2×10^{6}	≃5	≃0.14
13.35	1 530	8.3	185	350			1.9	0.365
25.3	2 300	3.7	620	450			0.73	0.95
47.5	7 750						9.8×10^{-2}	7.05
57.5	20 000						2.7×10^{-2}	25.6
67	44 000						7.4×10^{-3}	93.5
76	100 000						1.86×10^{-3}	372
84.8							4.1×10^{-4}	1690
92.6							6.3×10^{-5}	11 000

Table III. Kinetic and Equilibrium Parameters for the Reaction of Methoxide Ion with 4b in Methanol and Various Methanol–Me_2SO Mixtures at 20 °C

Solvent composition % Me_2SO by weight	1,3 complex 5b			1,1 complex 6b				
	k_3, $M^{-1}\,s^{-1}$	k_{-3}, s^{-1}	K_3, M^{-1}	k_2, $M^{-1}\,s^{-1}$	k_{-2}, s^{-1}	K_2, M^{-1}	k_{obsd}^{max}, s^{-1}	$t_{1/2}$, s
0				1.75	1.68×10^{-2}	101		
13.35				2.74	1.12×10^{-2}	245		
25.3				5.8	8×10^{-3}	720		
47.5	362	30	12	17			1.4	0.5
57.5	1 150	14.7	78	37			0.59	1.17
67	3 160	5.5	575	117			0.204	3.4
76	10 000						0.06	11.5
84.8	33 000						0.017	40.8
92.6	≃140 000						2.75×10^{-3}	2.5×10^{2}

methanol (see further in discussion) a ratio K_3^{5a}/K_3^{5b} of about 375 is obtained. These results clearly emphasize the much stronger electron-withdrawing character of the SO_2CF_3 group as compared with that of the NO_2 and SO_2CH_3 groups.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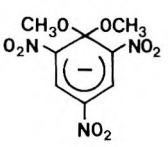
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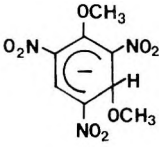
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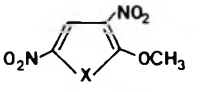
It is of interest to note that complexes **5a** and **6a** are the most stable benzenic 1,3 and 1,1 complexes which have ever been observed to form in methanol.

The differences in the ratios K_2^{6a}/K_2^{8} and K_3^{5a}/K_3^{9} reveal that the effect of the SO_2CF_3 group on the complex stability is greater when it is located in the para rather than in the ortho position of the sp^3 carbon. This behavior is essentially the same as that observed for the nitro group and therefore suggests a higher capacity of resonance stabilization by a para SO_2CF_3 group than by an ortho SO_2CF_3 group. This also confirms previous conclusions[9,17] that the SO_2CF_3 group exerts a large conjugative effect, presumably involving the d orbitals of the sulfur atoms,[18] in addition to an expected large inductive effect. In the present case, this would allow an extensive delocalization of the negative charge of the 1,1 complex **6a**, thus enhancing its stability.

The higher stability of **6a** and **5a** compared with that of trinitro analogues **8** and **9** or methylsulfonyl analogues **6b** and **5b** derives both from an increase in the rate of formation and a decrease in the rate of decomposition. For methoxide ion attack on the methoxyl-bearing carbon of the parent ethers, the second-order rate constant is 141 $M^{-1}\,s^{-1}$ for **4a** compared with 11.8 $M^{-1}\,s^{-1}$ for **7** and 1.75 $M^{-1}\,s^{-1}$ for **4b**. For attack on the unsubstituted 3 carbon, the second-order rate constants are 750 $M^{-1}\,s^{-1}$ for **4a**, 690 $M^{-1}\,s^{-1}$ for **7**, and 35 $M^{-1}\,s^{-1}$ for **4b**. This dependence of the rates on the substituent are of the same order of magnitude than those observed by Shein et al. in comparing the nucleophilic attack of methoxide ion on 2,4-dinitrochlorobenzene with that on related 4- (or 2-) trifluoromethylsulfonyl or methylsulfonyl 2- (or 4-) nitrochlorobenzenes.[10] A more noteworthy feature is the occurrence of methanol attack on the methoxyl-bearing carbon of **4a**. As shown by the simple calculation of each term of eq 9, the methanol attack contributes for about 10–15% to the rate of appearance of **6a** between pH 10 and 11. This is really a striking result since such a process appeared to be negligible in the pH range where the adducts **8** and **6b** are formed and was found to contribute only to a very small extent to the formation of the roughly similarly stable five-membered ring adducts **11** and **13**[15] (about 2–3% in the most favorable conditions for **13**). As can be seen in Table I, the methanol attack on **4a** is, however, much less significant than that which occurs on the methoxyl carbon of 4,6-dinitro-7-methoxybenzofuran (**14**) to give the more stable adduct **15**.[16]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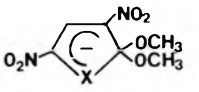
12 (X = Se)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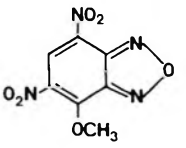
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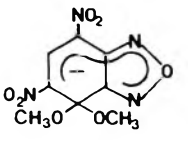
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Table IV. Effect of Substituent on the Rate and Equilibrium Constants for Formation and Decomposition of 1,1 and 1,3 Complexes in Pure Methanol

X	SO_2CF_3	NO_2	–N–	CN	SO_2CH_3	CF_3	Cl	F	H
k_2, M^{-1} s^{-1}	141[a]	11.8[b]	16.5[d]	2.82[e]	1.75[a]	0.4[h]	1.2×10^{-2}[h]	2.5×10^{-3}[h]	1.5×10^{-3}[h]
k_{-2}, s^{-1}	1.17×10^{-4}[a]	6.05×10^{-4}[b]	5.75×10^{-3}[d]	1.68×10^{-2}[a]	1.68×10^{-2}[a]	8×10^{-2}[h]	5[h]	30[h]	20[h]
K_2; M^{-1}	1.2×10^6[a]	19 500[b]	2870[d]	168[e]	101[a]	5[h] (2)[i,j]	2.5×10^{-3}[h] (4.3×10^{-3})[j]	8.5×10^{-5}[h]	7.5×10^{-5}[h] (9×10^{-5})[j]
$k_2^{SO_2CF_3}/k_2^X$	1	11.9	8.5	50	80	350	1.17×10^4	5.65×10^4	9.4×10^4
$k_{-2}^X/k_{-2}^{SO_2CF_3}$	1	5.2	49	144	144	585	4.3×10^4	2.56×10^5	1.7×10^5
$K_2^{SO_2CF_3}/K_2^X$	1	61.5	418	7.15×10^3	1.19×10^4	2.4×10^5	5×10^8	1.41×10^{10}	1.6×10^{10}
k_3, M^{-1} s^{-1}	750[a]	690[c]	275[d]	60[f]	35[g]	2.5[h]	2[h]	1[h]	
k_{-3}, s^{-1}	25[a]	270[c]	25[d]	420[f]	440[g]	1400[h]	2000[h]	5000[h]	
K_3, M^{-1}	30[a]	2.56[c]	11[d]	0.143[f]	0.08[g]	1.8×10^{-3}[h]	10^{-3}[h]	2×10^{-4}[h]	
$k_3^{SO_2CF_3}/k_3^X$	1	1.09	2.72	12.5	21.4	300	375	750	
$k_{-3}^X/k_{-3}^{SO_2CF_3}$	1	10.8	1	16.8	18	56	80	200	
$K_3^{SO_2CF_3}/K_3^X$	1	11.7	2.73	210	375	1.67×10^4	3×10^4	1.5×10^5	

[a] This work at 20 °C. [b] Calculated at 20 °C from ref 4b. [c] Calculated at 20 °C from ref 7. [d] Reference 6c. [e] Reference 6b. [f] Extrapolated from data in ref 6b. [g] Extrapolated from data of this work. [h] Extrapolated from data in ref 6a. [i] Reference 22. [j] Reference 21.

As pointed out by the following ratios, **6a** and **5a** decompose spontaneously more slowly than their nitro or methylsulfonyl analogues: $k_{-2}^{8}/k_{-2}^{6a} = 5$, $k_{-2}^{6b}/k_{-2}^{6a} = 144$, $k_{-3}^{9}/k_{-3}^{5a} = 10.8$, $k_{-3}^{5b}/k_{-3}^{5a} = 18$. The H^+-catalyzed decomposition of **6a** is similarly slower than that of 8 and **6b**: the ratios k_{-1}^{8}/k_{-1}^{6a} and k_{-1}^{6b}/k_{-1}^{6a} are equal to 1.7 and 28.3, respectively. Also, the high value of k_{-1} for **6a** should be noted with respect to those found for the similarly stable five-membered ring 1,1 adducts **11** and **13**. Whereas these latter decompose spontaneously 1.5- and 11-fold slower than **6a**, respectively, they have a much lower susceptibility to the H^+-catalyzed decomposition than **6a**: the ratios k_{-1}^{6a}/k_{-1}^{11} and k_{-1}^{6a}/k_{-1}^{13} are equal to 158 and 630, respectively. Unfortunately, the available data do not warrant an extensive discussion of possible reasons for this interesting contrast at this time.

Effect of Solvent. Adding Me_2SO to the methanolic solutions causes a strong increase in the equilibrium constants K_2 and K_3 for the formation of 1,1 complexes **6a** and **6b** and 1,3 complexes **5a** and **5b**. This reflects both an increase in the rate constants of formation k_2 and k_3 and a decrease in the rate constants of decomposition k_{-2} and k_{-3}, respectively. Rather than emphasizing these findings, which are quite similar to those previously found for other Meisenheimer complexes,[6,8,19] it is more interesting to point out some other striking features.

Let us turn our attention to Figure 5, where the available data for formation and decomposition of 1,1 and 1,3 complexes derived from all the substituted 4-X-2,6-dinitroanisoles studied to date are summarized. As can be seen, good parallel straight lines are obtained on plotting $\log k_2$, $\log k_3$ as well as $-\log k_{-2}$, $-\log k_{-3}$ vs. the molar fraction of Me_2SO, implying that the effect of solvent composition is approximately independent of the nature of the substituent and of the type of complex which is formed. This is in agreement with previous observations of the existence of such linear relationships between the specific rate or equilibrium constants of various Meisenheimer adducts and the amount of Me_2SO cosolvent.[6b,8,19,20] As a consequence, the *relative* thermodynamic stability of 1,1 and 1,3 complexes is practically unaffected by a change in the Me_2SO concentration, which is an interesting

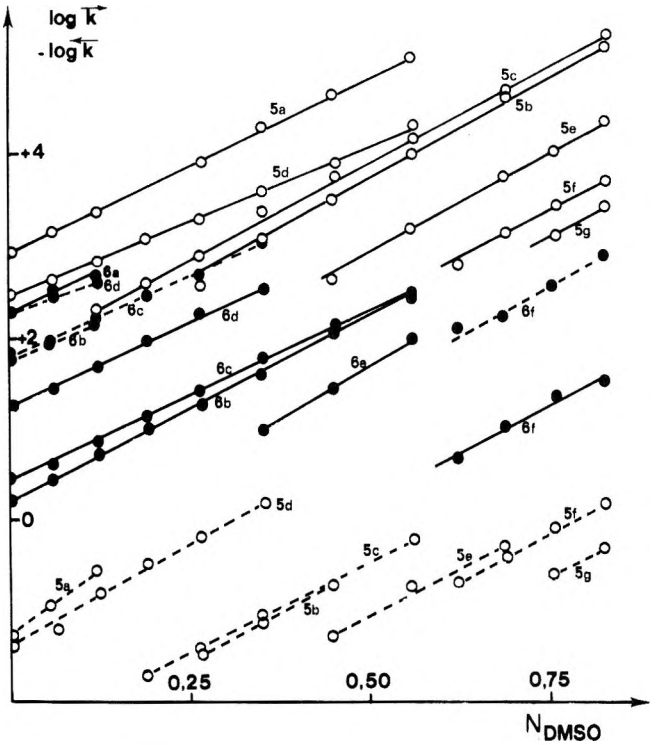

Figure 5. Plots of the rate constants for the formation $\vec{k}$ (—) and decomposition $\overleftarrow{k}$ (– – –) of 1,3 and 1,1 complexes against molar fraction of Me_2SO: **5a, 6a** (X = SO_2CF_3); **5b, 6b** (X = SO_2CH_3); **5c, 6c** (X = CN); **5d, 6d** (X = –N–); **5e, 6e** (X = CF_3); **5f, 6f** (X = Cl); **5g, 6g** (X = F).

result with respect to the lifetime of transient 1,3 complexes. As mentioned before, the maximum value of the observed first-order rate constant k''_{obsd} can be used as a measure for this lifetime. In view of the independence of the ratio K_2/K_3, eq 15 thus shows that the influence of Me_2SO on $k_{obsd}{}''^{max}$ is similar to that observed on the rate constant k_{-3} for the decomposition of 1,3 complexes. Increasing the Me_2SO con-

centration therefore results in a strong decrease in k_{obsd}^{max} which is paralleled by a strong increase in the lifetime of these transient species. Whereas the half-life of **6a** is about 0.14 s in methanol, it is almost 11 000 s in a mixture containing 92.6% Me_2SO, i.e., 10^5-fold greater than in the absence of Me_2SO cosolvent. Similarly, the half-life of **6b** is changing from 0.5 s in 47.5% Me_2SO to 250 s in 92.6% Me_2SO. These results, which are best appreciated on inspection of Tables II and III which list the $t_{1/2}$ values in the various mixtures, allow us to account for the possible NMR observation of such transient species in Me_2SO.[4b,5,21]

The linear correlations of Figure 5 are also useful to safely estimate rate and equilibrium constants not directly measurable in a given solvent. This is in particular the case in methanol where the values of k_2, k_{-2}, and K_2 for formation and decomposition of 1,1 complexes with X = CF_3, Cl, F, H as well as values of k_3, k_{-3}, and K_3 for formation and decomposition of 1,3 complexes with X = CN, SO_2CH_3, CF_3, Cl, F have thus been obtained by extrapolation of the data available in methanol–Me_2SO mixtures. In the case of X = CF_3, Cl, H the values so calculated for K_2 are equal to 5, 2.5×10^{-3}, and 7.5×10^{-5}, respectively, which compares fairly well with the values of 2, 4.3×10^{-3}, and 9×10^{-5} previously determined by using the acidity function method.[22,23] This agreement between these two sets of values further supports the reliability of the extrapolation procedure. All the calculated parameters, together with those of the complexes which could be directly studied in methanol, are summarized in Table IV. They allow a general analysis of the effect on the X substituent on the stabilities of 1,1 and 1,3 complexes in the 4-X-2,6-dinitroanisole series. First, we note that going from X = SO_3CF_3 to X = F results in a much larger decrease in the equilibrium constant K_2 for 1,1 complex formation than in the equilibrium constant K_3 for 1,3 complex formation: the ratios $K_2^{SO_2CF_3}/K_2^F$ and $K_3^{SO_2CF_3}/K_3^F$ are respectively equal to 1.6×10^{10} and 1.5×10^5. This difference in the effect of the substituent X on the equilibrium constants of 1,1 and 1,3 complexes, respectively, mainly reflects the well-known fact that complex stability is more sensitive to changes in the substituent para to the site of nucleophilic attack than ortho to it.[4,6,24] On the other hand, it appears from the ratios $k_2^{SO_2CF_3}/k_2^X$ and $k_{-2}^X/k_{-2}^{SO_2CF_3}$ that changes in the equilibrium constant K_2 for 1,1 complex formation are more dependent on changes in the rates of decomposition than of those in the rates of formation, suggesting a somewhat reactant-like transition state. When going from X = SO_2CF_3 to X = H, we note, however, that the changes in k_2 become more and more coresponsible for the changes in K_2, indicating that the transition state must progressively move closer to the complex as the electron-withdrawing power of the X substituent is decreased. Since complex stability is decreasing at the same time, such an effect would be consistent with Hammond's postulate.[25] Table IV shows also that the changes in the K_3 values for 1,3 complex formation are more dependent on the changes in k_3 than of those in k_{-3}, the difference between the two factors increasing with decreasing electron-withdrawing power of X. Again in agreement with Hammond's postulate, this now suggests a transition state which is more and more complex-like.

A rigorous discussion of the origin of the observed solvent effects on the rate parameters for formation and decomposition of complexes has to be made in terms of the changes in the activity coefficients of the reactants, transition states, and products.[19b,26,27] The rate constants k_2, k_3 and k_{-2}, k_{-3} in MeOH–Me_2SO mixtures are in fact related to those in pure methanol by the equations[19b,26]

$$k_2^{MeOH-Me_2SO} = k_2^{MeOH} \frac{\gamma'_{ether}\gamma'_{CH_3OK}}{\gamma'^{\ddagger}_2}$$

$$k_3^{MeOH-Me_2SO} = k_3^{MeOH} \frac{\gamma'_{ether}\gamma'_{CH_3OK}}{\gamma'^{\ddagger}_3}$$

$$k_{-2}^{MeOH-Me_2SO} = k_{-2}^{MeOH} \frac{\gamma'_{1,1\ complex}}{\gamma'^{\ddagger}_2}$$

$$k_{-3}^{MeOH-Me_2SO} = k_{-3}^{MeOH} \frac{\gamma'_{1,3\ complex}}{\gamma'^{\ddagger}_3}$$

where the γ''s represent the transfer activity coefficients for the various species, i.e., the activity coefficients in the mixed solvent compared to pure methanol as the standard state ($\gamma' = \gamma^{MeOH-Me_2SO}/\gamma^{MeOH}$). The fact that the solvent effects on the rate constants are independent of the substrates and of the type of complex thus suggests that the ratios $\gamma'_{ether}/\gamma'^{\ddagger}$ and $\gamma'_{complex}/\gamma'^{\ddagger}$ are themselves independent of these factors. Since Fendler et al.[25] have shown that the stabilizing effect of Me_2SO is in the order complex > transition state > parent ether and increases with increasing the Me_2SO concentration, one possibility would be that the relative changes in γ'_{ether}, $\gamma'^{\ddagger}$, and $\gamma'_{complex}$ are the same in a given mixture whatever the substrate and the formed complex may be. This is not unreasonable in the case of γ'_{ether} and $\gamma'_{complex}$ but this further supposes in the case of $\gamma'^{\ddagger}$ that the transition state would keep the same structure when changing the substituent in a given series (1,1 complex or 1,3 complex) or changing the series (1,1 complex and 1,3 complex). Such a conclusion is then inconsistent with those derived on the basis of a comparison of the contributions of changes in k and $\dot{k}$ values to the variations in the K values, and therefore with the application of Hammond's postulate to our results. Another possibility would be that the changes in γ'_{ether}, $\gamma'^{\ddagger}$, and $\gamma'_{complex}$ are dependent on the substrates and of the type of complex but that the ratios $\gamma'_{ether}/\gamma'^{\ddagger}$ and $\gamma'_{complex}/\gamma'^{\ddagger}$ are fortuitously the same. This would rule out, of course, any physical meaning to the correlations observed between log k values and the Me_2SO concentration but would not be inconsistent with changes in the structures of the transition states. Evidently, the experimental data do not permit us to choose between these two conflicting situations which point out that due care must therefore be taken in interpreting solvent effects observed on rate and equilibrium constants for formation and decomposition of Meisenheimer complexes.

Experimental Section

Materials. 2,6-Dinitro-4-trifluoromethylsulfonyl- and 4-methylsulfonylanisoles (**4a** and **4b**) were prepared as previously described:[5] **4a**, mp 59 °C; **4b**, mp 206 °C. Methanol and methanolic potassium methoxide solutions were prepared as previously described.[13a] The various buffers used for the rate measurements were purified according to classical methods. Buffers used were trichloroacetate (pH 4–5), dichloroacetate (pH 5–6.5), salicylate (pH 6.8–8.1), succinate (pH 8.3–9), benzoate (pH 8.6–9.7), 2,4,6-trichlorophenoxide (pH 9.8–10.6), 2,6-dichlorophenoxide (pH 10.7–11.5), 4-cyanophenoxide (pH 11.4–12.4), and 4-chlorophenoxide (pH 12.9–13.5).

Rate and pH Measurements. Stopped-flow determinations were performed on a Durrum stopped-flow spectrophotometer, the cell compartment of which was maintained to ±0.5 °C. Other kinetic measurements were made using a Beckman DB-G spectrophotometer. All kinetic runs were carried out under pseudo-first-order conditions with a substrate concentration of about 3×10^{-5} M. Rate constants are accurate to ±3%.

The pH was measured on a Radiometer Model pH meter according to a method previously reported.[13] The pH values are relative to the standard state in pure methanol.

Registry No.—**4a**, 19822-29-8; **4b**, 39880-50-7; **5a**, 35344-09-3; **5b**, 40203-33-6; **6a**, 35298-04-5; **6b**, 40203-26-7; methoxide ion, 3315-60-4.

References and Notes

(1) (a) ENSCP. Address to whom inquiries should be sent. (b) Faculté des Sciences et Techniques de Rouen.
(2) (a) K. L. Servis, *J. Am. Chem. Soc.*, **87**, 5495 (1965); (b) *ibid.*, **89**, 1508 (1967).
(3) M. R. Crampton and V. Gold, *J. Chem. Soc. B*, 893 (1966).

(4) (a) E. J. Fendler, J. H. Fendler, and C. E. Griffin, *Tetrahedron Lett.*, 5631 (1968); (b) *J. Org. Chem.*, **34**, 689 (1969).
(5) M. P. Simonnin, M. J. Pouet, F. Terrier, and C. A. Dearing, *Can. J. Chem.*, **50**, 3558 (1972).
(6) (a) F. Terrier and F. Millot, *Bull. Soc. Chim. Fr.*, 1743 (1970); (b) F. Terrier, C. A. Dearing, and R. Schaal in "Reaction Transition States", Gordon and Breach, London, 1973, p 137; (c) F. Terrier, A. P. Chatrousse, and R. Schaal, *J. Org. Chem.*, **37**, 3010 (1972).
(7) C. F. Bernasconi, *J. Am. Chem. Soc.*, **93**, 6975 (1971).
(8) F. Terrier, F. Millot, and R. Schaal, *J. Chem. Soc., Perkin Trans. 2*, 1192 (1972).
(9) W. A. Sheppard, *J. Am. Chem. Soc.*, **85**, 1314 (1963).
(10) (a) S. M. Shein, M. I. Krasnosel'skaya, and V. N. Boiko *Zh. Obshch. Khim.*, **36**, 2141 (1966); (b) S. M. Shein, V. A. Ignatov, L. A. Korzorez, and L. F. Chervatynk, *ibid.*, **37**, 114 (1967); (c) S. M. Shein and N. K. Danilova, *Zh. Org. Khim.*, **4**, 1940 (1968).
(11) For recent reviews on Meisenheimer complexes, see (a) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966); (b) E. Buncel, A. R. Norris, and K. E. Russell *Q. Rev., Chem. Soc.*, **22**, 123 (1968); (c) M. R. Crampton, *Adv. Phys. Org. Chem.*, **7**, 211 (1969); (d) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970); (e) C. F. Bernasconi, *MTP Int. Rev. Sci.: Org. Chem., Ser. One*, **3**, 33 (1973).
(12) F. Millot, J. Morel, and F. Terrier, *C. R. Acad. Sci., Ser. C*, **274**, 23 (1972).
(13) (a) J. C. Halle, F. Terrier, and R. Gaboriaud *Bull. Soc. Chim. Fr.*, **37** (1973); (b) F. Terrier, J. C. Halle, A. P. Chatrousse, and R. Schaal paper presented at the 4th IUPAC Meeting on Non-Aqueous Solvents, Vienna, July 1974.
(14) F. Terrier and F. Millot, unpublished results.
(15) F. Terrier, A. P. Chatrousse, C. Paulmier, and R. Schaal, *J. Org. Chem.*, **40**, 2911 (1975).
(16) A. P. Chatrousse and F. Terrier, *C. R. Acad. Sci., Ser. C*, **282**, 195 (1976).
(17) F. G. Bordwell, N. R. Vanier, W. S. Matthews, J. B. Hendrickson, and P. L. Skipper, *J. Am. Chem. Soc.*, **97**, 7160 (1975).
(18) (a) D. P. Craig and E. A. Magnsson, *J. Chem. Soc.*, 4895 (1956); (b) D. P. Craig and T. Thionnamachandran, *J. Chem. Phys.*, **43**, 4183 (1965).
(19) (a) E. J. Fendler, C. E. Griffin, and J. W. Larsen, *J. Org. Chem.*, **35**, 287 (1970); (b) J. H. Fendler and J. W. Larsen, *ibid.*, **37**, 2608 (1972); (c) W. L. Hinze, L. J. Liu, and J. H. Fendler, *J. Chem. Soc., Perkin Trans. 2*, 1751 (1975).
(20) C. F. Bernasconi and R. H. de Rossi, *J. Org. Chem.*, **38**, 500 (1973).
(21) F. Terrier, J. C. Halle, and M. P. Simonnin, *Org. Magn. Reson.*, **3**, 361 (1971).
(22) (a) M. R. Crampton, M. A. El Ghariani, and H. A. Khan, *J. Chem. Soc., Perkin Trans. 2*, 1178 (1972); (b) M. R. Crampton and H. A. Khan, *ibid.*, 1173 (1972).
(23) F. Terrier, *Ann. Chim. (Paris)*, **4**, 153 (1969).
(24) P. Caveng, P. B. Fisher, E. Heilbronner, A. I. Miller, and H. Zollinger, *Helv. Chim. Acta*, **50**, 848 (1967).
(25) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).
(26) E. J. Fendler, W. Ernsberger, and J. H. Fendler, *J. Org. Chem.*, **36**, 2333 (1971).
(27) J. H. Fendler, W. L. Hinze, and L. J. Liu, *J. Chem. Soc., Perkin Trans. 2*, 1768 (1975).

Conformational Analysis. 32. Conformational Energies of Methyl Sulfide, Methyl Sulfoxide, and Methyl Sulfone Groups[1]

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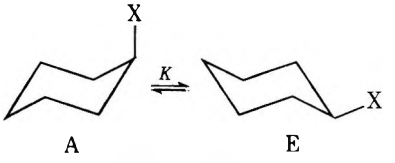
Conformational energy ($-\Delta G$) values for the title groups have been determined by low-temperature ^{13}C NMR signal area measurements. The values for CH_3SO_2, 2.5 kcal/mol, and CH_3SO, 1.2 kcal/mol, were determined by a "counterpoise" method, taking the ratio of the areas of the decoalesced spectra (at -95 ± 5 °C) of *cis*-4-methylcyclohexyl methyl sulfone and *cis*-4-methylcyclohexyl methyl sulfoxide and allowing for -1.7 kcal/mol as the ΔG value of the methyl group. The value for CH_3S, 1.0 kcal/mol, was determined both by an analogous method and by direct low-temperature ^{13}C NMR analysis of cyclohexyl methyl sulfide; it is in good agreement with the value in the literature.

Recently we reported[1] that the CH_3S group attached at C(5) in a 1,3-dioxane has a stronger preference for the equatorial conformation than it does when attached to a cyclohexyl ring.[2,3] In contrast, similarly placed methylsulfinyl (CH_3SO) and methylsulfonyl (CH_3SO_2) groups prefer the axial conformation. In the latter two cases, unfortunately, comparison with cyclohexyl methyl sulfoxide and sulfone was tenuous; in the case of the sulfone function, only a rather inaccurate value (2.5 kcal/mol) for phenylsulfonyl ($C_6H_5SO_2$) derived by NMR from an extremely one-sided equilibrium[4] was available; and the sulfoxide value[5] (1.9 kcal/mol) rested on the now discredited kinetic method. It is clear, however, even from the crude data, that cyclohexyl methyl sulfide, sulfoxide, and sulfone all exist with the sulfur function quite predominantly in the equatorial conformation.

The availability of ^{13}C NMR spectroscopy now makes it possible to determine, by signal area measurement at low temperature, conformational equilibria for a variety of substituents in a number of systems which were heretofore difficult to study.[6] However, measurement of signal areas[7] is difficult for conformations constituting less than 5% of the total. This difficulty can be obviated through use of a "counterpoise" method.[8] Thus, for cyclohexyl methyl sufide (**1**), it is adequate to measure the equilibrium shown in Scheme I, since the minor isomer constitutes about 6% of the total at -90 °C. But for cyclohexyl methyl sulfoxide (**2**), this value drops to 3.5% and for the sulfone **3** to much less than 1%; for the

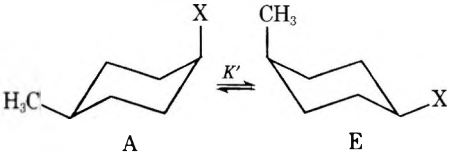
Scheme I



$\Delta G_X = -RT \ln K$

1, X = CH_3S
2, X = CH_3SO
3, X = CH_3SO_2

Scheme II



$\Delta G'_X = -RT \ln K'$

4, X = CH_3S
5, X = CH_3SO
6, X = CH_3SO_2

sulfoxide and sulfone functions it is desirable to measure the equilibrium shown in Scheme II, and this is preferable even for CH_3S. Here the equilibrium constants correspond to 12% of the minor isomer for **4**, 19% for **5**, and 10% for **6**, values

Table I. ^{13}C Signal Assignments in Compounds 1–15 (ppm from Me_4Si in $CDCl_3$)[a]

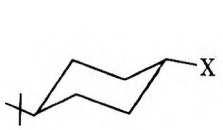
Compd	MeS	C(1)	C(2,6)[b]	C(3,5)[b]	C(4)	C(α)[c]	C(β)[d]
1	13.26	44.92	33.17	26.16	25.94		
	13.20[e]	44.94[e]	33.29[e]	26.24[e]	26.18[e]		
2	35.14	60.82	(26.07)[f]	(25.55)[f]	(25.16)[f]		
			(24.82)[f]	(25.40)[f]			
3	37.26	62.47	(25.07)[f]	(25.45)[f]	(25.07)[f]		
4	14.35	44.38	30.34	29.71	31.22	21.28	
5	36.31	61.29	24.25	30.23	30.03	20.44	
			22.44	30.75			
6	37.82	61.74	20.60	30.21	27.07	18.00	
7[e]	13.08	44.85	33.71	27.62	47.54	32.34	27.53
8	35.27	60.80	26.36	26.56	47.32	32.39	27.46
			25.28	26.36			
	35.21[e]	60.58[e]	26.27[e]	26.49[e]	47.25[e]	32.30[e]	27.43[e]
			25.07[e]	26.31[e]			
9	37.35	62.47	(26.08)[f]	(25.81)[f]	46.93	32.36	27.43
	37.38[e]	62.43[e]	(26.06)[e,f]	(25.79)[e,f]	46.92[e]	32.34[e]	27.42[e]
10[e]	14.73	44.29	31.09	21.96	48.41	32.54	27.48
10-d_4	14.72	43.97		21.75	48.35	32.55	27.48
11	37.10	61.49	27.17	23.14	47.69	32.57	27.36
			25.08	22.41			
	37.11[e]	61.33[e]	27.05[e]	23.07[e]	47.57[e]	32.49[e]	27.32[e]
11-d_4	37.08	61.08		22.88			
				22.16	47.52	32.52	27.34
12	39.68	57.76	25.12	22.14	47.06	32.58	27.44
	39.69[e]	57.79[e]	25.10[e]	22.13[e]	47.04[e]	32.56[e]	27.44[e]
12-d_4	39.68	57.46		21.94	46.93	32.58	27.45
13	13.19	44.58	33.24	35.31	32.16	22.35	
14	35.25	60.51	25.96	34.06	31.97	22.15	
			24.77	33.88			
15	37.42	62.24	25.40	33.52	31.59	21.99	

[a] In 8% solution unless otherwise indicated. [b] For the sulfoxides C(2,6) are diastereotopic and display two signals; the same is true for C(3,5). Assignment to one or other of the diastereotopic nuclei in each set has not been attempted. [c] CH_3 in methyl compounds, C_{quat} in *tert*-butyl compounds. [d] CH_3 in *tert*-butyl compounds. [e] In "concentrated" solution. [f] These assignments may have to be interchanged. However, the assignment of C(3,5) in **2** is supported by the calculations of conformational averaging of chemical shifts presented below.

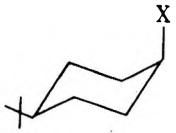
which are all easy to measure. For the equilibrium shown in Scheme II, $\Delta G' = \Delta G_X - \Delta G_{CH_3}$ whence $\Delta G_X = \Delta G' + \Delta G_{CH_3} = \Delta G' - 1.7$ kcal/mol, on the usual assumption that conformational energies are additive.

Results

The sulfides, sulfoxides, and sulfones **1–6** and the corresponding *trans*- and *cis*-4-*tert*-butyl analogues **7–12** and



7, X = CH_3S
8, X = CH_3SO
9, X = CH_3SO_2



10, X = CH_3S
11, X = CH_3SO
12, X = CH_3SO_2

trans-4-methyl analogues **13–15** (desired for spectral comparison) were prepared by standard literature methods (see

13, X = CH_3S
14, X = CH_3SO
15, X = CH_3SO_2

Experimental Section). The ^{13}C NMR spectra of these compounds are recorded in Table I. Signal assignments were made on the basis of off-resonance decoupling, intensity measurements, and parametrization. The *C*-methyl, C(4), and C(3,5) signals can be assigned on the basis of Grant's parameters for corresponding cyclohexanes with due allowance for the upfield shift of the X substituent in the axially substituted isomers **4, 5,** and **10–12**.[9] Data for *tert*-butylcyclohexane required for reference are on record.[10] The methyl group on the X substituent as well as C(1) and C(2,) were readily assigned among the remaining signals. Only in a few cases were signals too close together for secure assignment; such situations are indicated by parentheses in Table I.

In the case of three compounds (**10, 11,** and **12**) 2,2,6,6-tetradeuterated analogues were available whose spectra supported the assignments made for the protiated species. In some cases spectra were run at two concentrations; the effect of concentration is minor (≤0.2 ppm).

With the chemical shift information of the conformationally homogeneous (anancomeric) compounds **7–15** in hand, it became easy to assign chemical shifts to individual conformational isomers of compounds **1** and **4–6** at −90 °C. (The minor conformers in **2** and **3** were not seen in the low-temperature spectra, presumably because they are present in insufficient amounts.) The pertinent information is reported in Table II which includes (in parentheses) relative area measurements of the signals in question.

On the basis of the area ratios measured, ΔG^0 values were calculated at the appropriate temperatures. A listing of these data is presented in Table III, corrected, in the case of compounds **4–6**, by 1.7 kcal/mol (the ΔG value for methyl). In Table IV the averaged values for each of the three functional groups studied are compared with values in the literature.

It is possible, also to calculate the conformational equilibrium constants K and corresponding ΔG's from averaged chemical shifts by means of the equation $K = (\delta_a - \delta)/(\delta - \delta_e)$ developed by one of us.[11] Inspection of entries **7, 8, 10,** and **11**

Table II. Low-Temperature ^{13}C NMR Spectra of Compounds 1 and 4–6 (ppm Downfield from Me_4Si)

Compd	MeS	C(1)	C(2,6)	C(3,5)	C(4)	C(Me)
1A[a]	14.70 (1)	44.28	30.41 (1)	21.39 (1)	*b*	
1E[a]	13.27 (16)	44.78	33.42 (15.8)	26.90 (16.9)	26.14	
4A[c]	14.94 (6.64)	43.79 (7.57)	30.28	29.77	33.08	23.11 (8.12)
4E[c]	13.43 (1)	45.21 (1)	27.34	31.88	26.71	17.25 (1)
5A[d,e]	36.65 (3.93)	60.42	26.26 (4.55[f])	30.91	32.60	23.04 (4.55[f])
			24.65 (4.26)	30.16		
5E[d,e]	34.76 (1)	59.95	20.91 (1)	*b*	26.58	17.13 (1)
			18.40 (1)	*b*		
5A[g,e]	36.96 (4.23)	60.59	26.26	30.85	32.57	23.03
			24.59	30.03		
5E[g,e]	35.13 (1)	60.25	20.67	*b*	26.48	17.06
			18.56	*b*		
6A[h]	39.07 (1)	*b*	24.40 (1)	*b*	32.19	22.93 (1)
6E[h]	37.08 (9.05)	61.4	19.13 (8.78)	30.15	26.21	16.99 (8.98)
6A[d]	38.95 (1)	55.84 (1)	24.48 (1)	*b*	32.2	23.01 (1)
6E[d]	36.95 (11.1)	61.27 (8.89)	19.17 (9.06)	30.20	26.39	16.98 (10.2)
13[c,i]	13.35	44.40	33.17	35.24	32.42	22.73
	[13.07]	[44.83]	[33.69]	[35.74]	[32.63]	[22.55]

[a] In 1:1 acetone-d_6/trichloroethylene at −90 °C, concentration ca. 30%. [b] Not observed. [c] In 1:1 acetone-d_6/methylene chloride at −95 °C, concentration ca. 30%. [d] In 1:1 acetone-d_6/trichloroethylene at −100 °C, concentration ca. 20%. [e] See footnote *b*, Table I, regarding the doubled signals at C(3,5) and C(2,6). [f] After correction for an overlapping peak of the minor isomer. [g] In 1:1 acetone-d_6/methylene chloride at −95 °C, concentration ca. 20%. [h] In 1:1 acetone-d_6/methylene chloride at −90 °C, concentration ca. 20%. [i] This compound is anancomeric; the data were recorded to check effect of temperature and (cf. Table I) of solvent. The data in brackets were obtained at room temperature.

Table III. Calculated $-\Delta G^0$ Values (kcal/mol) for Sulfur Functions

		Signal integrated					
Compd	Temp, °C	MeS	C(1)	C(2,6)	C(3,5)	C(4)	C(Me)
1[a]	−90	1.01	n.d.[b]	1.00	1.03	n.d.	
4[c]	−95	1.03	0.98	n.d.	n.d.	n.d.	0.96
5[a]	−100	1.19	n.d.	1.18	n.d.	n.d.	1.18
5[c]	−95	1.22	n.d.	n.d.	n.d.	n.d.	n.d.
6[c]	−90	2.50	n.d.	2.49	n.d.	n.d.	2.50
6[a]	−100	2.53	2.45	2.46	n.d.	n.d.	2.50

[a] In acetone-d_6/CHCl=CCl_2. [b] Not determined, usually because the corresponding signal in the minor isomer was not seen or not well resolved. [c] In acetone-d_6/CH_2Cl_2.

in Table I discloses that, for the sulfides and sulfoxides, only C(3,5) provides an adequate spread ($\delta_e - \delta_a$) of chemical shifts to make such a calculation reliable. The shifts δ_e and δ_a may then be taken to be the shifts of C(3,5) in **7, 8** and **10, 11**, respectively, corrected by the known global β_e effect of a *tert*-butyl substituent of 0.59 ppm.[12] Insertion of these values, and the chemical shifts δ at C(3,5) for compounds **1** and **2** gives $K = (21.37 - 26.24)/(26.24 - 27.03) = 6.16$, $\Delta G = -1.08$ kcal/mol for CH_3S, and $K = 7.14$ or 9.67, $\Delta G = -1.16$ or −1.34 kcal/mol [depending on which of the two signals for the diastereotopic carbons at C(3,5) is chosen] for CH_3SO. The former value is in excellent agreement[13] with the low-temperature value (Table IV) and the agreement of the average of the latter values, −1.25 kcal/mol, with the value in Table IV is satisfactory also.[13] The calculation for the *cis*-4-methyl-substituted compounds **4–6** is more complex, since the anticipated shifts for the axial (A) and equatorial (E) conformers in Scheme II must be computed by applying the effect of the equatorial or axial methyl substituent to the shifts calculated (vide supra) for the A and E models in Scheme I. If this is done at C(3,5), it turns out, unfortunately, that the calculated shifts for the A and E isomers in Scheme II are nearly the same. Fortunately, for the sulfones (**6, 9, 12**) one can instead use the C(1) signals for which the corrections for the distant alkyl groups[12] are small: −0.28 ppm for *tert*-butyl, −0.30 for Me_a, and −0.48 for Me_e. With these values, $K = 5.88$, $\Delta G = -1.05$ kcal/mol for **6** which gives a $-\Delta G$ value of 2.75 kcal/mol for the sulfone group, in acceptable agreement with the low-temperature value.[13]

Table IV. $-\Delta G^0$ Values (kcal/mol) for Sulfur Functions

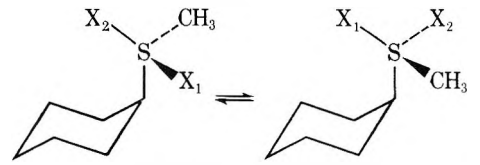
	CH_3S	CH_3SO	CH_3SO_2
This work[a]	1.00 ± 0.05	1.20 ± 0.05	2.50 ± 0.05
Lit.	1.07 ± 0.04[b]	(1.9[c])	(2.5[d])

[a] Values at −90° to −100 °C, in acetone-d_6/CHCl=CCl_2 or acetone-d_6/CH_2Cl_2. Because of the small temperature range and the apparent absence of variation in the two solvent systems, all values in Table III have been averaged. [b] Value for CD_3S at −79 °C in CS_2, ref 4. [c] Value of ref 6 for the phenylsulfinyl group; 0 °C, in 90% 2-propanol, determined by the kinetic method. [d] Value of ref 5 for the phenylsulfonyl group, room temperature in CCl_4.

Discussion

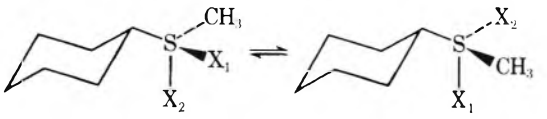
The $-\Delta G^0$ value at −90 °C for the methylthio group (Table IV) is in excellent agreement with that previously determined[4] by low-temperature ^1H NMR spectroscopy. The value previously determined by the chemical shift method in ^1H NMR, 0.7 kcal/mol,[3] is clearly too low, either because of inaccuracy of the measurement, or unsuitability of the model compounds,

Scheme III



X = O or unshared pair

sulfide	Me/CH_2	Me/CH_2
sulfoxides	Me/CH_2; O/CH_2	Me/CH_2; O inside
sulfone	Me/CH_2; O/CH_2; O inside	Me/CH_2; O/CH_2; O inside



sulfide	Me/CH_2	Me/CH_2
sulfoxides	Me/CH_2; O/CH_2	Me/CH_2; 2 O/CH_2
sulfone	Me/CH_2; 3 O/CH_2	Me/CH_2; 3 O/CH_2

sulfide	$2Me/CH_2$
sulfoxides	$2Me/CH_2$; O/CH_2
sulfone	$2Me/CH_2$; 2 O/CH_2

or both. The sulfone value is much larger, as would be expected from the fact that the unshared electron pair, which confronts the ring in the sulfide,[14] is supplanted by a space-requiring oxygen atom. In both of these cases, part of the equatorial preference is undoubtedly entropic. If one assumes that the axial CH_3S and CH_3SO_2 groups will avoid the conformation in which the methyl group points into the ring, each will have two mirror-image conformations ("methyl-out") and therefore an entropy of mixing of R ln 2. For the equatorial groups one has the choice of CH_3 gauche to one or two ring methylenes in the sulfide and the combinations of one CH_3 gauche and three O gauche or two CH_3 gauche and two O gauche in the sulfone (Scheme III). From the literature it appears that both the **CH_2**–C–S–**CH_3** gauche interaction[15] and the **CH_2**–C–S–**O** gauche interaction[16] are near zero. Therefore the entropy of mixing for the equatorial CH_3S and CH_3SO_2 groups will approach R ln 3 and the entropy difference in both cases will be almost R ln 3 − R ln 2 or 0.8 eu, contributing 0.24 kcal/mol to the conformational energy at room temperature.

It follows that the additional steric interaction of the "inside" oxygen of the axial sulfone is (2.50 − 0.24) − (1.00 − 0.24) or 1.50 kcal/mol.

The axial sulfoxide will therefore exist very largely (over 90%) with the pair confronting the ring and the methyl group and oxygen atom pointing out. For an individual enantiomer of the (chiral) sulfoxide this allows only a single rotational arrangement when CH_3SO is axial as against three (vide supra) when it is equatorial. The entropic advantage for equatorial CH_3SO will therefore be R ln 3 or 2.2 eu, 1.4 eu more than for CH_3S. Thus at −95 °C, if one assumes ΔH to be the same for CH_3S and CH_3SO, ΔG should be 0.25 kcal/mol more negative for the sulfoxide. This is in excellent agreement with the experimental findings (Table IV) showing that the rather primitive assumptions (equal ΔH for MeS and MeSO, three equally populated conformations for the equatorial groups) are at least grossly correct.

Experimental Section

The ^{13}C NMR spectra were recorded on a Varian XL-100 pulsed Fourier transform nuclear magnetic resonance spectrometer. Samples were dissolved in $CDCl_3$ with tetramethylsilane (2%) as an internal standard. ^1H NMR spectra were recorded on a Varian XL-100 or Jeolco C-60 HL NMR spectrometer. The proton and carbon chemical shifts of samples as 5–20% (w/3) solutions are presented in parts per million (δ) downfield from internal tetramethylsilane (Me_4Si), and these values are accurate to ±0.01 ppm unless otherwise indicated. The low-temperature ^{13}C spectra were recorded on a Varian XL-100 using a 50:50 mixture of CH_2Cl_2–CD_3COCD_3 (or CCl_2=CHCl–CD_3COCD_3) as solvent system with Me_4Si (at the same temperature) as internal standard. Melting points were obtained in an Electrothermal melting point apparatus. Analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind., and Galbraith Laboratories, Inc., Knoxville, Tenn.

The compounds required for this study were prepared either by following standard literature procedures or as described below.

4-Methylcyclohexyl-1,1-dithiol from 4-Methylcyclohexanone, *n*-Butylamine, and Hydrogen Sulfide. The procedure used was similar to that of Magnusson.[17] Fifty-six grams (0.5 mol) of 4-methylcyclohexanone and 5 g (0.068 mol) of *n*-butylamine were dissolved in 150 ml of THF in a 1-l. three-neck flask equipped with a stirrer, gas inlet tube, thermometer, and calcium chloride tube. Fifty grams of anhydrous potassium carbonate was added, stirring commenced, and the mixture was cooled to −20 °C. Hydrogen sulfide was passed into the reaction mixture for 1 h, the temperature allowed to rise to 0 °C, and H_2S passage continued for an additional 5 h. The K_2CO_3 was filtered and washed with THF and the washings were added to the reaction mixture which was then cooled to −20 °C and acidified with 2 N hydrochloric acid. The solution was extracted with ether (3 × 150 ml) and the combined organic layer was washed with a saturated solution of sodium bicarbonate and brine and dried over anhydrous $MgSO_4$.

The dried organic layer was concentrated to ca. 250 ml, and using 23 g of $LiAlH_4$ in 150 ml of THF, the dithiol was reduced to monothiol. (The $LiAlH_4$ reaction mixture was decomposed by the addition of 45 ml of water and 250 ml of 10% sulfuric acid.) The reaction mixture was extracted with THF and dried over anhydrous $MgSO_4$ and the solvent removed on a rotary evaporator. The residue was distilled to yield 39 g (60%) of 4-methylcyclohexyl mercaptan, bp 48 °C (5 Torr) [lit.[18] bp 74–75 °C (17 Torr)].

^1H NMR ($CDCl_3$) δ 0.87 (bd, 3 H, CH_3C), 0.97–2.1 (m, 9 H, $C_{2,6,3,5,4}$ H), 2.4–2.83 and 3.03–3.37 (broad m and narrow m, 1 H, C_1 H).

4-Methylcyclohexyl Methyl Sulfide. The procedure used was similar to that of Weibull.[19] Exactly 35 g (0.27 mol) of 4-methylcyclohexyl mercaptan was placed in a 500-ml flask equipped with a magnetic stirrer and reflux condenser. To this was added 30 g of sodium hydroxide in 130 ml of water and 50 ml of ethanol. Then 34 g (0.27 mol) of dimethyl sulfate was added all at once and stirring was commenced. An exothermic reaction immediately took place and the temperature rose to 60 °C. When the solution had cooled to room temperature it was extracted with ether (3 × 100 ml). The ether extracts were combined, washed once with water and once with saturated brine, and dried over anhydrous $MgSO_4$. The ethereal solution was filtered, the solvent removed (flash evaporator), and the oily residue distilled at reduced pressure to obtain 30 g (77%) of a 45:55 mixture of *cis*- and *trans*-4-methylcyclohexyl methyl sulfide, bp 58–59 °C (10 Torr). The diastereoisomers were separated using 20% QF-1 on Chromosorb A mesh 50–80, 10-ft column at 130 °C.

^1H NMR ($CDCl_3$) cis δ 0.83 (d, J = 5.5 Hz, 3 H, CH_3C), 1.18–1.75 (m, 9 H, CH_2's and C_4 H), 1.92 (s, 3 H, CH_3S), 2.54–2.75 (m, 1 H, C_1 H_e); trans δ 0.87 (d, J = 6 Hz, 3 H, CH_3C), 0.96–2.07 (m, 9 H, CH_2's and C_4H), 2.07 (s, 3 H, CH_3S), 2.27–2.6 (m, 1 H, C_1 H_a).

***cis*-4-Methylcyclohexyl Methyl Sulfoxide.** A mixture of 1.81 g (12.5 mmol) of sulfide and 2.8 g (13 mmol) of $NaIO_4$ in 30 ml of water was stirred at 0 °C in an ice bath for 9 h. The reaction mixture was then let stand overnight (15 hr) in an icebox. The solid was filtered and washed several times with methylene chloride. The methylene chloride solution was washed once with water and dried over anhydrous $MgSO_4$. The methylene chloride was removed (flash evaporator) to obtain 1.61 g of crude sulfoxide containing 1–2% of sulfone. The impurity was removed by adsorbing the crude material dissolved in ether on an alumina column and eluting the sulfone with ether. The pure sulfoxide was then obtained by eluting with chloroform and further purification was effected by sublimation at 60 °C (0.2 Torr) to give 1.25 g (62%) of sulfoxide, mp 58–59 °C (hygroscopic).

^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6 Hz, 3 H, CH_3C), 1.1–2.3 (m, 9 H, CH_2's and C_4 H), 2.45–2.75 (m, 1 H, C_1 H_e), 2.57 (s, 3 H, CH_5SO).

***trans*-4-Methylcyclohexyl Methyl Sulfoxide.** The trans sulfoxide was similarly obtained in 70% yield and recrystallized from pentane to give white plates, mp 66–67 °C.

^1H NMR ($CDCl_3$) δ 0.91 (d, J = 6 Hz, 3 H, CH_3C), 0.99–2.68 (m, 10 H, CH_2's and CH's), 2.53 (s, 3 H, CH_3SO).

***cis*-4-Methylcyclohexyl Methyl Sulfone.** A mixture of 0.72 g (5 mmol) of cis sulfide, 15 ml of 1:1 mixture of acetic acid–acetic anhydride, and 5 ml of 30% hydrogen peroxide was stirred for 3 h. Water (50 ml) was added to the reaction mixture which was then extracted with a 1:1 mixture of $CHCl_3$–CH_2Cl_2 (3 × 50 ml). The organic layer was washed with saturated solution of sodium bicarbonate and then once with water. The dried ($MgSO_4$) organic layer was concentrated (flash evaporator) to obtain crude sulfone which was purified by recrystallization from hexane to give 0.6 g (68%) of white solid, mp 71–72 °C.

^{1}H NMR ($CDCl_3$) δ 0.99 (d, J = 7 Hz, 3 H, CH_3C), 1.47–2.2 (m, 9 H, CH_2's and C_4 H), 2.71–2.95 (m, 1 H, C_1 H_e), 2.86 (s, 3 H, CH_3SO_2).

Anal. Calcd for $C_8H_{15}SO_2$: C, 54.51; H, 9.15. Found: C, 54.70; H, 9.03.

***trans*-4-Methylcyclohexyl Methyl Sulfone.** In a similar manner, 0.72 g (5 mmol) of trans sulfide yielded 0.62 g (71%) of sulfone after recrystallization from hexane, mp 100–101 °C.

^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.5 Hz, 3 H, CH_3C), 0.99–2.36 (m, 9 H, CH_2's and C_4H), 2.83 (s, 3 H, CH_3SO_2), 2.62–2.97 (m, 1 H, C_1 H_a).

Anal. Calcd for $C_8H_{16}SO_2$: C, 54.51; H, 9.15. Found: C, 54.24; H, 8.93.

***trans*-4-*tert*-Butylcyclohexyl Mercaptan.** This material was prepared by the procedure of Magnusson[17] as previously described,[3,20] and similarly as described above for the 4-methyl analogue. The yield of crude material was 84%, bp 98–99 °C (11.5 Torr). Gas chromatographic analysis indicated the composition to be 71.7% trans, 28.3% cis (10-ft QF-1 column at 150 °C). The material was purified either by distillation through a 48-in. double-vacuum-jacketed Podbielniak column at reduced pressure (10 Torr), using diphenylmethane as a chaser solvent (the trans isomer is the higher boiling), or (or followed by) oxidation to the disulfide by means of iodine in benzene. The disulfide was recrystallized from ethanol, mp 102–103 °C.

Anal. Calcd for $C_{20}H_{38}S_2$: C, 70.11; H, 11.18. Found: C, 70.05; H, 11.25.

The pure disulfide was reduced back to the trans mercaptan by means of lithium aluminum hydride in tetrahydrofuran[20] in 84% yield, bp 99.5–101 °C (10 Torr), n^{20}D 1.4861, purity (by GLC) > 99.5%.

***trans*-4-*tert*-Butylcyclohexyl Methyl Sulfide.** This thioether was prepared from the mercaptan as described for the 4-methyl analogue above, bp 114–115 °C (12 Torr), n^{20}D 1.4887 [lit.[21] bp 103–104 °C (7.5 Torr), n^{20}D 1.4885].

^{1}H NMR ($CDCl_3$) δ 0.86 [s, 9 H, $(CH_3)_3C$], 0.95–1.47 and 1.75–1.95 (m, 9 H, CH_2's and C_4 H), 2.09 (s, 3 H, CH_3S), 2.4 (broad m, 1 H, C_1 H).

Anal. Calcd for $C_{11}H_{22}S$: C, 70.89; H, 11.90. Found: C, 71.09: H, 11.99.

***cis*-4-*tert*-Butylcyclohexyl methyl sulfide** was prepared as previously described,[21] or by methylation[17] of the cis mercaptan (see below), bp 115.5–117 °C (16 Torr), n^{20}D 1.4871 [lit.[21] bp 99–100 °C (7.5 Torr), n^{20}D 1.4912].

^{1}H NMR ($CDCl_3$) δ 0.85 [s, 9 H, $(CH_3)_3C$], 0.95–1.95 (m, 9 H, CH_2's and C_4 H), 2.03 (s, 3 H, CH_3S), 3.01 (narrow m, 1 H, C_1 H).

***cis*-4-*tert*-Butylcyclohexyl Methyl Sulfoxide.** A solution of 3.72 g (20 mmol) of *cis*-4-*tert*-butylcyclohexyl methyl sulfide in 40 ml of *p*-dioxane was cooled in an ice bath and 4.28 g (20 mmol) of $NaIO_4$ in 40 ml of distilled water was slowly added over a period of 30 min with stirring. Stirring was continued for an additional 5 h at 0 °C, after which the reaction mixture was stored overnight in the refrigerator.

The mixture was poured into 100 ml of water and the sulfoxide was extracted with methylene chloride (3 × 50 ml). The methylene chloride was washed several times with water and then dried over anhydrous $MgSO_4$. The solvent was concentrated (flash evaporator) and the crude sulfoxide was recrystallized from hexane to give 2.57 g (64%) of pure sulfoxide, mp 152.5–153.5 °C.

^{1}H NMR ($CDCl_3$) δ 0.88 [s, 9 H, $(CH_3)_3C$], 0.96–2.06 (m, 9 H, CH_2's and C_4 H), 2.65 (s, 3 H, CH_3SO), 2.5–2.96 (m, 1 H, C_1 H_e).

***trans*-4-*tert*-Butylcyclohexyl Methyl Sulfoxide.** The trans isomer was obtained in an analogous fashion, except that the solution was stirred in a cold-water bath overnight instead of being stored in the refrigerator. The trans sulfoxide was recrystallized from ligroin to give 0.9 g (32% based on the amount of starting material recovered from the mother liquor: ca. 1.1 g of sulfide) of pure trans sulfoxide, mp 74–75 °C.

^{1}H NMR ($CDCl_3$) δ 0.87 [s, 9 H, $(CH_3)_3C$], 0.9–2.7 (m, 10 H, CH_2's, CH's), 2.5 (s, 3 H, CH_3SO).

***cis*-4-*tert*-Butylcyclohexyl-*2,2,6,6-d*$_4$ Methyl Sulfide.** The procedure used was similar to that described[21] for the undeuterated compound.

A solution of 1.6 g (10 mmol) of 2,2,6,6-tetradeuterio-*trans*-4-*tert*-butylcyclohexanol[22] was converted to 2.88 g (91%) of crude tosylate as described.[23]

The crude tosylate 2.88 g (9 mmol) in 20 ml of *N*-methylpyrrolidone was allowed to react with 30 ml (20 ml of *N*-methylpyrrolidone and 10 ml of methanol) of a 0.5 M solution of potassium methyl sulfide prepared by reaction of potassium with methanethiol and the resulting mixture was heated on a steam bath for 14 h. The reaction mixture was poured into a mixture of ice and aqueous HCl and extracted three times with 25-ml portions of CH_2Cl_2. The combined methylene chloride extracts were washed three times with water and dried over $MgSO_4$. Removal of methylene chloride yielded an oil which on distillation from Kugelrohr afforded 1.55 g (80%) of *cis*-4-*tert*-butyl-2,2,6,6-tetradeuteriocyclohexyl methyl sulfide, 15% of 4-*tert*-butylcyclohexene, and ca. 5% of unknown material.

The pure cis isomer was obtained by preparative gas chromatography.

^{1}H NMR ($CDCl_3$) δ 0.85 [s, 9 H, $(CH_3)_3C$], 1.0–1.6 (m, 5 H, $C_{3,5,4}$ H), 2.03 (s, 3 H, CH_3S), 2.97 (broad s, 1 H, C_1 H_e).

***cis*-4-*tert*-Butylcyclohexyl-*2,2,6,6-d*$_4$ Methyl Sulfoxide.** In a similar manner as described for the undeuterated compound, 0.3 g (1.6 mmol) of *cis*-4-*tert*-butylcyclohexyl-*2,2,6,6-d*$_4$ methyl sulfide yielded 0.22 g (67%) of sulfoxide after purification of the crude material by sublimation [ca. 100 °C (0.03 Torr)], mp 149.5–151 °C.

^{1}H NMR ($CDCl_3$) δ 0.85 [s, 9 H, $(CH_3)_3C$], 1.0–1.86 (m, 5 H, $C_{3,5,4}$ H), 2.52 (s, 3 H, CH_3SO), 2.7 (broad s, 1 H, C_1 H_e).

***cis*-4-*tert*-Butylcyclohexyl-*2,2,6,6-d*$_4$ Methyl Sulfone.** Using 2 ml of a 1:1 mixture of HOAc/Ac_2O and 1 ml of H_2O_2 (30%), from 150 mg (0.73 mmol) of sulfoxide, 130 mg (59%) of sulfone was obtained, mp 174.5–175.5 °C.

^{1}H NMR ($CDCl_3$) δ 0.83 [s, 9 H, $(CH_3)_3C$], 1.03–1.7 (m, 5 H, $C_{3,5,4}$ H), 2.8 (s, 3 H, CH_3SO_2), 2.97 (broad s, 1 H, C_1 H_e).

***cis*- and *trans*-4-*tert*-butylcyclohexyl sulfones** were prepared from the sulfides in 80 and 91% yield, respectively, in the manner described for the 4-methyl analogue. The cis isomer melted at 175.5–176.5 °C (lit.[3] 176.5–177.5 °C).

^{1}H NMR ($CDCl_3$) δ 0.88 [s, 9 H, $(CH_3)_3C$], 1.5–1.9 and 2.25–2.6 (m, 9 H, CH_2's and C_4 H), 2.91 (s, 3 H, CH_3SO_2), 3.09 (narrow m, 1 H, C_1 H_e).

The trans isomer melted at 136.5–137.5 °C (lit.[2] 136–137 °C).

^{1}H NMR ($CDCl_3$) δ 0.88 [s, 9 H, $(CH_3)_3C$], 0.93–2.4 (m, 9 H, CH_2's and C_4 H), 2.78 (s, 3 H, CH_3SO_2), 2.78–3.03 (broad m, 1 H, C_1 H_a).

Anal. Calcd for $C_{11}H_{22}O_2$: C, 60.55; H, 10.09. Found: cis isomer. C, 60.23; H, 10.19; trans isomer, C, 60.54; H, 10.21.

Cyclohexyl methyl sulfoxide and sulfone were prepared as described[24] from cyclohexyl methyl sulfide (Aldrich).

Sulfoxide: ir (neat) 1040 cm^{-1} (S–O) (lit.[24] 1040 cm^{-1}).

^{1}H NMR ($CDCl_3$) δ 1.03–2.2 (m, 10 H, $C_{2,3,4,5}$ H), 2.47 (s, 3 H, CH_3SO), 2.27–2.7 (m, 1 H, C_1H).

Sulfone: ir (neat) 1140 and 1310 cm^{-1} (lit.[24] 1138 and 1309 cm^{-1}).

^{1}H NMR ($CDCl_3$) δ 0.93–2.4 (m, 10 H, $C_{2,3,4,5}$ H), 2.75 (s, 3 H, CH_3SO_2), 2.5–2.96 (m, 1 H, C_1 H).

***cis*-4-*tert*-Butylcyclohexyl Mercaptan. *cis*-4-*tert*-Butylcyclohexyl Thiocyanate.** *trans*-4-*tert*-Butylcyclohexyl *p*-toluenesulfonate[23] (31.0 g, 0.10 mol) was placed in a 500-ml three-neck round-bottom flask equipped with reflux condenser and mechanical stirrer and dissolved in the minimum amount (ca. 150 ml) of hot 95% ethanol. After addition of 29.4 g (0.30 mol) of KSCN the mixture was stirred under reflux for 12 h, cooled, and filtered, the precipitated potassium salt being thoroughly washed with ethanol which was added to the original filtrate. The ethanol solution was concentrated to one-fourth its original volume, diluted with 100 ml of water, and extracted with three 100-ml portions of ether. The combined ether extracts were washed with saturated brine, dried over $MgSO_4$, filtered, and concentrated and the product was distilled, bp 119–120 °C (2.3 Torr), yield 6.01 g (30.6%).

***cis*-4-*tert*-Butylcyclohexyl Mercaptan.** To 31.8 ml of a 1.15 M ethereal lithium aluminum hydride solution (0.0365 mol) contained in a dry 250-ml round-bottom three-neck flask equipped with a reflux condenser protected by a drying tube, mechanical stirrer, and pressure-equalized addition funnel was added 7.18 g (0.0365 mol) of *cis*-4-*tert*-butylcyclohexyl thiocyanate in 100 ml of anhydrous ether dropwise and with stirring. After addition was complete stirring was continued for 0.5 h, the solution was cooled and hydrolyzed by careful addition of 10 ml of water, and the solids were dissolved by addition of 10% sulfuric acid. The product was worked up in standard fashion and the residue distilled, bp 104 °C (15 Torr), yield 3.46 g (55.3%).

Anal. Calcd for $C_{10}H_{20}S$: C, 69.70; H, 11.70. Found: C, 70.31; H, 11.62.

***cis*-4-*tert*-Butylcyclohexyl disulfide** was prepared in the same fashion as the trans isomer in 85% yield, mp 116–117 °C after two recrystallizations from ethanol.

Anal. Calcd for $C_{20}H_{38}S_2$: C, 70.11; H, 11.18. Found: C, 70.13; H, 11.14.

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Registry No.—**1**, 7133-37-1; **2**, 56051-02-6; **3**, 60260-74-4; **4**, 60260-75-5; **5**, 60260-76-6; **6**, 60260-77-7; **7**, 4934-66-1; **8**, 60260-78-8; **9**, 4943-25-3; **10**, 5004-79-5; **10**-d_4, 60260-79-9; **11**, 60260-80-2; **11**-d_4, 60260-81-3; **12**, 4943-24-2; **12**-d_4, 60260-82-4; **13**, 60260-83-5; **14**, 60260-84-6; **15**, 60260-85-7; 4-methylcyclohexanone, 589-92-4; hydrogen sulfide, 7783-06-4; 4-methylcyclohexyl-1,1-dithiol, 60260-86-8; 4-methylcyclohexyl mercaptan, 60260-87-9; *trans*-4-*tert*-butylcyclohexyl mercaptan, 60260-88-0; 4-*tert*-butylcyclohexyl disulfide, 60260-89-1; 2,2,6,6-tetradeuterio-*trans*-4-*tert*-butylcyclohexanol tosylate, 51933-09-6; *cis*-4-*tert*-butycyctohexyl thiocyanate, 60260-90-4; *trans*-4-*tert*-butycyclohexyl *p*-toluenesulfonate, 7453-05-6; *cis*-4-*tert*-butylcyclohexyl mercaptan, 53273-25-9; *cis*-4-*tert*-butylcyclohexyl disulfide, 60305-05-7.

References and Notes

(1) Part 31: M. K. Kaloustian, N. Dennis, S. Mager, S. A. Evans, F. Alcudia, and E. L. Eliel, *J. Am. Chem. Soc.*, **98**, 956 (1976).
(2) E. L. Eliel and B. P. Thill, *Chem. Ind. (London)*, 88 (1963).
(3) F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Am. Chem. Soc.*, **91**, 344 (1969).
(4) E. L. Eliel, unpublished results cited in J. A. Hirsch, *Top. Stereochem.*, **1**, 199 (1967). (The source of the data there indicated is in error.)
(5) E. L. Eliel, E. W. Della, and M. Rogič, *J. Org. Chem.*, **30**, 855 (1965).
(6) E.g., F. A. L. Anet, C. H. Bradley, and C. W. Buchanan, *J. Am. Chem. Soc.*, **93**, 258 (1971); O. A. Subbotin and N. M. Sergeyev, *J. Chem. Soc., Chem. Commun.*, 141 (1976).
(7) For an alternative method, see F. A. L. Anet, I. Yavari, I. J. Ferguson, A. R. Katritzky, M. Moreno-Mañas, and M. J. T. Robinson, *J. Chem. Soc., Chem. Commun.*, 399 (1976).
(8) E. L. Eliel, E. W. Della, and T. H. Williams, *Tetrahedron Lett.*, 831 (1963).
(9) Cf. D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **89**, 6612 (1967); **94**, 5318 (1972).
(10) J. D. Roberts, F. J. Weigert, J. L. Kroschwitz, and H. J. Reich, *J. Am. Chem. Soc.*, **92**, 1338 (1970).
(11) E. L. Eliel, *Chem. Ind. (London)*, 568 (1959).
(12) F. W. Vierhapper and R. L. Wilier, *Org. Magn. Reson.*, in press.
(13) In actual fact, since $\Delta S \neq 0$ (see following discussion), $-\Delta G$ should increase with temperature. The calculated increase for a 130 °C increase in temperature is, however, only 0.11 kcal/mol for the sulfide and sulfone and 0.18 kcal/mol for the sulfoxide, i.e., it may be hidden by the inherent imprecision of the data, which do, in fact, suggest some increase.
(14) Regarding the small "steric requirement" of an unshared pair, cf. E. L. Eliel and M. C. Knoeber, *J. Am. Chem. Soc.*, **90**, 3444 (1968).
(15) Both D. W. Scott, H. L. Finke, J. P. McCullough, M. E. Gross, K. D. Williamson, G. Waddington, and H. M. Huffman, *J. Am. Chem. Soc.*, **73**, 261 (1951), and M. Hayashi, T. Shimanouchi, and S. Mizushima, *J. Chem. Phys.*, **26**, 608 (1957), found nearly equal energy for the anti and gauche conformers of $CH_3SCH_2CH_3$.
(16) J. B. Lambert and R. G. Keske, *J. Org. Chem.*, **31**, 3429 (1966), find only a small difference in energy (0.18 kcal/mol) between the axial and equatorial conformation of thiane sulfoxide.
(17) B. Magnusson, *Acta Chem. Scand.*, **16**, 1536 (1962).
(18) R. D. Obolentsev, S. V. Netupskaya, L. K. Gladkova, V. G. Bukharov, and A. V. Mashkina, *Khim. Seraorg. Soedin. Soderzh. Neftyakh Nefteprod.*, 87–94 (1956); *Chem. Abstr.*, **54**, 250c (1960).
(19) B. Weibull, *Ark. Kemi, Mineral. Geol.*, **23A**, 1 (1946); *Chem. Abstr.*, **44**, 1427c (1950).
(20) B. P. Thill, Ph.D. Dissertation, University of Notre Dame, Notre Dame, Ind., 1964.
(21) E. S. Huyser and J. R. Jeffrey, *Tetrahedron*, **21**, 3083 (1965).
(22) E. L. Eliel and E. C. Gilbert, *J. Am. Chem. Soc.*, **91**, 5487 (1969).
(23) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).
(24) D. Barnard, J. M. Fabian, and H. P. Koch, *J. Chem. Soc.*, 2442 (1949).

Synthesis of the Monothiosquarate and 1,2-Dithiosquarate Ions and Their Derivatives

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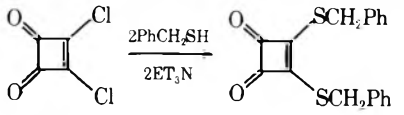
Reaction of diethyl squarate (diethoxycyclobutenedione) with 2 equiv of hydrosulfide ion gives the 1,2-dithiosquarate ion (DTS^{2-}) and reaction with 1 equiv gives the 3-ethoxycyclobutenedione-4-thiolate ion (**9**), which can be hydrolyzed to the monothiosquarate ion (MTS^{2-}). Thiosquarate ions are readily alkylated at sulfur to give alkylthio-substituted cyclobutenediones. For example, 3,4-bis(ethylthio)cyclobutenedione (**2b**) is prepared from DTS^{2-} and 3-ethoxy-4-ethylthiocyclobutenedione (**10b**) is obtained from **9**. Reaction of **10b** with 1 equiv of dimethylamine selectively replaces the ethoxy group, and reaction of **2b** with excess diethylamine gives a ring-opened product. The ir and ^1H NMR spectra of the compounds are discussed.

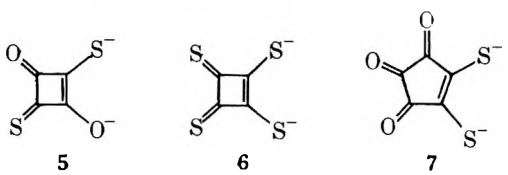
The monocyclic oxo carbon anions ($C_nO_n^{m-}$, n = 3–6), because of their unique electronic structures, have a number of unusual physical and chemical properties.[1,2] Several years ago we became interested in synthesizing sulfur analogues of oxo carbons and chose the four-membered ring series because of the chemistry already known for squaric acid (dihydroxycyclobutenedione) and its derivatives.[3] Addition–elimination reactions of oxygen and nitrogen nucleophiles were well known for cyclobutenediones with leaving groups on the vinyl carbons,[3–6] and some displacement reactions of sulfur nucleophiles have recently been reported.[7–14] For example, α-toluenethiol and dichlorocyclobutenedione (**1**) in the presence



1 **2a**

of base give 3,4-bis(benzylthio)cyclobutenedione (**2a**), a dithioester of squaric acid.[7,15]

Since our preliminary report of the monothiosquarate ion (**3**, MTS^{2-}) and the 1,2-dithiosquarate ion (**4**, DTS^{2-}),[7] others have reported the 1,3-dithiosquarate and tetrathiosquarate ions (**5** and **6**) and the 1,2-dithiocroconate ion (**7**).[14,16] In this



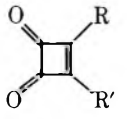
5 **6** **7**

paper the chemistry of MTS^{2-} and DTS^{2-} and related compounds is described.

Results and Discussion

Synthesis of Thiosquarates. The thiosquarate anions

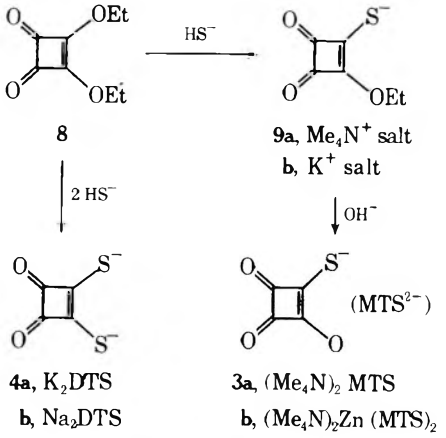
Table I. ^{1}H NMR Chemical Shifts (ppm) of Cyclobutenediones and Acetates



Registry no.	Compd	R	R′	δ OCH_2–	δ SCH_2–	δ NCH_3
5231-87-8	8	OEt	OEt	4.71		
52427-65-3	9a	OEt	$S^-Me_4N^+$	4.80		
60282-05-5	9b	OEt	S^-K^+	4.79		
52427-62-0	2b	SEt	SEt		3.46	
60282-06-6	10a	OEt	SMe	4.78	(2.85)[a]	
60282-07-7	10b	OEt	SEt	4.80	3.38	
60282-09-9	12	SMe	$O^-Me_4N^+$		(2.73)[a]	
19230-33-2	13	OEt	NMe_2	4.80		3.37, 3.23[b]
60282-10-2	11a	SMe	NMe_2		(2.93)[a]	3.38, 3.23
37669-71-9	11b	SEt	NMe_2		3.53	3.40, 3.25
		NMe_2	NMe_2			3.27[b]
	$CH_3C(=O)R$					
141-78-6		OEt		4.05		
625-60-5		SEt			2.84[c]	
127-19-5		NMe_2				2.94, 3.02

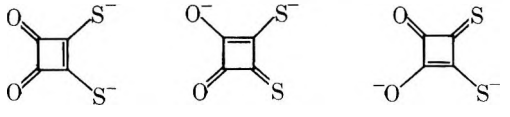
[a] *S*-Methyl groups. Add 0.6 ppm to compare to ethyl groups. [b] From ref 19. [c] R. Radeglia, S. Scheithauer, and R. Mayer, *Z. Naturforsch. B*, 24, 283 (1969).

MTS^{2-} and DTS^{2-} are synthesized by reactions of hydrosulfide ion and diethyl squarate (diethoxycyclobutenedione, 8). Two equivalents of potassium or sodium hydrosulfide convert diethyl squarate to DTS^{2-} in good yield.[7] With 1 equiv of potassium or tetramethylammonium hydrosulfide, displacement of one ethoxy group occurs, yielding the 3-ethoxycyclobutenedione-4-thiolate anion (**9**). Hydrolysis of **9** with



hydroxide is nearly quantitative, giving MTS^{2-} which has been isolated and characterized as the hygroscopic tetramethylammonium salt (**3a**) and as the ternary zinc salt **3b**.

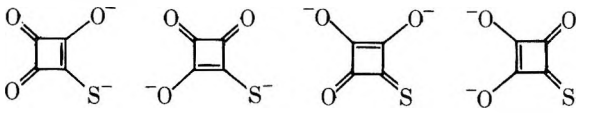
The symmetrical delocalized structure of the squarate ion was originally proposed because no carbonyl band was observed in the ir.[17] The DTS^{2-} ion has strong bands at 1705 and 1630 cm^{-1}, suggesting that **4** is the major resonance contributor to the structure of DTS^{2-}. However, the carbonyl stretching bands are shifted to higher frequency in the coordination complexes bonded through sulfur (1750–1655 cm^{-1}) and in the S-alkylated compounds **2a,b** (1770–1745 cm^{-1}).[7] Therefore resonance forms 4′ and 4″ may also contribute



4 4′ 4″

significantly to the structure of the free anion. The driving force for the incorporation of some carbon–sulfur double bond character may be the unfavorable α-dicarbonyl dipole interaction in **4** which is reduced in 4′ and 4″.

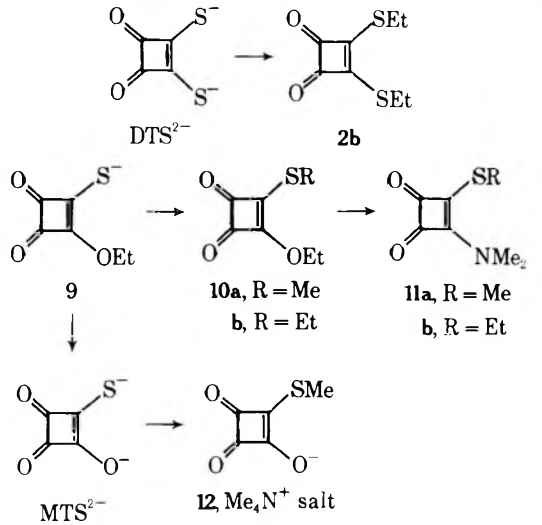
The MTS^{2-} ion has a higher frequency carbonyl band than DTS^{2-} (1735 vs. 1705 cm^{-1}). In this ion, the equivalent canonical forms **3** and **3′** can reduce the α-dicarbonyl interaction,



3 3′ 3″ 3‴

and incorporation of carbon–sulfur double bond character (3″ and 3‴) is not as important.

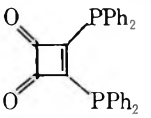
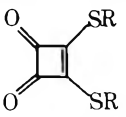
Reactions of Thiosquarate Anions. Alkylation of DTS^{2-} with iodoethane occurs rapidly, yielding 3,4-bis(ethylthio)-cyclobutenedione (**2b**) which has spectral properties similar



to those of **2a**, the dibenzyl dithioester.[7] The 3-ethoxycyclobutenedione-4-thiolate ion (**9**) is also easily alkylated, forming 3-ethoxy-4-alkylthiocyclobutenediones **10a,b**. Reaction of **10a,b** with 1 equiv of dimethylamine gives only displacement of the ethoxy groups, yielding 3-dimethylamino-4-alkylthiocyclobutenediones **11a,b**.[18] The MTS^{2-} ion reacts only at sulfur with excess iodomethane to form the S-methylated ion **12**.

The structural assignments for compounds **2** and **9**–**12** are clear from the ^{1}H NMR data summarized in Table I. The chemical shifts of the *O*-methylene and *S*-methylene protons are downfield from those of the corresponding acetates by

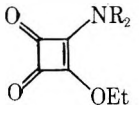
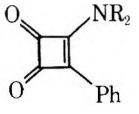
Table II. Infrared Spectra of Phosphorus- and Sulfur-Substituted Cyclobutenediones

	15	2a, R = $PhCH_2$	2b, R = Et
$\nu_{C=O}$, cm^{-1}	1770	1765	1770
	1760	1747	1747
ν_{C4}, cm^{-1}	1447	1453	1454
	1128	1124	1133

0.6–0.7 ppm, and dimethyl squaramides have *N*-methyls that appear 0.3–0.4 ppm downfield from dimethylacetamide.

Dialkylamino-substituted cyclobutenediones **13** and **14** undergo relatively slow rotation about the C–N bond, giving

13 **14**

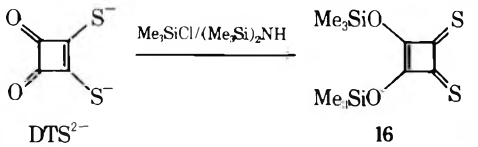
R = Me, Et, CH_2Ph

rise to nonequivalent alkyl groups in the ^1H NMR spectra.[19] Hindered rotation was also observed in the ^1H NMR spectra of **11a,b**, and a variable temperature study of **11b** showed coalescence of the *N*-methyls at 62.5 ± 1 °C, corresponding to an activation energy of 17.5 kcal/mol. Similar activation energies (15.7–17.3 kcal/mol) were found for the amides **13** and **14**.[19]

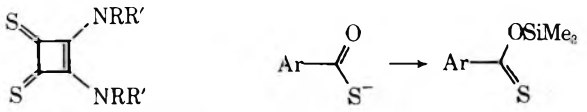
The ir spectra of cyclobutenediones with 2p-element substituents (CH_3, NR_2, OR) have two C=O stretching frequencies in the 1600–1900-cm^{-1} region and a strong C=C band at 1500–1600 cm^{-1}.[20] The ir spectra of 3-ethoxy-4-alkylthiocyclobutenediones **10a,b** and 3-dimethylamino-4-alkylthiocyclobutenediones **11a,b** are similar, having the expected C=O and C=C bands, but the spectra of 3,4-bis(alkylthio)cyclobutenediones **2a,b** lack the C=C band in the 1500–1600-cm^{-1} range. Compounds **2a,b** have in common four especially strong bands at frequencies very near those previously assigned to C=O and cyclobutene stretching modes in 3,4-bis(diphenylphosphino)cyclobutenedione[21] (**15**, Table II).

Protonation of DTS^{2-} gave a yellow solid with an S–H band in the ir, but rapid decomposition with loss of hydrogen sulfide discouraged further characterization.

Silylation of DTS^{2-} yielded an extremely moisture-sensitive red-orange compound (**16**) which readily dissolved in ether and carbon tetrachloride. Although **16** regenerated DTS^{2-} on



DTS^{2-} **16**

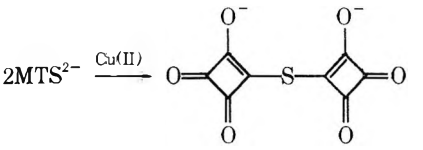


17a, R = H; R′ = cyclohexyl

b, R = R′ = Et

reaction with hydroxide, comparison of the ir spectrum with that of 3,4-bis(ethylthio)cyclobutenedione (**2b**) ruled out structural assignment as the *S,S′*-disilyl derivative. Comparison to the ir spectra of dithiosquaramides **17a,b**[22] and the report of O-silylation of potassium thiobenzoates[23] suggested that **16** was the O-silylated derivative of DTS^{2-}.[24]

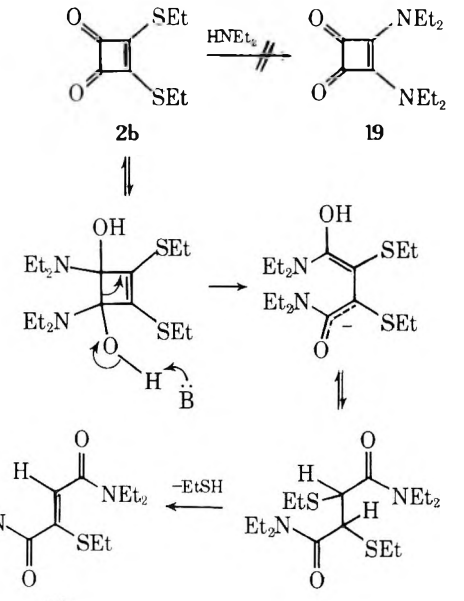
Reactions of DTS^{2-} and transition metal ions have led to interesting coordination compounds,[7,25] and the reaction of MTS^{2-} with aqueous copper(II) ion to give the bicyclic anion **18** has been reported.[13]



18

Reaction of Thiosquarate Esters with Amines. Reactions of dichlorocyclobutenedione (**1**) and diethyl squarate (**8**) resemble those of carboxylic acid chlorides and esters[3a,6] and carboxylic thioesters have long been known to react like esters.[26] To see if alkylthio groups could easily be removed from cyclobutenediones, several experiments were carried out. Reaction of 3-ethoxy-4-alkylthiocyclobutenediones **10a,b** with dimethylamine gave displacement of the ethoxy groups rather than the alkylthio groups (vide supra).

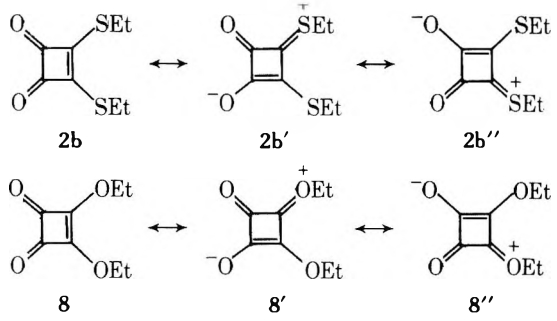
When 3,4-bis(ethylthio)cyclobutenedione (**2b**) was treated with an excess of diethylamine, formation of the expected squaramide **19** did not occur. The product in nearly quantitative yield was identified from spectral data as fumaramide **20**. The trans geometry was established by comparison of the observed chemical shift of the vinyl proton (δ 7.65) with the chemical shifts calculated from substituent constants[27] for fumaramide **20** (δ 7.64) and the corresponding maleamide (δ 6.86). The reaction probably proceeds by addition of amine to the carbonyl groups followed by base-catalyzed ring opening to a sulfur-stabilized enolate ion which can go on to the observed product.[28] Diphenylcyclobutenedione undergoes similar ring-opening reactions with ethanol and aromatic or acetylenic Grignard reagents.[29–31]



2b **19**

20

Nucleophilic addition at the carbonyl groups of 3,4-bis(ethylthio)cyclobutenedione (**2b**) rather than at the vinyl carbons as seen in the reactions of diethyl squarate (**8**)[3a,6] is consistent with a smaller contribution of dipolar resonance forms. Contributions by canonical forms **2b′**, **2b″**, **8′**, and **8″** are expected to decrease electron deficiency at the carbonyl carbons and make the vinyl carbons more susceptible to nucleophilic attack. Because of the much greater bond energy of carbon–oxygen double bonds than carbon–sulfur double bonds,[32] the dipolar resonance forms **2b′** and **2b″** should be much less important that **8′** and **8″**.



It has been pointed out (vide supra) that the ir spectra of dithioesters **2a,b** differ from spectra of cyclobutenediones with 2p-element substituents, and the observed reactivity of **2b** is quite different from that of diethyl squarate (8). Dithioesters **2a,b**, as well as other alkylthiocyclobutenediones, obviously have unique chemical properties which cannot necessarily be predicted from those of the alkoxycyclobutenediones.

Experimental Section

General Methods. The following instruments were used for spectral measurements: ^{1}H NMR, Varian A-60A; ir, Perkin-Elmer 457; uv–visible, Cary 14; mass spectra, AEI-MS 902, ionization potential 70 eV. Gas–liquid chromatography was carried out on a Barber-Coleman 5340 with a thermal conductivity detector. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points and boiling points are uncorrected.

Squaric acid was obtained from Aldrich or Columbia Organic Chemicals.

Diethyl squarate (8) was prepared by reaction of squaric acid and ethanol[3a,6] and had the following spectral properties: ir ($CHCl_3$) 1810 (m), 1735 (s), 1605 (s), 1480 (m), 1425 (m), 1380 (m), 1335 (m), 1080 (m), 1025 cm^{-1} (m); ^{1}H NMR (CCl_4) δ 4.71 (q, 2 H), 1.50 (t, 3 H); ^{1}H NMR (CD_3CN) δ 4.68 (q, 2 H), 1.40 (t, 3 H).

Dipotassium and Disodium 1,2-Dithiosquarate (4a,b). A 130-ml portion of 0.47 M anhydrous potassium methoxide in methanol (0.61 mol) was cooled to 0 °C and saturated with hydrogen sulfide. Addition of 5.1 g (0.27 mol) of diethyl squarate (8) was carried out over 15 min while stirring at 0 °C and hydrogen sulfide addition were continued. The reaction mixture was then stirred at 0 °C for 1 h, allowed to warm, and stirred at room temperature for 1 h, and heated at reflux for 0.5 h. Evaporation of solvent gave 7.8 g of yellow solid which was recrystallized from 100 ml of 90% aqueous methanol and dried ($CaSO_4$) to give 6.13 g (85%) of dipotassium 1,2-dithiosquarate monohydrate (**4a**): ir (KBr) 1705 (s), 1630 (s), 1340 (s), 1325 (s), 1205 (s), 920 (m), 565 cm^{-1} (m); uv–visible (water) λ_{max} 347 nm (log ϵ 4.42), 322 sh (4.30), 250 (4.12), 231 (4.04). Anal. Calcd for $C_4O_2S_2K_2{\cdot}H_2O$: C, 19.99; H, 0.84. Found: C, 19.89; H, 0.89.

Drying at 100 °C in vacuo removed ca. 0.33 mol of water. Anal. Calcd for $C_4O_2S_2K_2{\cdot}0.67H_2O$: C, 20.49; H, 0.60; S, 27.45. Found: C, 21.18; H, 0.58; S, 27.35.

Reaction of diethyl squarate with sodium hydrosulfide in ethanol under similar conditions, followed by recrystallization from aqueous ethanol and drying in vacuo at 100 °C, gave **4b** (80%) hydrated with ca. 2.67 mol of water. Anal. Calcd for $C_4O_2S_2Na_2{\cdot}2.67H_2O$: C, 20.16; H, 2.03; S, 26.92; O, 31.36. Found: C, 20.17; H, 2.25; S, 26.81; O, 31.33.

Tetramethylammonium 3-Ethoxycyclobutenedione-4-thiolate (9a). To a hydrogen sulfide saturated solution of 12 ml (0.033 mol) of 2.77 M tetramethylammonium hydroxide in methanol and 50 ml of absolute ethanol at 0 °C was added 5.1 g (0.030 mol) of diethyl squarate (8). The reaction mixture was then stirred at 0 °C for 1 h, allowed to warm to room temperature, and stirred for 1 h, and heated at reflux for 30 min. Evaporation of solvent gave a yellow solid which was recrystallized from 25 ml of absolute ethanol to give after drying ($CaSO_4$) 5.1 g (74%) of **9a:** mp 151–154 °C; ir (KBr) 3020 (w), 2970 (w), 1755 (s), 1675 (s), 1500 (s), 1445 (s), 1360 (s), 1315 (s), 1295 (s), 1260 (s), 1045 (s), 955 (s), 940 (s), 770 cm^{-1} (s); ^{1}H NMR (CD_3CN) δ 4.80 (q, 2 H), 3.15 (s, 12 H), 1.38 (t, 3 H); uv–visible (water) λ_{max} 316 nm (log ϵ 4.50). Anal. Calcd for $C_{10}H_{17}SNO_3$: C, 51.92; H, 7.41; N, 6.06; S, 13.86. Found: C, 52.03; H, 7.48; N, 6.11; S, 14.00.

Potassium 3-Ethoxycyclobutenedione-4-thiolate (9b). Under conditions similar to those used in the preparation of **9a,** 1.00 g (5.88 mmol) of diethyl squarate (8) was added to a solution of 6.00 ml (5.99 mmol) of 0.998 N methanolic potassium hydroxide and 20 ml of methanol saturated with hydrogen sulfide. Several recrystallizations from ethanol gave 0.75 g (65%) of **9b:** ir (KBr) 1755 (s), 1650 (s), 1510 (s), 1390 (m), 1305 (s), 1040 (m), 995 (m), 975 cm^{-1} (m); ^{1}H NMR (CD_3CN) δ 4.79 (q), 1.38 (t). Anal. Calcd for $C_6H_5O_3SK$: C, 36.72; H, 2.57. Found: C, 36.62; H, 2.48.

Bis(tetramethylammonium)zinc(II) Bis(monothiosquarate) (3b). A solution of 6.1 g (0.0264 mol) of **9a** and 9.0 ml (0.0249 mol) of 2.77 N methanolic tetramethylammonium hydroxide in 10 ml of water was heated at reflux until the pH of the solution became neutral (90 min). A solution of 3.71 g (0.0125 mol) of zinc nitrate hexahydrate in 10 ml water was added and the solution was heated for 20 min longer. Evaporation of water and methanol, recrystallization from ethanol, and repeated recrystallization from methanol gave 0.9 g (14%) of light yellow $(Me_4N)_2Zn(MTS)_2$ (**3b**): ir (KBr) 3010 (w), 1750 (s), 1650 (s), 1550 (s, br), 1480 (s), 1370 (s), 1280 (s), 1100 (m), 1040 (m), 950 (s), 800 (m), 680 cm^{-1} (m); uv–visible (water) λ_{max} 324 nm (log ϵ 4.81), 269 (4.34). Anal. Calcd for $C_{16}H_{24}O_6S_2N_2Zn$: C, 40.88; H, 5.15. Found: C, 40.86; H, 5.02.

Tetramethylammonium Monothiosquarate (3a). A solution of 5.0 g (0.022 mol) of tetramethylammonium 3-ethoxycyclobutenedione-4-thiolate (**9a**) and 12 ml (0.033 mol) of 2.75 M methanolic tetramethylammonium hydroxide in 35 ml of methanol and 5 ml of water were heated at reflux for 1 h. Methanol and water were removed under vacuum and the solid residue was recrystallized from absolute ethanol to yield 4.7 g (71%) of highly hygroscopic **3a:** ir (KBr) 3005 (w), 2950 (w), 1735 (s), 1590 (s), 1540 (s), 1485 (s), 1400 (m), 1280 (s), 1130 (m), 955 cm^{-1} (s).

When the uv–visible spectrum of a solution of **9a** and excess sodium hydroxide in water was monitored, nearly quantitative hydrolysis to the monothiosquarate ion was evidenced by the appearance in several hours of the following spectrum: λ_{max} 324 nm (log ϵ 4.49), 269 (3.99).

3,4-Bis(ethylthio)cyclobutenedione (2b). A solution of 31.0 g (0.129 mol) of dipotassium 1,2-dithiosquarate monohydrate (**4a**) in 200 ml of DMF and 20 ml of water was treated with 54.5 g (0.35 mol) of freshly distilled iodoethane. After stirring for 4.5 h at room temperature, the reaction mixture was added to 1 l. of water and extracted with one 400-ml and four 200-ml portions of pentane. The combined organic extracts were washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated, and the yellow liquid was distilled (85–90 °C, 0.05 Torr) to give 23.6 g (91%) of **2b.** GLC analysis (20% QF-1, 202 °C) showed one peak with a retention time of 22 min. The following data were obtained: ir (CCl_4) 1770 (s), 1747 (s), 1454 (s), 1421 (m), 1378 (m), 1265 (m), 1133 (s), 1078 (m), 1040 (m), 872 cm^{-1} (m); ^{1}H NMR (CCl_4) δ 3.46 (q, 2 H), 1.48 (t, 3 H); mass spectrum (10 eV) *m/e* (rel intensity) 204 (11), 203 (12), 202 (100, M$^+$), 174 (10), 148 (4), 147 (4), 146 (37); uv–visible (cyclohexane) λ_{max} 321 nm sh (log ϵ 4.22), 311 (4.36), 302 sh (4.29), 290 sh (4.17), 213 (4.07). Anal. Calcd for $C_8H_{10}S_2O_2$: C, 47.50; H, 4.98; S, 31.70. Found: C, 47.32; H, 4.88; S, 31.65.

3,4-Bis(benzylthio)cyclobutenedione (2a). A solution of 2.0 g (0.0171 mol) of α-toluenethiol and 2.4 g (0.0170 mol) of triethylamine in 5 ml of chloroform was added dropwise in 1 h to a stirred solution of 1.28 g (0.0085 mol) of dichlorocyclobutenedione (**1**)[33] at 0 °C and stirred for an additional 1 h. The reaction mixture was washed twice with 25 ml of 2% aqueous hydrochloric acid and twice with water, dried (Na_2SO_4), and evaporated to yield 2.8 g (103%) of a yellow oil, 75% **2a** by ^{1}H NMR. Several recrystallizations from hexane and hexane–benzene yielded 1.0 g (36%) of yellow **2a:** mp 69–70 °C; ir (CCl_4) 3060 (w), 3030 (w), 2915 (w), 2845 (w), 1765 (s), 1747 (s), 1495 (w), 1453 (s), 1415 (w), 1124 (s), 1070 (w), 690 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 7.24 (s, 5 H), 4.75 (s, 2 H); mass spectrum *m/e* (rel intensity) 326 (12, M$^+$), 235 (10, M$^+$ – C_7H_7, M* at 169.5), 207 (8), 123 (31), 91 (100), 65 (12).

3-Ethoxy-4-methylthiocyclobutenedione (10a). A solution of 2.31 g (0.0100 mol) of **9a** in 25 ml of acetonitrile was treated with 2.3 g (0.016 mol) of freshly distilled iodomethane. After the mixture had been stirred at room temperature for 20 min, solvent and excess iodomethane were evaporated. The residue was dissolved in 50 ml of water and extracted with one 75-ml and six 25-ml portions of hexane. The organic extracts were combined, dried (Na_2SO_4), and evaporated, and the residue Kugelrohr distilled (80–100 °C, 0.15 Torr) to yield 1.22 g (71%) of **10a** as a light yellow liquid: ^{1}H NMR ($CDCl_3$) δ 4.80 (q, 2 H), 2.85 (s, 3 H), 1.48 (t, 3 H); ir (CCl_4) 2980 (w), 2940 (w), 1790 (s), 1745 (s), 1565 (s), 1340 (m), 1315 (m), 1260 (m), 1035 cm^{-1} (m); mass spectrum *m/e* (rel intensity) 172 (34, M$^+$), 144 (24), 115 (84), 88 (45), 87 (100), 72 (10), 59 (22), 58 (23); *m/e* 172.01945 (calcd for $C_7H_8O_3S$, 172.01941).

3-Ethoxy-4-ethylthiocyclobutenedione (10b). To a solution of 1.00 g (4.32 mmol) of **9a** in 10 ml of dimethylformamide was added 0.97 ml (12 mmol) of freshly distilled iodoethane. The mixture was

stirred for 15 min and then partitioned between 25 ml of hexane and 35 ml of water. The aqueous layer was washed with five 25-ml portions of hexane and the combined organic layers were washed with 25 ml of saturated aqueous sodium chloride, dried ($MgSO_4$), concentrated, and Kugelrohr distilled (80–90 °C, 0.15 Torr) to give 0.63 g (78%) of **10b**. GLC (20% QF-1, 225 °C) showed one peak at 11.7 min. Analysis of samples purified by preparative GLC gave the following data: ir (CCl_4) 1785 (s), 1740 (s), 1560 (s), 1315 (m), 1255 (m), 1030 cm^{-1} (m); ^1H NMR (CCl_4) δ 4.78 (q, 2 H), 3.38 (q, 2 H), 1.50 (t, 3 H), 1.45 (t, 3 H); uv–visible (cyclohexane) λ_{max} 285 nm (log ϵ 4.34), 258 (3.98); mass spectrum (10 eV) *m/e* (rel intensity) 188 (8), 187 (12), 186 (100, M^+), 158 (62), 129 (20), 101 (9). Anal. Calcd for $C_8H_{10}SO_3$: C, 51.59; H, 5.41; S, 17.22. Found: C, 51.39; H, 5.25; S, 17.45.

3-Dimethylamino-4-methylthiocyclobutenedione (11a). A solution of 0.13 g (2.9 mmol) of dimethylamine in 10 ml of ether was added dropwise to a stirred solution of 0.50 g (2.9 mmol) of 3-ethoxy-4-methylthiocyclobutenedione (**10a**) in 10 ml of ether. After stirring at room temperature for 10 min, solvent was removed and the residue recrystallized from hexane/benzene to give 0.35 g (70%) of light yellow **11a**: mp 114–115 °C; ir ($CHCl_3$) 1780 (s), 1725 (m), 1710 (m), 1610 (s), 1425 (m), 1350 (m), 1320 (m), 1180 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 3.38 (s, 3 H), 3.23 (s, 3 H), 2.93 (s, 3 H); mass spectrum *m/e* (rel intensity) 173 (3), 172 (5), 171 (50, M^+), 143 (24), 115 (81), 100 (100), 95 (24), 85 (32), 81 (9), 70 (10); *m/e* 171.0353 (calcd for $C_7H_9NO_2S$, 171.0354). Anal. Calcd for $C_7H_9NO_2S$: C, 49.10; H, 5.30; N, 8.18; S, 18.73. Found: C, 49.12; H, 5.37; N, 8.09; S, 18.98.

3-Dimethylamino-4-ethylthiocyclobutenedione (11b). A solution of 0.200 g (1.07 mmol) of 3-ethoxy-4-ethylthiocyclobutenedione (**10b**) in 10 ml of methylene chloride was cooled to −78 °C and treated with 0.080 ml (1.2 mmol) of dimethylamine. The solution was allowed to warm slowly to room temperature in 30 min. ^1H NMR analysis of the crude product showed only peaks for **11b** plus a trace of an impurity at δ 3.0 (integration ca. 5% of triplet at δ 1.43). Recrystallization of the crude yellow oil from ether gave 0.155 g (78%) of **11b**: mp 58–60 °C (lit.[10] 59 °C); ir ($CHCl_3$) 1780 (s), 1715 (m), 1610 (s), 1425 (m), 1350 (m), 1175 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 3.53 (q, 2 H), 3.40 (s, 3 H), 3.25 (s, 3 H), 1.43 (t, 3 H); mass spectrum *m/e* (rel intensity) 185 (M^+, 75), 157 (8), 129 (65), 101 (31), 100 (100), 96 (30), 85 (31), 70 (10); *m/e* 185.05112 (calcd for $C_8H_{11}NO_2S$, 185.05105).

Variable temperature ^1H NMR measurements on **11b** in bromobenzene were carried out from room temperature to 100 °C. Temperatures were measured by thermocouple (±1 °C) before and after spectral determination. Coalescence of the *N*-methyls occurred at 62.5 °C, and, at 100 °C, a single sharp peak was observed for **11a,b** at δ 2.90.

Tetramethylammonium 3-Methylthiocyclobutenedion-4-olate (12). A solution of 13.0 g (5.62 mmol) of tetramethylammonium 3-ethoxycyclobutenedione-4-thiolate (**9a**) and 2.0 ml (5.54 mmol) of 2.77 N methanolic tetramethylammonium hydroxide in 10 ml of methanol and 2.0 ml of water was heated at reflux in the dark for 3 h. Solvents were evaporated and the crude tetramethylammonium monothiosquarate (**3a**) obtained was dissolved in 10 ml of Me_2SO and 2 ml of water and treated with 2.1 g (15 mmol) of freshly distilled iodomethane. After stirring at room temperature for 10 min, the mixture was filtered by suction. Water and Me_2SO were removed by Kugelrohr distillation, leaving 1.09 g (89%) of crude **12**. Recrystallization from dichloromethane gave 0.89 g (73%) of **12** as a yellow solid: mp 112–116 °C; ir (KBr) 3020 (w), 2940 (w), 1760 (s), 1690 (s), 1670 (s), 1605 (sh), 1565 (s), 1490 (m), 1330 (m), 1270 (s), 1120 (m), 1055 (m), 960 (m), 950 (s), 930 cm^{-1} (m); ^1H NMR (CD_3CN) δ 3.31 (s, 12 H), 2.73 (s, 3 H); uv–visible (water) λ_{max} 310 nm (log ϵ 4.30), 257 (4.11). Anal. Calcd for $C_9H_{15}NO_3S$: C, 49.75; H, 6.96; N, 6.45; S, 14.76. Found: C, 49.67; H, 6.97; N, 6.43; S, 14.54.

Silylation of DTS^{2-}. A 2.34-g (0.010 mol) sample of **4a** found to have the formula $K_2C_4O_2S_2 \cdot 0.67H_2O$ was suspended in 50 ml of dry ether and stirred under dry nitrogen in the dark with 5.1 ml (0.040 mol) of trimethylchlorosilane and 1.0 ml (0.005 mol) of hexamethyldisilazane for 5 days. The resulting red-orange solution was filtered in a glove bag and a known fraction of the clear filtrate was added to excess aqueous potassium hydroxide. Measurement of the uv–visible spectrum and comparison to the spectrum of DTS^{2-} indicated that the ethereal filtrate contained disilylated DTS^{2-} in 82% yield. Evaporation of ether and excess silylating agent from the filtrate yielded a red-orange, highly moisture-sensitive oil: ir (CCl_4) 2960 (m), 1665 (s), 1425 (s), 1335 (s), 1295 (s), 1255 (s), 1110 (m), 1100 (m), 980 (s), 940 cm^{-1} (m).

3,4-Bis(cyclohexylamino)cyclobutenedithione (17a) and 3,4-bis(diethylamino)cyclobutenedithione (17b) were prepared by the reported method.[3a,22] Compound **17a** was prepared in 80% yield using hexamethylphosphoric triamide as solvent and recrystallized from Me_2SO: mp 348–350 °C (darkens at 290 °C); ir (Nujol) 3230 (m), 3170 (m), 3120 (m), 1705 (s), 1570 (s), 1330 (s), 1270 (s), 1250 (s), 1230 (s), 1140 (m), 1080 (m), 945 (m), 885 cm^{-1} (m); mass spectrum *m/e* (rel intensity) 308 (M^+, 53), 225 (23), 193 (15), 183 (11), 145 (14), 144 (26), 143 (32), 116 (18), 111 (14), 105 (13), 83 (38), 55 (100), 44 (58). Anal. Calcd for $C_{16}H_{24}N_2S_2$: C, 62.29; H, 7.84; N, 9.08; S, 20.79. Found: C, 62.25; H, 7.81; N, 8.97; S, 20.85.

Compound **17b** was prepared in 24% yield using THF as solvent and recrystallized from benzene: mp 160–162 °C; ir (Nujol) 1675 (s), 1550 (s), 1310 (s), 1270 (s), 1250 (s), 1205 (m), 1170 (s), 1100 (m), 1070 (m), 1055 (m), 1010 (m), 795 (m), 560 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 3.89 (q, 2 H), 1.33 (t, 3 H); uv–visible (MeOH) λ_{max} 403 nm (log ϵ 4.60), 371 sh (4.48), 283 (4.34); mass spectrum *m/e* (rel intensity) 258 (11), 257 (16), 256 (100, M^+), 241 (5), 227 (36), 213 (16), 170 (18), 140 (17), 128 (11), 116 (14), 112 (11), 110 (11), 88 (16), 84 (30), 72 (45). Anal. Calcd for $C_{12}H_{20}N_2S_2$: C, 56.20; H, 7.86; N, 10.92; S, 25.01. Found: C, 56.16; H, 7.82; N, 10.97; S, 25.01.

***N,N,N',N'*-Tetraethyl-2-ethylthiofumaramide (20).** A solution of 0.40 g (2.0 mmol) of 3,4-bis(ethylthio)cyclobutenedione (**2b**) and 0.58 g (8.0 mmol) of diethylamine in 10 ml of ether was stirred at room temperature for 2.5 h. Evaporation of solvent and Kugelrohr distillation of the residue (135–140 °C, 0.1 Torr) gave 0.55 g (95%) of **20**: ^1H NMR (CCl_4) δ 7.65 (s, 1 H), 3.72 (q, broad, J = 7 Hz, 4 H), 3.39 (q, J = 7 Hz, 2 H), 3.17 (q, J = 7 Hz, 2 H), 2.64 (q, J = 8 Hz, 2 H), 1.0–1.5 (m, 15 H); ir (neat) 2980 (m), 1630 (s), 1580 (s), 1555 (s), 1450 (m), 1330 (m), 1220 (m), 1115 cm^{-1} (m); mass spectrum *m/e* (rel intensity) 286 (13), 187 (13), 186 (100), 158 (61), 129 (15), 128 (15), 126 (15), 114 (35), 100 (10), 98 (27), 97 (14), 96 (19), 86 (11), 82 (10), 72 (22), 68 (10), 59 (11), 56 (38); *m/e* 286.1727 (calcd for $C_{14}H_{26}N_2O_2S$, 286.1715). Anal. Calcd for $C_{14}H_{26}N_2O_2S$: C, 58.71; H, 9.15; N, 9.78; S, 11.19. Found: C, 58.57; H, 8.97; N, 9.76; S, 10.96.

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Registry No.—**1**, 2892-63-9; **2a**, 52427-63-1; **3a**, 52427-67-5; **3b**, 58288-49-6; **4a**, 52427-61-9; **4b**, 52427-60-8; **15**, 41006-27-3; **16**, 60282-11-3; **17a**, 60282-12-4; **17b**, 60282-13-5; **20**, 60282-14-6; squaric acid, 2892-51-5.

References and Notes

(1) D. Eggerding and R. West, *J. Am. Chem. Soc.*, **97**, 207 (1975); **98**, 3641 (1976).
(2) For general reviews of the oxocarbons see (a) R. West and J. Niu, "Nonbenzenoid Aromatics", Vol. 1, J. P. Snyder, Ed., Academic Press, New York, N.Y., 1969, Chapter 6; (b) R. West and J. Niu, "The Chemistry of the Carbonyl Group", Vol. 2, J. Zabicky, Ed., Interscience, New York, N.Y., 1970, Chapter 4.
(3) (a) G. Maahs and P. Hegenberg, *Angew. Chem., Int. Ed. Engl.*, **5**, 889 (1966); (b) H. E. Sprenger and W. Ziegenbein, *ibid.*, **7**, 530 (1968).
(4) W. Ried and A. H. Schmidt, *Angew. Chem., Int. Ed. Engl.*, **11**, 997 (1972).
(5) E. J. Smutny, M. C. Caserio, and J. D. Roberts, *J. Am. Chem. Soc.*, **82**, 1793 (1960).
(6) S. Cohen and S. G. Cohen, *J. Am. Chem. Soc.*, **88**, 1533 (1966).
(7) D. Coucouvanis, F. J. Hollander, R. West, and D. Eggerding, *J. Am. Chem. Soc.*, **96**, 3006 (1974).
(8) W. Ried and A. H. Schmidt, *Justus Liebigs Ann. Chem.*, **742**, 116 (1970).
(9) A. H. Schmidt, W. Ried, P. Pustolemsek, and H. Dietschmann, *Angew. Chem., Int. Ed. Engl.*, **11**, 142 (1972).
(10) G. Seitz and H. Morck, *Chimia*, **26**, 368 (1972).
(11) G. Seitz, R. Schmiedel, and K. Mann, *Synthesis*, 578 (1974).
(12) G. Seitz, H. Morck, K. Mann, and R. Schmiedel, *Chem.-Ztg.*, **98**, 459 (1974).
(13) D. Eggerding, J. L. Straub, and R. West, *Tetrahedron Lett.*, 3589 (1975).
(14) G. Seitz, K. Mann, R. Schmiedel, and R. Matusch, *Chem.-Ztg.*, **99**, 90 (1975); R. Allmann, T. Debaerdemaeker, K. Mann, R. Matusch, R. Schmiedel, and G. Seitz, *Chem. Ber.*, **109**, 2208 (1976).
(15) 3,4-Bis(methylthio)cyclobutenedione has recently been prepared from **1** and methanethiol and by another route. See ref 11.
(16) R. F. X. Williams, Abstracts, 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1975, No. INOR-033.
(17) S. Cohen, J. R. Lacher, and J. D. Park, *J. Am. Chem. Soc.*, **81**, 3480 (1959).
(18) Compound **11b** has been prepared by another method (ref 10), but only the melting point was reported.
(19) J. E. Thorpe, *J. Chem. Soc. B*, 435, 1534 (1968).
(20) F. G. Baglin and C. B. Rose, *Spectrochim. Acta, Part A*, **26**, 2293 (1970).
(21) H. J. Becher, D. Fenske, and E. Langer, *Chem. Ber.*, **106**, 177 (1973).
(22) The preparation of dithiosquaramides was first reported w thout detail in ref 3a. See also ref 12; G. Seitz, K. Mann, and R. Schmiedel, *Chem.-Ztg.*, **99**, 332 (1975).
(23) S. Kato, W. Akada, M. Mizuta, and Y. Ishii, *Bull. Chem. Soc. Jpn.*, **46**, 244 (1973).

(24) We have been unsuccessful in preparing the corresponding *O,O'*-diethyl derivative of DTS^{2-} by treatment of diethyl squarate (**8**) with B_2S_3 [F. M. Dean, J. Goodchild, and A. W. Hill, *J. Chem. Soc. C*, 2192 (1969)] or P_4S_{10}.
(25) F. J. Hollander and D. Coucouvanis, *J. Am. Chem. Soc.*, **96**, 5646 (1974); D. G. Holah and D. Coucouvanis, *ibid.*, **97**, 6917 (1975); D. Coucouvanis, D. G. Holah, and F. J. Hollander, *Inorg. Chem.*, **14**, 2657 (1975); D. Coucouvanis, D. Swenson, N. C. Baenziger, D. G. Holah, A. Kostikas, A. Simopoulos, and V. Petrouleas, *J. Am. Chem. Soc.*, **98**, 5721 (1976).
(26) E. E. Reid, "Organic Chemistry of Bivalent Sulfur", Vol. IV, Chemical Publishing Co., New York, N.Y., 1962, pp 31–33.
(27) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966).
(28) Since no reaction had occurred after 18 h when **2b** was dissolved in ethanol, a diketene intermediate is not involved. Ring opening could also occur after addition of only one molecule of amine to give a ketene enolate which could go on to the observed product.
(29) A. T. Blomquist and E. A. LaLancette, *J. Am. Chem. Soc.*, **83**, 1387 (1961).
(30) W. Ried and R. Lantzsch, *Chem. Ber.*, **104**, 679 (1971).
(31) E. Müller and A. Huth, *Tetrahedron Lett.*, 1031, 1035, 4359 (1972); *Chem.-Ztg.*, **96**, 585 (1972); J. Hambrecht, H. Straub, and E. Müller, *Chem. Ber.*, **107**, 3962 (1974).
(32) T. L. Cottrell, "The Strengths of Chemical Bonds", 2d ed, Butterworths, London, 1958, pp 270–289, Table 11.5.1.
(33) R. C. DeSelms, C. J. Fox, and R. C. Riordan, *Tetrahedron Lett.*, 781 (1970).

Crystal and Molecular Structure of *trans*-Biphthalyl, $C_{16}H_8O_4$. Reaction of Substituted Phthalic Anhydrides with Trialkyl Phosphites

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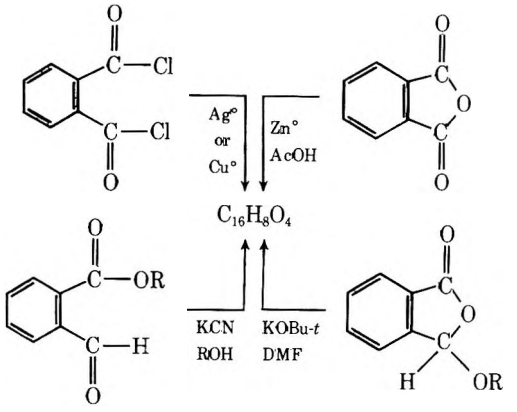
The crystal and molecular structure of *trans*-biphthalyl, the main product of the reaction of phthalic anhydride with triethyl phosphite, has been elucidated by x-ray crystallographic techniques. The yellow substance crystallizes in the monoclinic system, space group $P2_{1/c}$ with four asymmetric units per unit cell. The structure was refined by full-matrix least-squares techniques to a final R factor on F of 3.5% based on 571 observations above background. The molecule is planar, and some of the bond angles formed by the trigonal carbon atoms are significantly larger ($\Delta \sim 12°$) than the normal 120° value. It is suggested that the flexibility inherent in C–C–C, C–C–O, and C–O–C bond angles permits (a) the observed angle expansions which are required to allow for coplanarity of the chromophore O=C–C=C–C=C–C=C–C=O in the crowded molecule; and (b) the observed angle contractions, which are required to establish the five-membered rings. This effect accounts for the existence of octaphenyl-, octachloro-, and octabromo-*trans*-biphthalyl, although there is no assurance that the octahalo compounds have completely planar molecules.

The classical researches on the structure of phthalic anhydride, phthaloyl chloride, phthalaldehydic esters, and 3-alkoxyphthalides (Scheme I) led to a series of yellow and

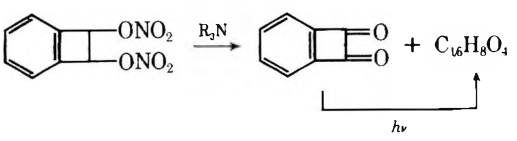
Scheme I



colorless isomers of the formula $C_{16}H_8O_4$, known as "biphthalyls".[2,3] Some of those experiments were later repeated[4] and extended.[5]

Structurally related $C_{16}H_8O_4$ compounds have been recently obtained from benzocyclobutene-1,2-diol dinitrate[6] (Scheme II), and from the photolysis[7-9] of benzocyclobutadienoquinone.[6]

Scheme II



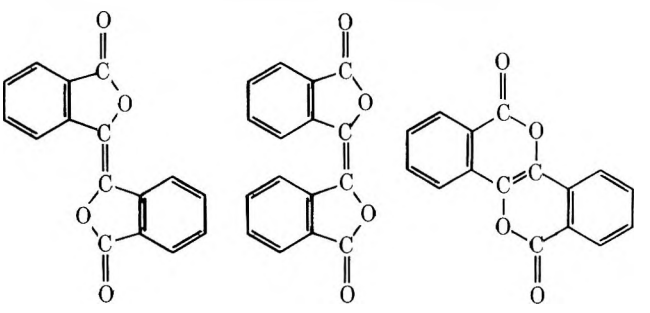
The biphthalyls were initially formulated as the trans and cis isomers, **1** and **2**, of the bis-γ-lactone of *o,o'*-dicarboxybenzoin.[2,3] However, the work of Cava[6] and of Bird[10] suggests that, with one exception,[7,8] the colorless substance designated as *cis*-BP (**2**)[11] is identical with the biisocoumarin (**3**) that was obtained as a by-product of the benzocyclobutadienoquinone synthesis[6] (Scheme II). Thus, the *acid-catalyzed* isomerization

$$\text{yellow } trans\text{-BP (1)} \xrightarrow{H(+)} \text{colorless "}cis\text{-BP (2)"}\ ^{5}$$

is actually

$$trans\text{-BP (1)} \xrightarrow{H(+)} \text{biisocoumarin (3)}^{10}$$

Scalar molecular models disclose an increasing degree of intramolecular crowding in the series: **3** < **1** ≪ **2**. Nevertheless (and this constitutes the exception mentioned above), Staab[7,8] has reported the isolation of authentic *cis*-BP (**2**, 5%), together with **1** (25%) and **3** (4%) from the photolysis of benzocyclo-

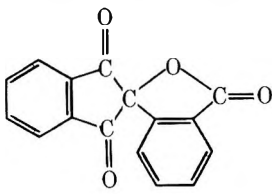


1 **2** **3**

butadienoquinone.[6] The thermal *cis*-**2** → *trans*-**1** isomerization was observed at 200 °C.

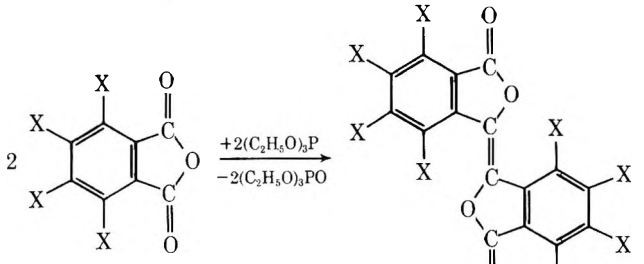
In 1959 we reported the deoxygenative coupling of PA[11] to *trans*-BP (**1**), by means of triethyl phosphite.[12,13] Bird and Wong[14] confirmed these results, and made the significant observation that biisocoumarin[6] (**3**) was formed as a by-product in about 25% yield. These authors,[15] as well as Markgraf et al.,[16] have extended the biphthalyl condensation to thiophthalic anhydride.

There is in the literature a fourth related $C_{16}H_8O_4$ isomer, the spirolactone[17] **4**. This substance was obtained by Brown[9]



4

(but not by Staab[7,8]) from the photolysis of benzocyclobutadienoquinone, and has been isomerized into *trans*-BP (**1**), thermally[17] (250–300 °C), and on heating with tertiary amines.[9,17,18]



5, X = H
6, X = Cl
7, X = Br
8, X = C_6H_5

1, X = H
9, X = Cl
10, X = Br
11, X = C_6H_5

The present investigation had three purposes: (1) to study the molecular structure of yellow BP (**1**) by x-ray crystallography; (2) to confirm the BP structure (**9**) previously assigned[13] to the yellow-orange crystals obtained from tetrachloro-PA (**6**) and triethyl phosphite, and to extend the reaction to other hindered PA derivatives, **7** and **8**; (3) to correlate the new and the published data in order to arrive at a rational explanation for the formation of *trans*- and *cis*-BP, and of biisocoumarin, in the various reactions mentioned above.

Experimental Section

Reaction of Phthalic Anhydride with Triethyl Phosphite. A mixture of phthalic anhydride and freshly distilled triethyl phosphite (½ mol ratio) was stirred under argon for 24 h at ca. 190 °C. A third molar equivalent of the phosphite was introduced, and the mixture was stirred for an additional 24-h period. The crystals which separated at 20 °C were collected, and were washed repeatedly with warm benzene; they represented 65% of the expected *trans*-BP (**1**), mp ca. 350 °C (see Table II). The pale-yellow crystals used in the x-ray analysis were obtained after recrystallization from mesitylene.

The mother liquid which remained after filtration of the *trans*-BP (**1**) was distilled under vacuum to remove triethyl phosphate. Unreacted phthalic anhydride was recovered by sublimation, and the residue was submitted to TLC (Table II). A spot attributed to biisocoumarin (**3**) was observed at R_f 0.48; the remaining **1** gave a spot at R_f 0.61, and there was a relatively weak spot at R_f 0.37.

The crystals of **1** obtained from xylene or from mesitylene sublimed at ca. 260 °C during slow heating on a hot stage. In open capillary, sublimation was also detected at ca. 260 °C. The sublimate resublimed at about the same temperature. On relatively rapid heating, the material melted to a clear liquid at 352–354 °C. When a sealed tube containing crystals of *trans*-biphthalyl was immersed in a bath preheated to 370 °C and the sample was kept for 2.5 h at that temperature, a clear melt was produced. This melt resolidified to a material which proved to be identical with the initial **1**, according to ir spectrum (Nujol mull) and TLC behavior.

Crystal Data. *trans*-Biphthalyl, $C_{16}H_8O_4$: monoclinic; $P2_{1/c}$; a = 10.196 (6), b = 3.778 (3), c = 15.090 (8) Å, $\cos\beta = -0.1228$ (2); ($\lambda_{CuK\alpha}$ = 1.5418 Å at 21 °C); Z = 2 (half a molecule per asymmetric unit); d_{calcd} = 1.52 g cm^{-3}, d_{meas} (by flotation in benzene–diiodomethane) = 1.50 (1) g cm^{-3}; μ(Cu Kα) = 9.38 cm^{-1}.

Data Collection and Structure Refinement. Precession and Weissenberg photographs of the ($hk0$), (hkl), ($0kl$), ($1kl$), and ($h0l$) zones showed systematic absences ($h0l$) for l odd and ($0k0$) for k odd implying space group $C_{2h}^5 = P2_{1/c}$. The cell dimensions were determined by a least-squares fit of the observed 2θ angles for 26 reflections centered automatically on a four-circle diffractometer.

Intensity data were collected from a light yellow crystal of rectangular prismatic habit and dimensions 0.3 × 0.1 × 0.05 mm. The crystal was mounted on a glass fiber and oriented along b^* (the prism axis). Data were obtained on a computer-controlled Picker four-circle diffractometer[19] using nickel-filtered Cu Kα radiation. Two independent sets of data (hkl and $\bar{h}kl$) were collected for 2θ (Cu Kα) < 55°. The 1337 observations gave 571 independent reflections with $F_o^2 > 3\sigma_{count}(F_o^2)$ with $\sigma(F_o^2)$ being based on Poisson counting statistics. The intensities of two standard reflections were measured periodically, and there was no evidence of crystal deterioration. Data were collected by θ–2θ step scans using a fixed scan width $\Delta 2\theta$ = 2.00° and a step size $\delta 2\theta$ of 0.02°. The center of the scan range was set at the Bragg angle calculated for 1.5418 Å. Background was measured as the average of the first and last ten points of the scan. The take-off angle was 3.0° and pulse height–pulse shape discrimination system was used.

Structure factors were derived in the usual way; no absorption correction was necessary. Normalized structure factors (E's) were used in a multiple solution direct methods technique as described by Germain, Main, and Woolfson[20] to determine phases from which an E map revealed the coordinates of all nonhydrogen atoms. The structure was refined by full-matrix least squares, minimizing the function $\Sigma w\Delta^2$ with $\Delta = |F_o| - |F_c|$ with weights $w = 4F_o^2/\sigma^2(F_o)^2$ and $\sigma^2(F_o^2) = \sigma_{count}^2(I) + (0.03F^2)^2$. All hydrogen atom positions were located by difference Fourier synthesis following isotropic refinement. The atomic scattering factors for all nonhydrogen atoms were taken from a standard source,[21] while that for hydrogen atoms was the best spherically averaged value of Stewart et al.[22]

The final least-squares cycles included anisotropic thermal parameters for the nonhydrogen atoms and individual isotropic thermal parameters on the hydrogen atoms. The final values of $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_2 = \{[w||F_o| - |F_c||^2]/\Sigma wF_o^2\}^{1/2}$ were 0.035 and 0.043, respectively,[23] and the error in an observation of unit weight was 2.34. The maximum density in a final difference electron density synthesis was 0.15 electrons Å^{-3}, approximately 25% of the height of a hydrogen atom. The final parameters are presented in Table III.[24]

Reaction of Tetrasubstituted Phthalic Anhydrides with Triethyl Phosphite. Tetrachloro-PA (**6**) or tetrabromo-PA (**7**) was mixed with 10 molar equiv of triethyl phosphite and the mixture was stirred, under N_2, for 5 min at 155 °C. The mixture was cooled, and the yellow crystals were filtered off and washed repeatedly with warm benzene, for octachloro-BP (**9**), or with warm toluene for octabromo-BP (**10**). A mixture of tetraphenyl-PA (**8**) and triethyl phosphite (10 molar equiv) was stirred for 48 h at 180 °C, and the crystals of octaphenyl-BP (**11**) were washed with warm benzene. Additional data are furnished in Table II.

Anal. Calcd for $C_{16}O_4Br_8$: C, 21.5; Br, 71.4. Found: C, 21.3; Br, 71.2. Calcd for $C_{64}H_{40}O_4$: C, 88.0; H, 4.6. Found: C, 88.0; H, 4.7.

The octahalo-BP undergo extensive decomposition on prolonged heating with trialkyl phosphites.

Reaction of Biphthalyls with Concentrated Sulfuric Acid. *trans*-BP (**1**) was mixed with concentrated H_2SO_4, and the mixture was stirred for 2 h at 140 °C, cooled to 20 °C, and poured into ice. The colorless crystals of crude biisocoumarin (**3**) (ca. 50%) were purified as described;[10] cf. Table II. The same procedure was applied to the octachloro- and octabromo-BP (**9** and **10**) but in those cases no pure new compound could be isolated.

Results and Discussion

Molecular Structure of *trans*-BP (1). The structure and numbering system for the atoms in an individual molecule, whose two halves are related by the center of symmetry, are shown in Figure 1. The 50% probability vibrational ellipsoids

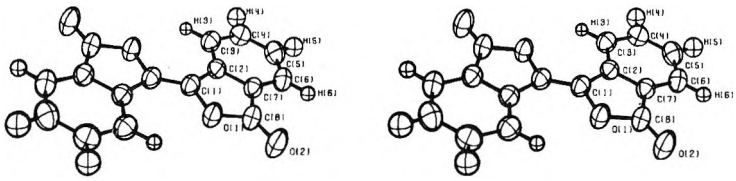


Figure 1. Stereoscopic drawing of an isolated molecule of *trans*-biphthalyl (1), $C_{16}H_8O_4$. The 50% probability ellipsoids are shown (hydrogen atoms are isotropic).

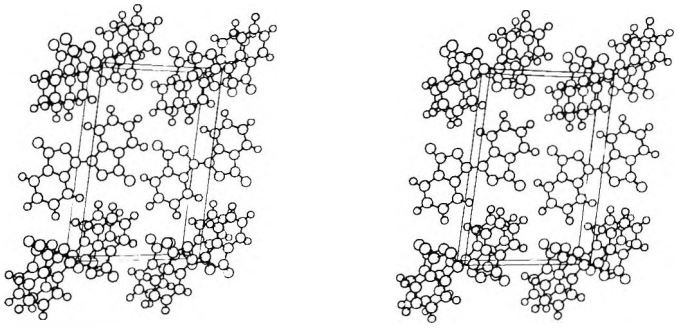
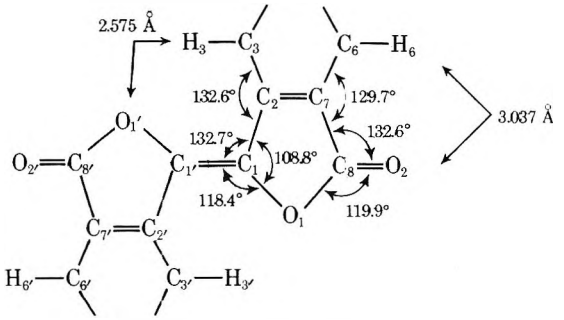


Figure 2. Stereoscopic drawing showing the contents of the unit cell with all molecules, $C_{16}H_8O_4$, completed ($Z = 2$). In addition, there are two complete molecules no parts of which lie within the unit cell; these appear at the far upper left and near lower right hand corners, and are included to show the packing arrangement. The asymmetric unit consists of half a molecule (or $C_8H_4O_2$), and there are four asymmetric units per unit cell. The view is approximately along *b*, and *c* is vertical.

are also displayed in Figure 1. The packing of the molecules in the crystal is depicted in Figure 2. The interatomic distances, bond angles, and their standard deviations are summarized in Table I and were calculated from the positional parameters given in Table III[24] and the correlation matrix. Some significant least-squares planes are presented in Table IV.[24]

The data confirm the structure and the configuration assigned to the main product of the reaction of phthalic anhydride with triethyl phosphite.[12,13] The molecule of *trans*-BP (1) is perfectly planar, as shown in Table IV.[24] The bond distances are unexceptional, and the most interesting features of the molecule reside in the bond angles which are emphasized in the partial formula.



Angles C(1′)–C(1)–C(2) and C(1)–C(2)–C(3) are significantly larger than the trigonal 120° value. Angle O(1)–C(1)–C(2) is smaller than 120°. The net effect of these bond angle deformations is to move H(3) away from O(1′). The nonbonded distance H(3)–O(1′) is 2.575 Å, while the estimated[25] van der Waals radii for H and O are about 1.1 and 1.40 Å, respectively. There is enough available space in the planar molecule to accommodate at least a hydrogen atom on the aromatic C(3) position.

A second set of expanded bond angles included O(2)–C(8)–C(7) and C(8)–C(7)–C(6), and this effect increases the separation between H(6) and O(2); cf. the nonbonded distance H(6)–O(2).

Table I. Bond Distances (Å) and Angles (Deg)

Distances		Angles	
		A. In Five-Membered Ring	
C(1)–C(1′)[a]	1.329 (4)	C(1′)[a]–C(1)–C(2)	132.7 (3)
C(1)–C(2)	1.452 (3)	C(1′)–C(1)–O(1)	118.4 (3)
C(2)–C(7)	1.388 (3)	C(1)–C(2)–C(3)	132.6 (2)
C(7)–C(8)	1.460 (3)	C(1)–C(2)–C(7)	106.7 (2)
C(8)–O(1)	1.395 (3)	C(2)–C(7)–C(8)	108.4 (2)
O(1)–C(1)	1.397 (3)	C(7)–C(8)–O(1)	107.4 (2)
O(2)–C(8)	1.196 (3)	C(8)–O(1)–C(1)	108.6 (2)
		O(1)–C(1)–C(2)	108.8 (2)
		O(2)–C(8)–C(7)	132.6 (2)
		O(2)–C(8)–O(1)	119.9 (2)
		C(8)–C(7)–C(6)	129.7 (2)
		B. In Six Membered Ring[b]	
C–C	1.386 (6)	C–C–C	120.0 (22)
C–H	0.99 (3)	H–C–C	120.0 (80)

[a] Atom C(1′) is related to C(1) by the center of symmetry. [b] These are average quantities. The estimated standard deviation in parentheses is the larger of an individual deviation or the standard deviation as calculated on the assumption of equivalence.

Table II. Properties of *trans*-Biphthalyl, Biisocoumarin, and Some Octasubstituted Biphthalyls

Compd	Subst X	Mp, °C	Ir bands,[a] cm^{-1} C=O	R_f[b]	Yield,[c] %
		Biphthalyls			
1	H	352–354[d]	1780	0.61	65
9	Cl	375–377[e]	1780 1730		44
10	Br	408–409[f]	1780 1730		40
11	C_6H_5	407–409[g]	1780	0.79	45
		Biisocoumarin[h]			
3	H	330–334[i]	1720[j]	0.48	

[a] Nujol mulls. [b] On unactivated silica gel plates, using toluene (1) or toluene–ethyl acetate, 19:1 (11). No suitable solvent was found for **9** or **10**. [c] Based on the corresponding phthalic anhydride. [d] From xylene or mesitylene. The crystals sublime at ca. 260 °C; the melting point was obtained on rapid heating, in open or sealed capillaries. [e] From *o*-dichlorobenzene. [f] Before and after repeated washings with warm toluene. [g] Before and after repeated washings with warm benzene. [h] Prepared as described in ref 10. [i] From toluene. [j] A sharp band at 1175 cm^{-1} is useful for characterization purposes.

The five-membered rings have bond angles which are close to those of the regular pentagon (108°).

It appears that the flexibility inherent in C–C–C, C–C–O, and C–O–C bond systems permit the bond angle expansions which are required to allow for the coplanarity of the chromophore O=C–C=C–C=C–C=C–C=O in the relatively

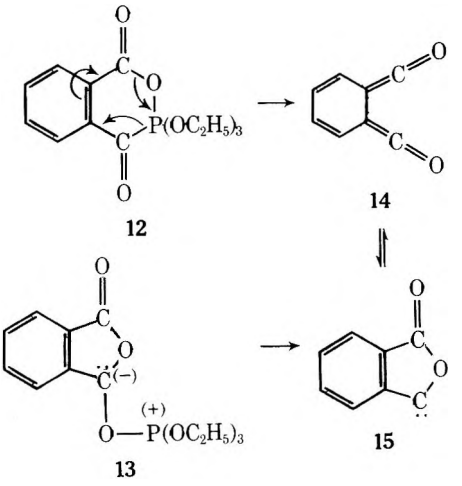
crowded *trans*-BP (1). This angle flexibility permits also the contractions which are required to establish the five-membered rings in the shape of a regular pentagon.

There are no unusual intermolecular distances in the crystals of *trans*-BP (1); however, the packing shows an interesting feature (cf. Figure 2). Pairs of molecules (at the upper and lower edges of the figure) are perfectly stacked, but other pairs (in the middle of the figure) are not stacked with respect to each other or in relation to the stacked pairs. This relatively inefficient packing may account for the sublimation that is observed at about 260 °C. We speculate that there could be another phase transition above this temperature leading to a more efficient packing which would account for the observed melting point of 352–354 °C. However, the postulated second phase transition was not detected in the present investigation.

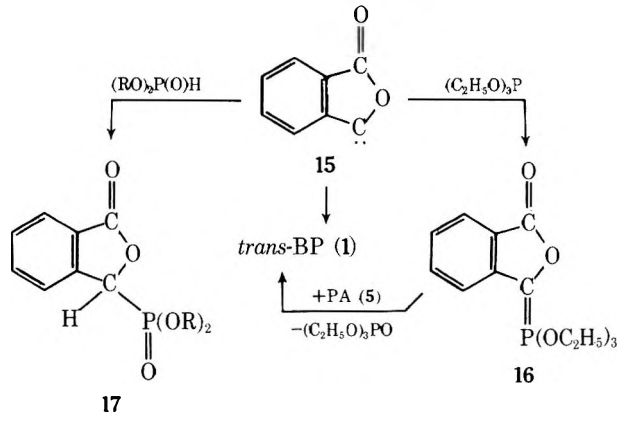
Reaction of Tetrasubstituted Phthalic Anhydrides with Triethyl Phosphite. The data in Table II support the conclusion that the yellow-orange substance isolated from the reaction of tetraphenyl-PA (8) is also the *trans*-BP derivative, 11. The estimated[25] half-width of the benzene ring is 1.85 Å; and with a van der Waals radius of 1.40 Å for the divalent oxygen, it is evident that a planar octaphenyl derivative 11 analogous to 1 requires even greater bond angle deformations than those observed in 1. Yet the similarities of the C=O stretching bands of 11 and 1, as well as the color of the two substances, suggest similar molecular structures.

The steric problem may be comparable or worse for the octachloro-*trans*-BP (9) (Cl radius[25] ~1.80 Å), and much worse for the octabromo-*trans*-BP (10) (Br radius ~1.95 Å). The Nujol mulls of the analytical samples of both yellow octahalo derivatives exhibited two carbonyl bands. Repeated recrystallizations of the chloro compound, 9, did not alter the spectrum. The bromo compound, 10, could not be recrystallized. Neither halogen derivative could be analyzed by TLC for lack of solubility. It is possible, but unlikely, that the 1730-cm^{-1} peak is due to contamination of the crystals with the corresponding octahalobiisocoumarin (analogous to 3). The latter compounds, however, could not be made from the reaction of concentrated sulfuric acid with the octahalo-BP (9 and 10). If the two C=O bands in the spectra of 9 and 10 result, indeed, from the pure compounds, the phenomenon may indicate that these very crowed molecules are not entirely planar. In the planar *trans*-BP (1) the two carbonyl groups are aligned in opposite directions, and the symmetric vibration mode does not result in a change in dipole moment; consequently, one expects only a single carbonyl band, due to the asymmetric mode, despite the fact that extensive vibrational coupling is taking place, of the type that is responsible for the well-known doublet in symmetrical anhydrides.[26] This restriction need not apply if the molecule is not entirely planar. All efforts to obtain single crystals of 9 or 10 suitable for x-ray analysis have failed.

Mechanisms of the Biphthalyl Condensation and Related Reactions. We suggested the possible intervention of the bisketene (14)[12] and the related carbene (15)[12,13] in the formation of *trans*-BP (1) from PA (5) and triethyl phosphite. These hypothetical intermediates may arise via a cyclic oxyphosphorane[12,27] (12), or via a dipolar 1:1 adduct[13] (13), which represent the attack by the phosphite at the carbon or at the oxygen of the carbonyl function of PA (5), respectively. The reactions of trivalent phosphorus compounds with carbonyl functions can give rise to a variety of products[28] which may be pictured as arising from the two types of 1:1 adducts, X_3P^+–C–O^- and X_3P^+–O–C^-. Apparently, these adducts can be subject to relative rapid equilibration, rearrangements, eliminations, and additions of other reagents, including a second molecule of the carbonyl compound.[28] In the biphthalyl condensation, which occurs at relatively high temperature, there are no compelling reasons to exclude either of these modes of attacks by the phosphite on PA (5) as the source of the carbene (15).

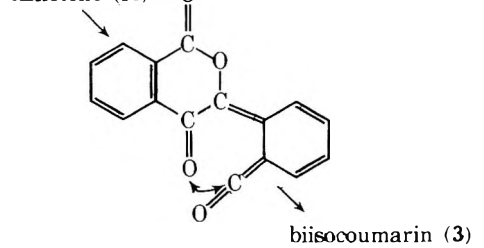


The *trans*-BP (1) may arise by direct dimerization of the carbene (15),[12,13] or via the phosphite ylide (16)[29] which represents the trapping of the carbene (15) by the phosphite. From the ylide (16) and PA (5), *trans*-BP (1) is formed through the steps of the Wittig olefin synthesis.[29] The phthalidephosphonate (17), which is observed when dialkyl phosphites are present during the reaction of PA (5) with trialkyl phosphites, represents the trapping of the carbene by dialkyl phosphite.



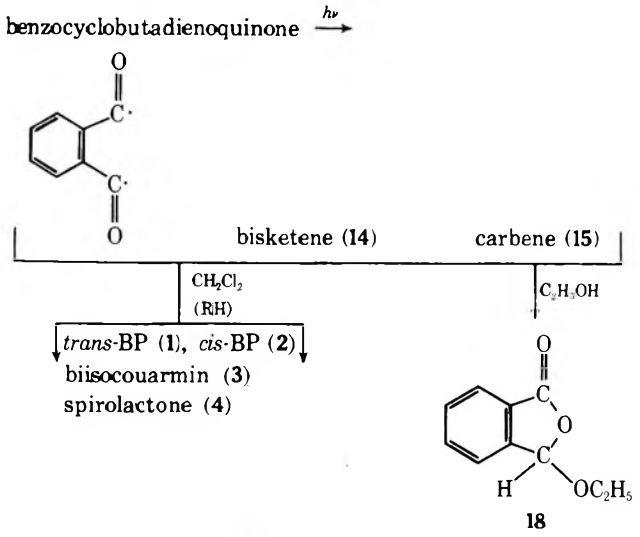
The biisocoumarin (3) recently detected by Bird[14] among the by-products of the biphthalyl condensation may result from a dimerization of the bisketene (14, Scheme III).

Scheme III



In support of the bisketene (14) ⇌ carbene (15) hypothesis, one can mention the results of the photolysis[7-9] of the quinone[6] as has been pointed out by Stabb[7,8] and by Brown[9] (Scheme IV). The dimerization of the carbene (15) to *trans*- and *cis*-BP (1 and 2), and of the ketene (14) to biisocoumarin (3), as well as the carbene insertion on the quinone to give the spirolactone (4), are reasonable. The trapping of the carbene by ethanol to give the 3-alkoxyphthalide[7,8] (18, Scheme IV) provides an analogy for the similar trapping by dialkyl phosphite.

Scheme IV



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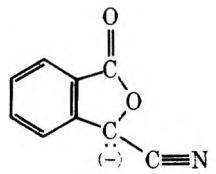
The carbene (15) is a likely intermediate in the early work[2,3] with phthaloyl chloride (Scheme I). Moreover, the formation of *trans*-BP (1) and/or biisocoumarin (3) from phthalaldehydic esters[2,3] or from 3-alkoxyphthalides[5] (Scheme I) suggest also a carbenoid mechanism (via 19 and 20).



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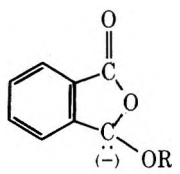

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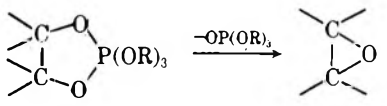
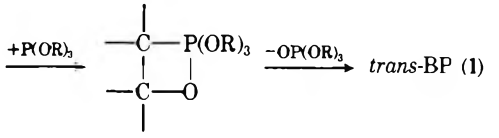
The formation of *trans*-BP (1) from the phosphite ylide (16) via the Wittig reaction[29] seems more reasonable than the simple carbene dimerization, and has been favored by several authors.[10,14-16,30] Phosphite ylides are known[31,32] and there is precedent for the formation of certain phthalylidene derivatives from phosphine ylides and phthalic anhydride.[33] However, neither the phosphite ylide (16), nor the carbene (15) are *mandatory* intermediates in the biphthalyl condensation. There is a reasonable pathway in which the dipolar ion (13) adds to PA (5) carbonyl to yield the 1,3,2-dioxaphospholane (21).[34] Subsequent steps have precedent, in other related reactions of cyclic oxyphosphoranes.[27-29] as was recognized by Markgraf.[16] The 1,2-oxaphosphetane (23)[35] depicted in this pathway is the intermediate in the Wittig olefin synthesis.



21 22



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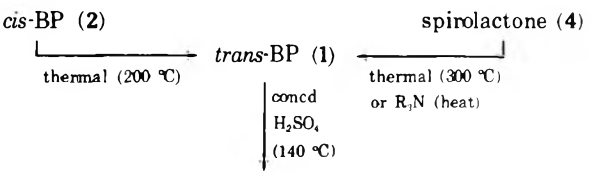
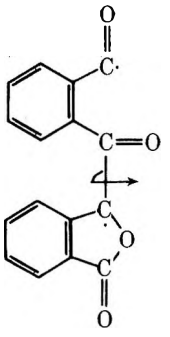
In view of the intramolecular crowding revealed by the x-ray analysis of the unsubstituted *trans*-BP (1), one may raise the question of prohibitive steric hindrance in the various intermediates discussed above, the 1,2-oxaphosphetane (23), 1,3,2-dioxaphospholane (21), and epoxide[36] (22). In that case, the direct carbene dimerization could still provide a plausible mechanism for the biphthalyl condensation.

Several isomerizations of the various $C_{16}H_8O_4$ structures discussed above have been discussed:



The homolytic acyl–oxygen bond cleavage required in the cis → trans isomerization[6,7] could be facilitated by resonance stabilization in species 24. A similar effect in species 25 would



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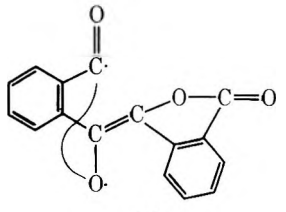
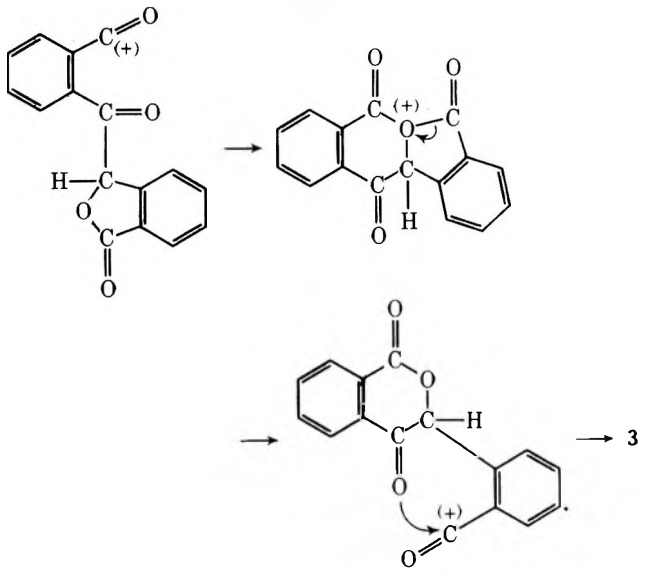


25

account for the thermal spirolactone *trans*-BP rearrangement;[9,17] this picture is analogous to that suggested[9] for the amine catalysis of that reaction.

We have found that *trans*-BP (1) and octachloro-BP (9) are recovered unchanged after heating to 370 and 175 °C, respectively, and have verified the acid-catalyzed *trans*-BP (1) → biisocoumarin (3) isomerization,[10] which could simply be an acylium cation mediated rearrangement, Scheme V.

Scheme V



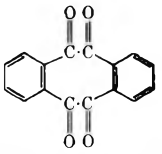
Registry No.—**1**, 19357-64-3; **3**, 7433-92-3; **5**, 85-44-9; **6**, 117-08-8; **7**, 632-79-1; **8**, 4741-53-1; **9**, 60260-50-6; **10**, 60260-51-7; **11**, 60260-52-8; triethyl phosphate, 122-52-1.

Supplementary Material Available. Positional and thermal parameters (Table III) and equations of best least-squares planes (Table IV) (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) State University of New York at Stony Brook. Research supported by Grant GM 20672 from the National Institute of General Medical Sciences, and Grant MPS73-04944 from the National Science Foundation; (b) Brookhaven National Laboratory; (c) address correspondence to this author at the Department of Chemistry, Windham College, Putney, Vt.

(2) "Diphthalyl, $C_{16}H_8O_4$" was first mentioned by E. Ador, *Justus Liebigs Ann. Chem.*, **164**, 229 (1872), who formulated it as a bis-1,2-diketone. The



bis-γ-lactone alternative was proposed by C. Graebe, *Ber.*, **15**, 1673 (1882); J. Wislicenus, *ibid.*, **17**, 2178 (1884); C. Graebe and H. Guye, *ibid.*, **17**, 2851 (1884); and C. Graebe and H. Schmalgigaug, *Justus Liebigs Ann. Chem.*, **228**, 126 (1885). Graebe's "yellow" crystals had mp 334–335 °C (from phenol), while Wiscilenus' "colorless" crystals had mp 320 °C (from acetic acid). A later sample of "yellow" crystals by P. Karrer, W. Werli, E. Biedermann, and M. dalla Vedov,, *Helv. Chim. Acta*, **11**, 233 (1928), had mp 335 °C (from benzene).

(3) For a review of the early literature, see Beilstein, "Handbuch der Organischen Chemie", 4th ed, J. Springer, Berlin: (a) **19**, 176 (1910); (b) **I**, 688 (1919); (c) II, 192 (1929).
(4) J. C. Sauer, R. D. Cramer, V. A. Engelhardt, T. A. Ford, H. E. Holmquist, and B. W. Howk, *J. Am. Chem. Soc.*, **81**, 3677 (1959).
(5) H. D. Becker, *J. Org. Chem.*, **29**, 3070 (1964).
(6) M. P. Cava, D. R. Napier, and R. J. Pohl, *J. Am. Chem. Soc.*, **85**, 2076 (1963).
(7) H. A. Staab and J. Ipaktschi, *Tetrahedron Lett.*, 583 (1966).
(8) H. A. Stabb and J. Ipaktschi, *Chem. Ber.*, **101**, 1457 (1968).
(9) R. F. C. Brown and R. K. Solly, *Tetrahedron Lett.*, 169 (1966).
(10) C. W. Bird and D. Y. Wong, *Tetrahedron*, **31**, 31 (1975).
(11) BP = biphthalyl; PA = phthalic anhydride.
(12) F. Ramirez, H. Yamanaka, and O. H. Basedow, *J. Org. Chem.*, **24**, 1838 (1959). The yellow BP, mp 352–354 °C (xylene), was erroneously drawn in the cis configuration; cf., however, the correct trans configuration in ref 13.
(13) F. Ramirez, H. Yamanaka, and O. H. Basedow, *J. Am. Chem. Soc.*, **83**, 173 (1961).
(14) C. W. Bird and D. Y. Wong, *Organomet. Chem. Synth.*, **1**, 421 (1972).
(15) C. W. Bird and D. Y. Wong, *Chem. Commun.*, 932 (1969).
(16) J. H. Markgraf, C. I. Heller, and Noyes L. Avery, III, *J. Org. Chem.*, **35**, 1588 (1970).
(17) M. Pailer, H. Woerther and A. Meller, *Monatsh. Chem.*, **92**, 1037 (1961).
(18) In view of the relatively low melting point of the yellow product, 334 °C, vs. that of pure *trans*-BP (**1**), it is possible that some biisocoumarin (**3**) was also formed in the pyrolysis of spirolactone **4**.
(19) Unpublished results.
(20) G. Germain, P. Main, and M. M. Woofson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970); *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(21) "International Tables for X-Ray Crystallography", Vol. 3, Kynoch Press, Birmingham, England, 1962, Table 3.3.1 A.
(22) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).
(23) These values were 0.117 and 0.176 before addition of hydrogen atoms and anisotropic refinement.
(24) See paragraph at end of paper regarding supplementary material.
(25) L. Pauling, "The Nature of the Chemical Bond", 3d ed, Cornell University Press, Ithaca, N.Y., 1960.
(26) L. J. Bellamy, "Advances in Infrared Group Frequencies", Methuen, London, 1968, p 128.
(27) F. Ramirez, *Acc. Chem. Res.*, **1**, 168 (1968).
(28) For a recent review see F. Ramirez, *Synthesis*, 90 (1974).
(29) IUPAC Conference on Phosphorus Compounds, Heidelberg, Germany, May 1963; F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964); cf. p 367.
(30) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry", Academic Press, New York, N.Y., 1965, p 185.
(31) (a) F. Ramirez, O. P. Madan, and C. P. Smith, *Tetrahedron Lett.*, 201 (1965); (b) *J. Org. Chem.*, **30**, 2284 (1965).
(32) F. Ramirez, A. S. Gulati, and C. P. Smith, *J. Am. Chem. Soc.*, **89**, 6283 (1967).
(33) P. A. Chopard, R. F. Hudson, and R. J. G. Searle, *Tetrahedron Lett.*, 2357 (1965).
(34) F. Ramirez and N. Ramanathan, *J. Org. Chem.*, **26**, 3041 (1961).
(35) A direct conversion of **21** into **23** by attack of $(RO)_3P$ on the carbon of **21** and elimination of $(RO)_3PO$ is conceivable.
(36) In principle the carbene **15** could be trapped by PA (**5**) to give the epoxide **22** directly.

Notes

On the Catalytic Role of the Carboxyl Group in the Hydrolysis of *o*-Carboxybenzyl Bromide

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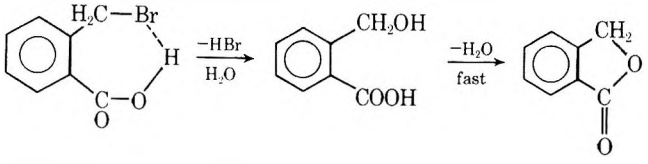
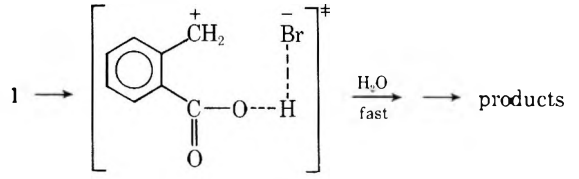
Received October 1, 1975

Of the isomeric carboxybenzyl bromides, *o*-carboxybenzyl bromide (**1**) is known to undergo solvolytic reactions many times more rapidly than *p*-carboxybenzyl bromide (**2**).[1] This difference—the ortho isomer (**1**) reacts some 84–87 times as fast as the para isomer (**2**)—reverses the usual order of reac-



tivity among isomers of this type. Although differences are rarely this dramatic, the para isomer is nearly always more reactive.[2] The greater reactivity of **1** is attributed to internal participation by the un-ionized carboxyl group.[3] Such participation is not possible for **2** because of unfavorable molecular geometry. Manifestly the equation above does not show how the solvent acts.

Solvolyses of benzyl halides have been studied extensively.[4] The findings cannot be interpreted in terms of simple SN1 or simple SN2 mechanisms. It has been suggested that the mechanisms of benzyl halide solvolysis be interpreted as SN2 (**1**) and SN2 (**2**); in the former, bond ionization plays the predominant role, while the latter is more like the conventional SN2 type, nucleophilic attack being more important.[5] Two possible transition states can be postulated for the particular reaction now being discussed:



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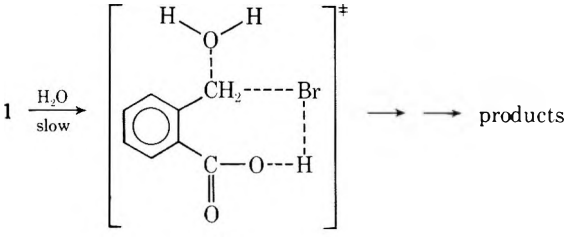

II

If the reaction proceeds through the transition state I, sufficient stretching of the reactive bond must occur to produce an ion-pair-like species. The subsequent nucleophilic attack on the ion is expected to be very fast. In this case, the carboxyl group can be said to act as an electrophilic catalyst. Reactions proceeding through this state should be little affected by nucleophiles but appreciably sensitive to the ionic strength or dielectric constant of the solvent medium. If the reaction goes through the transition state II, less bond stretching is required. The reactive bond is stretched only enough to in-

Table I. Effect of Added Nucleophiles on Solvolysis Rate Constants for Carboxybenzyl Bromides and Benzyl Bromide in 50% Aqueous Dioxane[a]

pH	[Buffer] mol/l.	$10^5 k_s$, s^{-1} o-Carboxybenzyl bromide (1)	p-Carboxybenzyl bromide (2)	Benzyl bromide
		Hydroxylamine/Hydroxylamine Hydrochloride		
7.10	0.500	480 ± 6	335 ± 1	252 ± 9
	0.375	446 ± 6	228 ± 2	123 ± 2
	0.250	463 ± 9	125 ± 5	61.6 ± 1.9
		Morpholine/Morpholine Hydrochloride		
7.05	0.500	364 ± 6	239 ± 13	147 ± 3
	0.375	359 ± 6	87.0 ± 0.3	92.8 ± 0.4
	0.250	370 ± 14	22.9 ± 1.0	52.4 ± 2.5
		Sodium Acetate/Acetic Acid		
5.68	0.500	246 ± 5	32.8 ± 0.8	30.7 ± 0.7
	0.350	248 ± 1	30.0 ± 0.0	25.2 ± 0.2
	0.200	241 ± 1	24.0 ± 0.3	18.3 ± 0.4

[a] Temperature 40.0 °C and total ion concentration maintained at 1 M with NaCl.

Table II. Effect of Added Salt on Hydrolysis Rate Constants for Carboxybenzyl Bromides and Benzyl Bromide in Aqueous Dioxane, 60.4 °C

Aqueous dioxane, %	$[KNO_3]$, mol/l.	$10^5 k_s^-$, s^{-1} o-Carboxybenzyl bromide (1)	p-Carboxybenzyl bromide (2)	Benzyl bromide
80	0.000	30.7 ± 0.8	0.272 ± 0.008	0.626 ± 0.010
	0.050	39.6 ± 0.6	0.328 ± 0.011	0.659 ± 0.018
	0.100	43.2 ± 0.4	0.364 ± 0.003	0.701 ± 0.015
	0.150	44.3 ± 0.6	0.405 ± 0.014	0.743 ± 0.031
	0.000[a]	68.5 ± 0.4	0.740 ± 0.005	
	0.000[b]	13.4 ± 0.1		
60	0.000	114 ± 0	1.81 ± 0.02	
	0.000[a]	217 ± 3	5.01 ± 0.05	
	0.000[b]	56.9 ± 0.5	0.722 ± 0.021	
50	0.000	183 ± 9	3.56 ± 0.12	4.50 ± 0.16
	0.100	187 ± 7	4.24 ± 0.08	10.8 ± 0.2
	0.300	195 ± 5	5.45 ± 0.19	20.9 ± 0.8
	0.500	210 ± 3	6.75 ± 0.14	32.5 ± 0.5
	0.750	210 ± 3		
	1.000		7.12 ± 0.09	
	0.000[a]	325 ± 9	8.74 ± 0.14	
	0.000[c]	86.1 ± 3.8		

[a] Temperature 70.6 °C. [b] Temperature 50.6 °C. [c] Temperature 40.0 °C.

crease the charge polarization so that nucleophilic attack in the rate-determining step is facilitated. In this case the carboxyl group can be said to act as a general acid catalyst.

We report here a series of experiments in which the nucleophilicity and ionic strength of the media have been varied and the resulting rate constants determined. From these data, we have tried to interpret the catalytic role of the carboxyl group in the solvolysis of o-carboxybenzyl bromide.

Results and Discussion

The carboxybenzyl bromides (1 and 2) and benzyl bromide were solvolyzed in 50% aqueous dioxane in which one of three nucleophiles was initially present. The nucleophiles used were hydroxylamine, morpholine, and acetate anion, each in the form of a buffer containing the free base and conjugate acid. Sodium chloride was added to give uniform ionic strength. In these experiments (Table I) the benzyl halides reacted at a convenient rate with all the nucleophiles used and the pseudo-first-order rate plots were linear through 3 half-lives. The rates of reaction for 2 and benzyl bromide increase linearly with the nucleophile concentration, total buffer concentration, while the rate of reaction of 1 is independent of the nucleophile concentration (Figure 1). It should be noted, also, that the behavior of the ortho isomer toward varying nucleophile concentration is not dependent on the amount of un-ionized carboxyl group present. The amount of un-ionized carboxyl group present at pH 5.68 is significantly greater than the amount present at pH 7.1.[6] This independence suggests that the reaction of 1 is proceeding predominantly by SN1 while on the other hand 2 and benzyl bromide react by SN2. Additional support for this hypothesis is obtained by comparing the ratios of the solvolysis rates of 1 and 2 in glacial acetic acid and aqueous ethanol, respectively. Jones and Thornton have suggested that the ratio, r, of solvolysis rates in the solvents of different nucleophilicities but the same ionizing power (i.e., the same Y value) measures the nucleophilic sensitivity of a substrate relative to *tert*-butyl chloride.[7] Solvolysis of this substance is used as a standard for reference because it is judged to need little nucleophilic assistance. In general, r values for primary substrates are considerably larger. Consequently larger ratios are expected for substrates reacting by SN2 mechanisms. The ratios calculated for 1 and

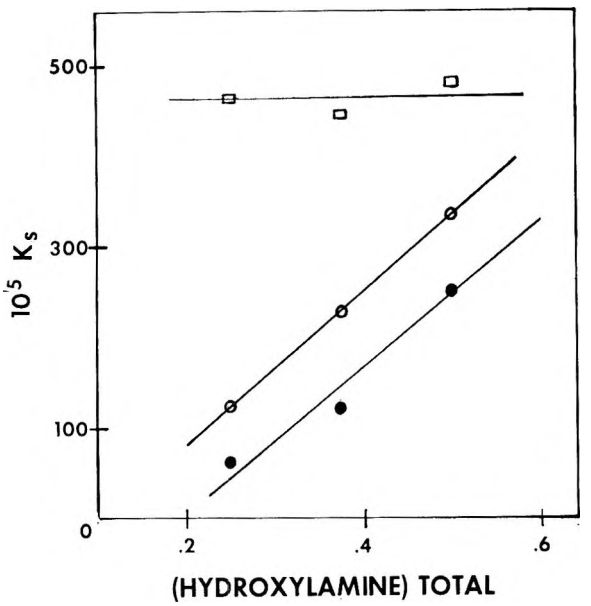

Figure 1. Solvolysis rate constants vs. total buffer concentration for 1 (□), 2 (○), and benzyl bromide (●) in hydroxylamine buffer, pH 7.1.

2 were 24 and 254, respectively.[8] The smaller r for 1 indicates appreciably less sensitivity to nucleophilic attack; this is consistent with the prior inference of a SN1 reaction mechanism.

Further information about the transition state of 1 was sought by determining the effect of varying ionic strength. Potassium nitrate was added to solutions of 50 and 80% aqueous dioxane and the rate constants determined (Table II). In 80% aqueous dioxane, the effect of adding 0.1 M KNO_3 initially is to increase the rate constant by 41% for **1**, by 34% for 2, and by 12% for benzyl bromide. These values are within the range of increase expected for a SN1 reaction.[9] The magnitude of a salt effect for either SN1 or SN2 reactions is expected to be greater in a medium of low dielectric constant since charges operate more effectively in media of low dielectric constant.[10] This inverse relationship between magnitude of salt effect and dielectric constant of the medium is observed for 1; in 50% aqueous dioxane, addition of 0.1 M KNO_3 initially increases the rate constant only 2% as compared to 41% in 80% aqueous dioxane. The increases in rate constants due to salt effects for 2 and benzyl bromide in 50% aqueous dioxane are 19 and 40%, respectively, values considerably larger than for 1. Furthermore, as the salt concentration is increased to the saturation point in 50% dioxane, the rate constants for 2 and benzyl bromide continue to increase significantly. These results are sufficiently different from those anticipated to merit further examination.

Although we cannot exclude the possibility that an ordinary salt effect is responsible for these observed differences in the rate constants, it is probable that these differences result from differences in the relative contributions of the SN1 and SN2 components in the reactions of 2 and benzyl bromide. If an increase in salt concentration can increase the ability of the medium to stabilize a SN1 transition state without significantly changing its ability to stabilize a SN2 transition state, it is probable that any change in the relative contribution of the two component reactions will favor the SN1 component with little concurrent suppression of the SN2 component. We have already inferred that the reactions of 2 and benzyl bromide proceed chiefly by SN2. Accordingly, as addition of salt increases the ionizing power of the medium, the SN1 components of these reactions should increase, too. Thus overall rate constants for these hydrolyses are expected to increase. Since

Table III. Activation Parameters for Hydrolysis of *o*- and *p*-Carboxybenzyl Bromides

	o-Carboxybenzyl bromide (1)		*p*-Carboxybenzyl bromide (2)	
Solvent	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
80% aqueous dioxane	17.3	−22.9	21.2	−20.1
60% aqueous dioxane	14.1	−30.0	21.7	−15.3
50% aqueous dioxane	8.81	−30.8	19.4	−20.8

1 reacts initially chiefly via SN1, the overall rate enhancement is not so evident. The activation parameters for the hydrolyses of 1 and 2, shown in Table III, are consistent with reactions by different mechanisms for the two isomers.

These data, then, support the hypothesis that *o*-carboxybenzyl bromide is hydrolyzed in aqueous dioxane by SN1 mechanism. The more rapid hydrolysis of *o*-carboxybenzyl bromide as compared with its para isomer is attributed to the action of the *o*-carboxyl group as an intramolecular electrophilic catalyst.

Experimental Section

Materials. The isomeric carboxybenzyl bromides were prepared from the corresponding toluic acid according to previously published procedures.[1] Other compounds employed were all reagent grade or were recrystallized before using.

Kinetics. All solvents used were purified according to standard procedures and distilled in all-glass apparatus. The mixed solvents (v/v) were prepared at room temperature, i.e., 80% dioxane—20 volumes of water and 80 volumes of dioxane.

In most runs, the method used in investigating the rates of hydrolysis of the various bromo compounds were essentially the same as that employed in previous investigations.[1,3] The change in reactant or product concentration was also followed spectrophotometrically. In these cases, the sample solution was placed in the thermostated cell in a Beckman DB spectrophotometer. The reactions were generally followed to about 80% of completion. At least three separate runs were made to determine all rate constants. Solvolysis rate constants were determined using the equation

$$\ln([RBr]_i/[RBr]_t) = k_s t$$

The k_s values were determined using a least-squares computer program.

Registry No.—1, 7115-89-1; 2, 6232-88-8; benzyl bromide, 100-39-0.

References and Notes

(1) A. Singh, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **84**, 1179 (1962).
(2) (a) S. C. J. Oliver, *Recl. Trav. Chim. Pays-Bas*, **49**, 697 (1930); (b) G. M. Bennett and B. Jones, *J. Chem. Soc.*, 1815 (1935).
(3) The question of carboxylate vs. free carboxyl participation has been dealt with previously: L. Chauffe, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, **31**, 3758 (1966).
(4) (a) E. R. Thornton, "Solvolysis Mechanisms", Ronald Press, New York, N.Y., 1968, p 160; (b) A. Streitwieser, Jr., "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962, p 74.
(5) K. J. Laidler and R. Martin, *Int. J. Chem. Kinet.*, **1**, 113 (1969).
(6) The K_a values of toluic acids are 10^{-4}–10^{-5} in water and 10^{-9}–10^{-11} in 82% aqueous dioxane. It is assumed that the K_a values for the brominated toluic acids would be of similar magnitude. H. S. Hormed and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions", Reinhold, New York, N.Y., 1958, p 581.
(7) T. C. Jones and E. R. Thornton, *J. Am. Chem. Soc.*, **89**, 4863 (1967).
(8) The solvents were 2.0 M H_2O in glacial acetic acid and 91% aqueous ethanol. Both solvents have a Y value of −0.863.
(9) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2d ed, Cornell University Press, Ithaca, N.Y., 1969, p 491.
(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Rinehart and Winston, New York, N.Y., 1959, p 257.

Electron-Impact and Pyrolytic Eliminations from 4-*tert*-Butylcyclohexyl Xanthates

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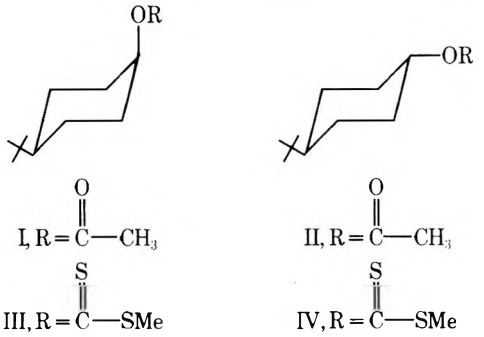
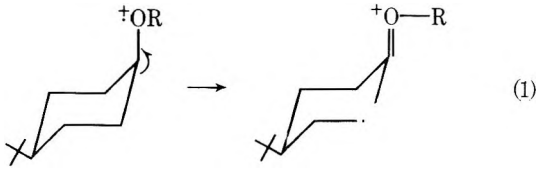
The electron-impact induced[1] and pyrolytic[2a,3] eliminations of xanthic acid from *S*-methyl xanthates are formally analogous to each other, and to the electron-impact induced[4] and pyrolytic[2b-e,3] eliminations of acetic acid from acetates. These reactions proceed largely through six-membered cyclic transition states, and involve predominant elimination of a β hydrogen. A recent investigation of the reactions of *cis*- and *trans*-4-*tert*-butylcyclohexyl acetate confirmed that the pyrolytic elimination of acetic acid occurs with clean cis stereochemistry for these compounds.[5] In contrast, the electron-impact induced elimination from *trans*-4-*tert*-butylcyclohexyl acetate (II) occurs with very predominant elimination



of the trans equatorial hydrogen ($k_{ax}/k_{eq} \approx 0.26$).[5] This dichotomy was considered to be evidence for a nonconcerted mechanism for the electron-impact induced process, although other explanations could not be excluded.[5,6] Further, although the electron-impact induced elimination from the cis axial acetate I was predominantly cis ($k_{ax}/k_{eq} = 0.51$), the reaction was less stereospecific than the fragmentation of the equatorial acetate II. An equatorial acetate group can approach either a cis or trans hydrogen well within the requisite 1.8 Å[7] for hydrogen abstraction; in contrast, if the cyclohexyl ring remains intact and in its stable chair conformer, an axial acetate group can only approach the cis equatorial hydrogen atom. There was little basis to decide whether the considerable trans elimination actually observed was attributable to cyclohexyl ring cleavage (eq 1), to fragmentation through

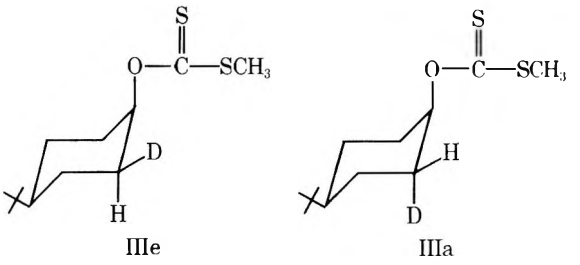


(1)

high-energy boatlike conformers, or to operation of an electronic effect favoring trans abstraction when the product is an ionized alkene.

An investigation into the stereochemistry of the electron-impact induced reactions of the *S*-methyl xanthates III and IV was initiated to shed light on the generality and origins of these effects. The pioneering study of the mass spectral behavior of cyclohexyl-*S*-methyl xanthates permits no firm conclusions about the stereochemistry of reaction of axial and equatorial derivatives.[1] The compounds studied (*cis*- and *trans*-2-methylcyclohexyl-*S*-methyl xanthate) can each exist in two stable chair conformers. Depending on the conformer distribution after ionization and the relative rates of reaction of axial and equatorial derivatives, these xanthates might behave as equatorial or axial esters; information about such factors is, of course, lacking. However, the early study demonstrated that xanthate mass spectra typically exhibit an intense peak corresponding to ionized alkene, that the reaction is largely site specific for β hydrogen abstraction, and that it generates a significant metastable peak. Preliminary studies on unlabeled *cis*-4-*tert*-butylcyclohexyl-*S*-methyl xanthate (III) and the -2,2,6,6-d_4 analogue were consistent with these observations. The ionized alkene was formed with 91–96% elimination of deuterioacetic acid as the ionizing voltage was varied from 70 eV to threshold; similarly, the fragmentation of *trans*-4-*tert*-butylcyclohexyl-*S*-methyl xanthate-2,2,6,6-d_4 is 81–90% site specific. The ionized alkene peak is the base peak in the spectra of III and IV at 70 eV, and its formation generates intense first and second field-free region metastables.

The stereochemistry of electron impact induced xanthic acid elimination from *cis*-4-*tert*-butylcyclohexyl-*S*-methyl xanthate was assessed from the mass spectra of *cis*-4-*tert*-butylcyclohexyl-*S*-methyl xanthate-*cis*-2-*d* (IIIe) and -*trans*-2-*d* (IIIa). The intensity ratio $[M - DOC_2S_2H_3]\cdot^+/[M - HOC_2S_2H_3]\cdot^+$ in the two spectra is related to the stereochemistry of the eliminations. If the reasonable assumptions are made that the isotope effects for abstraction of an equatorial and an axial deuterium are similar, and that secondary isotope effects can be ignored, a modification of Curtin's analysis[4a,8] can be applied. Thus, for example, for IIIe



IIIe IIIa

$$\frac{[M - DOC_2S_2H_3]\cdot^+}{[M - HOC_2S_2H_3]\cdot^+} = \frac{k_{eq}I}{k_{eq} + 2k_{ax} + k_i}$$

For IIIa

$$\frac{[M - DOC_2S_2H_3]\cdot^+}{[M - HOC_2S_2H_3]\cdot^+} = \frac{k_{ax}I}{k_{ax} + 2k_{eq} + k_i}$$

For *cis*-4-*tert*-butylcyclohexyl-*S*-methyl xanthate-2,2,6,6-d_4

$$\frac{[M - DOC_2S_3H_3]\cdot^+}{[M - HOC_2S_2H_3]\cdot^+} = \frac{[2k_{eq} + 2k_{ax}]I}{k_i}$$

In all three equations k_{eq} and k_{ax} are the rate constants (averaged over all ions energies) for abstraction of a γ-equatorial hydrogen and a γ-axial hydrogen, respectively, k_i is the rate constant for hydrogen elimination from other than the γ position, and I is the isotope effect (k_D/k_H). These equations can be solved for k_{ax}/k_{eq}, the relative rates of axial and equatorial hydrogen abstraction. The results of these calculations appear in Table I.

These experiments demonstrate that cis elimination is the very predominant mode of reaction of the axial xanthate III; at 14 eV, cis elimination is about 30 times as facile as trans elimination. The much more extensive trans elimination observed in the mass spectrum of the acetate I is most plausibly attributed to the greater facility of the α-cleavage process for acetates, since conformational populations and electronic effects should be similar for these closely related reactions. Comparison of the mass spectra of the acetate (V) and xanthate (VI) derived from 4-heptanol demonstrates that α-cleavage is a much more favorable process for the former

Table I. Electron-Impact Induced Elimination of Xanthic Acid from Stereospecifically Labeled 4-*tert*-Butylcyclohexyl-*S*-methyl Xanthates

Registry no.	Compd	Isotopic purity	Ionizing voltage, eV[a]	D loss/H loss[b,c]	k_{ax}/k_{eq}[c]
60239-10-3	*cis*-4-*tert*-Butylcyclohexyl-*S*-methyl xanthate-*cis*-2-*d* (IIIe)	98% D	70	0.375 ± 0.015	
			12	0.39 ± 0.03	
					0.06 ± 0.03 (70)
					0.03 ± 0.03 (12)
60239-11-4	*cis*-4-*tert*-Butylcyclohexyl-*S*-methyl xanthate-*trans*-2-*d* (IIIa)	98.7% D	70	0.033 ± 0.006	
			12	0.007 ± 0.006	
60239-12-5	*trans*-4-*tert*-Butylcyclohexyl-*S*-methyl xanthate-*trans*-2-*d* (IVe)	97.5% D	*d*	0.11 ± 0.002	
					1.6 ± 0.2
60239-13-6	*trans*-4-*tert*-Butylcyclohexyl-*S*-methyl xanthate-*cis*-2-*d* (IVa)	98% D	*d*	0.21 ± 0.002	

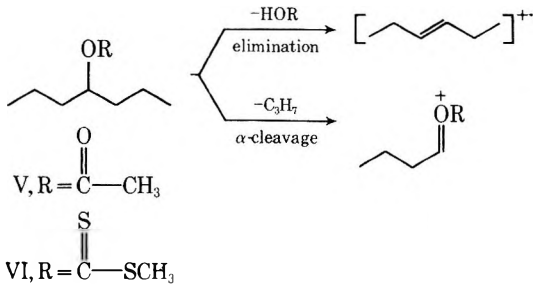
[a] Ionizing voltages are nominal. [b] All data are corrected for isotopic impurities and the occurrence of a small amount of 1,3 and 1,4 elimination. [c] Error limits represent the extreme values observed in at least three separate measurements. [d] Independent of ionizing voltage between 70 and 12 eV.

Table II. First and Second Field-Free Region Metastable Ion Intensities from Stereospecifically Labeled 4-*tert*-Butylcyclohexyl-*S*-methyl Xanthates

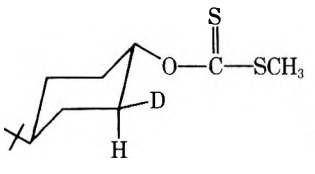
Compd	Transition	(m_1^*)[a]	(m_2^*)[b]
cis-4-*tert*-Butylcyclohexyl-*S*-methyl xanthate-*cis*-2-*d* (IIIe)	$\frac{247 \rightarrow 139}{247 \rightarrow 138}$	0.34 ± 0.02	0.30 ± 0.05
cis-4-*tert*-Butylcyclohexyl-*S*-methyl xanthate *trans*-2-*d* (IIIa)	$\frac{247 \rightarrow 139}{247 \rightarrow 138}$	0.025 ± 0.02	0.08 ± 0.05
trans-4-*tert*-Butylcyclohexyl-*S*-methyl xanthate-*trans*-2-*d* (IVe)	$\frac{247 \rightarrow 139}{247 \rightarrow 138}$	0.11 ± 0.01	0.15 ± 0.05
trans-4-*tert*-Butylcyclohexyl-*S*-methyl xanthate *trans*-2-*d* (IVa)	$\frac{247 \rightarrow 139}{247 \rightarrow 138}$	0.22 ± 0.01	0.25 ± 0.05

[a] Error limits represent the extreme ratios observed in at least four measurements. [b] Data obtained from repeated measurements on chart paper. Error limits are estimated.

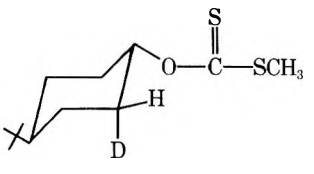
compound. In acyclic compounds, the α-cleavage process is readily detected since it generates a fragment ion; thus, the intensity ratio $[M - C_3H_7]^+/[M - HOR]^{\cdot+}$ is a measure of the relative rates of the α-cleavage and elimination reactions. The ratio is ca. 2.0 at all ionizing voltages in the spectrum of acetate V; in contrast, it is less than 0.05 in the mass spectrum of xanthate VI.



The stereochemistry of the electron-impact induced elimination of xanthic acid from *trans*-4-*tert*-butylcyclohexyl-*S*-methyl xanthate was assessed from the spectra of the *trans*-2-*d* (IVe), *cis*-2-*d* (IVa) and 2,2,6,6-d_4 derivatives. As



IVe



IVa

the results in Table I indicate, the equatorial xanthate fragments with little stereospecificity. This result is not surprising. The carbon–sulfur double bond of the xanthate IV should be much longer than the carbon–oxygen double bond of the acetate II.[9] Since sulfur–hydrogen single bonds are typically much longer than oxygen–hydrogen single bonds,[9] hydrogen migration to the thion sulfur may occur over longer distances than migration to the carbonyl oxygen. Both effects will weaken steric interactions between the cyclohexyl ring and the abstracting group in the transition states for hydrogen abstraction. It is notable, however, that the xanthate IV exhibits a slight preference for cis elimination (k_{ax}/k_{eq} = 1.6), in contrast to the preferential trans elimination of the acetate II (k_{ax}/k_{eq} = 0.26). In light of existing uncertainties about the mechanism of xanthate fragmentation, it is pointless to speculate about the origin of the small energy differences that correspond to a rate ratio of 1.6. However, these experiments do demonstrate that trans elimination from equatorial ester derivatives is not a general phenomenon.

An unusual[10] aspect of the electron-impact induced behavior of the xanthates III and IV is that their spectra exhibit intense first[11] and second field free region metastable peaks for loss of xanthic acid. Thus, the stereochemistry of the reaction can be studied as a function of ion lifetime. The results of these studies appear in Table II. Within experimental error, there is no difference between the stereospecificity of xanthic acid elimination at 70 eV and in the metastable regions. This result is unexpected, since metastable ions should be less energetic, and are expected to fragment with greater stereospecificity than ions decomposing in the source.[12] Further

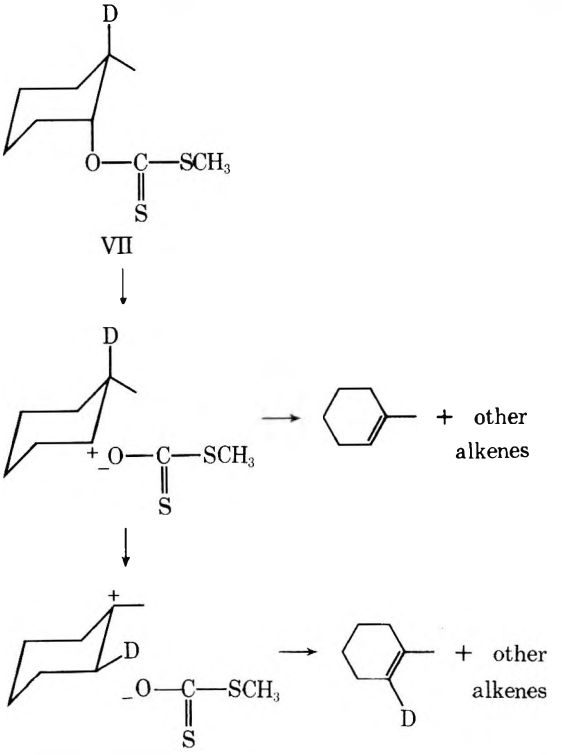
Table III. Pyrolytic Elimination of Xanthic Acid from Stereospecifically Labeled 4-*tert*-Butylcyclohexyl-*S*-methyl Xanthates

Compd	D loss/H loss[a,b]	k_{ax}/k_{eq}	*I*
cis-4-*tert*-Butycyclohexyl-*S*-methyl xanthate-*cis*-2-*d* (IIIe)	0.025 ± 0.015		
		0.08 ± 0.05	1.65 ± 0.2
cis-4-*tert*-Butylcyclohexyl-*S*-methyl xanthate-*trans*-2-*d* (IIIa)	0.53 ± 0.02		
trans-4-*tert*-Butylcyclohexyl-*S*-methyl xanthate-*trans*-2-*d* (IVe)	0.47 ± 0.01		
		0.04 ± 0.04	2.0 ± 0.2
trans-4-*tert*-Butylcyclohexyl-*S*-methyl xanthate-*cis*-2-*d* (IVa)	0.01 ± 0.01		

[a] Numbers appearing in this table were obtained by injecting 5-μl sample onto a stainless steel column at 300 °C. Injection onto a Pyrex glass column gave values which agreed within experimental error. [b] Error limits represent extreme values observed in at least three pyrolyses.

experiments will be required to establish the generality of this result. It may simply reflect the existence of a competing hydrogen–deuterium randomization process whose rate is fortuitously close to that of the elimination process among the metastable ions.

The pyrolytic elimination of xanthic acid has been much more thoroughly investigated than the electron-impact induced reaction. There is considerable evidence to indicate that the concerted cyclic E_i mechanism is not the exclusive elimination pathway.[2] Perhaps the most thoroughly studied reaction is the pyrolysis of *cis*- and *trans*-2-methylcyclohexyl-*S*-methyl xanthates.[3] The trans isomer pyrolyzes with a normal isotope effect ($k_H/k_D \approx 1.6$) and gives the expected products. In contrast, pyrolysis of the cis isomer VII generates



an olefin mixture containing 28% Δ′-methylcyclohexene; this alkene is 44% monodeuterated, and the isotope effect for its formation is 1. These effects were rationalized by postulating a carbonium ion intermediate which either loses a proton or deuteron directly, or isomerizes to the more stable carbonium ion. Other cases of net trans elimination have been reported.[2] It is notable that in every case where such anomalous behavior has been reported in the cyclohexyl ring system, an α carbon was substituted such that cis elimination to form the more stable alkene product was impossible. It appeared worthwhile to measure the facility of the trans elimination process in a cyclohexyl system devoid of alkene stabilizing groups on the α carbon. The results of pyrolyzing the labeled *S*-methyl xanthates IIIe, IIIa, IIIe, and IVa appear in Table III. Interestingly, these experiments demonstrate that the pyrolysis of cyclohexyl-*S*-methyl xanthates unsubstituted at the α carbon occurs with predominant cis elimination and normal isotope effects regardless of the stereochemistry of the starting xanthate. Thus, the unusual effects observed in earlier studies must be strongly facilitated by α substituents. Trans elimination is only a minor pathway to alkene formation in the pyrolysis of cyclohexyl-*S*-methyl xanthates unsubstituted at the α carbons. Further, these experiments demonstrate that the pyrolytic and electron-impact induced eliminations of xanthic acid from *cis*- and *trans*-4-*tert*-butylcyclohexyl-*S*-methyl xanthate occur with similar stereochemistry.

Experimental Section

Xanthate mass spectra were obtained on an AEI MS902 mass spectrometer using a direct insertion technique. The source temperature was maintained below 40 °C during all measurements. Pyrolyses were accomplished by injection of neat 5-μl samples of the *S*-methyl xanthates onto a 10-ft glass or stainless steel column (0.25 in. o.d.) mounted in a Hewlett-Packard 5450 gas chromatograph maintained at 300 °C. Helium flow rate was adjusted to allow a reaction time of ca. 5 min. Under these conditions, reaction was essentially complete. The 4-*tert*-butylcyclohexene was isolated by preparative gas chromatography performed on a Hewlett-Packard 5750 gas chromatograph containing a 6 ft × 0.125 in. column packed with 10% UCW 98 on 80–100 Chromosorb S and maintained at 130 °C. The isotopic composition of the alkene was determined by repeated mass spectral measurements.

NMR spectra were obtained using deuteriochloroform solvents on a Varian Model A-60 spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to a tetramethylsilane internal standard.

trans-4-*tert*-Butylcyclohexanol-*cis*-2-*d* and -*trans*-2-*d* and *cis*-4-*tert*-butylcyclohexanol-*cis*-2-*d* and -*trans*-2-*d* were prepared as already described.[5] Conversion to the corresponding *S*-methyl xanthates were accomplished by analogy to the procedure of Briggs and Djerassi.[1,3]

***trans*-4-*tert*-Butylcyclohexyl-*S*-methyl xanthate (IV)** was purified by preparative TLC (silica gel, hexane, repeated elution) or preparative gas chromatography (on a 10 ft × 0.125 in. Teflon-lined column packed with 3% OV-210 on 80/100 Chromosorb W-HP at 130 °C). The resulting white solid exhibited mp 45–46 °C; NMR δ 0.87 [9 H, s, $(CH_3)_3C$–], 2.53 (3 H, s, CH_3S), 5.44 (1 H, m, broad, HCOCS–), 0.88–2.5 (9 H, aliphatic H); mass spectrum, M^+ at 246.1103 ($C_{12}H_{22}S_2O$ requires 246.1112).

***cis*-4-*tert*-Butylcyclohexyl-*S*-methyl xanthate (III)** was purified similarly. A sample exhibited mp 56–57 °C; NMR δ 0.87 [9 H, s, $(CH_3)_3C$–], 2.53 (3 H, s, CH_3S), 5.83 (1 H, m, HCOCS–), 0.88–2.5 (9 H, aliphatic H); mass spectrum, M^+ at 246.116 ($C_{12}H_{22}S_2O$ requires 246.1112).

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Registry No.—III, 60239-14-7; IV, 60239-15-8.

References and Notes

(1) W. S. Briggs and C. Djerassi, *J. Org. Chem.*, **33**, 1612 (1968).
(2) (a) H. R. Nace, *Org. React.*, **12**, 57 (1962); (b) C. H. Depuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960); (c) D. V. Banthorpe, "Elimination Reactions", Vol. 2, Elsevier, Amsterdam, 1963, Chapter 7; (d) W. H. Saunders, Jr., and F. Cockerill, "Mechanisms of Elimination Reactions", Wiley, New York, N.Y., 1973, Chapter 8; (e) C. C. Beard, "Organic Reactions in Steroid Chemistry", Vol. 1, J. Fried and J. A. Edwards, Ed., Van Nostrand-Reinhold, Princeton, N.J., 1972, p 34.
(3) W. S. Briggs and C. Djerassi, *J. Org. Chem.*, **33**, 1625 (1968).
(4) See, for example, (a) M. M. Green, J. M. Moldowan, and J. G. McGrew II, *J. Org. Chem.*, **39**, 2166 (1974); (b) M. M. Green, J. M. Moldowan, D. J. Hart, and J. M. Krakower, *J. Am. Chem. Soc.*, **92**, 3491 (1970); (c) Z. M. Akhtar, C. E. Brion, and L. D. Hall, *Org. Mass Spectrom.*, **8**, 189 (1974); (d) W. Benz and K. Biemann, *J. Am. Chem. Soc.*, **86**, 2375 (1964).
(5) G. Eadon, P. Gold, and E. Bacon, *J. Am. Chem. Soc.*, **97**, 5184 (1975).
(6) G. Eadon, E. Bacon, and P. Gold, *J. Org. Chem.*, **41**, 171 (1976).
(7) D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2091 (1963); C. Djerassi, G. von Mutzenberger, J. Fajkos, D. H. Williams, and H. Budzikiewicz, *ibid.*, **87**, 817 (1965); C. Djerassi and L. Tökes, *ibid.*, **88**, 536 (1966); L. Tökes, R. T. LaLonde, and C. Djerassi, *J. Org. Chem.*, **32**, 1020 (1967).
(8) D. Y. Curtin and D. B. Kellom, *J. Am. Chem. Soc.*, **75**, 6011 (1953).
(9) "International Tables for X-Ray Crystallography", Kynoch Press, Birmingham, England, 1952.
(10) The acetates and malonates do not exhibit significant metastables (cf. ref 5). See also, G. Eadon, submitted for publication.
(11) M. Barber and R. M. Elliott, 12th Annual Conference on Mass Spectrometry and Allied Topics, Committee E-14, A.S.T.M., Montreal, Canada, 1964.
(12) See, for example, R. G. Cooks, J. H. Beynon, R. M. Caprioli, and G. R. Lester, "Metastable Ions", Elsevier, Amsterdam, 1973, p 207.

A Special-Salt Effect upon the Hydride Shift during the Acetolysis of Cyclohexyl Tosylate

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Lambert and Putz[1b] have recently suggested from stereochemical studies that the substitution product formed during the acetolysis of cyclohexyl tosylate arises from nucleophilic attack on an intimate ion pair (IIP). This interpretation is based upon the observation that cyclohexyl acetate was selectively formed with inversion of configuration. To our knowledge, this is the only study of the intermediate(s) leading to substitution on an unsubstituted cyclohexyl system, although Winstein and Holness[2] had previously suggested similar behavior in the solvolysis of *trans*-4-*tert*-butylcyclohexyl tosylate. On the other hand, Elakovich and Traynham[3] concluded from a study of the special salt effect that the cyclohexyl acetate was formed from a solvent separated ion pair (SSIP) during a chlorinolysis in acetic acid. With the exception of the work discussed above, most reports on the cyclohexyl system have been oriented toward the study of the possible conformation of the transition state.[4]

In this paper we report studies involving the special-salt effect and hydride shifts which are directed toward the elucidation of the product determining intermediates in the acetolysis of cyclohexyl tosylate. The results of the acetolysis of 2,2,6,6-tetradeuteriocyclohexyl tosylate at 50 °C are summarized in Table I.

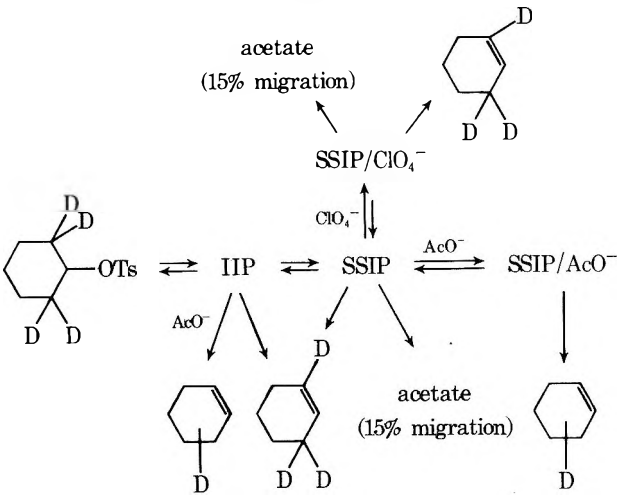
Substitution. The observation that the 0.13 D at position 1 of unreacted tosylate in the absence of $LiClO_4$ is suppressed by the presence of this salt clearly suggests the intermediacy of an external ion pair. Although Winstein[5] did not observe a special salt effect upon the rate of similar reactions, a contradiction does not necessarily exist. The special salt effect upon each of various reaction steps can sometimes be hidden in measurement of the overall rate since not all of the individual rate constants play a rate-determining role. Winstein, himself, recognized this as he admitted the possibility of external return, especially in the light of a very large normal salt effect (b = 37.2 at 50 °C). In terms of Winstein's[6] classic scheme

$$RX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\text{IIP}}{R^+X^-} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{\text{SSIP}}{R^+//X^-} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} R^+ + X^- \quad (1)$$

this result indicates that the equilibrium goes at least as far as the SSIP, suggesting the possibility of a reaction involving such a species, even in the absence of $LiClO_4$.

The intermediacy of a SSIP in the substitution reactions seems logical upon consideration of the following results. There is no change in the extent of deuterium scrambling in the acetate buffered reaction upon the inclusion of $LiClO_4$ in the reaction mixture. Observation of two identical patterns of deuterium scrambling for products arising from two different kinds of ion pairs is unlikely.[7] Since addition of $LiClO_4$ presumably increases the SSIP/IIP rates, the observed increase in the substitution/elimination (S/E) ratio upon addition of this salt suggests that the SSIP is more prone to substitution than the IIP.

Scheme I

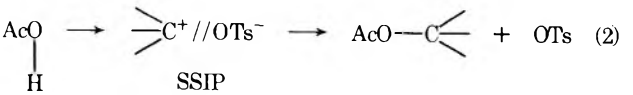


The present suggestion that the SSIP might be an intermediate in the substitution may, at first, seem in contradiction with the stereoselective inversion reported by Putz and Lambert.[1b] Nevertheless, there exists no definitive proof that a SSIP intermediate cannot react with such stereoselectivity, especially if the nucleophile is not the particular solvent molecule thought to separate the ions. In fact, reaction of a SSIP to form an inverted alcohol has been recently proposed by Shiner et al.[8] Such a possibility has also been recently suggested in two recent reformulations of the original Winstein equilibrium.[9,10]

We suggest two possible mechanisms that are consistent with substitution of a SSIP with inversion of configuration:

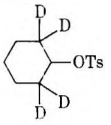
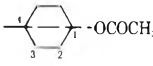
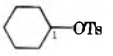
(a) The nucleophile could be an acetic acid that attacks the SSIP from the rear. This idea is in accord with a recent suggestion by Schleyer et al.[9]

(b) Another possibility is the simple collapse of the so-called anion–cation-stabilized intermediate (ACSI) which has recently been proposed by one of us as an alternative model for the SSIP[10] (reaction 3).

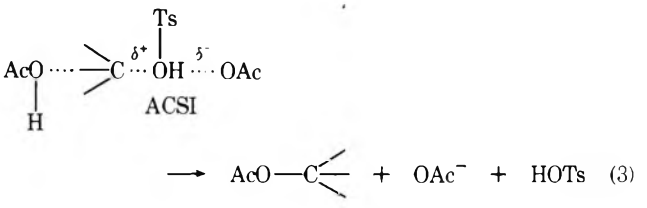


(2)

Table I. Extent of Migration during Acetolysis

0.03 M  D_T[a] = 3.95 7 days at 50 °C in 1.4 M anhydrous acetic acid		Number of atoms of deuterium per atom of hydrogen at position 1,2 . . . and total deuterium D_T[a]											
		Cyclohexyl acetate 					Cyclohexene 				Recovered tosylate 		
	S/E[b]	1	2	3	4	D_T	1	2	3	D_T	1	D_T	% ROTs recovered
With base 0.053 M CH_3COOK	10/90	0.15	0.86	0.07	0	3.96	0.40	0.38	0.21	3.17	0.13	3.97	10
With base and perchlorate 0.053 M CH_3COOK 0.0053 M ClO_4Li	45/55	0.15	0.86	0.07	0	3.96	0.51	0.49	0.03	3.08	0	3.97	10
Without base	30/70[c]	0.26[c]				3.75[c]	0.50	0.47	0	2.89	0.05[c]	3.84[c]	60[c]

[a] Quantitative isotopic distributions were done by NMR and MS errors are ±3%. [b] Substitution/elimination ratio is determined chromatographically. [c] These results are not significant since both HOTs and HOAc add to cyclohexene under these conditions.



Elimination. The elimination reaction at 50 °C (in the presence of KOAc and absence of $LiClO_4$) yields cyclohexene that exhibits a substantially greater amount of hydride shift than for the substitution product. Addition of $LiClO_4$ suppresses these shifts to a great extent. The cyclohexene produced exhibits a deuterium distribution consistent with that observed for the cyclohexyl acetate if we assume that k_H/k_D for the proton transfer from carbocation to base is reasonably small. These results clearly suggest the intermediacy of different species for the eliminations in two cases. Analysis of the three different sets of reaction conditions used can be interpreted in terms of the different kinds of SSIP's which might serve as possible intermediates: (a) $R^+//OTs^-$ in the absence of KOAc and $LiClO_4$; (b) $R^+//OTs^-$ and $R^+//OAc^-$ in the presence of KOAc; (c) $R^+//ClO_4^-$ in the presence of both KOAc and $LiClO_4$.

The extensive migration observed in the presence of KOAc might be related to the relatively strong basicity of the OAc^- anion. This particular point will be developed in a further and more detailed paper.

In conclusion, the most important point to emphasize is that $LiClO_4$ and KOAc can have a significant effect upon the extent of hydride migration and the product distribution of the acetolysis of cyclohexyl tosylate. Furthermore, it seems reasonable that both the substitution and elimination products are formed via the intermediacy of a SSIP.

Experimental Section

The reaction products were analyzed by GLC on a Girdel Model 75 chromatograph using a 3 m × 2 mm column of 20% PEG 20M on 60–80 mesh Chromosorb W NAW.

Cyclohexyl acetate and cyclohexene were purified by preparative GLC on an Aerograph Autoprep 700 using a 3 m × 6 mm column of the same packing.

The isotopic purity of the cyclohexanone was verified by mass spectroscopy on an EAI Model MS 12. Deuterium substitution in the products was measured by integration of the ^1H NMR signals vs. those of an internal standard using a Perkin-Elmer R12B spectrometer. Evaluation of this method using known amounts of a very pure nondeuterated sample indicated an error range of 1–3% depending upon the concentrations.

Cyclohexanone-*2,2,6,6-d*$_4$ (I). This compound was produced according to the method discussed by Hammond and Warkentin.[11] After three exchanges with D_2O and triethylamine a product 98.5% D (94% d_4 and 6% d_3) was obtained.

Cyclohexanol-*2,2,6,6-d*$_4$ (II). A solution of 30 g (0.3 mol) of I in anhydrous ether was added dropwise to a suspension of 15 g (0.04 mol) of $LiAlH_4$ in 300 ml of anhydrous ether. The reaction mixture was refluxed overnight, cooled, and hydrolyzed with 10% HCl, then extracted with ether. The ethereal solution was neutralized with $NaHCO_3$, washed with water, dried with anhydrous Na_2SO_4, and then distilled, yield 21 g (0.21 mol), 70% of II.

Cyclohexyl Tosylate-*2,2,6,6-d*$_4$ (III). Toluenesulfonyl chloride (19 g, 0.1 mol) was added to a stirred solution of 8 g (0.08 mol) of II in 80 ml of anhydrous pyridine maintained in an ice bath. Stirring was continued for 2 h, after which the reaction mixture was let stand for 18 h at room temperature. The mixture was then recooled in an ice bath after which 350 g of ice was slowly added. The precipitate was filtered, washed with cold water, and dried. Recrystallization from petroleum ether gave 16 g (0.06 mol) of III (85% yield, mp 43.5 °C).

Acetolysis.[12] III (8 g, 0.03 mol) was added to 80 ml of anhydrous acetic acid containing 5.2 g (0.053 mol) of anhydrous potassium acetate (acetolysis in the presence of base) and 0.56 g (0.0053 mol) of $LiClO_4$ (acetolysis in the presence of $LiClO_4$). The mixture was stirred for 7 days at 50 °C in a thermostated reactor fitted with a reflux condensor. At the end of the reaction period, the mixture was cooled in an ice–water bath, neutralized to pH 8 with chilled 30% KOH, and then extracted with ether. The collected ether layers were washed with water, dried, then analyzed by GLC to determine S/E. The ether was then distilled taking care to keep the liquid temperature below 45 °C. Cyclohexene and cyclohexyl acetate were separated from the unreacted tosylate by vacuum distillation and trapped with liquid nitrogen. These products were then separated and purified by preparative GLC. The unreacted tosylate was recrystallized from petroleum ether.

^1H NMR Analysis of Solvolysis Products. The extent of deuteration was determined using the following internal standard: trichloroethylene (for the acetate); the phenyl protons of the tosyl group (for the tosylate); chloroform (for cyclohexene); bromobenzene (for total deuterium interpretation). The relative amounts of deuteration in the various positions of cyclohexyl acetate were determined by integration of simplified spectra obtained upon the addition of a shift reagent, $Eu(DPM)_3$. Each value in Table I represents an average of two or three experiments, each of which was integrated ten times.

The error in the integration was of the order of 1% of the proton signal in the most favorable cases (those where total proton content was measured) and 2–3% in the less favorable cases (where proton content per position was measured). These errors, when translated into deuterium content, are approximately the following: (a) total D in cyclohexene, ±0.06 D; (b) total D in cyclohexyl tosylate or acetate, ±0.10 D; (c) D per position in cyclohexyl acetate, ±0.02 D; (d) D per position in cyclohexene, ±0.03 D. The small deuterium content in position 3 of cyclohexene formed in the presence of $LiClO_4$ was specifically confirmed by 270-MHz spectra.

Registry No.—I, 1006-03-7; II, 21273-03-0; III, 98-59-9; toluenesulfonyl chloride, 967-93-1; potassium acetate, 127-08-2; $LiClO_4$, 7791-03-9.

References and Notes

(1) (a) Professeur Associé, Universite Pierre et Marie Curie (Paris VI), 1974–1975. Department of Chemistry, Hunter College of the City University of New York, New York, N.Y. 10021. (b) J. B. Lambert and G. J. Putz, *J. Am. Chem. Soc.*, **95**, 6313 (1973).
(2) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).
(3) S. D. Elakovich and J. G. Traynham, *J. Org. Chem.*, **38**, 873 (1973).
(4) (a) H. Kwart and T. Takeshita, *J. Am. Chem. Soc.*, **86**, 1161 (1964); (b) V. J. Shiner, Jr., and G. J. Jewett, *ibid.*, **87**, 1383 (1965); (c) *ibid.*, **87**, 1382 (1965); (d) N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc. B*, 355 (1968); (e) J. L. Mateos, C. Perez, and H. Kwart, *Chem. Commun.*, 125 (1967); (f) W. H. Saunders, Jr., and K. T. Finley, *J. Am. Chem. Soc.*, **87**, 1384 (1965); (g) M. Tichy, J. Hapala, and J. Sicher, *Tetrahedron Lett.*, 3739, (1969); (h) J. E. Nordlander, J. M. Blank, and S. P. Jinda , *ibid.*, 3477 (1969); (i) J. E. Nordlander and T. J. McCrary, Jr., *J. Am. Chem. Soc.* **94**, 5133 (1972).
(5) A. J. Fainberg and S. Winstein, *J. Am. Chem. Soc.*, **78**, 2780 (1956).
(6) S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck, and G. C. Robinson, *J. Am. Chem. Soc.*, **78**, 328 (1956).
(7) S. Winstein, B. Appel, R. Baker, and A. Diaz, *Chem. Soc., Spec. Publ.*, **No. 19**, 109 (1965).
(8) K. Humski, V. Sendijarevic and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **95**, 7722 (1973).
(9) D. J. Raber, J. M. Harris, and P. v. R. Schleyer, "Ions and Ion Pairs in Organic Reactions", Vol. 2, M. Szwarc, Ed., Wiley, New York, N.Y., 1974, p 247.
(10) J. J. Dannenberg, *J. Am. Chem. Soc.*, **98**, 6261 (1976).
(11) G. S. Hammond and J. Warkentin, *J. Am. Chem. Soc.*, **83**, 2554 (1961).
(12) T. N. Shatkina, E. V. Leont'eva, and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, **177**, 373 (1967).

Structure and Reactivity in the Reduction of Cycloalkenes and Cycloalkadienes by Diimide[1]

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The reduction of alkenes by diimide is believed to consist of a single step in which the diimide, formed in situ, transfers a pair of hydrogen atoms to the olefinic center by a synchronous suprafacial process via a transition state of negligible ionic character.[2-5] The relative rates of diimide reductions of nearly 40 cyclic, exocyclic, and acyclic alkenes have been determined by Garbisch, Schildcrout, Patterson, and Sprecher.[6] They concluded that the major factors that contribute to the differences in reactivity are torsional strain, bond angle bending strain, and the α-alkyl substituent effect and, in support, cited the good agreement between the calculated and observed values for the relative rates. Bird, Franzus, and Surridge[7] concluded that the relative rate of reduction of the nonconjugated dienes (nonbornadienes) is a function of the degree of substitution of the double bond attacked. In our previous paper[8] we proposed that Garbisch's general approach (for estimating the contribution of torsional strain and bond angle strain to the relative reactivities of alkenes) can be extended to conjugated dienes by an appropriate estimate of the conjugation energy which diminishes as the geometry of the conjugated system departs from planarity.[8,9]

To provide additional information on the effect of ring size upon the reactivity of cycloalkadienes, we have determined the relative rate constants for the sequential reduction of some conjugated and nonconjugated cycloalkadienes to the derived cycloalkenes and cycloalkanes, and through a series of competitive reactions, the relative rates of reduction of cycloalkenes and cycloalkadienes of different ring size ($C_5 \rightarrow C_{12}$). The reductions were carried out at 25 °C with diimide which was generated from the decomposition of azodicarboxylic acid produced by the slow addition of a methanol solution of acetic acid to potassium azodicarboxylate in methanol.[7,8]

Results and Discussion

The competitive reductions of cycloalkenes by diimide generated from the decarboxylation of azodicarboxylic acid at 25 °C yielded relative rate constants whose values are compared in Table I to those calculated and found experimentally by Garbisch et al.[6] Each constant represents the average obtained from six to ten samples of the reaction mixtures which were removed at arbitrary intervals of time in each experiment. Some cross checks were done to verify the relative rates obtained indirectly. Since our experiments were done at 25 °C, rather than 80 °C, the relative rates were found to be larger than those reported by Garbisch et al.[6] but the general trend in the observed relative reactivities of the alkenes is in good agreement. Cyclopentene, cycloheptene, and *cis*-cyclooctene are considerably more reactive than cyclohexene and, according to Garbisch et al., *cis*-cyclononene and *cis*-cyclododecene are only slightly more reactive.[6] Bicyclo[2.2.1]heptene and *trans*-cyclooctene are by far the most reactive of the alkenes, a fact that is attributed to the unusually large bond angle bending and torsional strains (estimated to be 23.6 and 17.8 kcal/mole, respectively),[10] which are relieved in part upon reaching the transition state. The highly strained *trans*-cyclooctene is 22 000 times more reactive than cyclohexene at 25 °C.

For the 12-member ring, the cis isomer, which possesses a very low strain energy,[6] was found to react 1.4 times as fast as cyclohexene while Garbisch reports a relative rate of 0.6 (calculated 1.5).[6] However, the trans isomer was found to react eight times as fast, a fact attributed again to the relief of torsional strain as well as to the absence of the vicinal methylene–methylene interactions which are present in the cis isomer.

With respect to ring size, the trend found for the cycloalkadienes, however, was opposite to that of the cycloalkenes (Table II). The most reactive compound was 1,3-cyclohexadiene while cyclopentadiene, 1,3-cycloheptadiene, and 1,3-cyclooctadiene were reduced more slowly. Indeed the conjugated 1,3-cyclohexadiene was reported by Siegel, Forman, Fisher, and Johnson[8] to be more reactive than the corresponding nonconjugated diene as well as cyclohexene, when the rates are adjusted for the reactivity per double bond. They suggested that the expected rate-diminishing effect of conjugation in this instance is small because of the nonplanarity of the conjugated system which is due to internal torsional and bond angle strains.[8,9] The lower reactivity of other cyclic dienes relative to 1,3-cyclohexadiene arises because the decreased torsional strains in those dienes not only permits a more effective conjugative interaction in the diene (rate diminishing) but also results in a smaller driving force from the release of torsional strain at the transition state.

Ring size (Table II) influences the relative reactivity toward diimide of nonconjugated dienes in a manner which indicates the importance of the release of torsional strain as a driving force. Thus 1,5-cyclooctadiene, which has been estimated to have a torsional strain energy of 13.3 kcal/mol,[10] was found to react five times as fast as 1,3-cyclooctadiene while the unconjugated 1,4-cyclohexadiene, whose torsional strain appears to be relatively small,[9] has a lower reactivity than the corresponding conjugated diene, 1,3-cyclohexadiene.

The determination of the relative reactivity of a particular cyclic diene and the resulting monoene was obtained directly as before (Table III).[8] While for 1,3- and 1,4-cyclohexadiene, the reactivity (per double bond) of the diene is greater or equal to that of the monoene, the other cycloalkadienes examined are less restrictive per double bond than the corresponding monoene. This fact suggests again that although conjugation is important in tending to lower the reactivity of the alkenyl double bond, torsional strain (as in 1,3-cyclohexadiene) may

Table I. Summary of Relative Rates (Cross Checks) in the Reduction of Cycloalkenes with Diimide at 25 °C[a]

Registry no. (A)	Alkene A	Alkene B	k_A/k_B[b] (direct)	k_A/k_6[b]	k_a/k_6[c] (Garbisch et al.) 80 °C
142-29-0	c-C_5	c-C_6[f]	22 ± 1.5	22 ± 1.5	15.5
628-92-2	c-C_7	c-C_6	18 ± 1.0	18 ± 1.0	12.1
931-87-3	c-C_8 (cis)	c-C_7	1.69 ± 0.2	30.4 ± 0.9[d]	17.0
931-89-5	c-C_8 (trans)	c-C_7	1200 ± 80	$2.2 \times 10^3 \pm 500$[d]	
	c-C_8 (cis)	c-C_6	30.5 ± 1.0	30.5 ± 1.0	17.0
	c-C_8 (trans)	c-C_8 (cis)	740 ± 30	$2.2 \times 10^3 \pm 500$[d]	
1129-89-1	c-C_{12} (cis)	c-C_8 (cis)	0.05 ± 0.01	1.46 ± 0.3	0.64[e]
1468-75-5	c-C_{12} (trans)	c-C_8 (cis)	0.26 ± 0.12	8.0 ± 0.5	
279-23-2	Bicyclo[2.2.1]-C_7	c-C_6	690 ± 20	690 ± 20	
	Bicyclo[2.2.1]-C_7	c-C_7	36 ± 3	648 ± 40[d]	4.5×10^2
	Bicyclo[2.2.1]-C_7	c-C_8 (cis)	24 ± 2	732 ± 50	4.5×10^2
1192-37-6	Methylenecyclohexane	Methylenecyclopentane[g]	1.8 ± 0.3		3.5

[a] Diimide generated from decomposition of azodicarboxylic acid at 25 °C. [b] k_6 is for cyclohexene. [c] See ref 6. [d] Calculated from $k_A/k_6 = (k_A/k_B)(k_B/k_6)$. [e] Calculated value according to Garbisch et al. should be 1.5 (ref 6). [f] Registry no., 110-83-8. [g] Registry no., 1528-30-9.

Table II. Relative Rates for Competitive Reduction of Cyclic Dienes to Monoenes with Diimide Generated at 25 °C[a]

Registry no. A	Registry no. B	Dienes A	Dienes B	k_A/k_B (direct)	k_{6D}/k_A[b,c] (indirect)
592-57-4	542-92-7	1,3-Cyclohexadiene	Cyclopentadiene	2.0 ± 0.15	(1.00)
	628-41-1	1,3-Cyclohexadiene	1,4-Cyclohexadiene	22 ± 2.0	
				25.0[d]	
		1,3-Cyclohexadiene	1,3-Cycloheptadiene	9.0 ± 1.0	
	1700-10-3	1,3-Cyclohexadiene	1,3-Cyclooctadiene	27 ± 2	
4054-38-0		1,3-Cycloheptadiene	1,3-Cyclooctadiene	3.2 ± 0.6	8.6
111-78-4		1,5-Cyclooctadiene	1,3-Cyclooctadiene	5.5 ± 1.0	5.0
		1,3-Cyclohexadiene	1,5-Cyclooctadiene	5.0 ± 0.5	

[a] Diimide generated from decomposition of azodicarboxylic acid at 25 °C. [b] k_{6D} is for 1,3-cyclohexadiene reduced to cyclohexene. [c] Calculated from $k_A/k_{6D} = (k_A/k_B)(k_B/k_{6D})$. [d] From ref 8.

Table III. Relative Reactivities of Cycloalkadienes and Product Monoenes in the Reduction of Diimide at 25 °C[a]

diene $\xrightarrow{k_1}$ monoene $\xrightarrow{k_2}$ saturated

Diene	Monoene	k_2/k_1[b]
c-C_5-diene	Cyclopentene	1.75 ± 0.3
1,3-c-C_6-diene	Cyclohexene	0.04[c]
1,4-c-C_6-diene	Cyclohexene	0.45 ± 0.1
1,3-c-C_7-diene	Cycloheptene	6.5 ± 0.9
1,3-c-C_8-diene	*cis*-cyclooctene	35 ± 4.0

[a] Diimide generated from the decomposition of azodicarboxylic acid. [b] *Per double bond*, the relative reactivities are 3.5, 0.08, 0.9, 13, and 70 (in descending order in the table). [c] Value obtained from ref 8.

reduce the planarity of the conjugated system and thus the conjugative interaction as well.

Experimental Section

Dienes and Alkenes. The cycloalkenes and cycloalkadienes were purchased from Chemical Samples Co. or Aldrich Co. and used without further purification except for 1,5-cyclooctadiene and *cis*- and *trans*-cyclododecene, which were obtained from Columbian Carbon Co. and were redistilled before use. The identity of each compound was checked by examining its NMR and infrared spectra and its purity was at least 99% as determined by GLC.

Reduction with Diimide. Competitive reductions with diimide generated from the decarboxylation of azodicarboxylic acid in methanol at 25 °C followed the procedure of Bird et al.[7] with relatively minor modifications.[8]

Analytical Procedure. The mixtures were analyzed by GLC (flame ionization detector) on either a 45 ft × 0.125 in. column of 2.5% Carbowax 600 and 2.5% Carbowax 750 on Chromosorb W (AW) 60/80 mesh (for the cyclic dienes and products) or a 300 ft × 0.02 in. capillary column coated with 10% Apiezon L. All peaks were identified by comparison with mixtures of authentic standards and the molar response factor of each component was determined. The peak areas were obtained with a digital integrator, Varian Model 485. The calculations of the relative rate constants from competitive reductions or the consecutive reactions of a diene were obtained by the equations and methods described in our previous paper.[8]

Registry No.—Diimide, 3618-05-1.

References and Notes

(1) (a) Support from a grant from the National Science Foundation, CHE-76-01785, is gratefully acknowledged. (b) Ms. Anne Tramp assisted with the preliminary experiments on the monoenes.
(2) S. Hünig, H. R. Müller, and W. Thier, *Angew. Chem., Int. Ed. Engl.*, **4**, 271 (1965).
(3) S. Hunig, H. R. Muller, and W. Thier, *Tetrahedron Lett.*, 11, 353 (1961).
(4) E. J. Corey, and W. L. Mock, *J. Am. Chem. Soc.*, **84**, 685 (1962).
(5) E. J. Corey, D. J. Pasto, and W. L. Mock, *J. Am. Chem. Soc.*, **83**, 2957 (1961).
(6) E. W. Garbisch, Jr., S. M. Schildcrout, D. B. Patterson, and C. M. Sprecher, *J. Am. Chem. Soc.*, **87**, 2932 (1965).
(7) W. C. Baird, Jr., B. Franzus, and J. H. Surridge, *J. Am. Chem. Soc.*, **89**, 410 (1967).
(8) S. Siegel, M. Foreman, R. P. Fisher, and S. E. Johnson, *J. Org. Chem.*, **40**, 3599 (1975).
(9) N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.*, **95**, 3893 (1973).
(10) N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.*, **94**, 5734 (1972).

An Improved Route for the Synthesis of 1-Amino-2-methylnaphthalene[1]

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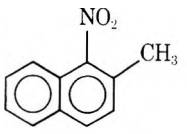
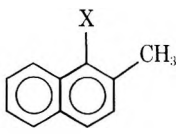
When a chemist wishes to prepare a primary aromatic amine the classic approach has been to nitrate the nucleus in question and then to reduce the nitro compound thus obtained. In this paper we show that if 1-amino-2-methylnaphthalene is the desired compound, an alternate approach is preferable. 1-Amino-2-methylnaphthalene was needed as a precursor to several disubstituted naphthalenes of interest in the synthesis of compounds desired for testing in the cancer program.

In the first place, nitration is a reaction which often proceeds with less selectivity than many other electrophilic aromatic substitution reactions. This means that often the nitration product is a mixture of isomers. Frequently the yield of crude nitration product is cited and also the melting point of the desired isomer but too often there is no indication of what yield of pure isomer is to be expected. Furthermore, the products of nitration are quite sensitive to the nitrating species.[3] In the present case, nitration of 2-methylnaphthalene near 0 °C has been reported[4] to yield 58% of 1-nitro-2-methylnaphthalene (1) (plus 42% of an unknown mixture of



1 (X = NO_2)



2 (X = Br)
3 (X = COOH)
4 (X = NH_2)

other nitro-2-methylnaphthalenes) and to yield **1**, mp 80–81 °C, in unspecified yield from 60% of solid nitro compound.[5] That even the 58% of 1-nitro-2-methylnaphthalene was not pure is indicated by the fact that monobromination of the 1-amino-2-methylnaphthalene produced by reduction of **1** needed several recrystallizations to afford a pure sample of 1-amino-4-bromo-2-methylnaphthalene in 31% yield[6] (some impurities may have resulted from the bromination procedure). In our experience with the nitration of 2-methylnaphthalene, we have found that the yield varies from run to run and that recrystallization to obtain pure **1** is tedious and accompanied by large diminutions in yield. Accordingly we have developed the method described below.

Bromination[7] of 2-methylnaphthalene affords an 88% yield of almost pure 1-bromo-2-methylnaphthalene (**2**). This material is converted via the Grignard reagent into 2-methyl-1-naphthoic acid (**3**), shown to be almost pure by subjecting to acid-catalyzed esterification. Acids other than **3** are esterified and hence easily separated from the sterically hindered acid, **3**, which is obtained pure in 77% overall yield from **2**. Finally, **3** is converted into 1-amino-2-methylnaphthalene (**4**) in high yield (see Experimental Section) by treating a sulfuric acid solution (90.8% by weight) with sodium azide. Because **4** is sensitive to air it is best converted to the *N*-formyl derivative, **5**, if it is to be brominated.

The extreme sensitivity to sulfuric acid strength of the Schmidt reaction in converting **3** to **4** is noteworthy. If 96% sulfuric acid was used, the amine formed was sulfonated and only water-soluble products were obtained. If 90% sulfuric acid (possibly weaker as no titration was performed) was used, mostly unchanged **3** was recovered. The best yield was obtained with 90.8% sulfuric acid by weight, but no other reactions in which titrated H_2SO_4 was used were studied.

We believe that the route we have developed is preferable to the nitration route because higher yields of purer product may be obtained even though an extra step is involved. It is noteworthy that separation of the desired isomer is accomplished by taking advantage of chemical reactivity (the inability of the desired acid, **3**, to be esterified) rather than having to rely on a physical method, i.e., recrystallization, for purification of **1**.

Experimental Section

1-Bromo-2-methylnaphthalene (2). A solution of 320 g of bromine in 180 ml of acetic acid was added during 3 h to a well-stirred solution of 284 g of 2-methylnaphthalene[8] in 375 ml of glacial acetic acid containing 10 g of $AlCl_3$ and 1 ml of pyridine (the rate of bromination is less if the pyridine is omitted). After 2 more h the mixture was poured into 1.5 l. of water and the product taken into 1:1 ether–benzene. After a conventional workup (which included a wash with $NaHSO_3$) the solvent was removed on a rotary evaporator and the residue was vacuum distilled through a short column to yield 409 g (92%) of **2**, bp 148–149 °C (8 mm). In other runs when material having a slightly larger distilling range was collected some further purification procedures were applied prior to attempting to prepare the Grignard reagent. One procedure involved boiling with a small amount of aqueous alcoholic KOH followed by washing the solvent-free product thus obtained with 75% H_2SO_4 until no color was observed in the H_2SO_4 layer. Whether or not this purification is advisable could be found out by treating a small amount of crude **2** with alcoholic $AgNO_3$. If no precipitate of AgBr was formed no side-chain bromination had occurred and then alkaline treatment is unnecessary. The other procedure involved shaking a chloroform solution of crude **2** with portions of 75% H_2SO_4 as often as color was formed in the H_2SO_4 layer. The product was then recovered and distilled. Overall yields of 83–88% of pure **2** suitable for facile conversion to Grignard reagent were the rule.

2-Methyl-1-naphthoic Acid (3). In a typical reaction, a solution of 155 g of **2** in 400 ml of ether containing 2 ml of ethylene dibromide was added to a stirred mixture of 20 g of Mg and 180 ml of ether (previously activated by treatment with a small amount of ethylene dibromide[9]) during 2 h. As soon as a trace of oily layer was apparent sufficient benzene was added to dissolve the oily layer. In all about 200 ml of benzene was needed. After being held at reflux for 1 h the cooled Grignard reagent was poured rapidly on crushed solid CO_2 (a large but unmeasured excess) in a 4-l. beaker. A conventional workup, which included extraction of the acid by 15% KOH solution, yielded crude **3** which was promptly treated with ethanol, benzene, and an acid catalyst at reflux under a phase-separating head. After several hours at reflux (the amount of acid esterified by this treatment is so small that a second layer is not seen in the head) the pure acid is recovered by a conventional workup as an almost colorless solid, mp 125–127 °C (lit.[10] mp 126–127 °C), in 77–80% overall yield from **2**. The small amount of ester recovered from the neutral fraction had two components [NMR CH_3 peaks when methanol was used for esterification at 1.18 ppm (minor component) and 1.23 ppm].

1-Amino-2-methylnaphthalene (4). Our best results were obtained by adding 7.8 ml of water to 100 ml of commercial concentrated H_2SO_4 (97% by titration). To a stirred solution of 25 g of **3** in 200 ml of 90.8% H_2SO_4 held at 0–5 °C was added 13 g of NaN_3 in small portions during 2 h. After another 3 h the yellow-orange solution was poured on 500 ml of ice and water. The mixture was made basic by the addition of 900 ml of 40% NaOH. The amine was taken into ether–benzene and after the usual workup was distilled to yield 16.2 g (77%) of pure **4**, bp 150 °C (4 mm) [lit.[11] bp 141–143 °C (5 mm)]. In smaller runs (5 g of **3**) higher yields (80–85%) were occasionally obtained and on a larger run (65 g) the yield dropped to 70%. The amine darkens rapidly on standing and should be used as soon as convenient.

Registry No.—**2**, 2586-62-1; **3**, 1575-96-8; **4**, 2246-44-8; 2-methylnaphthalene, 91-57-6.

References and Notes

(1) This work was supported by Grant CA-07394 and by Contract CP 43248 of the National Cancer Institute.
(2) Postdoctoral Research Associates.
(3) J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, "Nitration and Aromatic Reactivity", Cambridge University Press, New York, N.Y., 1971.
(4) V. Vesely and J. Kapp, *Recl. Trav. Chim. Pays-Bas*, **44**, 360, (1925).

(5) H. E. Fierz-David and E. Mannhart, *Helv. Chim. Acta*, **20**, 1024 (1973).
(6) (a) R. Adams and A. A. Albert, *J. Am. Chem. Soc.*, **64**, 1475 (1942); (b) A. Fischer, W. J. Mitchell, G. S. Ogilvie, J. Packer, J. E. Packer, and J. Vaughan, *J. Chem. Soc.*, 1426 (1958).
(7) An improved bromination in acetic acid containing a small amount of pyridine is described in the Ph.D. Thesis of A. I. Kosak, The Ohio State University, 1948, and in the Experimental Section.
(8) Technical grade, 98.5%, obtained from the Chemical Samples Co., Columbus, Ohio.
(9) D. E. Pearson, D. Cowan, and J. D. Beckler, *J. Org. Chem.*, **24**, 504 (1959).
(10) R. Adams and L. O. Binder, *J. Am. Chem. Soc.*, **63**, 2773 (1941).
(11) M. S. Newman and S. Blum, *J. Med. Chem.*, **7**, 466 (1964).

A Convenient Synthesis of 1,2-Naphthalic Anhydride[1]

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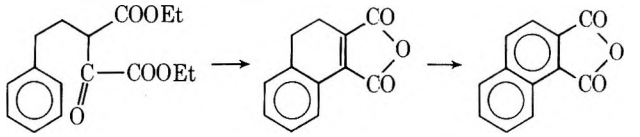
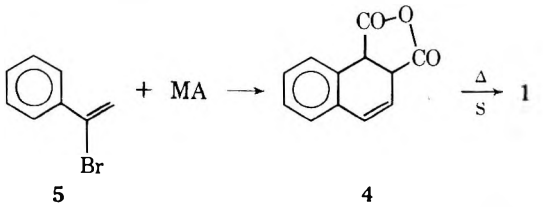
1,2-Naphthalic anhydride (**1**) has long been used for the elaboration of compounds in the benz[*a*]anthracene series.[3] An early synthesis of **1** involved cyclization of ethyl 3-carboethoxy-2-oxo-5-phenylpentanoate (**2**) to 3,4-dihydronaphthalene-1,2-dicarboxylic acid anhydride (**3**) followed by aromatization by heating with sulfur.[4] Later, 1,2-dihydronaphthalene-1,2-dicarboxylic anhydride (**4**), together with a small amount of **1**, were prepared by heating α-bromostyrene (**5**) with maleic anhydride[5] but no developmental work on this route to **1** has been reported. An attempt to convert β-bromostyrene to **4** by heating with maleic anhydride failed.[6] We have tried to use α-chlorostyrene instead of **5** but obtained none of the desired **4**. In this note we record our observations on an improved preparation of **1** by the styrene route.



2 **3** **1**

We have converted styrene dibromide to **5**, by using phase transfer catalysis.[7] In the final dehydrogenation of **4** by heating with sulfur, we have found that the **1** produced always contains some sulfur compound which is not removed by recrystallization. However, by boiling **1** in aqueous alkali, acidification, and cyclization to the anhydride pure sulfur-free **1** can be obtained in satisfactory overall yield.



5 **4**

In our opinion it is much easier to prepare quantities of **1** by the styrene route than by the earlier cyclization of the keto diester[4] as it is relatively simple to carry out the reactions involved on a large (2–3 mol) scale.

Experimental Section

α-Bromostyrene (5). In the best experiment, a solution of 336 g of bromine in 250 ml of $CHCl_3$ was added to a cooled (ca. 5 °C) solution of 208 g of freshly distilled styrene in 250 ml of $CHCl_3$. The temperature was not allowed to rise above 15 °C but cooling to 5 °C near the end is not advisable because the product will crystallize prematurely. After all of the bromine was added the reaction mixture was allowed to stand at room temperature for 1 h. The solvent was then removed to constant weight on a rotary evaporator. The yield of styrene dibromide is practically quantitative.

In the best of many runs, a solution of the crude styrene dibromide thus obtained in 800 ml of benzene was added fairly rapidly to a well-stirred mixture at 70 °C of 528 g of KOH, 800 ml of water, and 10 g of Aliquat 336.[8] The mixture was held at reflux for 3 h.[9] After cooling, the benzene layer was washed with water and saturated salt solution, passed through a cone of anhydrous $MgSO_4$, and fractionally distilled to afford 301 g (82.7%) of **5**, bp 80–83 °C (10 mm). In other similar runs which varied in detail yields of 52–79% were obtained. The yield is somewhat dependent on the skill of the operator in conducting a rapid distillation. If the distillation is conducted too slowly thermal decomposition occurs and the yield is lower. The use of a hot salt bath and a free flame to hasten distillation is recommended.[10]

1,2-Naphthalic Anhydride (1). In the best of many runs, a solution of 408 g of **5** and 326 g of maleic anhydride in 1.5 l. of xylene was refluxed for 48 h (to ensure escape of most of the HBr formed). The solvent was then distilled and the residue was rapidly vacuum distilled to yield crude **4**, bp 150–165 °C (1 mm), which was immediately placed in a Claisen flask with 71 g of sulfur. The mixture was heated rapidly to 230–235 °C with a salt bath and held at this temperature for 1 h, then at 250 °C for 1 h. Rapid vacuum distillation afforded 300 g (69%) of crude **1**, mp in the 160–164 °C range. The yields in this step varied from 63 to 75% (small-scale run). This product contains sulfur-containing impurities and cannot be effectively purified by crystallization. The best method of purification involved heating at reflux for 4 h 131.5 g of crude **1** with excess 20% NaOH. On acidification of the filtered solution followed by heating of the acid with 1 l. of $(Ac)_2O$, there was obtained 116.9 g (89%) of **1** in three crops. The melting points lay in the 165–167 °C range and this material was suitable for further work. No sulfur was present as shown by the absence of *m/e* over 198.

Registry No.—**1**, 5343-99-7; **4**, 60224-29-5; **5**, 98-81-7; styrene, 100-42-5; styrene dibromide, 93-52-7; maleic anhydride, 108-31-6.

References and Notes

(1) This work was supported by Grant CA-07394 and by Contract NO1-CP-43248 from the National Cancer Institute.
(2) Postdoctoral Research Associate.
(3) L. F. Fieser and M. S. Newman, *J. Am. Chem. Soc.*, **58**, 2376 (1936).
(4) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Cos.*, **57**, 1851 (1935); "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, pp 194, 423.
(5) K. Alder and K. Triebenech, *Ber.*, **87**, 237 (1954).
(6) F. Bergmann and J. Szmuszkowicz, *J. Am. Chem. Soc.*, **69**, 1777 (1947).
(7) C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971).
(8) Aliquat 336, methyltricaprylammonium chloride, McKerson Corp., Minneapolis, Minn.
(9) Refluxing for longer times results in the formation of larger amounts of phenylacetylene, bp below 75 °C (10 mm).
(10) The technique is described in M. S. Newman, "An Advanced Organic Laboratory Course", Macmillan, New York, N.Y., 1972, pp 23, 35.

The Chemistry of a Ketene–Sulfur Dioxide Adduct. 3. Reactions with Azines

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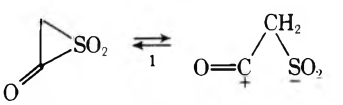
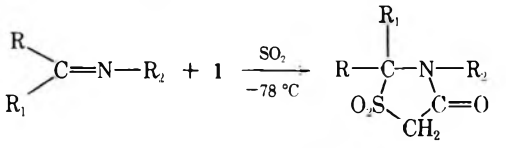
The cycloadditions of imines with ketene–sulfur dioxide adduct (**1**)[1b,c] to give substituted thiazolidin-4-one 1,1-dioxides was described in earlier publications,[1a,b] and extended by Kagan et al.[2] to substituted ketenes. More recently, Bellus reported that ketenes containing carbanion stabilizing substituents, generated in situ in the presence of sulfur dioxide,



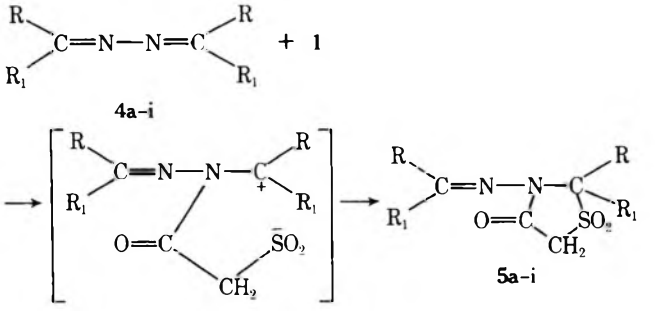
also gave the corresponding substituted thiazolidin-4-one 1,1-dioxides, when treated with benzylideneaniline.[3]

The reaction of imines with **1** was first shown to occur with benzylideneaniline,[1a,b] but we have since found that other compounds containing the imino function also react readily, thereby illustrating the generality of this reaction.



2, R = C_6H_5; R_1 = H; R_2 = CH_3
3, R, R_1 = 9-fluorenyl; R_2 = C_6H_5

In order to further extend the reactions of the ketene–sulfur dioxide adduct to other dipolarophiles, we have examined the reactions of both aldehyde and ketone azines (**4a–i**) with **1** at −78 °C, in liquid sulfur dioxide, and observed the following results.



4a–i

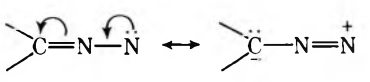
5a–i

a, R = 2-furyl	R_1 = H
b, R = 5-methyl-2-furyl	R_1 = H
c, R = 2-thienyl	R_1 = H
d, R = phenyl	R_1 = H
e, R = 3,4-dimethoxyphenyl	R_1 = H
f, R = 3-methoxyphenyl	R_1 = H
g, R = styryl	R_1 = H
h, R = furyl	R_1 = CH_3
i, R = phenyl	R_1 = CH_3

In contrast with two recent reports,[4,5] ketone azines underwent cyclization with **1**. This observation not only supports the existence of a ketene–sulfur dioxide adduct,[1b,c] since diphenyl ketene in ether was found unreactive, but also suggests that **1** is a reactive 1,3-dipolar species.

In all cases (**5a–i**), the reaction took place at only one of the two available azomethine functions. This finding is in agreement with previously unpublished observations that hydrazones from either aldehydes or ketones do not react with **1** under a variety of conditions. Starting material was quantitatively recovered from these reactions along with ketene polymer. The azomethine group of the hydrazone structural unit (>C=N–N–) is inert to **1**, ketenes, and alkoxydiazenium salts, although in the latter case a reaction occurred on the amino nitrogen.[5]

Although the reason for this lack of reactivity has not been established, it is possible that delocalization of the type shown



would decrease both the nucleophilicity of the carbon–nitrogen double bond and the electron deficiency of the carbon. This delocalization is similar to that observed in the anion of hydrazones in Wolff–Kishner reductions. In the azine, once cycloaddition has occurred at one of the azomethine groups, the product is structurally analogous to a hydrazone and therefore capable of similar delocalization.

Aldehyde and ketone azines containing aliphatic substituents polymerized under the conditions used.

Experimental Section

Ir spectra were recorded on a Perkin-Elmer Model 137 Infracord and NMR spectra were recorded on a Varian A-60A spectrometer with tetramethylsilane as an internal standard. All melting points were determined on a Thomas-Hoover Unimelt apparatus and are corrected. Ketene was generated by the pyrolysis of acetone over a nichrome coil at 500–700 °C in a calibrated ketene generator and collected at dry ice–acetone temperature. Anhydrous grade sulfur dioxide was obtained from commercial sources and dried further by first bubbling it through concentrated sulfuric acid and then a column containing calcium chloride, phosphorus pentoxide, and indicator grade calcium sulfate desiccants at which point it was condensed at −78 °C for use. With one exception, **4b**, all aldehyde and ketone azines (**4a–i**) were known compounds.

Reactions of Imines with 1. 3′-Phenyl-4′-oxospiro[fluorene-9,2′-thiazolidine] 1′,1′-Dioxide (3). Fluorenylideneaniline (0.2 g, 0.001 mol) was mixed with 100 ml of liquid sulfur dioxide at −78 °C. Ketene was then generated and bubbled through the suspension for 15 min at a rate of 0.24 mol/h. When the addition was completed, the delivery tube was replaced with a stopper. The suspension was stirred for 1 h at room temperature whereupon excess sulfur dioxide was removed in vacuo and the residue was heated with 15 ml of methanol, separated, washed with cold methanol, and recrystallized from acetic acid to give 0.22 g (80% yield) of **3**, mp 264–265 °C. Anal. Calcd for $C_{21}H_{15}NSO_3$: C, 69.80; H, 4.16; N, 3.88; S, 8.86. Found: C, 69.64; H, 4.14; N, 3.80; S, 9.06. Ir (KBr) 1675 (C=O), 1340 and 1140 cm^{-1} (SO_2); NMR (Me_2SO-d_6) δ 5.00 (s, 2 H, CH_2), 6.65–7.30 (m, 5 H, NC_6H_5), and 7.30–8.00 (m, 8 H, fluorene nucleus).

2-Phenyl-3-methyl-4-thiazolidinone 1,1-Dioxide (2). Benzylidenemethylamine (12 g, 0.1 mol) was mixed with 100 ml of liquid sulfur dioxide at −78 °C. Ketene was generated and bubbled through the suspension for 30 min at a rate of 0.30 mol/h. The reaction mixture was then treated as described for 3 with the exception that the residue was treated with 800 ml of diethyl ether instead of methanol. The product was recrystallized from ethanol to give pure **2**, mp 121.5–123.5 °C. Anal. Calcd for $C_{10}H_{11}NSO_3$: C, 53.33; H, 4.88; N, 6.22; S, 14.00. Found: C, 53.02; H, 5.18; N, 6.23; S, 14.12. Ir (KBr) 1675 (C=O), 1320 and 1130 cm^{-1} (SO_2); NMR (acetone-d_6) δ 2.90 (s, 3 H, NCH_3), 4.00 (s, 2 H, CH_2), 5.85 (s, 1 H, CH), and 7.50 (m, 5 H, C_6H_5).

5-Methyl-2-furfuraldehyde Azine (4b). A solution of 1.6 g (0.05 mol) of 95% hydrazine in 10 ml of absolute ethanol was added dropwise to a stirred solution of 11.0 g (0.10 mol) of 5-methyl-2-furfuraldehyde in 20 ml of absolute ethanol. The precipitate that formed on cooling was collected and recrystallized from absolute ethanol to give 20.1 g (93% yield) of yellow needles: mp 114–115 °C; ir (KBr) 1630 (C=N) and 1580 cm^{-1} (C=C); NMR ($CDCl_3$) δ 2.45 (s, 3 H, CH_3), 6.10–7.00 (q, 2 H, furyl), and 8.70 (s, 1 H, CH=N). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.67; H, 5.56; N, 12.96. Found: C, 66.53; H, 5.76; N, 12.71.

General Procedure for the Reaction of 1 with Azines. Sulfur dioxide (25 ml) was condensed at −78 °C into a two-necked flask fitted with a Dewar condenser filled with a dry ice–acetone mixture. Ketene was then generated and bubbled into the flask for 30 min at the rate of 0.25 mol/h. A solution containing the appropriate azine (0.015 mol) in 25 ml of methylene chloride was then added dropwise to the solution of **1** over a period of 10 min. The reaction mixture was then warmed to room temperature, and stirred for 2 h. Methylene chloride and excess sulfur dioxide were removed under reduced pressure and the resulting residue was triturated with absolute methanol or ethanol. The solid that formed was removed by filtration and recrystallized from acetone. Additional product could be obtained by evaporation of the mother liquor. Yields of products ranged between 69 and 97%.

2-(2-Furyl)-3-[(furfurylidene)amino]-4-thiazolidinone 1,1-Dioxide (5a). The reaction was carried out as described for **5a** using 2.82 g (0.015 mol) of **4a**.[6] Methanol was added to the residue at 0 °C to afford a white solid which was recrystallized from acetone to give 4.27 g (97% yield) of **5a**: mp 160–161 °C dec; ir (KBr) 1700 (C=O), 1625 (C=N), 1320 and 1145 cm^{-1} (SO_2); NMR (Me_2SO-d_6) δ 4.69 (s, 2 H, CH_2), 7.10 (s, 1 H, CH), 6.50–7.90 (m, 6 H, furyl), and 8.30 (s, 1 H, CH=N). Anal. Calcd for $C_{12}H_{10}N_2SO_5$: C, 48.98; H, 3.40; N, 9.52; S, 10.88. Found: C, 49.08; H, 3.38; N, 9.46; S, 11.12.

2-(5-Methyl-2-furyl)-3-[(5-methylfurfurylidene)amino]-4-thiazolidinone 1,1-Dioxide (5b). The reaction was carried out as described for **5a** using 3.24 g (0.015 mol) of **4b**. Addition of methanol to the reaction mixture at 0 °C gave a white solid which was recrys-

tallized from acetone to yield 4.30 g of **5b** (89% yield): mp 161–162 °C dec; ir (KBr) 1725 (C=O), 1625 (C=N), 1320, and 1145 cm^{-1} (SO_2); NMR (Me_2SO-d_6) δ 2.22 (s, 3 H, CH_3), 2.42 (s, 3 H, CH_3), 4.60 (s, 2 H, CH_2), 6.00–7.00 (m, 4 H, furyl), and 8.15 (s, 1 H, CH=N). Anal. Calcd for $C_{14}H_{14}N_2O_5S$: C, 52.18; H, 4.38; N, 8.69; S, 9.93. Found: C, 52.29; H, 4.51; N, 8.84; S, 9.95.

2-(2-Thienyl)-3-[(thenylidene)amino]-4-thiazolidinone 1,1-Dioxide (5c). The procedure described for **5a** was employed with 3.3 g (0.015 mol) of **4c**.[7] The reaction mixture was treated with methanol at 0 °C to give 4.41 g (90% yield) of **5c** as a white solid which was recrystallized from a 1:1 mixture of acetone–carbon tetrachloride: mp 160–161 °C dec; ir (KBr) 1700 (C=O), 1600 (C=N), 1310, and 1145 cm^{-1} (SO_2); NMR (Me_2SO-d_6) δ 4.72 (broad s, 2 H, CH_2), 7.00–8.00 (m, 7 H, thienyl and H-2), and 8.60 (s, 1 H, CH=N). Anal. Calcd for $C_{12}H_{10}N_2S_3O_3$: C, 44.17; H, 3.07; N, 8.59; S, 29.45. Found: C, 44.17; H, 3.07; N, 8.43; S, 29.22.

2-(Phenyl)-3-[(benzylidene)amino]-4-thiazolidinone 1,1-Dioxide (5d). This reaction was carried out as described for **5a** using 3.12 g (0.015 mol) of **4d**.[6] Addition of methanol to the reaction mixture, at 0 °C, gave 3.15 g of **5d** (67% yield). The product was recrystallized from a 1:1 mixture of chloroform–acetone: mp 199–201 °C; ir (KBr) 1700 (C=O), 1600 (C=N), 1310, and 1140 cm^{-1} (SO_2); NMR (Me_2SO-d_6) δ 4.70 (broad s, 2 H, CH_2), 6.85 (s, 1 H, H-2), 7.50 (s, 10 H, phenyl), 8.15 (s, 1 H, CH=N). Anal. Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.15; H, 4.46; N, 8.92; S, 10.19. Found: C, 61.22; H, 4.65; N, 9.10; S, 10.24.

2-(3,4-Dimethoxyphenyl)-3-[(veratrylidene)amino]-4-thiazolidinone 1,1-Dioxide (5e). The same procedure described for **5a** was used with 4.92 g (0.015 mol) of **4e**.[8] Addition of methanol yielded 6.18 g (95% yield) of **5e**. This compound was recrystallized from acetone: mp 164–166 °C; ir (KBr), 1710 (C=O), 1600 (C=N), 1310, and 1140 cm^{-1} (SO_2); NMR (Me_2SO-d_6) δ 3.8 (s, 12 H, OCH_3), δ_A 4.72, δ_B 4.53 (q, 2 H, J_{AB} = 17 Hz, CH_2), 6.70 (s, 1H, CH), 7.20–7.30 (m, 8 H, phenyl), and 8.25 (s, 1 H, CH=N). Anal. Calcd for $C_{20}H_{22}N_2SO_7$: C, 55.30; H, 5.10; N, 6.45; S, 7.37. Found: C, 55.44; H, 5.15; N, 6.34; S, 7.66.

2-(3-Methoxyphenyl)-3-[(3-methoxybenzylidene)amino]-4-thiazolidinone 1,1-Dioxide (5f). The same procedure described for **5a** was followed with 4.02 g (0.015 mol) of **4f**.[9] The white solid obtained was recrystallized from acetone to give 4.77 g of **5f** (85% yield): mp 155–156 °C; ir (KBr) 1710 (C=O), 1600 (C=N), 1320 and 1135 cm^{-1} (SO_2); NMR (Me_2SO-d_6) δ_A 4.88, δ_B 4.70 (q, 2 H, J_{AB} = 17.5 Hz, CH_2), 3.75 (s, 3 H, OCH_3), 6.85 (s, 1 H, CH), 6.90–7.60 (m, 8 H, phenyl), and 8.25 (s, 1 H, CH=N). Anal. Calcd for $C_{18}H_{18}N_2O_5S$: C, 57.75; H, 4.85; N, 7.48; S, 8.55. Found: C, 57.49; H, 4.72; N, 7.28; S, 8.68.

2-*trans*-Styryl-3-[(cinnamylidene)amino]-4-thiazolidinone 1,1-Dioxide (5g). The procedure described for **5a** was followed using *trans*-cinnamaldehyde azine[6] (3.90 g, 0.015 mol). The product obtained was recrystallized from acetone to afford 4.40 g (80% yield) of **5g**: mp 153–155 °C dec; ir (KBr) 1720 (C=O), 1640 (C=C), 1590 (C=N), 1330, and 1140 cm^{-1} (SO_2); NMR (Me_2SO-d_6) δ_A 4.77, δ_B 4.58 (9, 2 H, J_{AB} = 17 Hz, CH_2), 6.30–7.83 (m, 15 H, aromatic and olefinic protons), 8.45 (q, 1 H, CH=N). Anal. Calcd for $C_{20}H_{18}N_2SO_3$: C, 65.57; H, 4.95; N, 7.65; S, 8.74. Found: C, 65.27; H, 5.23; N, 7.80; S, 8.80.

2-(2-Furyl)-2-methyl-3-[(α-methylfurfurylidene)amino]-4-thiazolidinone 1,1-Dioxide (5h). This reaction was carried out as described for **5a** using 3.24 g (0.015 mol) of **4h**.[7] The product separated as a white solid and was recrystallized from acetone to afford 4.12 g (85% yield) of **5h**: mp 189–190 °C dec; ir (KBr) 1700 (C=O), 1600 (C=N), 1325, and 1145 cm^{-1} (SO_2); NMR (Me_2SO-d_6) δ 1.90 (s, 3 H, CH_3), 2.20 (s, 3 H, $=CCH_3$), 4.54 (d, 2 H, CH_2), and 6.50–7.90 (m, 6 H, furyl). Anal. Calcd for $C_{14}H_{14}N_2O_5S$: C, 52.18; H, 4.38; N, 8.28; S, 9.93. Found: C, 52.34; H, 4.50; N, 8.48; S, 9.92.

2-Methyl-2-phenyl-3-[(α-methylbenzylidene)amino]-4-thiazolidinone 1,1-Dioxide (5i). The procedure described for **5a** was carried out using 3.54 g (0.015 mol) of **4i**:[10] mp 174–175 °C; ir (KBr) 1710 (C=O), 1600 (C=N), 1305, and 1145 cm^{-1} (SO_2); NMR (Me_2SO-d_6) δ 2.10 (s, 3 H, CH_3), 2.14 (s, 3 H, $=CCH_3$), δ_A 4.67, δ_B 4.48 (q, 2 H, J_{AB} = 17 Hz, CH_2), and 7.45 (s, 10 H, phenyl). Anal. Calcd for $C_{18}H_{18}N_2O_3S$: C, 63.15; H, 5.30; N, 8.18; S, 9.35. Found: C, 63.44; H, 5.46; N, 8.07; S, 9.60.

Registry No.—**1**, 27393-94-8; **2**, 43056-12-8; **3**, 60253-51-2; **4a**, 5428-37-5; **4b**, 60253-52-3; **4c**, 24523-46-4; **4d**, 588-68-1; **4e**, 17745-86-7; **4f**, 40252-74-2; **4g**, 13362-71-5; **4h**, 24523-53-3; **4i**, 729-43-1; **5a**, 60253-53-4; **5b**, 60253-54-5; **5c**, 60253-55-6; **5d**, 60253-56-7; **5e**, 60253-57-8; **5f**, 60253-58-9; **5g**, 60253-59-0; **5h**, 60253-60-3; **5i**, 60253-61-4; fluorenylideneaniline, 10183-82-1; sulfur dioxide, 7446-09-5; ketene, 463-51-4; benzylidenemethylamine, 622-29-7; hydrazine, 302-01-2; 5-methyl-2-furfuraldehyde, 620-02-0.

References and Notes

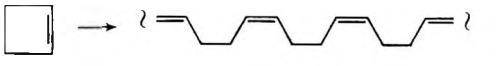
(1) (a) A. Gomes and M. M. Joullié, *Chem. Commun.*, 935 (1967); (b) *J. Heterocycl. Chem.*, **6**, 729 (1969); (c) J. M. Bohen and M. M. Joullié, *J. Org. Chem.*, **38**, 2652 (1973).
(2) J. M. Decazes, J. L. Luche, and H. B. Kagan, *Tetrahedron Lett.*, 3633 (1972).
(3) D. Bellus, *Helv. Chim. Acta*, **58**, 2509 (1975).
(4) S. Satsumabayashi, S. Motoki, and H. Nakano, *J. Org. Chem.*, **41**, 156 (1976).
(5) S. S. Mathur and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 2474 (1975).
(6) E. R. Blout and R. M. Gofstein, *J. Am. Chem. Soc.*, **67**, 13 (1945).
(7) O. Tsuge, M. Tashiro, and K. Horama, *Nippon Kagaku Zasshi*, **90**, 572 (1969).
(8) N. K. Kotchetkov and L. A. Vorotnikova, *Zh. Obshch. Khim.*, **26**, 1143 (1956).
(9) T. Curtius, *J. Prakt. Chem.*, **85**, 393 (1912).
(10) A. Dornow and W. Bartsch, *Justus Liebigs Ann. Chem.*, **602**, 23 (1957).

Cyclobutene Derivatives as Isoprene Equivalents in Terpene Synthesis. The Metathesis of 1-Methylcyclobutene

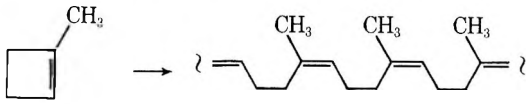
Summary: The metathesis of 1-methylcyclobutene leads to head-to-tail isoprenoid homologation and can convert the monoterpene geraniol acetate into the sesquiterpene farnesol acetate.

Sir: As part of a general program of natural products synthesis, a portion of our efforts are directed toward uncovering *fundamentally new approaches* to terpene synthesis. This is a difficult task, since terpene chemistry is a mature science and the head-to-tail linking of isoprene units has long been an objective of organic synthesis.[1,2] A new and potentially quite general approach to terpenoid synthesis involves the use of 1-methylcyclobutene (**1**) as an isoprene synthon. This molecule contains the five carbons required for an isoprene unit as well as ~26-kcal/mol strain energy[4] to drive reactions to completion.[5] We have recently described[3] the synthesis of terpenoid 1,3-dienes using cyclobutenes as reactive isoprene synthons. Since 1,5-dienes are more common (geraniol, farnesol, squalene, etc.), we now disclose a method for "insertion" of an isoprene unit into an unactivated double bond, resulting in the head-to-tail linking of isoprene units.

The olefin metathesis reaction[6] has been the object of a flurry of recent activity, with only limited application to natural products synthesis.[7] Since Dall'Asta had reported the metathetical polymerization of cyclobutenes to 1,5-dienes[8a] (eq 1), we felt that this unique reaction might have application to terpene chemistry.



(1)



(2)

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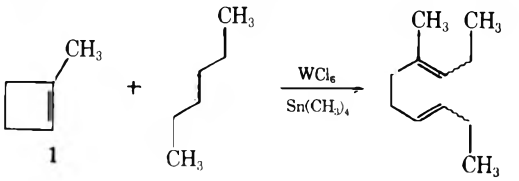
1-Methylcyclobutene (**1**) reacts exothermically[9] with the metathesis catalyst $WCl_6/Sn(CH_3)_4$[10] giving a polymer (eq 2) whose gross structure is that of polyisoprene (natural rubber).[8b] After this work was completed, a detailed examination of the metathetical polymerization of 1-methylcyclobutene was published.[11] The polymer produced is 84–87% *Z* and more importantly 10.1/1 head-to-tail, the regioisomerism crucial for the production of terpenoid products. Based on the currently accepted mechanism,[6a] the selectivity is a consequence of factors which favor a more highly substituted metallocarbene.[12]

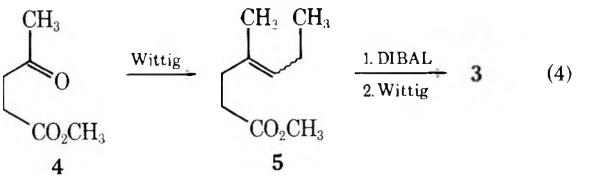
At the outset a model system was investigated which avoids regioisomer problems. The crossed metathesis of 1-methylcyclobutene (**1**) with excess 3-hexene (**2**) in chlorobenzene gives compound **3** in 20–30% yields[13,14] (eq 3). Compound **3**



(3)

1 **2** **3**

(a mixture of *E*/*Z* isomers) was prepared by an independent route shown in eq 4. Wittig reaction of methyl levulinate gives

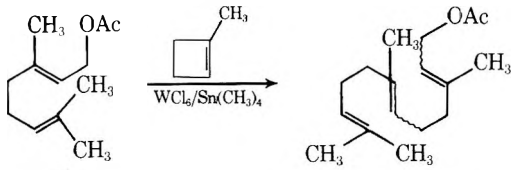


(4)

4 **5**

the unsaturated ester **5** which was converted to **3** via the aldehyde. The materials were identical from the two pathways.[15]

The interconversion of terpenes was then attempted. There are few reports in the literature concerning the metathesis of trisubstituted olefins.[16] Presumably because of steric hindrance they react much slower. In addition, there seems to be no systematic study of the effect of functional groups on the metathesis reaction.[17] Since alcohols quench the metathesis catalyst the corresponding acetates were used, and appear to be compatible.[18] When geraniol acetate (**6**) and excess **1** were reacted [$WCl_6/Sn(CH_3)_4$ in chlorobenzene] for prolonged periods and the polymer was precipitated with methanol, 1–2% farnesol acetate (**7**) (*E*/*Z* isomers) could be detected



6 **7**

(GC/MS). A mechanistic rationale for formation of farnesol acetate involves metathesis[12] at the 6,7 double bond of geranyl acetate (metathesis at the 2,3 double bond is degenerate.)

Although far from being preparatively useful at this time, we feel that investigation of some of the newer soluble catalysts, isolable carbene initiators[19] or the photochemically initiated metathesis,[20] possibly with other protecting groups may lead to a viable terpene homologation. Further applications of this unique reaction to terpene synthesis will form the basis of subsequent reports.

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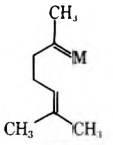
References and Notes

(1) A. F. Thomas, "The Total Synthesis of Natural Products", Vol. 2, J. Apsimon, Ed., Wiley, New York, N.Y., 1973.
(2) See, for example, S. R. Wilson, K. M. Jernberg, and D. T. Mao, *J. Org. Chem.*, **41**, 3209 (1976), and ref 3.
(3) S. R. Wilson and L. R. Phillips, *Tetrahedron Lett.*, 3047 (1975).
(4) R. B. Turner, P. Goebel, B. J. Mallon, W. von E. Doering, J. F. Coburn, Jr., and M. Pomerantz, *J. Am. Chem. Soc.*, **90**, 4315 (1968).
(5) For example, thermolysis of **1** gives isoprene itself: H. M. Frey, *Trans. Faraday Soc.*, **58**, 957 (1962).
(6) The olefin metathesis reaction has been the subject of a number of major review articles: (a) N. Calderon, E. A. Ofstead, and W. A. Judy, *Angew Chem., Int. Ed. Engl.*, **15**, 401 (1976); (b) R. Streck, *Chem. Ztg.*, **99**, 397 (1975); (c) L. Hocks, *Bull. Soc. Chim. Fr.*, 1893 (1975); (d) R. J. Haines and G. J. Leigh, *Chem. Soc. Rev.*, **4**, 155 (1975); (e) J. C. Mol and J. A. Moulijn, *Adv. Catal.*, **24**, 131 (1975); (f) W. B. Hughes, *Organomet. Chem. Synth.*, **1**, 341 (1972); (g) N. Calderon, *Acc. Chem. Res.*, **5**, 127 (1972); (h) R. L. Banks, *Top. Curr. Chem.*, **25**, 39 (1972); (i) M. L. Khidekel, A. D. Shebaldova, and I. V. Kalechits, *Russ. Chem. Rev. (Engl. Transl.)*, **40**, 669 (1971); (j) G. C. Bailey, *Catal. Rev.*, **3**, 37 (1969).
(7) (a) L. G. Wideman, *J. Org. Chem.*, **33**, 4541 (1968); (b) F. W. Kuepper and R. Streck, *Chem. Ztg.*, **99**, 464 (1975); (c) R. Rossi, *Chim. Ind. (Milan)*, **57**, 242 (1975) [*Chem. Abstr.*, **84** 73557f (1976)].

(8) (a) G. Dall'Asta, *J. Polym. Sci., Part A-1*, **6**, 2397 (1968), and references cited therein. (b) Dall'Asta reported the polymerization of 1-methylcyclobutene, but the polymer was largely saturated: G. Dall'Asta and R. Manetti, *Atti Acad. Naz. Lincei Rend. Cl. Sci. Fis. Mat. Nat.*, **41**, 351 (1966) [*Chem. Abstr.*, **67** 33003q (1967).
(9) The metathesis reaction has been capricious in our hands; sometimes the reaction is inexplicably slow.
(10) An astonishing variety of catalyst recipes have been reported.[6] We have chosen the mixture $WCl_6/Sn(CH_3)_4$ because of its reported compatability with esters.[17b]
(11) T. J. Katz, J. McGinnis, and C. Altus, *J. Am. Chem. Soc.*, **98**, 606 (1976).
(12) The reactive (chain carrying) metallocarbene derived from 1-methylcyclobutene is **8**.



8

(13) All new compounds possessed spectral and analytical data in accord with the assigned structures.
(14) A cyclobutene/hexene/catalyst ratio of 8/44/1 was used.
(15) Only two isomers could be resolved (mol wt, 152.1558 and 152.1563) by VPC. Materials from the two pathways possessed identical spectral data and retention times on a 200-ft. DB-TCP capillary column. We have not established the configuration about the double bonds.
(16) (a) T. Katz, Abstracts, 172nd National Meeting of the American Chemical Society, San Francisco, Calif., Aug 1976, INOR81; (b) C. P. Pinazzi, I. Guilmet, and D. Reyx, *Tetrahedron Lett.*, 989 (1976); (c) R. Rossi, P. Diversi, A. Lucherini, and L. Porri, *ibid.*, 879 (1974); (d) British Patent 1125529 [*Chem. Abstr.*, **69**, 105851f (1968)].
(17) There are scattered reports of the metathesis of functionalized olefins. (a) Nitrile: G. Foster, *Chem. Abstr.*, **75**, 63172b (1971). (b) Ester: P. B. van Dam, M. C. Mittelmeijer, and C. Boelhouwer, *Chem. Commun.*, 1221 (1972); P. B. van Dam, M. C. Mittelmeijer, and C. Boelhouwer, *J. Am. Oil Chem. Soc.*, **51**, 389 (1974); W. Ast, G. Rheinwald, and R. Kerber, *Makromol. Chem.*, **177**, 39 (1976). (c) Acids: K. Hummel and Y. Imanoglu, *Colloid Polym. Sci.*, **253**, 225 (1975); *Chem. Abstr.*, **83**, 96094w (1975).
(18) Geraniol acetate is relatively stable in the presence of active metathesis catalyst $WCl_6/Sn(CH_3)_4$. Catalyst activity was checked by injecting aliquots of 2-pentene. Within minutes at room temperature 2-butene and 3-hexene are produced.
(19) J. McGinnis, T. J. Katz, and S. Hurwitz, *J. Am. Chem. Soc.*, **98**, 605 (1976).
(20) (a) P. Krausz, F. Garnier, and J. E. Dubois, *J. Am. Chem. Soc.*, **97**, 437 (1975); (b) S. Warwel and W. Laarz, *Chem. Ztg.*, **99**, 502 (1975); (c) A. Agapiou and E. McNelis, *Chem. Commun.*, 187 (1975).

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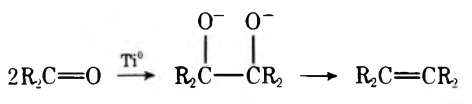
Synthesis of Unsymmetrical Olefins by Titanium(0) Induced Mixed Carbonyl Coupling. Some Comments on the Mechanism of the Pinacol Reaction

Summary: Unsymmetrical olefins can be synthesized in useful yields by titanium induced ketone coupling if one component is used in excess. Mixed coupling is particularly efficient for diaryl ketones, and a mechanism is proposed to account for this.

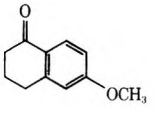
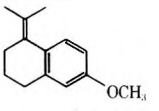
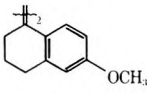
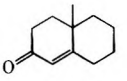
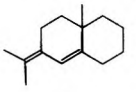
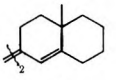
Sir: We recently reported an improved carbonyl coupling procedure employing active titanium(0). Olefins were isolated in high yields.[1] Since the reaction occurs by a two-step pathway involving initial reductive dimerization of the carbonyl to a pinacol, followed by deoxygenation to olefin, one might expect the intermolecular version of this reaction to be limited to the synthesis of symmetrical olefins.



Pinacol formation is generally presumed to occur by dimerization of anion radicals,[2] and the synthesis of unsymmetrical olefins by our method therefore requires that we be able to carry out mixed pinacol couplings. There is little information in the literature concerning mixed pinacol reactions,[3-6] but the few scattered reports that do exist indicate that one generally obtains a mixture of the three possible pinacols in a nearly statistical ratio. Recently, while this work was in progress, another report appeared describing several mixed pinacol reactions. Again, the mixed products appear to be found in approximately statistical amounts, although complete product analyses were not reported.[7]

We felt, therefore, that our olefin-forming reaction would probably only be synthetically useful in cases where an excess of one inexpensive carbonyl component could be used and where the major olefinic by-product could be easily removed. Acetone is the obvious choice as one component of the reaction since it may be used in excess and its self-coupling product,

Table I. Titanium Induced Mixed Coupling Reactions between Acetone and Other Ketones (Acetone/Ketone, 4:1)

Entry	Ketone	Products	Isolated yield, %[a]
1	Adamantanone	Isopropylideneadamantane	63
		Biadamantylidene	12
2	4-*tert*-Butylcyclohexanone	4-*tert*-Butylisopropylidenecyclohexane	55
		Bi-4-*tert*-butylcyclohexylidene	22
3	3-Cholestanone	3-Isopropylidenecholestane	54
		Bi-3-cholesterylidene	29
4	Cycloheptanone	Isopropylidenecycloheptane	50
		Bicycloheptylidene	26
5	1-Indanone	1-Isopropylideneindan	71
		Bi-1-indanylidene	24
6	Acetophenone	2-Methyl-3-phenyl-2-butene	65
		2,3-Diphenyl-2-butene	16
7	Benzophenone	1,1-Diphenyl-2-methylpropene	94
		Tetraphenylethylene	tr
8	Fluorenone	Isoptropylidenefluorene	84
		Bifluorenylidene	0
9		 + 	85 + 9
10		 + 	67 + 26
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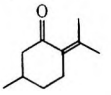
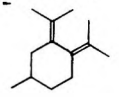
12			55

[a] The crude product mixtures were purified by column chromatography on silica gel and the products identified by spectral methods (NMR, MS).

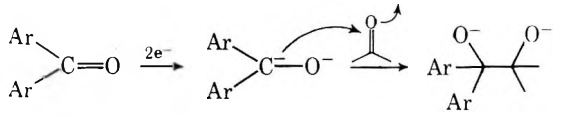
tetramethylethylene, is volatile. We therefore examined unsymmetrical olefin formation by reaction of acetone with other ketones. Our results are given in Table I.

In all cases, the isopropylidene products can be isolated in synthetically useful yields. The isopropylidene group is a common structural unit of many sesquiterpenes, and, since the Wittig reaction is not applicable to the synthesis of these tetrasubstituted olefins, this one-step mixed coupling may prove of value. Further, the synthesis and spectroscopic study of *vic*-diisopropylidene compounds such as that derived from pulegone (reaction 12) has been an active field recently,[8] and the present synthesis is quite efficient.

In examining these results, we were struck by the fact that, while mixed coupling of acetone with most other ketones gave the mixed product in a nearly statistical amount, reaction with the diaryl ketones, benzophenone and fluorenone, gave essentially *only* mixed product. Indeed, even when acetone and benzophenone were reacted in equimolar amounts, mixed coupling was still highly favored.

This is most surprising when one considers that the reduction potentials (E_{redn}) of benzophenone and fluorenone are both 1.0–1.5 V less negative than that of acetone.[9] One would expect the corresponding anion radicals to form more rapidly than that of acetone, leading to a preponderance of symmetrical coupling. Since this is not the case, we consider it unlikely that the mixed pinacol reaction of acetone with diaryl ketones is in fact a radical coupling process.

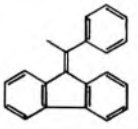
An alternate mechanistic hypothesis can be devised. Stabilized radical anions, such as those derived from diaryl ketones, are known to reduce further to dianions, and the E_{redn} for this second reduction is less negative than E_{redn} for acetone.[9] We suggest that these dianions are formed and that mixed coupling results by nucleophilic addition to acetone.



While we have no evidence to suggest that normal pinacol reactions between similar species are other than radical couplings, the nucleophilic addition of a stabilized dianion to a free ketone may well be general for mixed reactions in which one component is much more easily reduced than the other. This then suggests that our olefin synthesis need not be limited to cases where one inexpensive component is used in excess. Rather, we ought to be able to obtain good yields of mixed coupling of any two ketones as long as one component reduces to a dianion before the other reduces to an anion radical. We have carried out several such reactions successfully and the results are given in Table II.

In a representative procedure, anhydrous $TiCl_3$ (2.87 g, 18.6 mmol) was slurried in 30 ml of dry dimethoxyethane under argon, and lithium[10] pieces (0.45 g, 65 mg-atoms) were added. After 1-h reflux, the black mixture was cooled, and a solution of benzophenone (0.42 g, 2.3 mmol) and cyclohexanone (0.226 g, 2.3 mmol) in 2.0 ml of dimethoxyethane was added. The mixture was stirred for 2 h at room temperature and then refluxed for 20 h. After the mixture cooled to room temperature, 50 ml of petroleum ether was added over 15 min. The organic layer was decanted from the black residue, filtered through a 1-cm pad of Florisil, and concentrated. Chromatography on 15 g of silica gel gave bicyclohexylidene (11 mg, 6%, hexane elution), cyclohexylidenediphenylmethane (445 mg, 78%, hexane/benzene elution), and tetraphenylethylene (74 mg, 19%, benzene elution).

Table II. Titanium Induced Mixed Carbonyl Couplings of Diaryl Ketones with Other Partners (Ratio of Ketones, 1:1).

Entry	Ketones	Products	Isolated yield, %
1	Benzophenone + acetone	1,1-Diphenyl-2-methylpropene	81
		Tetraphenylethylene	14
2	Benzophenone + cyclohexanone	Cyclohexylidenediphenylmethane	78
		Tetraphenylethylene	19
		Bicyclohexylidene	6
3	Benzophenone + 3-cholestanone	3-Cholesterylidenediphenylmethane	82
		Tetraphenylethylene	14
		Bi-3-cholesterylidene	5
4	Benzophenone + hexanal	1,1-Diphenyl-1-heptene	84
		Tetraphenylethylene	9
		6-Dodecene	8
5	Benzophenone + di-*tert*-butyl ketone	Tetraphenylethylene	90
6	Fluorenone + acetone	Isopropylidenefluorene	74
		Bifluorenylidene	8
7	Fluorenone + cycloheptane	Cycloheptylidenefluorene	77
		Bifluorenylidene	7
		Bicycloheptylidene	17
8	Fluorenone + acetophenone		70
		2,3-Diphenyl-2-butene	15
		Bifluorenylidene	8

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

References and Notes

(1) J. E. McMurry and M. P. Fleming, *J. Org. Chem.*, **41**, 896 (1976).
(2) See H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, New York, N.Y., 1972, pp 167–169.
(3) J. Wiemann, *C. R. Hebd. Seances Acad. Sci.*, **212**, 764 (1941).
(4) N. V. Elagina and N. D. Zelinskii, *Dokl. Akad. Nauk SSSR*, **71**, 293 (1950); *Chem. Abstr.* **44**, 7786*b* (1950).
(5) M. J. Allen, J. A. Siragusa, and W. Pierson, *J. Chem. Soc.*, 1045 (1960).
(6) D. G. Botteron and G. Wood, *J. Org. Chem.*, **30**, 3871 (1955).
(7) E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, *J. Org. Chem.*, **41**, 260 (1976).
(8) L. W. Jelinski and E. W. Kiefer, *J. Am. Chem. Soc.*, **98**, 282 (1976), and references therein.
(9) For a table of reduction potentials of organic substrates, see L. Meites, "Polarographic Techniques", 2nd ed, Interscience Publishers, New York, N.Y., 1965.
(10) In our original publication[1] we used potassium metal to effect this reduction. We have subsequently found lithium to be nearly as effective and far safer to use.

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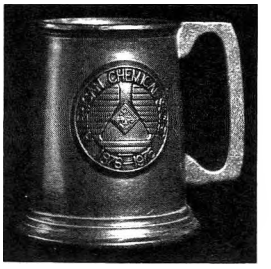

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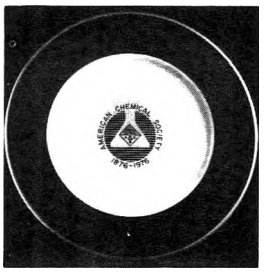

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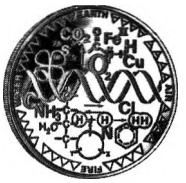

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$CH_3OCH_2CH_2OCH_2Cl$

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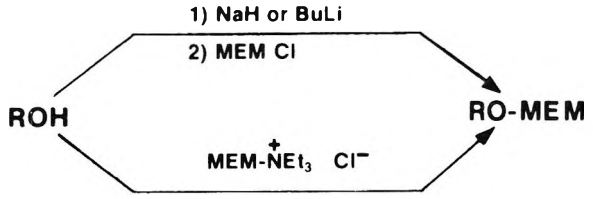
The recent introduction[1] of **β-methoxyethoxymethyl (MEM) ethers** as protected derivatives of primary, secondary, and tertiary alcohols provides a valuable addition to the organic chemist's armamentarium of protective methods. Because of the ease of formation and specificity of cleavage conditions, the **MEM group** serves as a valuable addition to the more traditional hydroxyl protecting groups such as tetrahydropyranyl and benzyl.

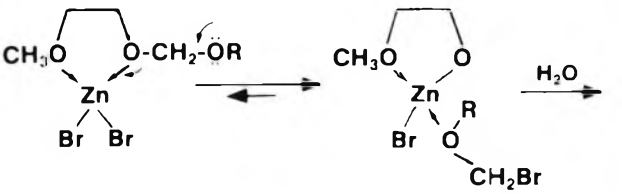
MEM ethers are stable to strong bases, organometallic reagents, oxidizing agents and mild acids.

The formation of **MEM ethers** can be effected either under aprotic basic conditions by reaction of the sodium or lithium salt of the alcohol with **MEM chloride** in THF or dimethoxyethane, or under aprotic neutral conditions by reaction of the alcohol with **MEM-triethylammonium chloride** in acetonitrile. Although the ammonium salt is hygroscopic, it can be prepared readily from **MEM chloride** and triethylamine.



MEM ethers can also be prepared from the alcohol and **MEM chloride** in the presence of diisopropylethylamine in CH_2Cl_2. Yields of the MEM derivatives by these methods are excellent, usually exceeding 90%.

MEM ethers are cleaved by either anhydrous zinc bromide or titanium tetrachloride in methylene chloride solution at room temperature. The specificity of the cleavage conditions is hypothesized to be due to the formation of a cyclic complex with the Lewis acid ($ZnBr_2$, $TiCl_4$) which facilitates the cleavage of the



ROH + $CH_2(OH)_2$ + $CH_3OCH_2CH_2OH$

MEM ether. Thus, the cleavage of methoxymethyl ethers is markedly slower than that of the corresponding MEM derivative under the same conditions. THP, benzyl, acetyl, benzoyl, *t*-butyldimethylsilyl and other silyl protecting groups are readily and selectively cleaved in the presence of **MEM ethers.**

Reference:

1) E.J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 809 (1976).

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