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

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

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

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

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

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

"Approved."

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THE JOURNAL OF Organic Chemistry

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SEPTEMBER 17, 1976

Reactions Involving Electron Transfer. 9. Reaction of Lithium Dimethylcuprate with Alkyl Aryl Ketones[1]

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Received March 3, 1976

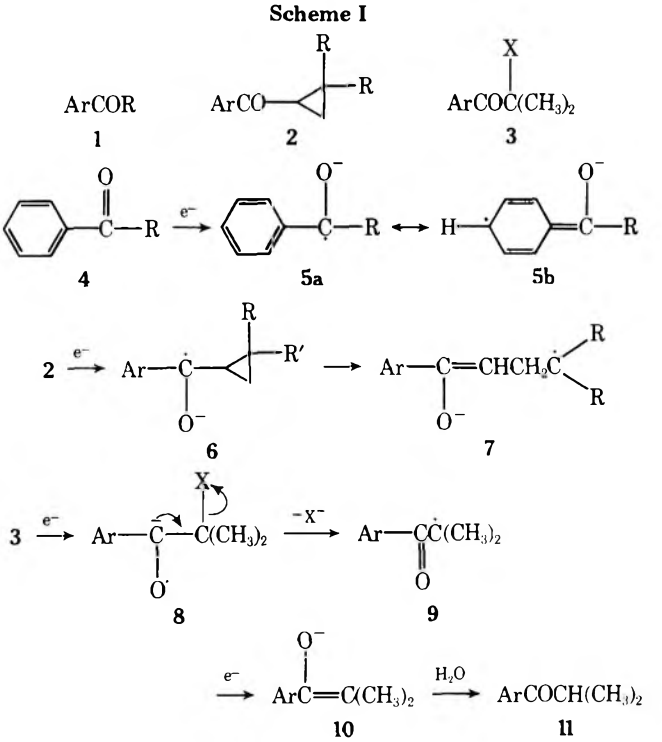
The reactions of several aryl alkyl ketones **12–15, 22–24,** and **40–42** with Me_2CuLi have been studied. Each of these ketones has a sufficiently positive reduction potential so that reduction by Me_2CuLi to form an anion radical is energetically feasible. The major products formed from those ketones whose anion radicals are relatively stable were the 1,2-addition products. This 1,2-addition reaction was significantly slower than the conjugate addition of Me_2CuLi to α,β-unsaturated ketones. The aryl alkyl ketones **41** and **42,** whose anion radicals are relatively unstable, reacted rapidly with Me_2CuLi to form the product of reductive elimination rather than 1,2 addition.

Previous study[2] of the reaction of Me_2CuLi with carbonyl compounds revealed that α,β-unsaturated carbonyl compounds having reduction potentials within the range −1.4 to −2.35 V (vs. SCE in an aprotic solvent) could be expected to react by way of an initial electron-transfer step to form products derived from the net conjugate addition of a methyl anion to the unsaturated carbonyl compound. Substrates with less negative reduction potentials (more easily reduced) yielded reduction rather than addition products while substrates with more negative reduction potentials (more difficulty reduced) either failed to react with Me_2CuLi or reacted, with liberation of CH_4, to form the metal enolate of the starting unsaturated ketone. Saturated ketones (which have reduction potentials more negative than −2.9 V) reacted with Me_2CuLi either with evolution of CH_4 to form the metal enolates of the ketones or by a very slow process leading to 1,2 addition.[2c]

Since aryl alkyl ketones typically have reduction potentials in the range −1.8 to −2.2 V (vs. SCE in an aprotic solvent),[3] these compounds appeared to be substrates that might react with Me_2CuLi by a process that involved an initial electron transfer step. To learn what types of products might result, we have studied the reaction of Me_2CuLi with three types of aryl alkyl ketone systems **1–3** (Scheme I). Reaction of ketones of type **1** (e.g., **4**) by an electron-transfer process would yield anion radicals **5** in which spin density would be distributed between the carbonyl carbon atom (**5a**) and various positions of the aromatic ring (e.g., **5b**).[4] Thus, further reaction of such an intermediate could introduce a methyl substituent either at the carbonyl carbon atom or at one of the positions in the aromatic ring.[5]

Reaction of Me_2CuLi with an aryl cyclopropyl ketone **2** offered the possibility that an intermediate anion radical **6** might rearrange to the structurally isomeric ion radical **7** prior to further reaction. Provided that this rearrangement occurred within a time period of 10^{-3} s or less,[2b,6] rearranged addition products derived from ion radical **7** might be expected.

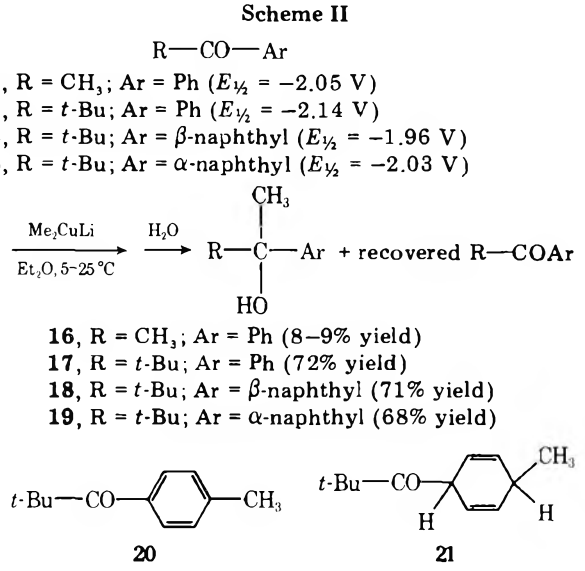
Scheme I



Compounds of the type **3,** where X is a group that can be lost as a relatively stable anion, offered the possibility that an intermediate anion radical might eliminate an anion X^- provided that this elimination would occur within time periods of the order of 10^{-3} s or less. The elimination of X^- would yield an easily reduced radical **9** that would be expected to react with additional Me_2CuLi to form the enolate **10** and finally the reduction product **11**.[2,7]

Ketones **12–15** (Scheme II) were studied as examples of aryl alkyl ketones of type **1.** Acetophenone (**12**) reacted relatively

Scheme II

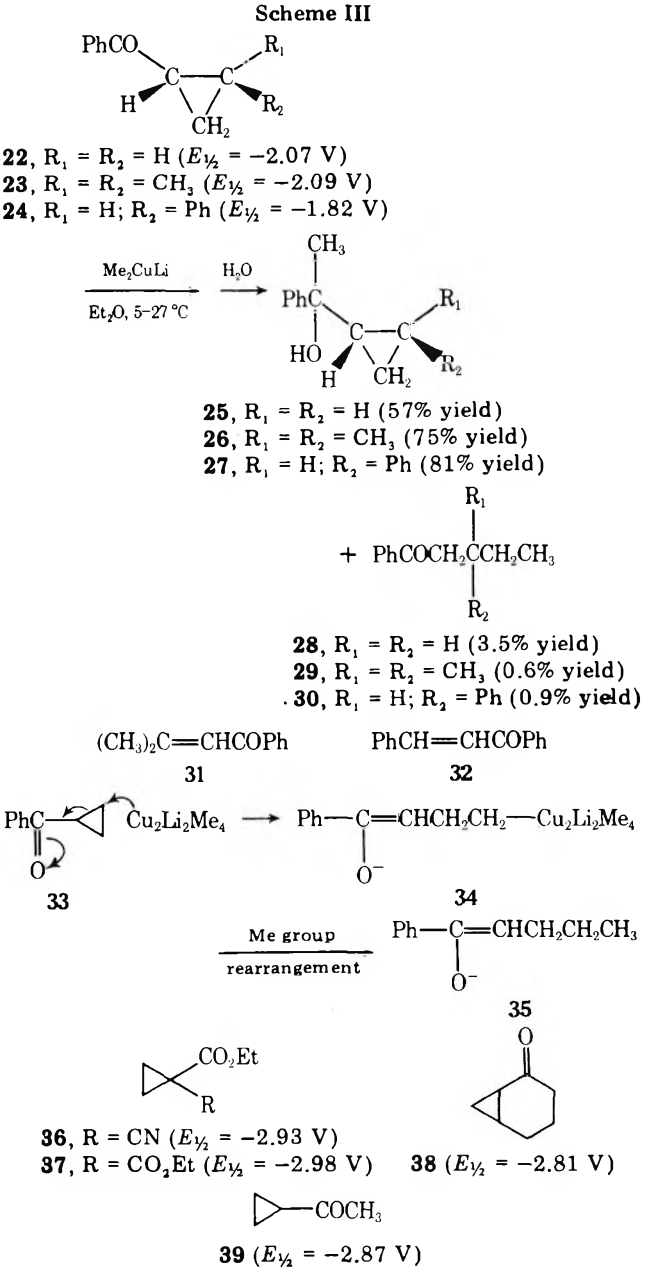


rapidly with Me_2CuLi with evolution of gas and precipitation of $(MeCu)_n$. The predominant reaction was formation of the enolate of ketone **12**; the 1,2 adduct **16** was obtained in only 8–9% yield after reaction periods of either 11 min or 3.5 h with excess Me_2CuLi.[8] This major side reaction leading to enolate formation is also observed[2c] in reaction of Me_2CuLi with aliphatic methyl ketones and *n*-alkyl ketones. To avoid this side reaction, the nonenolizable ketones **13–15** were used for further study. Each compound underwent a relatively slow reaction with Me_2CuLi to form the 1,2 adducts **17–19.** Minor components detected in these reaction mixtures were the unchanged ketones **13–15** and/or olefinic products derived from dehydration of the alcohols **17–19.** Examination of these minor compounds by mass spectrometry gave no indication that ring-methylated products, such as **20** or **21** from ketone **13,** were present. Consequently, we conclude that if anion radicals of the type **5** are intermediates in these reactions, recombination with the cluster $[Me_4Cu_2Li_2]\cdot^+$ occurs only at the carbonyl carbon atom (structure **5a**) that appears to be the site of highest spin density in these intermediates. It should be noted that each of the ketones **12–15** has a reduction potential (see Scheme II and Table I) within the range (less negative than −2.2 V) where electron transfer from Me_2CuLi is feasible. Furthermore, the anion radicals formed from these ketones **12–15** are relatively stable with half-lives greater than 0.1 s (see Table I).

We next examined the reactions of Me_2CuLi with ketones **22–24** (Scheme III) as representative aryl cyclopropyl ketones **2.** In each case these ketones **22–24** underwent a relatively slow reaction with Me_2CuLi to form mainly the 1,2 adducts **25–27.** However, small amounts of ring-opened by-products **28–30** were also formed. The structures of each of these by-products **28–30** were established by comparison with authentic samples, samples of ketones **29** and **30** being obtained by CuCl-catalyzed conjugate addition of EtMgBr to the enones **31** and **32.** The reduction potentials (Scheme III and Table I) of each of the ketones **22–24** lie in the range −1.8 to −2.1 V. The anion radicals **6** formed from ketones **22** and **23** are relatively stable with half-lives of 4–5 s (Table I) but the half-life of the anion radical from ketone **24** is much less ($<10^{-2}$ s).[9]

Several facts indicate that the minor ring opened products **28–30** *are not derived from an anion radical intermediate* **6** by rearrangement **6** → **7** followed by recombination of **7** with $[Me_4Cu_2Li_2]\cdot^+$. Thus, the greatest amount of ring-opened product **28** is obtained from ketone **22** whose anion radical rearranges (**6** → **7**) very slowly and in which the rearranged radical ion **7** (R = R′ = H) has no stabilizing substituents. Not only do stabilizing substituents (as in ketones **23** and **24**) diminish the yields of ring-opened products, but the products **29** and **30** obtained are derived from addition of a methyl group to the cyclopropane carbon atom with no stabilizing substituents. All of these observations are better explained by a relatively slow direct nucleophilic attack of the cuprate at the least substituted cyclopropane carbon atom as illustrated in structures **33** → **34** → **35.** This process is, of course, analogous to the nucleophilic displacement believed operative in the reaction of cuprates with alkyl halides or epoxides.[2d,10] This type of nucleophilic displacement readily accounts for the slow ring opening observed when various cyclopropyl esters (e.g., **36** and **37**) react with Me_2CuLi.[11] Although the reduction potentials of these esters **36** and **37** are clearly too negative for an electron-transfer process to be probable, the fact that aliphatic nitriles and esters fail to react with Me_2CuLi[2c,11e] would clearly allow time for a slow nucleophilic ring opening process analogous to **33** → **34** → **35.** Although aliphatic cyclopropyl ketones such as **38** and **39** have less negative reduction potentials than the esters **36** and **37,** each of the ketones **38**[11b] and **39**[5b] failed to undergo any opening with Me_2CuLi and the ketones were recovered. Since both of these ketones have relatively acidic α-CH_2 groups, we suspect that the failure to observe a slow ring opening in these cases

Scheme III



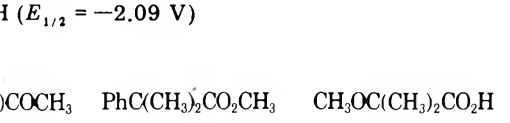
is attributable to the rapid conversion of each ketone to its enolate by the cuprate reagent.[12]

The last type of aryl alkyl ketones to be examined were the α-substituted ketones **40–42** (Scheme IV). Although the ac-

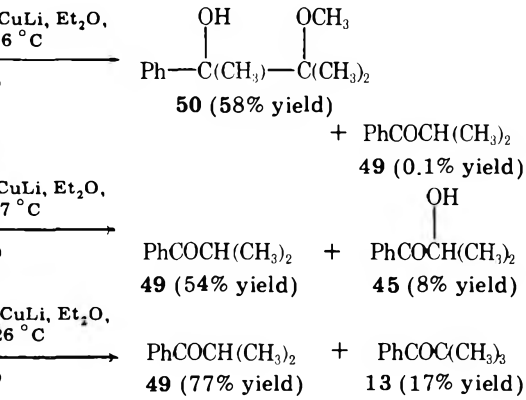
Scheme IV

40, X = OCH_3 ($E_{1/2}$ = −2.03 V)
41, X = $OCOCH_3$ ($E_{1/2}$ = −1.80 V)
42, X = Br
45, X = OH
49, X = H ($E_{1/2}$ = −2.09 V)

43, X = $OCOCH_3$
44, X = OCH_3



46 **47** **48**



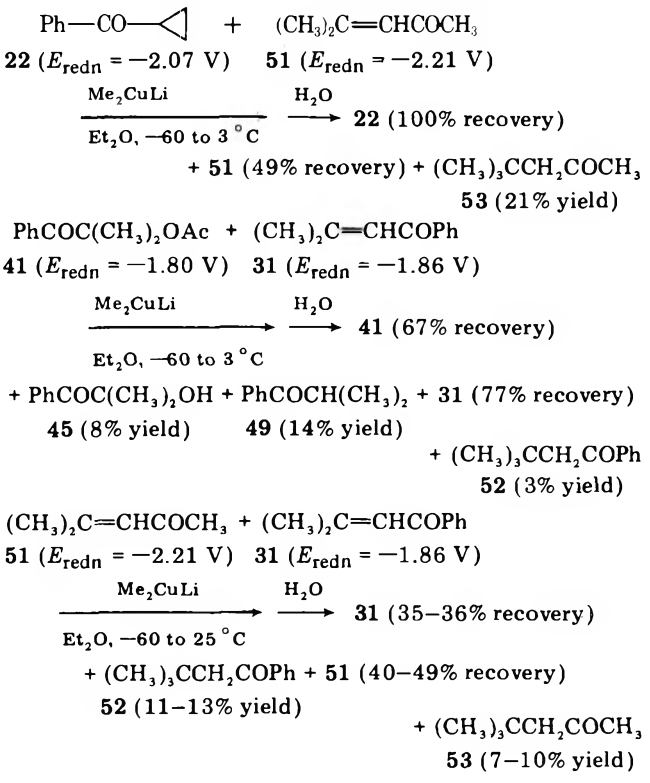
etoxy ketone **41** was readily prepared by reaction of the bromo ketone **42** with KOAc (presumably via the unstable epoxide **43**), the analogous reaction of the bromo ketone **42** with NaOMe yielded not the reported[13] methoxy ketone **40** but rather the epoxy ether **44**. Acid-catalyzed hydrolysis of the epoxy ether **44** yielded the ketol **45** and acid-catalyzed rearrangement of **44** yielded the methoxy ketone **46**. Silver nitrate catalyzed solvolysis of the bromo ketone **42** in MeOH produced a mixture of the desired methoxy ketone **40** (ca. 10% of the mixture) and the rearranged ester **47** (ca. 90% of the mixture). In view of these problems, we finally synthesized the methoxy ketone **40** by reaction of the methoxy acid **48** with excess PhLi. Although the reduction potentials (Scheme IV and Table I) of ketones **40** and **41** were similar, the half-life (see Table I) of the ketyl **8** derived from the methoxy ketone **40** ($t_{1/2}$ 0.7 s) was distinctly longer than the half-life ($<10^{-2}$ s) for the ketyl **8** from the acetoxy ketone **41**. The instability of the bromo ketone **42** in our solvent–electrolyte system prevented us from obtaining satisfactory electrochemical data for this compound.

Although the methoxy ketone **40** reacted with Me_2CuLi to form the 1,2 adduct **50** accompanied by only traces of the reduction product **49**, the analogous reaction with the acetoxy ketone **41** yielded primarily the reduced ketone **49**. This differing behavior of ketones **40** and **41** with Me_2CuLi is analogous to the differing behavior[7c] of a 4-alkoxy-2-cyclohexen-1-one (conjugate addition) and a 4-acetoxy-2-cyclohexen-1-one (reductive elimination) with Me_2CuLi. In both cases, reductive elimination, presumably by the sequence **8** → **9** → **10** → **11**, is observed only if a reasonably good leaving group X is present so that the initial elimination **8** → **9** can occur within the lifetime (ca. 10^{-3} s)[2b,d,6] of the anion radical in a cuprate reaction. Thus, the different reactions of ketones **40** and **41** seem to be determined not by a mechanistic difference in the first step of the reaction but rather by the relative stabilities of the initially formed radical ions **8**.

As might be expected, the bromo ketone **42** with an even better leaving group as a substituent reacted with Me_2CuLi to form mainly the reduction product **49** accompanied by a minor amount of the ketone **13** in which substitution of a methyl group for bromine has occurred. The formation of both reduction and substitution products upon reaction of α-bromo ketones with cuprates has been observed in a number of cases.[14] The substitution products (such as **13** from **42**) are presumably formed[14c] by reaction of the enolate **10** with CH_3X (X = I or Br), this methyl halide being formed in the reaction mixture[7a] from reaction of the halide ion present (I^- or Br^-) with an oxidized derivative of the cuprate such as $[Me_4Cu_2Li_2]\cdot^+$ or $[Me_4Cu_2Li_2]^{2+}$.

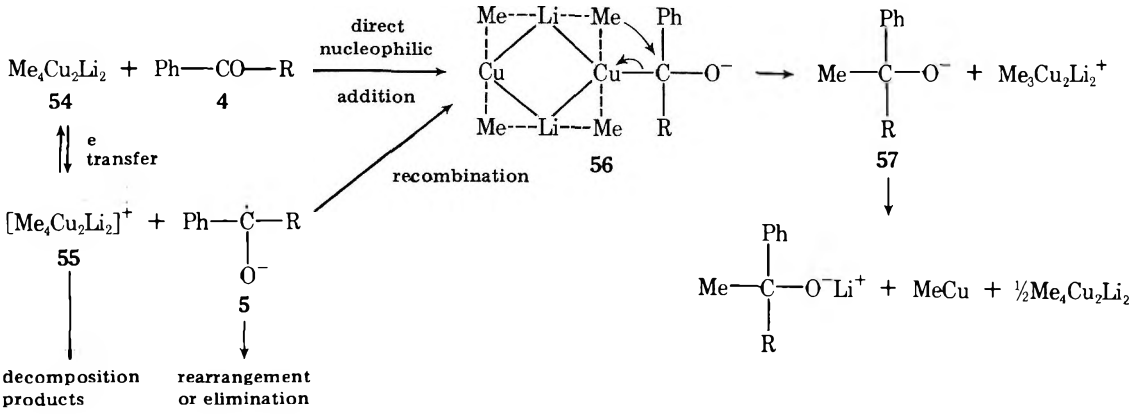
Finally, to obtain estimates of the relative rates at which Me_2CuLi reacts with typical enones and with aryl alkyl ketones, we performed the competition experiments summarized in Scheme V. In a competition between an enone **51** and an

Scheme V. Competition Experiments in Which the Ketone Reactants Are Present in Excess



aryl alkyl ketone **22** that reacts to give a 1,2 adduct, addition of Me_2CuLi to the enone was clearly more rapid. The same conclusion has been derived from a related study[15] of a competitive reaction of Me_2CuLi with a mixture of the enone **31** and PhCOPh (E_{redn} = −1.80 V, reacts with Me_2CuLi to give mainly a 1,2 adduct). In a competition reaction involving an enone **31** and an aryl alkyl ketone **41** whose anion radical undergoes a rapid secondary reaction, the overall rates of the two processes were similar with the reaction involving reductive elimination (**41** → **49**) being slightly more rapid. In each of the foregoing rate comparisons, ketones having comparable E_{redn} values were compared. In conjugate additions of Me_2CuLi to enones the relative reaction rates appear not to be directly related to E_{redn} values. Thus, the relative rates of conjugate addition of Me_2CuLi to the two enones **31** and **51** were similar although the E_{redn} values differ by 0.35 V. Although experimental difficulties in this competition experiment (see Experimental Section) created some ambiguity

Scheme VI



in our results, the reaction of Me_2CuLi with the more easily reduced enone **31** does appear to be slightly faster than the reaction with enone **51**.

From these studies we conclude that if the radical anion **5** (Scheme VI) derived from an aryl alkyl ketone **4** can undergo a further intramolecular reaction within a time period of 10^{-3} s or less, reaction of this ketone **4** with Me_2CuLi is likely to form a reduced or a rearranged product in a reaction that is comparable in rate to the conjugate addition of Me_2CuLi to an enone. However, if the anion radical **5** does not undergo a rapid intramolecular reaction, reaction of the ketone **4** with Me_2CuLi will yield a 1,2 adduct via a reaction path that is significantly slower than conjugate addition of Me_2CuLi to an enone. There appear to be at least two reaction pathways (Scheme VI) that can lead to the 1,2 adduct **57**. One pathway is a direct nucleophilic addition of the cuprate cluster **54** to the ketone to form an intermediate **56** that can rearrange to form the 1,2 adduct **57**. This process, which is analogous to the mechanism believed operative[10] in the relatively slow reaction of cuprates with alkyl halides, seems most probable for the slow 1,2 addition of cuprates to difficulty reduced (E_{redn} more negative than −2.8 V) saturated ketones. With the more easily reduced aryl alkyl ketones, a second process involving initial electron transfer to form intermediates **5** and **55** followed by recombination to form the intermediate **56** is a reasonable alternative. Although we are inclined to favor this second pathway (**4** → **5** → **56** → **57**), it should be noted that the recombination step (**5** + **55** → **56**) must be slow to be consistent with the relative reaction rates observed. This slow recombination rate could be attributed to the fact that a relatively small amount of the *total spin density* in the ketyl **5** is centered at the carbonyl carbon atom.[4] By contrast, a significantly larger fraction of the *total spin density* in ketyls derived from α,β-unsaturated ketones is centered at the β-carbon atom.[2] Also, in species such as **7** and **9** derived from rearrangement of or elimination of an anion from a radical anion, the bulk of the spin density will be located at a single carbon atom. To decide if this conjecture has merit, we clearly need more information about the relationship between spin densities in ion radical intermediates and their rates of recombination.

Experimental Section[16]

Preparation or Purification of the Starting Materials. All anhydrous ethereal solvents were freshly distilled from $LiAlH_4$, commercial Et_2O solutions of MeLi (halide free, Foote Mineral Co.) were standardized by a double titration procedure,[17] and the colorless, crystalline complex, Me_2SCuBr, was prepared from commercial CuBr (Fisher Scientific) as previously described.[2c] Commercial samples of ketones **12**, **22**, and **39** were purified by distillation and the ketone **13** was obtained from PhCOCl by a literature procedure.[18] This same procedure[18] was used with β-$C_{10}H_7COCl$ and with α-$C_{10}H_7COCl$ to obtain ketones **14** and **15**. The ketone **15** was obtained in 72% yield as colorless needles from hexane: mp 74–75 °C [recrystallization raised the mp to 76–77 °C (lit.[19] mp 73–74 °C)]; ir (CCl_4) 1688 cm^{-1} (C=O); uv max (95% EtOH) 220 nm (ϵ 65 000) and 282 (5600) with shoulders at 271 (5100) and 293 (5100); NMR (CCl_4) δ 7.1–7.9 (7 H, m, aryl CH) and 1.23 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 212 (M^+, 14), 155 (100), 127 (36), 77 (4), and 57 (4).

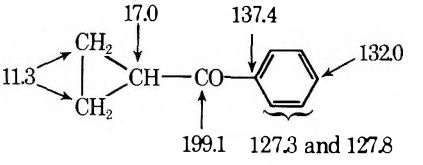
The ketone **14** was obtained in 88% yield as a pale yellow liquid, bp 134–136 °C (0.8 mm) [lit.[19] bp 184–186 °C (16 mm)], that solidified on cooling, mp 55–59 °C. Recrystallization from hexane afforded the pure ketone **14** as colorless prisms: mp 59–60 °C (lit.[20] mp 66 °C); ir (CCl_4) 1675 cm^{-1} (C=O); uv max (95% EtOH) 213 nm (ϵ 29 700), 222 (26 700), 242 (33 600), 248 (32 500), and 283 (6910); NMR (CCl_4) δ 7.3–8.3 (7 H, m, aryl CH) and 1.40 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 212 (M^+, 17), 156 (13), 155 (100), 128 (5), 127 (32), 126 (4), 97 (3), 57 (3), and 41 (5).

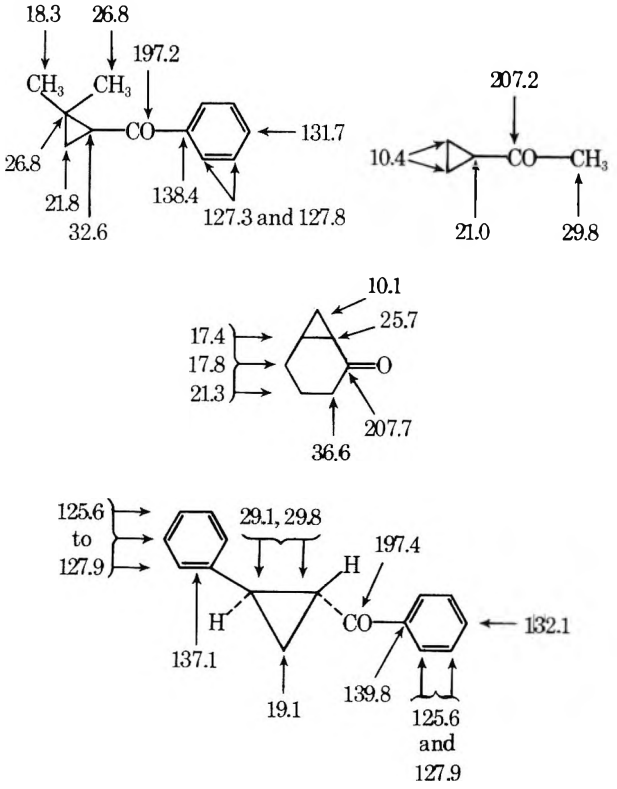
Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.84; H, 7.62.

Ketones **38** and **24** were prepared by previously described procedures.[21] The bicyclic ketone **38** was obtained in 51% yield as a colorless liquid: bp 96 °C (18 mm); $n^{25}D$ 1.4898 [lit.[22] bp 90 °C (15 mm)]; ir (CCl_4) 1691 cm^{-1} (C=O);[23] NMR (CCl_4) δ 0.8–1.4 (2 H, m, cyclopropyl CH_2) and 1.5–2.5 (8 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 110 (M^+, 73), 82 (48), 81 (55), 68 (53), 67 (58), 55 (66), 54 (100), 53 (33), 41 (34), and 39 (68). The ketone **24** was obtained in 54% yield as colorless needles from hexane: mp 43–44 °C[24d] (lit. mp 45.5–50,[21] 45–48,[24a] 45,[24b] 43–45 °C[24c]); ir ($CHCl_3$) 1667 cm^{-1} (conjugated C=O); uv max (95% EtOH) 244 nm (ϵ 20 200); NMR ($CDCl_3$) δ 7.1–8.2 (10 H, m, aryl CH), 2.5–3.1 (2 H, m, benzylic CH and COCH), and 1.3–2.1 (2 H, m, CH_2); mass spectrum *m/e* (rel intensity) 222 (M^+, 100), 221 (58), 117 (67), 116 (57), 115 (75), 106 (26), 105 (94), 91 (40), 78 (32), 77 (86), and 51 (32).

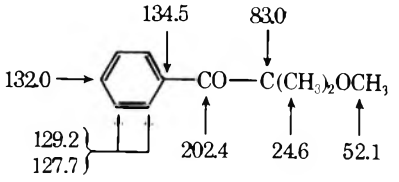
An authentic sample of the ketone **23** was obtained as a colorless liquid:[25] ir (CCl_4) 1675 cm^{-1} (C=O); uv max (95% EtOH) 245 nm (ϵ 13 000); NMR (CCl_4) δ 7.2–8.0 (5 H, m, aryl CH), 2.2–2.6 (1 H, m, CHCO), and 0.6–1.8 (8 H, m, cyclopropyl CH_2 and two CH_3 singlets at 1.05 and 1.33); mass spectrum *m/e* (rel intensity) 174 (M^+, 75), 159 (30), 154 (39), 115 (23), 106 (23), 105 (100), 77 (65), 51 (25), and 41 (20). The cyclopropyl ketone **22** had the following spectral properties: ir (CCl_4) 1670 cm^{-1} (C=O); uv max (95% EtOH) 242 nm (ϵ 23 200) and 273 (1830); NMR (CCl_4) δ 7.0–8.0 (5 H, m, aryl CH), 2.3–2.9 (1 H, m, COCH), and 0.7–1.4 (4 H, m, cyclopropyl CH_2); mass spectrum *m/e* (rel intensity) 146 (M^+, 72), 145 (25), 106 (26), 105 (100), 77 (73), 69 (23), 51 (36), 43 (38), 41 (22), and 39 (30). The spectral properties of the cyclopropyl ketone **39** were ir (CCl_4) 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.48 (3 H, s, $COCH_3$), 2.0–2.5 (1 H, m, CHCO), and 0.8–1.3 (4 H, m, cyclopropyl CH_2); mass spectrum *m/e* (rel intensity) 84 (M^+, 74), 83 (21), 69 (100), 43 (92), 42 (30), 41 (72), and 39 (61).

The natural abundance ^{13}C NMR spectra of the various cyclopropyl ketones **22–24**, **38**, and **39**, determined in $CDCl_3$ solution, are summarized in the following structures. In each case off-resonance decoupling was used to support the assignments given.





Preparation of the Methoxy Ketone 40. A solution of $NaOCH_3$ [from 2.45 g (107 mg-atoms) of Na] and 8.41 g (50.3 mmol) of α-bromoisobutyric acid in 75 ml of MeOH was stirred at 26 °C for 3 h and then refluxed for 1.5 h. After the reaction mixture had been concentrated it was partitioned between Et_2O and saturated aqueous HCl. The ethereal solution was dried (Na_2SO_4) and concentrated to leave 5.16 g of pale yellow liquid. Fractional distillation separated 3.85 g (65%) of the methoxy acid **48** as a colorless liquid: bp 95–96 °C (19 mm); $n^{25}D$ 1.4188 [lit.[26] bp 99.5 °C (18 mm)]; ir (CCl_4) 2980 (broad, associated OH) and 1710 cm^{-1} (carboxyl C=O); NMR (CCl_4) δ 10.16 (1 H, s, OH), 3.27 (3 H, s, OCH_3), and 1.40 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 118 (M^+, <1), 103 (2), 73 (100), 59 (8), 57 (8), 45 (10), 43 (29), and 41 (26). To a cold (−45 °C) solution of 1.21 g (10.2 mmol) of the acid **48** in 15 ml of Et_2O was added, dropwise with stirring and cooling during 10 min, 10 ml of an Et_2O solution containing 10.7 mmol of PhLi. The resulting mixture was warmed to −10 °C and an additional 9.5 ml of Et_2O solution containing 10 mmol of PhLi was added, dropwise and with stirring while the reaction mixture was kept at −10 to 1 °C. After the reaction mixture had been stirred at 1 °C for 15 min, it was warmed to 27 °C and poured, with vigorous stirring, into dilute aqueous HCl. After the aqueous phase had been saturated with NaCl, the mixture was extracted with Et_2O and the Et_2O extract was washed with aqueous $NaHCO_3$ and with aqueous NaCl and dried (Na_2SO_4). Concentration left 1.67 g of pale yellow liquid that was chromatographed on silica gel to separate 329 mg of early fractions containing PhPh and other impurities followed by 1.36 g (75%) of fractions (eluted with Et_2O–hexane mixtures, 2:98 v/v) containing (GLC, Carbowax 20M on Porasil) the ketone **40.** A collected (GLC) sample of the ketone **40** was obtained as a colorless liquid: $n^{25}D$ 1.5094; ir (CCl_4) 1680 cm^{-1} (conjugated C=O); NMR (CCl_4) δ 8.1–8.4 (2 H, m, aryl CH), 7.3–7.6 (3 H, m, aryl CH), 3.13 (3 H, s, OCH_3), and 1.43 (6 H, s, CH_3); uv max (95% EtOH) 247 nm (ϵ 10 200), 280 (shoulder, 1020), and 330 (72); mass spectrum *m/e* (rel intensity) 178 (M^+, <1), 105 (9), 77 (12), and 73 (100). The natural abundance ^{13}C NMR spectrum of the ketone **40** in $CDCl_3$ solution is summarized in the following structure.



Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.87; H, 7.78.

To examine a reaction reported[13] to form the methoxy ketone **40,** a mixture of NaOMe [from 409 mg (17.8 mg-atoms) of Na] and 3.45 g (15.2 mmol) of the bromo ketone **42** in 20 ml of Et_2O was stirred for 16 h at 25 °C and then partitioned between Et_2O and aqueous NaCl. The Et_2O solution was dried and concentrated to leave 2.54 g of a pale yellow liquid that contained no halogen and exhibited no ir absorption in the 6-μ region attributable to a carbonyl group. A 203-mg aliquot of the product was distilled under reduced pressure (0.6 mm) in a short-path still to separate 159 mg (78%) of the epoxy ether **44** as a colorless liquid: $n^{25}D$ 1.4898; ir (CCl_4) no OH or C=O absorption in the 3- and 6-μ regions; NMR (CCl_4) δ 7.1–7.6 (5 H, m, aryl CH), 3.14 (3 H, s, OCH_3), 1.48 (3 H, s, CH_3), and 0.97 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity) 178 (M^+, <1), 105 (100), 77 (45), 73 (14), and 43 (15); uv (95% EtOH), series of weak maxima (ϵ 64–727) in the region 244–281 nm.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.03; H, 7.94.

An attempt to obtain the pure epoxy ether **44** by GLC collection (silicone SE-30 on Chromosorb P) resulted in isomerization to the methoxy ketone **46** that was collected as a colorless liquid: $n^{25}D$ 1.5049; ir (CCl_4) 1720 cm^{-1} (C=O); NMR (CCl_4) δ 7.1–7.6 (5 H, m, aryl CH), 3.28 (3 H, s, OCH_3), 1.97 (3 H, s, CH_3CO), and 1.55 (3 H, s, CH_3); uv max (95% EtOH) 255 nm (ϵ 810) and 291 (256); mass spectrum *m/e* (rel intensity) 135 (52), 105 (10), 77 (21), and 43 (100).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.20; H, 7.94.

A solution of 792 mg (4.45 mmol) of epoxy ether **44** and 0.15 ml of aqueous 36% HCl in 10 ml of MeOH was stirred at 27 °C for 80 min and then partitioned between Et_2O and aqueous NaCl. After the Et_2O solution had been washed with H_2O and with aqueous NaCl and dried (Na_2SO_4), concentration left 667 mg of the crude hydroxy ketone **45** as a pale yellow liquid. A 150-mg aliquot of the crude product was distilled at 0.05 mm in a short-path still to separate 124 mg (75% yield) of the hydroxy ketone **45** as a colorless liquid: $n^{25}D$ 1.5260 [lit. $n^{25}D$ 1.5276,[27a] bp 91–93 °C (0.7 mm),[27a] 120 °C (3 mm)[27b]]; ir (CCl_4) 3590, 3460 (OH), and 1670 cm^{-1} (C=O); uv max (95% EtOH) 244 nm (ϵ 7190) and 325 (63); NMR (CCl_4) δ 7.2–8.2 (5 H, m, aryl CH), 3.85 (1 H, broad, OH, exchanged with D_2O), and 1.50 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 164 (M^+, <1), 121 (50), 106 (23), 105 (30), 77 (30), 59 (97), and 43 (100).

To explore the possible synthesis of the methoxy ketone **40** by reaction of the bromo ketone **42** with Ag^+ ion in MeOH solution,[28] a solution of 510 mg (3.0 mmol) of $AgNO_3$, 0.6 ml of H_2O, and 647 mg (2.85 mmol) of the bromo ketone **42** in 11 ml of MeOH was stirred in the dark for 30 min during which time a white precipitate separated. The mixture was filtered and the filtrate was partitioned between Et_2O and aqueous NaCl. After the Et_2O solution had been dried ($NaSO_4$), concentration left 419 mg of yellow liquid that contained (GLC, Carbowax 20M on Porasil) the ester **47** (ca. 90%, retention time 22.4 min) and the methoxy ketone **40** (ca. 10%, 25.6 min). A collected (GLC) sample of the ketone **40** was identified with the previously described material by comparison of ir and mass spectra and GLC retention times. A collected (GLC) sample of the ester **47** was obtained as a colorless liquid: $n^{25}D$ 1.5040; ir (CCl_4) 1735 cm^{-1} (ester C=O); uv (95% EtOH), a series of weak maxima (ϵ 408–831) in the region 248–262 nm with intense end absorption; NMR (CCl_4) δ 7.1–7.4 (5 H, m, aryl CH), 3.60 (3 H, s, OCH_3), and 1.53 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 178 (M^+, 17), 119 (100), 91 (45), 77 (15), and 41 (20).

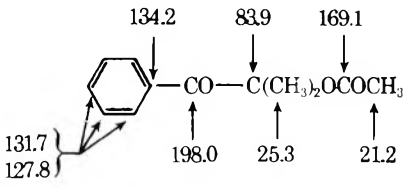
Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.12; H, 7.93.

Preparation of the Acetoxy Ketone 41. A solution of 10.00 g (44 mmol) of the bromo ketone **42** and 7.2 g (73 mmol) of KOAc in 75 ml of 95% EtOH was refluxed for 19 h and then cooled, filtered, and partitioned between Et_2O and aqueous NaCl. After the Et_2O solution had been dried (Na_2SO_4) and concentrated, distillation of the residual yellow liquid (7.75 g) separated 2.90 g of an early fraction, bp 82–90 °C (0.9–1.3 mm), containing (NMR analysis) a mixture of the acetoxy ketone **41** and an olefinic impurity. The subsequent distillation fraction (3.05 g), bp 90–96 °C (0.9–1.3 mm), containing the desired product was crystallized from hexane to separate 2.52 g (28%) of the acetoxy ketone **41** as white needles: mp 59–60 °C (lit.[29] mp 61 °C); ir (CCl_4) 1742 (ester C=O) and 1690 cm^{-1} (conjugated C=O); uv max (95% EtOH) 249 nm (ϵ 13 300), 269 (1000), and 314 (96); NMR (CCl_4) δ 7.8–8.1 (2 H, m, aryl CH), 7.2–7.5 (3 H, m, aryl CH), 1.88 (3 H, s, $COCH_3$), and 1.66 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 206 (M^+, <1), 163 (59), 106 (16), 105 (100), 101 (17), 77 (45), 59 (32), and 43 (51). The natural abundance ^{13}C NMR spectrum of the ketone **41** in $CDCl_3$ solution is summarized in the following structure.

Table I. Electrochemical Reduction of the Ketones at 25 °C in DMF Solution Containing 0.5 M n-Bu_4NBF_4

Registry no.	Ketone (concn, M × 10^3)	Polarography $E_{1/2}$, V vs. SCE	Polarography n	Polarography i_d, μA	Cyclic voltammetry $E_{1/2}$, V vs. SCE	Cyclic voltammetry Half-life, s
98-86-2	**12** (6.3)	−2.05	1.1	17–18	−2.12	0.2
938-16-9	**13** (5.6–5.8)	−2.14	1.0	17–25	−2.15	3
		−2.82	ca. 2	23		
7270-99-7	**14** (2.9–3.1)	−1.96	1.0	8–11	−1.95	>10
		−2.44	1.1	6–7	*a*	*a*
25540-73-2	**15** (3.8–4.8)	−2.03	1.1	14–18	−2.04	3
		−2.41	1.0	4	*a*	*a*
765-43-5	**39** (7.6–11.7)	ca. −2.87[b]			*a*	*a*
5771-58-4	**38** (7.6–8.3)	ca. −2.81[b]			*a*	*a*
3481-02-5	**22** (3.6–6.6)	−2.07	1.1	15–18	−2.08	ca. 5
		−2.73	1.4	12		
5685-43-8	**23** (2.6–4.3)	−2.09	1.1	9–16	−2.09	4
1145-92-2	**24** (1.8–4.2)	−1.82	0.8	8–23	−1.85	$<10^{-2}$
5650-07-7	**31** (6.4–7.0)	−1.86	0.9	11–25	−1.89	0.7
141-79-7	**51** (8.0–10.2)	−2.21	0.9	15–26	−2.26	0.07
611-70-1	**49** (3.8–6.2)	−2.09	1.1	12–22	−2.09	0.3
		−2.73	1.3	5–13		
7476-41-7	**41** (6.1–6.2)	−1.80[c]	1.0	22–24	−1.83[d]	$<10^{-2}$
59671-36-2	**40** (6.2)	−2.03	1.2	32–35	−2.01	0.7
		−2.76	1.2	16–21		

[a] Value not determined. [b] Since the reduction wave for this ketone was almost as negative as the reduction wave for the supporting electrolyte, only approximate $E_{1/2}$ values could be obtained. [c] An additional wave with $E_{1/2} = -2.10$ V corresponding to the formation and reduction of ketone **49** was also observed. [d] At slow scan rates (<10 V/s), the cyclic voltammetry scans also exhibited a reversible reduction wave, with $E_{1/2} = -2.10$ V, corresponding to the formation and reversible reduction of the ketone **49**.



Electrochemical Measurements. The polarographic and cyclic voltammetry measurements employed a custom-made polarographic module, utilizing solid-state amplifiers, that followed the typical three electrode design. Descriptions of the cells, working electrodes, reference electrodes, and reagent purification procedures have been published previously.[30] In all cases the solvent was anhydrous DMF containing 0.5 M n-$Bu_4N^+BF_4^-$ as the supporting electrolyte. Previously described procedures[30b,31] were used to estimate the $E_{1/2}$ values and half-lives from cyclic voltammetry measurements. The results of these measurements are summarized in Table I. Since the reduction waves for the saturated cyclopropyl ketones **38** and **39** were almost as negative as the discharge potential for the supporting electrolyte, only approximate $E_{1/2}$ values were obtained from the polarographic measurements and it was not possible to obtain data for these two ketones by cyclic voltammetry.

Reactions with Me_2CuLi. A. Ketone 13. To a solution of Me_2CuLi, prepared by adding 10.1 ml of an Et_2O solution containing 18 mmol of MeLi to a solution of 1.77 g (8.6 mmol) of Me_2SCuBr in 12 ml of Et_2O and 9 ml of Me_2S, was added 1.00 g (6.2 mmol) of the ketone **13** in 2 ml of Et_2O. The resulting solution, from which yellow $(MeCu)_n$ began to precipitate within 5 min, was stirred at 27 °C for 1 h and then partitioned between Et_2O and an aqueous solution of NH_4Cl and NH_3. The ethereal layer was dried and concentrated to leave 966 mg of crude liquid product. After an aliquot of the product had been mixed with a known weight of internal standard (n-$C_8H_{17}Ph$), GLC analysis (silicone SE-30 on Chromosorb P) indicated the presence of the unchanged ketone **13** (retention time 4.5 min, 10% recovery), the alcohol **17** (6.5 min, 72% yield), and n-$C_8H_{17}Ph$ (10.4 min). The mixture of the ketone **13** (R_f 0.48) and the alcohol **17** (R_f 0.34) was separated by preparative TLC [silica gel with an Et_2O–pentane (1:19 v/v) eluent] and the alcohol fraction was distilled under reduced pressure in a short-path still to separate the alcohol **17** as a colorless liquid: bp 140–141 °C (18 mm); $n^{25}D$ 1.5123 [lit.[32] bp 116–117 °C (15 mm), $n^{25}D$ 1.5135]; ir (CCl_4) 3590 cm^{-1} (OH); uv (95% EtOH) series of weak maxima (ε 125–204) in the region 247–254 nm; NMR (CCl_4) δ 6.9–7.5 (5 H, m, aryl CH), 1.4–1.6 (4 H, OH and CH_3 singlet at 1.52), and 0.88 (9 H, s, t-Bu); mass spectrum m/e (rel intensity) 160 ($M^+ - H_2O$, 16), 145 (49), 121 (100), 105 (42), 91 (20), 77 (35), 57 (21), 51 (21), 43 (65), and 41 (20).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.83; H, 10.18.

Reaction of 969 mg (5.98 mmol) of the ketone **13** with 6.58 mmol of MeLi in 24 ml of Et_2O afforded 1.02 g (96%) of the alcohol **17**, $n^{25}D$ 1.5145, that was identified with the previously described sample by comparison of ir and NMR spectra.

The ketone fraction from the preparative TLC separation was identified as ketone **13** by comparison of ir and mass spectra. The absence of peaks in the mass spectrum at m/e values larger than 162 (e.g., 176 and 178) indicated the absence of ketone products in which a CH_3 group had been added to the aromatic ring.

B. Ketone 14. To a cold (4 °C) solution of Me_2CuLi, from 10.0 mmol of MeLi, 1.03 g (5.0 mmol) of Me_2SCuBr, 4 ml of Me_2S, and 5.9 ml of Et_2O, was added 336 mg (1.6 mmol) of ketone **14** in 4 ml of Et_2O. The reaction solution was stirred at 0–8 °C for 1 h, during which time a small amount of yellow $(MeCu)_n$ precipitated, and then at 25 °C for 16 h. After the usual isolation procedure, the crude liquid product was subjected to preparative TLC (silica gel with an Et_2O–pentane eluent, 1:19 v/v) to separate 28 mg of a ketone fraction and 269 mg of an alcohol fraction (eluted second). The alcohol fraction was distilled in a short-path still at 0.4 mm to separate 260 mg (71%) of the alcohol **18** as a light yellow liquid, $n^{25}D$ 1.5843. This material crystallized on standing and was recrystallized from pentane at low temperatures to separate the pure alcohol **18** as colorless needles: mp 57.5–59 °C; ir (CCl_4) 3595 cm^{-1} (OH); uv max (Et_2O) 224 nm (ε 94 300) with a series of weak maxima (ε 3250–5190) in the region 248–288 nm; NMR (CCl_4) δ 7.3–8.0 (7 H, m, aryl CH), 1.67 (3 H, s, CH_3), 1.57 (1 H, s, OH, exchanged with D_2O), and 0.97 (9 H, s, t-Bu); mass spectrum m/e (rel intensity) 228 (M^+, 33), 172 (53), 171 (100), 155 (41), 153 (22), 129 (25), 128 (58), 127 (40), 77 (20), and 57 (40).

Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.09; H, 8.84.

An authentic sample of the alcohol **18**, mp 58–59 °C, was obtained in 64% yield by reaction of the ketone **14** with excess ethereal MeLi for 30 min at 25 °C. The two samples were identified by a mixture melting point determination and by comparison of ir, NMR, and uv spectra.

The crude ketone fraction (28 mg) from the TLC separation contained (GLC, silicone SE-30 on Chromosorb P) the ketone **14** (retention time 14.0 min, ca. 73% of the mixture) accompanied by two more rapidly eluted components (10.2 min, ca. 14%, and 11.7 min, ca. 13%), believed to be olefins derived from the alcohol **18**. The mass spectrum of this mixture exhibited abundant peaks corresponding to the ketone **14** with a less abundant peak at m/e 210 attributable

to an olefin formed from alcohol **18**. There were no higher mass peaks that would be expected from ketones in which a Me group had been added to the aromatic ring of ketone **14**.

C. Ketone 15. A cold (5 °C) solution of Me_2CuLi, from 11.9 mmol of MeLi, 1.23 g (6.0 mmol) of Me_2SCuBr, 6 ml of Me_2S, and 7.3 ml of Et_2O, was treated with 424 mg (2.0 mmol) of the ketone **15** in 5 ml of Et_2O. The resulting mixture was stirred at 5–10 °C for 1 h and at 25 °C for 18 h and then subjected to the usual isolation procedure. The crude liquid product (500 mg) was subjected to preparative TLC (silica gel with an Et_2O–pentane eluent, 1:19 v/v) to separate 70 mg of an unidentified hydrocarbon fraction (ir analysis) and 410 mg of an alcohol fraction (eluted second). A 375-mg aliquot of the alcohol fraction was distilled in a short-path still at 1.6 mm to separate 282 mg (68%) of the alcohol **19** as a viscous yellow liquid: n^{25}D 1.5892; ir (CCl_4) 3590 cm^{-1} (OH); uv max (Et_2O) 224 nm (ϵ 79 000) with a series of weak maxima (ϵ 4780–8410) in the region 260–295 nm; NMR (CCl_4) δ 7.1–7.9 (7 H, m, aryl CH), 1.77 (3 H, s, CH_3), 1.70 (1 H, s, OH, exchanged with D_2O), and 0.99 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 210 ($M^+ - H_2O$, 49), 195 (50), 171 (51), 170 (25), 165 (37), 155 (70), 154 (100), 153 (94), 152 (83), 151 (24), 127 (53), 57 (32), 56 (28), 43 (28), and 41 (28).

Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.38; H, 8.90.

Reaction of the ketone **15** with excess ethereal MeLi at 25 °C for 1 h yielded 81% of the alcohol **19** as a viscous liquid, n^{25}D 1.5880, that was identified with the previously described sample by comparison of ir, NMR, and uv spectra.

D. Ketone 22. To a cold (4 °C) solution of Me_2CuLi, from 9.3 mmol of MeLi, 1.01 g (4.9 mmol) of Me_2SCuBr, 5.3 ml of Me_2S, and 5.7 ml of Et_2O, was added a solution of 512 mg (3.5 mmol) of ketone **22** in 1 ml of Et_2O. As the ketone was added an exothermic reaction occurred with precipitation of $(MeCu)_n$. The mixture was stirred at 27 °C for 3.5 h and then subjected to the usual isolation procedure to separate 476 mg of crude product as a yellow liquid. A 454-mg aliquot of this product was chromatographed on silica gel to separate 18 mg (3.5%) of ketone **28** (eluted with hexane, identified with an authentic sample by comparison of ir, NMR, and mass spectra and GLC retention times), followed by 29 mg of fractions (eluted with hexane) containing (GLC, silicone DC-10 on Chromosorb P) a mixture of ketone **22** (retention time 9.1 min) and ketone **28** (9.6 min) and 54 mg (11%) of ketone **22** (eluted with 2% Et_2O in hexane, identified by comparison of GLC retention times and ir and mass spectra). Subsequent chromatography fractions, eluted with 2% Et_2O in hexane, contained 289 mg (57%) of the crude alcohol **25**. A 120-mg aliquot was distilled at 0.5 mm in a short-path still to separate 86 mg of the pure alcohol **25** as a colorless liquid: n^{25}D 1.5332; ir (CCl_4) 3590 cm^{-1} (OH); uv (95% EtOH), series of weak maxima (ϵ 75–187) in the region 247–267 nm; NMR (CCl_4) δ 7.0–7.5 (5 H, m, aryl CH), 1.60 (1 H, s, OH, exchanged with D_2O), 1.41 (3 H, s, CH_3), 0.9–1.3 (1 H, m, cyclopropyl CH), and 0.2–0.5 (4 H, m, cyclopropyl CH_2); mass spectrum *m/e* (rel intensity) 147 (22), 144 (43), 143 (26), 134 (100), 129 (81), 128 (45), 121 (32), 115 (30), 105 (44), 103 (30), 91 (43), 77 (40), 51 (23), 43 (43), and 39 (20).

Reaction of the ketone **22** with excess ethereal MeLi at 26 °C for 2 h yielded 79% of the alcohol **25** as a colorless liquid, n^{25}D 1.5330 [lit.[33] bp 78–81 °C (0.3 mm), n^{27}D 1.5324], that was identified with the previously described sample by comparison of ir, NMR, and mass spectra.

E. Ketone 23. To a cold (3 °C) solution of Me_2CuLi, from 9.3 mmol of MeLi, 1.02 g (4.9 mmol) of Me_2SCuBr, 5.0 ml of Me_2S, and 6.0 ml of Et_2O, was added a solution of 613 mg (3.5 mmol) of the ketone **23** in 2.0 ml of Et_2O. During the addition, a mildly exothermic reaction occurred with precipitation of $(MeCu)_n$. After the mixture had been stirred at 27 °C for 4.5 h, it was subjected to the usual isolation procedure to give 640 mg of crude product as a pale yellow liquid. A 610-mg aliquot of this product was chromatographed on silica gel with an Et_2O–petroleum ether eluent (1:99 v/v) to separate 76 mg of early fractions containing (ir analysis) a mixture of alcohol and ketone products. Subsequent fractions contained 467 mg (75%) of the alcohol **26**. A 130-mg portion of the alcohol was distilled in a short-path still to separate 95 mg of the pure alcohol **26** as a colorless liquid: n^{25}D 1.5145; ir (CCl_4) 3610 cm^{-1} (OH); uv (95% EtOH), series of weak maxima (ϵ 92–257) in the region 240–266 nm; NMR (CCl_4) δ 7.1–7.6 (5 H, m, aryl CH), 0.8–1.7 (11 H, m, cyclopropyl CH, OH, and three CH_3 singlets at 1.54, 1.04, and 0.88), and 0.2–0.7 (2 H, m, cyclopropyl CH); mass spectrum *m/e* (rel intensity) 172 (46), 157 (100), 143 (38), 142 (50), 134 (27), 129 (58), 128 (39), 115 (46), 91 (41), and 77 (29).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.11; H, 9.58.

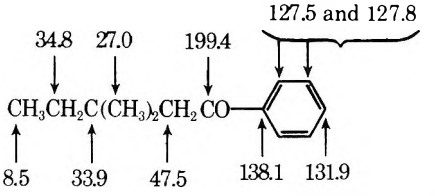
Reaction of the ketone **23** with excess ethereal MeLi at 27 °C for 3 h yielded 90% of the alcohol **26** as a colorless liquid, n^{25}D 1.5155, that was identified with the previously described sample by comparison of ir, NMR, and mass spectra and TLC R_f values on silica gel.

The early chromatographic fractions (70 mg) were rechromatographed on silica gel to separate 9 mg of an early fraction containing (GLC, silicone SE-30 on Porasil) the starting ketone **23** (retention time 16.0 min, ca. 60% of the mixture) and the ketone **29** (22.2 min, ca. 40% of the mixture corresponding to a 0.6% yield). Subsequent chromatographic fractions contained 22 mg of the starting ketone **23** (GLC analysis) and 30 mg of the alcohol **26**. A collected (GLC) sample of the ketone **29** was identified with a subsequently described authentic sample by comparison of mass spectra and GLC retention times.

An authentic sample of the ketone **29** was prepared from β,β-dimethylacryloyl chloride: bp 78–82 °C (42 mm); n^{25}D 1.4750 [lit.[34] bp 59–61 °C (30 mm)]; ir (CCl_4) 1785, 1755 (C=O), and 1620 cm^{-1} (C=C); NMR (CCl_4) δ 6.03 (1 H, m, vinyl CH), 2.15 (3 H, broad, CH_3), and 1.98 (3 H, broad, CH_3). To a cold (−8 °C) solution of 13.5 g (114 mmol) of this acid chloride in 25 ml of Et_2O was added, dropwise and with stirring, 75 ml of an ethereal solution of PhMgBr (prepared from 100 mmol of PhBr). After the resulting solution had been stirred for 30 min, it was quenched with H_2O and then partitioned between Et_2O and aqueous NaCl. The organic solution was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried (Na_2SO_4) concentrated, and distilled to separate 7.15 g (45%) of β,β-dimethylacrylophenone (**31**) as a pale yellow liquid: bp 89–93 °C (1.2 mm); n^{25}D 1.5598 [lit. bp 104–106 °C (5 mm),[34] 120–121 °C (4 mm),[35] n^{23}D 1.5579,[34] n^{19}D 1.5598[35]]; ir (CCl_4) 1665 (C=O) and 1615 cm^{-1} (C=C); uv max (95% EtOH) 259 nm (ϵ 19 700) and 346 (155); NMR (CCl_4) δ 7.2–8.0 (5 H, m, aryl CH), 6.69 (1 H, broad, vinyl CH), 2.20 (3 H, broad, CH_3), and 1.96 (3 H, broad, CH_3); mass spectrum *m/e* (rel intensity) 160 (M^+, 72), 159 (100), 145 (83), 115 (40), 105 (72), 83 (64), 77 (81), 55 (38), 51 (59), and 39 (42). A cold (2 °C) solution of EtMgBr, prepared from 1.80 g (75 mg-atoms) of Mg, 10.9 g (100 mmol) of EtBr, and 75 ml of Et_2O, was treated successively with 91 mg (1.0 mmol) of CuCl and a solution of 4.80 g (30 mmol) of the enone **31** in 25 ml of Et_2O. The resulting mixture was stirred for 2.5 h while it was allowed to warm to 27 °C and then the mixture was partitioned between Et_2O and cold dilute aqueous H_2SO_4. The ethereal solution was washed with aqueous NaCl, dried, and concentrated to leave 5.30 g (93%) of crude product as a pale yellow oil containing (GLC, silicone SE-30 on Porasil) one major component, the ketone **29** (retention time 23.8 min). A collected (GLC) sample of the pure ketone **29** was obtained as a colorless liquid: n^{25}D 1.5100; ir (CCl_4) 1692 and 1680 cm^{-1} (conjugated C=O);[36] uv max (95% EtOH) 241 nm (ϵ 10 300) and 277 (1190); NMR (CCl_4) δ 7.3–8.1 (5 H, m, aryl CH), 2.80 (2 H, s, CH_2CO), and 0.7–1.7 [11 H, m, CH_3CH_2 and a $C(CH_3)_2$ singlet at 1.00]; mass spectrum *m/e* (rel intensity) 190 (M^+, 6), 120 [PhC(OH)=CH_2^+, 100], 105 (90), and 77 (36).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.00; H, 9.55.

The natural abundance ^{13}C NMR spectrum of ketone **29**, determined in $CDCl_3$, is summarized in the following formula.



F. Ketone 24. To a cold (4 °C) solution of Me_2CuLi, from 6.8 mmol of MeLi, 0.73 g (3.5 mmol) of Me_2SCuBr, 4.0 ml of Me_2S, and 6.0 ml of Et_2O, was added a solution of 560 mg (2.5 mmol) of ketone **24** in 3.0 ml of Et_2O. The addition was accompanied by a mild exothermic reaction and precipitation of $(MeCu)_n$ began within 20 min. After the reaction mixture had been stirred for 5 h at 27 °C, it was subjected to the usual isolation procedure to give 572 mg of crude product as a yellow liquid. A 565-mg aliquot of this product was chromatographed on silica gel with Et_2O–hexane mixtures as eluents. After separation of 28 mg of early fractions containing (GLC) a mixture of ketones **24** (ca. 4% recovery) and **30** (ca. 0.9% yield), the next fraction contained 36 mg (6% recovery) of the starting ketone **24**, mp 42.5–43 °C, identified by a mixture melting point determination and by comparison of ir, NMR, and mass spectra and GLC retention times. Subsequent fractions contained 484 mg (81%) of the alcohol **27** as a colorless liquid: n^{25}D 1.5805; ir ($CHCl_3$) 3580 and 3460 cm^{-1} (OH); uv (95% EtOH), series of weak maxima (ϵ 440–900) in the region 249–272 nm; NMR ($CDCl_3$) δ 6.9–7.6 (10 H, m, aryl CH), 1.8–2.2 (1 H, m, benzylic CH), 1.70 (1 H, s, OH, exchanged with D_2O), and 0.6–1.6 (6 H, m, cyclo-

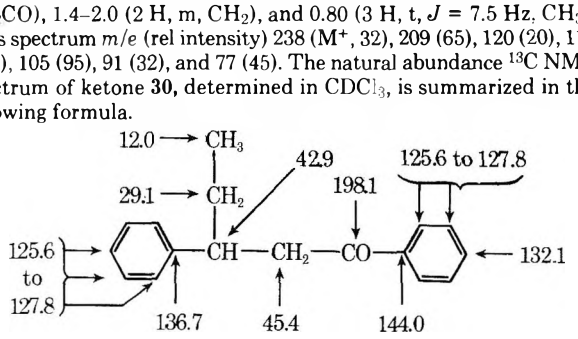
propyl CH and a CH_3 singlet at 1.55); mass spectrum *m/e* (rel intensity) 221 (16), 220 (78), 205 (96), 142 (26), 134 (32), 130 (81), 129 (100), 128 (72), 115 (73), 106 (59), 105 (66), 103 (31), 91 (40), 77 (66), and 51 (37).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.71; H, 7.65.

Reaction of the ketone **24** with excess ethereal MeLi at 26 °C for 2 h yielded, after column chromatography, 94% of the alcohol **27** as a colorless liquid, $n^{25}D$ 1.5790, that was identified with the previously described sample by comparison of ir, NMR, and mass spectra.

The early chromatographic fractions (23 mg) were rechromatographed on silica gel to separate in early fractions 3 mg of the ketone **30** followed by 11.5 mg of fractions containing (GLC, silicone SE-30 on Porasil) both ketone **30** (retention time 29.4 min) and ketone **24** (34.4 mm), and 5 mg of ketone **24.** Recrystallization of the crude ketone **30** from EtOH afforded 1 mg of the pure ketone **30**, mp 57–58 °C, that was identified with the subsequently described authentic sample by a mixture melting point determination and by comparison of ir and mass spectra.

To obtain an authentic sample of ketone **30,** a cold (6 °C) solution of EtMgBr, prepared from 21.8 g (200 mmol) of EtBr, 3.60 g (150 mg-atoms) of Mg, and 75 ml of Et_2O, was treated successively with 0.20 g (2 mmol) of CuCl and a solution of 12.48 g (60 mmol) of ketone **32** in 20 ml of Et_2O. The mixture was stirred for 3 h while it was allowed to warm to 25 °C and then it was partitioned between Et_2O and cold, dilute aqueous H_2SO_4. the organic layer was washed with aqueous NaCl, dried, and concentrated to leave 12.4 g (87%) of the crude ketone **30** as a yellow liquid that solidified on standing. A 1.80-g aliquot of the crude product was chromatographed on Al_2O_3 with a pentane eluent to separate 1.15 g of the ketone **30** as a colorless solid. Recrystallization from EtOH afforded the ketone **30** as colorless needles: mp 59–60 °C (lit.[37] mp 63 °C); ir ($CHCl_3$) 1682 cm^{-1} (conjugated C=O); uv max (95% EtOH) 243 nm (ϵ 13 400); NMR ($CDCl_3$) δ 7.1–8.2 (10 H, m, aryl CH), 3.1–3.4 (3 H, m, benzylic CH and CH_2CO), 1.4–2.0 (2 H, m, CH_2), and 0.80 (3 H, t, J = 7.5 Hz, CH_3); mass spectrum *m/e* (rel intensity) 238 (M^+, 32), 209 (65), 120 (20), 118 (100), 105 (95), 91 (32), and 77 (45). The natural abundance ^{13}C NMR spectrum of ketone **30,** determined in $CDCl_3$, is summarized in the following formula.



G. Ketone 12. A cold (5 °C) solution of Me_2CuLi, from 10.7 mmol of MeLi, 1.25 g (6.06 mmol) of Me_2SCuBr, 6.5 ml of Me_2S, and 8.5 ml of Et_2O, was treated with a solution of 563 mg (4.69 mmol) of ketone **12** in 3 ml of Et_2O. The addition was accompanied by a mildly exothermic reaction with evolution of gas (presumably CH_4) and precipitation of $(MeCu)_n$. After the mixture had been stirred at 27 °C for 3.5 h, it was subjected to the usual isolation procedure to separate 532 mg of crude product as a pale yellow oil. A 434-mg aliquot was chromatographed on silica gel with an Et_2O–hexane eluent (1:19 to 1:3 v/v) to separate 354 mg (77% recovery) of starting ketone **12** followed by 46 mg (9%) of the alcohol **16.** Both products were identified with authentic samples by comparison of ir, NMR, and either mass spectra (for alcohol **16**) or GLC retention times (for ketone **12**). A comparable experiment was performed with a solution of 540 mg (4.5 mmol) of ketone **12** and a cold (4 °C) solution of Me_2CuLi, from 1.66 g (8 mmol) of Me_2SCuBr, 14 mmol of MeLi, 8 ml of Me_2S, and 7 ml of Et_2O. After reaction for 11 min at 4–8 °C [with gas evolution and precipitation of $(MeCu)_n$], a 446-mg aliquot of the crude liquid product (484 mg) was chromatographed to separate 357 mg (72% recovery) of ketone **12** and 48 mg (8%) of the alcohol **16,** $n^{25}D$ 1.5159.

An authentic sample of the alcohol **16,** prepared by reaction of ketone **12** with excess ethereal MeLi, was obtained as a colorless liquid: $n^{25}D$ 1.5169 [lit. bp 60–65 °C (4 mm),[38a] $n^{27}D$ 1.510,[38a] $n^{35}D$ 1.51502[38b]]; ir (CCl_4) 3590 and 3420 cm^{-1} (OH); NMR (CCl_4) δ 7.0–7.6 (5 H, m, aryl CH), 2.18 (1 H, s, OH, exchanged with D_2O), and 1.47 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity), 136 (M^+, 1), 121 (25), 105 (3), 78 (6), 77 (9), 59 (4), 51 (10), and 43 (100); uv (95% EtOH), series of weak maxima (ϵ 78–177) in the region 239–265 nm.

H. Ketone 31. To a cold (4 °C) solution of Me_2CuLi, from 1.03 g (5.0 mmol) of Me_2SCuBr, 8.6 mmol of MeLi, 6 ml of Me_2S, and 9 ml of Et_2O, was added, dropwise with stirring and cooling, a solution of 480 mg (3.0 mmol) of the ketone **31** in 4 ml of Et_2O. As the ketone **31** was added a mildly exothermic reaction occurred with precipitation of $(MeCu)_n$. The resulting cold (8 °C) mixture was stirred for 15 min at 4–8 °C and then subjected to the usual isolation procedure. The crude product, 490 mg of yellow liquid, contained (ir and NMR analyses) the ketone **52.** A 157-mg aliquot was distilled at 0.9 mm in a short-path still to separate 135 mg (80%) of the ketone **52:** $n^{25}D$ 1.5078 [lit.[36] bp 112–114 °C (10 mm), $n^{25}D$ 1.5056]; ir (CCl_4) 1690 and 1675 cm^{-1} (C=O); NMR (CCl_4) δ 7.2–8.0 (5 H, m, aryl CH), 2.79 (2 H, s, CH_2CO), and 1.05 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 176 (M^+, 12), 120 (56), 105 (100), 77 (54), 57 (15), 51 (25), and 41 (19). This product, which exhibited a single GLC peak (silicone SE-30 on Chromosorb P), was identified with an authentic sample[36] by comparison of ir and NMR spectra and GLC retention times.

I. Ketone 51. To a cold (5 °C) solution of Me_2CuLi, from 1.144 g (5.57 mmol) of Me_2SCuBr, 10 mmol of MeLi, 6 ml of Me_2S, and 7 ml of Et_2O, was added, dropwise with stirring and cooling, a solution of 394 mg (4.00 mmol) of the enone **51** in 5 ml of Et_2O. The reaction mixture, which warmed to 11 °C with precipitation of $(MeCu)_n$ during this addition, was stirred at 5–11 °C for 15 min and then subjected to the usual isolation procedure. The crude product, 407 mg (89%) of yellow liquid containing (ir and NMR analyses) the ketone **53,** was distilled at 20 mm in a short-path still to separate 280 mg (61%) of the ketone **53:** $n^{25}D$ 1.4034 (lit. bp 125–126 °C;[39a] $n^{31}D$ 1.3989;[39a] $n^{25}D$ 1.4018[39b]); ir (CCl_4) 1715 cm^{-1} (C=O); NMR (CCl_4) δ 2.27 (2 H, s, CH_2CO), 2.03 (3 H, s, CH_3CO), and 1.00 (9 H, s, *t*-Bu). This product was identified with an authentic sample[39a] by comparison of ir and NMR spectra and GLC retention times.

J. Bromo Ketone 42. A cold (5 °C) solution of Me_2CuLi, from 1.025 g (5.0 mmol) of Me_2SCuBr, 9.6 mmol of MeLi, 7 ml of Me_2S, and 9 ml of Et_2O, was treated with a solution of 690 mg (3.04 mmol) of the bromo ketone **42** in 3 ml of Et_2O. After the addition [accompanied by an exothermic reaction and precipitation of $(MeCu)_n$] was complete, the mixture was stirred for 30 min at 5 °C and for 90 min at 26 °C and then subjected to the usual isolation procedure. After the crude product (405 mg of yellow liquid) had been mixed with a weighed amount of internal standard (n-$C_{11}H_{24}$), analysis (GLC, silicone SE-30 on Porasil) indicated the presence of n-$C_{11}H_{24}$ (retention time 11.7 min), ketone **49** (18.8 min, 77% yield), and ketone **13** (22.2 min, 17% yield). Collected (GLC) samples of ketones **13** and **49** were identified with authentic samples by comparison of GLC retention times and ir and mass spectra.

K. Methoxy Ketone 40. To a cold (5 °C) solution of Me_2CuLi, from 1.028 g (5.0 mmol) of Me_2SCuBr, 9.45 mmol of MeLi, 6 ml of Me_2S, and 9 ml of Et_2O, was added, dropwise and with stirring, a solution of 540 mg (3.03 mmol) of the methoxy ketone **40** in 4 ml of Et_2O. The mixture, from which $(MeCu)_n$ began to precipitate immediately, was stirred at 4–7 °C for 30 min and at 26 °C for 1 h and then subjected to the usual isolation procedure. A 506-mg aliquot of the crude product (510 mg of yellow liquid) was chromatographed on silica gel with Et_2O–hexane mixtures as the eluent. After separation of 202 mg of early fractions containing mixtures of ketone and alcohol products, the subsequent fractions contained 312 mg (53%) of the alcohol **50** as a colorless liquid. Short-path distillation of a 95-mg aliquot of this product under reduced pressure afforded 75 mg of the pure liquid alcohol **50:** $n^{25}D$ 1.5131; ir (CCl_4) 3600 and 3550 cm^{-1} (OH); NMR (CCl_4) δ 7.0–7.6 (5 H, m, aryl CH), 3.22 (3 H, s, OCH_3), 2.82 (1 H, s, OH, exchanged with D_2O), 1.53 (3 H, s, CH_3), 1.32 (3 H, s, CH_3), and 0.98 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity) 194 (M^+, <1), 121 (5), 105 (2), 77 (4), 74 (5), 73 (100), and 43 (22), uv (95% EtOH), series of weak maxima (δ 236–440) in the region 247–264 nm.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.18; H, 9.35.

Reaction of the ketone **40** with excess ethereal MeLi at 27 °C for 1.5 h followed by isolation of the crude neutral product and chromatography on silica gel afforded 92% of the alcohol **50** as a colorless liquid, $n^{25}D$ 1.5118–1.5120, that was identified with the previously described sample by comparison of ir, NMR, and mass spectra.

A 185-mg portion of the first fraction from the initial chromatography was rechromatographed on silica gel to separate an additional 29 mg of the pure alcohol **50** (total yield 58%), 95 mg of fractions containing (ir and NMR analysis) mainly the alcohol **50,** and 22 mg of early fractions that contained (GLC, Carbowax 20M on Chromosorb P) the starting ketone **40** (ca. 83%, retention time 22.4 min) accompanied by ca. 2% (corresponding to a 0.1% yield) of the ketone **49** (14.8 min) and ca. 15% of the alcohol **50** (42.6 min). A collected (GLC) sample of the ketone **49** was identified with an authentic sample by comparison of GLC retention times and mass spectra.

L. Acetoxy Ketone 41. To a cold (3–5 °C) solution of Me_2CuLi, from 1.03 g (5.0 mmol) of Me_2SCuBr, 9.6 mmol of MeLi, 9 ml of Et_2O, and 6 ml of Me_2S, was added, dropwise and with stirring, a solution

of 618 mg (3.0 mmol) of the ketone **41** in 2 ml of Et_2O. The resulting solution, from which $(MeCu)_n$ began to precipitate immediately, was stirred at 3–5 °C for 40 min and at 27 °C for 80 min and then subjected to the usual isolation procedure. A 420-mg aliquot of the crude liquid product (426 mg) was subjected to preparative TLC on silica gel (E. Merck, no. PF 254) with an Et_2O–hexane eluent (3:25 v/v, three successive elutions). The fastest moving band (R_f 0.63) contained 169 mg (39%) of the ketone **49** as a colorless liquid identified with an authentic sample by comparison of the R_f values and ir, NMR, and mass spectra. The second TLC band (R_f 0.32) contained 128 mg of liquid that was crystallized from hexane to separate 94 mg (15% recovery) of the starting acetoxy ketone **41**, mp 59–60 °C, that was identified with an authentic sample by a mixture melting point determination and by comparison of ir, NMR, and mass spectra. The slowest moving band (R_f 0.18) contained 39 mg (8%) of the hydroxy ketone **45** as a pale yellow liquid that was identified with a previously described sample by comparison of ir, NMR, and mass spectra.

In a comparable experiment reaction of 4.8 mmol of Me_2CuLi with 532 mg (2.58 mmol) of the acetoxy ketone **41** for 2 h at 3–5 °C and for 2.5 h at 25 °C yielded 361 mg of crude liquid product that was mixed with a known weight of internal standard (n-$C_{11}H_{24}$). The crude product contained (GLC, silicone SE-30 on Chromosorb P) n-$C_{11}H_{24}$ (retention time 11.2 min), the ketone **49** (54% yield, 18.0 min), and two minor unidentified components (26.6 and 58.4 min). A collected (GLC) sample of the ketone **49** was identified with an authentic sample by comparison of GLC retention times and ir, NMR, and mass spectra.

Competition Experiments with Me_2CuLi. A. Ketones 22 and 51. A solution of Me_2CuLi, prepared at 4 °C from 216 mg (1.05 mmol) of Me_2SCuBr in 1.6 ml of Me_2S and 2 ml of Et_2O and 2.04 mmol of MeLi in 3 ml of Et_2O, was cooled to −70 °C. While the solution was maintained at −60 to −70 °C,[40] a solution of 301 mg (2.06 mmol) of the ketone **22** and 207 mg (2.11 mmol) of the ketone **51** in 2 ml of Et_2O was added dropwise and with stirring. After the solution had been stirred for 15 min at −60 to −70 °C (during which time no reaction was apparent), it was allowed to warm to 3 °C during approximately 5 min; separation of significant quantities of $(MeCu)_n$ from the reaction solution occurred as the temperature rose above −35 °C. After the mixture had been stirred at 3 °C for 45 min, it was subjected to the usual isolation procedure; aliquots of the crude product were mixed with known amounts of an internal standard (either tetralin or n-$C_{12}H_{26}$) and subjected to GLC analysis (Carbowax 20M on Porasil). Employing a GLC analysis at 85 °C, the mixture contained ketone **53** (retention time 3.8 min, 21% yield), ketone **51** (6.6 min, 49% recovery), and n-$C_{12}H_{26}$ (11.0 min). At higher temperatures (158 °C), GLC analysis indicated the presence of tetralin (7.0 min) and ketone **22** (28.6 min, 100% recovery). Collected (GLC) samples of each of the ketones **22, 51,** and **53** were identified with authentic samples by comparison of GLC retention times and mass spectra.

B. Ketones 31 and 41. A solution of Me_2CuLi, from 209 mg (1.02 mmol) of Me_2SCuBr in 1.5 ml of Me_2S and 2 ml of Et_2O and 2.8 ml of an Et_2O solution containing 1.96 mmol of MeLi, was cooled to −72 °C and then a solution of 321 mg (2.0 mmol) of enone **31** and 411 mg (2.0 mmol) of acetoxy ketone **41** in 3 ml of Et_2O was added, dropwise with stirring and cooling. After the resulting orange solution had been stirred at −60 °C for 10 min,[40] it was allowed to warm to 3 °C during 5 min. Precipitation of $(MeCu)_n$ from the solution was observed as the temperature rose above −35 °C. The resulting mixture was stirred at 3 °C for 35 min and then subjected to the usual isolation procedure. The crude liquid product was mixed with a known weight of internal standard (tetralin) and subjected to GLC analysis (Carbowax 20M on Porasil). The product contained (GLC) tetralin (retention time 5.6 min), ketone **49** (9.3 min, 14% yield), ketone **52** (13.6 min, 3% yield), enone **31** (25.7 min, 77% recovery), hydroxy ketone **45** (32.1 min, ca. 8% yield), and the acetoxy ketone **41** (38.8 min, 67% recovery). Collected (GLC) samples of ketones **31, 49, 41, 45,** and **52** were identified with authentic samples by comparison of GLC retention time and mass spectra.

C. Ketones 31 and 51. After a solution of Me_2CuLi, prepared at 4 °C from 216 mg (1.05 mmol) of Me_2SCuBr in 1.5 ml of Me_2S and 2 ml of Et_2O and 2.04 mmol of MeLi in 3 ml of Et_2O, had been cooled to −70 °C, the solution was maintained at −60 to −70 °C[40] while a solution of 324 mg (2.03 mmol) of ketone **31** and 201 mg (2.05 mmol) of ketone **51** in 2 ml of Et_2O was added, dropwise, with stirring. After the resulting orange-colored mixture had been stirred at −70 °C for 10 min, it was warmed to 4 °C during approximately 5 min. During this warming, the orange color faded and a yellow precipitate of $(MeCu)_n$ separated as the solution was warmed above −30 °C. The reaction mixture was stirred at 4 °C for 25 min and at 27 °C for 20 min and then subjected to the usual isolation procedure. Aliquots of the crude product were mixed with known amounts of an internal standard (tetralin or n-$C_{12}H_{26}$) for GLC analysis (Carbowax 20M on Porasil). Analysis (GLC) at 85 °C indicated the presence of ketone **53** (retention time 3.9 min, 10% yield), ketone **51** (6.9 min, 49% recovery), and n-$C_{12}H_{26}$ (12.6 min). Analysis (GLC) at 170 °C indicated the presence of tetralin (retention time 5.7 min), ketone **52** (14.2 min, 11% yield), and ketone **31** (26.2 min, 36% recovery). Collected (GLC) samples of ketones **31, 51, 52,** and **53** were identified with authentic samples by comparison of GLC retention times and mass spectra.

Repetition of this experiment resulted in the following yields of products or reactants: **31,** 35%; **51,** 40%; **52,** 13%; and **53,** 7.4%. These consistently low yields (or recoveries) of products and reactants indicated that portions of these materials were being converted to higher molecular weight materials that were not eluted in our GLC analysis. This is presumably the result of Michael and/or aldol condensation of the product enolate anions with the excess enones present in the reaction mixture. In an effort to minimize this problem, a series of comparable reactions were performed in which the mixtures were quenched after shorter reaction times at lower reaction temperatures. In an experiment in which a cold reaction solution was warmed to −30 °C, stirred at −30 °C for 30 min, and then quenched, the yields were 93% of **31,** 86% of **51,** 6% of **52,** and 0.9% of **53.** When the reaction solution was warmed from −70 to −20 °C during 10 min and then quenched immediately, the yields were 96% of **31,** 86% of **51,** 3.8% of **52,** and 1.4% of **53.** When the cold (−70 °C) reaction solution was warmed to −10 °C during 10 min, stirred at −10 °C for 10 min, and then quenched, the yields were 97% of **31,** 79% of **51,** 3% of **52,** and 0.7% of **53.** Thus, it appears that the reaction of the more easily reduced enone **31** with Me_2CuLi is slightly more rapid than the corresponding reaction with the enone **51.**

Registry No.—**16,** 617-94-7; **17,** 21811-48-3; **18,** 59671-37-3; **19,** 59671-38-4; **25,** 5558-04-3; **26,** 59671-39-5; **27,** 59671-40-8; **28,** 1009-14-9; **29,** 59671-41-9; **30,** 1454-61-1; **32,** 94-41-7; **42,** 10409-54-8; **44,** 13694-96-7; **45,** 7473-98-5; **46,** 18913-16-1; **47,** 57625-74-8; **48,** 13836-62-9; **50,** 59671-42-0; **52,** 31366-07-1; **53,** 590-50-1; α-bromoisobutyric acid, 2052-01-9; Me_2CuLi, 15681-48-8.

References and Notes

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(2) (a) H. O. House and M. J. Umen, *J. Org. Chem.*, **38,** 3893 (1973); *J. Am. Chem. Soc.*, **94,** 5495 (1972); (b) H. O. House and P. D. Weeks, *ibid.*, **97,** 2770, 2778, 2785 (1975); (c) H. O. House, C.-Y. Chu, J. M. Wilkins, and M. J. Umen, *J. Org. Chem.*, **40,** 1460 (1975); (d) For a brief review, see H. O. House, *Acc. Chem. Res.*, **9,** 59 (1976).

(3) For an extensive survey of electrode potentials, see H. Siegerman in "Technique of Electroorganic Synthesis", Part II, N. L. Weinberg, Ed., Wiley-Interscience, New York, N.Y., 1975, pp 667–1056.

(4) The hyperfine coupling constants observed in the EPR spectra of benzaldehyde and acetophenone anion radicals suggest that about one-third of the spin density is centered at the carbonyl carbon atom with the remainder being distributed among the ortho, meta, and para positions of the benzene ring: P. B. Ayscough, "Electron Spin Resonance in Chemistry", Methuen, London, 1967, pp 274–279.

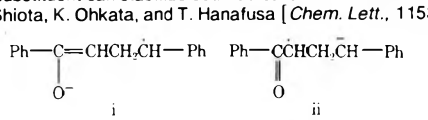
(5) One apparent example of this possibility is the reaction of various benzophenone derivatives with *t*-BuMgCl to form both products with the *t*-Bu group bound to the carbonyl carbon atom and dihydroaromatic products with the *t*-Bu group at the ortho or para position of the dihydroaromatic ring. T. Holm and I. Crossland, *Acta Chem. Scand.*, **25,** 59 (1971).

(6) (a) H. O. House and K. A. J. Snoble, *J. Org. Chem.*, following paper in this issue; (b) J. A. Marshall and R. A. Ruden, *ibid.*, **37,** 659 (1972).

(7) For examples of this type of reaction sequence with enones, see (a) D. J. Hannah and R. A. J. Smith, *Tetrahedron Lett.*, 187 (1975); (b) A. Nilsson and A. Ronlán, *ibid.*, 1107 (1975); (c) R. A. Ruden and W. E. Litterer, *ibid.*, 2043 (1975).

(8) E. Barreiro, J. L. Luche, J. Zweig, and P. Crabbé [*Tetrahedron Lett.*, 2353 (1975)] also reported obtaining only a low yield (13%) of the adduct **16** from ketone **12.** These authors obtained good yields (>90%) of 1,2 adducts from reaction of Me_2CuLi with both aromatic and aliphatic aldehydes.

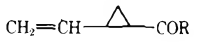
(9) The substantial decrease in the stability of the ketyl **6** with a phenyl substituent (from ketone **24**) when compared with the analogous ketyl with two methyl substituents (from ketone **23**) presumably reflects the fact that the phenyl substituent can stabilize both radical and carbanionic structures i and ii. H. Shiota, K. Ohkata, and T. Hanafusa [*Chem. Lett.*, 1153 (1974)]



i ii

have reported that exhaustive reduction of ketones **22** and **23** with Na in NH_3 yielded alkylated cyclopropanes whereas the comparable reduction of ketone **24** yielded 1,4-diphenylbutane. Although the latter result could be regarded as an example of the ion radical rearrangement 6 → **7,** the facts that ketone **24** reacts with Me_2CuLi without appreciable ring opening

and that anion radical intermediates appear to have longer lifetimes in cuprate reactions than in metal-NH_3 reductions (ref 2b,d) lead us to believe that this ring opening occurred after initial reduction of the carbonyl group.
(10) (a) H. O. House, *Proc. Robert A. Welch Found. Conf. Chem. Res.*, **16**, 101-149 (1973); (b) C. R. Johnson, R. W. Herr, and D. M. Wieland, *J. Org. Chem.*, **38**, 4263 (1973).
(11) For various examples of this reaction, see (a) E. J. Corey and P. L. Fuchs, *J. Am. Chem. Soc.*, **94**, 4014 (1972); (b) G. Daviaud and P. Miginiac, *Tetrahedron Lett.*, 997 (1972); (c) R. D. Clark and C. H. Heathcock, *ibid.*, 529 (1975); (d) P. A. Grieco and R. Finkelhor, *J. Org. Chem.*, **38**, 2100 (1973); (e) For a study of the reactions of Me_2CuLi with other esters, see S. A. Humphrey, J. L. Herrmann, and R. H. Schlessinger, *Chem. Commun.*, 1244 (1971).
(12) N. Miyaura, M. Itoh, N. Sasaki, and A. Suzuki [*Synthesis*, 317 (1975)] have reported successful ring opening reactions with cuprates and ketones of the type iii. We presume that these reactions, like the analogous reaction



iii, R = Me, Ph

iv

with iv (see ref 11d), are instances in which nucleophilic ring opening with cuprate reagents is sufficiently rapid to compete with other possible side reactions.
(13) J. G. Aston, J. T. Clarke, K. A. Burgess, and R. B. Greenburg, *J. Am. Chem. Soc.*, **64**, 300 (1942).
(14) For examples and leading references, see (a) C. Lion and J. E. Dubois, *Tetrahedron*, **31**, 1223, 1227 (1975); (b) G. H. Posner, J. J. Sterling, C. E. Whitte*, C. M. Lentz, and D. J. Brunelle, *J. Am. Chem. Soc.*, **97**, 107 (1975); (c) J. E. Dubois, P. Fournier, and C. Lion, *Tetrahedron Lett.*, 4263 (1975).
(15) H. O. House and C. Y. Chu, *J. Org. Chem.*, accompanying paper in this issue.
(16) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The ^1H NMR spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60-A NMR spectrometer and the ^{13}C NMR spectra were determined at 100 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) Model RMU-7 or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.
(17) G. M. Whitesides, C. P. Casey, and J. K. Krieger, *J. Am. Chem. Soc.*, **93**, 1379 (1971).
(18) (a) G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 7788 (1973); (b) G. H. Posner and C. E. Whitten, *Org. Synth.*, **55**, 122 (1975).
(19) V. Volmar, *C. R. Acad. Sci.*, **150**, 1174 (1910); *Chem. Abstr.*, **4**, 2098 (1910).
(20) P. Ramart-Lucas and J. Hoch, *Bull. Soc. Chim. Fr.*, 422 (1952).
(21) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
(22) J. M. Conia, J. C. Limasset, and P. Amice, *Bull. Soc. Chim. Fr.*, 3981 (1969).
(23) Our product was identified with an authentic sample by comparison of ir spectra. We are grateful to Professor James A. Marshall for providing this authentic sample.
(24) (a) C. R. Johnson, R. A. Kirchoff, R. J. Reischer, and G. F. Katekar, *J. Am. Chem. Soc.*, **95**, 4287 (1973); (b) F. Rocquet and A. Sevin, *Bull. Soc. Chim. Fr.*, 888 (1974); (c) U. Mende, B. Radüchel, W. Skuballa, and H. Vorbrüggen, *Tetrahedron Lett.*, 629 (1975); (d) In order to separate the ketone **24** from small amounts of residual starting benzalacetophenone, the product was initially purified by chromatography on alumina with pentane as an eluent.
(25) We are grateful to Professor Erling Grovenstein and Dr. Leslie Gelbaum for an authentic sample of this ketone. It was prepared by the addition of PhMgBr to 1-cyano-2,2-dimethylcyclopropane [E. R. Nelson, M. Maienthal, L. A. Lane, and A. A. Benderly, *J. Am. Chem. Soc.*, **79**, 3467 (1957)]. The preparation of this ketone has been described by J. M. Watson, J. L. Irvine, and R. M. Roberts, *ibid.*, **95**, 3348 (1973).
(26) M. Oki and M. Hirota, *Bull. Chem. Soc. Jpn.*, **36**, 290 (1963).
(27) (a) C. L. Stevens, P. Blumbergs, and M. Munk, *J. Org. Chem.*, **28**, 331 (1963); (b) S. Hunig and G. Weihner, *Synthesis*, 391 (1975).
(28) For examples and leading references concerning the reaction of α-bromo ketones with Ag^+ ion to form either esters or α-alkoxy ketones, see (a) D. N. Kevill and N. H. Cromwell, *J. Org. Chem.*, **29**, 499 (1964); (b) D. J. Pasto and K. Garves, *ibid.*, **32**, 778 (1967); (c) D. Baudry and M. Charpentier-Morize, *Tetrahedron Lett.*, 3013 (1973); D. Baudry J. P. Begue, and M. Charpentier-Morize, *ibid.*, 4707 (1970); J. P. Begue, M. Charpentier, and C. Pardo, *Tetrahedron*, **31**, 1919 (1975).
(29) K. von Auwers and H. Mauss, *Biochem. Z.*, **192**, 200 (1928).
(30) (a) H. O. House and E. F. Kinloch, *J. Org. Chem.*, **39**, 1173 (1974); (b) H. O. House, D. Koepsell, and W. Jaeger, *ibid.*, **38**, 1167 (1973).
(31) (a) K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger, and D. K. Roe, *J. Am. Chem. Soc.*, **92**, 2783 (1970); (b) R. N. Adams, "Electrochemistry at Solid Electrodes", Marcel Dekker, New York, N.Y., 1969, pp 143-158.
(32) Ramart-Lucas, *Ann. Chim. (Paris)*, **30**, 353 (1913).
(33) A. Maercker and J. D. Roberts, *J. Am. Chem. Soc.*, **88**, 1742 (1966).
(34) L. I. Smith and V. A. Engelhardt, *J. Am. Chem. Soc.*, **71**, 2671 (1949).
(35) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2012 (1950).
(36) The doublet observed for the carbonyl peak of ketone **29**, which is analogous to the doublet at 1691 and 1677 cm^{-1} observed for $PhCOCH_2Bu$-*t* [H. O. House and E. J. Grubbs, *J. Am. Chem. Soc.*, **81**, 4733 (1959)], is apparently attributable either to the presence of two conformations of these ketones or to Fermi resonance.
(37) (a) A. C. Lespagnol, J. Claude, and M. Cazin, *Bull. Soc. Chim. Fr.*, 1507 (1964); (b) E. Middleton, *J. Am. Chem. Soc.*, **45**, 2763 (1923).
(38) (a) L. B. Jones and J. P. Foster, *J. Org. Chem.*, **35**, 1777 (1970); (b) R. R. Dreisbach and R. A. Martin, *Ind. Eng. Chem.*, **41**, 2875, 2877 (1949).
(39) (a) H. O. House, E. J. Grubbs, and W. F. Gannon, *J. Am. Chem. Soc.*, **82**, 4099 (1960); (b) W. A. Mosher and J. C. Cox, *ibid.*, **72**, 3701 (1950).
(40) Since neither of the ketones used reacts with Me_2CuLi at -60 °C, this procedure was followed to ensure complete mixing of the cuprate and the ketones before any reaction occurred.

Reactions Involving Electron Transfer. 10. The Use of β-Cyclopropyl α,β-Unsaturated Ketones to Detect Anion Radical Intermediates[1]

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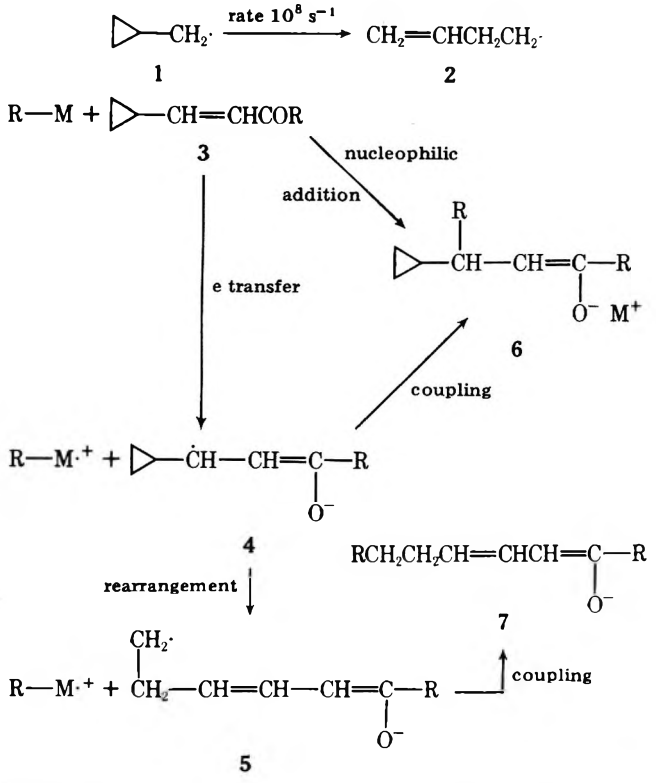
The cyclopropyl enone **16** has been prepared as an example of an enone whose anion radical **39** will have a geometry very favorable for the rearrangement **39** → **40**. Reaction of this enone **16** with Me_2CuLi yielded a mixture of rearranged product **33** (72% of the product) and unrearranged product **32** (28% of the product). This observation is considered compelling evidence that this reaction is proceeding by an initial electron transfer step rather than a direct nucleophilic addition. As part of the synthesis of the enone **16**, a new procedure was developed for the dehydration of the aldol intermediate **25** or **26** to form mainly the α,β isomer **16** rather than the β,γ isomer **30**.

Among various experimental tests that might be applied to distinguish between addition reactions proceeding by a polar nucleophilic addition and by a two-stage reaction involving initial electron transfer,[2] we were encouraged to study β-cyclopropyl α,β-unsaturated ketones **3** as reaction substrates because of the rapidity with which a cyclopropylcarbinyl radical **1** (see Scheme I) rearranges to a 3-butenyl radical **2**.[3] The nucleophilic addition of an organometallic reagent RM (or other nucleophile) to such an enone **3** could be expected to form an unrearranged product **6**. However, if the initial step

Scheme I

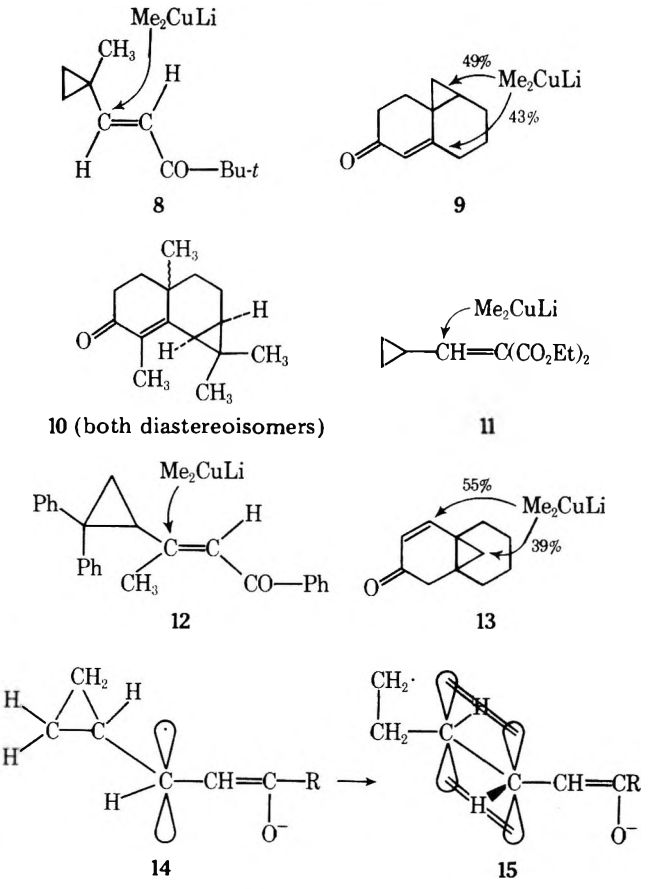


involved transfer of only an electron, the resulting anion radical intermediate **4** could follow two different pathways leading to addition products. In cases where recombination of the ion radical intermediates was *faster* than the intramolecular rearrangement **4** → **5** of the anion radical **4**, the same unrearranged product **6** would result. Alternatively, if the rate of rearrangement **4** → **5** was *faster than* or *comparable to* the rate of coupling of the ion radical intermediates, then at least part of the product would be the rearranged adduct **7** rather than **6**. This later result would be particularly useful in supplying evidence that the electron-transfer step lies on the reaction path leading to an addition product and is not merely a parasitic equilibrium that is unrelated to the formation of addition products.

For this experimental test to be useful, it was clear that the lifetime of the anion radical **4** formed in a two-stage addition process must be sufficient to permit the rearrangement **4** → **5** to be at least competitive with the recombination of ion radical intermediates. Earlier study[4] of this idea employed conjugate addition of lithium dimethylcuprate and conjugate reduction with solutions of lithium in ammonia as model reactions that almost certainly involve an initial electron transfer.[2] Among the β-cyclopropyl enones **8**–**10** (Scheme II) examined, cyclic voltammetry measurements indicated the half-lives of the anion radicals from these enones to be **8**, 10^{-2} s; **9**, 10^{-3} s; **10**, $<10^{-3}$ s. Thus, the delocalization of the unpaired electron possible in the enone anion radicals **4**, but not in radical **1**, resulted in rearrangement **4** → **5** being slower than **1** → **2** by a factor of 10^4–10^6.

Since both enone systems **8**[4] and **10**[5] were reduced without rearrangement by Li–NH_3 solutions, we concluded that the lifetime of the enone anion radical present in these reactions was $<10^{-4}$ s. In reactions with Me_2CuLi (see Scheme II), only unrearranged product was isolated from enone **8** whereas about equal amounts of rearranged and unrearranged product were obtained from enone **9**.[6] These observations suggested a lifetime of about 10^{-3} s for the enone anion radical formed during these Me_2CuLi–enone reactions. In other studies involving Me_2CuLi addition, both of the unsaturated carbonyl compounds **11**[7] and **12**[8] gave unrearranged addition products

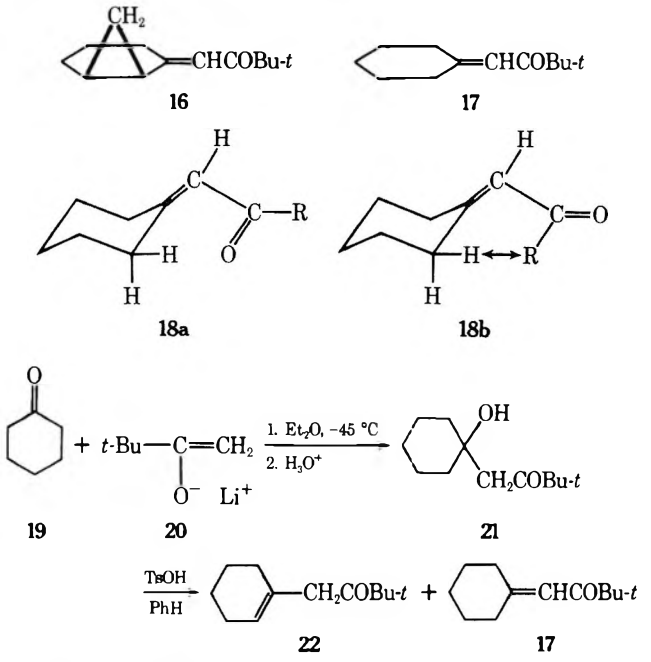
Scheme II



whereas the enone **13**[6] gave comparable amounts of rearranged and unrearranged products. These various results suggest that the anion radical rearrangement **4** → **5** is definitely more rapid with anion radicals derived from the polycyclic enones **9**, **10**, and **13** than with the anion radicals from unsaturated carbonyl compounds **8**, **11**, and **12**. Since even the enone **12**, containing two phenyl substituents that could stabilize a rearranged radical ion (cf. **5**), gave an unrearranged product with Me_2CuLi,[8] the presence of substituents on the cyclopropane ring is apparently not particularly effective in increasing the rate of the rearrangement **4** → **5**. Instead, it appeared that the appropriate structural feature to enhance this rate of rearrangement **4** → **5** would be to prepare cyclopropyl enones whose structures would maintain the geometry of the anion radical indicated in structure **14**. This arrangement **14**, with one cyclopropyl C–C bond and the p orbital at the β carbon in the same plane and approximately parallel, would offer the best opportunity for continuous orbital overlap during the rearrangement **14** → **15**. Such a geometrical arrangement is maintained in each of the enones **9**, **10**, and **13** but is not required in systems **8**, **11**, and **12**.

Since rapid rearrangement **4** → **5** is one of the requirements of a β-cyclopropyl enone system **3** if it is to be useful in testing for an anion radical intermediate, we sought to prepare an enone system **3**, different from the octalone derivatives **9**, **10**, and **13**, that would meet the geometrical requirements of structure **14**. This paper describes the preparation of such a derivative, the β-cyclopropyl enone **16**, as well as the related model substance **17** (Scheme III). Both of these compounds, like previously studied α-cyclohexylidene ketones and esters,[9] are believed to exist in the cisoid conformation **18a** in order to avoid a serious nonbonding interaction (arrow in structure **18b**) that would be present in the transoid conformation **18b**. Thus, although the enone **16** and the decalones **9**, **10**, and **13** share the geometric feature (structure **14**) believed appropriate for rapid rearrangement **14** → **15** of the anion radical,

Scheme III



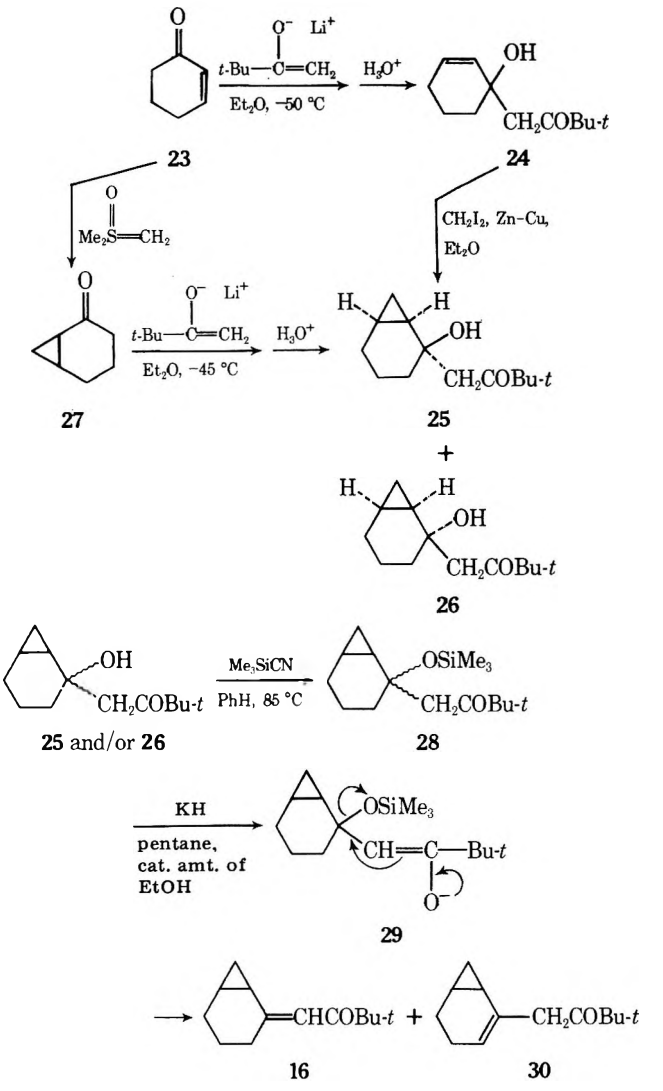
in other respects the cisoid enone **16** and the transoid enones **9**, **10**, and **13** have quite different geometries.

The model enone **17** was readily synthesized (Scheme III) by use of a directed aldol condensation[10] followed by acid-catalyzed dehydration of the hydroxy ketone **21**. Although prolonged contact with this acid catalyst gave a mixture of enones **17** and **22** containing mainly the more stable β,γ isomer **22**, under carefully controlled dehydration conditions the initially formed conjugated isomer **17** was the major reaction product.

We had hoped to obtain the cyclopropyl enone **16** by an analogous process involving initial aldol condensation of the enolate **20** with the cyclopropyl ketone **27** (Scheme IV). Unfortunately, in spite of considerable experimentation, we were able to effect this aldol condensation only in ca. 25% yield with the remaining bicyclic ketone **27** being recovered unchanged. The products from this aldol reaction were the diastereoisomeric ketols **25** (minor product) and **26** (major product). A more satisfactory route to these ketols **25** and **26** involved initial condensation of the enolate **20** with cyclohexenone (**23**) to yield the hydroxy ketone **24**.[11] Reaction of this allylic alcohol **24** with the CH_2I_2–Zn–Cu reagent[12] afforded a mixture of the diastereoisomeric ketols **25** (major) and **26** (minor). The major diastereoisomer formed in this reaction was assigned the stereochemistry **25** based on the expectation[12] that the cyclopropyl CH_2 group should be introduced cis to the allylic hydroxyl group.

Our efforts to obtain the desired enone **16** by acid-catalyzed dehydration of the ketols **25** and/or **26** also posed an unexpected difficulty since the ketols **25** and **26** dehydrated only under conditions more vigorous than those required to dehydrate the model ketol **21**. As a result all of our successful acid-catalyzed dehydration experiments yielded mixtures of enones **16** and **30** in which the more stable β,γ isomer **30** was the major product. To circumvent this problem we elected to convert the acid- and base-labile ketols **25** and **26** to their trimethylsilyl ethers **28**. Although the conventional silylating procedures were unsatisfactory, heating the ketols **25** and **26** with Me_3SiCN with escape of the HCN as it formed did allow us to achieve the desired silylation under essentially neutral conditions. Subsequent reaction of the β-trimethylsilyloxy ketone **28** with KH and a catalytic amount of EtOH effected the desired elimination (see structure **29**) to give a mixture of enones **16** and **30** containing primarily the desired conjugated

Scheme IV

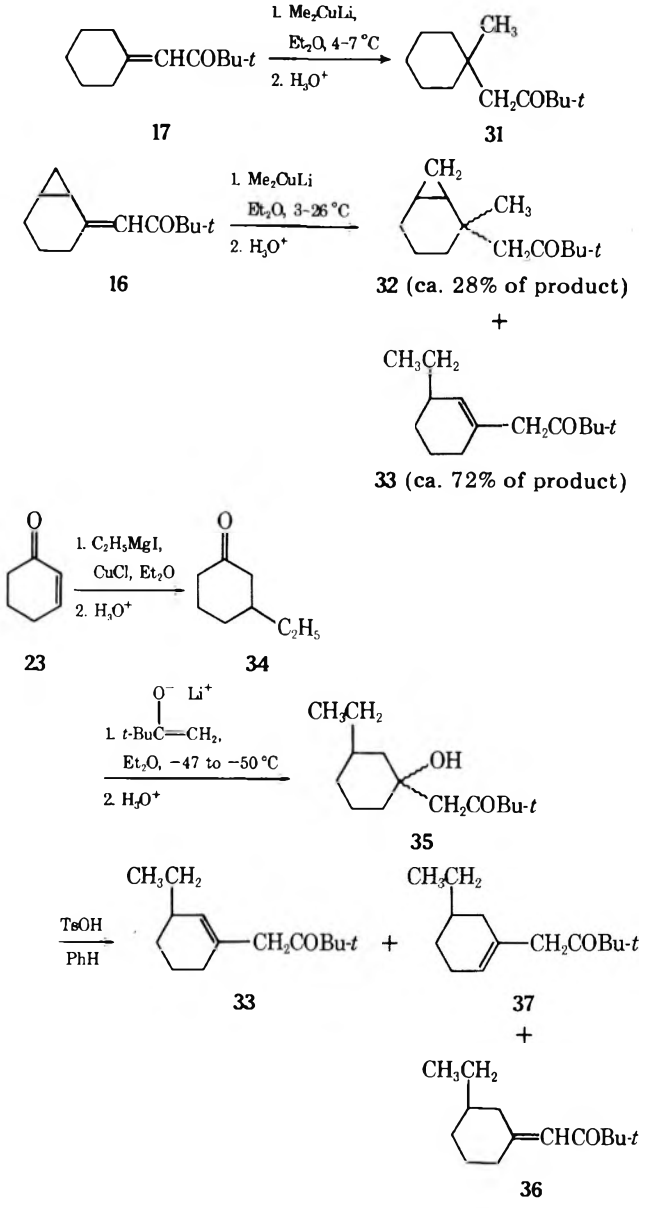


isomer **16**. It is appropriate to note that the ketone **28**, formed in the presence of Me_3SiCN (which is an efficient scavenger for alcohol impurities), failed to react with the KH suspension to form the enolate **29** until a catalytic amount of alcohol was added. These observations suggest that KH, like NaH,[13] does not react directly with ketones to form enolates but rather reacts with some alcohol present to form a potassium alkoxide that abstracts a proton from the ketone.

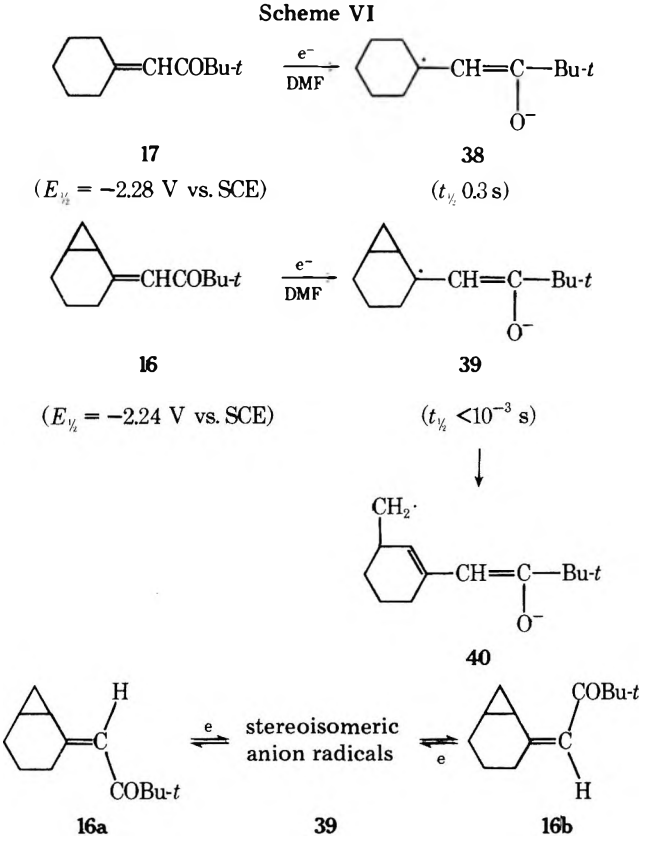
Reaction of the model enone **17** with Me_2CuLi formed the expected conjugate addition product **31** (Scheme V). The same reaction with the cyclopropyl enone **16** afforded a mixture of structurally isomeric products in which the unrearranged adduct **32** (a mixture of diastereoisomers) was the minor product accompanied by the rearranged adduct **33**. To establish the structure of the rearranged product **33**, the crude ketol **35**, obtained from ketone **34** and enolate **20**, was dehydrated with acid to yield a mixture of the rearranged adduct **33** and at least two other products believed to be the isomeric enones **36** and **37**.

Although the polarographic reduction potentials of the two enones **16** and **17** (Scheme VI) were approximately the same, reduction by cyclic voltammetry demonstrated that the stabilities of the initial anion radical products **38** and **39** were very different. In particular, the half-life ($<10^{-3}$ s) of the anion radical **39** derived from the cyclopropyl enone **16** was significantly less than the half-life for **38** (0.3 s) and was comparable to the values previously observed for the octalone derivatives **9** and **10**. Both this observation and the fact that the enone **16** reacted with Me_2CuLi to form mainly rearranged product **33**

Scheme V



Scheme VI



are consistent with the hypothesis that the anion radical rearrangement **4** → **5** can be expected to be most rapid when the anion radical is held in the geometric arrangement shown in structure **14.**

Thus, in the reaction of Me_2CuLi with the various cyclopropyl enones **8, 9,** and **16,** there is a clear relationship between the stability of the enone anion radicals and the formation of a rearranged product. Consequently, the reaction of the cyclopropyl enone **16** with Me_2CuLi to form mainly the rearranged adduct **33** provides compelling evidence that *the major reaction pathway in this case involves initial formation of an anion radical intermediate* **39** *and not initial nucleophilic addition to enone* (as in structure **6,** Scheme I).

A stereochemical result of incidental interest was also observed in the reaction of enone **16** with Me_2CuLi. After preparation of the enone **16** (Scheme IV), purification by a combination of preparative liquid chromatography and low temperature crystallization separated the two geometrical isomers **16a** and **16b** of enone **16.** We have tentatively assigned stereochemistry to these isomers **16a** [λ_{max} 263 nm (ε 14 800), eluted first from silica gel] and **16b** [λ_{max} 264 nm (ε 9260), eluted second from silica gel] based on the assumption that isomer **16a** will have less steric hinderance to coplanarity so that its ultraviolet absorption maximum would be expected to have a larger extinction coefficient. In agreement with this sterochemical assignment, the NMR spectrum of isomer **16a** exhibits a signal for the allylic CH_2 group at unusually low field as expected[9] for this isomer **16a** in a cisoid conformation **18a.** Similarly, the NMR spectrum of isomer **16b** (also in the cisoid conformation **18a**) exhibits a signal for the allylic cyclopropyl CH group at unusually low field. After reaction of this enone (12% **16a** and 88% **16b**) with Me_2CuLi, the small amount of enone **16** recovered contained appreciable amounts of both stereoisomers (29% **16a** and 71% **16b**). Although the mechanistic significance of this observation is dubious, the result is compatible with our previous observations[2,14] that a catalytic amount of an anion radical (e.g., **39**) can catalyze the interconversion of stereoisomeric enones such as **16a** and **16b.**

This observation does raise the question: is the stereochemical isomerization of β-cyclopropyl enones **16a** ⇌ **16b,** catalyzed by electron exchange with a small amount of the anion radical **39,** faster than the structural isomerization **39** → **40?** Earlier indirect evidence[2,14] had suggested that this was the case. To explore this question in a more direct manner, a DMF solution of the enone **16b** (which was stable if not electrolyzed) was subjected to partial controlled-potential electrolysis to convert approximately 1% of the enone **16b** to its anion radical **39.** The enone **16** recovered from this partial electrolysis was a mixture of 37% of isomer **16a** and 63% isomer **16b.** Partial isomerization of the conjugated enones **16** to the more stable β,α isomer **30** also occurred as a result of catalysis by the base produced during the partial electrolysis. However, several control experiments (see Experimental Section) established that further equilibration accompanying this base-catalyzed isomerization **16** → **30** could not account for the amount of stereochemical isomerization **16b** → **16a** observed in the partial electrolysis experiment. Consequently, these observations provide direct evidence that the interconversion of stereoisomeric enones such as **16a** and **16b** by electron exchange with their anion radical **39** is more rapid than anion radical structural isomerizations such as **39** → **40.**

Experimental Section[15]

Aldol Condensation with Cyclohexanone (19). To a cold (−45 °C) pink-orange solution of *i*-Pr_2NLi, prepared by the dropwise addition of 15.7 ml of a hexane solution containing 24 mmol of *n*-BuLi to a cold (−72 °C), stirred solution of 2.593 g (25.6 mmol) of *i*-Pr_2NH and several milligrams of 2,2′-bipyridyl (an indicator) in 54 ml of Et_2O, was added, dropwise and with stirring, 2.319 g (23.2 mmol) of pinacolone. After the resulting yellow-orange solution of the enolate **20** had been stirred at −45 °C for 50 min, a solution of 2.310 g (23.5 mmol) of cyclohexanone (**19**) in 5 ml of Et_2O was added to the cold solution, dropwise and with stirring during 8 min. After the resulting pale yellow solution had been stirred at −45 °C for 15 min, it was poured into 150 ml of cold (0 °C) aqueous 1 M HCl. The combined Et_2O layer and Et_2O extract of the aqueous phase were washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and concentrated. The residual crude aldol product **21**, 4.535 g of white solid, was recrystallized from pentane to separate 3.604 g (78.5%) of the pure aldol **21** as white needles: mp 61–62 °C; ir (CCl_4) 3490 (OH) and 1692 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.17 (1 H, s, OH, exchanged with D_2O), 2.61 (2 H, s, CH_2CO), 1.2–2.0 (10 H, m, aliphatic CH), and 1.11 (9 H, s, *t*-Bu); uv max (95% EtOH) 290.5 nm (ϵ 37); mass spectrum *m/e* (rel intensity) 198 (M^+, 1), 180 (11), 141 (30), 123 (86), 100 (55), 99 (85), 98 (70), 95 (30), 85 (51), 83 (21), 81 (88), 70 (37), 69 (45), 67 (24), 57 (100), 56 (40), 55 (77), 53 (23), 43 (62), 42 (61), 41 (65), and 39 (46).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.78; H, 11.20.

A series of small-scale experiments were performed in which solutions of 0.5 mmol of the aldol **21** in 4.2 ml of PhH were mixed with various amounts of *p*-TsOH and refluxed for various periods of time. The resulting mixtures were partitioned between Et_2O and aqueous $NaHCO_3$ and the Et_2O solutions were dried, concentrated, and analyzed by NMR (CCl_4) employing the vinyl CH signals at δ 6.13 (attributable to **17**) and 5.38 (attributable to **22**). With 0.5 mmol of the aldol **21**, 0.026 mmol (5 mol %) of *p*-TsOH, and a reflux period of 30 min, dehydration was complete and the mixture contained ca. 77% of the conjugated olefin **17** and ca. 23% of the unconjugated olefin **22**. With less acid catalyst or shorter reaction times, the dehydration was incomplete while longer reaction times resulted in mixtures containing increased amounts of the unconjugated isomer **22**. The mixture of isomers could also be analyzed by use of GLC (TCEP on Chromosorb P) using peaks for olefins **17** (retention time 21.8 min) and **22** (25.0 min), although some interconversion of **17** and **22** during GLC analysis was observed.

After a solution of 1.986 g (10.0 mmol) of the aldol **21** and 104 mg (0.55 mmol) of *p*-TsOH in 84 ml of PhH had refluxed for 36 min with continuous separation of H_2O and then subjected to the previously described isolation procedure, 1.913 g of the crude mixture (GLC) of olefins **17** (ca. 83%) and **22** (ca. 17%) was obtained. Fractional crystallization of this mixture from pentane at dry ice temperatures enriched the conjugated isomer **17** in the crystalline fractions and the nonconjugated isomer **22** in the mother liquors. After two crystallizations, the pure (ir analysis) conjugated isomer **17** was obtained as 1.226 g (70%) of colorless liquid, $n^{25}D$ 1.4797. A collected (GLC) sample of the conjugated olefin **17** was obtained as a colorless liquid: $n^{25}D$ 1.4801;[16] ir (CCl_4) 1680 (conjugated C=O) and 1618 cm^{-1} (conjugated C=C); uv max (95% EtOH) 238 nm (ϵ 14 500) and 324.5 (102); NMR (CCl_4) δ 6.13 (1 H, m, vinyl CH), 1.4–3.1 (10 H, m, aliphatic CH), and 1.10 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 180 (M^+, 10), 123 (100), 95 (16), 55 (28), 54 (23), and 41 (17).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.82; H, 11.20.

A collected (GLC) sample of the unconjugated olefin **22** was obtained as a colorless liquid: $n^{25}D$ 1.4673; ir (CCl_4) 1710 cm^{-1} (C=O); uv max (95% EtOH) 293.5 nm (ϵ 71); NMR (CCl_4) δ 5.38 (1 H, m, vinyl CH), 3.02 (2 H, broad s, CH_2CO), 1.3–2.3 (8 H, m, aliphatic CH), and 1.09 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 180 (M^+, 8), 123 (14), 85 (25), 57 (100), 41 (18), and 40 (17).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.95; H, 11.18.

Aldol Condensation with Cyclohexenone (23). To a cold (−50 °C) solution of *i*-Pr_2NLi, from 10.70 g (106 mmol) of *i*-PrNH, 67 ml of a hexane solution containing 105 mmol of *n*-BuLi, and 150 ml of Et_2O, was added, dropwise and with stirring, 10.22 g (102 mmol) of pinacolone. After the enolate solution had been stirred at −50 °C for 45 min, a solution of 9.886 g (103 mmol) of cyclohexenone (**23**) in 20 ml of Et_2O was added, dropwise and with stirring during 5 min. After the reaction solution had been stirred at −50 °C for 10 min, it was poured into cold (0 °C), aqueous 1 M HCl and then subjected to the previously described isolation procedure. The crude neutral liquid product was concentrated at 85 °C and 0.05 mm pressure to leave 18.58 g (93%) of the crude aldol product **24** as a yellow liquid. Two crystallizations from pentane at −50 °C separated 6.63 g (33%) of the aldol product **24** as colorless plates, mp 26–29 °C. An additional crystallization gave the aldol product **24** as colorless plates, mp 31–33 °C, that appeared to react rapidly if exposed to air: ir (CCl_4) 3490 (OH) and 1690 cm^{-1} (C=O); uv max (95% EtOH) 292.5 nm (ϵ 19); NMR (CCl_4) δ 5.3–5.8 (2 H, m, vinyl CH), 3.83 (1 H, broad s, OH), 2.60 (2 H, s, CH_2CO), 1.3–2.3 (6 H, m, aliphatic CH), and 1.10 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 178 (2), 121 (7), 100 (11), 97 (16), 96 (17), 68 (92), 57 (100), 43 (50), 42 (25), 41 (100), 40 (34), and 39 (75).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.36; H, 10.28.

Preparation of the Hydroxy Ketone 25. To a suspension of 7.204 g of Zn–Cu couple[17] in 35 ml of Et_2O containing several milligrams of I_2 was added, dropwise and with stirring during 10 min, 23.11 g (86 mmol) of CH_2I_2. After the resulting mixture had been heated to 40 °C for 70 min, a solution of 7.791 g (39.7 mmol) of the hydroxy olefin **24** in 8 ml of Et_2O was added, dropwise and with stirring during 22 min. After the reaction mixture had been refluxed for 23 h, it was partitioned between Et_2O and aqueous NH_4Cl. The Et_2O solution was washed successively with aqueous K_2CO_3 and with aqueous NaCl and then dried over Na_2SO_4 and concentrated (finally at 48 °C and 0.4 mm to remove CH_2I_2). The residual yellow oil, 7.290 g, which slowly solidified on standing, was fractionally recrystallized from pentane at −25 °C to separate 2.477 g (29.7%) of the pure hydroxy ketone **25** as white needles: mp 47.7–48.4 °C; ir (CCl_4), 3510 (OH), 3060 (cyclopropyl CH), and 1695 cm^{-1} (C=O); uv max (95% EtOH) 294 nm (ϵ 34); NMR (CCl_4) δ 3.61 (1 H, broad s, OH), 2.76 (2 H, s, CH_2CO), 1.1–2.0 (8 H, m, aliphatic CH), 1.14 (9 H, s, *t*-Bu), and 0.3–0.8 (2 H, m, cyclopropyl CH_2); mass spectrum *m/e* (rel intensity) 210 (M^+, 1), 110 (18), 67 (23), 57 (100), 55 (36), 54 (30), 43 (31), 41 (59), and 39 (27).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.25; H, 10.56.

The NMR spectrum of the crude product, before separation of ketone **25** by recrystallization, suggests that in addition to the major product, ketone **25**, a small amount of the stereoisomeric ketone **26** is also present.

Preparation of the Hydroxy Ketone 26. A previously described procedure[18] was used to convert cyclohexenone (**23**) to the cyclopropyl ketone **27** (57% yield), bp 36–37 °C (0.25–0.3 mm), $n^{25}D$ 1.4871 [lit. bp 91 °C (15 mm),[19a] $n^{25}D$ 1.4878[19b]]. To a cold (−45 °C) solution of *i*-Pr_2NLi, from 526 mg (5.20 mmol) of *i*-Pr_2NH, 3.18 ml of a hexane solution containing 4.99 mmol of *n*-BuLi, and 50 ml of Et_2O, was added, dropwise and with stirring, 519 mg (5.18 mmol) of pinacolone. After the cold solution of the enolate **20** had been stirred for 38 min, a solution of 598 mg (5.43 mmol) of the cyclopropyl ketone **27** in 2 ml of Et_2O was added, dropwise and with stirring during 1.8 min. The resulting solution was stirred at −45 to −50 °C for 15 min and then poured into 50 ml of cold (0 °C) aqueous 1 M HCl and subjected to the usual isolation procedure. The concentration of the crude neutral product was completed with warming at 0.1 mm pressure to facilitate removal of the unchanged pinacolone and cyclopropyl ketone **27**. Analysis (NMR) of the residual crude product suggested that the total yield of aldol product was about 25% and that the crude product contained mainly the hydroxy ketone **26** accompanied by minor amounts of the stereoisomer **25**. Crystallization of this crude product from cold pentane separated 142 mg (13.5%) of the pure hydroxy ketone **26** as white plates: mp 60–61 °C; ir (CCl_4) 3490 (OH), 3060 (cyclopropyl CH), and 1695 cm^{-1} (C=O); uv max (95% EtOH) 292 nm (ϵ 30); NMR (CCl_4) δ 3.99 (1 H, broad s, OH), an AB pattern (J = 17 Hz) with signals at 2.79 and 2.44 (2 H, CH_2CO), 1.0–2.0 (17 H, m, aliphatic CH including a *t*-Bu singlet at 1.12) and multiplets at 0.5–0.9 and −0.4 to −0.1 (2 H, cyclopropyl CH_2); mass spectrum *m/e* (rel intensity) 192 (3), 135 (12), 110 (19), 100 (17), 67 (20), 57 (100), 55 (24), 54 (25), 43 (26), 41 (52), 40 (27), and 39 (24).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.23; H, 10.56.

Preparation of the Unsaturated Ketones 16 and 30. Preliminary experiments in which PhH solutions of the ketols **25** and **26** and TsOH were heated for varying periods of time indicated that the conditions required to dehydrate the ketols also caused isomerization of the conjugated enone **16** to its β,γ isomer **30** so that the product mixture contained mainly ketone **30**. To explore an alternative procedure, Me_3SiCN was prepared by a published procedure[20] in which a mixture of 116.2 mg (0.44 mmol) of 18-crown-6 polyether, 6.596 g (101 mmol) of anhydrous KCN, 12 g (0.11 mmol) of Me_3SiCl, and 20 ml of anhydrous CH_2Cl_2 was refluxed with stirring for 36 h. Fractional distillation of the mixture through a 10-cm Vigreux column separated 3.712

g (37%) of Me_3SiCN as a colorless liquid: bp 114–116.5 °C (lit. bp 114–117,[21a] 117.9–118.2[21b]); ir (CCl_4) 2195 cm^{-1} (C≡N); NMR (CCl_4) δ 0.33 (s, CH_2Si). A solution of 2.095 g (9.96 mmol) of the hydroxy ketones **25** and **26** in 3.0 ml of Me_3SiCN and 1.0 ml of PhH was heated to 85 °C under an N_2 atmosphere for 20 h and then concentrated under reduced pressure and shaken with a mixture of 30 ml of pentane and 30 ml of cold (0 °C) aqueous buffer (pH 7) to remove any residual Me_3SiCN.[22] The pentane solution was dried (Na_2SO_4) and concentrated to leave 2.23 g (97%) of the crude siloxy ketone **28** as a yellow liquid: NMR (CCl_4) δ 2.87 (s), 2.6–2.7 (m, CH_2CO of two diastereoisomers in a ratio of ca. 6:1), 0.9–2.2 (m, aliphatic CH including a *t*-Bu singlet at 1.10), and 0.05–0.8 [m, cyclopropyl CH including a $(CH_3)_3SiO$ singlet at 0.09].

To a cold (−5 °C) solution of 2.21 g (7.82 mmol) of the siloxy ketone **28** and 2.5 μl (0.07 mmol) of EtOH[22] in 20 ml of pentane was added, portionwise and with stirring during 2.5 min, 316 mg (7.9 mmol) of KH (washed with pentane). The cold, orange-colored reaction mixture was stirred for an additional 5.5 min and then poured into 30 ml of cold (0 °C) aqueous buffer (pH 7) and extracted with pentane. The pentane extract was washed with aqueous NaCl, dried (Na_2SO_4), and concentrated to leave 1.61 g of yellow liquid containing (NMR analysis) the conjugated enone **16** (ca. 75%, a mixture of stereoisomers) and the isomeric ketone **30** (ca. 25%). This mixture was subjected to fractional crystallization from pentane at −70 °C to separate 624 mg of the enone **16** (a mixture of stereoisomers) that melted as it warmed to room temperature to form a colorless liquid, $n^{25}D$ 1.5092. The mother liquors from this fractional crystallization were subjected to preparative liquid chromatography (silica gel with 1.5% Et_2O in hexane as an eluent) to separate early fractions containing the unconjugated ketone **30** and later fractions containing the conjugated isomers **16**. Fractional crystallization of these latter fractions from pentane at −70 °C separated an additional 228 mg of the enones **16** (total yield 852 mg or 56%): ir (CCl_4) 1675 (conjugated C=O) and 1595 cm^{-1} (conjugated C=C);[23] uv max (95% EtOH) 264 nm (ε 11 900) and 330 (shoulder, 168); NMR (CCl_4) δ 6.37 (t, *J* = 2.0 Hz, vinyl CH of minor stereoisomer) and 6.1–6.3 (m, vinyl CH of major stereoisomer, total 1 H), 2.0–3.2 (2 H, m, allylic CH_2 including an apparent triplet of doublets, *J* = 2.0 and 6.5 Hz, at 2.70 shown by decoupling to be the allylic CH_2 group of the minor stereoisomer), and 0.4–2.0 (19 H, m, aliphatic CH including a *t*-Bu singlet at 1.09); mass spectrum *m/e* (rel intensity) 192 (M^+, 9), 177 (8), 138 (33), 135 (50), 107 (60), 93 (38), 91 (50), 79 (100), 77 (39), 57 (65), 41 (98), and 39 (66). Analysis by GLC (Apiezon M on Chromosorb P) exhibited partially resolved peaks with retention times of 9.7 (major) and 11.0 min (minor) corresponding to the two stereoisomers tentatively assigned structures **16b** and **16a**, respectively.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.34; H, 10.75.

The liquid chromatography fractions containing (GLC, Apiezon M on Chromosorb P) mainly the unconjugated enone **30** (retention time 8.6 min) with lesser amounts of the stereoisomeric conjugated enones **16b** (11.2 min) and **16a** (12.4 min) were used to collect (GLC) a pure sample of the unconjugated enone **30** as a colorless liquid: $n^{25}D$ 1.4841; ir (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 5.1–5.3 (1 H, m, vinyl CH), 3.1–3.3 (2 H, m, CH_2CO), 0.9–2.2 (15 H, m, aliphatic CH including a *t*-Bu singlet at 1.12), and 0.4–0.9 (2 H, m, cyclopropyl CH_2); mass spectrum *m/e* (rel intensity) 192 (M^+, 1), 91 (9), 79 (10), 77 (7), 57 (100), 41 (24), and 39 (13).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.96; H, 10.45.

The analysis of mixtures of the unconjugated enone **30** and the stereoisomeric conjugated enones **16a** and **16b** (not resolved) could be obtained both by the previously described GLC analysis and by integration of that portion of the NMR spectrum containing the vinyl CH signals. Since neither of these methods was well suited for determining the composition of mixtures of the stereoisomeric enones **16a** and **16b**, the composition of mixtures of these stereoisomeric enones **16** was determined by high-pressure liquid chromatography (HPLC) employing a Waters liquid chromatograph, Model ALC-202, fitted with a uv detector (254 nm), a 30-cm μ-Porasil column, and 2.5% (by volume) of $CHCl_3$ in pentane as an eluent. Known amounts of $PhCOCH_3$ were added as an internal standard and the apparatus was calibrated with known mixtures prepared from pure samples of $PhCOCH_3$, **16a**, and **16b**. The retention times were **30**, 4.3 min; **16a**, 6.2 min; **16b**, 6.8 min; and $PhCOCH_3$, 9.0 min. Mixtures of the stereoisomeric enones **16** were separated by preparative low-pressure (15 psi) liquid chromatography employing columns packed with silica gel (E. Merck) and eluted with 1.5% (by volume) of Et_2O in hexane. The early fractions containing (HPLC) the isomer **16a** were subjected to low-temperature crystallization from pentane to separate the enone, tentatively assigned stereochemistry **16a**, as colorless crystals: mp 26.5–27.5 °C; uv max (95% EtOH) 263 nm (ε 14 800); ir (CCl_4) 1671 (less intense, C=O) and 1588 cm^{-1} (more intense, C=C); NMR (CCl_4) δ 6.33 (1 H, t, *J* = 1.9 Hz, vinyl CH), 2.67 (2 H, apparently a triplet of doublets, *J* = 1.9 and 6.3 Hz, allylic CH_2), and 0.6–2.1 (17 H, m, aliphatic CH including a *t*-Bu singlet at 1.10); mass spectrum *m/e* (rel intensity) 192 (M^+, 23), 177 (5), 135 (93), 107 (19), 93 (22), 91 (22), 79 (32), 57 (100), 55 (22), 41 (55), and 39 (32).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.19; H, 10.51.

The later chromatography fractions containing (HPLC) isomer **16b** were subjected to low-temperature crystallization to separate the enone, tentatively assigned stereochemistry **16b**, as colorless crystals: mp 12.5–13.5 °C; uv max (95% EtOH) 264 nm (ε 9260); ir (CCl_4) 1671 (less intense, C=O) and 1595 cm^{-1} (more intense, C=C); NMR (CCl_4) δ 6.20 (1 H, broad, vinyl CH), 2.7–3.2 (1 H, m, allylic cyclopropyl CH), 0.9–2.3 (17 H, m, aliphatic CH including a *t*-Bu singlet at 1.10), and 0.4–0.7 (1 H, m, one H of cyclopropyl CH_2, shown by a spin-decoupling experiment to be coupled to the low-field allylic cyclopropyl CH signal); mass spectrum *m/e* (rel intensity) 192 (M^+, 28), 177 (11), 138 (48), 135 (100), 107 (22), 93 (27), 91 (26), 79 (42), 57 (40), 55 (24), 41 (71), and 39 (34).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.18; H, 10.50.

Reaction of Enone 17 with Me_2CuLi. To a cold (4 °C) solution of Me_2CuLi, from 875 mg (4.25 mmol) of Me_2SCuBr, and 7.8 mmol of MeLi in 17 ml of Et_2O and 5 ml of Me_2S, was added, dropwise with stirring and cooling, a solution of 546 mg (3.03 mol) of the enone **17** in 1.5 ml of Et_2O. The reaction solution, from which yellow $(MeCu)_n$ began to precipitate after 10 s, was stirred at 4–7 °C for 40 min and then partitioned between Et_2O and an aqueous solution (pH 8) of NH_4Cl and NH_3. The ethereal layer was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried and concentrated. The residual liquid (630 mg) was chromatographed on silica gel with an Et_2O–hexane eluent (1:130 v/v) to separate 518 mg (87%) of the pure ketone **31** as a colorless liquid: $n^{25}D$ 1.4564; ir (CCl_4) 1705 cm^{-1} (C=O); uv max (95% EtOH) 295 nm (ε 30); NMR (CCl_4) δ 2.33 (2 H, s, CH_2CO), 1.2–1.8 (10 H, m, CH_2), 1.07 (9 H, s, *t*-Bu), and 1.00 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity) 196 (M^+, 2), 139 (31), 97 (100), 69 (10), 57 (13), 55 (24), and 41 (13).

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.56; H, 12.34.

Reaction of the Enone 16 with Me_2CuLi. To a cold (3 °C) solution of Me_2CuLi, from 719 mg (3.50 mmol) of Me_2SCuBr, 7.0 mmol of MeLi, 5 ml of Me_2S, and 14.4 ml of Et_2O, was added a solution of 490 mg (2.55 mmol) of the enone **16** in 1.1 ml of Et_2O. The resulting solution was stirred at 3 °C for 4 h, during which time a precipitate of $(MeCu)_n$ slowly separated, and at 26 °C for 45 min. After the resulting mixture had been partitioned between Et_2O and an aqueous solution (pH8) of NH_3 and NH_4Cl, the ethereal phase was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried and concentrated. The crude product (520 mg of pale yellow liquid) contained (GLC, Carbowax 20M on Chromosorb P) mainly a mixture of the adducts **32** and **33** (unresolved, retention time 5.9 min) accompanied by minor amounts of the enones **16** (9.6 min) and the unconjugated enone **30** (7.4 min) and three minor unidentified materials (3.0, 3.4, and 4.6 min). On a second GLC column (TCEP on Chromosorb P), the components eluted were the three minor unidentified materials (retention times 6.1, 8.0, and 11.6 min), the stereoisomeric ketones **32** (19.7 and 20.4 min, ca. 28% of the product), the enone **33** (24.0 min, ca. 72% of the product), the unconjugated isomer **30** of the starting material (34.6 min), and the starting enones **16** (45.1 min, isomers not resolved).

A 372-mg aliquot of this product was subjected to preparative low-pressure liquid chromatography (LC) employing a column packed with silica gel and an Et_2O–hexane eluent (1:66 v/v). After separation of initial fractions (14 mg) containing (GLC) the minor, unidentified materials, the next fraction, amounting to 56.5 mg (15% yield), contained the stereoisomeric ketones **32** as a colorless liquid: ir (CCl_4) 3060 (cyclopropyl CH) and 1705 cm^{-1} (C=O); NMR (CCl_4) δ 2.2–2.6 (2 H, m, CH_2CO) and 0.3–2.2 [22 H, m, aliphatic CH including singlets for the minor stereoisomer at 1.13 (*t*-Bu) and 1.06 (CH_3) and singlets for the major stereoisomer at 1.26 (CH_3) and 1.12 (*t*-Bu)]; mass spectrum *m/e* (rel intensity) 208 (M^+, 30), 193 (100), 151 (36), 109 (83), 81 (20), 67 (40), 57 (59), and 41 (28); calcd for $C_{14}H_{24}O$; 208.1827; found; 208.1847.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 81.02; H, 11.79.

The next LC fractions eluted (148.8 mg or 39% yield) contained (GLC) the β,λ-unsaturated ketone **33** as a colorless liquid: $n^{25}D$ 1.4665;

ir (CCl_4) 1710 cm^{-1} (C=O); uv max (95% EtOH) 295 nm (ϵ 82); NMR (CCl_4) δ 5.29 (1 H, broad, vinyl CH), 3.05 (2 H, broad, CH_2CO), and 0.5–2.2 (21 H, m, aliphatic CH including at *t*-Bu singlet at 1.10); mass spectrum *m/e* (rel intensity) 208 (M^+, 4), 79 (38), 57 (100), and 41 (20); calcd for $C_{14}H_{24}O$, 208.1827; found, 208.1847.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 81.01; H, 11.80.

The next LC fraction (20 mg or 4% yield) contained (GLC) the unconjugated isomer **30** of the starting enone **16**. The material was identified with the previously described sample by comparison of GLC retention times and ir and NMR spectra. The final LC fraction (58 mg or 12% recovery) contained (GLC, ir and NMR analysis) a mixture of starting enones **16**. Although the starting enone **16** for this reaction contained (HPLC) mainly one stereoisomer (12% **16a** and 88% **16b**), the enone sample recovered from this reaction contained (HPLC) substantial amounts of both stereoisomers (29% **16a** and 71% **16b**).

Synthesis of the Enone 33. A cold (−4 °C), stirred solution of EtMgI, from 3.65 g (150 mg-atoms) of Mg, 25.0 g (160 mmol) of EtI, and 45 ml of Et_2O, was treated with 219 mg (2.2 mmol) of CuCl and then a solution of 9.62 g (100 mmol) of 2-cyclohexenone in 20 ml of Et_2O was added, dropwise with stirring and cooling during 85 min. After the addition was complete, the mixture was stirred for 30 min while it was allowed to warm to room temperature and then the mixture was added slowly to a vigorously stirred mixture of 150 g of ice and 80 ml of aqueous 10% H_2SO_4. The resulting mixture was extracted with Et_2O and the ethereal extract was washed with aqueous $Na_2S_2O_3$, dried, concentrated, and fractionally distilled to separate 7.145 g (57%) of the ketone **34** as a pale yellow liquid: bp 44–45 °C (0.8 mm) [lit.[24] bp 190 °C (732 mm)], $n^{25}D$ 1.4493; ir (CCl_4) 1712 cm^{-1} (C=O); uv max (95% EtOH) 285 nm (ϵ 21); NMR (CCl_4) δ 0.8–2.5 (m, aliphatic CH); mass spectrum *m/e* (rel intensity) 126 (M^+, 39), 98 (22), 97 (79), 83 (100), 82 (27), 70 (35), 69 (26), 56 (20), 55 (87), 42 (28), 41 (82), and 39 (39).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.06; H, 11.18.

To a cold (−47 to −50 °C) solution of the enolate **20**, from 4.68 g (46.2 mmol) of *i*-Pr_2NH, 75 ml of Et_2O, 25.3 ml of a hexane solution containing 45.8 mmol of *n*-BuLi, and 4.48 g (44.7 mmol) of *t*-$BuCOCH_3$, was added, dropwise with stirring and cooling during 4 min, a solution of 5.34 g (42.3 mmol) of the ketone **34** in 8 ml of Et_2O. The resulting cold (−47 to −50 °C) solution was stirred for an additional 7 min and then poured into cold (0 °C) aqueous 1 M HCl and extracted with Et_2O. The ethereal extract was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried and concentrated. The residual pale yellow liquid (10.6 g) was fractionally crystallized from pentane at −70 °C to separate the crude aldol **35** as white crystals that melted below 25 °C to give the aldol **35** (presumably a mixture of diastereoisomers) as a colorless liquid: ir (CCl_4) 3495 (associated OH) and 1690 cm^{-1} (hydrogen bonded C=O); NMR (CCl_4) δ 3.64 (1 H, broad, OH), 2.48 (2 H, s, CH_2CO), and 0.7–2.1 (23 H, m, aliphatic CH including a *t*-Bu singlet at 1.11).

A solution of 52.2 mg (0.27 mmol) of $TsOH \cdot H_2O$ and 1.174 g (5.12 mmol) of the hydroxy ketone **35** in 41 ml of PhH was refluxed for 46 min and then partitioned between Et_2O and aqueous $NaHCO_3$. The crude product (1.075 g of yellow liquid) recovered from the Et_2O solution contained (ir and GLC, TCEP on Chromosorb P) mainly a component (retention time 22.3 min) believed to be the conjugated isomer **36** with lesser amounts of the enone **33** (23.6 min) and a component believed to be enone **37** (25.6 min). A 1.039-g aliquot of this crude product mixture in 41 ml of PhH containing 194 mg (1.02 mmol) of $TsOH \cdot H_2O$ was refluxed for 1.5 h and subjected to the same isolation procedure to yield 993 mg of yellow liquid containing the same three components noted above but with the major products being the β,γ isomers **33** and **37**. A collected (GLC) sample of the component believed to be enone **37** was obtained as a colorless liquid: ir (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 5.2–5.5 (1 H, m, vinyl CH), 3.04 (2 H, broad, CH_2CO), and 0.8–2.3 (21 H, m, aliphatic CH including a *t*-Bu singlet at 1.11); mass spectrum *m/e* (rel intensity) 208 (M^+, 4), 151 (11), 57 (100), and 41 (16); calcd for $C_{14}H_{24}O$, 208.1827; found, 208.1847.

A collected (GLC) sample of the enone **33** was identified with the previously described sample by comparison of GLC retention times and NMR and mass spectra.

Electrochemical Measurements. The polarography, cyclic voltammetry, and electrolysis measurements employed a custom-made polarographic module, utilizing solid-state amplifiers, that followed the typical three-electrode design. Descriptions of the cells, working electrodes, reference electrodes, and reagent purification procedures have been published previously.[25] In all cases the solvent was anhydrous DMF containing 0.5 M *n*-$Bu_4N^+BF_4^-$ as the supporting electrolyte. Previously described procedures[25b,c,26] were used to estimate $E_{1/2}$ values and half-lives from cyclic voltammetry measurements.

Solutions of the enone **17** (2.5–5.4 × 10^{-3} M), upon polarographic reduction, exhibited $E_{1/2}$ −2.28 V vs. SCE (n = 1.2, i_d = 5–15 μA). Cyclic voltammetry indicated the reduction ($E_{1/2}$ −2.29 V vs. SCE) to be reversible at moderate scan rates (1 V/s) with the anion radical having an estimated half-life of 0.3 s. Polarographic reduction of solutions of the enone **16** (3.0–5.1 × 10^{-3} M) gave $E_{1/2}$ = −2.24 V vs. SCE (n = 1.4, i_d = 9–18 μA). Cyclic voltammetry measurements on these solutions exhibited only a cathodic current peak with no evidence for reversibility up to scan rates of 500 V/s. We therefore estimate the half-life of the radical anion from enone **16** to be less than 10^{-3} s.

The preparative electrolysis experiments employed a previously described[25c] three-compartment H-cell with a Pt anode, a Hg-pool cathode, and an SCE reference electrode fitted with a salt bridge. The potential between the reference electrode and the cathode was measured with a high-input impedance buffer amplifier connected to a digital voltmeter and the current passing through the cell was measured by continuously monitoring the potential drop across a precision resistor in series with the cell circuit. After a solution containing 0.42 M *n*-Bu_4NBF_4 in anhydrous DMF had been placed in each cell compartment, a potential (−2.4 V vs. SCE) was applied to reduce any impurities present and then 246 mg (1.28 mmol) of the enone **16b** was added to the catholyte (total volume 10 ml). A potential (−2.1 V vs. SCE) was applied to the cell and reduction was to proceed for 8 min at which time 1.50 × 10^{-5} Faradays of current (sufficient to reduce 1.2% of the enone **16** to its anion radical **39** and/or **40**) had passed through the cell. The catholyte solution was then removed and partitioned between H_2O and pentane. After the organic phase had been dried (Na_2SO_4) and concentrated, the crude liquid product (244 mg) contained (GLC and NMR analysis) ca. 53% of the unconjugated enone **30** and ca. 47% of the conjugated enones **16**. After an aliquot of the crude product had been mixed with a known amount of internal standard ($PhCOCH_3$) for HPLC analysis, the calculated yields of the stereoisomeric enones were 19% of **16a** (37% of the recovered enone **16**) and 32% of enone **16b** (63% of the recovered enone **16**).

In this electrochemical experiment both interconversion of the gemetrically isomeric enones **16a** and **16b** and structural isomerization of the conjugated enones **16** to the *more stable* unconjugated enone **30** were occurring. The latter structural isomerization is presumably catalyzed by the base(s) generated on further electrochemical reduction of the rearranged anion radical **40**. Several control experiments were performed to establish the cause of the geometrical isomerism **16a** ⇌ **16b**. When a 17.7-mg (0.92 mmol) sample of the enone **16b** (containing 2.3% of **16a**) was stirred at 25 °C in 1.0 ml of a DMF solution containing 0.41 M *n*-Bu_4NBF_4 for 1 h and subjected to the same isolation and analysis procedures used in the electrochemical experiment, the crude recovered enone **16b** (22 mg) contained 2.4% of the stereoisomer **16a**. In another experiment, 1.0 ml of a 0.42 M solution of *n*-Bu_4NBF_4 in DMF was treated with 0.002 mmol of *n*-BuLi and then 28 mg (0.14 mmol) of the enone **16b** (containing 7.0% of stereoisomer **16a**) was added. After this solution had been stirred for 20 min at 25 °C, the recovered crude enone **16b** (22 mg) contained 7.3% of the stereoisomer **16a**. To explore the effect of a higher concentration of base, 22 mg (0.11 mmol) of the enone **16b** (containing 7.2% of stereoisomer **16a**) was added to 1.0 ml of a solution prepared from 0.42 M *n*-Bu_4NBF_4 in DMF and 0.05 mmol of *n*-BuLi and the solution was stirred at 25 °C for 20 min. The yields (HPLC analysis) of enones **16** in the crude liquid product (40 mg) were 10% of enone **16a** (15% of the recovered enones **16**) and 56% of enone **16b** (85% of the recovered enones **16**). The crude liquid product contained (NMR analyses) ca. 61% of the stereoisomeric enones **16** and ca. 39% of the unconjugated enone **30**. These observations strongly suggest that the rapid stereochemical isomerization **16b** → **16a** observed in the electrochemical experiment was caused by the presence of the anion radical **39** and not by the small amount of base generated during the partial electrolysis.

Registry No.—**16a**, 59671-43-1; **16b**, 59671-44-2; **17**, 775-10-0; **19**, 108-94-1; **20**, 34865-75-3; **21**, 59671-45-3; **22**, 775-09-7; **23**, 930-68-7; **24**, 59671-46-4; **25**, 59671-47-5; **26**, 59671-48-6; **27**, 5771-58-4; **28** isomer A, 59671-49-7; **28** isomer B, 59686-32-7; **30**, 59671-50-0; **31**, 59671-51-1; **32** isomer A, 59671-52-2; **32** isomer B, 59671-53-3; **33**, 59671-54-4; **34**, 22461-89-8; *cis*-**35**, 59671-55-5; *trans*-**35**, 59671-56-6; **37**, 59671-57-7; *i*-Pr_2NLi, 4111-54-0; pinacolone, 75-97-8; Me_3SiCN, 7677-24-9; Me_2CuLi, 15681-48-8.

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Reactions Involving Electron Transfer. 11. Reaction of Lithium Dimethylcuprate with Diaryl Ketones[1]

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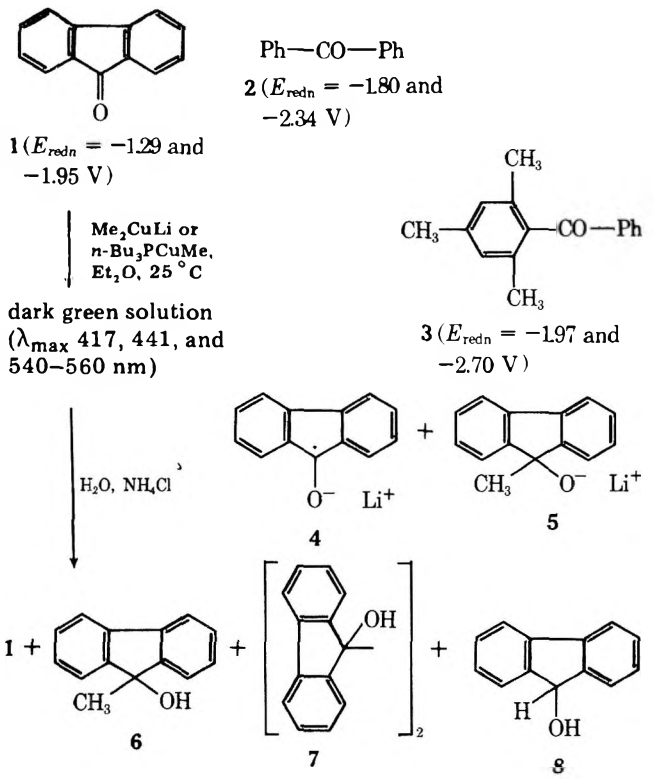
When cold, colorless solutions of PhCOPh and Me_2CuLi were mixed, an intermediate red-colored solution was formed. When this red solution, thought to arise from a charge-transfer absorption, was allowed to warm above 0 °C, a deep blue solution was formed and yellow $(MeCu)_n$ precipitated. This solution contained a mixture of the blue ketyl, $Ph_2C\text{-}O^-Li^+$, and the salt of the 1,2 adduct **9**. When the more hindered diaryl ketone **3**, selected to retard 1,2 addition, was mixed with Me_2CuLi a yellow solution was formed that underwent no further change even at 25 °C. However, treatment of ketone **3** with a cold solution containing both Me_2CuLi and MeLi produced an initial yellow solution that turned red with precipitation of $(MeCu)_n$ as the solution was warmed above 0 °C. This red solution contained a mixture of the red ketyl **16** and the salt of the 1,2 adduct **14**. The observations with ketone **3** and mixtures of Me_2CuLi and MeLi suggest the formation of at least a small concentration of some more powerful reducing agent such as Me_4CuLi_3.

As noted in a recent paper,[2] it was of interest to examine the reactions of lithium dimethylcuprate (Me_2CuLi or $Me_4Cu_2Li_2$)[3] with alkyl aryl ketones (typical E_{redn} values −1.8 to −2.2 V) and with diaryl ketones (typical E_{redn} values −1.8 to −2.0 V) because the reduction potentials (E_{redn}) of these ketone substrates are sufficiently positive to permit[4] reactions with Me_2CuLi by a process involving an initial electron transfer step. Our study of reactions with alkyl aryl ketones is described elsewhere[2] and this paper describes our observations when the diaryl ketones 1–3 (Scheme I) were treated with Me_2CuLi.

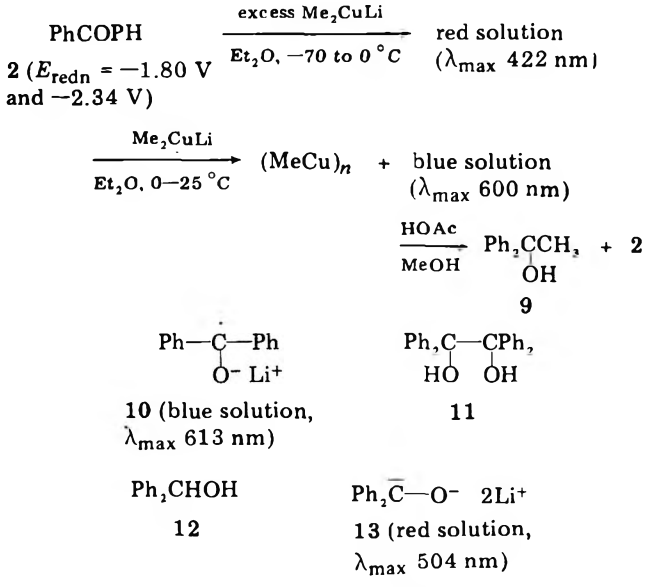
Some time ago we reported[5] that treatment of either Me_2CuLi or $MeCuP(Bu\text{-}n)_3$ with the very easily reduced[6] diaryl ketone **1** (Scheme I) formed immediately a deep green colored ethereal solution containing (EPR) a paramagnetic species. Hydrolysis of this solution yielded a mixture containing approximately equal amounts of the alcohol **6** and the diol **7** as well as minor amounts of the alcohol **8** and the starting ketone **1**. These observations indicate that the reaction of the ketone **1** with Me_2CuLi formed approximately equal amounts of the 1,2 adduct **5** and the ketyl **4**. This mixture, containing excess Me_2CuLi, underwent further change only very slowly.

Since reduction of the ketone **1** to the ketyl **4** occurs with unusual ease (E_{redn} = −1.29 V), we were concerned that the formation of the anion radical **4** in this case might not be indicative of the behavior with typical enones having E_{redn} values in the range −1.6 to −2.4 V. Consequently, we have examined the analogous reaction with benzophenone (**2**, E_{redn} = −1.80 and −2.34 V).[7] As summarized in Scheme II, mixing

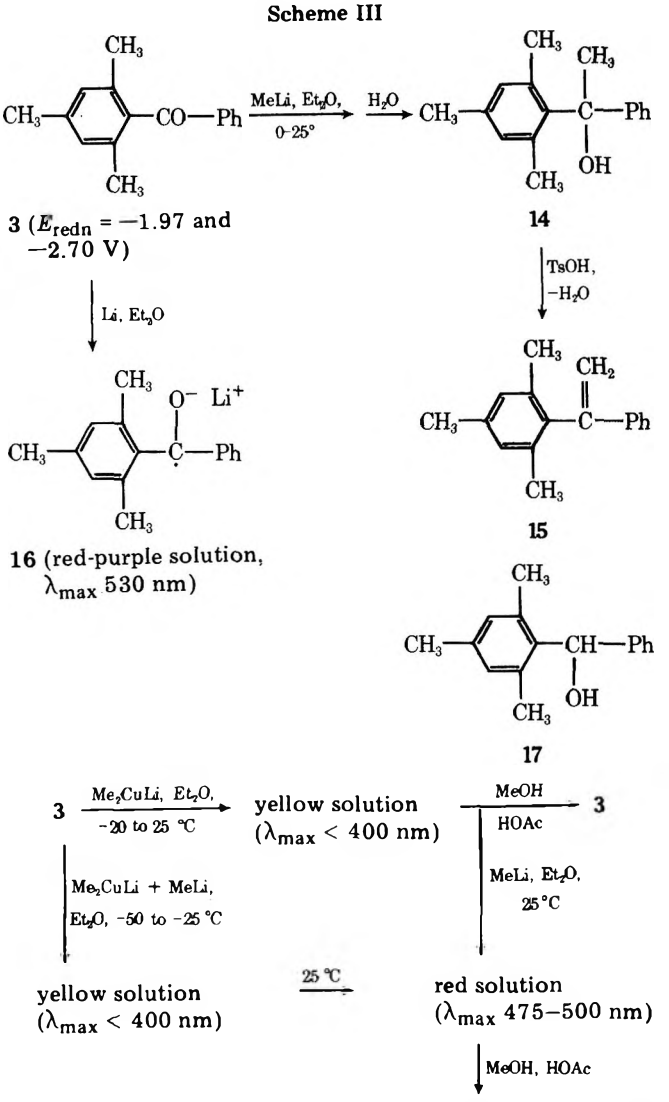
Scheme I



Scheme II



Scheme III



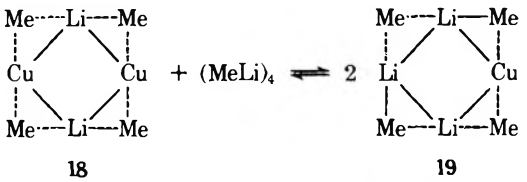
colorless solutions of PhCOPh and Me_2CuLi resulted in the immediate formation of a red solution. Although this red solution was stable for hours at low temperatures (−20 to −70 °C), when it was warmed to 0 °C, precipitation of yellow $(MeCu)_n$ began and the supernatant solution slowly changed from red to deep blue. The blue solution, containing excess Me_2CuLi and a yellow precipitate of $(MeCu)_n$, was stable for periods of at least 30 min at 25 °C. Examination of both the visible spectrum[8] and the EPR spectrum established that the blue species in the final solution was the lithium ketyl **10**. Quenching this solution yielded the alcohol **9** and the starting ketone **2** (formed by oxidation of ketyl **10** during the quenching process). The amounts of products **9** and **2** formed indicated that ca. 80% of the starting ketone **2** had been converted to the salt of the 1,2 adduct **9** and the remaining ketone **2** (ca. 20%) had been reduced to the ketyl **10**. Both of these changes had occurred during the period when the initially formed red solution was converted to a blue solution with precipitation of $(MeCu)_n$. Quenching the initial red solution yielded only unchanged ketone **2**. Although an ethereal solution of the dilithium salt **13** of benzophenone dianion is red (λ_{max} 504 nm), the visible absorption spectrum of **13** does not correspond to the spectrum of the red intermediate from benzophenone (**2**). Furthermore, quenching a solution of the dianion **13** yielded mainly alcohol **12** accompanied by lesser amounts of diol **11** and ketone **2** from oxidation during the quenching process. Consequently, the foregoing observations suggest that the initially formed red solution does not contain any substantial concentration of either the dianion **13** or any species in which a new carbon–carbon or carbon–metal bond has been formed. We have noted previously[9a] that a transient *red-to-orange* color has often been observed *before the precipitation of* $(MeCu)_n$ begins when phenyl-substituted enones are mixed with Me_2CuLi in ether solution. Thus, it seemed possible that this initially formed red species might be an intermediate in the formation of an anion radical (e.g., **10** from **2**) and/or an addition product (e.g., **9** from **2**).

To explore further the possibility of observing a stepwise sequence of reactions with Me_2CuLi and diaryl ketones, we examined the reaction with the more hindered ketone **3** in the hope that we could retard or inhibit 1,2 addition. This ketone **3** is a member of a well-studied[10] family of 2,6-disubstituted phenyl ketones in which the steric bulk of the two ortho methyl groups causes the molecule to adopt a conformation with the 2,4,6-trisubstituted phenyl ring perpendicular to the

plane of the carbonyl group. In this conformation, the two ortho methyl groups shield both sides of the carbonyl carbon atom. Mixing the ketone **3** (Scheme III) with an ethereal solution of MeLi (with or without LiBr) at −70 °C produced a yellow solution (λ_{max} <400 nm) from which the unchanged ketone **3** was recovered after quenching with a MeOH–HOAc mixture. When this yellow solution was warmed before quenching, above −10 °C the solution acquired a yellow-brown color (shoulder at ca. 500 nm) and subsequent quenching yielded the alcohol **14** also characterized as the olefin **15**.[11] Reaction of the ketone **3** with Li in Et_2O afforded a relatively stable red-to-purple solution of the ketyl **16** (λ_{max} 530 nm, intense EPR signal, g = 2.0024). On long standing, this red color slowly faded (presumably H^+ abstraction from the solvent); after hydrolysis the unchanged ketone **3** and the alcohol **17** were isolated.

When the ketone **3** was added to a solution of Me_2CuLi (containing no excess MeLi) at −20 °C, the resulting yellow solution exhibited no evidence (visible spectrum or EPR spectrum) for the formation of the ketyl **16**. Even when this solution was warmed to 25 °C, no visible absorption attributable to the ketyl **16** was observed and quenching the yellow solution afforded the unchanged ketone **3**. When the ketone **3** was added to a cold (−50 °C) solution of equimolar amounts of Me_2CuLi and MeLi, the resulting yellow solution exhibited no visible absorption attributable to the ketyl **16** and only a very weak EPR signal. However, as the solution was warmed above 0 °C, the solution deposited $(MeCu)_n$ and developed both an intense red color (λ_{max} 475–500 nm)[8] and an intense EPR signal (g = 2.0020) both attributable to the ketyl **16**. Quenching this red solution afforded a mixture of the alcohol **14** (ca. 20% of the product) and the ketone **3** (ca. 80% of the product). The various spectral changes and products observed in these reactions of either ketone **2** or **3** with a cuprate reagent were not significantly different when performed with solutions of cuprate reagents that either did or did not contain dissolved LiBr.[8]

These latter observations suggest that although neither Me_2CuLi nor MeLi in Et_2O solution is a sufficiently good reductant to reduce the ketone **3** to its ketyl **16**, some species formed when Et_2O solutions of Me_2CuLi and MeLi are mixed is capable of effecting this reduction. A recent report[12] of differing stereochemistry for the methyl carbinols formed by reaction of substituted cyclohexanones with MeLi and with a mixture of MeLi and Me_2CuLi could also be interpreted as evidence for the formation of this information would be the existence of equilibrium between the usual dimeric cuprate



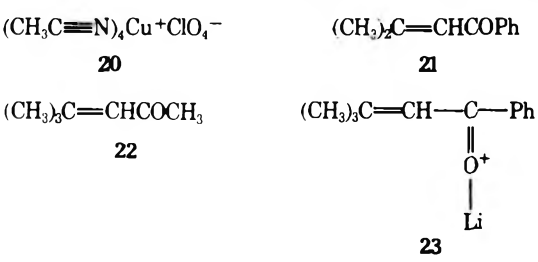
18 **19**

formulation **18** ($Me_4Cu_2Li_2$) and a small amount of a related organometallic cluster **19** having the composition Me_4CuLi_3. Such species are analogous to the mixed aggregate formed from MeLi and lithium halides.[13] If the species **19** (Me_4CuLi_3) is a more powerful reductant than $Me_4Cu_2Li_2$ (**18**) our observations with ketone **3** are readily explained.

However, the equilibrium concentration of an aggregate such as **19** appears to be small. In an earlier ^1H NMR study[5] when an Et_2O solution of MeLi and Me_2CuLi was cooled below −60 °C, the average ^1H NMR signal for the equilibrating methyl groups separated into two signals corresponding in position to the separate ^1H NMR signals for Me_2CuLi and MeLi but no signal was observed for a third species. We have now also examined the natural abundance ^{13}C NMR spectra for solutions of MeLi, Me_2CuLi, and a mixture of the two. At room temperature an Et_2O solution of MeLi exhibited a single line at −13.4 ppm for the equilibrating methyl groups. As the solution was cooled below 0 °C this line began to broaden and at −40 °C appeared as a set of overlapping multiplets ($J_{^{13}C-^7Li}$ = 15 Hz) corresponding to a ten-line multiplet (Me group bound to three equivalent ^7Li atoms) and a seven-line multiplet (Me group bound to two ^7Li atoms and one ^6Li atom).[14] An Et_2O solution containing Me_2CuLi at 35 °C exhibited a single ^{13}C NMR line at −9.6 ppm; this line remained narrow as the solution was cooled to −60 °C but did begin to broaden as the solution was further cooled to −80 °C. Unfortunately, the concentrated solution being used became so viscous at temperatures below −80 °C that we were unable to obtain satisfactory ^{13}C NMR data at lower temperatures.

An Et_2O solution containing a mixture of MeLi and Me_2CuLi (average composition Me_4CuLi_3) at 35 °C exhibited a single ^{13}C NMR peak (−11.1 ppm) corresponding to rapidly exchanging methyl groups. As the solution was cooled this peak broadened and at −40 °C appeared as two partially separated broad peaks at −9.0 and −13.1 ppm. Further cooling of these rather concentrated solutions to −60 °C resulted in precipitation of the MeLi and left a single narrow peak at −8.8 ppm corresponding to the solution of Me_2CuLi. Although this result was less definitive than the ^1H NMR data, we again observed no obvious signal attributable to a third organometallic species. Lack of solubility of the MeLi prevented us from obtaining meaningful measurements at lower temperatures.

To explore possible causes for the initial red color developed when PhCOPh (**2**) was mixed with Me_2CuLi (or the yellow color observed when ketone **3** was mixed with Me_2CuLi) we examined the ^{13}C NMR spectra, the Raman spectra, and/or the visible spectra of solutions obtained by adding one of the ketones **2** or **3** to solutions of $LiClO_4$, to solutions of several Cu(II) compounds [$CuBr_2$, $Cu(OAc)_2$, $Cu(acac)_2$], and to solutions of the Cu(I) complex **20**.[15] We observed no evidence



indicating the formation of complexes between the ketones **2** or **3** and any of the Cu(I) or Cu(II) compounds examined. Although we observed no new absorption in the Raman spectra or visible spectra of solutions prepared by adding one of the ketones **2**, **3**, **21**, or **22** to an Et_2O solution of $LiClO_4$, the ^{13}C NMR spectra of these solutions did exhibit a small (3–6 ppm) downfield shift of the signals attributable to the carbonyl groups of each ketone. The ^{13}C NMR signals for β-carbon atoms of the α,β-unsaturated ketones **21** and **22** were also shifted downfield 4–5 ppm when excess $LiClO_4$ was added to the Et_2O solutions. These observations suggest that in ethereal solvents, at least partial coordination of these ketones with Li^+ cation (e.g., structure **23**) does occur resulting in some reduction of the electron density at the carbonyl carbon atom and at the β-carbon atom of the enones **21** and **22**.

We used various spectrometric techniques to examine the colored solutions obtained immediately after adding one of the ketones **2** or **3** to a cold solution of Me_2CuLi. The EPR spectra of these solutions indicated that no appreciable concentration of one of the ketyls **10** or **16** was present. The Raman spectrum of the red solution from ketone **2** exhibited

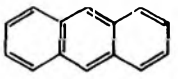
C=C and C=O absorption that did not differ significantly from that observed for a solution of the ketone **2** in pure Et_2O. The ^1H and ^{13}C NMR spectra of these solutions were also very similar to the spectra of various separate components. In the ^{13}C NMR spectra of the colored solutions from ketones **2** and **3**, the signals attributable to the Me_2CuLi, the carbonyl carbon atom, and the aromatic para carbon atoms of the aryl rings were somewhat broader than the other NMR signals and the signals for the carbonyl carbon atoms were shifted to slightly (3–5 ppm) lower field. Thus, all of our data suggests that the species responsible for the red or yellow color in these initial solutions is present at low concentration and the bulk of the reactants, Me_2CuLi and ketone **2** or **3**, remain unchanged. All of this information is compatible with the idea that the initial colors observed in these solutions arise from charge-transfer absorption bands which need not bear any particular relationship to the subsequent reduction of the ketones **2** and **3** by cuprate reagents to form ketyls **10** and **16**.

Our previous observations,[4,9] indicating a relationship between the E_{redn} values for various unsaturated carbonyl compounds and their reaction with Me_2CuLi suggested that the oxidation of Me_2CuLi could be formulated as shown in Scheme IV. In an effort to measure directly the electrode

Scheme IV

$Me_4Cu_2Li_2$ (**18**) $\xrightarrow[-1.8 \text{ to } -2.0 \text{ V}]{-e^-}$ $[Me_4Cu_2Li_2]^+$ (**24**)

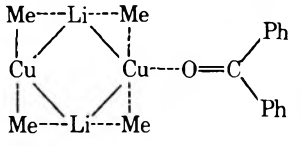
$\xrightarrow[-1.0 \text{ to } -1.2 \text{ V}]{-e^-}$ $[Me_4Cu_2Li_2]^{+2}$ (**25**) $\longrightarrow$ Me—Me + $2Li^+$ + 2MeCu



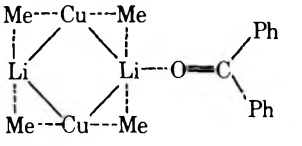
26 ($E_{redn} = -1.93$ V)

PhCH=CHCN

27 ($E_{redn} = -1.84$ V)



28



29

potentials associated with the changes **18** → **24** → **25**, we have prepared solutions of Me_2CuLi in DME containing LiBr or $LiClO_4$ and in DMF containing n-Bu_4NBF_4 and examined their electrochemical behavior by cyclic voltammetry. In no case did we observe significant oxidation or reduction currents within the potential range −0.5 to −2.5 V. Analysis of these solutions by NMR established that Me_2CuLi was present and addition of anthracene (**26**) to a DMF solution of Me_2CuLi allowed us to obtain a typical cyclic voltammetry curve for this hydrocarbon **26**. Consequently, our failure to observe the electrochemical oxidation of **18** does not appear to be attributable either to decomposition of the cuprate or to a problem (e.g., electrode coating) with the electrochemical apparatus. In spite of these electrochemical results it is clear from the chemical reactions described that Me_2CuLi is capable of reducing both ketones **1** and **2** to the corresponding ketyls **4** and **10**. We believe that the most reasonable explanation of this apparent dilemma is to postulate that the transfer of an electron from the cuprate to a metal electrode surface is kinetically very slow. This postulate gains credibility when considered in light of the behavior of possible substrates **26** and **27** with Me_2CuLi. Although both the hydrocarbon **26** ($E_{redn} = -1.93$ V) and the nitrile **27** ($E_{redn} = -1.84$ V) are reduced at approximately the same potential as PhCOPh ($E_{redn} = -1.80$ V), both of these substrates **26** and **27** fail to react with an etheral solution of Me_2CuLi at 0–10 °C and are recovered unchanged. Because of these various observations, we are led to suggest that a necessary first step in the transfer of an electron from a cuprate to a substrate is the formation of a coordination complex such as **28** or **29**. Subsequent transfer of an electron could occur by a process analogous to an inner-sphere electron transfer mechanism in redox reactions of metal ions.

It is noteworthy that the substrates that are effective in abstracting an electron from cuprate reagents (carbonyl compounds, certain sulfones,[16] nitro compounds,[17] quinones,[17] O_2[17]) all contain a terminal oxygen atom that might be used to form complexes similar to **28** or **29**.

It was of interest to compare the rate of reaction of PhCOPh with Me_2CuLi to form the alcohol **9** with a typical conjugate addition of Me_2CuLi to an enone. For this comparison, we performed a competition experiment in which a limited amount (0.9 molar equiv) of Me_2CuLi was allowed to react with a mixture of 1 molar equiv of PhCOPh and 1 molar equiv of the enone **21** (Scheme V). This enone **21**, which has almost

Scheme V

PhCOPh + $(CH_3)_2C$=CHCOPh

2 ($E_{redn} = -1.80$ V) **21** ($E_{redn} = -1.86$ V)

$\xrightarrow[-70 \text{ to } 22 \text{ °C}]{Me_2CuLi,\ Et_2O.}$ $\xrightarrow[HOAc]{MeOH}$ **2** (90% recovery)

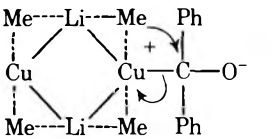
+ **21** (23% recovery) + Ph_2CCH_3 (OH) + $(CH_3)_3CCH_2COPh$

9 (4% yield) **30** (64% yield)

the same E_{redn} value as PhCOPh, is known[2] to react with Me_2CuLi to form the conjugate adduct **30**. Furthermore, when the enone **21** is mixed with a cold (−60 to −70 °C) solution of Me_2CuLi, a red solution is obtained immediately. As this solution is warmed, reaction occurs with precipitation of $(MeCu)_n$ and loss of the red color to give the adduct **30**. When this competition experiment was performed by mixing the reactants at −70 °C and then warming them until reaction occurred, the major materials isolated were the adduct **30** and the unchanged ketone **2** with lesser amounts of the enone **21** and only a small amount of the alcohol **9**. From these results, we conclude that reaction of Me_2CuLi with the enone **21** is *at least* 15 times as rapid as addition to PhCOPh. As a result of this experiment and related experiments with aryl alkyl ketones,[2] we conclude that 1,2 additions of Me_2CuLi both to diaryl ketones and to aryl alkyl ketones are significantly slower than conjugate additions of Me_2CuLi to enones.

The present studies provide even more compelling evidence than the related study of Me_2CuLi with aryl alkyl ketones[2] that Me_2CuLi does transfer an electron to an easily reducible ketone such as **2** (Scheme VI). The point of uncertainty in

Scheme VI

$Me_4Cu_2Li_2$ (**18**) + PhCOPh (**2**) $\xrightarrow{\text{nucleophilic addition}}$ 

32

e transfer ↓ ; recombination ↗

$[Me_4Cu_2Li_2]^+$ (**24**) + Ph—$\dot{C}$(O$^-$)—Ph (**10**)

$Ph_2C(Me)—O^-$ + $Me_3Cu_2Li_2^+$

$Ph_2C(Me)—O^-Li^+$ + MeCu + ½$Me_4Cu_2Li_2$

31

both studies is what relationship this electron-transfer process bears to the formation of a 1,2 adduct (e.g., **31** from **2**). Our data do not exclude a possible competing nucleophilic addition of the cuprate **18** to the ketone **2** to form an intermediate **32** that would be expected to yield the 1,2 adduct **31**. Of course the same intermediate **32** (leading to **31**) could be formed by recombination of the ion radical intermediates **10** and **24** produced by electron transfer. While our data do not unambiguously distinguish between these pathways to the 1,2 adduct **31**, it is appropriate to note that with both ketones **2** and **3** studied we have observed the formation of a 1,2 adduct only under reaction conditions where the corresponding ketyl (e.g., **10**) is also being generated. Thus, both the observations reported here and the related studies with aryl alkyl ketones[2] provide circumstantial evidence supporting the idea that the predominant reaction pathway in all of these reactions involves an initial electron-transfer step. In the present studies with diaryl ketones, it would appear that the recombination step **24** + **10** → **32** is particularly slow allowing a significant amount of the oxidized cuprate intermediate **24** to decompose before recombination can occur. As a result, appreciable concentrations of the ketyls such as **10** accumulate in the reaction mixture.

Experimental Section[18]

Preparation or Purification of Starting Materials. All ethereal solvents were freshly distilled from $LiAlH_4$, commercial Et_2O solutions of MeLi (halide free, Foote Mineral Co.) were standardized by a double titration procedure,[19] and the colorless, crystalline complex, Me_2SCuBr, was prepared from commercial CuBr (Fisher Scientific) as previously described.[9b] Ethereal solutions of MeLi containing an equimolar amount of LiBr were prepared from CH_3Br in the usual way.[20] A typical solution contained[19] 1.00 M MeLi. Previously described[21] procedures were also used to obtain pure DMF,[21] n-Bu_4NBF_4,[21] and $LiClO_4(DME)_2$.[7,22] Commercial "anhydrous" LiBr (City Chemical Corp.) was recrystallized repeatedly from DME (8.0 g of LiBr per 15 ml of DME) to give the complex, $LiBr(DME)_2$,[22] as white cubes. Commercial samples of the ketone **2**, mp 46–48 °C, and alcohols **12**, mp 65.5–66 °C, and **11**, mp 184–186 °C (dependent on rate of heating), were used (with purification[23] when necessary) and an authentic sample of the alcohol **9**, mp 80–81.5 °C, was available from previous work.[23,24] The ketone **3**, prepared by the acylation of mesitylene with PhCOCl and $AlCl_3$, was obtained in 94% yield as a colorless liquid: bp 195–197 °C (20 mm); $n^{25}D$ 1.5779 [lit. bp 120–122 °C (0.5 mm),[25a] 180–182 °C (11 mm)[25b]]; ir (CCl_4) 1672 cm^{-1} (C=O); NMR (CCl_4) δ 7.1–7.9 (5 H, m, aryl CH), 6.79 (2 H, s, aryl CH), 2.26 (3 H, s, aryl CH_3), and 2.00 (6 H, s, aryl CH_3); uv max (95% EtOH) 248 nm (ε 7500) and 285 (shoulder, 1200). Utilizing previously described[21,26] apparatus and procedures, the polarographic reduction of solutions of the ketone **3** ($3–8 \times 10^{-3}$ M) in DMF containing 0.5 M n-Bu_4NBF_4 was measured. The $E_{1/2}$ values observed were −1.97 V vs. SCE (n = 0.6, i_d = 22–57 μA) and −2.70 V vs. SCE (n = 0.6, i_d = 13–26 μA).[27] The preparation and characterization of ketones **21** and **30** are described elsewhere.[2]

To analyze mixtures of the ketone **2** and alcohols **9**, **11**, and **12**, we employed high-pressure liquid chromatography (HPLC) with a C-18 Corasil column and CH_3CN–H_2O (2:3 v/v) as a reverse-phase eluent. With this system and an eluent flow rate of 4 ml/min, the retention times of the components were **12**, 1.0 min; **9**, 1.3 min; **2**, 1.5 min; **11**, 4.8 min; and naphthalene (an internal standard), 1.9 min. Better resolution of the first three components eluted was obtained with an eluent flow rate of 1 ml/min where the retention times were **12**, 3.9 min; **9**, 4.9 min; **2**, 6.5 min; and naphthalene (an internal standard), 7.8 min. For quantitative analysis of the various mixtures, response factors for the uv detector (254 nm) were obtained with known mixtures of authentic samples. Mixtures containing compounds **2**, **9**, **11**, and **12** could also be analyzed by TLC and NMR analyses. With an alumina TLC coating and benzene as an eluent, the R_f values were **2**, 0.68; **9**, 0.54; **12**, 0.42; and **11**, 0.62. The NMR spectra (CCl_4) of all the components **2**, **9**, **11**, and **12** exhibited an aryl CH multiplet within the region δ 7.0–8.0; in addition the carbinol **9** exhibited singlets at δ 1.83 (CH_3) and 1.93 (OH), the carbinol **12** exhibited broad peaks at δ 5.68 (benzylic CH) and 2.04 (OH), and the diol **11** exhibited at broad peak at δ 3.2 (OH).

Reaction of PhCOPh (2) with Me_2CuLi. A. Product Studies. To a cold (0 °C) solution of Me_2CuLi, prepared from 1110 mg (5.4 mmol) of Me_2SCuBr and 10.8 mmol of MeLi in 10.2 ml of Et_2O, was added a solution of 900 mg (4.94 mmol) of ketone **2** in 3 ml of Et_2O. The resulting solution, which immediately turned dark red, was stirred at 0 °C for 10 min and then at 25 °C for 30 min. The solution remained red during the 10 min at 0 °C but changed progressively to green and then to a blue color with a yellow precipitate as the solution was warmed from 0 to 25 °C. The blue solution (containing a yellow precipitate) exhibited no further change during a 60-min period at 25 °C. Then 8 ml of MeOH–HOAc (1:1 v/v, N_2 passed through the solution to remove dissolved O_2) was added, and the mixture was partitioned between Et_2O and an aqueous solution (pH 8) of NH_3 and NH_4Cl. The Et_2O layer was washed with aqueous $NaHCO_3$, dried, and concentrated to leave 846 mg of crude product as a yellow liquid that contained (HPLC with added naphthalene as an internal standard and NMR analysis) the ketone **2** (17% recovery) and the carbinol **9** (70% yield); neither the alcohol **12** nor the diol **11** was detected (HPLC analysis) in the crude product.

In a comparable reaction a solution (at 25 °C) of 5.4 mmol of Me_2CuLi in 10.2 ml of Et_2O was treated with a solution of 400 mg (2.2 mmol) of PhCOPh in 3.0 ml of Et_2O and the resulting mixture was stirred at 25 °C for 20 min. During this reaction period the initial reaction mixture was a deep red solution that turned green as a yellow precipitate began to separate. Within 5 min, the separation of the yellow precipitate was complete leaving a deep blue colored supernatant liquid. After the reaction mixture had been partitioned between Et_2O and water, the crude neutral organic product was isolated as 390 mg of yellow liquid containing (HPLC and NMR analysis) the ketone **2** (22% recovery) and the carbinol **9** (63% yield). The same procedure was repeated with 5.4 mmol of Me_2CuLi and 900 mg (4.94 mmol) of the ketone **2** in 13.2 ml of Et_2O to give 890 mg of crude liquid product containing (TLC, HPLC, and NMR analysis) the ketone **2** (26% recovery) and the alcohol **9** (53% yield). A portion of the crude product was chromatographed on alumina to separate 121 mg of early fractions (eluted with PhH) containing (TLC and NMR analysis) ketone **2**, 162 mg of intermediate fractions (mixtures of **2** and **9**, eluted with PhH), and 109 mg of fractions (eluted with PhH and PhH–Et_2O) containing (TLC and NMR analysis) the carbinol **9**. Recrystallization of the early fractions from Et_2O–hexane separated 86 mg of pure PhCOPh, mp 46–48 °C, and recrystallization of the late fractions from PhH separated 64 mg of the carbinol **9**, mp 80–81 °C.

To explore the effect of LiBr on this reaction, a previously described[28] procedure was used to obtain a solution of Me_2CuLi that did not contain an equimolar amount of a lithium halide. Reaction of 2.2 ml of an Et_2O solution containing 1.54 mmol of MeLi with a solution of 310 mg (1.50 mmol) of Me_2SCuBr in 2 ml of Et_2O and 2 ml of Me_2S yielded a yellow precipitate of $(MeCu)_n$ which was separated by centrifugation, washed with 2 ml of Et_2O, and then treated with 2.0 ml of an Et_2O solution containing 1.4 mmol of MeLi to give a colorless solution of halide-free Me_2CuLi. After this solution of Me_2CuLi had been cooled to 0 °C, it was treated with a solution of 220 mg (1.21 mmol) of PhCOPh in 2 ml of Et_2O. The resulting red solution was warmed from 0 to 25 °C during 20 min (during which time a yellow precipitate separated and the solution turned blue) and then quenched with 4 ml of a MeOH–HOAc mixture (deoxygenated with N_2). After the usual isolation procedure, analysis (HPLC with added internal standard) of the crude product (211 mg of colorless liquid) indicated the presence of the alcohol **9** (39% yield) and the ketone **2** (53% recovery).

In another experiment, a cold (−20 °C) solution of 2.14 mmol of Me_2CuLi in 8 ml of Et_2O was treated with a solution of 350 mg (1.92 mmol) of PhCOPh in 3 ml of Et_2O and the resulting solution was stirred at −20 °C for 20 min. After this solution had been quenched with 5 ml of MeOH–HOAc (1:1 v/v, flushed with N_2 to remove O_2), it was partitioned between Et_2O and an aqueous solution of NH_3 and NH_4Cl. The ethereal solution was washed with aqueous NaCl, dried, and concentrated to leave 327 mg of colorless liquid that contained (HPLC and NMR analyses) the starting ketone **2** (93% recovery) but none of the alcohols **9**, **11**, or **12**.

B. Studies of the Visible and EPR Spectra. To obtain authentic samples of the dianion **13** and the ketyl **10**, the following procedures were employed.[29]

A solution of the dianion **13** was obtained by stirring a solution of 1.276 g (7.0 mmol) of PhCOPh in 30 ml of Et_2O with 0.4 g (56 mg-atoms) of Li wire at 25 °C for 18 h. The solution initially turned a blue color corresponding to the ketyl **10** and then slowly became dark red in color as the dianion **13** formed. The solution was quenched with 5 ml of MeOH–HOAc (1:1 v/v, flushed with N_2 to remove O_2) and subjected to the usual isolation procedure to separate 1.28 mg of crude neutral product containing (HPLC and NMR analysis) ketone **2** (22% recovery) and alcohols **12** (30% yield) and **11** (47% yield). A portion

of the same solution of dianion **13** was diluted with Et_2O containing 0.3 mmol of MeLi (a scavenger for O_2 and protic impurities) and then exhibited a visible absorption maximum at 504 nm with an absorbance of 0.71 corresponding to ϵ 2100 if conversion of **2** to the dianion **13** (maximum concentration 3.39×10^{-4} M) was complete. When excess ethereal Me_2CuLi was added to this solution, the principal maximum (at 504 nm) remained with a new shoulder at ca. 590 nm. When an ethereal solution of the dianion **13** was deliberately oxidized by adding O_2 (air) to the cell, the solution changed from red to blue in color with loss of the absorption maximum at 504 nm and the appearance of a new maximum at 614 nm corresponding to the ketyl **10**. Further oxidation gave a colorless solution of PhCOPh. The reported[29] maximum for an Et_2O solution of the dianion **13** is 494 nm (ϵ 25 000).

A solution of the ketyl **10** was obtained[29] by treating 96 mg (0.26 mmol) of the pinacol **11** in 25 ml of Et_2O with 1.2 ml of an Et_2O solution containing 1.15 mmol of MeLi. After the resulting blue solution had been stirred at 25 °C for 20 min, it was quenched with 10 ml of MeOH–HOAc (1:1 v/v, flushed with N_2 to remove O_2) and subjected to the usual isolation procedure to separate 98 mg of crude neutral product as a yellow liquid containing (TLC, HPLC, and NMR analysis) the ketone **2** (ca. 44%) and the alcohols **12** (ca. 3%) and **11** (ca. 53%). A comparable solution of the ketyl **10** from 96 mg (0.26 mmol) of the pinacol **11** and 1.2 mmol of MeLi (halide free) in 1.2 ml of Et_2O exhibited a maximum at 613 nm with an absorbance of 0.71 corresponding to ϵ 213 if all of the pinacol **11** was converted to ketyl **10**. The reported[29] absorption maximum for an Et_2O solution of the ketyl **10** is 600 nm (whether the MeLi used contained LiBr was not stated).[8] When the ketyl **10** was prepared from diol **11** and MeLi containing LiBr, the absorption maximum was 598 nm. An analogous blue solution of the ketyl **10**, prepared from 7.3 mg (0.02 mmol) of the diol **11**, and 1.0 mmol of MeLi (halide free) in 11 ml of Et_2O exhibited an intense EPR signal[30] with g = 2.0028. In certain of the preparations of this ketyl **10**, partial resolution of the hyperfine structure was achieved.[31]

When the Et_2O solution of PhCOPh was added to a cold (−20 °C) ethereal solution of excess 0.2 M Me_2CuLi (from halide-free MeLi and Me_2SCuBr) in a uv cell and the resulting red solution was scanned rapidly, a broad peak was observed at 422 nm. As the solution warmed, with corresponding color changes from red to yellow to green to blue, the peak at 422 nm was gradually replaced by a new maximum at 600–610 nm corresponding to the ketyl **10**. When 1 equiv of PhCOPh was added to an Et_2O solution of Me_2CuLi at 25 °C, the initial scan of the resulting blue solution exhibited a maximum at 600 nm corresponding to the ketyl **10**. Similarly, as a cold (−78 °C) red solution, prepared from 45 mg (0.22 mmol) of Me_2SCuBr, 0.4 mmol of MeLi, 40 mg (0.2 mmol) of ketone **2**, and 2 ml of Et_2O exhibited a weak EPR signal (g = 2.0027)[30] that increased in intensity substantially as the solution was warmed to 25 °C and became blue in color.

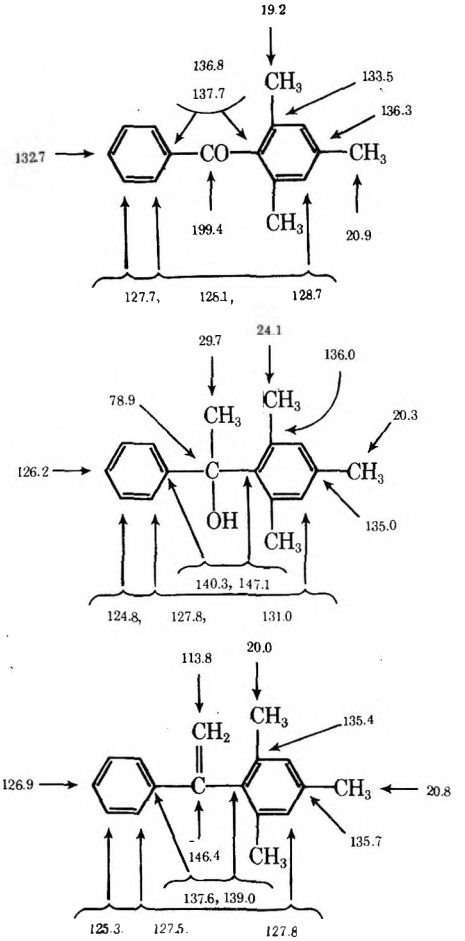
Reactions of Ketone 3. A. With MeLi. To a cold (0 °C) solution of 1.80 g (8.04 mmol) of the ketone **3** in 10 ml of Et_2O was added, dropwise and with stirring, 15 ml of an Et_2O solution containing 10.5 mmol of halide-free MeLi. The resulting yellowish-brown solution was stirred at 25 °C for 25 min and then partitioned between Et_2O and H_2O. After the organic layer had been dried and concentrated, the crude product, 1.86 g of yellow liquid, contained (ir, NMR, and TLC analysis, silica gel with Et_2O–pentane (1:9 v/v) as eluent) mainly the alcohol **14** (R_f 0.28) accompanied by a small amount of the starting ketone **3** (R_f 0.48). Chromatography on silica gel with an Et_2O–pentane eluent (1:24 v/v) separated 1.563 g (81%) of the liquid alcohol **14**. A portion of the product was distilled in a short-path still to separate the alcohol **14** as a pale yellow liquid: bp 145–147 °C (1.1 mm); n^{25}D 1.5776; ir (CCl_4) 3595 cm^{-1} (OH); uv (95% EtOH) a series of weak maxima (ϵ 393 or less) in the region 245–260 nm; NMR (CCl_4) δ 7.0–7.4 (5 H, m, phenyl CH), 6.68 (2 H, s, aryl CH), 2.18 (3 H, s, aryl CH_3), 2.10 (6 H, s, aryl CH_3), 1.88 (3 H, s, CH_3CO), and 1.68 (1 H, s, OH, exchanged with D_2O); mass spectrum m/e (rel intensity) 240 (M^+, <1), 223 (13), 222 (58), 208 (18), 207 (100), 206 (18), 192 (45), 191 (12), and 96 (11).

Anal. Calcd for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found: C, 84.98; H, 8.40.

In another experiment, a solution of 168 mg (0.75 mmol) of the ketone **3** in 5 ml of Et_2O was maintained at −70 °C during the addition of 1.2 ml of an Et_2O solution containing 0.84 mmol of halide-free MeLi. The resulting yellow-colored solution was stirred at −70 °C for 1 h and then quenched with a cold mixture of MeOH and HOAc (5:1 v/v) and subjected to the usual isolation procedure. The crude liquid product (167 mg) contained (ir and NMR analyses) the starting ketone **3** and no alcohol **14** was detected. A comparable experiment was performed by preparing a cold (−70 °C) solution of 1.0 mmol of ketone **3** and 2.0 mmol of MeLi (containing LiBr) in 10 ml of Et_2O. This pale yellow solution, which exhibited no significant absorbtion above 400 nm, was allowed to warm slowly. At ca. −10 °C the solution became yellowish-brown in color and exhibited intense absorption below 450 nm with a shoulder at ca. 500 nm. Thus, the color and absorption of the reaction solution from ketone **3** and MeLi are comparable in the presence or in the absence of LiBr.

Mixtures of the alcohol **14** and the ketone **3** could also be analyzed by GLC (Carbowax 20M on Chromosorb P), the products elected being the olefin **15** (retention time 2.4 min, from dehydration of the alcohol **14**) and the ketone **3** (5.2 min). A sample of the olefin **15**, collected (GLC) after injection of the alcohol **14**, was obtained as a colorless liquid, n^{25}D 1.5833, that was identified with the subsequently described sample by comparison of GLC retention times and NMR spectra. After a solution of 377 mg (1.57 mmol) of the alcohol **14** and 50 mg of p-$CH_3C_6H_4SO_3H$ in 25 ml of PhH had refluxed for 30 min, the solution was washed with aqueous $NaHCO_3$, dried, and concentrated. Distillation of the residual liquid in a short-path still separated 247 mg (71%) of the olefin **15** as a pale yellow liquid: bp 122–125 °C (0.7 mm); n^{25}D 1.5830 [lit.[11] bp 120 °C (3 mm), n^{20}D 1.5835]; ir (CCl_4) 1613 (C=C) and 905 cm^{-1} (C=CH_2); uv max (95% EtOH) 247 nm (ϵ 6500); NMR (CCl_4) δ 7.1–7.4 (5 H, m, phenyl CH), 6.81 (2 H, s, aryl CH), 5.92 (1 H, d, J = 1.5 Hz, vinyl CH), 5.04 (1 H, d, J = 1.5 Hz, vinyl CH), 2.27 (3 H, s, aryl CH_3), and 2.07 (6 H, s, aryl CH_3); mass spectrum m/e (rel intensity) 222 (M^+, 48), 208 (20), 207 (100), 206 (20), 192 (58), and 41 (19).

The natural abundance ^{13}C NMR spectra ($CDCl_3$ solution) of the ketone **3**, the alcohol **14**, and the olefin **15** are summarized in the following formulas. The assignments are compatible with relative peak areas and with off-resonance decoupling measurements.



B. With Me_2CuLi. To 10 ml of a solution (at 25 °C) of 5.0 mmol of Me_2CuLi was added, dropwise with stirring, 684 mg (3.0 mmol) of the ketone **3**. The resulting yellow solution was stirred at 25 °C for 30 min. A comparable yellow solution exhibited broad absorption at 380–400 nm with no resolved absorption peak at longer wavelength. When excess ethereal MeLi was added to this yellow solution, the solution developed a red color and exhibited a new absorption maximum within the range 510–525 nm. After the yellow reaction solution had been subjected to the usual isolation procedure, the crude liquid product contained (GLC and NMR analysis) the starting ketone **3** but no alcohol **14** was detected. In a comparable experiment where

the solution of Me_2CuLi and ketone **3** was stirred at 25 °C for 18 h, the crude product isolated again contained (GLC) only the starting ketone **3.**

A comparable yellow solution was obtained by adding 45 mg (0.2 mmol) of the ketone **3** in 1 ml of Et_2O to a cold (−50 °C) solution of Me_2CuLi, from 205 mg (1.0 mmol) of Me_2SCuBr, 1.8 mmol of MeLi (containing LiBr), and 11.8 ml of Et_2O. At −20 °C this solution exhibited no EPR signal.[30] After the solution had been warmed to 25 °C during 40 min, the resulting yellow solution exhibited a very weak EPR signal, g = 2.0020, corresponding to the subsequently described ketyl **16.**

C. With the Reagent from Me_2CuLi and MeLi. To a solution (at 25 °C), prepared from 411 mg (2.0 mmol) of Me_2SCuBr, 6.0 mmol of MeLi, and 10 ml of Et_2O, was added a solution of 400 mg (1.79 mmol) of the ketone **3** and 2 ml of Et_2O. The resulting dark red solution was stirred at 25 °C for 30 min and then quenched with MeOH–HOAc (1:1 v/v, flushed with N_2) and subjected to the usual isolation procedure. The crude liquid product contained (NMR and GLC analyses) ca. 20% of the alcohol **14** and ca. 80% of the ketone **3.** Collected (GLC) samples of the ketone **3** and the olefin **15** (from dehydration of alcohol **14** in the GLC apparatus) were identified with previously described samples by comparison of GLC retention times and NMR and mass spectra.

When 23 mg (0.10 mmol) of ketone **3** was added to a cold (−50 °C) solution, from 0.49 mmol of Me_2CuBr, 1.4 mmol of MeLi (containing LiBr), and 10 ml of Et_2O, a yellow solution was obtained that remained yellow and exhibited no absorption maximum at longer wavelength than 400 nm as the solution was warmed to −20 °C. As the solution was further warmed to 25 °C, a red color developed and a new maximum appeared at ca. 475 nm. In a similar experiment where the ketone **3** was added to a solution (at 25 °C) of the reagent, Me_2CuLi + MeLi prepared with halide-free MeLi, the red solution exhibited a maximum at ca. 500 nm corresponding more closely to the absorption observed for the subsequently described ketyl **16** in the absence of LiBr.[8]

Similarly when a cold (−50 °C) solution, from 1.0 mmol of Me_2S-CuBr, 2.9 mmol of MeLi (containing LiBr), 0.11 mmol of ketone **3,** and 11 ml of Et_2O, was examined at −20 °C, it exhibited an EPR signal[30] of only moderate intensity corresponding to the ketyl **16.** When the solution was warmed to 25 °C, the intensity of the EPR signal (at g = 2.0020) attributable to the ketyl **16** increased approximately 100-fold.

D. With Li. A solution of 700 mg (3.12 mmol) of the ketone **3** in 35 ml of Et_2O was stirred with 260 mg (37.1 mg-atoms) of Li wire under an argon atmosphere for 6 h at which time the gradually increasing absorbance of the red-purple solution had become constant. The solution of the ketyl **16** exhibited a maximum at 530 nm; the absorbance value corresponded to ϵ 930 if conversion of the ketone **3** to the ketyl **16** were complete. A comparable solution of the ketyl **16** exhibited a strong EPR signal, g = 2.0024,[30] with partial resolution of hyperfine structure.[32]

After a comparable red solution, from 700 mg (3.12 mmol) of the ketone **3** and 260 mg (37.1 mg-atoms) of Li in 35 ml of Et_2O, had been stirred for 10 days, the red color had faded to leave a yellow solution. This solution was quenched with MeOH–HOAc (1:1 v/v, flushed with N_2) and subjected to the usual isolation procedure. The crude liquid product (682 mg) contained (ir and NMR analysis) a mixture of the ketone **3** (ca. 20%) and the alocohol **17** (ca. 80%). Chromatography on silica gel with Et_2O–hexane (1:24 v/v) separated 367 mg of the alcohol **17** as a pale yellow liquid: $n^{25}D$ 1.5819 [lit. bp 138–139 °C (0.5 mm)[33a]]; ir (CCl_4) 3610 cm^{-1} (OH); NMR (CCl_4) δ 7.1–7.3 (5 H, m, phenyl CH), 6.74 (2 H, s, aryl CH), 6.17 (1 H, s, carbinol CH), 2.21 (3 H, s, aryl CH_3), 2.12 (6 H, s, aryl CH_3), and 2.04 (1H, broad, OH); uv (95% EtOH) shoulder at 216 nm (ϵ 17 300) with a series of weak maxima (ϵ 400 or less) in the region 257–274 nm;[33b] mass spectrum m/e (rel intensity) 226 (M^+, 30), 208 (30), 207 (25), 193 (100), 178 (28), 149 (39), 147 (47), 121 (47), 105 (98), 91 (41), 79 (38), 77 (85), and 51 (28).

Competitive Reaction of Me_2CuLi with Ketones 2 and 21. A solution of Me_2CuLi, from 925 mg (4.5 mmol) of Me_2SCuBr, 9.0 mmol of MeLi, and 8.6 ml of Et_2O, was cooled to −72 °C and a solution of 910 mg (5.0 mmol) of PhCOPh and 800 mg (5.0 mmol) of ketone **21** in 4.0 ml of Et_2O was added, dropwise and with stirring while the temperature was maintained at −65 to −72 °C. After the resulting red solution had been stirred for 5 min at −70 °C, it was allowed to warm slowly with stirring. At ca. −40 °C separation of $(MeCu)_n$ from the red solution began and when the solution had warmed to −20 °C, the solution was pale yellow with a copious precipitate of $(MeCu)_n$. The resulting mixture was warmed to 22 °C (with no further change in appearance) and then quenched with a MeOH–HOAc mixture and then filtered and partitioned between Et_2O and H_2O. The ethereal layer was washed with an aqueous solution (pH 8) of NH_3 and NH_4Cl and then dried and concentrated to leave 1.74 g of crude product as a pale yellow liquid. An aliquot of the crude product was mixed with naphthalene (an internal standard for HPLC analysis, C-18 Corasil column with CH_3CN–H_2O, 1:3 v/v, as eluent). The product contained (ir, NMR, and LC analyses) the carbinol **9** (retention time 3.3 min, ca. 4% yield), the ketone **21** (3.8 min, 23% recovery), the ketone **2** (4.8 min, 90% recovery), naphthalene (6.5 min), and the ketone **30** (64% yield).

Reaction of Me_2CuLi with Cinnamonitrile (27). To a cold (0 °C) solution of Me_2CuLi, from 1110 mg (5.4 mmol) of Me_2SCuBr, 10.8 mmol of MeLi, 5.0 ml of Me_2S, and 10.2 ml of Et_2O, was added a solution of 568 mg (4.4 mmol) of the nitrile **27** in 2 ml of Et_2O. After the yellow-orange solution had been stirred at 0 °C for 20 min, a 3.0-ml aliquot was removed and partitioned between H_2O and Et_2O. The crude neutral product obtained from the Et_2O solution amounted to 109 mg of yellow liquid with NMR absorption corresponding to the starting nitrile **27.**[34] The remainder of the reaction solution was stirred at 25 °C for 1 h and then subjected to the same isolation product. The crude product, 669 mg of red viscous liquid, was chromatographed on silica gel with Et_2O–hexane mixture as eluents. Early fractions eluted with Et_2O–hexane (1:4 v/v) provided 195 mg of crude product that contained (NMR analysis) mainly the starting nitrile **27.** Later chromatographic fractions exhibited broad, ill-defined NMR absorption and appeared to be a mixture of polymeric materials that contained no product from conjugate addition.

Earlier studies in our laboratory by Dr. Michael J. Umen had indicated that ethereal solutions of Me_2CuLi did not react with anthracene (**26**). To examine the behavior of this hydrocarbon **26** with a mixed reagent, a solution with the average composition Me_4CuLi_3 was prepared from 411 mg (2.0 mmol) of Me_2SCuBr and 8.0 mmol of halide-free MeLi in 4.5 ml of Et_2O. This solution was treated with a solution of 267 mg (1.5 mmol) of anthracene (**26**) in 5 ml of PhH and the resulting solution was stirred at 25 °C for 1 h and then subjected to the usual isolation procedure. The crude organic product (192 mg of colorless solid) had NMR absorption corresponding to unchanged anthracene (**26**). Analysis by GLC (Carbowax 20M on Chromosorb P) indicated the presence of anthracene (**26,** retention time 10.0 min) and no peak was observed corresponding to 9-methylanthracene (16.0 min).

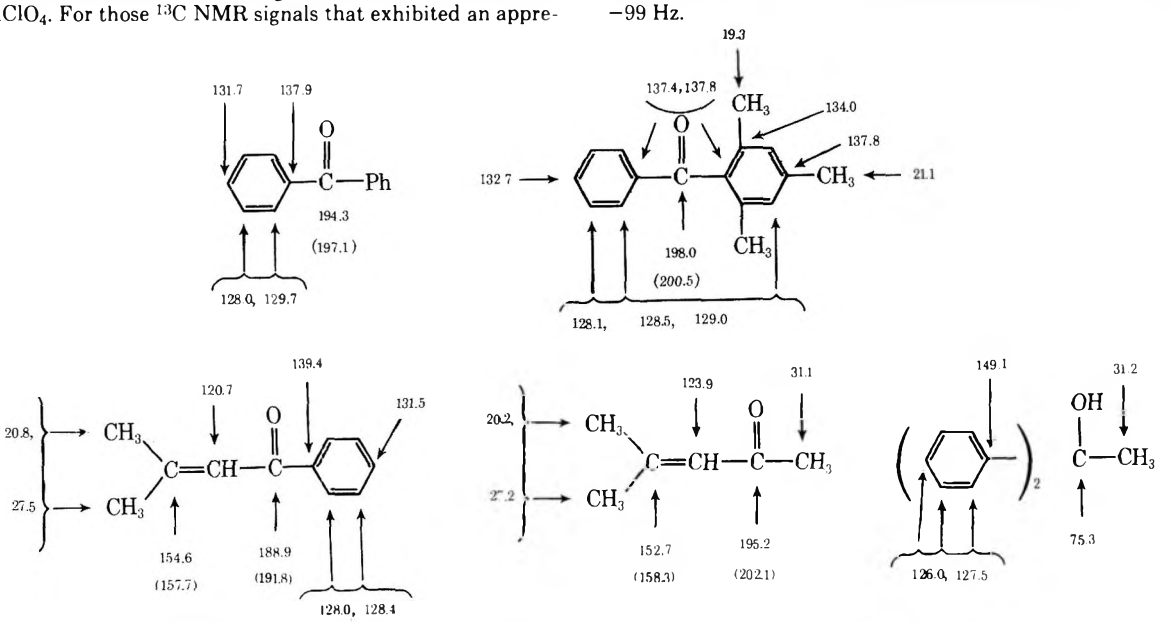
Preparation of the Complex 20. Following a previously described[15] procedure, a mixture of 572 mg (4.0 mmol) of Cu_2O, 1.31 g (32 mmol) of CH_3CN, 4.6 ml of aqueous 70% $HClO_4$ (32 mmol), and 25 ml of H_2O was refluxed under a N_2 atmosphere for 10 min and then allowed to cool. Colorless crystals of the complex **20** that separated were recrystallized from an H_2O–CH_3CN mixture to separate 851 mg (37%) of the complex **20** as colorless prisms. A CH_3CN solution of the complex **20** exhibited end absorption with ϵ 11 000 at 231 nm. Addition of either ketone **2** or ketone **3** to this solution produced no visible color and the uv spectrum of the mixtures showed only absorption bands attributable to the complex **20** and the added ketone **2** or **3.**

A series of experiments were performed in which solutions containing 0.01–0.5 molar equiv of various Cu(II) salts (with added solubilizing ligands) were mixed with 1.0 molar equiv of Ph_2CO. The Cu salts examined included $BrCuSMe_2$ in $CDCl_3$, $CuBr_2$ in DME and in CH_3CN, $Cu(OAc)_2$ in $CDCl_3$, and $Cu(acac)_2$ in $CDCl_3$. In all cases we observed no color change indicating an interaction between Ph_2CO and the Cu(II) compound. Also, even in the presence of substantial concentrations of the paramagnetic Cu(II) compounds, the ^{13}C NMR signals for Ph_2CO did not exhibit a substantial shifting or broadening; only the ^{13}C NMR signals for various added ligands or solvents were broadened. Thus, we found no evidence for significant association between these Cu(II) compounds and Ph_2CO.

Raman Spectra of Reactants.[35] The Raman spectrum of an Et_2O solution of PhCOPh exhibited peaks at 1669 (C=O) and 1604 cm^{-1} (phenyl) with the region 1430–1510 cm^{-1} being obscured by absorption of the solvent, Et_2O.[36] The Raman spectrum of a solution of 45 mg (0.25 mmol) of the ketone **2** and 28 mg (0.26 mmol) of $LiClO_4$ in 0.50 ml of Et_2O exhibited comparable peaks at 1668 and 1603 cm^{-1}. Similarly, a solution of 36 mg (0.16 mmol) of ketone **3** in 0.70 ml of Et_2O exhibited Raman peaks at 1682 (C=O) and 1603 cm^{-1} (phenyl ring) and a solution of 230 mg (1.03 mmol) of ketone **3** and 230 mg (2.2 mmol) of $LiClO_4$ in 1.0 ml of Et_2O exhibited comparable peaks at 1681 and 1603 cm^{-1}. The Raman spectrum of a cold (−40 °C) red solution obtained from addition of PhCOPh to an Et_2O solution of Me_2CuLi exhibited bands at 1671 and 1604 cm^{-1} suggesting that the concentration of the species responsible for the red color is small.

NMR Studies. A. Reactants. The subsequently described natural abundance of ^{13}C NMR spectra were measured in Et_2O with added C_6D_6 (ca. 20% by volume to provide a "lock" signal) and Me_4Si as an

internal standard; the ^{13}C NMR lines arising from these solvents were found at 15.4 and 65.7 ppm (Et_2O signals) and at 126.6, 127.5, and 128.5 ppm (C_6D_6 signals). The assignments indicated are consistent with relative peak intensities and with off-resonance decoupling measurements. The ^{13}C NMR data for ketones **2**, **3**, **21**, and **22** were also measured in a solution containing 1.0–1.5 molar equiv of anhydrous $LiClO_4$. For those ^{13}C NMR signals that exhibited an appreciable shift (more than 1 ppm), the values in the presence of added $LiClO_4$ are indicated in parentheses. It will be noted that added $LiClO_4$ causes an appreciable downfield shift in the ^{13}C NMR signal for only the carbonyl carbon atom of the diaryl ketones **2** and **3** whereas both the carbonyl carbon atoms and the β-carbon atoms of the enones **21** and **22** undergo an appreciable downfield shift in signal.



A 1.6 M solution of halide-free MeLi in 1.5 mol of Et_2O containing 0.2 ml of C_6D_6 and 0.2 ml of Me_4Si exhibited a single ^{13}C NMR line for the MeLi at −13.4 ppm when measured at 35 °C. As the solution was cooled to 0 °C, this line broadened (half-band width 60 Hz). Upon further cooling to −40 °C, this line appeared as a multiplet centered at −13.2 ppm. This multiplet appeared to consist of a more intense ten-line pattern (eight of the ten lines were clearly resolved, $J_{^{13}C-^{7}Li}$ = 15 Hz) expected[14] for a Me group bound to three equivalent ^7Li atoms. Superimposed upon this ten-line multiplet was a less intense seven-line multiplet ($J_{^{13}C-^{7}Li}$ = 15 Hz), the pattern expected for approximately 20% of the Me groups that are bound to a tetrahedral face defined by two ^7Li atoms and one ^6Li atom. A solution of Me_2CuLi, prepared from 4 ml of an Et_2O solution containing 7.08 mmol of halide-free MeLi, 728 mg (3.64 mmol) of $BrCuSMe_2$, 0.3 ml of C_6D_6, and 0.2 ml of Me_4Si, exhibited a single ^{13}C NMR line for the Me groups at −9.6 ppm when measured at 35 °C. As the solution was cooled to −60 °C the half-band widths for the Me signals of Me_4Si and Me_2CuLi remained the same. Upon further cooling to −80 °C, the Me signal for Me_2CuLi (at −8.4 ppm) had a half-band width of 10 Hz while the half-band width for the Me_4Si signal was 5 Hz. Upon further cooling, the solutions became sufficiently viscous that all of the lines in the spectrum were seriously broadened.

A solution corresponding in stoichiometry to the composition Me_4CuLi_3 was prepared from 411 mg (2.0 mmol) of Me_2SCuBr, 4.5 ml of an Et_2O solution containing 8.0 mmol of halide-free MeLi, 0.2 ml of C_6D_6, and 0.1 ml of Me_4Si. As had been observed previously[5] in the ^1H NMR spectrum, the ^{13}C NMR spectrum of this solution at 35 °C exhibited a single peak at −11.1 ppm corresponding to the average signal for all of the methyl groups present in the organometallic reagent. As this solution was cooled, the peak broadened and at −40 °C had separated into two broad partially resolved peaks at −9.0 and −13.1 ppm. Further cooling to −60 °C was accompanied by precipitation of the MeLi to leave a single sharp signal at −8.8 ppm corresponding to the Me_2CuLi that remained in solution. These observations are compatible with the earlier ^1H NMR observations[5] where the signal at −78 Hz for the rapidly equilibrating Me groups separated into two signals at −72 and −112 Hz when the solution was cooled to −62.5 °C. As noted in earlier work,[5] the ^1H NMR signals for solutions (at 35 °C) of MeLi and Me_2CuLi were found as singlets at −110.5 and −57 Hz (half-band width 2.5 Hz) and the addition of extra MeLi to the Me_2CuLi solution moved the position of the ^1H NMR singlet (−57 Hz) to higher field. The ^1H and ^{13}C NMR signals for the Me_2S present in the Me_2CuLi solutions (prepared from Me_2SCuBr) were located at δ 2.00 and 17.8 ppm, respectively. A solution of MeLi in a mixture of Et_2O and DME containing excess $LiClO_4$ exhibited an ^1H NMR MeLi signal at −124 Hz. A comparable solution of Me_2CuLi in Et_2O and DME containing excess $LiClO_4$ exhibited an ^1H NMR signal at −99 Hz.

B. Reaction of PhCOPh with Me_2CuLi. A cold (ca. −60 °C) solution of Me_2CuLi, from 0.22 mmol of Me_2SCuBr and ca. 0.5 mmol of MeLi in 0.4 ml of Et_2O, containing Me_4Si was treated with 1 molar equiv of PhCOPh; the resulting red solution exhibited an ^1H NMR CH_3 singlet at −62 Hz with a half-band width of 2.5 Hz. When a second molar equiv of PhCOPh was added to the cold, red solution, the Me signal was shifted to −51.5 Hz. The remainder of the spectrum of this cold red solution exhibited peaks attributable to Et_2O, Me_2S, and PhCOPh but none of the alcohol product **9** was detected.

When a cold (−20 °C) solution of 3.0 mmol of Me_2CuLi in 3.3 ml of Et_2O containing 0.2 ml of C_6D_6 and 0.2 ml of Me_4Si was treated with 558 mg (3.0 mmol) of PhCOPh, the resulting red solution exhibited ^{13}C NMR signals attributable to Me_2CuLi and to PhCOPh at −9.3, 127.6, 128.5, 130.9, 135.8, and 199.6 ppm. In this spectrum, the signals at −9.3 (cuprate Me signals), 130.9 (*p*-C atoms of PhCOPh), and 199.6 ppm (C=O) were significantly broader than the other signals in the spectrum. This experiment was repeated with a cold (−30 to −40 °C) solution prepared from 250 mg (1.37 mmol) of PhCOPh and 1.46 mmol of the previously described *halide-free* Me_2CuLi in 1.0 ml of Et_2O. The ^{13}C NMR values observed, −9.6, 128.5, 130.7, 132.6, 136.3, and 198.9 ppm, were comparable to those observed in a reaction solution containing LiBr.

A solution prepared from 500 mg (2.75 mmol) of PhCOPh, 10 mg (0.027 mmol) of the diol **11**, 0.2 ml of C_6D_6, 0.3 ml of Me_4Si, and 1.0 ml of Et_2O was treated with 0.4 ml of an Et_2O solution containing 0.28 mmol of MeLi. The ^{13}C NMR spectrum of the resulting blue solution (containing PhCOPh and less than 0.02 molar equiv of the ketyl **10**) exhibited only peaks attributable to the solvents (Et_2O, C_6D_6, and Me_4Si). When the solution was exposed to air to oxidize the ketyl **10**, the blue color was discharged and the ^{13}C NMR spectrum then exhibited all of the additional peaks from the dissolved ketone **2**.

C. Reaction of Ketone 3 with Me_2CuLi. A cold (−20 °C) solution containing 3.0 mmol of Me_2CuLi, 0.2 ml of C_6D_6, and 0.2 ml of Me_4Si in 3.3 ml of Et_2O was treated with 672 mg (3.0 mmol) of the ketone **3**. The resulting yellow solution exhibited the following ^{13}C NMR signals attributable to the ketone **3** and Me_2CuLi: −9.6, 19.4, 21.2, 128.2, 129.2, 129.9, 133.4, 135.1, 135.7, 138.6, and 203.4 ppm. The signals at −9.6 (cuprate Me groups), 129.9, 135.1, and 203.4 ppm (C=O) were broadened when compared with the remaining signals in the spectrum. In a comparable experiment, a cold (0 °C) solution prepared from **3** and *halide-free* Me_2CuLi exhibited a carbonyl ^{13}C NMR signal at 202.3 ppm.

A solution of 500 mg (2.3 mmol) of the ketone **3** in 1 ml of Et_2O containing C_6D_6 and Me_4Si was stirred with 100 mg of Li wire until a red solution (a mixture of ketone **3** and ketyl **16**) was obtained. The ^{13}C NMR spectrum of the mixture exhibited broadened peaks attributable to C_6D_6, Et_2O, and Me_4Si, but no signals attributable to the ketone **3** were observed.

Electrochemical Measurements. Cyclic voltammetry measurements utilized previously described[7,21b] procedures, cells, and electrodes. A series of attempts were made to measure directly by cyclic voltammetry the electrode potential associated with the oxidation of Me_2CuLi, employing previously described combinations of either a bare Pt or Hg-coated Pt working electrode with a saturated calomel reference electrode fitted with appropriate salt bridges and a Pt wire as the counter electrode. For solvents and supporting electrolytes the combinations examined were 0.5 M n-Bu_4NBF_4 in DMF, 0.4 M LiBr in DME, and 0.5 M $LiClO_4$ in DME. Before use, the solutions of LiBr and $LiClO_4$ in DME were treated with small amounts of ethereal MeLi (as a scavenger for O_2 and protic impurities) and then centrifuged. Aliquots of ethereal Me_2CuLi (ca. 1 M) were added to these solvent–electrolyte systems and the resulting solutions were scanned by cyclic voltammetry from −0.5 V to −2.5 V vs. SCE. In no case were any oxidative or reductive current peaks observed that could be attributed to Me_2CuLi. In two cases ($LiClO_4$–DME–Et_2O and n-BuN_4BF_4–DMF–Et_2O) portions of the solutions were examined by ^1H NMR spectra to establish that the CH_3 peak attributable to Me_2CuLi was still present in these solutions being examined electrochemically. Since we have found that anthracene (**26**, $E_{1/2}$ = −1.93 and −2.48 V vs. SCE)[21b] does not react with ethereal Me_2CuLi at 25 °C, it was possible to perform another control experiment. A solution of Me_2CuLi, from 0.30 g (1.5 mmol) of Me_2SCuBr and 2.9 mmol of MeLi in 2 ml of Et_2O, was mixed with 3 ml of DMF containing 0.5 M n-Bu_4NBF_4. Although this solution, whose ^1H NMR spectrum established that Me_2CuLi was still present in the DMF solution, exhibited no oxidative or reductive peak in the region −0.5 to −2.5 V, when anthracene was added to the solution a cyclic voltammetry scan characteristic[21b] of the reversible reduction of anthracene to its radical anion was readily observed.

Registry No.—**2**, 119-61-9; **3**, 954-16-5; **9**, 599-67-7; **14**, 59671-58-8; **15**, 1667-02-3; **16**, 59671-59-9; **17**, 21945-75-5; **20**, 14057-91-1; **21**, 5650-07-7; **27**, 4360-47-8; Me_2CuLi, 15681-48-8; MeLi, 917-54-4.

References and Notes

(1) This research has been supported by Public Health Service Grant 9-RO1-GM-20197 from the National Institute of General Medical Sciences. The execution of this research was also assisted by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.

(2) H. O. House, A. V. Prabhu, J. M. Wilkins, and L. F. Lee, *J. Org. Chem.*, accompanying paper in this issue.

(3) Although several lines of evidence, summarized in ref 4, suggest that this reagent has a dimeric structure ($Me_4Cu_2Li_2$), analogous to $(MeLi)_4$, both for convenience and in accord with current practice [G. H. Posner, *Org. React.*, **19**, 1 (1972); **22**, 253 (1975)] we will continue to refer to this reagent as a monomer (Me_2CuLi) unless the nature of the discussion requires use of the dimeric formulation for clarity.

(4) For a recent summary, see H. O. House, *Acc. Chem. Res.*, **9**, 59 (1976).

(5) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

(6) H. O. House, L. E. Huber, and M. J. Umen, *J. Am. Chem. Soc.*, **94**, 8471 (1972).

(7) H. O. House and P. D. Weeks, *J. Am. Chem. Soc.*, **97**, 2785 (1975).

(8) The visible absorption maxima of Et_2O solutions of both ketyls **10** and **16** were shifted to shorter wavelengths when LiBr was present in the solutions. This phenomenon has been noted and discussed previously by P. G. Powell and E. Warhurst, *Trans. Faraday Soc.*, **58**, 953 (1962).

(9) (a) H. O. House and M. J. Umen, *J. Org. Chem.*, **38**, 3893 (1973); (b) H. O. House, C. Y. Chu, J. M. Wilkins, and M. J. Umen, *ibid.*, **40**, 1460 (1975).

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(34) This result corresponds to our previous observation[9a] that cinnamonitrile is recovered unchanged after treatment with etheral Me_2CuLi at 0–10 °C for 20 min.

(35) The Raman spectra were determined with a Spex monochromator, Model 1401, employing a CR-3 argon ion laser as a light source. We are indebted to Professor Nai-Teng Yu and his associates for performing these measurements.

(36) The analogous infrared bands for DME solutions of $Ph_2C{=}O$ and $Ph_2C{-}O^-Na^+$ (or K^+) are reported to be 1664 (C=O) and 1598 cm^{-1} (Ph) and 1554 (C=O) and 1581 cm^{-1} (Ph), respectively. The C=O absorption for $Ph_2C{-}O^-Li^+$ in DME was found to be 1563 cm^{-1} in concentrated solution and 1617 cm^{-1} in dilute solution. See (a) D. H. Eargle, Jr., and E. W. Cox, "The Alkali Metals", *Chem. Soc., Spec. Publ.*, **No. 22**, 116–124 (1967); (b) D. H. Eargle, Jr., *J. Chem. Soc. B*, 1556 (1970); (c) D. H. Eargle, Jr., and R. Emrich, *J. Org. Chem.*, **35**, 3744 (1970).

Allyl Alcohol to Saturated Ketone Isomerizations in the Presence of Alkali Metal or *n*-Butyllithium

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Propiophenone (**2**) is formed when α-vinylbenzyl alcohol (**3**) is treated with 2 equiv of either *n*-butyllithium or sodium–potassium alloy in DME. The mechanism of both reactions appears to be the same; namely, an intermediate dianion **6** is formed which rapidly undergoes intermolecular chain proton transfers with another ion (**5**) generating propiophenone enolate ion.

One of the methods of preparing allyllithium involves treating allyl phenyl ether with lithium metal in THF solvent.[2] In doing this reaction, we observed than a small amount (ca. 5%) of propiophenone was also produced (eq 1). The yield of

$$\underset{\mathbf{1}}{PhOCH_2CH{=}CH_2} + Li \xrightarrow[-5\,^\circ C]{THF} PhOLi + CH_2{=}CHCH_2Li + \underset{\mathbf{2}}{PhCCH_2CH_3} \quad (1)$$

ketone increased to over 50% when *n*-butyllithium was used in place of the lithium metal.[3] Based on some quenching studies, we proposed the mechanism shown in Scheme I for the *n*-butyllithium reaction.

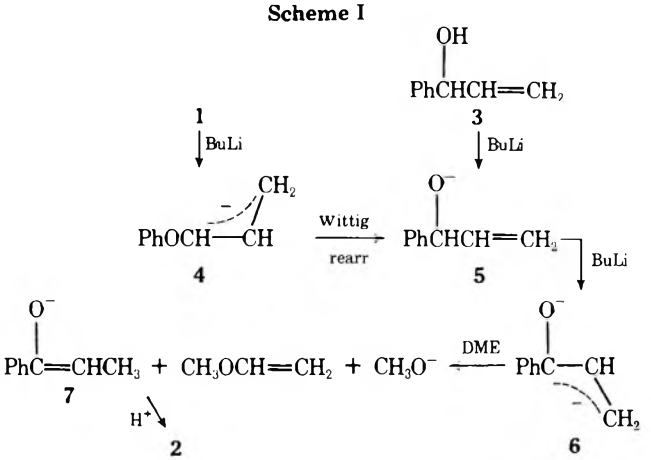
The dianion **6**, which is present in the *n*-butyllithium reaction, could be a useful synthetic intermediate toward the production of specifically alkylated ketones. However, the quenching studies on allyl phenyl ether showed that the dianion (because of its reactivity) never achieved a very high concentration in the reaction mixture. A change to nonpolar solvents, like hexane, changed the whole course of the *n*-butyllithium reactions of allyl phenyl ether[3] and α-vinylbenzyl alcohol (**3**).[4]

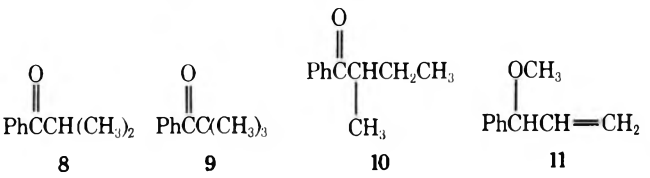
This paper will bring out some additional details about the reactivity of dianion **6** and its conversion (in ether solvents) to propiophenone. Also, some facts concerning the mechanism of the alkali metal promoted isomerizations of **1** and **3** will be presented.

Results

***n*-Butyllithium Reaction.** In order to demonstrate the presence of a dianion intermediate, α-vinylbenzyl alcohol (**3**) was treated with 2 equiv of *n*-butyllithium in DME (dimethoxyethane) and periodically quenched with methyl iodide. Three methylated products, **8**–**10**, were observed. The results are shown in Figure 1. The starting material had all reacted 1 min after mixing (the first sampling), giving rise to a 80:20 mixture of enolate ion **7** and dianion **6**.[5] There was then a slow conversion of dianion **6** to ion **7**, presumably by way of proton abstraction from the solvent, as shown in Scheme I. None of the expected methylated product, **11**, of alkoxide ion **5** was observed, even in the first sampling.

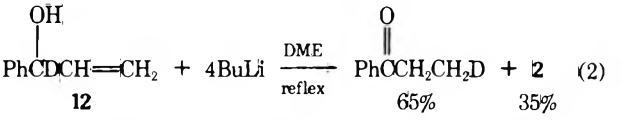
Scheme I





8 **9** **10** **11**

In order to determine what is happening in the first minute of this reaction, the rearrangement of α-deuterio-α-vinylbenzyl alcohol (**12**) was examined. The necessary deuterated alcohol was prepared from α-deuteriobenzaldehyde and vinylmagnesium bromide. Using the conditions normally employed for rearranging **3**, the deuterated analogue gave no ketone and was recovered with deuterium intact. A similar behavior was observed when α,α-dideuterioallyl phenyl ether was treated with *n*-butyllithium.[3,6]



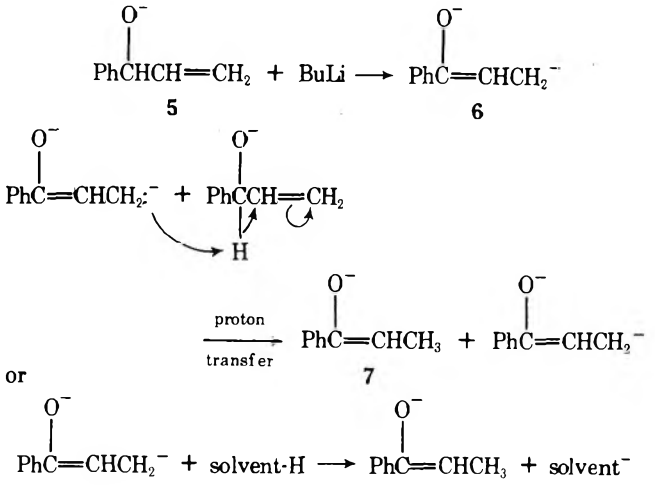
(2)

Under forcing conditions, deuterated alcohol **12** could be rearranged to propiophenone. By a combination of mass and NMR spectra, it was apparent that the propiophenone had 65% of one deuterium atom on the methyl group (eq 2). If the dianion **6** was solely produced by proton abstraction by *n*-butyllithium from alkoxide **5** (Scheme I), there should be no deuterium present in the product ketone. Also, the mechanistically unlikely *intramolecular* 1,3-hydrogen atom transfer within ion **5** can be ruled out in that (a) less than 1 equiv of *n*-butyllithium to α-vinylbenzyl alcohol gives no ketone and (b) excess methyllithium, a base capable of generating **5** from **3**, affords no ketone.

The most plausible explanation of the quenching and deuterium labeling experiments is that the dianion can, in a very rapid reaction, undergo *intermolecular* proton transfers with alkoxide **5**, generating another dianion and propiophenone enolate ion (Scheme II).

For every dianion produced by *n*-butyllithium proton abstraction from **5**, there are many more dianions being produced and destroyed in the chain process. The amount of *n*-butyllithium abstraction vs. chain process can be estimated by (a) the amount of nondeuterated propiophenone produced from **12**, ca. 35%, and (b) the relative amount of dianion remaining (determined by the quenching results) after the first minute of reaction, ca. 20%. The fact that the two estimates do not totally agree can be accounted for by assuming that the dianion, once formed from deuterated alcohol **12**, will be slow to undergo intermolecular deuterium transfer as opposed to reaction with the solvent. Because of this isotope effect, the

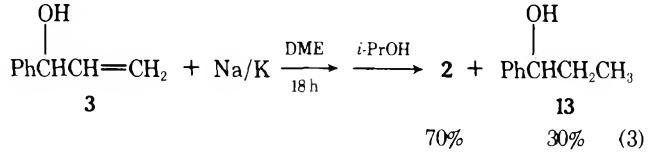
Scheme II



quenching results probably more accurately reflect the degree of proton abstraction by *n*-butyllithium vs. chain process. Even this crude estimate does not depict the true situation in that concentration changes occurring during the course of the reaction disfavor the chain process; i.e., near the end of the reaction, at low alkoxide (**5**) concentrations, the *n*-butyllithium concentration will be high and dianion concentration should still be low.

To summarize, in the reaction of α-vinylbenzyl alcohol with 2 equiv of *n*-butyllithium in DME, a dianion is produced which rapidly undergoes chain proton transfers, followed by a slower reaction with solvent, to give propiophenone (enolate). Based on this conclusion it seems highly unlikely that a dianion like **6** could ever be generated in significant quantities to be a useful synthetic intermediate.

Alkali Metal Reactions. The 5% yield of propiophenone obtained with allyl phenyl ether and lithium metal in THF (eq 1) can be improved to 25% using sodium–potassium alloy in DME. With α-vinylbenzyl alcohol as the starting material, a quantitative production of a 70:30 mixture of propiophenone and 1-phenyl-1-propanol (**13**) was observed (eq 3). The rearrangement of α-vinyl-*p*-methylbenzyl alcohol or allyl *p*-tolyl ether with Na/K alloy in DME gave *p*-methylpropiophenone; consequently, rearrangement occurred without positional changes in the aryl ring.



A methyl iodide quenching study of allyl phenyl ether and Na/K alloy gave anisole, **8**, **9**, **11**, and 1-methoxy-1-phenylpropane (the methylated derivative of **13**). Similarly, α-vinylbenzyl alcohol was methylated at regular time intervals to afford **8**, **9**, and 1-methoxy-1-phenylpropane. This latter reaction was so rapid that no **11** (the methylated product of the starting material) could be detected in the first 2-min sample. The methylated product of dianion **6**, namely **10**, could not be detected (thermal conductivity VPC on concentrated samples) in either case.

The deuterated alcohol **12** was treated with Na/K alloy under the usual room temperature conditions to give, after isopropyl alcohol quenching, unchanged starting material. However, refluxing the mixture for 36 h afforded the usual 70:30 mixture of propiophenone and 1-phenyl-1-propanol. The observed deuterium distribution in the products is shown in eq 4.

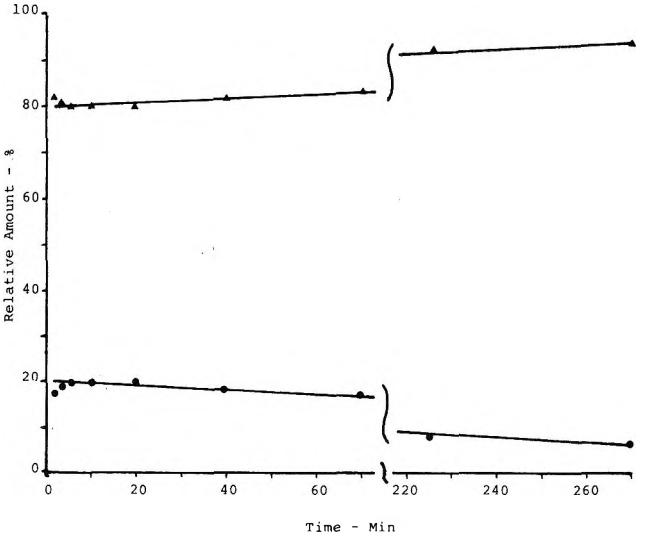
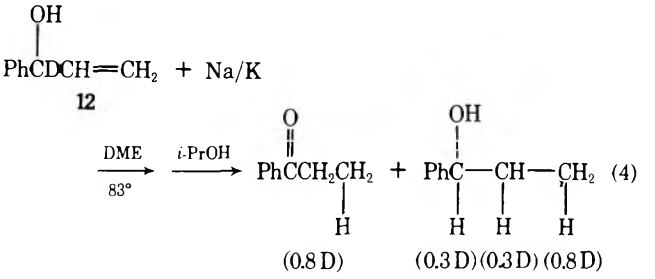


Figure 1. The isomerization of α-vinylbenzyl alcohol (**3**) with 2 equiv of *n*-butyllithium at 25 °C followed by quenching with methyl iodide: ●, amount of α-methylbutyrophenone (**10**); ▲, combined amount of isobutyrophenone (**8**) and pivalophenone (**9**).



The location of 0.8 of one deuterium in the methyl group of propiophenone was easily deduced by a combination of mass and NMR spectra; there appears to be no deuterium in the ring nor at the methylene position. The deuterium distribution in the alcohol was not as easily arrived at. This alcohol, like most others, has a characteristic weak molecular ion region, populated by M − 1, M − 2, etc., peaks in its mass spectrum which made it practically impossible to get an exact deuterium count. A sample of the alcohol was oxidized with CrO_3–H_2SO_4–H_2O to propiophenone. This latter sample of propiophenone was identical in spectral properties with the 0.8 D sample. The oxidation reaction would not only remove the benzylic hydrogen (or deuterium) but should also effectively exchange, via an acid-catalyzed enolization, any deuterium at the methylene position. However, with the knowledge that 80% of one hydrogen on the methylene group was a deuterium, the NMR spectrum of the deuterated 1-phenyl-1-propanol product became much easier to interpret and clearly showed the approximate 0.3 D at each of the other two aliphatic carbons. A spectrum run in the presence of $Eu(fod)_3$ shift reagent showed no deuteriums atoms at any position in the phenyl ring. Isomerization of α-vinylbenzyl alcohol-*O*-*d* gave nondeuterated propiophenone.

Except for the lack of any methylated product **10** in the quenching studies and the appearance of the saturated alcohol **13**, there seems to be a great deal of similarity in the *n*-butyllithium and alkali metal promoted isomerizations of α-vinylbenzyl alcohol. Both exceptions can be explained while staying in the context of a dianion intermediate.

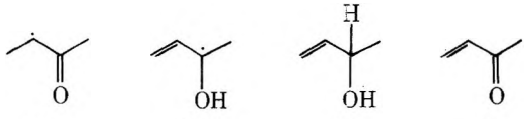
The dianion produced in the *n*-butyllithium reactions (which can be detected) has lithium for a counterion while the alloy reaction would have sodium or potassium counterions. It is well known that organolithium reagents are more stable than the corresponding organosodium or -potassium reagents,

presumably because of a greater degree of covalent bonding in the former case. Conceivably, the alloy reaction could produce a sodium–potassium dianion which is so reactive that it undergoes proton abstraction reactions, as in Scheme II, so rapidly that it never achieves an appreciable concentration or is gone before our first sampling. The greater degree of deuterium found in the propiophenone produced from **12** and Na/K alloy, as compared to the *n*-butyllithium reaction, would indicate that there are more chain proton transfers occurring in the former reaction.

The saturated alcohol **13** is probably a secondary product, arising from the reduction of propiophenone (enolate). This statement is based on the fact that both the alcohol and ketone have the same percent deuterium in their methyl groups. Reducing conditions are present; Na/K alloy in DME is commonly employed in radical anion reactions, where reduction products are frequently observed. Also, sodium hydride or species like this may be present. Sodium hydride has been reported to reduce ketones to alcohols.[7] Treating α-vinylbenzyl alcohol with sodium hydride in refluxing DME afforded nearly a 50:50 mixture of propiophenone and 1-phenyl-1-propanol (**13**).

Some of the saturated alcohol may arise during the isopropyl alcohol quench, via Meerwein–Ponndorf–Verley pathway.[8] Reaction of propiophenone with Na/K alloy, followed by quenching with isopropyl alcohol, gave **13** in yields ranging from 15 to 40% (depending on the order of mixing). It is obvious that all of the saturated alcohol does not result from a reductive quench since methyl iodide quenches show the presence of **13**; also, quenching with *tert*-butyl alcohol (with no α-protons) gave a 80:20 mixture of **2** and **13**.

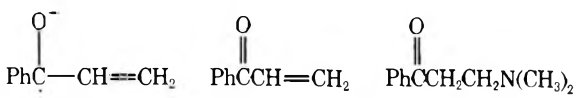
An alternative mechanism for the alloy-promoted isomerizations could involve radicals or radical anion intermediates. As previously mentioned, the conditions were conducive to this type of reaction; bright colors were observed and a reduction product was isolated. Eadon and Shiekh[9] claim that radicals **14** and **15** are intermediates in the copper-catalyzed



14 **15** **16** **17**

rearrangement of 3-buten-2-ol (**16**) to methyl vinyl ketone (**17**). They also observed a 1,3-intermolecular deuterium atom transfer (~80%), showing a large isotope effect.

The radical anion **18** could conceivably be an intermediate in the Na/K reactions. A couple of attempts were made to prove its existence in the alloy reactions. One attempt utilized acrylophenone (**19**) (prepared from amine **20**)[10] and sodium



18 **19** **20**

naphthalide, a radical anion which is capable of proton abstractions from weak acids.[11] By using 1.1 equiv of sodium naphthalide to 0.1 equiv of α-vinylbenzyl alcohol, the alkoxide ion **5** should be produced with 0.1 equiv of sodium naphthalide remaining. Addition of a small amount of acrylophenone should then generate a low concentration of ketyl **18**. When these conditions were used, no rearrangement products were observed; alcohol **3** was recovered.

Since ketyl **18** should be fairly stable, one may be able to generate it by treating ion **5** with a peroxide. Consequently, α-vinylbenzyl alcohol was mixed with 1 equiv of methyllithium (a reagent which does not rearrange the alcohol) and then a small amount of benzoyl peroxide. Refluxing this solution in the presence of a strong light source gave nothing but recovered starting material.

To summarize, the evidence gathered in the Na/K alloy reactions point toward a mechanism involving a very reactive dianion intermediate which follows the reactions outlined in Scheme II. The fact that a strong base like sodium hydride gives the same reaction products as does Na/K alloy indicates that the latter is also probably acting as a strong base. The yields in the Na/K alloy reaction with allyl phenyl ether suggests that extensions of this reaction for the synthesis of ketones will not prove useful, principally because the accompanying cleavage reactions dominate. However, the yields in the alloy-promoted isomerization of α-vinylbenzyl alcohol hint that extensions of this type of reaction may be synthetically useful.

Experimental Section

All boiling points and melting points were uncorrected. Infrared spectra were determined with a Perkin-Elmer spectrophotometer, Model 137-B. NMR spectra were obtained on a Varian Associates A-60A spectrometer, using Me_4Si as the internal standard and carbon tetrachloride as the solvent. Mass spectra were obtained using a CEC-21-104 mass spectrometer. Gas chromatographic analyses and preparative VPC were performed on a 6 ft × 0.25 in. aluminum column packed with 20% silicon rubber (SE-30) on 60–80 mesh Chromosorb W or a 13 ft × 0.25 in. aluminum column packed with 5% diethylene glycol succinate (DEGS) on 30–60 mesh Chromosorb W, or a 6 ft × 0.25 in. aluminum column packed with 20% Reoplex 400 (polyester) on 60–80 mesh Chromosorb W, using a F & M Model 700 gas chromatograph. Anhydrous solvents, such as dimethoxyethane (DME) and *p*-dioxane, were dried over metallic sodium and potassium and distilled immediately before use.

Propiophenone, allyl phenyl ether, 1-phenyl-1-propanol, and isobutyrophenone were commercially available[12] and *p*-methylpropiophenone has been previously described by us.[3] The procedure of Delaby and Lecomte[13] was used to prepare α-vinylbenzyl alcohol and α-vinyl-*p*-methylbenzyl alcohol.

General Procedure for the Sodium–Potassium Alloy Isomerizations. Sodium (0.36 g, 15.7 mg-atoms) and potassium (0.61 g, 15.6 mg-atoms) were fused together in some refluxing anhydrous DME. After the flask was cooled with an ice–water bath, a solution of 15.7 mmol of allyl phenyl ether (or derivative) or α-vinylbenzyl alcohol (or derivative) in DME was added. The mixture was stirred under a nitrogen atmosphere at room temperature for 18 h. [In the cases of deuterated analogues the mixture was refluxed (83 °C).] The DME solution was then filtered through a fritted funnel and quenched with 15 ml of 2-propanol. The solution was further diluted with water and extracted with 3 × 50 ml of ether. The combined ether extracts were washed with a brine solution, dried over magnesium sulfate, and concentrated on a rotary evaporator. A short-path vacuum distillation afforded a colorless liquid which was analyzed by gas chromatography and NMR. Small samples of the various components of the mixture were usually obtained by preparative VPC and analyzed by ir, NMR, and mass spectra.

The variable time quenching experiments were performed as follows. The substrate to be isomerized, allyl phenyl ether or α-vinylbenzyl alcohol, was added rapidly to a vigorously stirred ice-cold suspension of Na/K alloy in DME in a three-neck round-bottom flask under a nitrogen atmosphere. One minute after initial mixing a sample was withdrawn with a disposable pipet and added to an Erlenmeyer flask containing an excess of methyl iodide in DME. Additional samples were treated the same way at periodic time intervals, i.e., 2, 4, 8, 15, 20, 30, 60, 90, 120, etc., min, after the start. The quenched samples were then analyzed directly by VPC, using retention time comparisons with known samples for identification purposes and the area under the peak for approximate calculation of the relative amounts. The thermal responses of the components, which were generally isomers of each other, in the VPC traces were not calibrated; thus, the relative areas on the traces may not have represented the relative molar proportions of the volatile components. However, our principal objective was to determine the presence of 2-methylbutyrophenone (**10**)[3] in any of the samples and in no case (even in concentrated samples at high attenuation) was a peak indicative of **10** observed.

1-Methoxy-1-phenylpropane. This was the only compound that

was observed in the methyl iodide quenches which was not already characterized.[3] It was obtained by preparative VPC (SE-30), as were the other "known" components, to confirm its structure. Subsequently, a sample of the compound was prepared independently as described next.

To a solution of 4.0 g (29.5 mmol) of 1-phenyl-1-propanol in 30 ml of anhydrous ether was added 1.26 g (33 mmol) of commercial sodium amide. After the solution was stirred for 3 h, 3.2 ml (50 mmol) of methyl iodide was added. The solution was stirred for another 4.5 h and then poured into water. The aqueous layer was separated and extracted with two 10-ml portions of ether. The combined ether extracts were dried, flash evaporated, and vacuum distilled to give 2 ml of liquid, bp 48–69 °C (2 mm) [lit.[14] bp 76–77 °C (24 mm)]. On analysis by VPC and NMR, this was found to be a mixture of the starting alcohol and 1-methoxy-1-phenylpropane. The mixture was separated by preparative VPC. The spectral properties of 1-methoxy-1-phenylpropane were ir (film) 9.12 (C–O–C), 13.02, 13.22, and 14.16 μ (Ph); NMR (CCl_4) δ 0.88 (t, 3, J = 7 Hz, C–CH_3), 1.70 (m, 2, –CH_2–), 3.15 (s, 3, –OCH_3), 3.95 (t, 1, J = 6.5 Hz, $CHCH_2$–) and 7.22 (s, 5, Ph).

1-Vinylbenzyl Alcohol-*1-d* (12). The necessary starting material, benzaldehyde-*formyl*-d_1, was prepared by a known procedure[15] and based on NMR and mass spectral analysis was about 98% d_1. A solution of 7.2 g (68 mmol) of vinyl bromide in 20 ml of anhydrous THF was added, with vigorous stirring, to 1.1 g (91 mg-atoms) of magnesium turnings, under nitrogen, over a period of 1 h. An acetone–dry ice cold finger condenser was used to prevent the vinyl bromide from escaping. Formation of the Grignard reagent was completed by external heating (45–55 °C) for an additional 3 h. The Grignard reagent was cooled to room temperature and then a solution of 4.0 g (36 mmol) of benzaldehyde-*formyl-d* in 25 ml of THF was added over the course of 0.5 h. The mixture was stirred under nitrogen for 16 h and decomposed with 10 ml of cold, saturated NH_4Cl. The THF solution was decanted from the caked residue which was triturated with 4 × 25 ml of ether. The combined THF–ether solution was dried over $MgSO_4$, concentrated, and distilled to give 4.0 g (80%) of a colorless liquid: bp 77–85 °C (1.5 mm); ir (film) 3500 (OH), 1060 (C–O), 990 (C=CH_2), and 700 cm^{-1} (Ph); NMR (CCl_4) δ 7.18 (s, 5, Ph), 5.90 (d of d, J = 17 and 9.7 Hz, 1, –CH=CH_2), 5.13 (d of d, J = 17 and 2 Hz, 1, trans CH=CH_2), 5.01 (d of d, J = 9.7 and 2 Hz, 1, cis CH=CH_2), and 3.78 (s, 1, OH); mass spectrum (70 eV) *m/e* (rel intensity) 135 (74), 134 (82), 116 (31), 108 (33), 105 (75), 93 (57), 92 (54), 80 (100), 79 (43), 78 (87), 77 (74), 55 (37), 51 (69), 39 (31), and 27 (49).

Isomerization of α-Vinylbenzyl Alcohol (3). A. With Na/K Alloy, Quenched with 2-Propanol. The general procedure afforded a mixture of 70% propiophenone and 30% 1-phenyl-1-propanol, as proven by preparative VPC and comparison of spectral properties to those of known samples.[13]

B. With Na/K Alloy, Quenched with *tert*-Butyl Alcohol. The general procedure was used except for the substitution of *tert*-butyl alcohol for 2-propanol. Analysis by VPC showed 81% propiophenone and 19% 1-phenyl-1-propanol.

C. With Sodium Naphthalide. According to a procedure of Scott,[17] a dark green solution of sodium naphthalide was prepared from 2.5 g (19 mmol) of naphthalene and 0.6 g (26 mg-atoms) of sodium in 25 ml of DME. To this green solution was added 2.2 g (16.4 mmol) of α-vinylbenzyl alcohol and 4 drops of acrylophenone.[10,16] After stirring at room temperature for 18 h the green color was discharged by adding water. The solution was extracted with 2 × 50 ml of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated on a rotary evaporator. VPC analysis showed only naphthalene and α-vinylbenzyl alcohol.

D. With Sodium Hydride. To a suspension of 0.97 g (40 mmol) of sodium hydride in DME was added, with stirring, 5.3 g (40 mmol) of α-vinylbenzyl alcohol. After refluxing for 20 h, the solution was diluted with water and extracted with ether. The ether extract was dried over $MgSO_4$ and concentrated. VPC analysis showed 46% of propiophenone and 54% of 1-phenyl-1-propanol.

E. With *n*-Butyllithium. To a cold (0 °C) solution of 3.0 g (22.4 mmol) of α-vinylbenzyl alcohol in 20 ml of DME was rapidly added 44.8 mmol of *n*-butyllithium in hexane. A vigorous reaction occurred and the reaction mixture became red. The cooling bath was removed and the mixture allowed to warm to room temperature (25 °C). Samples were withdrawn at regular time intervals, quenched with methyl iodide, diluted with ether, and washed with water. The ether solutions were concentrated and chromatographed (SE-30).

From matching retention times, it was possible to prove the presence of isobutyrophenone (8), pivalophenone (9), and α-methylbutyrophenone (10). The results are shown in Figure 1.

Reduction of Propiophenone with Na/K alloy and 2-Propanol. Potassium (0.50 g, 12.8 mg-atoms) and sodium (0.30 g, 12.8 mg-atoms) were fused together in refluxing DME. After cooling to 5 °C, 1.72 g (12.8 mmol) of propiophenone was added. The solution was stirred at room temperature for 18 h. A 5-ml sample was withdrawn, by means of a syringe, and *added* to 1 ml of 2-propanol. Water and ether were added and the ether layer separated, dried over $MgSO_4$, and concentrated. VPC analysis showed 85% propiophenone and 15% α-vinylbenzyl alcohol.

The remaining residue in the flask *was treated with* 15 ml of 2-propanol until all the metal had disappeared (1 h). Ether and water were added and the ether layer separated, dried over $MgSO_4$, and concentrated to give 1.50 g of a colorless liquid: VPC analysis showed 57% propiophenone and 43% α-vinylbenzyl alcohol.

Isomerization of 1-Vinylbenzyl Alcohol-*1-d* (12). A. With Na/K Alloy. The general procedure, employing refluxing DME for 36 h, gave, after quenching with 2-propanol, 1.2 g of colorless liquid. Analysis by VPC showed 70% propiophenone and 30% 1-phenyl-1-propanol. The VPC separated sample of propiophenone showed ir (film) 1710 (C=O), 747 and 692 cm^{-1} (Ph); NMR (CCl_4) δ 7.80–8.05 (m, 2, ortho protons), 7.15–7.55 (m, 3, meta and para protons), 2.70–3.12 (m, 2, –CH_2),[18] and 0.98–1.33 (m, 2.2, –CH_D);[19] mass spectrum (70 eV) *m/e* (rel intensity) 136 (2), 135 (13), 134 (5), 105 (100), 77 (51), 51 (25), 50 (9), 29 (3), and 27 (8). A comparison of this mass spectrum with that of a nondeuterated sample of propiophenone indicated a deuterium distribution of 27% d_0, 69% d_1, and 4% d_2.

The NMR spectrum of the VPC separated sample of the deuterated 1-phenyl-1-propanol showed, in comparison to an authentic, undeuterated sample, a singlet at 7.18 for the aromatic protons (area 110), a broad triplet at 4.38 (J = 7.0 Hz, area 14), a singlet at 2.83 (area 26) for the hydroxy proton, a broad multiplet at 1.56 (area 37), and a multiplet at 0.83 ppm (area 49). Sufficient amount of $Eu(fod)_3$ (67.7 mg) was added so that the benzyl, ortho, and meta and para protons were well resolved. The relative integrated areas under ortho:benzyl:meta and para:methylene:methyl were 36:12.3:55:31:40, respectively. Assuming that there are no deuterium atoms in the phenyl ring gives a relative ratio of 2.0:0.7:3.0:1.7:2.2 for the above-mentioned protons.

The NMR sample was concentrated to remove CCl_4 and diluted with ether. The solution was cooled to 0 °C and CrO_3–H_2SO_4 solution was added dropwise until a red color persisted. The red color was discharged by the addition of 2-propanol. The ether solution was filtered, washed with 1 ml of water, dried over $MgSO_4$, and concentrated. A VPC separated sample showed that it was propiophenone; its NMR and mass spectra were identical with those of the deuterated propiophenone. From the NMR spectrum of propiophenone, the deuterium distribution in 1-phenyl-1-propanol was determined: 0.32 at the benzylic position, 0.28 at the methylene position, and 0.80 at the methyl position.

B. With *n*-Butyllithium. To a cold (5 °C) solution of 0.13 g (0.9 mmol) of 1-vinylbenzyl alcohol-*1*-d_1 in 15 ml of anhydrous DME was added a hexane solution of 4.0 mmol of *n*-butyllithium. The mixture was refluxed under nitrogen for 4 h and then stirred at room temperature for 14 h. The mixture was poured into 25 ml of water and extracted with 2 × 50 ml of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated to yield 107 μl of a liquid. VPC analysis (DEGS) showed 87% propiophenone and five other unidentified components totaling 13%. No detectable amount of 1-phenyl-1-propanol was found. After purification by preparative VPC, the sample showed the following spectral characteristics: NMR (CCl_4) 7.78–8.03 (m, 2.0, ortho protons), 7.18–7.53 (m, 3.0, meta and para protons), 2.70–3.12 (m, 2.0, –CH_2–), and 0.99–1.34 ppm (m, 2.4, –CH_2D);[20] mass spectrum (70 eV) *m/e* (rel intensity) 136 (3), 135 (11), 134 (6), 105 (100), 77 (60), 51 (29), 50 (13), 29 (5), and 27 (8), By comparison to the nondeuterated propiophenone spectrum, a deuterium distribution was arrived at: 34% d_0, 56% d_1, and 9% d_2.

Isomerization of α-Vinylbenzyl Alcohol-*O-d* with Na/K Alloy. To 6 ml of heavy water was added 2 g of α-vinylbenzyl alcohol (3) and a catalytic amount of sodium. This mixture was stirred overnight and extracted with two 8-ml portions of ether. The combined ether extracts were dried, flash evaporated, and vacuum distilled to give 3-*O-d*. Its NMR spectrum did not show any alcoholic hydrogen. Rearrangement of this by way of the general procedure gave propiophenone containing no deuterium (NMR).

Treatment of α-Vinylbenzyl Alcohol Salt with Benzoyl Peroxide. To a solution of 1.34 g (10 mmol) of 3 in cold DME was added 4.2 ml (10 mmol) of a solution of methyllithium in ether. After the solution was stirred for 15 min, 0.242 g (1 mmol) of benzoyl peroxide was added. A dark red color developed. The solution was then refluxed overnight under a 150-W light bulb. The usual workup, after vacuum distillation, gave 0.4 g of liquid, bp 40–110 °C (2 mm). Based on VPC and NMR, the liquid was principally starting alcohol 3.

Registry No.—**2**, 93-55-0; **3**, 4393-06-0; **12**, 33716-94-8; 1-phenyl-1-propanol, 93-54-9; sodium amide, 7782-92-5; 1-methoxy-1-phenylpropane, 59588-12-4; benzaldehyde-*formyl-d*, 3592-47-0; α-vinylbenzyl alcohol-*O-d*, 59588-11-3.

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(6) The exact reason for this large isotope effect is unknown. It is conceivable that dianion generation could have a large isotope effect, based on the evidence that certain monoanion formations have exhibited isotope effects of $k_H/k_D = 24$ at −50 °C [A. Wright and R. West, *J. Am. Chem. Soc.*, **96**, 3227 (1974)]. In the allyl phenyl ether case the α deuteriums appear to not only retart isomerization but also divert the starting material toward competing reactions.
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(18) The multiplet pattern consisted of an intense triplet ($J = 7$ Hz, vicinal H–H), which was further split (equal intensity triplet, $J = 0.7$ Hz, vicinal H–D), and a weaker quartet ($J = 7$ Hz, vicinal H–H).
(19) The pattern is definitely that of a triplet ($J \approx 7$ Hz), which is further split. It appears that there is some unsplit triplet superimposed on a triplet which is further split into an equally intense triplet ($J \approx 2$ Hz, geminal H–D).
(20) The patterns of the methylene and methyl groups were similar to the previously described deuterated propiophenone,[18,19] but obviously different with the respect to the amount of deuterium on the methyl group. The methylene quartet (reflecting the nondeuterated propiophenone component) and triplet, which was further split (reflecting the $-CH_2CH_2D$ unit), were closer to the same intensity.

Synthesis of Optically Active Dialkylarylsulfonium Salts from Alkyl Aryl Sulfoxides[1]

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Treatment of alkoxysulfonium salts, prepared by O-alkylation of optically active methyl, ethyl, and *n*-butyl *p*-tolyl sulfoxides, with alkyl Grignard or alkylcadmium reagents gave optically active *n*-butylmethyl-*p*-tolyl-, *n*-butylethyl-*p*-tolyl-, and ethylmethyl-*p*-tolylsulfonium salts. Racemic phenyl-o-tolyl-*p*-tolyl- and ethylphenyl-*p*-tolylsulfonium salts were formed from optically active alkoxyphenyl-*p*-tolylsulfonium salts. Trialkylsulfonium salts were not formed when alkoxydialkylsulfonium salts were treated with alkyl Grignard or alkylcadmium reagents. The chiroptic properties of the dialkyl-*p*-tolylsulfonium salts are discussed.

Optically active sulfonium salts, formerly accessible only by resolution, may be synthesized by treating optically active O-alkylated sulfoxides with organocadmium or Grignard reagents (eq 1).[3] This reaction has recently been shown to proceed with inversion of configuration

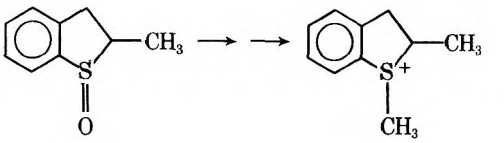
$$RR'S{=}O \rightarrow RR'S^+{-}OR''' \rightarrow RR'R''S^+ \qquad (1)$$

although partial racemization of the alkoxysulfonium salt may lower the enantiomeric purity of the product.[4]

This article reports on the study of this reaction for the synthesis of dialkylaryl-, triaryl-, alkyldiaryl-, and trialkylsulfonium salts and on the chiroptic properties of dialkylarylsulfonium salts. In principle, a given sulfonium salt may be prepared from any one of three sulfoxides. That is, any one of the three groups around sulfur could come from the organometallic reagent while the other two originate from the sulfoxide. But in fact, only alkoxyalkylaryl- and alkoxydiarylsulfonium salts ($RArS{-}OR^+$, $Ar_2S{-}OR^+$) react as in eq 1; alkoxydialkyl sulfonium salts (R_2SOR^+) do not.

Results and Discussion

Dialkylarylsulfonium Salts. Treatment of alkoxysulfonium salts, derived from (*R*)-alkyl *p*-tolyl sulfoxides, with alkylcadmium or Grignard reagents yields optically active dialkyl-*p*-tolylsulfonium salts (Table I). Since the cyclic analogues *cis*- and *trans*-**4** yield sulfonium salts *trans*- and *cis*-**5** with predominant inversion at sulfur (eq 2), we assume that acyclic compounds behave similarly.[4] This assumption is



(2)

4 **5**

strengthened by the reactions depicted by eq 3–6. Enantiomeric sulfonium salts are produced in each pair of reactions (eq 3 and 4, 5 and 6) from sulfoxides of known absolute configuration, thus establishing a common stereochemical process. These results, and the fact that displacement of alkoxy

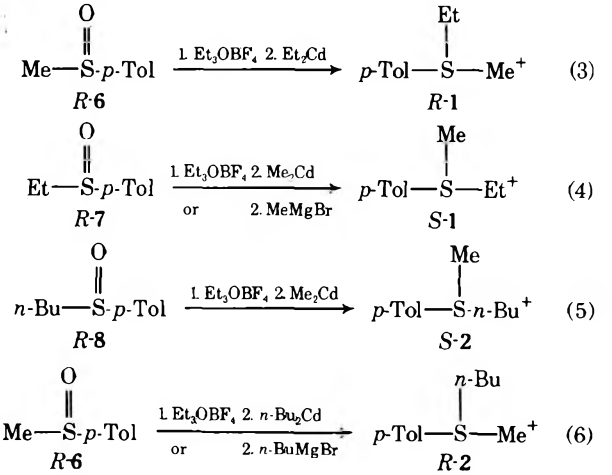


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Table I. Dialkyl-*p*-tolylsulfonium Salts (*p*-TolR′R″SX) Prepared from (*R*)-Alkoxyalkyl-*p*-tolylsulfonium Salts (*p*-TolR″SOR‴$^+$)

Sulfonium salt[a]	R′	R″	R‴O	X$^-$	Mp, °C	$[\alpha]^{25}$D	Yield, %[b]	Registry no.
R-1	Et	Me	EtO	TNBS$^-$	199–200	−5.6[c]	57[d]	59710-76-8
			MeO	BF_4^-	Oil	−15.8[e]	51[f]	59710-77-9
			MeO	Ph_4B^-	168–170	−10.5[c]	39[f]	59710-78-0
			EtO	Br^-	Oil	−115[g,e]	25[f]	59710-79-1
S-1	Me	Et	EtO	TNBS$^-$	208–209	19.2[c]	16[h]	59710-81-5
			MeO	BF_4^-	Oil	21.2[e]	59[f]	59710-82-6
			MeO	Ph_4B^-	168–170	9.0[c]	53[f]	59710-83-7
			EtO	Ph_4B^-	167–169	4.8[c]	7[h]	
			EtO	Ph_4B^-	165–166	7.8[c]	9[i]	
			EtO	Br^-	Oil	230[g,e]	72[f]	59710-84-8
R-2	*n*-Bu	Me	EtO	TNBS$^-$	136–142	−6.6[c]	10[h]	59751-79-0
			EtO	Ph_4B^-	100–110	−10.7[c]	10[h]	59751-80-3
			EtO	Ph_4B^-	119–121	−17.5[c]	9[i]	
S-2	Me	*n*-Bu	EtO	TNBS$^-$	149–150	7.6[c]	75[j]	34586-95-3
R-3	*n*-Bu	Et	EtO	TNBS$^-$	148–150	−6.2[c]	11[i]	59710-86-0
S-3	Et	*n*-Bu	MeO	BF_4^-	Oil	8.7[e]	59[k]	59710-88-2
			MeO	Ph_4B^-	140–142	10.2[c]	64[f]	59710-89-3

[a] The TNBS (2,4,6-trinitrobenzenesulfonate) and tetraphenylborate salts analyzed within 0.3% of theory for C and H. [b] Based on sulfoxide. [c] In acetone. [d] Distilled Et_2Cd, room temperature, 3 h (ref 3). [e] In ethanol. [f] Distilled R'_2Cd, room temperature, 2 h. [g] 290 nm. [h] Undistilled R'_2Cd, room temperature, 20 min. [i] R′MgBr, −78 °C, 1 h. [j] Distilled Me_2Cd, room temperature, 40 h (ref 3). [k] Distilled R'_2Cd, room temperature, 20 min.

groups from acyclic tricoordinate S(IV) generally proceeds with inversion, justify our generalization.[5]

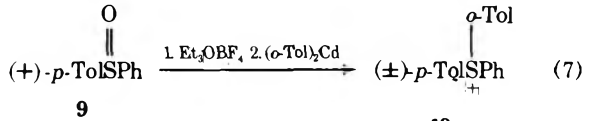
If Grignard reagents or organocadmium reagents are used, the chemical yields of sulfonium salts are around 10%; but if distilled, halide-free alkylcadmiums are employed, the yields improve to ca. 50–70% (Table I). Competing racemization reactions of the alkoxysulfonium salts may be important so the sulfonium salts produced are probably not optically pure. This is particularly true in the case of the distilled organocadmium reagents which react more slowly than Grignard reagents. In any event, the sulfonium salts are of unknown optical purity no matter which organometallic is used in their synthesis.

The sulfonium salts do not racemize at room temperature, nor are they destroyed by the organometallic reagents under the reaction conditions, but isolation as the bromide should be avoided. Use of the nonnucleophilic tetrafluoroborate anion is prefered to minimize any decomposition of the sulfonium salt during workup.[4]

Other systems were employed in an attempt to prepare dialkylarylsulfonium salts. When *N*-tosyl-*S*-methyl-*S*-phenylsulfilimine was alkylated with methyl fluorosulfonate and treated with *n*-butylmagnesium bromide, none of the desired sulfonium salt was obtained. The products isolated include the parent sulfilimine, *N*-methyl-*p*-toluenesulfonamide, and methyl phenyl sulfoxide. An analogous reaction with *N*-tosyl-*S*-phenyl-*S*-ethylsulfilimine gave similar results.

Several sulfoxides have been alkylated with a 1-bromoadamantane.[6] Treatment of 1-adamantoxymethyl-*p*-tolylsulfonium salts with ethylcadmium over a 20-min period at room temperature gave the desired sulfonium salt 1 in only 6% yield, but after 15 h the yield was 100%.

Triarylsulfonium Salts. Triarylsulfonium salts have been prepared from the reaction of alkoxydiarylsulfonium salts with aryl Grignard reagents, but the salts obtained were always racemic.[7] The evidence suggested a low barrier to pyramidal inversion with consequent rapid racemization at room temperature although other causes could not be completely ruled out. We carried out a synthesis using an arylcadmium reagent and also obtained a racemic product (eq 7). Since Grignard and organocadmium reagents both react with inversion at sulfur (eq 3–6) in the synthesis of dialkylarylsulfonium salts and would be expected to do so in the analogous triaryl case, the formation of a racemic product further supports the idea of a low barrier. Darwish recently estimated the half-life for triarylsulfonium salts undergoing pyramidal inversion to be 15 min in methanol at 25 °C.[8]



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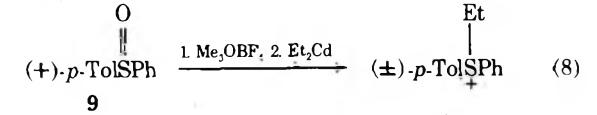
Alkyldiarylsulfonium Salts. One alkyldiarylsulfonium salt was prepared (eq 8), but it was racemic. Darwish and Scott



9 11 (8)

studied the racemization of ethyl-*p*-anisylphenylsulfonium salt and observed a half-life of about 2.3 h in methanol at 25 °C.[8]

Trialkylsulfonium Salts. The alkylation of racemic or optically active dialkyl sulfoxides (cyclic or acyclic) followed by treatment with Grignard or organocadmium reagents at varying temperatures and reaction times failed to yield any sulfonium salt. The main product was the parent sulfoxide, which was often isolated as a 1:1 adduct of sulfoxide and 2,4,6-trinitrobenzenesulfonic acid, the anion used in the attempted isolation of the sulfonium salt.

A number of model experiments were undertaken to explain this observation. The reaction of (±)-methoxy-*n*-butylmethylsulfonium tetrafluoroborate with ethylcadmium indicated that propane was formed, so attack at the alkoxy carbon was definitely occurring. Triethylsulfonium tetrafluoroborate was stable to treatment with methylcadmium; no propane or ethylene was formed and the salt was recovered in quantitative yield. The same result was obtained on treatment with methoxide ion (methylcadmium followed by the addition of an aliquot of methanol).

Thus, the reaction of O-alkylated dialkyl sulfoxides with alkylmagnesium, alkylcadmium, or dialkylmagnesium reagents does not form trialkylsulfonium salts. If the salts were formed, they would have been isolated since they are stable under the reaction conditions.

Table II. ORD, CD, and Uv Measurements on Dialkyl-*p*-tolylsulfonium Salts

Mode	Salt[a]	Anion	Concn[b]	P[c]	T[c]	P	T	P	T	P	T	P	T
ORD	*S*-1	BF_4^-	0.004–0.04	272 (400)	269 (200)	260 (815)	258 (800)	240 (1200)					
ORD	*R*-1	BF_4^-	0.006–0.06	272 (−500)	269 (−350)	262 (−700)	257.5 (−600)	238 (−3400)					
ORD	*S*-1	Br^-	0.05	271.5 (480)	269.5 (340)	267.8 (580)	265.5 (560)	241.6 (1820)					
ORD	*R*-1	Br^-	0.05	271 (−176)	267.5 (−120)	262.5 (−355)	260 (−352)	241.5 (−724)					
ORD	*S*-3	BF_4^-	0.045	275.5 (130)	270.5 (110)	265 (120)	258.5 (64)	237 (660)					
CD	*S*-1	BF_4^-	0.004–0.04	274 (−1800)	272 (−1300)	265 (−2120)	258 (−1600)	255 (−1700)					
CD	*R*-1	BF_4^-	0.006–0.06	270 (1750)	268 (1720)	265 (2130)	263 (1200)	255 (3330)					
CD	*S*-1	Br^-	0.05	274 (−2940)	269 (−1470)	267.5 (−2500)	255 (−494)	252.5 (−611)					
CD	*R*-1	Br^-	0.05	273.2 (1400)	268 (1175)	265 (1410)	263 (423)	250 (1434)					
CD	*S*-3	BF_4^-	0.045	273.5 (−2500)	271 (−2200)	264 (−2900)	257 (−2750)	250 (−3600)					
CD	*R*-1	BF_4^-	0.04						200[d] (−8600)	230 (34 000)	215 (22 000)		
Uv	1	BF_4^-	0.0004–0.004	274.5 (1800)	272 (1460)	266.5 (1900)	262.5 (1700)	255 (1720)	253.5 (1700)	229 (20 000)	218 (11 000)		
Uv	1	Br^-	0.002–0.009	274 (1375)	272 (1050)	266 (1615)	257.5 (1350)	254 (1375)	251 (1300)	230 (9000)			
Uv	3	BF_4^-	0.0046	275 (1100)	273 (950)	266 (1350)	263 (1320)	254 (1650)	253 (1630)				

[a] Configuration of predominant enantiomer. [b] g/ml in ethanol. [c] P = peak; T = trough. Wavelengths are in nm; values in parentheses are for molecular rotation (ORD), molecular ellipticity (CD), and molar extinction coefficients (uv). [d] In methanol.

Table III. ^{1}H NMR Parameters of Sulfonium Tetraphenylborates[a]

Sulfonium salt	SCH_3	SCH_2CH_3	$S(CH_2)_3CH_3$	SCH_2	$SCH_2CH_2CH_3$	$-C_6H_4CH_3$	ArH	Anion Ph
1	3.28 s	1.24 t (8)		3.64 m		2.44 s	7.8 q (8.5)	7.04 m
2	3.19 s		0.81 t (5.5)	3.52 m	1.37 m	2.33 s	7.5 q (8)	6.8 m
3		1.17 t (6)	0.84 t (6)	3.72 m	1.44 m	2.44 s	7.8 q (8)	7.08 m
10						2.44 s	7.7 m	7.02 m
						2.52		
11		1.24 t (8)		2.9 m		2.68 s	7.52 m	7.52 m

[a] Chemical shifts are in parts per million from internal Me_4Si in Me_2SO-d_6 except for 11, which was run in CH_2Cl_2 with external Me_4Si. Coupling constants are in hertz and enclosed in parentheses.

When the *O*-adamantyl derivatives of dimethyl, di-*n*-butyl, methyl *n*-butyl, and pentamethylene sulfoxides were treated with alkylcadmiums, no trialkylsulfonium salts were isolated; the products were the parent sulfoxide, adamantanol, and uncharacterized substances, probably sulfides.

Chiroptic Properties of Dialkyl-*p*-tolylsulfonium Salts. The first reported ORD and CD spectral data for sulfonium salts are listed in Table II.

The uv spectra of dialkyl-*p*-tolylsulfonium salts exhibit primary or ^1L_a bands at ca. 230 nm and less intense secondary or ^1L_b bands at 250–280 nm arising from the aromatic chromophore.[9] Cotton effects (CE) were recorded in the 250–280-nm region, but the low rotation and high absorptivity of the salts made measurements at lower wavelengths difficult. We were successful in measuring only one short wavelength CE, the one for (−)-*R*-1 bromide. The longer wavelength data exhibited a fair amount of experimental error as can be seen by comparing the ORD and CD data for enantiomers.

The longer wavelength (^1L_b) CE correspond fairly well with the uv maxima, e.g., Figure 1, while the oppositely signed shorter wavelength CE observed for (−)-*R*-1 tetrafluoroborate corresponds to the ^1L_a absorption.

Although positive ORD curves are associated with the (+)-*S* enantiomers, the CD curves are negative, showing that the ^1L_b CE are actually negative. The positive rotation at 589 nm is caused by the tail of a strong positive CE associated with the primary bands. Thus, the (+)-*S* enantiomers give rise to negative CE in the 250–280-nm region and the (−)-*R* isomer to positive CE.

Experimental Section

Instrumentation. NMR spectra, obtained on a Varian A-60 or Jeolco HM-100 spectrometer, are reported in Table III. Optical rotations, optical rotatory dispersion curves, and circular dichroism curves were obtained on a Cary 60 recording spectrophotopolarimeter; optical rotations were also taken on a Carl Zeiss 0.005° photoelectric precision polarimeter. Uv spectra were recorded on a Cary Model 14 recording spectrophotometer. Ir spectra were obtained on a Perkin-Elmer Model 337 grating infrared spectrophotometer. Melting points, determined on a Hoover capillary melting point apparatus, are uncorrected. Microanalyses were determined by Mrs. L. Heavner, Mrs. D. Cardin, and Miss G. Lambert on a F & M Model 185 carbon, hydrogen, nitrogen analyzer.

Dialkyl-*p*-tolylsulfonium salts were prepared from optically active O-methylated and O-ethylated sulfoxides in three ways: by the use of distilled methyl- or ethylcadmium,[10] by undistilled organocadmium reagents, or by Grignard reagents. An example of each method is given. Racemic salts were prepared by alkylation of sulfides with triethyl- or trimethyloxonium tetrafluoroborate or methyl fluorosulfonate. Optically active sulfoxides of high optical purity were synthesized by treating (−)-menthyl-(*S*)-*p*-toluenesulfinate with the appropriate Grignard reagent.[11]

1. (*S*)-(+)-Ethylmethyl-*p*-tolylsulfonium Tetraphenylborate (1). (*R*)-Ethyl *p*-tolyl sulfoxide (1.0 g, 5.9 mmol, $[\alpha]^{25}D$ 186.6°, acetone) was methylated using trimethyloxonium tetrafluoroborate (0.96 g, 6.5 mmol) in nitromethane.

The solution was concentrated and (*R*)-methoxyethyl-*p*-tolylsulfonium tetrafluoroborate was precipitated by addition of an excess of ether. The salt was purified by dissolution in methylene chloride followed by precipitation with ether. After several repetitions, 1.27 g (80%) of the salt was obtained as a thick yellow oil.

Distilled methylcadmium in ether (3 ml, 6.18 mmol, 30% excess, 2.08 M) was added with rapid stirring to a methylene chloride solution of the oil. After 20 min at room temperature, the excess cadmium reagent was hydrolyzed with 5% sulfuric acid, and the entire mixture was extracted with water. The aqueous layers were saturated with ca. 20 g of sodium tetrafluoroborate and extracted with five 25-ml portions of methylene chloride. The organic layer was dried over magnesium sulfate and concentrated on the rotary evaporator to give the tetrafluoroborate as a thick yellow oil. It was purified by dissolution in methylene chloride followed by precipitation with ether as above. After drying in vacuo, 0.88 g (73%) of (*S*)-(+)-ethylmethyl-*p*-tolylsulfonium tetrafluoroborate was obtained.

The tetrafluoroborate (0.2 g, 0.79 mmol) was converted to the tetraphenylborate by mixing acetone solutions of the sulfonium salt and sodium tetraphenylborate and adding ether. After several reprecipitations there remained 0.33 g (90% yield).

2. (*S*)-(+)-Ethylmethyl-p-tolylsulfonium Salt (1). (*R*)-Ethyl *p*-tolyl sulfoxide (1.00 g, 5.94 mmol, $[\alpha]^{25}D$ +185.7°, acetone) was ethylated with triethyloxonium tetrafluoroborate (1.19 g, 6.26 mmol) in methylene chloride. Methylcadmium prepared from cadmium chloride (2.00 g, 10.9 mmol) and methylmagnesium bromide (7.4 ml, 21.8 mmol, 3.0 M in ether) was added at 0 °C. After 15 min, the mixture was poured into water and extracted with ether. Several grams of sodium bromide were added. The aqueous layer was acidified with 5% hydrochloric acid and then extracted several times with chloroform. Concentration on the rotary evaporator without external warming gave 1.06 g (72.3%) of crude bromide.

The 2,4,6-trinitrobenzenesulfonate salt was obtained from the crude bromide (0.53 g) in acetone–ether using 2,4,6-trinitrobenzenesulfonic acid to yield 0.22 g (22%).

The tetraphenylborate salt was prepared in a similar way from sodium tetraphenylborate (0.74 g) and the crude bromide (0.53 g) in acetone, yield 0.10 g (9.6%).

3. (*S*)-(+)-Ethylmethyl-*p*-tolylsulfonium Tetraphenylborate (1). (*R*)-Ethyl *p*-tolyl sulfoxide (1.0 g, 5.9 mmol, $[\alpha]^{25}D$ 185.7°, acetone) was ethylated with triethyloxonium tetrafluoroborate (1.32 g, 6.6 mmol) in methylene chloride. Methylmagnesium bromide (2.0 ml, 6 mmol, 3.0 M) was added slowly at −78 °C. After hydrolysis with 5% sulfuric acid, the entire mixture was extracted with an equal volume of ether and the two layers were separated. The aqueous layer was saturated with sodium bromide (ca. 35 g) and extracted with chloroform. Concentration gave 0.52 g (40%) of the crude sulfonium bromide as a yellow oil. The bromide was converted to the tetraphenylborate as above.

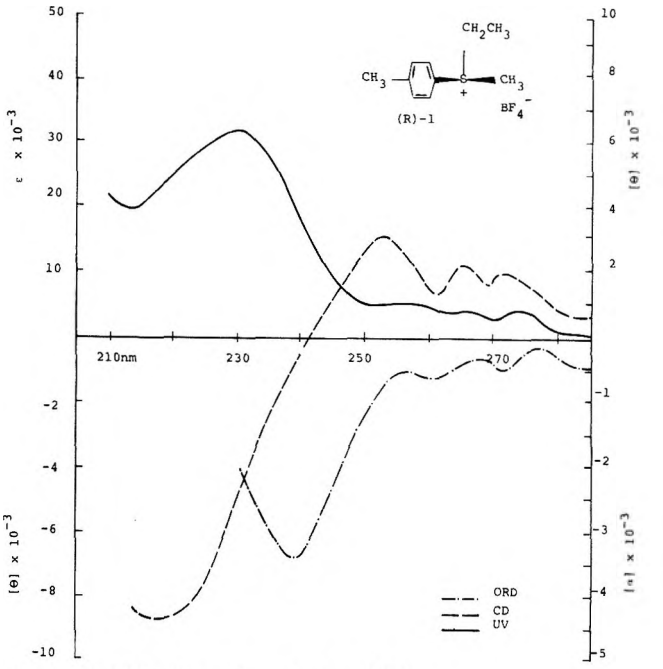


Figure 1. ORD, CD, and uv spectra of *R*-1.

(*S*)-(+)-Ethylmethyl-*p*-tolylsulfonium Tetraphenylborate (1) via Adamantoxysulfonium Salts. (+)-Adamantoxymethyl-*p*-tolylsulfonium hexafluoroantimonate (0.45 g, 0.856 mmol) in methylene chloride was treated with diethylcadmium (0.32 ml, 0.856 mmol, 2.75 M). After 24 h at room temperature, the mixture was worked up as above. (+)-Ethylmethyl-*p*-tolylsulfonium tetrafluoroborate was isolated as a thick yellow oil, yield 0.22 g (100%). The tetrafluoroborate was converted to the tetraphenylborate in the normal way with a 70% recovery, mp 169–171 °C (EtOH).

(*R*)-(−)-Ethylmethyl-*p*-tolylsulfonium tetrafluoroborate was prepared in a similar way (54% yield). It contained very slight amounts of impurities which could not be removed even after repeated recrystallizations. No further work was performed on the compound.

Attempted Preparation of Optically Active Phenyl-*o*-tolyl-*p*-tolylsulfonium Tetraphenylborate (10). (*R*)-Phenyl *p*-tolyl sulfoxide (1.3 g, 6.02 mmol, $[\alpha]^{25}D$ 21.05°, acetone) was ethylated with triethyloxonium tetrafluoroborate (1.25 g, 6.6 mmol) in methylene chloride. Undistilled di-o-tolylcadmium (6.02 mmol) was introduced at 0 °C. After 1.5 h, the usual workup yielded 2.6 g (100%) of the crude sulfonium bromide as a thick yellow oil.

The bromide (oil) was converted to the tetraphenylborate (solid) as above yielding 0.5 g (20%) of the desired product, mp 171–174 °C (acetone–ether), $[\alpha]^{25}D$ 0°.

(±)-Phenyl-o-tolyl-*p*-tolylsulfonium Tetraphenylborate (10). (±)-Phenyl *p*-tolyl sulfoxide (1.3 g, 6.0 mmol) was ethylated with triethyloxonium tetrafluoroborate (1.25 g, 6.6 mmol) in methylene chloride and then treated with *o*-tolylmagnesium bromide (2.22 ml, 6 mmol, 2.7 M) according to the procedure outlined for the attempted preparation of optically active phenyl o-tolyl-*p*-tolylsulfonium tetraphenylborate (see above) with the following modification: the organometallic and alkylated sulfoxide were allowed to react at −78 °C for 1 h. (±)-Phenyl-*o*-tolyl-*p*-tolylsulfonium tetraphenylborate was isolated in 46% yield (1.42 g), mp 172.5–174 °C (acetone–ether).

Anal. Calcd for $C_{44}H_{39}BS$: C, 86.54, H, 6.43. Found: C, 86.25; H, 6.35.

Attempted Preparation of Optically Active Ethylphenyl-*p*-tolylsulfonium Tetraphenylborate (11). (*R*)-Phenyl *p*-tolyl sulfoxide (0.63 g 2.87 mmol, $[\alpha]^{25}D$ 15.24°, acetone) was ethylated as above and the ethoxysulfonium salt purified by precipitation from methylene chloride–ether, to give 0.55 g (60%) as a thick oil. Diethylcadmium (4.32 ml, 2.66 mmol, 0.6 M, 50% excess) was added to the oil in methylene chloride. After 20 min at room temperature, the mixture was worked up using sodium tetrafluoroborate to give 0.4 g (73%) of (±)-ethylphenyl-*p*-tolylsulfonium tetrafluoroborate (11), which was converted to the tetraphenylborate as above, 0.7 g (80% yield).

Anal. Calcd for $C_{39}H_{37}SB$: C, 85.38, H, 6.80. Found: C, 85.87; H, 6.54.

Attempted Preparation of Racemic and Optically Active Trialkylsulfonium Salts from O-Alkylated Sulfoxides. Treatment of O-alkylated dialkyl sulfoxides (racemic or optically active) with Grignard reagents at −78 °C for 1 h or alkylcadmium reagents for 20 min at room temperature using the procedure for the preparation of dialkylarylsulfonium salt (see above) failed to yield the desired trialkylsulfonium salts. The products isolated include starting sulfoxide (partially racemized in the case of optically active sulfoxides), the corresponding sulfide, and some unidentified products. The sulfoxides were often isolated as a 1:1 complex with 2,4,6-trinitrobenzenesulfonic acid, the anion which was used in the attempted isolation of the sulfonium salt. A number of variations in the reaction conditions including changes in temperature, reaction time, organometallic, leaving group, and anion resulted in no sulfonium salt.

Attempted Preparation of Racemic Sulfonium Salts from N-Methylated Sulfilimines. *N*-Tosyl-*S*-methyl-*S*-phenylsulfilimine (1 g, 3.4 mmol) in methylene chloride was methylated with methyl fluorosulfonate (0.52 g, 3.4 mmol). *n*-Butylmagnesium bromide (1.45 ml, 3.4 mmol, 2.4 M) was added at −78 °C. Workup as above using sodium bromide yielded a crude yellow oil which consisted of *N*-tosyl-*S*-methyl-*S*-phenylsulfilimine, *N*-methyl-*p*-toluenesulfonamide, and methyl phenyl sulfoxide (TLC, NMR). None of the desired product was obtained.

Repetition of the reaction with *N*-tosyl-*S*-phenyl-*S*-ethylsulfilimine and ethylcadmium yielded analogous results.

Dialkyl- and Adamantoxyalkylarylsulfonium Salts.[6] The procedure outlined for the preparation of (±)-adamantoxymethyl-*p*-tolylsulfonium perchlorate will serve to illustrate the general method employed in the synthesis of the title compounds.

Methyl *p*-tolyl sulfoxide (1.08 g, 7 mmol) in methylene chloride was added to silver perchlorate (1.44 g, 7 mmol). 1-Bromoadamantane (1.5 g, 7 mmol) in methylene chloride was added with the exclusion of light over a 15-min period. After the addition, the mixture was allowed to stand for 1 h at room temperature. The silver bromide produced was removed by filtration. Adamantoxymethylsulfonium perchlorate (1.42 g, 53%) was obtained as a fluffy white solid by precipitation from methylene chloride–ether, mp 153–155 °C dec.

Anal. Calcd for $C_{18}H_{25}O_5SCl$: C, 55.59; H, 6.48. Found: C, 55.7; H, 6.58.

The hexafluoroantimonate salts were prepared and purified in an analogous way by use of silver hexafluoroantimonate. Other salts prepared according to this procedure include (+)-adamantoxymethyl-*p*-tolylsulfonium hexafluoroantimonate (53%), mp 124–126 °C (methylene chloride–ether), $[\alpha]^{25}D$ 68.37° (c 1, acetone).

Anal. Calcd for $C_{18}H_{25}SSbF_6$: C, 41.16; H, 4.80. Found: C, 41.12; H, 4.80.

(±)-Adamantoxymethyl-*n*-propylsulfonium hexafluoroantimonate (20%), mp 110–112 °C (methylene chloride–ether).

Anal. Calcd for $C_{14}H_{25}SSbF_6$: C, 35.24; H, 5.28. Found: C, 35.17; H, 5.11.

Attempted Preparation of Racemic Trialkylsulfonium Salts from Adamantoxydialkylsulfonium Salts. Treatment of adamantoxydialkylsulfonium salts with dialkylcadmium reagents at room temperature for ca. 24 h, using the procedure described for the preparation of dialkylarylsulfonium salts, failed to yield the desired trialkylsulfonium salts. Starting sulfoxides, adamantanol, and several unidentified by-products were isolated (TLC, NMR). The sulfoxides were often isolated as a 1:1 complex with 2,4,6-trinitrobenzenesulfonic acid, the anion used in the attempted isolation of the sulfonium salt. Reactions were also attempted for a 20-min period at room temperature with negative results.

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Registry No.—*S*-**2** Ph_4B^-, 59751-81-4; *R*-**3** Ph_4B^-, 59710-90-6; *R*-**6**, 1519-39-7; *R*-**7**, 1519-40-0; *R*-**8**, 20288-49-7; **9**, 16491-20-6; (±)-**10** Br^-, 59710-91-7; (±)-**10** Ph_4B^-, 59710-93-9; **11** BF_4^-, 59710-95-1; **11** Ph_4B^-, 59710-96-2; trimethyloxonium tetrafluoroborate, 420-37-1; (*R*)-methoxyethyl-*p*-tolylsulfonium BF_4^-, 59710-98-4; sodium Ph_4B^-, 143-66-8; triethyloxonium BF_4^-, 368-39-8; sodium bromide, 7647-15-6; 2,4,6-trinitrobenzenesulfonic acid, 2508-19-2; (+)-adamantoxymethyl-*p*-tolylsulfonium hexafluoroantimonate, 59711-00-1; silver perchlorate, 7783-93-9; 1-bromoadamantane, 768-90-1; (±)-adamantoxymethyl-*p*-tolylsulfonium perchlorate, 59711-02-3; silver hexafluoroantimonate, 26042-64-8; (±)-adamantoxymethyl-*n*-propylsulfonium hexafluoroantimonate, 59711-04-5.

References and Notes

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Solvolysis of Arylsulfonylmethyl Perchlorates in Dioxane–Water, *tert*-Butyl Alcohol–Water, and Acetonitrile–Water. An Analysis of Solvent Effects on a Water-Catalyzed Process

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This paper presents a study of the water-catalyzed hydrolysis of two covalent arysulfonylmethyl perchlorates (involving rate-determining proton transfer to water) in dioxane–H_2O, *t*-BuOH–H_2O, and CH_3CN–H_2O. The characteristic kinetic behavior for each aqueous binary is discussed in terms of the variation of the activation parameters $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ as a function of the mole fraction of water (n_{H_2O}). Addition of the weak Bronsted bases dioxane and CH_3CN markedly increases the kinetic basicity of water. It is proposed that the magnitude of the effect is correlated with the amount of polarization of the water molecule as a result of hydrogen bonding to the organic cosolvent. Thermodynamic data for transfer of a model substrate **3** from H_2O to the aqueous mixtures support the idea that especially in *t*-BuOH–H_2O effects due to changes in "water structure" should be invoked to explain the remarkable extrema observed for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in the region of high water concentration. Possible biochemical implications are briefly indicated.

Few systematic studies have been made of the effect of solvent composition upon rates and activation parameters of hydrolysis reactions involving proton transfer to or from water in the rate-determining step.[1-4] Recently, we have reported that the neutral hydrolysis of covalent arylsulfonylmethyl perchlorates, which is subject to efficient general base catalysis by water[5] (Scheme I), may be a useful probe for such studies.[2,4]

Scheme I

$$\underset{\text{1, Ar = } p\text{-}NO_2C_6H_4;\ \text{2, Ar = } p\text{-}CH_3C_6H_4}{ArSO_2CH_2OClO_3} + H_2O \xrightarrow{\text{slow}} [ArSO_2\bar{C}HOClO_3] + H_3O^+$$

$$[ArSO_2\bar{C}HOClO_3] \xrightarrow[H_2O]{\text{fast}} ArSO_2H + HCOOH + ClO_3^-$$

The hypothesis was advanced that the peculiar behavior of the kinetic parameters as a function of solvent composition can be rationalized by assuming that the diffusionally averaged "water structure"[6] is one of the factors determining $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in mixed aqueous solvents of high water concentration.[2] It was also argued that the water-catalyzed process depicted in Scheme I is by no means a *general* probe for the kinetic basicity of mixed aqueous solutions.[4]

In this paper we report a more detailed analysis of the trends in $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ for hydrolysis of **1** and **2** as a function of solvent composition in dioxane–H_2O, *t*-BuOH–H_2O, and CH_3CN–H_2O using transition-state theory. The data provide a deeper insight into the propensity of water molecules to deprotonate pseudoacids like **1** and **2** under conditions of changing water–water hydrogen bonding interaction. In addition, the present results may possess relevance for our understanding of microenvironmental factors at the active sites of enzymes which catalyze C–H bond fission.[7,8]

Results

Hydrolysis of 1, 1a, and 2 in 1,4-Dioxane–H_2O Mixtures.[9] Pseudo-first-order rate constants (k_{obsd}), second-order rate constants ($k_2 = k_{obsd}\, c_{H_2O}^{-1}$), and activation parameters for hydrolysis of **1**, **1a** (p-$NO_2C_6H_4SO_2CD_2OClO_3$), and **2** in dioxane–H_2O mixtures of varying mole fraction of water (n_{H_2O}) are shown in Table I. Plots of log $k_{obsd}/k_{obsd}^{H_2O}$ and log $k_2/k_2^{H_2O}$ vs. n_{H_2O} are given for **1** in Figures 1 and 2, respectively, and $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ are plotted as a function of n_{H_2O} in Figure 3. These data all pertain to water-induced processes because the substrates are stable in anhydrous dioxane for a long time.[5] Since **1** and **2** exhibit closely similar trends in their data, the following discussion will be largely limited to **1**. Two observations are particularly noteworthy: firstly, the nearly constant value of $k_2/k_2^{H_2O}$ between n_{H_2O} = 0.2–0.8, and secondly, the extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ around n_{H_2O} = 0.7. Upon the first addition of dioxane to water, the rate enhancement is governed by a decrease of $\Delta H^{\ddagger}$ which is only partly compensated by a decrease of $\Delta S^{\ddagger}$. Below n_{H_2O} = 0.7 almost completely compensatory changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are observed. Between n_{H_2O} = 0.7 and 0.5 these changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are in opposite direction to those found in the region n_{H_2O} = 0.7–1.0. Hydrolysis of **1** and **2** in the region n_{H_2O} = 0.8–1.0 is associated with real isokinetic temperatures (**1**, T_c = 375 ± 10 K; **2**, T_c = 369 ± 10 K) as indicated by application of Petersen's criterium.[10]

The substantial changes of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ with n_{H_2O} for hydrolysis in dioxane–H_2O may be contrasted with the small changes of these quantities of activation for ethanolysis of **1** in dioxane–EtOH (Table II). In the latter solvent system there is no initial increase of k_{obsd}/k_{obsd}^{EtOH} upon the first addition of dioxane to ethanol (Figure 1). It should also be noted that k_{obsd} is only moderately sensitive to changes in the dielectric constant of the medium.[2b]

Solvolysis of 1 in *t*-BuOH–H_2O Mixtures.[9] The kinetic data for solvolysis of **1** in *t*-BuOH–H_2O are listed in Table III. A plot of log $k_{obsd}/k_{obsd}^{H_2O}$ vs. n_{H_2O} is shown in Figure 1. It should be emphasized that the k_{obsd} values for the *t*-BuOH–H_2O mixtures represent the sum of the rate constants for hydrolysis and alcoholysis, which are, in the respective pure solvents, of the same order of magnitude (Table III). Interestingly, k_{obsd} increases sharply upon the first addition of *t*-BuOH to H_2O until k_{obsd} reaches around n_{H_2O} = 0.9 a value well above that for solvolysis in either pure water or pure *t*-BuOH. Between n_{H_2O} = 0.9–0.2 k_{obsd} is nearly constant and then, below n_{H_2O} = 0.2, falls off rapidly to the value for alcoholysis in pure *t*-BuOH. A rather similar behavior of k_{obsd} as a function of n_{H_2O} has been observed for solvolysis in EtOH–H_2O and in glycol–H_2O although in these solvent systems the rate increase upon initial addition of the alcohol is appreciably smaller.[2]

The variation of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ as a function of solvent composition shows mirror image behavior, as for hydrolysis in dioxane–water, but now extrema are located at n_{H_2O} = 0.85 (Figure 4). Clearly the increase in rate between n_{H_2O} = 1.0 and 0.85 is the result of a decrease in $\Delta H^{\ddagger}$ which is incompletely compensated by a decrease in $\Delta S^{\ddagger}$. Almost perfect $\Delta H^{\ddagger}$–$\Delta S^{\ddagger}$ compensation occurs in the region n_{H_2O} = 0.9–0.1. Below n_{H_2O} = 0.1 the increase of $\Delta G^{\ddagger}$ is caused by an endothermic change in $\Delta H^{\ddagger}$.

Table I. Rate Constants and Activation Parameters for the Neutral Hydrolysis of 1, 1a, and 2 in Dioxane–H_2O[a] at 25 ± 0.04 °C

Compd	n_{H_2O}	$k_{obsd} \times 10^4$, s^{-1}[b]	$k_2 \times 10^6$, $M^{-1} s^{-1}$[c]	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	k_H/k_D[d]
1	1.00	32.5	58.6	18.4	− 8	
1	0.98	44.7	88.7	17.9	− 9	
1	0.90	111	306	15.6	−15	
1	0.80	164	645	14.0	−20	
1	0.75	166	770	13.3	−22	
1	0.70	148	804	13.0	−23	
1	0.65	135	864	13.0	−23	
1	0.58	106	859	13.8	−22	
1	0.50	79.4	811	14.3	−20	
1	0.30	35.2	788	14.0	−23	
1	0.20	19.9	736	12.5	−29	
1a	1.00	5.7	10.3	19.2	− 9	5.6
1a	0.80	25.4	98.1	14.6	−22	6.4
1a	0.50	12.5	129	15.3	−21	6.4
1a	0.30	5.5	120	14.6	−24	6.2
1	1.00[e]	18.4	33.3	18.6	− 9	1.7[f]
1	0.80	104	402	13.7	−22	1.6[f]
1	0.50	54.8	561	14.0	−22	1.5[f]
1	0.30	25.6	555	12.2	−29	1.6[f]
2	1.00	6.10	11.0	19.7	− 7	6.2[g]
2	0.98	7.23	14.2	18.5	−11	
2	0.90	13.3	36.0	17.0	−15	
2	0.80	17.0	65.6	14.4	−23	7.7
2	0.75	15.2	69.4	15.0	−21	
2	0.65	11.0	69.2	15.3	−21	
2	0.50	6.92	71.3	15.7	−21	7.3
2	0.30	2.88	62.6			7.1
2	0.20	1.71	61.1	14.0	−29	

[a] Containing 10^{-3} M HCl. [b] Pseudo-first-order rate constant. [c] $k_2 = k_{obsd} C_{H_2O}^{-1}$. [d] Primary kinetic deuterium isotope effect. [e] n_{D_2O}. [f] Solvent deuterium isotope effect, k_{H_2O}/k_{D_2O}. [g] $k_{H_2O}/k_{D_2O} = 1.7$.

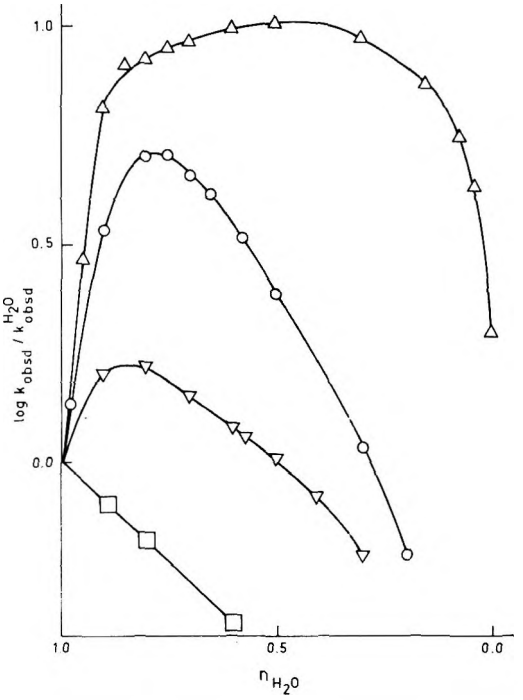
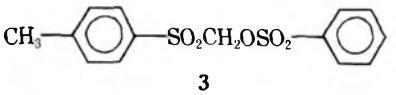


Figure 1. Plot of log $k_{obsd}/k_{obsd}^{H_2O}$ vs. n_{H_2O} for the neutral hydrolysis of 1 in *t*-BuOH–H_2O (△), dioxane–H_2O (○), CH_3CN–H_2O (▽), and dioxane–EtOH (□). In the last case log k_{obsd}/k_{obsd}^{EtOH} is plotted as a function of n_{EtOH}.

Hydrolysis of 1 in CH_3CN–H_2O Mixtures. Kinetic data for hydrolysis of 1 in CH_3CN–H_2O mixtures are summarized in Table IV. The data comprise the region n_{H_2O} = 0.3–1.0; 1 is not solvolyzed in pure CH_3CN, as expected. As shown in Figure 1, there is a small increase of k_{obsd} upon going from pure water to n_{H_2O} ca. 0.8, further addition of CH_3CN then results in a smooth decrease. The modest increase of k_2 upon increasing concentration of CH_3CN is displayed in Figure 2. A striking difference with the results for solvolysis in dioxane–H_2O and *t*-BuOH–H_2O is the absence of extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in the region of high water concentration (Figure 5) although again $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ vary as a function of n_{H_2O} in a compensating fashion.

Thermodynamic Parameters of Transfer for 3. Unfortunately the perchlorates 1 and 2 are too readily hydrolyzed to allow the determination of thermodynamic quantities for transfer from water to the aqueous mixtures employed in the kinetic studies. Therefore we have chosen the less reactive sulfonate 3[11] as a reasonable model compound for 1 and 2.



3

Justification for this choice is found in Cox's observation[12] that for such different substrates as ethyl acetate, acetone, benzene, and trimethyl phosphate the enthalpies ($\Delta H_{tr}°$) and entropies ($\Delta S_{tr}°$) for transfer from water to various aqueous mixtures show trends which are similar in their gross features.[13] The thermodynamic parameters $\Delta G_{tr}°$, $\Delta H_{tr}°$, and $\Delta S_{tr}°$ for transfer of 3 were obtained from solubility measurements and are tabulated in Table V. Figure 6 shows a plot of $\Delta H_{tr}°$ and $-T\Delta S_{tr}°$ as a function of n_{H_2O} for the three solvent systems. The plots clearly reveal mirror image behavior. Most noteworthy are the pronounced extrema in $\Delta H_{tr}°$ and $\Delta S_{tr}°$ at n_{H_2O} = 0.95 for *t*-BuOH–H_2O.

Discussion

Solvent Effects on $\Delta G^{\ddagger}$. Since the $\Delta G^{\ddagger}$ value for solvolysis

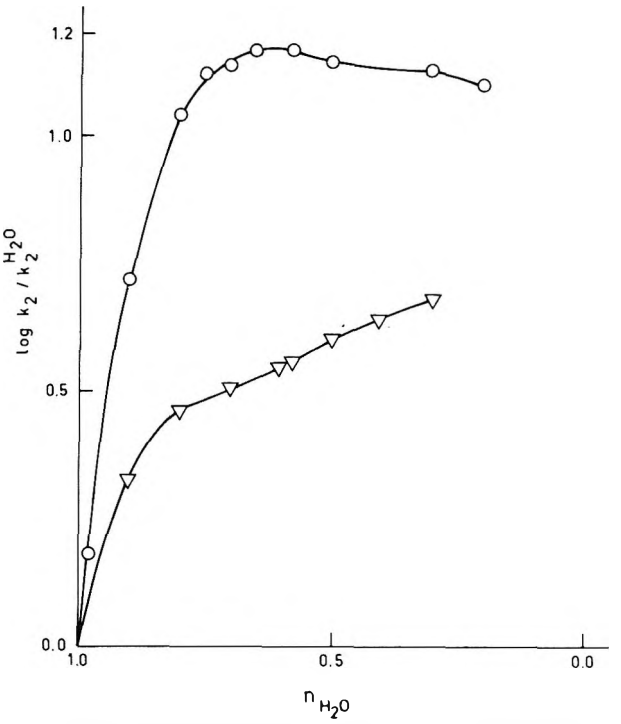


Figure 2. Plot of log $k_2/k_2^{H_2O}$ vs. n_{H_2O} for the neutral hydrolysis of 1 in dioxane–H_2O (○) and in CH_3CN–H_2O (▽).

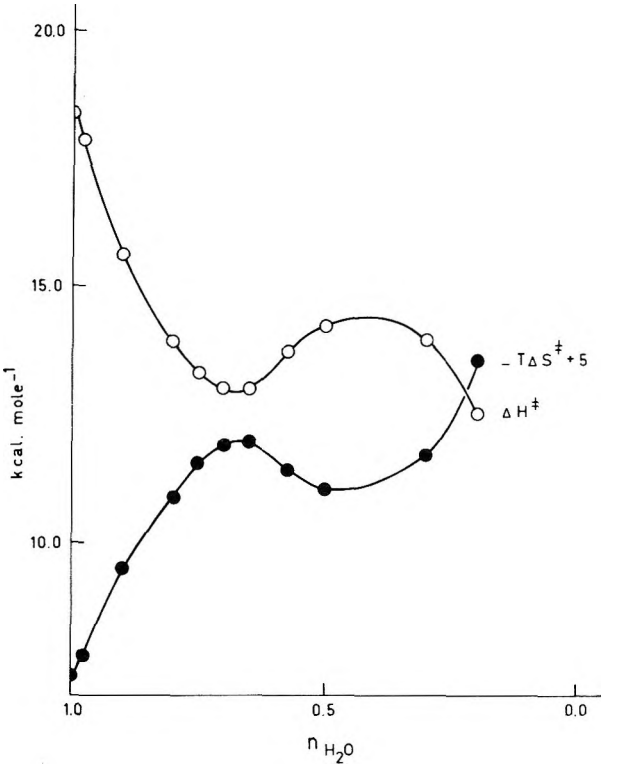


Figure 3. Plot of $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ vs. n_{H_2O} for the neutral hydrolysis of 1 in dioxane–H_2O.

of 1 and 2 measures the "kinetic basicity" of the reaction medium,[14] it is remarkable that the first addition of the weak Bronsted bases dioxane and CH_3CN to water lead to enhanced reaction rates as expressed in the k_2 values (Figure 2). These results serve to indicate that the activation process is strongly affected by solvation factors.[15] From previous work it seems evident that proton transfer in the transition state is far from complete since the Bronsted β is ca. 0.5.[5] In addition, the rather small negative entropy of activation for hydrolysis in

Table II. Rate Constants and Activation Parameters for the Neutral Hydrolysis of 1 in Dioxane–EtOH[a] at 25 ± 0.04 °C

n_{EtOH}	$k_{obsd} \times 10^4$, s^{-1}[b]	$k_2 \times 10^6$, $M^{-1}\,s^{-1}$[c]	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
1.00	45.1	207	15.8	−16
0.90	36.1	201	16.3	−15
0.80	30.3	206	16.3	−15
0.60	19.1	200	16.1	−17

[a] Containing 10^{-3} M HCl. [b] Pseudo-first-order rate constant. [c] $k_2 = k_{obsd} c_{EtOH}^{-1}$.

Table III. Pseudo-First-Order Rate Constants (k_{obsd}) and Activation Parameters for the Neutral Hydrolysis of 1 in t-BuOH–H_2O[a] at 25 ± 0.04 °C

n_{H_2O}	$k_{obsd} \times 10^4$, s^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	k_H/k_D[b]
1.00	32.5	18.4	− 8	5.6
0.95	95.5	16.9	−11	
0.90	214	14.5	−18	
0.85	269	13.2	−22	
0.80	275	14.0	−19	
0.75	288	14.1	−18	
0.70	299	14.0	−19	
0.60	320	13.4	−21	
0.50	331	13.1	−21	
0.30	306	12.8	−23	6.1
0.15	240	12.6	−24	
0.075	180	12.7	−24	
0.040	138	12.9	−24	
0.0	64.6	14.6	−20	

[a] Containing 10^{-3} M HCl. [b] Primary kinetic deuterium isotope effect, k_{obsd} (1)/k_{obsd} (1a).

Table IV. Rate Constants and Activation Parameters for the Neutral Hydrolysis of 1 in CH_3CN–H_2O[a] at 25 ± 0.04 °C

n_{H_2O}	$k_{obsd} \times 10^4$, s^{-1}[b]	$k_2 \times 10^6$, $M^{-1}\,s^{-1}$[c]	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
1.00	32.5	58.6	18.4	−8
0.90	51.9	124	17.1	−12
0.80	54.3[d]	169	16.2	−15
0.70	46.2	188	15.6	−17
0.60	39.0	207	15.5	−18
0.58	37.2	212	15.4	−18
0.50	33.1	234	14.6	−21
0.41	26.9	256	14.4	−22
0.30	19.8	278	14.0	−24

[a] Containing 10^{-3} M HCl. [b] Pseudo-first-order rate constant. [c] $k_2 = k_{obsd} C_{H_2O}^{-1}$. [d] $k_{H_2O}/k_{D_2O} = 1.9$, $k_H/k_D = 6.4$.

pure water (−8 eu) reveals that no drastic change in the solvation pattern is required to reach the transition state for proton transfer to water. Since 1 and 2 should be considered as "pseudoacids",[16] it is reasonable to assume that only one water molecule will be tightly bound in the transition state and that the rate of deprotonation will not be seriously affected by the necessity of substrate desolvation. The proposed transition state structure also implies that solvation of the dispersed negative charge at the α-sulfonyl carbon atom is relatively unimportant.[4] Because proton transfer from 1 and 2 in dioxane–H_2O and CH_3CN–H_2O occurs only to water molecules,[17] we suggest that the increase in the kinetic basicity of water in these solvents should be ascribed to water–organic

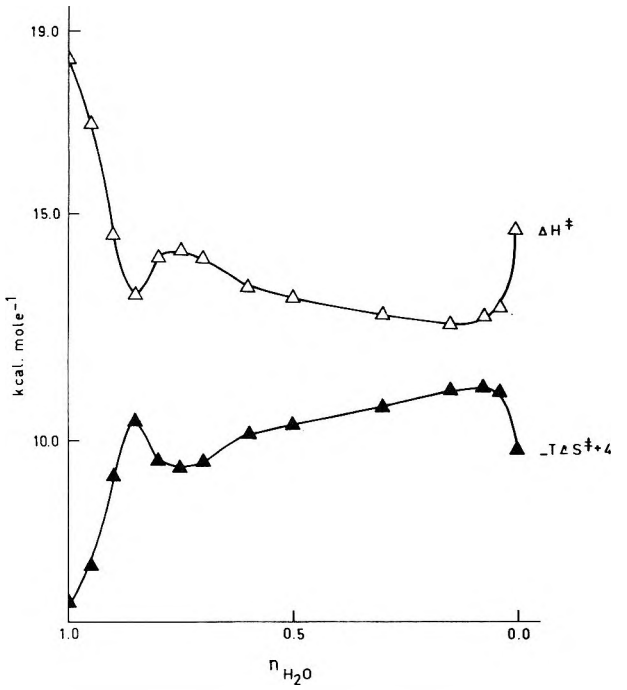


Figure 4. Plot of $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ vs. n_{H_2O} for the neutral hydrolysis of 1 in t-BuOH–H_2O.

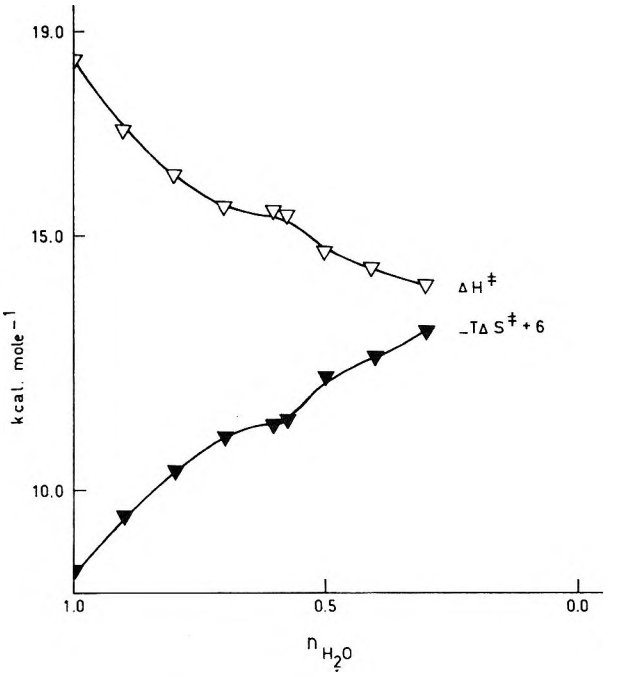
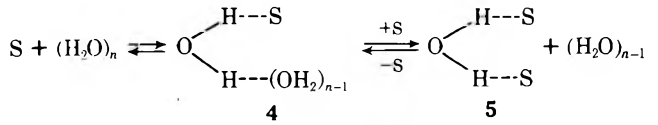


Figure 5. Plot of $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ vs. n_{H_2O} for the neutral hydrolysis of 1 in CH_3CN–H_2O.

solvent hydrogen bonding interactions in complexes of type **4** and **5**. This type of association apparently results in an en-



S = dioxane, CH_3CN

hanced electron density at the water oxygen atom as compared with that in water–water hydrogen bond complexes. Experimental evidence for the intrinsic high hydrogen bonding capability (high proton affinity) of ether molecules like dioxane has been obtained from gas-phase ion equilibria.[18] In these studies it was shown that the interaction of H_3O^+ with three ether molecules is more favorable than with three water molecules. Acetonitrile has also a greater proton affinity than water. In the light of these data for the gas phase, it is interesting to see that the curves of k_2 as a function of n_{H_2O} for hydrolysis of 1 in dioxane–H_2O and CH_3CN–H_2O show a strong conformity (Figure 2), except for the size of the effect, which is smaller for CH_3CN. The low kinetic basicities of dioxane and CH_3CN molecules themselves, either in the pure liquid or in their aqueous solutions, find their explanation in their aprotic character which strongly discourages proton transfer to these molecules because of the associated highly unfavorable $\Delta S^{\ddagger}$ values. Our results therefore reinforce the idea[19] that the relatively high Bronsted basicity of water in aqueous solutions, despite its low gas-phase proton affinity, is largely due to the presence of extensive three-dimensional hydrogen bond networks and its associated low entropy. As a consequence, the loss of entropy associated with proton transfer to water will be less than for proton transfer to less associated solvent molecules although the latter may form hydrogen bonds of comparable enthalpy as water does. In addition to this effect, cooperative hydrogen bonding between water molecules will also enhance the hydrogen bond basicity of water in the enthalpic sense.[20] Support for the idea that the enhanced rates in the water-rich dioxane–H_2O and CH_3CN–H_2O mixtures are due to a predominating transition state effect, is found in the exothermic ΔG_{tr}° values for these solvent systems given in Table V.

An explanation for the rate–solvent composition profile for solvolysis of 1 in t-BuOH–H_2O[21] may be given along similar lines but now the situation is still more complex because the organic cosolvents also functions as an efficient Bronsted base. The rate enhancement in the region n_{H_2O} = 1.0–0.8 will be due to transition state stabilization as suggested by the ΔG_{tr}° data in Table V. Apparently, transition state solvation is promoted by the formation of water–t-BuOH hydrogen bond complexes at the expense of water–water interactions in the bulk solvent. Support for this conclusion is found in the strongly *reduced* rates of solvolysis of 1 in 2,2,2-trifluoroethanol (TFE)–H_2O mixtures (n_{H_2O} = 0.827, $k_{obsd} = 69.3 \times 10^{-5}$ s^{-1}, $k_2 = 26.9 \times 10^{-6}$ M^{-1} s^{-1}, $\Delta H^{\ddagger}$ = 17.6 kcal mol^{-1}, $\Delta S^{\ddagger} = -14$ eu). Now the alcohol is only a weak hydrogen bond acceptor and formation of complexes like **4** and **5** (S = TFE) is much less favorable.

The nearly constant k_2 values and activation parameters for ethanolysis of 1 in dioxane–EtOH (n_{EtOH} = 0.6–1.0; Table II) are understandable in view of the relatively small differences in gas-phase proton affinities between EtOH and most cyclic ethers[18] and the absence of large three-dimensional hydrogen bond structures in liquid EtOH.[21,22] The minor role which solvent polarity plays in determining the rates of solvolysis is readily reconciled with a transition state occurring early on the reaction coordinate (vide supra).

Since the above discussion of the trends in the rates as a function of solvent composition is perforce qualitative, we cannot decide, at the moment, whether or not a secondary effect is imposed on $\Delta G^{\ddagger}$ by changes in the diffusionally averaged "water structure" induced by the organic cosolvent in the region of high water concentration.[23] In the following section it will be argued that the $\Delta H^{\ddagger}$–$\Delta S^{\ddagger}$ compensation phenomena observed in t-BuOH–H_2O and possibly in dioxane–H_2O, respond to "water structure" perturbation but the possibility remains that $\Delta G^{\ddagger}$ is (almost) insensitive to changes in solvent structural integrity. In this context it is significant to note that in t-BuOH–H_2O the maximum rate is reached at a higher n_{H_2O} than in EtOH–H_2O.[2] This correlates with the

Table V. Thermodynamic Quantities of Transfer for 3 from Water to Aqueous Solvent Mixtures (25 °C)

Solvent mixture	n_{H_2O}	$\Delta H_{tr}°$, kcal mol^{-1}	$\Delta S_{tr}°$, eu	$\Delta G_{tr}°$, kcal mol^{-1}
Dioxane–H_2O	0.95	−0.2	+5	−1.75
Dioxane–H_2O	0.90	+0.2	+11	−2.90
Dioxane–H_2O	0.875	−0.5	+10	−3.40
t-BuOH–H_2O	0.95	+6.5	+27	−1.43
t-BuOH–H_2O	0.90	+4.4	+23	−2.36
t-BuOH–H_2O	0.80	−1.2	+8	−3.48
CH_3CN–H_2O	0.95	+0.6	+6	−1.23
CH_3CN–H_2O	0.925	+1.3	+11	−1.87
CH_3CN–H_2O	0.875	−1.4	+8	−3.68

higher n_{H_2O} for the maximum in "water structure" in *t*-BuOH–H_2O in comparison with that in EtOH–H_2O.

Solvent Effect on $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. The data shown for the three solvent systems in Tables I, III, and IV reveal that the first addition of organic cosolvent to water leads to smaller $\Delta H^{\ddagger}$ values. In the previous section it was proposed that these lower $\Delta H^{\ddagger}$ values manifest an enhanced kinetic basicity of water as a result of cosolvent-induced, stronger C–H···OH_2 interaction in the transition state. Invariably, this exothermic shift of $\Delta H^{\ddagger}$ is largely compensated by an endothermic shift of $\Delta S^{\ddagger}$. This is expected for stronger binding of water in the transition state resulting in more extensive solvent reorientation. Compensatory behavior of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ is characteristic for many chemical processes in aqueous solutions.[24,25] On the basis of this concept, one would expect that $\Delta H^{\ddagger}$ changes smoothly upon lowering n_{H_2O}. The change in $\Delta G^{\ddagger}$ is then dependent on whether the reaction is enthalpy or entropy controlled. This situation is encountered for hydrolysis of **1** in CH_3CN–H_2O (Figure 5). For this solvent system it is known that there is no initial "structure-making" effect by small amounts of CH_3CN.[26,27] In sharp contrast, the $\Delta H^{\ddagger}$–$\Delta S^{\ddagger}$ pattern for solvolysis in dioxane–H_2O and *t*-BuOH–H_2O shows marked extrema at n_{H_2O} = 0.7 and 0.85, respectively (Figures 3 and 4). We suggest that these minima may find a reasonable explanation by consideration of effects due to changes in the diffusionally averaged "water structure" induced by the organic addendum.[28] Before proceeding to a qualitative interpretation of the trends in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, we will first consider the thermodynamic quantities of transfer for the model substrate **3** (Table V). It appears that for *t*-BuOH–H_2O pronounced extrema occur in $\Delta H_{tr}°$ and $\Delta S_{tr}°$ at n_{H_2O} = 0.95 which nearly coincides with the n_{H_2O} of 0.92 for maximal "water structure" as indicated by studies employing such techniques as low angle x-ray scattering,[29] ultrasound absorption,[30] and measurements of molar excess functions.[21] Since water–water hydrogen bonding will be stronger than solute–water hydrogen bonding,[31] the large and positive $\Delta H_{tr}°$ for n_{H_2O} = 0.95 will reflect the increase in enthalpy necessary under conditions of enhanced "water structure" for forming a cavity in the solvent to accommodate the solute. Despite this large $\Delta H_{tr}°$, the transfer of **3** is exothermic ($\Delta G_{tr}°$ = −1.43 kcal mol^{-1} at n_{H_2O} = 0.95) because of a dominant and positive $\Delta S_{tr}°$. We contend that this is the result of a release of strongly hydrogen bonded water molecules consistent with the occurrence of hydrophobic contacts between **3** and *t*-BuOH. As expected,[23] this entropy effect will reach an extremum at the n_{H_2O} of maximum structural integrity of the solvent. Since highly "structured water" is present around the active sites of several enzymes (as revealed by x-ray diffraction studies[8,32,33]), one wonders how far a similar entropy effect also operates on the binding process of the substrate to the active site. For example, it is known that the strongly ordered water molecules present in the groovelike active site of

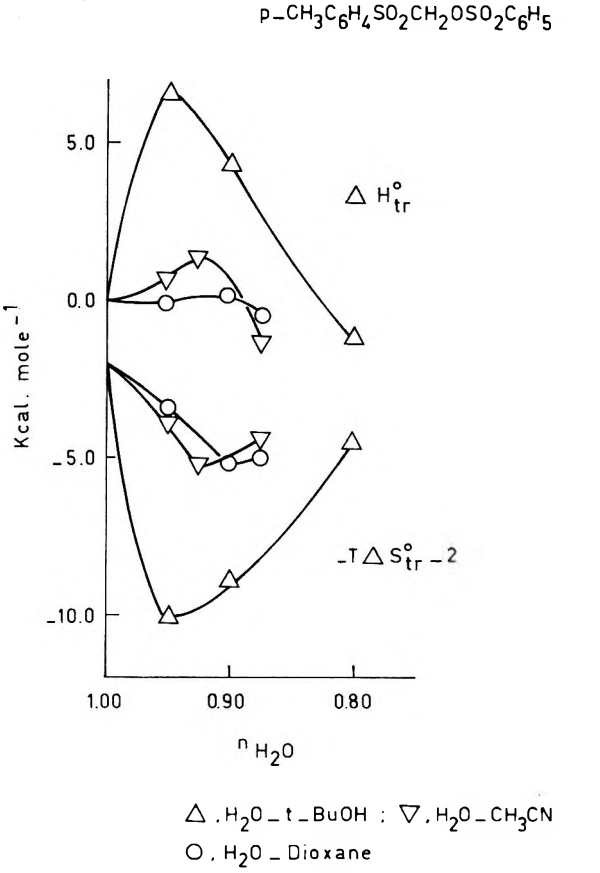


Figure 6. Plot of $\Delta H_{tr}°$ and $-T\Delta S_{tr}°$ vs. n_{H_2O} for transfer of **3** at 25 °C.

papain[34] are displaced by the substrate upon formation of the Michaelis complex. Notwithstanding the limitations of the above theory for aqueous binaries,[35] we like to suggest that a loss of the amount of solvent "structure" may help to overcome the unfavorable entropy inherent in bringing the substrate to the binding site.

The extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for solvolysis of **1** in *t*-BuOH–H_2O occur at a somewhat lower water concentration (n_{H_2O} = 0.85) than that of maximum water–water hydrogen bonding. Most likely, however, these extrema also reflect solvation effects originating from changes in "water structure".[36] We infer that the extrema arise because these "water structure" effects differ for the initial state and the transition state. This will be mainly due to the fact that for the transition state the loss of enthalpy as a result of cavity formation will be partly offset by strong CH···OH_2 interaction and which will increase with enhanced "water structure".[20] In view of the complex factors which affect the hydrolysis of **1** in *t*-BuOH–H_2O one would not expect, a priori, that the extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ and the maximum in "structuredness" of the solvent occur at exactly the same n_{H_2O}. In the hydrolysis of **1** and **2** "water structure" effects only modulate primary solvation changes induced by addition of the organic cosolvent and these effects should only be invoked to explain the extrema of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in the water-rich region.

The sharp increase of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in *t*-BuOH–H_2O below n_{H_2O} = 0.1 is remarkable. A similar behavior has been observed in a few other studies. According to Caldin and Bennetto,[37] and in agreement with Franks and Ives,[21] the addition of small quantities of water to alcohols leads to a stronger hydrogen bonded structure, build around water molecules, as compared with that in the unperturbed alcohol. It seems likely that the dramatic changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ reflect this solvent structuring effect.

In the dioxane–H_2O system the compensatory changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ between $n_{H_2O} = 0.2$ and 1.0 are qualitatively similar to those in t-BuOH–H_2O but now extrema are reached at $n_{H_2O} = 0.7$. Despite some controversy in the literature,[38] many authors agree that the presence of small amounts of dioxane enhances water–water interactions or, at least, does not break "water structure".[39,40] This is indicated by, for instance, dielectric relaxation times,[41,42] enthalpies of mixing,[43] ultrasound absorption,[44] and self-diffusion coefficients.[42] Consequently, the extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ may find their explanation in similar effects as proposed for t-BuOH–H_2O.[45] The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for ethanolysis of **1** in dioxane–EtOH exhibit only small and smooth changes for n_{EtOH} = 0.6–1.0 and serve to indicate the much more pronounced role of solvation effects in dioxane–H_2O. However, there remains some ambiguity in the explanation of the kinetic data in dioxane–H_2O because of the less well characterized structural properties of this solvent and the possibility that the apolar dioxane molecules preferentially solvate **1** and/or the transition state to an unknown extent.[46]

Experimental Section

Materials. Compounds **1–3** were prepared by methods described previously.[5,11] The water used in all experiments was demineralized and distilled twice in an all-quartz distillation unit. Deuterium oxide (99.75% D_2O) was purchased from Merck AG (Uvasol quality) and was used as such. The organic solvents were of the highest grade available, usually obtained from Merck AG. 1,4-Dioxane was filtered through active, neutral alumina in a nitrogen atmosphere and was stored under nitrogen at 0 °C. The solvent mixtures were all made up by weight.

Kinetic Measurements. Pseudo-first-order rate constants (reproducible to within 2%) were obtained using the uv technique described previously.[2] Solvolysis was accurately first order for more than 3 half-lives. All hydrolyses were carried out in the presence of small amounts of HCl (Tables I–IV) in order to suppress catalysis by OH^-. The thermodynamic quantities of activation were calculated from k_{obsd} values at three to five temperatures between 25 and 45 °C. In all cases excellent Arrhenius plots were found. The accuracy of $\Delta H^{\ddagger}$ is usually ±0.3 kcal mol^{-1} and of $\Delta S^{\ddagger}$ ±1 eu. Since only trends in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are discussed in this paper, the problem of the choice of the standard state in the calculation of $\Delta S^{\ddagger}$ is not relevant.

Thermodynamic Quantities of Transfer. Heats of transfer ($\Delta H_{tr}°$) for **3** (Table V) were obtained from solubility measurements between 15 and 30 °C following the procedure of Jolicoeur and Lacroix[47] with small modifications. (1) Saturated solutions were prepared by stirring the solution containing excess of **3** for 8–12 h. No solvolysis of **3** was observed during this period. (2) For the measurements of the absorbance, the samples were diluted with 96% ethanol (λ_{max} 223.5 nm, 20-mm quartz cells).

Since the transfer parameters for **3** are being discussed in connection with activation parameters for hydrolysis of **1** and **2**, we note that the corresponding thermodynamic quantities for transfer of one water molecule will be very small in comparison with the values listed in Table V.

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Registry No.—**1**, 26452-84-6; **1a**, 59711-29-4; **2**, 14894-56-5; **3**, 31081-09-1.

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(17) This is also indicated by the magnitude of the solvent deuterium isotope effect, k_{H_2O}/k_{D_2O}, which hardly depends on n_{H_2O}.
(18) (a) E. P. Grimsrud and P. Kebarle, *J. Am. Chem. Soc.*, **95**, 7939 (1973); (b) K. Hiraoka, E. P. Grimsrud, and P. Kebarle, *ibid.*, **96**, 3359 (1974).
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(20) J. E. Gordon, *J. Am. Chem. Soc.*, **94**, 650 (1972), and references cited therein.
(21) For an excellent review of the peculiar properties of alcohol–water mixtures, see F. Franks and D. J. G. Ives, *Q. Rev., Chem. Soc.*, **20**, 1 (1966).
(22) As expected, addition of TFE to EtOH leads to slower solvolysis. At n_{EtOH} = 0.80 in TFE–EtOH $k_{obsd} = 209 \times 10^{-5}$ s^{-1}, $k_2 = 148 \times 10^{-6}$ l. mol^{-1} s^{-1}, $\Delta H^{\ddagger} = 16.8$ kcal mol^{-1}, and $\Delta S^{\ddagger} = -14$ eu.
(23) (a) The leading reference on water and aqueous solutions is "Water, a Comprehensive Treatise", Vol. 1–5, F. Franks, Ed., Plenum Press, New York, N.Y., 1973–1975; (b) see also ref 6b and D. Eisenberg and W. Kauzmann, "The Structure and Properties of Water", Oxford University Press, London, 1969.
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(26) (a) D. A. Armitage, M. J. Blandamer, M. J. Foster, N. J. Hidden, K. W. Marcom, M. C. R. Symons, and M. J. Wootten, *Trans. Faraday Soc.*, **64**, 1193 (1968); (b) B. G. Wada and S. Umeda, *Bull. Chem. Soc. Jpn.*, **35**, 1797 (1962).
(27) It has been suggested that "water structure" is relatively unaltered in the region n_{H_2O} = 1.0–0.84, gradual disruption taking place below n_{H_2O} = 0.84; see M. F. Stennikova, G. M. Poltoratskii, and M. P. Mitschenko, *J. Strukt. Chem.*, **13**, 127 (1972). The shallow maximum in the $\Delta H_r°-n_{H_2O}$ plot (Figure 6) may be rationalized by assuming that the first amounts of CH_3CN are placed into the voids in the "water structure". This is not possible for a molecule of much greater size like **3**.
(28) Classic papers on this subject are (a) H. S. Frank and M. W. Evans, *J. Chem. Phys.*, **13**, 507 (1945); (b) G. Némethy and H. A. Scheraga, *ibid.*, **36**, 3382, 3401 (1962).
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(30) M. J. Blandamer, ref 23a, Vol. 2, Chapter 9.
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(32) For a review of protein–water interactions, see H. J. C. Berendsen, "FEBS, Enzymes: Structure and Function", Vol. 29, J. Drenth, R. A. Oosterbaan, and C. Veeger, Ed., Elsevier, Amsterdam, 1972, p 19.
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(37) E. F. Caldin and H. P. Bennetto, *J. Solution Chem.*, **2**, 217 (1973).
(38) See, for example, (a) A. Ben-Naim and M. Yaacobi, *J. Phys. Chem.*, **79**, 1263 (1975); (b) F. Cennamo and E. Tartaglione, *Nuovo Cimento*, **11**, 401 (1959).
(39) P. F. Waters and S. Jaffer, *J. Chem. Soc., Chem. Commun.*, 529 (1975).
(40) Raman spectroscopic evidence suggests "structure breaking" below n_{H_2O} = 0.67; see Y. I. Naberukhin and S. I. Shuiskii, *J. Strukt. Chem.*, **8**, 544 (1967).
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(44) G. G. Hammes and W. Knoche, *J. Chem. Phys.*, **45**, 4041 (1966).
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Fluorodesulfurization. A New Reaction for the Formation of Carbon–Fluorine Bonds

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The reactions of 2-aminothiols and thiol amino acids in liquid hydrogen fluoride solution with either fluoroxytrifluoromethane, chlorine, *N*-chlorosuccinimide, or a fluorine–helium mixture are described. The cleavage of the carbon–sulfur bond with concomitant formation of a carbon–fluorine bond is observed, affording the synthesis of aminoalkyl fluorides and fluoro amino acids. D-Penicillamine (**1**) was converted to 3-fluoro-D-valine (**2**) in near-quantitative yield while other amino thiols, following more complex pathways, furnish lower yields of the respective fluoro products. The proposed mechanisms involve highly oxidized forms of sulfur such as dihalosulfonium salts or trifluorosulfur dications. These very electropositive sulfur moieties should be very good leaving groups, reacting with hydrogen fluoride, either in a unimolecular sense as in the case of penicillamine, or possibly via a bimolecular mode, as in the case of cysteine. In either case, the solvent appears to be the source of fluorine in the carbon–fluorine bond. Finally, there is described a carbocation-type conversion of some alcohols to thiols which can be effected by reacting the appropriate alcohols with hydrogen sulfide in liquid hydrogen fluoride.

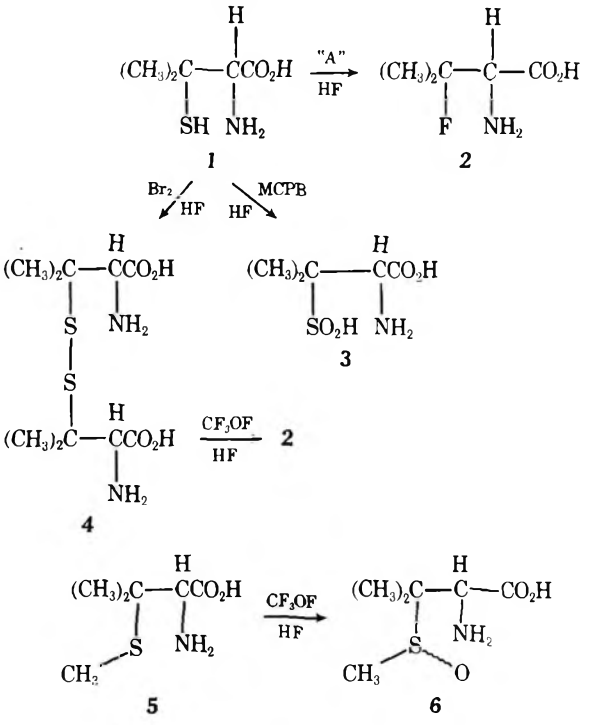
It has been known for a long time that carbon–sulfur bonds of thiols may be cleaved by chlorine[1] or bromine[2] and that a carbon–chlorine or carbon–bromine bond results from such a reaction. We wish to report that fluorine, and in some cases chlorine, *N*-chlorosuccinimide, or fluoroxytrifluoromethane can effect an analogous reaction when these reagents are reacted with amino thiols in liquid hydrogen fluoride. These reactions provide another method for the formation of carbon–fluorine bonds, especially in those molecules containing an amine, which being protonated in the highly acidic medium[3a] is protected from oxidation[3b] by the reagents. It allows the synthesis of certain fluorinated amino acids which, in some cases, would be very difficult to prepare.[4] We propose the name "fluorodesulfurization" for this reaction.

A. Reactions with Fluoroxytrifluoromethane, *N*-Chlorosuccinimide, and Chlorine. Photofluorination[3b] of D-penicillamine (**1**) in liquid HF at −78 °C with fluoroxytrifluoromethane (CF_3OF) afforded not the expected 4-fluoro-D-penicillamine, but rather a high yield of a substance characterized as 3-fluoro-D-valine (**2**). The structural assignment was made on the basis of its elemental analysis, its NMR spectrum, and a comparison (electrophoretic mobility and chromatographic retention time) with a sample of 3-fluorovaline obtained by photofluorination of L-valine.[5] Since $[\alpha]_D$ for **2** was equal to and of opposite sign to the $[\alpha]_D$ of the photofluorination product, it is probable that there is no involvement of C-2 in the reaction.

Subsequently, it was shown that these conversions of penicillamine proceeded equally well in the dark, at −78 or 0 °C, and that the conversion did not require CF_3OF but could also be effected with chlorine (Cl_2) or *N*-chlorosuccinimide (NCS). The stoichiometry was defined using NCS, of which 2 mol were required. However, when **1** was treated with *m*-chloroperbenzoic acid (MCPBA) or with bromine in liquid HF, **2** was not obtained but the products were penicillaminesulfinic acid[6] (**3**) and penicillamine disulfide[7] (**4**), respectively.

A consideration of related compounds other than thiols led us to react **4** and *S*-methylpenicillamine[8] (**5**) with CF_3OF. From the former, there was obtained a quantitative yield of **2** while from the latter two diastereomeric sulfoxides,[9] **6**, could be isolated. Elemental sulfur[10] is the major by-product (ca. 60% isolated yield) when **1** or **4** was reacted with CF_3OF but sulfur was not found when the reagent was NCS or Cl_2. When **1** was reacted with CF_3OF in trifluoroacetic acid (TFA), as opposed to HF, a number of products were formed but no trace of **2** was observed. Some of these transformations are outlined in Scheme I.

Scheme I. Reactions of Penicillamine and Relatives



"A" = either CF_3OF, NCS, or Cl_2

***B.* Reactions with a Fluorine–Helium Mixture.** It was hoped that the application of this chemistry to the cysteine (**7**) system would provide another route to 3-fluoroalanine (**9**) but none of the latter was found when **7** or cystine (**8**) was reacted with CF_3OF, NCS, or Cl_2 under a variety of conditions. Rather, with these reagents, there was obtained a mixture of cysteinesulfinic acid[11] (**11**) and cystine 1,1-dioxide[12] (**12**). **9** was obtained when F_2/He (1:4 v/v) was used as the reagent in HF/HBF_4 solvent and **7** as the substrate in which case a 33% yield of **9** and a 3% yield of 3,3-difluoroalanine[13] (**10**) were isolated. When **8** was reacted with F_2/He, only **11** was obtained and no **9** or **10** was detected. These transformations are outlined in Scheme II. Table I outlines the results of these reagents with other substrates.

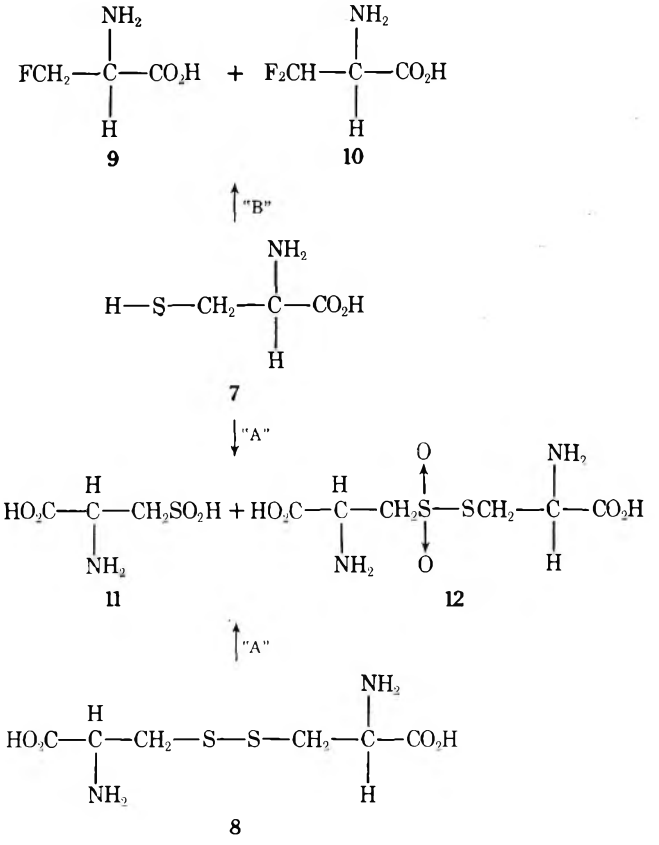
It should be noted that in contrast to the S-substituted compounds **4** and **5**, the 2,2-di-*n*-butyl-1,3-dithiolane[14] (Table I) produced the *gem*-difluoro compound. The next higher substituted compound, 1,1,1-tris(ethylthio)octane[15] (Table

Table I. Reactions of Various Sulfur Compounds in Liquid Hydrogen Fluoride with Fluorodesulfurization Reagents

Substrate	Reagent[a]	Product	Yield,[b] %
D-Penicillamine	A	3-Fluoro-D-valine	94
β-Mercaptophenylalanine	C	β-Fluorophenylalanine[c]	34
L-Cysteine	B	3-Fluoro-L-alanine	33
		3,3-Difluoro-L-alanine[d]	3
L-Cysteine	C	Cysteinesulfinic acid[e]	60
		Cystine 1,1-dioxide[f]	13.7
2-Diethylaminoethanethiol	B	2-Diethylaminoethyl fluoride	25
		2-Diethylamino-1,1-difluoroethane	3
N,α-Dimethyl-β-mercaptophenethylamine	A	N,α-Dimethyl-β-fluorophenethylamine	*g*
Homocysteine lactone	B	Homocystine 1,1-dioxide[h]	30
1,1,1-Tris(ethylthio)octane	A	1,1-Bis(ethylthio)-1-octene	*i*
3-Mercapto-3-methylbutyric acid	A	3,3-Dimethylacrylic acid	80[j]
2-Mercaptosuccinic acid	B	Succinic acid	17
2,2-Dibutyl-1,3-dithiolane	A	5,5-Difluorononane	50[k]

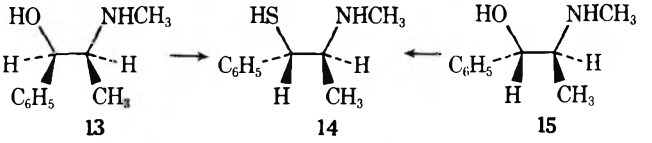
[a] Reagent A = CF_3OF; reagent B = F_2/He (1:4 v/v); reagent C = Cl_2 or NCS. [b] Unless otherwise stated, yields are isolated ones. [c] NMR and Spinco-Beckman amino acid analysis indicate one isomer. [d] Reference 13. [e] Reference 11. [f] Reference 12. [g] Could not be isolated analytically pure. [h] Identified by elemental analysis and NMR. [i] Identified by mass spectrum and NMR. [j] NMR yield. [k] Elemental analysis indicates 90% purity. Structural assignment made by mass spectral and NMR analysis.

Scheme II. Reactions of Cysteine and Cystine



I), afforded the ketene mercaptal, a result which may be caused by the fact that the starting material does not dissolve in liquid HF. Nitrogen heterocycles containing a thiol functionality are a readily available structural type, and thus 4-methyl-2-mercaptothiazole, 1-methyl-2-mercaptoimidazole, and 2-mercapto-6-hydroxypurine were subjected to a variety of fluorodesulfurization conditions. However, in no case was a carbon–fluorine bond formed. Finally when **5** was reacted with F_2/He, several products were obtained including a 40% yield of **2** (cf. CF_3OF reaction with **5**).

C. Thiolation in Liquid HF. Useful methods require readily available starting materials and therefore a thiolation method was developed which allows select alcohols to be transformed into thiols. It involves reacting the alcohol, dissolved in liquid HF, with hydrogen sulfide and has furnished DL-penicillamine (yield 60% by amino acid analysis) from DL-3-hydroxyvaline, and DL-β-mercaptophenylalanine (34% yield) from *threo*-DL-phenylserine. The stereochemistry of the reaction was defined by the isolation of *threo*-(+)-phenyl-2-methylaminopropanethiol[16] (**14**) from both (−)-ephedrine and (+)-pseudoephedrine (**15**):



The reaction also gave 7 mol % of bis(1-phenyl-2-methylaminopropyl) sulfide.[17]

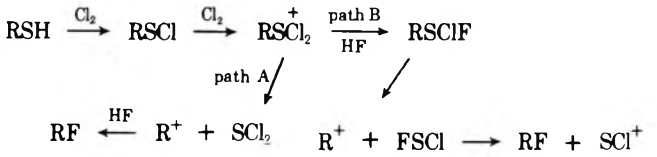
Discussion

The chlorinolytic cleavage of carbon–sulfur (C–S) bonds is well documented and a C–S bond rupture effected by bromine has been suggested but no carbon–fluorine bonds have been made by this route. Compounds in the cysteine–cystine system have been converted to their 3-chloroalanine analogues.[1b,c] These reactions were carried out with suspensions of hydrochlorides in methylene chloride and their mechanistic relevance to the reactions presented here is questionable.

Reactions with CF_3OF, NCS, Cl_2. We have arbitrarily divided our mechanistic considerations into two types: those reactions which *require* F_2/He and those which may be effected by CF_3OF, Cl_2, or NCS, reagents of lower oxidizing potential. It is probable that the reactions with the latter group of reagents have similar pathways and that they involve a heterolytic rupture of the C–S bond. Such an ionic, as opposed to a radical, pathway may be inferred by a consideration of the redox potentials of the species involved. That is, if a radical mechanism obtained, then at some point a fluoride ion would have to be oxidized to a fluorine atom and this is not possible with these reagents (e.g., Cl_2). Based on dielectric constant correlations, Norcross and Martin[1c] suggested ionic intermediates in the chlorinolysis of cysteine and cystine esters. That the intermediates are carbocations may be inferred from the successful fluorodesulfurization of tertiary and benzylic types and the failure of heterocyclic thiols to undergo this reaction.

The simplest view of the C–F bond forming step would involve discharge of the carbocation, formed in the penultimate step, by fluoride ion (path A, Scheme III). However, one can

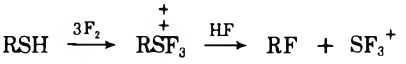
Scheme III. Possible Mechanistic Pathways for the Fluorodesulfurization Reaction



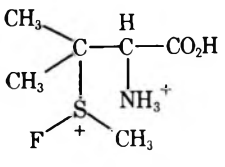
also envision a fluorine species being transferred from sulfur in an SNi process (path B).

Our preference is for path A since (1) it is probable that the carbon-bound fluorine originates in the HF solvent, a view supported by the finding that **2** is not formed when **1** is reacted with CF_3OF in trifluoroacetic acid, and (2) path B would require a fluorine–chlorine ligand interchange at sulfur when chlorine is the reagent. Although supporting evidence is not available, such an interchange seems unlikely considering the nature of some of the by-products: thus, no elemental sulfur was observed when chlorine was the reagent. This is consistent with the formation of sulfur dichloride, a stable molecule. Sulfur dichloride was identified by Norcross and Martin[1b] as a by-product. Sulfur difluoride, on the other hand, is known to rapidly disproportionate to sulfur and sulfur tetrafluoride,[18] thus accounting for the presence of sulfur in the CF_3OF reaction. The chemistry of mixed or complex sulfur halides or oxyhalides has not yet been established and the definitive statement about this mechanistic aspect will come when the by-products are identified in situ.

Reactions with F_2/He. The requirement of primary thiols such as cysteine for the more powerful oxidizer, F_2/He, may reflect the need of such systems for more potent leaving groups. Oxidation to the dihalosulfonium species by Cl_2, NCS, or CF_3OF affords only a singly positive ion, whose sulfur moiety may not be a good enough leaving group to compensate for the higher energy of an incipient primary carbocation. On the other hand, F_2/He could oxidize the sulfur to a dispositive species whose greatly enhanced leaving tendency could give rise to a primary carbocation or suffer ready bimolecular displacement by a fluoride ion:



Such a process would lead to an SF_3^+ ion, whose existence in liquid HF has been demonstrated.[19] Further support for the critical electropositive nature of the leaving group comes from the results of reactions of *S*-methylpenicillamine (**5**). Its failure to be converted to **2** by CF_3OF indicates that the inductive effect of the methyl group in an intermediate such as **16** is enough to vitiate the reaction, whereas an intermediate



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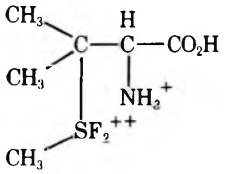

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such as **17** formed in the F_2/He reaction can overcome these difficulties. The difluorinated compounds such as **10** can be explained by an elimination of HF followed by addition of fluoride to carbon forming an α-fluorosulfenyl fluoride which reacts further.

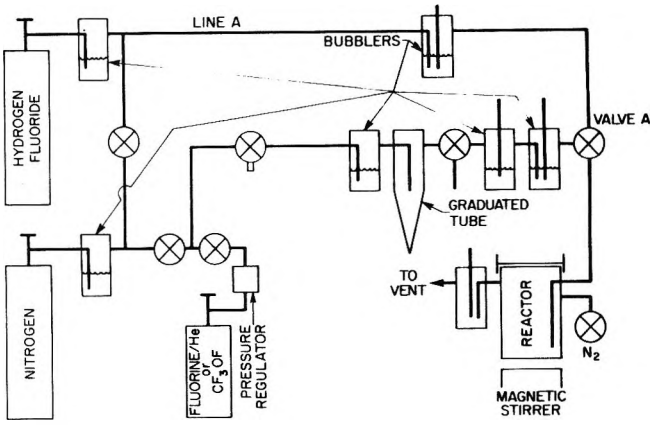
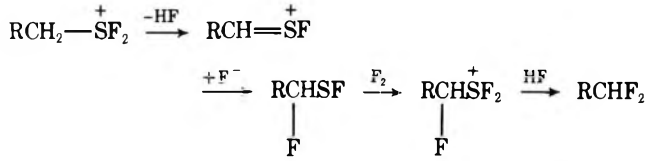


Figure 1.



This type of transformation has analogies in the reaction of *n*-butyl disulfide with silver difluoride yielding 1-fluorobutyl sulfur trifluoride[20a] and also in the chemistry of chlorosulfonium salts.[20b]

The Thiolation Reaction. It seems fairly clear that the thiolation reaction involves a carbocation mechanism. This is supported by a consideration of the structural types that undergo the reaction (e.g., tertiary and benzylic alcohols) and the stereochemical results (in which diastereomeric alcohols afford the same product). Additionally, the structural types which do not react are those which would afford less stable carbocations on C–OH cleavage. Thus threonine was recovered unchanged from the usual reaction conditions. The synthesis of the tertiary sulfide, felinine,[21] probably follows a similar mechanistic pathway.

Experimental Section

^{1}H NMR spectra (60 and 100 MHz) were obtained on Varian T-60 and HA-100 spectrometers, respectively, using tetramethylsilane or 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard. ^{19}F NMR spectra were obtained on either a Varian T-60 fitted with a 56.4-MHz transmitter and receiver or a JEOL C60HL spectrometer. In either case, trifluoroacetic acid or $CFCl_3$ was used as an internal standard and trifluoroacetic acid assumes the value $\phi = 77.0$. Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. F_2/He (1:4 v/v) was obtained from Matheson Gas Products, East Rutherford, N.J.; fluoroxytrifluoromethane from PCR, Gainesville, Fla.

Caution: The herein described technique for handling hydrogen fluoride is relatively safe as it does *not* involve transfer of *liquid* HF. A well-ventilated hood is indispensable for this type of work. The operator should wear face shield as well as rubber gloves. With these precautions, handling of HF, F/He, and CF_3OF proved in our laboratory to be routine and safe. Instructions of suppliers for safe handling of these reagents should be observed. First aid treatment of HF burns has been described.[23]

Fluorodesulfurization. General Procedure. The flow diagram of the apparatus is illustrated in Figure 1. (The design of this equipment and its modus operandi is in essence the same as described in ref 3a, with some improvements in details.) The reactor[3a] and bubblers are constructed from polychlorotrifluoroethylene (Kel-F); the valves are of polytetrafluoroethylene (Hamilton Co., P.O. Box 307, Whittier, Calif. 90608) (Teflon) and the connecting tubes were constructed of Teflon, polyethylene, and glass. The bubbler liquid was Halocarbon Oil (a blend of completely halogenated chlorofluorocarbons, Halocarbon Products Corp., Hackensack, N.J.). The glass graduated tube had to be replaced after four to five runs when CF_3OF was used.

Substrates were sealed in the reactor which was purged with N_2 throughout the reaction. The reactor was immersed in a −78 °C bath

(dry ice–acetone) and hydrogen fluoride gas was introduced via line A. After the requisite amount of liquid had been condensed, line A was purged with N_2 to avoid condensation of the remaining HF. Valve A was then closed to line A. F_2/He or CF_3OF was then introduced into the reactor either directly by reading the pressure drop on a regulator, or by condensation (with CF_3OF only) with a liquid N_2 bath in the graduated tube and measuring the liquid volume. When Cl_2 was used, it was condensed and measured using a −78 °C bath. Addition of NCS was accomplished by opening the top of the reactor under a vigorous stream of N_2 and adding in one portion.

After completion of the reaction, N_2 was introduced via the train until all the HF was removed from the reactor. The residue was generally dissolved in hydrochloric acid (ca. 2.5 N) and concentrated in a rotary evaporator. At this point, the desired analytical measurements (e.g., NMR, amino acid analysis) were made. The residues were then chromatographed, generally on Dowex 50X8 cation exchange resin (200–400 mesh), by applying the residue to the column and eluting with water until no fluoride ion could be detected in the effluent with fluoride ion test paper (Macherey, Nagel & Co.). Elution was continued by increasing the concentration of HCl in the eluent from 0.2 N to 4 N. A Teflon bellows pump was used and 15–20-ml fractions were collected. Concentration of fractions containing ninhydrin-positive materials was effected in vacuo (bath temperature <40 °C).

3-Fluoro-D-valine. D-penicillamine (1.49 g, 10 mmol) was sealed into the reactor, a slight nitrogen pressure applied, placed in a −78 °C bath, and 35 ml of liquid hydrogen fluoride was condensed resulting in the dissolution of the amino acid. The −78 °C bath was replaced with an ice bath, and approximately 30 mmol of fluoroxytrifluoromethane (85% purity) (the amount ascertained by a pressure drop on a gauge) was introduced through the inductor tube.

After the completion of the addition, an aliquot revealed the absence of starting material and only had NMR resonances corresponding to 3-fluorovaline. The HF was evaporated in a stream of nitrogen and the residue was taken up in concentrated HCl and concentrated in vacuo to yield 1.62 g of 3-fluoro-D-valine hydrochloride (94%).

The free amino acid was isolated by dissolving 1.52 g of the hydrochloride in 7 ml of water, decolorizing with 100 mg of Darco G-60, and filtering through Celite. The filtrate was cooled, treated with 0.7 ml of pyridine, and diluted with 20 ml of 2-propanol. There was obtained 560 mg of 3-fluoro-D-valine (44% overall) as white plates. An analytical sample was obtained by recrystallization from water–2-propanol: 60-MHz NMR (D_2O–DCl) δ 1.53 (d, 3 H, J = 22.5 Hz), 1.68 (d, 3 H, J = 24 Hz), 4.38 (d, 1 H, J = 14 Hz); $[\alpha]D$ −6.1° (c 2.5, 1 N HCl); ^{19}F NMR (D_2O–DCl) 14 lines centered at ϕ 143.5. Anal. Calcd for $C_5H_{10}NFO_2$: C, 44.44; H, 7.41; N, 10.35; F, 14.07. Found: C, 43.93; H, 7.30; N, 9.95; F, 14.31.

(+)-*threo*-1-Phenyl-2-methylaminopropanethiol Hydrochloride. A. From (−)-Ephedrine. The reactor was charged with 16.5 g of (−)-ephedrine (100 mmol), sealed under N_2, and after cooling to −78 °C was dissolved in 200 ml of liquid HF. Then H_2S was passed through the solution for 2 h at −78 °C and at 0 °C for 1 h. The HF was evaporated in a stream of nitrogen overnight and the residue was dissolved in concentrated HCl.

The solution was evaporated to 20 g of a semisolid which was dissolved in 30 ml of H_2O and basified with 70 ml of 2.5 N NaOH. The mixture was extracted with 100 ml of ether, and the aqueous layer was acidified with 11 ml of concentrated HCl and concentrated to dryness. The residue was extracted with hot ethanol and on addition of ether, 8.67 g of (+)-*threo*-1-phenyl-2-methylaminopropanethiol hydrochloride (40%), mp 175–177 °C dec, was obtained. For analysis it was recrystallized from acetonitrile: mp 178–180 °C dec; 60-MHz NMR (D_2O) δ 1.25 (d, 3 H, J = 6.2 Hz), 2.90 (s, 3 H), 3.78 (m, 1 H), 4.23 (d, 1 H, J = 10 Hz), 7.50 (s, 5 H); $[\alpha]D$ +88.9° (c 1.45 ethanol). Anal. Calcd for $C_{10}H_{16}NSCl$: C, 55.17; H, 7.36; N, 6.44; S, 14.71. Found: C, 55.41; H, 7.24; N, 6.21; S, 14.91.

The above ether extract was saturated with gaseous HCl at 0 °C, and the precipitate was slurried with acetonitrile to afford 2.9 g of the bis(1-phenyl-2-methylaminopropyl) sulfide dihydrochloride, mp 236–238 °C dec. An analytical sample was prepared by recrystallization from ethanol–ether: mp 236–237 °C dec; 60-MHz NMR (D_2O–DCl) δ 1.10 (broad doublet, 6 H, J = 5.6 Hz), 2.57 (s, 6 H) 3.80 (m, 4 H), 7.53 (s, 10 H). Anal. Calcd for $C_{20}H_{30}N_2SCl_2$: C, 59.85; H, 7.48; N, 6.98; S, 7.90; Cl, 17.71. Found: C, 60.02; H, 7.45; N, 6.14; S, 7.71; Cl, 18.02.

B. From Pseudoephedrine. (+)-Pseudoephedrine (1.65 g, 10 mmol) was dissolved in 20 ml of liquid HF in the usual reactor and H_2S bubbled through the solution at −78 °C for 1 h and at 0 °C for 2 h. The HF was evaporated in a stream of nitrogen, and the residue taken up in concentrated HCl, concentrated to dryness, and triturated with acetonitrile, affording 500 mg of (+)-*threo*-1-phenyl-2-methylaminopropanethiol hydrochloride, mp 177.5–179.5 °C dec, $[\alpha]D$ +86.9° (c 1.85, ethanol). Addition of ether to the acetonitrile supernatant yielded a second crop of 500 mg, mp 173–175 °C dec. The combined yield (1 g) was 46% of theory.

β-Mercapto-DL-phenylalanine. The reactor was charged with 15 g of DL-*threo*-phenylserine (83 mmol) which was then dissolved in 150 ml of liquid hydrogen fluoride at −78 °C. The solution was saturated with H_2S continuously for 1.5 h at −78 °C and for an additional 3 h at 0 °C. The HF and H_2S were removed in a stream of nitrogen at room temperature (overnight). The residue was dissolved in 75 ml of H_2O and after cooling in an ice bath was saturated with gaseous HCl. The precipitate which was formed was collected, redissolved in 50 ml of H_2O, and again saturated with HCl at 0 °C. The precipitate was filtered, washed with ether, and dried, affording 6.5 g of β-mercapto-DL-phenylalanine hydrochloride (34%) which showed a single peak on amino acid analysis and a single spot on electrophoresis (10% acetic acid buffer). Analytically pure material was prepared as follows: a 2-g sample was covered with 15 ml of concentrated HCl, warmed, and dissolved with addition of about 15 ml of methanol. After filtering the solution there was added an additional 15 ml of concentrated HCl, causing 1.18 g of analytically pure β-mercaptophenylalanine hydrochloride, mp 222–223 °C dec, to crystallize. Anal. Calcd for $C_9H_{12}NO_2SCl$: C, 46.25; H, 5.14; N, 5.97; S, 13.71. Found: C, 46.58; H, 5.44; N, 5.93; S, 13.30.

β-Fluoro-DL-phenylalanine. The reactor was charged with 1.167 g of β-mercapto-DL-phenylalanine (5 mmol), and dissolved in 20 ml of liquid HF at −78 °C. When solution was complete, 1.468 g of *N*-chlorosuccinimide (11 mmol) was added in one portion. The resultant solution was stirred at −78 °C for 10 min and at 0 °C for an additional 15 min; 5 ml was removed and quenched on ice for an alternate workup. The remainder of the HF solution was rapidly evaporated in a stream of nitrogen at 0 °C and the residue was taken up in a small quantity of H_2O and applied to a 100-ml Dowex 50X8 (200–400 mesh) column. The column was eluted with H_2O (300 ml), 0.5 N HCl (300 ml), and then continuously with 1 N HCl.

Fractions 119–135 afforded 300 mg of β-fluoro-DL-phenylalanine hydrochloride (34%): 60-MHz NMR (D_2O–DCl) δ 4.75 (d of d, 1 H, J = 26, 4 Hz), 6.33 (d of d, 1 H, J = 45, 5 Hz), 7.53 (s, 5 H). Anal. Calcd for $C_9H_{11}NO_2FCl$: C, 49.25; H, 5.01; N, 6.37; F, 8.65. Found: C, 48.76; H, 5.31; N, 6.35; F, 8.30.

The free amino acid was obtained by dissolving 30 mg of the hydrochloride in about 0.1 ml of H_2O, cooling, adding 0.011 ml of pyridine, and washing with H_2O–2-propanol (1:1). β-Fluoro-DL-phenylalanine (13 mg) was obtained, mp 173–174 °C. Anal. Calcd for $C_9H_{10}NO_2F$: C, 59.10; H, 5.46; N, 7.56; F, 10.37. Found: C, 58.36; H, 5.42; N, 7.52; F, 10.26.

Reaction of Cysteine with Fluorine–Helium. 3-Fluoro-L-alanine and 3,3-Difluoro-L-alanine. The reactor was charged with 1.50 g of anhydrous L-cysteine hydrochloride (9.5 mmol), cooled to −78 °C, and 50 ml of liquid hydrogen fluoride condensed into the reactor. This was evaporated at room temperature in a stream of nitrogen to remove HCl. The residue was redissolved the same way in 50 ml of HF and the solution was saturated at −78 °C with gaseous boron trifluoride. After the −78 °C bath was exchanged for an ice bath, a fluorine/helium mixture (1:4 v/v) was bubbled through the solution (ca. 2 bubbles/s) for 3 h.

The solution was evaporated with a stream of nitrogen and one-half of the residue was chromatographed on 100 ml of Dowex 50X8 cation exchange resin column (200–400 mesh) eluting with water and then with 0.5 N HCl. Concentration of fractions 65–77 afforded 230 mg of 3-fluoro-L-alanine hydrochloride (33%). Paper electrophoresis (10% aqueous acetic acid) showed it to be one substance. Its NMR spectrum was identical with that of an authentic sample. This 230 mg was dissolved in 1 ml of H_2O, cooled, and treated with 0.127 ml of pyridine and 3 ml of 2-propanol affording 139 mg of 3-fluoro-L-alanine[22] (81% recovery from the hydrochloride), $[\alpha]D$ +9.9° (c 3, 1 N HCl). Anal. Calcd for $C_3H_6NO_2F$: C, 33.65; H, 5.65; N, 13.08; F, 17.74. Found: C, 33.28; H, 5.90; N, 12.88; F, 17.63.

Fractions 54–56 were concentrated to give 20 mg of 3,3-difluoro-L-alanine hydrochloride (3%), a substance previously prepared in these laboratories:[13] 60-MHz NMR (D_2O–DCl) δ 4.77 (4 lines, 1, J_{HF} = 24.6, J_{HH} = 2 Hz), 6.56 (t of d, 1, J_{HF} = 52 Hz); ^{19}F NMR ϕ_A 125.5 (m, J_{FF} = 285 Hz), ϕ_B 129.9.

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analyses, and Mr. C. Homnick for the Spinco Beckman amino acid analysis.

Registry No.—D-Penicillamine, 52-67-5; hydrogen fluoride, 7664-39-3; fluoroxytrifluoromethane, 373-91-1; 3-fluoro-D-valine hydrochloride, 59752-73-7; 3-fluoro-D-valine, 59752-74-8; (−)-ephedrine, 299-42-3; (+)-*threo*-1-phenyl-2-methylaminopropanethiol hydrochloride, 59752-75-9; bis(1-phenyl-2-methylaminopropyl) sulfide dihydrochloride, 59738-51-1; (+)-pseudoephedrine, 90-82-4; DL-*threo*-phenylserine, 2584-75-0; β-mercapto-DL-phenylalanine hydrochloride, 59779-79-2; *N*-chlorosuccinimide, 128-09-6; β-fluoro-DL-phenylalanine hydrochloride, 59729-21-4; β-fluoro-DL-phenylalanine, 57362-93-3; L-cysteine hydrochloride, 52-89-1; 3-fluoro-L-alanine hydrochloride, 59729-22-5; 3-fluoro-L-alanine, 35455-21-1; 3,3-difluoro-L-alanine, 59729-23-6; 2-diethylaminoethanethiol, 100-38-9; *N*,α-dimethyl-β-mercaptophenethylamine, 4389-42-8; homocysteine lactone, 2338-04-7; 3-mercapto-3-methylbutyric acid, 59729-24-7; 2-mercaptosuccinic acid, 70-49-5; 2,2-dibutyl-1,3-dithiolane, 59729-25-8; cysteinesulfinic acid, 1115-65-7; cystine 1,1-dioxide, 30452-69-8; 2-diethylaminoethyl fluoride, 369-60-8; 2-diethylamino-1,1-difluoroethane, 59729-26-9; *N*,α-dimethyl-β-fluorophenethylamine, 59729-27-0; homocystine 1,1-dioxide, 59729-28-1; 1,1-bis(ethylthio)-1-octene, 13880-01-8; 3,3-dimethylacrylic acid, 541-47-9; succinic acid, 110-15-6; 5,5-difluorononane, 59729-29-2.

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(5) To be published.
(6) The product was identified by NMR, electrophoretic migration to the positive electrode (10% acetic acid system, ninhydrin visualization), and a positive starch–iodide reaction.
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Effect of Hydrogen Bonding and Solvent on the Conformational Preferences of Some 4-Hydroxythioxanthene *S*-Oxides

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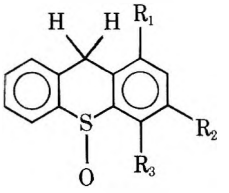
For a series of 4-hydroxythioxanthene *S*-oxides, it is shown by ^{1}H NMR spectroscopy that these molecules preferentially exist in conformations in which the sulfinyl oxygen is pseudoequatorial (e′) in chloroform but pseudoaxial (a′) in dimethyl sulfoxide solutions. Intra- vs. intermolecular hydrogen bonding is used to explain these observations. This is the first observation where the equilibrium between two possible conformations of a thioxanthene *S*-oxide type molecule has been altered such that either conformation can be preferred. The temperature dependence in the ^{1}H NMR spectrum was also examined.

The solution conformational preferences of thioxanthene *S*-oxide and its various substituted derivatives have been the subject of recent interest.[1-4] A number of conclusions have been made concerning the conformational dispositions of these molecules in solution.[5] The sulfinyl oxygen prefers to be in a pseudoequatorial position (10e′) (in a rapid conformational equilibrium) in thioxanthene *S*-oxide[3] (II, R = H). However, when a substituent (e.g., R = chloro, methyl) is placed in the 4 position peri to the sulfinyl moiety, the sulfinyl oxygen prefers the 10a′ position[3] (I). This is a result of steric repulsive interactions and demonstrates the larger steric requirement of sulfinyl oxygen vs. the sulfur lone pair. Thus, "the efficacy of peri substituents in altering the conformation of these (and related) systems"[3] was concluded.

Proton magnetic resonance (^{1}H NMR) spectroscopy has been the primary tool in making conformational assignments in these systems and several ^{1}H NMR parameters have become definitive in assigning preferred conformations in the thioxanthene *S*-oxide systems. When the 10e′ position (II) is preferred, the 9-H_a′ absorption appears upfield and broadened[2,3] relative to the 9-H_e′ absorption. It is broadened owing to long-range coupling to the peri (1,8) protons[2,3] as substantiated by decoupling experiments. Alternatively, when the 10a′ position (I) is preferred, the 9-H_a′ absorption appears downfield and broadened relative to the 9-H_e′ absorption. It appears downfield owing to the large deshielding effect of the 10a′ sulfinyl group. In addition, these criteria and the conformational preferences do not appear to depend significantly upon solvent, e.g., benzene, chloroform, or dimethyl sulfoxide (Me_2SO).[2,4]

In our search for new polymer additives, we began an investigation of some 4-hydroxythioxanthene *S*-oxide compounds. In the course of characterizing these compounds, we have shown (1) that a hydroxy group at C-4 does not necessarily drive the sulfinyl oxygen into the 10a′ position, (2) that solvent is sufficient for changing the conformational prefer-

Table I. Chemical Shifts of the C-9 Methylene Protons in Some Thioxanthene *S*-Oxides

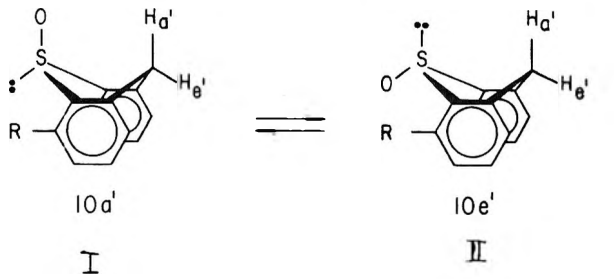


				Chemical shift[a-c]						
				$CDCl_3$			Me_2SO-d_6			
Compd	R_1	R_2	R_3	H_a'	H_e'	A[d]	H_a'	H_e'	A[d]	Ref
1	H	H	H	3.79 (b)	4.16	3.97				*e*
2	CH_3	H	CH_3	4.67 (b)	4.10	4.38				*f*
3	CH_3	H	OH	*g*	*g*		4.28[h]		4.28	This work
4	CH_3	CH_3	OH	3.29 (b)	4.17	3.73	4.38 (b)	4.02	4.20	This work
5	Cl	H	OH	3.48 (b)	4.63	4.05	4.47[h]		4.47	This work

[a] Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. [b] This number represents the center of the doublet, calculated from $\delta_A - \delta_B = \sqrt{(\nu_4 - \nu_1)(\nu_3 - \nu_2)}$. The coupling constants are of the order of 17–18 Hz. [c] The letter b indicates that that absorption is broadened compared to the other. [d] This number represents the mathematical center of the AB quartet pattern and is included in the table to show the downfield shift of the methylene protons in the 10a′ conformer. [e] Reference 3. [f] J. L. Herrmann, Ph.D. Dissertation, Case Western Reserve University, 1970. [g] These values could not be determined due to poor solubility. [h] This number represents a broad singlet resulting from accidental equivalence of the H_a' and H_e' absorptions.

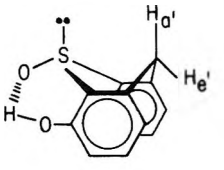
ences of these compounds, and (3) the first examples in which the same thioxanthene *S*-oxide molecule can be caused to exist preferentially in either of its two conformations.

Compounds 1 and 2 (Table I) are representative of the 10e′ (II) and 10a′ (I) conformations, respectively. The H_a' absorption is upfield and broadened in 1 and downfield and broadened in 2 compared to their respective H_e' absorptions (vide infra). Compounds 4 and 5 (and presumably 3) follow the same pattern in $CDCl_3$ as 1, which establishes their conformations as 10e′ (II). Apparently, strong intramolecular hydrogen bonding[6] between the sulfinyl and hydroxyl groups overpowers a steric or dipolar repulsive interaction, stabilizing the 10e′ conformer (III). However, in Me_2SO-d_6 solutions 4



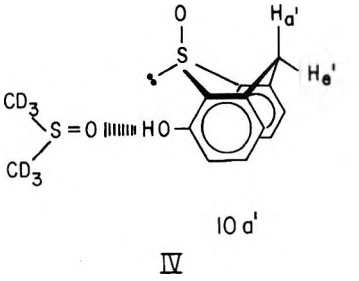
10a′ I

10e′ II



10e′ III

exhibits a pattern similar to that of 2 (10a′) in $CDCl_3$, indicating that a conformational shift has occurred in changing solvents. Indeed, while the C-9 proton absorptions of 3 and 5 are accidentally equivalent in Me_2SO-d_6, there is a net downfield shift in the absorptions (compare *A* values in Table I). Thus, compounds 3, 4, and 5 exist in the 10a′ conformation (I) in Me_2SO-d_6. Presumably, the sulfinyl group of Me_2SO competes better for the hydroxyl group in 3, 4, and 5 than does the sulfinyl group of the molecule itself, breaking the intramolecular hydrogen bond. When this occurs, the steric bulk of the solvated hydroxyl group forces the 10e′ sulfinyl group into the 10a′ position (IV). This results in a deshielding of the H_a' absorption.[3] Thus, solvent can be important in determining the conformations of these types of heterocycles.

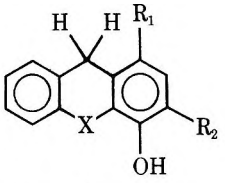


10a′ IV

To lend credence to these conclusions, the effect of solvent on the hydroxyl proton absorptions in the sulfoxides and their corresponding sulfides was examined. The exact position of hydroxyl protons is dependent upon temperature and concentration, as well as solvent.[7] The chemical shifts of the hydroxyl protons shown in Table II were determined at approximately the same temperature (35 °C) and concentration (20% w/v) in each solvent. Therefore, any gross changes in position (in a particular solvent) should reflect changes in structure, i.e., hydrogen bonding. It is seen that the hydroxyl proton absorptions of the sulfoxides are shifted downfield by ~3 ppm compared to their corresponding sulfides in $CDCl_3$. This suggests that strong intramolecular hydrogen bonds exist between the 10e′ sulfinyl oxygen and the hydroxyl proton in the sulfoxides but at best only weak ones (between sulfur lone pair and hydroxyl) in the sulfides. However, in Me_2SO-d_6, all the hydroxy protons are shifted into the 9.5–11-ppm region, suggesting that all are bound strongly to solvent. This is certainly in tune with the deductions reached above.

Since the strength of hydrogen bonding is dependent upon temperature,[8] an examination of the ^1H NMR spectrum of the C-9 protons of the sulfoxides vs. temperature might prove revealing. An increase in temperature should weaken and break the hydrogen bond between the sulfinyl and hydroxyl groups (in a nonpolar solvent), resulting in a conformational shift from II to I. We examined the ^1H NMR spectrum of 4 in *o*-dichlorobenzene from 60 to 170 °C. The only alteration in

Table II. Chemical Shifts of the Hydroxyl Proton in Some 4-Hydroxythioxanthenes and Their *S*-Oxides



Compd		Registry no.		Chemical shift (OH) [a]			
				$CDCl_3$		Me_2SO-d_6	
R_1	R_2	X = S	X = SO	X = S	X = SO	X = S	X = SO
CH_3	H	59803-16-6	59803-19-9	5.17	*b*	9.74	10.42
CH_3	CH_3	59803-17-7	59803-20-2	5.20	9.42	*c*	9.47
Cl	H	59803-18-8	59803-21-3	5.39	8.7 [d]	10.38	11.06

[a] Chemical shifts are reported in parts per million downfield from internal Me_4Si. [b] Insoluble. [c] Was not determined. [d] Extremely broad absorption.

the C-9 proton absorptions was a continual downfield shift of these absorptions (H_e', 9 Hz; H_a', 14 Hz). The upfield absorption remained broadened while the downfield one remained narrow indicating the H_a' and H_e' protons, respectively. Thus, even at 170 °C, the hydrogen bond is sufficiently strong to hold **4** in the $10_e'$ conformation.

In conclusion, these experiments have demonstrated the first examples wherein the two limiting conformations (in a rapid conformational equilibrium) of the same thioxanthene *S*-oxide molecule have been observed and that hydrogen bonding and solvent play the crucial role in establishing these conformations.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are not corrected. The ir spectra were taken as KBr pellets (except where indicated) on a Perkin-Elmer Model 467. All ^1H NMR spectra were obtained on a Varian Model A-60 spectrometer. Microanalyses were performed by Avon Lake Technical Center, B. F. Goodrich Co., Avon Lake, Ohio, and Huffman Labs, Inc., Wheatridge, Colo. All TLC analyses were performed on Analtech, Inc. precoated glass plates of silica gel using benzene or chloroform as eluent and uv light or iodine vapor for visualization. The silica gel used in column chromatography was Woelm silica gel, 70–230 mesh.

1-Methyl-4-hydroxythioxanthene (6). Diborane (40 ml of a 1.0 M solution in THF, 0.04 mol) was added by syringe to a stirred solution of 1-methyl-4-hydroxythioxanthone[9] (5.0 g, 0.02 mol) in 100 ml of THF at 0–5 °C under nitrogen. This mixture was stirred at 0–5 °C for 2 h, at ambient temperature overnight, and at reflux for 2 h. Ice and then water were added, the THF was evaporated, and the resulting mixture was extracted with chloroform. The extracts were dried ($MgSO_4$) and evaporated to afford a dark oil. Column chromatography on silica gel (100 g) using chloroform as eluent yielded 2.92 g (62%) of an oil which slowly crystallized to a tan solid: mp 99–101 °C; ir (neat) 3430, 1475, 1205, 810, 750 cm^{-1}; NMR ($CDCl_3$) δ 2.32 (3 H, s), 3.77 (2 H, s), 5.17 (1 H, s), 6.65 (1 H, d, J = 8 Hz), 6.95 (1 H, d, J = 8 Hz), 6.98–7.52 (4 H, m). Anal. Calcd for $C_{14}H_{12}OS$: C, 73.64; H, 5.31; S, 14.04. Found: C, 73.61; H, 5.41; S, 14.16.

1-Methyl-4-hydroxythioxanthene *S*-Oxide (3). A solution of *m*-chloroperbenzoic acid (6.68 g, 0.034 mol) in CH_2Cl_2 (120 ml) was added dropwise to a cold (0–5 °C) solution of **6** (7.72 g, 0.034 mol) in CH_2Cl_2 (35 ml). After stirring overnight, the mixture was warmed to room temperature and washed with a saturated solution of $NaHCO_3$ (2 × 100 ml) and water (100 ml). Drying ($MgSO_4$) and evaporation of the solvent led to 6.2 g (75%) of a white solid, mp 192–196 °C. Recrystallization from ethanol afforded TLC pure **3**: mp 205–206 °C dec; ir 3040 (OH), 970 cm^{-1} (S–O); NMR (Me_2SO-d_6) δ 2.35 (3 H, s), 4.28 (2 H, s), 6.86 (1 H, d, J = 8.5 Hz), 7.22 (1 H, d, J = 8.5 Hz), 7.35–7.92 (4, H, m), 10.42 (1 H, s). Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.12. Found: C, 68.79; H, 4.78; S, 12.98.

1-Chloro-4-hydroxythioxanthene (8). 1-Chloro-4-hydroxythioxanthone[10] was reduced as in the preparation of **6** to give a 92% yield of an off-white solid, mp 122–124 °C. Recrystallization from benzene afforded TLC pure **8**: mp 125–126 °C; ir 3400, 800, 735 cm^{-1}; NMR ($CDCl_3$) δ 3.99 (2 H, s), 5.39 (1 H, s), 6.67 (1 H, d, J = 8.5 Hz), 7.10 (1 H, d, J = 8.5 Hz), 7.0–7.5 (4 H, m). Anal. Calcd for $C_{13}H_9ClOS$: C, 62.78; H, 3.65; Cl, 14.25; S, 12.89. Found: C, 62.94; H, 3.40; Cl, 14.43; S, 12.99.

1-Chloro-4-hydroxythioxanthene *S*-Oxide (5). **8** was oxidized as in the preparation of **3** to afford an 89% yield of a light brown solid, mp 161–174 °C. Recrystallization from ethyl acetate gave TLC pure tan **5**: mp 191–193 °C dec; ir ~3000 (OH), 1432, 1308, 970 (S–O), 818, 755 cm^{-1}; NMR ($CDCl_3$) δ 3.48 (1 H, d, J = 17.6 Hz), 4.63 (1 H, d, J = 17.6 Hz), 6.78 (1 H, d, J = 9 Hz), 7.31 (1 H, d, J = 9 Hz), 7.49–7.97 (4 H, m), 8.67 (1 H, broad). Anal. Calcd for $C_{13}H_9ClO_2S$: C, 58.98; H, 3.43; Cl, 13.39; S, 12.11. Found: C, 59.21; H, 3.26; Cl, 13.58; S, 11.79.

1,3-Dimethyl-4-hydroxythioxanthene (7). A. 1,3-Dimethyl-4-hydroxythioxanthone. This compound was made from 2,4-dimethylphenol and thiosalicyclic acid by a procedure similar to that used to make 1-methyl-4-hydroxythioxanthone.[9] After recrystallization of the crude material from acetic acid, there was obtained a 32% yield of green product:[11] mp 252–255 °C; ir 3230, 1593, 1583, 1175, 860, 745 cm^{-1}; NMR (Me_2SO-d_6, 100 °C)[13] δ 2.35 (3 H, s), 2.75 (3 H, s), 7.03 (1 H, s), 7.3–7.7 (3 H, m), 8.2–8.5 (1 H, m).

B. 1,3-Dimethyl-4-hydroxythioxanthene (7). The product from **A** was reduced as in the preparation of **6** to give, after column chromatography (100 g of silica gel, $CHCl_3$ eluent), a 53% yield of amber oil: ir (neat) 3490, 1468, 1195, 1075, 752 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (3 H, s), 2.32 (3 H, s), 3.75 (2 H, s), 5.20 (1 H, s), 6.83 (1 H, s), 7.02–7.54 (4 H, m). This material was relatively unstable, turning green in light and air. A good elemental analysis could not be obtained.

1,3-Dimethyl-4-hydroxythioxanthene *S*-Oxide (4). **7** was oxidized as in the preparation of **3** to afford a 96% of yellow crude product, mp 136–157 °C. Two recrystallizations from ethanol gave a white solid: mp 158–163 °C; ir ~3020 (OH), 1278, 960 cm^{-1} (S–O); NMR ($CDCl_3$) δ 2.17 (3 H, s), 2.31 (3 H, s), 3.29 (1 H, d, J = 17 Hz), 4.17 (1 H, d, J = 17 Hz), 6.95 (1 H, s), 7.3–7.90 (4 H, m), 9.42 (1 H, broad). Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.41. Found: C, 69.39; H, 5.24; S, 12.44.

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Registry No.—1-Methyl-4-hydroxythioxanthone, 21896-76-4; *m*-chloroperbenzoic acid, 5106-10-5; 1-chloro-4-hydroxythioxanthone, 59803-22-4; 1,3-dimethyl-4-hydroxythioxanthone, 59803-23-5.

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The SN1 Hydrolysis of Isothioureas. 1

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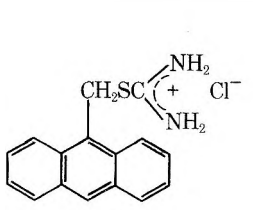
The hydrolysis of certain arylmethylisothioureas in water was studied. Evidence is presented which indicates that 9-anthrylmethylisothiourea (1), 10-methyl-9-anthrylmethylisothiourea (2), and 7(10)-benzanthrylmethylisothiourea (3) hydrolyze under acidic conditions by an SN1 mechanism. Support for this mechanism arises from a significant thiourea ("common ion") effect and from differences in the reactivity of 1–3, which can only be rationalized on the basis of a carbonium ion mediated mechanism.

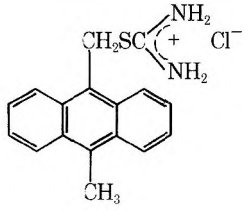
Recently there has been much interest in investigating the mechanistic details of hydrolysis reactions in pure water.[1] The development of sensitive conductance methods has allowed the accurate determination of hydrolysis rates for organic halides and sulfonates in water, which otherwise would have been difficult to study by conventional titrimetric methods. Most hydrolytic investigations have been conducted in mixed solvent systems, which avoided the analytical difficulties associated with the low aqueous solubilities of organic nonelectrolytes and moderated the high reactivity of many organic halides. Despite the development of more sensitive analytical techniques, low solubility remains as a major barrier to the systematic study of the hydrolysis of many compounds in water. Thus, correlations of reactivity with structure have been conducted in partially aqueous solvent systems, and comparison of results from different investigators is difficult because of the wide variety of solvent systems employed.

This report describes our investigations into the hydrolysis of certain arylmethylisothioureas in water. The isothiouronium moiety represents a new type of leaving group for an SN1 reaction. The proposed SN1 mechanism for these isothioureas is shown in Scheme I.

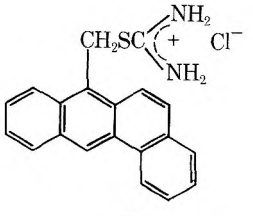
The compounds studied as their hydrochloride salts are 9-anthrylmethylisothiourea (1), 10-methyl-9-anthrylmethylisothiourea (2), and 7(10)-benzanthrylmethylisothiourea (3). These isothioureas are moderately soluble in water at a pH below their pK_a where they exist in the cationic



1

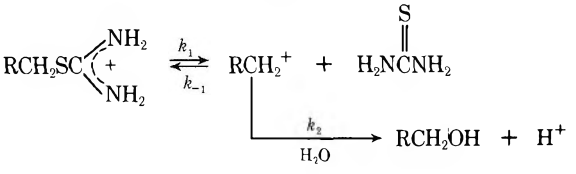


2



3

Scheme I



isothiouronium form. Isothioureas normally decompose to thiols in alkaline media,[2] but no information is available on their stability in acidic media.

Experimental Section

9-Anthrylmethylisothiourea Hydrochloride (1). 9-Anthraldehyde was synthesized by the Vilsmeier method.[3] Reduction of 9-anthraldehyde with sodium borohydride in refluxing methanol gave 9-hydroxymethylanthracene.[4] The 9-hydroxymethylanthracene was dissolved in benzene and chlorinated by passing hydrogen chloride gas into the solution. The 9-chloromethylanthracene was not isolated because direct addition of excess thiourea in ethanol to this solution with refluxing gave 1 as a yellow precipitate. The isolated solid 1 was mixed with a small amount of water and ultrasonified to dissolve any excess thiourea which may have contaminated the product. The slurry was filtered and, after drying, 1 melted with decomposition at 213–215 °C. Anal. Calcd for $C_{16}H_{17}ClN_2OS$ (monohydrate): C, 59.9; H, 5.34; H_2O, 5.61. Found: C, 60.13; H, 5.25; H_2O, 5.20.

10-Methyl-9-anthrylmethylisothiourea Hydrochloride (2). 10-Methyl-9-chloromethylanthracene was synthesized by chloromethylation of 9-methylanthracene.[5] The resulting chloromethyl compound, after recrystallization, was refluxed with a slight excess of thiourea in benzene. A yellow precipitate of 2 formed, which was isolated and washed with water in a manner similar to 1. After drying, 2 melted with decomposition at 208–210 °C. Anal. Calcd for $C_{17}H_{17}ClN_2S$: C, 64.44; H, 5.41. Found: C, 64.31; H, 5.50.

7(10)-Benzanthrylmethylisothiourea Hydrochloride (3). The procedure of Wood and Fieser[6] was followed in synthesizing 3. Chloromethylation of benzanthracene produced 7(10)-chloromethylbenzanthracene,[7] which was reacted with thiourea to give 3, which melted with decomposition at 212–215 °C (reported 213–214 °C).

Other Isothioureas. Benzylisothiourea hydrochloride (4) was available commercially and was used as received. 1-Naphthylmethylisothiourea hydrochloride (5) was synthesized by reacting 1-chloromethylnaphthalene with thiourea.[8] 9-Phenanthrylmethylisothiourea hydrochloride (6) was obtained similarly by reacting 9-chloromethylphenanthrene with thiourea.

Kinetic Methods. Two methods were used to follow the hydrolysis of isothioureas. One method depended on hydrogen ion production, while the other depended on a change in the uv-visible absorption spectrum as hydrolysis proceeded.

The production of hydrogen ion was followed with a pH stat by recording the volume of 0.01 M potassium hydroxide required to maintain the reaction solution at pH 5. The reaction solution temperature was maintained by circulating oil from a constant temperature bath through a stoppered jacketed beaker. The stopper contained holes for the pH-electrode, buret tip, and thermometer, but otherwise was tight fitting to minimize evaporation at the high temperature (50–80 °C) of most of the kinetic studies. First-order rate constants were obtained from semilogarithmic plots of the titrant volumes ($V_\infty - V_t$) by graphical estimation and least-square computer fits.

Rates of hydrolysis were determined spectrophotometrically using the absorbance measured at the spectral peaks of the arylmethylisothioureas between 350 and 405 nm. These studies were conducted by extracting the hydrolysis end products (arylmethyl alcohols) with ethyl ether from reaction solution samples, leaving the intact cationic isothioureas in the aqueous phase. From semilogarithmic plots of the remaining absorbance at one of the spectral maxima, as a function of time, were obtained first-order rate constants. This method was generally preferred over the pH-stat method at low temperatures because the lower reaction rates required sampling over long periods of time to accurately establish the rate.

Reaction solutions usually contained 0.001 M KCl, but for others, dilute acetate or succinate buffers were used. The aqueous medium did not affect the kinetics, unless the pH was outside of the range from 2 to 7 or high buffer or salt concentrations were used. The apparent solubility of these isothioureas became a problem in the presence of inorganic salt concentrations greater than 0.05 M. Apparently, these isothioureas form insoluble salts upon the addition of organic or inorganic salts at concentrations greater than 0.05 M, whereas the free base precipitated out of solution above pH 7.

Thiourea Effect. Evidence for a carbonium ion intermediate can be obtained by observing a common-ion effect.[9] For the hydrolysis of isothioureas, thiourea can be considered to be the "common ion". Reagent grade thiourea was initially added to reaction solutions, and the hydrolysis reaction followed by the uv or pH-stat method. For the general SN1 mechanism in Scheme I the rate expression is

$$\frac{d[RX]}{dt} = \frac{k_1k_2[RX][H_2O]}{k_2[H_2O] + k_{-1}[X]} = \frac{k_1[RX]}{1 + \alpha[X]} = k_{obsd}[RX]$$

where RX = isothiourea, X = thiourea, $\alpha = k_{-1}/k_2[H_2O]$, k_{obsd} = observed rate constant, k_1 = initial rate constant at [X] = 0. Solving for α, which is a measure of the magnitude of the common-ion effect, gives

$$\alpha = \frac{1}{[X]}\left[\frac{k_1}{k_{obsd}} - 1\right] = \frac{k_1 - k_{obsd}}{k_{obsd}[X]}$$

Generally the more stable the intermediate carbonium ion in question, the larger α is.

Results and Discussion

9-Anthrylmethylisothiourea Hydrochloride (1). Initial kinetic studies with 1 were conducted by the uv–visible spectral method with dilute (0.01–0.02 M) acetate or succinate buffers. Such dilute buffer concentrations were required because of the solubility problem mentioned previously. Initial studies were also made by the pH-stat method, which required no buffer. It was apparent that the hydrolysis rate was independent of pH or buffer type under acidic conditions. Therefore, further kinetic studies by the uv–visible spectral method were made in the absence of buffer with the solution being initially adjusted to pH 5 with dilute HCl so that the results could be directly compared to studies made by the pH-stat method. The rate constants for hydrolysis at various temperatures and the activation parameters are summarized in Table I.

The addition of thiourea to reaction solutions of 1 produced dramatic reductions in the observed rate of hydrolysis. The observed rate constants are summarized in Table II for three temperatures. In addition to the observed rate reductions, it is apparent that the magnitude of the retardation is greater at lower temperatures for a particular thiourea concentration. The first measurement of α for an SN1 halide hydrolysis was conducted on benzhydryl halides,[10] for which values of 10–10^2 were obtained. For 1, α ranges from 200 to 500 (Table II), which is the same order of magnitude as α for the SN1 hydrolysis of triphenylmethyl chloride.[11] Such large values of α for 1 lend strong support to the proposed SN1 mechanism.

Table I. Hydrolysis Rate Constants for Arylmethylisothiourea Hydrochlorides (1, 2, 3)

Temp, °C	$10^4 k$, s^{-1} 9-Anthryl (1)	10-Methyl-9-anthryl (2)	7(10)-Benzanthryl (3)
81			3.50
77	23.00		2.10
72			1.30
67	7.00		0.74
62			0.34
57	1.70	51.10	0.18
52		26.50	
47	0.43	13.50	
37	0.10	4.50	
27	0.03	1.10	
17		0.24	
E_a, kcal/mol	28.2	25.4	28.6
S_a, cal/mol K	+7.8	+5.8	+4.3

Support for the proposed carbonium ion mediated hydrolysis of 1 also is obtained from the fact that the 9-anthrylmethyl carbonium ion produced by dissociation of the thiouronium moiety has been shown to be quite stable by both hydrolysis studies on arylmethyl chlorides[12] and by theoretical molecular orbital calculations.[13] The high stability of the 9-anthrylmethyl carbonium ion arises from its ability to effectively delocalize its positive charge away from the methylene carbon from which the leaving group has departed.

10-Methyl-9-anthrylmethylisothiourea Hydrochloride (2). Hydrolysis of 2 proceeds to 10-methyl-9-hydroxymethylanthracene which is similar to 9-hydroxymethylanthracene obtained from the hydrolysis of 1. A significant increase in hydrolysis rate (15–20-fold) was observed for 2 compared to that for 1 (Table I).

An unusual feature of the semilogarithmic hydrolysis plots of 2 was significant curvature after initial linear portions. This behavior has been observed for the hydrolysis of 9-anthrylmethyl halides[14,15] and can be attributed to a mass-law effect. This nonlinear behavior has only been seen previously for highly reactive 9-anthrylmethyl halides because of the high stability of their carbonium ion. Such an effect for 2, in our work, is essentially the observation of a thiourea ("common ion") effect at a very low thiourea concentration. Thus the observed curvature as hydrolysis progresses is due to an increasing thiourea concentration producing an increasing retardation in rate.

Addition of thiourea to reaction solutions of 2 produced larger reductions in the observed hydrolysis rate constants than were observed for 1. These rate constants are summarized in Table II. In a typical hydrolysis study, the initial concentration of 2 was 6×10^{-4} M, which would produce 6×10^{-4} M thiourea upon complete hydrolysis. Since 1×10^{-3} M thiourea produces an initial rate reduction of one-half, it is apparent that even the thiourea produced after partial hydrolysis can cause an appreciable reduction in the observed hydrolysis rate.

The high reactivity of 2 is easily rationalized by the proposed SN1 mechanism and cannot be accounted for by an SN2 mechanism. The accelerative effect of a *p*-methyl group on a typical SN2 reaction can only be expected to be a factor of 2 or 3.[16] For an SN1 reaction, on the other hand, the accelerative effect of a *p*-methyl group is usually an order of magnitude or higher. This acceleration results from the greater

Table II. Thiourea Effect on Arylmethylisothiourea Hydrochlorides at Various Temperatures (1, 2)[a]

Thiourea concn, M	$10^4 k_{obsd}$, s^{-1}			
	9-Anthryl (1)			10-Methyl-9-anthryl (2),
	57 °C	66 °C	77 °C	52 °C
0	1.700	5.70	23.0	26.5
0.001				12.9 (1050)
0.005				3.5 (1320)
0.010	0.280 (500)	1.40 (350)	6.7 (250)	1.4 (1800)
0.100	0.033 (480)	0.18 (310)	1.1 (220)	0.2 (1210)

[a] The numbers in parentheses are α values ($k_{-1}/k_2[H_2O]$).

Table III. Molecular Orbital Calculations on Arylmethyl Carbonium Ions

Ar in $ArCH_2^+$	Reactivity $10^4 k$, s^{-1}, at 62 °C	Charge on $-CH_2^+$	
		CNDO	Huckel (ω = 1.1)
Phenyl		+0.410	+0.411
1-Naphthyl		+0.310	+0.309
9-Phenanthryl		+0.292	+0.295
9-Anthryl	3.61		+0.191
7(10)-Benzanthryl	0.336		+0.201
10-Methyl-9-anthryl	77.8		+0.175

electronic sensitivity of an SN1 reaction, mediated by a positively charged carbonium ion that is resonantly stabilized by an aromatic nucleus. The *p*-methyl group has the ability to increase the resonance stability of the carbonium ion through hyperconjugation.[17]

This type of interaction has been accounted for by the use of the Hammett σ^+ substituent constants, proposed for reactions in which a developing positive charge interacts with a π electron or aromatic system.[18] For a pure SN1 reaction a ρ of at least -4 is required and the σ^+ value for a *p*-methyl group is -0.31. Combining these values gives

$$\log\left(\frac{k_{p\text{-}CH_3}}{k_{mono}}\right) = \rho\sigma+ = (-4)(-0.31) = 1.24$$

$$\frac{k_{p\text{-}CH_3}}{k_{mono}} = 10^{1.24} = 17.4$$

This ratio is in agreement with the observed factor of 15–20 obtained for the increase in hydrolysis rate of **2** over **1**.

The thiourea effect for **2**, as mentioned previously, is two to three times higher than for **1**. Values for α, shown in Table II, range from 1000 to 1800 which indicate an even higher carbonium ion stability than the 9-anthrylmethyl carbonium ion. These α values approach the highest observed for an SN1 reaction, which are in the range of 1000–4000 for 4,4′-disubstituted diphenylmethyl chlorides.[19] This information supports the concept that structural changes which enhance the stability of a carbonium ion also increase α and thus α appears to be a reflection of the stability of the intermediate carbonium ions.

From an alternate point of view, α can be considered to be a measure of the discrimination of the carbonium ion for nucleophiles. Thus α, which is a ratio of k_{-1} to k_2 [H_2O], is a measure of the ability of the 9-anthrylmethyl carbonium ion to discriminate between thiourea and water as nucleophiles. To correct for the concentration of water, α should be multiplied by 55.5, which then would make α the ratio of two true second-order rate constants. With this correction, the magnitude of α becomes 10^4–10^5. This value reflects the ratio of the nucleophilicities of thiourea and water for the 9-anthrylmethyl carbonium ion, which is approximately the same magnitude as the ratio of their nucleophilicities in a standard SN2 reaction.[20] This suggests that the 9-anthrylmethyl carbonium ion is stable enough so that α becomes a measure of the intrinsic nucleophilicities of thiourea and water.

7(10)-Benzanthrylmethylisothiourea Hydrochloride (3). The hydrolysis rate of **3** was determined by the pH-stat method and the rate constants and activation parameters are summarized in Table I. Essentially the same activation energy is obtained for **3** as **1** with its lower reactivity arising from a less positive activation entropy.

The lower reactivity of **3** compared to **1** and **2** is in agreement with the poorer ability of the benzanthryl aromatic system to delocalize a charge away from the exocyclic methylene carbon of the carbonium ion. The rate of SN1 hydrolysis of arylmethyl halides has been shown to be dependent upon their ability to delocalize the positive charge away from the exocyclic atom from which the leaving group has departed.[21] Hydrolysis rates for limiting SN1 hydrolyses can then be compared to parameters calculated from molecular orbital theory. Recent work[22] has shown a linear correlation between σ^+ substituent constants and the charge on the exocyclic $-CH_2$ group of polycyclic arylmethyl carbonium ions. Such correlations indicate that a lower charge on this $-CH_2$ group corresponds to a higher SN1 reactivity because of greater charge delocalization through the π-electron system.

Molecular orbital calculations on the carbonium ions produced by the polycyclic arylmethylisothioureas investigated in this study show the same correlations. Omega–Huckel[23,24] and CNDO/2[25] calculations were used to calculate the charges on the arylmethyl carbonium ions and each gave comparable results for the smaller aromatic systems. The Omega–Huckel method was used exclusively for the larger carbonium ions because of the limited size of the CNDO/2 computer program.[26] For the 10-methyl-9-anthrylmethyl carbonium ion, a heteroatom model[27] was used which accounted for the stabilizing effect of the *p*-methyl group. The charges for representative aromatic systems obtained from these calculations are shown in Table III along with the hydrolysis rate constants at 62 °C. The lower reactivity of **3** compared to **1** as mentioned above is in keeping with the higher charge on the exocyclic $-CH_2$ group of the intermediate carbonium ion. The higher reactivity of **2** also correlates with its lower localized charge.

The other arylmethyl systems shown in Table III were investigated as their respective isothioureas. The benzyl-, 1-naphthylmethyl-, and 9-phenanthrylmethylisothioureas were subjected to hydrolytic conditions but none showed hydrolysis characteristic of **1**–**3**. Referring to the charges in Table III calculated for these hypothetical carbonium ions, it is evident that a significantly higher positive charge is localized on their exocyclic methylene groups as compared to **1**–**3**. Thus the nonreactivity of these three compounds can be ascribed to the lower stability of the carbonium ion produced and the higher energy requirement to remove the thiourea moiety from the higher localized charge. Using as a comparison the hydrolysis rates of the corresponding arylmethyl halides indicates that

9-anthrylmethyl chloride hydrolyzes 10^3–10^5 times faster than 9-phenanthrylmethyl chloride.[28] If this large reactivity difference can be applied to the relative reactivity for isothiourea hydrolysis, a rate of hydrolysis is predicted that would be practically undetectable for 9-phenanthrylmethylisothiourea under our experimental conditions.

Such large differences in reactivity for arylmethylisothioureas indicates that nucleophilic assistance does not make a significant contribution to this type of hydrolysis. If water was acting as a direct nucleophile in displacing the isothiourea moiety, there should not be such large differences in reactivity among different arylmethyl systems. The polycyclic aromatic ring should not alter greatly the ability to undergo an SN2 hydrolysis since the exocyclic methylene group electronically and sterically is only slightly altered with different aromatic rings. As an example, in the SN2 reaction in which chloride is displaced by iodide in anhydrous acetone, the difference in reactivity between 9-phenanthrylmethyl chloride and 9-anthrylmethyl chloride is only a factor of 10.[29] Such a mechanism would not, therefore, account for the large observed difference in the hydrolytic reactivity of the comparable isothioureas. Only an SN1 mechanism can account for such variation in reactivity because of pronounced differences in the carbonium ion stability of the various arylmethyl systems studied.

Conclusions

This investigation was undertaken in an attempt to determine the mechanism of hydrolysis of certain arylmethylisothioureas. Evidence has been presented to show that this hydrolysis proceeds by an SN1 mechanism with thiourea as the leaving group. Substituent effects and the observed activation parameters lend strong support to this proposal. As a comparison, the only well-characterized hydrolysis, in pure water, involving a sulfur leaving group (i.e., carbon–sulfur bond cleavage), is that of *tert*-butyldimethylsulfonium iodide,[30] which has an activation energy of 31.56 kcal/mol and an activation entropy of +15.74 cal/(mol K). This hydrolysis reaction was shown to be SN1 and its activation energy and entropy are of the same sign and approximately the same magnitude as those for the hydrolysis of 1–3. Although comparisons of activation parameters are insufficient evidence on which to base a mechanism, they provide further support for our proposed carbonium ion mediated hydrolysis.

Alterations in the arylmethyl group, to which the isothiourea moiety is attached, altered reactivity in a predictable fashion if an SN1 mechanism is operative and molecular orbital calculations correlated well with the predicted order of reactivity of the arylmethylisothioureas. The arylmethylisothioureas that would produce arylmethyl carbonium ions with high charge delocalization showed much higher hydrolytic reactivity and the unreactivity of other arylmethylisothioureas (i.e., benzyl-, 1-naphthylmethyl-, and 9-phenanthrylmethyl-) can also be understood on the basis of these molecular orbital calculations.

This investigation has thus shown that thiourea is a new leaving group for SN1 solvolyses. Because of their moderate aqueous solubility, the arylmethylisothioureas offered the opportunity of studying an SN1 hydrolysis in a purely aqueous medium. The generally higher stability of the isothiourea compounds compared to the corresponding arylmethyl halides allowed study of the hydrolytic reactivity of the 9-anthrylmethyl ring system in a purely aqueous environment. These ring systems have only been studied previously in organic solvents of low water content, because of their high hydrolytic reactivity as halides. The following paper will report on the effect of modifications of the leaving group on hydrolytic reactivity and on the reactivity of an allylic isothiourea.[31]

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The SN1 Hydrolysis of Isothioureas. 2

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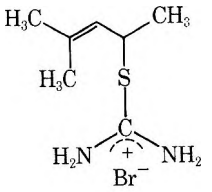
The hydrolysis of an allylic isothiourea and the hydrolytic effect of structural modifications on the isothiourea moiety were studied. The allylic isothiourea 1,3-dimethyl-2-butenylisothiourea (**1**) was found to be much more reactive than arylmethylisothioureas. Various *N*-methylisothioureas (**2–4**) and an isoselenourea (**5**) were studied to determine how alterations directly on the isothiourea affect reactivity. Such studies further support an SN1 mechanism for isothiourea hydrolysis proposed previously.[1]

In the preceding paper,[1] evidence was presented for an SN1 hydrolysis of certain arylmethylisothioureas in a purely aqueous medium. Our previous work indicated that thiourea is a new leaving group for SN1 hydrolyses. These compounds offer the opportunity to study hydrolysis in pure water because of their moderate aqueous solubility. This advantage is significant, because the correlation of SN1 hydrolysis studies from one investigator to another is made difficult by the wide variety of mixed solvent systems employed.

This report will extend the applicability of our proposed mechanism to a wider variety of compounds. An allylic isothiourea, 1,3-dimethyl-2-butenylisothiourea hydrobromide (**1**), was studied to further investigate a previous proposal[2]



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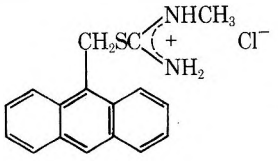
that **1** hydrolyzed by an SN1 mechanism. No detailed study of the mechanism of the hydrolysis was undertaken but **1** was found to hydrolyze quickly in water producing an allylic alcohol, thiourea, and hydrogen ion.

We also will report on the effect of modifications of the isothiouronium moiety on hydrolytic reactivity. Various *N*-methyl-substituted 9-anthrylmethylisothioureas (**2–4**) were



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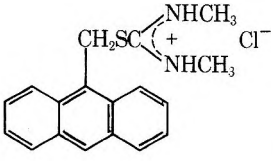

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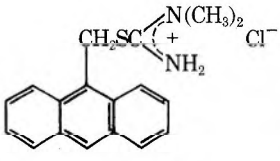

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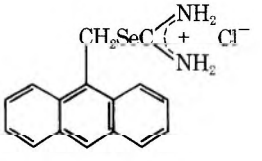

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studied as well as 9-anthrylmethylisoselenourea (**5**), in which selenium substitutes for sulfur in the isouronium moiety.

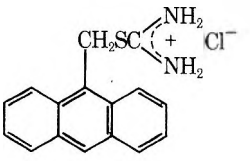
Experimental Section

1,3-Dimethyl-2-butenylisothiourea Hydrobromide (1). The procedure of Saville[2] was used to synthesize **1** by the reaction of thiourea with 2-methylpenta-1,3-diene catalyzed by concentrated hydrobromic acid. The 2-methylpenta-1,3-diene was prepared by dehydration of 2-methylpentane-2,4-diol using aniline and hydrobromic acid. The 2-methylpenta-1,3-diene (bp 76 °C) was purified by fractional distillation.

Crude **1** was washed with cold dilute hydrobromic acid, suspended in acetone, filtered, and dried over paraffin chips in a desiccator. The white, crystalline product melts at 124–125 °C (Saville reports 133.5–134.3 °C). Anal. Calcd for $C_7H_{15}BrN_2S$: C, 35.15; H, 6.32. Found: C, 35.21; H, 6.25.

Two similar allylic isothioureas, allylisothiourea hydrochloride (**6**) and 2-methylallylisothiourea hydrochloride (**7**), were used as received from Eastman Organic Chemicals.

***N*-Methyl-Substituted 9-Anthrylmethylisothiourea Hydrochlorides (2–4).** *N*-Methyl, *N,N*-dimethyl, and *N,N'*-dimethyl analogues of 9-anthrylmethylisothiourea hydrochloride were synthesized in a manner similar to 9-anthrylmethylisothiourea hydrochloride (**8**)



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reported in our previous paper.[1] The appropriate N-substituted thiourea was used in place of thiourea.

N-Methyl-9-anthrylmethylisothiourea hydrochloride (**2**) melted with decomposition at 206–209 °C. Anal. Calcd for $C_{17}H_{17}ClN_2S$: C, 64.44; H, 5.41. Found: C, 64.25; H, 5.25.

N,N'-Dimethyl-9-anthrylmethylisothiourea hydrochloride (**3**) melted with decomposition at 205–207 °C. Anal. Calcd for $C_{18}H_{19}ClN_2S$: C, 65.34; H, 5.79. Found: C, 63.43; H, 5.60. The impurity in this compound did not affect the hydrolysis kinetic data.

N,N-Dimethyl-9-anthrylmethylisothiourea hydrochloride (**4**) melted with decomposition at 204–207 °C. Anal. Calcd for $C_{18}H_{19}ClN_2S$: C, 65.34; H, 5.79. Found: C, 65.22; H, 5.83.

9-Anthrylmethylisoselenourea Hydrochloride (5). The synthesis of **5** is analogous to the synthesis of 9-anthrylmethylisothiourea hydrochloride (**8**)[1] except that thiourea is replaced by selenourea. Selenourea is difficult to use because of its instability. It apparently decomposes in solution by reacting with dissolved oxygen and, therefore, reaction solutions were deoxygenated prior to the introduction of selenourea. Commercial samples of selenourea were contaminated with free selenium, which was removed by filtration of the selenourea before adding it to the reaction solution. The resulting yellow isoselenourea hydrochloride (**5**) melted with decomposition at 185–188 °C. Anal. Calcd for $C_{16}H_{17}ClN_2OSe$ (monohydrate): C, 52.26; H, 4.66; H_2O, 4.91. Found: C, 52.18; H, 4.54; H_2O, 5.17.

Kinetic Method. The pH-stat technique described in the preceding paper[1] was used for each compound. The titrant volume added as a function of time was used to obtain first-order rate constants. The thiourea effect was studied, for **1**, by adding thiourea to reaction solutions of **1** and measuring the apparent reduction in hydrolysis rate. The analysis of the results for the thiourea effect has been previously discussed.[1]

Results and Discussion

1,3-Dimethyl-2-butenylisothiourea Hydrobromide (1). **1** hydrolyzes much faster (50–300-fold) than any of the arylmethylisothioureas reported on previously.[1] Using the pH-stat technique, anthrylmethylisothioureas require reaction temperatures greater than 50 °C for hydrolysis to occur at an appreciable rate, while **1** is so reactive that its hydrolysis can only be followed conveniently at temperatures below 40 °C. Table I summarizes the hydrolysis rate constants and activation parameters obtained for **1**. The higher reactivity of **1** is encompassed in the activation entropy, which is +21.22

Table I. Hydrolysis Rate Constants for Various Isothioureas and an Isoselenourea

	$10^4 k$, s^{-1}					
		9-Anthrylmethyl				
Temp, °C	1,3-dimethyl-2-butenyl (1)	Unsubstd (8)[a]	*N*-Methyl (2)	*N,N'*-Dimethyl (3)	*N,N*-Dimethyl (4)	Seleno (5)
74			11.6	20.9		
67		7.00	5.4	9.8	7.3	15.6
62			2.5	5.3	3.7	9.6
57		1.70	1.3	2.7	2.0	4.1
52	290.5					1.6
47	142.2	0.43				0.7
42	68.0					
37	31.8	0.10				
27	6.4	0.03				
17	1.2					
E_a, kcal/mol	28.9	28.2	28.2	28.2	28.2	36.8
S_a, cal/mol K	+21.2	+7.8	+7.0	+8.4	+7.8	+35.3
pK_a[b]		−1.19	−1.12	−1.32	−1.08	

[a] See ref 1. [b] pK_a of the N-substituted thiourea.

Table II. Kinetic Salt and Thiourea Effects on the Hydrolysis of 1,3-Dimethyl-2-butenylisothiourea Hydrobromide (1)[a]

Concn, M	$10^4 k$, s^{-1}	Concn, M	$10^4 k$, s^{-1}
0	12.8	1.00 $NaClO_4$	19.9
0.10 KCl	12.8	0.01 Thiourea	12.5 (2.6)[b]
0.50 KCl	16.2	0.10 Thiourea	10.6 (2.0)
1.00 KCl	21.1	1.00 Thiourea	6.6 (0.9)
0.10 $NaClO_4$	13.3		

[a] 30 °C. [b] Parenthetical values are α ($k_{-1}/k_2[H_2O]$).

cal/(mol K) compared to +7.77 cal/(mol K) for **8**. Similar hydrolysis studies with **6** and **7** gave no hydrolysis under the same conditions where **1** hydrolyzed readily, and even by elevating the temperature to force hydrolysis, only the thiol-producing reaction was detected.[3]

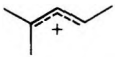
It has been shown that an increase in ionic strength assists reactions in which a molecule dissociates into ions in the rate-determining step.[4] The ionic strength effect on the hydrolysis of anthrylmethylisothioureas could not be studied because the addition of salt depresses their solubility appreciably, but **1** is very soluble in water and its solubility is relatively unaffected by the addition of salt. It was, therefore, thought that it would be worthwhile to investigate the effect of added salt on the hydrolysis rate of **1** as a further test of the SN1 mechanism proposed for isothiourea hydrolysis. Table II summarizes the hydrolysis rate constants obtained at various concentrations of potassium chloride and sodium perchlorate up to 1.0 M.

The effect of thiourea added to reaction solutions of arylmethylisothioureas[1] was used as a measure of the "common ion" effect, which is observed with the SN1 solvolysis of organic halides. The effect of initially added thiourea on the hydrolysis rate of **1** was investigated up to 1.0 M thiourea and Table II summarizes the observed hydrolysis rate constants.

The kinetic information presented for **1** indicates hydrolytic properties that are quite different from those of the arylmethylisothioureas. Its behavior can best be discussed in relation to the hydrolysis of allylic halides, which have shown evidence for both SN1 and SN2 mechanisms.[5] Allyl chloride was observed to be more reactive than the corresponding saturated alkyl chloride, but its solvolysis rate is dependent on the entering nucleophile in certain solvents.[5] The higher reactivity is attributed to the allyl cation in which the positive charge is resonantly distributed, while the dependency upon the entering nucleophile indicates that under some solvolytic conditions the allyl carbonium ion is not fully developed and allyl chloride requires nucleophilic assistance.

Methyl-substituted allyl chlorides show definite SN1 character and diminishing SN2 character. In 50% aqueous ethanol, α,α-dimethylallyl chloride and γ,γ-dimethylallyl chloride are 1.3×10^5 and 5.5×10^5 times more reactive than allyl chloride, respectively.[6] They are also less sensitive to the nature of the entering nucleophile, while being more sensitive to the solvent ionizing power. In formic acid, containing 0.5% water, a common ion effect was observed in the hydrolysis of various substituted allyl chlorides due to the chloride ion produced in the reaction.

The available evidence indicates that, while allyl halides may react by SN1 or SN2 mechanisms, alkyl substituted allyl halides react by an SN1 mechanism except under extreme conditions where only the SN2 mechanism is possible. Hydrolysis of **1** by an SN1 reaction would produce, as an intermediate, the trimethylallyl carbonium ion (**9**) which would be



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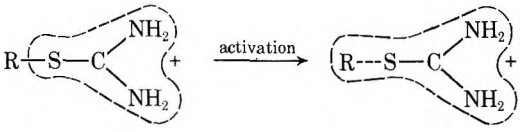
quite stable. The lack of hydrolysis for allylisothiourea (**6**) and 2-methylallylisothiourea (**7**) indicates that a sufficiently stable carbonium ion is not produced from these isothioureas.

The modest acceleration for the hydrolysis of **1** due to the addition of salt does not apparently correlate with the significant positive salt effects seen in other SN1 hydrolyses. Typically, Ingold has observed rate accelerations of 30–50% at 0.1 M salt concentrations for the hydrolysis of *tert*-butyl bromide and benzhydryl halides.[7] Recently a more detailed study of specific salt effects on SN1 solvolyses has been reported[8] and, generally, it was observed that the rate of hydrolysis increases linearly with ionic strength for halide salts, while with perchlorates greater rate accelerations are observed.

For **1** only a 4–6% increase in hydrolysis rate is seen up to a 0.1 M concentration of either potassium chloride or sodium perchlorate. Above 0.1 M the increase in rate seems to be more pronounced with an increase of 60–70% at a 1.0 M concentration. These results indicate that the SN1 hydrolysis of an isothiourea does not follow the ionic strength behavior of alkyl halide hydrolysis. For alkyl halides the SN1 transition state involves the separation of two charged species—the carbonium ion and anionic halide. For the isothioureas, on the other

hand, the transition state involves only one charged species—the carbonium ion—and one dipolar species—thiourea. The ionic strength effect on such a dissociation would be smaller than that expected for the separation of two charged species.

Above a salt concentration of 0.1 M, the observed rate accelerations could be due to either an effect on the transition state or the initial state. It is unlikely that an increased salt concentration would assist in a transition state that is dispersing charge. In proceeding from the cationic isothiourea to the transition state in which the carbon–sulfur bond is being stretched, positive charge is being actually spread over a larger area as depicted below. Increasing ionic strength should de-



crease slightly the stability of the transition state of such a molecule. The salt effect on the initial state (cationic isothiourea) may be the important factor in the observed rate acceleration, since at high ionic strengths, it is known that the activity coefficients of many salts increase rather than decrease. Such an effect could be operative in increasing the activity of the cationic isothiourea, which would be reflected in a hydrolysis rate acceleration. In general, the kinetic effect of high concentration salt cannot be predicted, a priori, and thus the origin of the ionic strength effect is only speculative.

In addition to an apparently anomalous salt effect on hydrolysis, 1 exhibits only a minor "common ion" effect. With 0.1 M thiourea the reduction in hydrolysis rate is only 15% while other arylmethylisothioureas exhibit reductions of 85–99% at this concentration.[1] Even at the highest concentration of 1.0 M thiourea, the rate reduction is only 50%. Values for α ($k_{-1}/k_2[H_2O]$) are also given in Table II and it appears that α decreases as the thiourea concentration increases but it is questionable whether these decreases are significant. At low thiourea concentrations the rate reductions are small and small errors in the apparent rate constants would produce large deviations in α. Additionally, at a high thiourea concentration (1.0 M), the hydrolytic properties of the aqueous solution have changed due to the large amount of added solute and thus α would depend on both the thiourea effect and the effect of the altered solvent on the hydrolysis rate.

For 1, α is at least an order of magnitude lower than α determined for other arylmethylisothioureas.[1] Apparently, although the trimethylallyl carbonium ion produced in this reaction is very stable, it poorly discriminates between thiourea and water nucleophiles, which may be the result of a strongly held hydration layer hindering penetration by a potential nucleophile. In the trimethylallyl carbonium ion, the positive charge is shared by fewer atoms than in the anthrylmethyl carbonium ion, where the positive charge is delocalized over 15 atoms. The trimethylallyl carbonium ion could hold its hydration sphere more strongly because of its higher charge density. Such a hydration sphere around carbonium ions has been suggested by the pioneering work of Ingold,[9] which indicated that the reaction of the carbonium ion with water is a multimolecular cooperative reaction of the hydration sphere with the carbonium ion. With a strongly held hydration layer an effective barrier to entering nucleophiles is present. Also a strong interaction between the carbonium ion and its hydration layer should facilitate surmounting the activation barrier for the reaction of water and carbonium ion.

Even though 1 exhibits its own unusual kinetic behavior, its behavior can be rationalized in terms of the previously proposed SN1 mechanism for arylmethylisothioureas. These studies on 1 extend the general applicability of the proposed SN1 hydrolysis mechanism to a different class of isothioureas. Thus the carbonium ion mediated hydrolysis of arylmethylisothioureas is not peculiar to them alone, but can be applied to other isothioureas which produce sufficiently stable carbonium ions.

N-Substituted 9-Anthrylmethylisothiourea Hydrochlorides (2, 3, 4). Table I summarizes the hydrolysis rate constants and activation parameters obtained for each *N*-methylmonoisothiourea (2–4). These compounds apparently have the same activation energy (28.2 kcal/mol) as 8 with the differences in hydrolysis rate being encompassed in their activation entropies.

In considering solvolysis reactions, the relative ability of various leaving groups to depart from carbon is an important factor in controlling hydrolysis rates. The ability of a group to leave a developing carbonium ion can be correlated with the pK_a of the conjugate acid of the leaving group.[10] This correlation is reasonable, since the pK_a of an acid represents the ability of a base to separate from a hydronium ion, which is analogous to a base separating from a carbonium ion.

The hydrolysis rate of 3 is significantly faster than that for 8 while 2 hydrolyzes significantly slower. These results correlate well with the pK_a's of the corresponding thioureas (Table I)[11] except for 4. Apparently, 4 does not follow the reactivity correlation with pK_a, because its hydrolysis rate is identical with 8 at the three temperatures studied, while the pK_a correlation predicts that 4 should hydrolyze slower than 2. The anomaly in this case may be due to steric factors arising from the two methyl groups being attached to the same nitrogen. Isothioureas have been shown to be freely rotating about the alkyl carbon–sulfur bond,[12] but substituents on the isothiourea nitrogens or in the alkyl moiety hinder this rotation[12] and may hold the molecule in one conformation, if they are sufficiently bulky. Molecular models show that the substitution of two methyl groups on one nitrogen can hinder free rotation in 4. Steric hindrance could create an energy barrier to rotation creating a strain upon rotation in the alkyl carbon–sulfur bond which would facilitate bond breaking in the SN1 ionization step.

Other than the abnormality in reactivity observed for 4, methyl additions to the isothiourea moiety add further confirmation to the proposed carbonium ion mechanism.[1] Minor alterations in leaving group structure would not produce such a pronounced effect on the hydrolysis rate in an SN2 reaction. Only a small charge separation is involved in the transition state for a SN2 mechanism which would not be as sensitive to the individual ionization properties of each methyl-substituted thiourea.

9-Anthrylmethylisoselenourea Hydrochloride (5). The hydrolysis rate constants and activation parameters for 5 are summarized in Table I. With the N-substituted isothioureas (2–4) there is a correlation between reactivity and pK_a of the corresponding thiourea. This pK_a relationship is applicable because only small perturbations are made in the leaving group. The methyl substitutions influence the carbon–sulfur bond indirectly through an inductive effect, while replacement of sulfur by selenium is a more significant perturbation of the leaving group. The isoselenourea (5) has a larger activation energy than its corresponding sulfur analogue (8), which is in keeping with the isouronium moiety being the leaving group in a SN1 hydrolysis mechanism. Selenium is larger and more polarizable than sulfur, and it is reasonable to assume that energetically it should be more difficult for selenourea to depart from the developing carbonium ion. This greater energy requirement is seen in the 8 kcal/mol higher activation energy for the isoselenourea (5) over the equivalent isothiourea (8). The very positive activation entropy may indicate higher

initial solvation for **5**, contributing to the high activation entropy when hydration water is released in the activated state.

Conclusions

The evidence presented in this and the previous report[1] supports our proposal that thiourea is a new leaving group for SN1 hydrolyses. In this report we have included studies on a reactive allylic isothiourea and the effect of alterations of the leaving group. These additional studies extend the applicability of the SN1 mechanism originally proposed for arylmethylisothioureas and indicate that perturbations of the leaving group are in agreement with a carbonium ion mediated mechanism.

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Registry No.—**1**, 59473-89-1; **2**, 59473-90-4; **3**, 59473-91-5; **4**, 59473-92-6; **5**, 59473-93-7.

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Synthesis of the β-Adrenergic Blocking Agent Timolol from Optically Active Precursors

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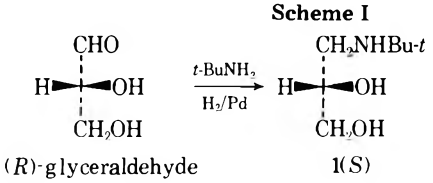
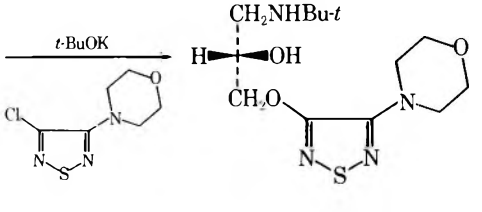
The synthesis of the β-adrenergic blocking agent, timolol, from optically active precursors is described and confirmation of its absolute configuration is presented.

The biological activity of 3-(3-*tert*-butylamino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole (**2**),[1] a potent β-adrenergic blocking agent, resides mainly in one of the enantiomers, the levorotatory hemimaleate salt. The active isomer, timolol maleate, was previously obtained via chemical resolution, and on the basis of the stereochemistry of compounds interacting with the adrenergic receptor was presumed to have the *S* configuration[1]. Since other β-blocking agents such as propranolol[2] and practolol[3] possess the *S* configuration, it seems likely that the stereoisomeric relationship of timolol with (*R*)-glyceraldehyde as depicted in Scheme I should obtain. We have indeed found this to be the case and wish to report a convenient synthesis of timolol from optically active precursors. Catalytic hydrogenation of (*R*)-glyceraldehyde over palladium in the presence of *tert*-butylamine produced 54% of (*S*)-3-*tert*-butylamino-1,2-propandiol (**1**). This in turn

Scheme I



(*R*)-glyceraldehyde 1(*S*)



2(*S*)

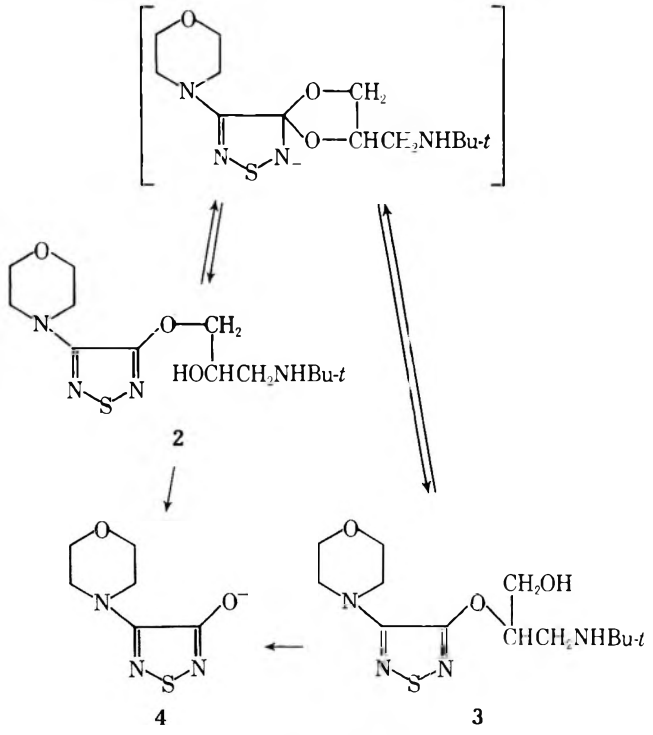
was condensed with 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole in the presence of potassium *tert*-butoxide to afford a low yield of optically pure timolol, isolated as the levorotatory maleate salt.

This procedure was short and convenient for laboratory purposes but suffered from two shortcomings: low yields and the commercial unavailability of glyceraldehyde. Low yields in the etherification step (**1** → **2**) were found to be a consequence of the base instability of compound **2**. Strong base effects the equilibration of **2** and **3** (Smiles rearrangement) as well as the concomitant loss of the side chain from **2** and **3** giving the anion of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (**4**). These transformations are illustrated in Scheme II. In order to circumvent these side reactions the secondary alcohol functionality of **1** was protected by reaction with benzaldehyde yielding oxazolidine **8**. Subsequent reaction of **8** with 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole in the presence of potassium *tert*-butoxide followed by acid hydrolysis gave timolol in 50% yield.

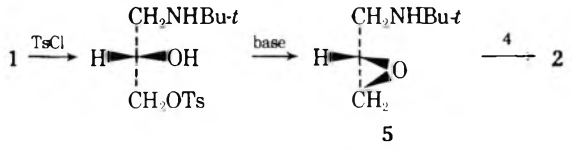
Scheme III depicts an alternate mode for introducing the aminopropanediol side chain utilizing optically active epoxide **5**. When the epoxide **5** was allowed to react with the sodium salt of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole, **2** was produced in 36% yield.

To obviate the need for (*R*)-glyceraldehyde, an alternate synthesis of aminoglycol **1** was devised (Scheme IV). Cleavage of D-mannitol-1,2,5,6-bisacetonide (**6**)[5] with lead tetraacetate conveniently afforded 2 equiv of (*R*)-glyceraldehyde acetonide (**7**). Reductive alkylation with *tert*-butylamine and subsequent hydrolysis gave a 70% overall yield of **1** without isolation of the intermediates. Optimum conditions for conducting the reductive alkylation were achieved by slow addition of alde-

Scheme II



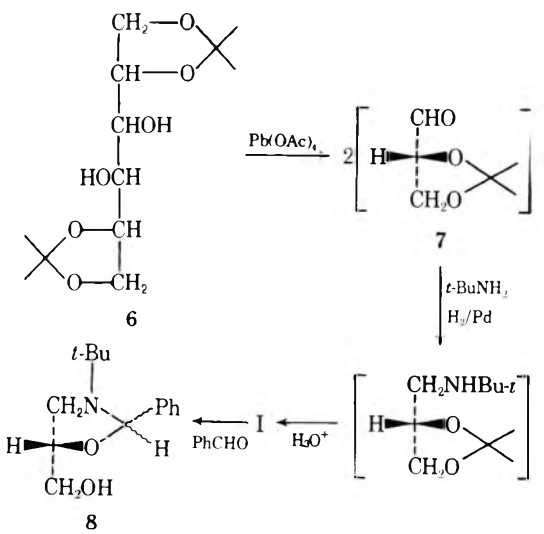
Scheme III



hyde to *tert*-butylamine during the course of the catalytic reduction.[6] In this manner, reduction of the aldehyde as well as racemization of the intermediate imine were minimized.

In conclusion, a practical synthesis of timolol has been achieved through the agency of optically active precursors and its absolute configuration has been confirmed. These procedures are also of potential utility in the synthesis of other β-adrenergic blocking agents in the biologically active *S* configuration utilizing either electrophilic or nucleophilic optically active reagents for elaboration of the side chain. These methods coupled with the method used by Danilewicz and Kemp[3] for the synthesis of (*R*)-practolol via **7** allow the introduction of the aminopropanol side chain in either the *R* or *S* configuration.

Scheme IV



Experimental Section

All melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Boiling ranges are similarly uncorrected. Infrared spectra were determined on a Perkin-Elmer Infracord Model 137 as Nujol mulls. Rotations were measured on a Perkin-Elmer Model 141 polarimeter. NMR spectra were determined on a Varian Model A-60A; proton shifts, δ, are relative to internal Me_4Si reference. Uv spectra were obtained on a Perkin-Elmer Model 202.

3-Chloro-4-(*N*-morpholino)-1,2,5-thiadiazole. 3,4-Dichloro-1,2,5-thiadiazole[4] (100.0 g, 0.645 mol) was added dropwise over a 30-min period at 105–110 °C to 224 ml (2.58 mol) of morpholine (mild exotherm). After addition the reaction mixture was stirred for 2 h at 105–110 °C, cooled to 15 °C, and quenched with 250 ml of water. The mixture was made acidic with 250 ml of concentrated hydrochloric acid. The insoluble oil soon crystallized to a heavy solid which was isolated by filtration and washed well with water. After drying in vacuo at 35 °C, 125.5 g (97%) of the morpholine derivative was obtained, mp 43–45 °C. NMR ($CDCl_3$) showed two symmetrical multiplets, δ 3.5 ppm (CH_2NCH_2), the second at 3.9 ppm ($-CH_2OCH_2-$). An analytical sample was prepared by recrystallization from ethanol, mp 43–45 °C. Anal. Calcd for $C_6H_8ClN_3OS$: C, 35.04; H, 3.92; N, 20.43; Cl, 17.24. Found: C, 35.27; H, 3.88; N, 19.90; Cl, 17.30.

3-Hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (4). 3-Chloro-4-(*N*-morpholino)-1,2,5-thiadiazole (125.5 g, 0.610 mol) was added to 1 l. of 2.5 N sodium hydroxide and 100 ml of dimethyl sulfoxide. The reaction mixture was refluxed with stirring for 3 h. The solution was cooled to 15 °C and rendered acidic with 250 ml of concentrated hydrochloric acid. The precipitated hydroxy compound was filtered at 15 °C, washed well with water, and dried in a Dietert dryer, yielding 108.7 g (95%) of **4**, mp 198–200 °C dec, equiv wt 189 (calcd, 187). The NMR (Me_2SO-d_6) showed two symmetrical multiplets at δ 3.3 ($-CH_2NCH_2-$) and 3.45 ppm ($-CH_2OCH_2-$). The active proton was too broad to be observed. Anal. Calcd for $C_6H_9N_3O_2S$: C, 38.49; H, 4.85; N, 22.44. Found: C, 38.64; H, 4.76; N, 22.49.

(*S*)-(−)-3-*tert*-Butylamino-1,2-propanediol (1). Method A. To a solution of 12.48 g (0.17 mol) of *tert*-butylamine in 50 ml of methanol was added 1.0 g of 5% palladium on carbon and the mixture shaken under hydrogen (45 psi initial) as a solution of 5.0 g (0.056 mol) of (*R*)-glyceraldehyde in 20 ml of methanol was added dropwise. Hydrogen uptake ceased after 24 h (48 of 53 lb theory consumed). After separation of the catalyst by filtration and washing twice with 5-ml portions of methanol the combined filtrates were concentrated in vacuo to a viscous, yellow oil. This oil was covered with 25 ml of ether and scratched to induce crystallization. The resulting solid was isolated by filtration and dried in vacuo at 25 °C to afford 7.1 g of crude **1**, mp 55–65 °C. After recrystallizing from *n*-hexane 4.47 g (54%) of **1**, mp 81–83 °C, $[\alpha]_D$ −30.1° (1 N aqueous HCl), was obtained. The NMR showed a singlet at δ 1.1 ppm [$-C(CH_3)_3$], a distorted doublet at 2.6 ppm ($-CH_2N-$), a complex multiplet at 3.6 ppm (CHOH, NH), distorted singlet at 4.0 ppm ($-CH_2O-$). Anal. Calcd for $C_7H_{17}NO_2$: C, 57.10; H, 11.64; N, 9.51. Found: C, 57.36; H, 11.58; N, 9.73.

Method B. A solution of 36.4 g (0.138 mol) of 1,2,5,6-diisopropylidenemannitol[5] in 175 ml of anhydrous tetrahydrofuran was treated with 61.6 g (0.139 mol) of lead tetraacetate. The addition was made in portions over a 20-min period at 15–20 °C (slightly exothermic). After the addition the mixture was stirred for 40 min at 25 °C and the reaction tested negative with potassium iodide–starch paper. The mixture was cooled to 0 °C, aged 10 min, and filtered into an ice-cooled receiver, washing the precipitate with 35 ml of cold tetrahydrofuran. The filtrate (containing isopropylidene-(*R*)-glyceraldehyde) was added dropwise over a 1-h period during hydrogenation to a mixture of 103 ml of *tert*-butylamine, 103 ml of methanol, and 7.2 g of 5% palladium on carbon in a hydrogenation apparatus under 3 atm hydrogen pressure. The mixture was hydrogenated at ambient temperature until the absorption of hydrogen ceased. The catalyst was filtered (ice-cooled receiver) and washed with 52 ml of methanol. The filtrate was treated with 350 ml of 6 N hydrochloric acid (cooling), and the mixture was distilled until a vapor temperature of 98 ± 1 °C was reached, and then refluxed for 1 h. The solution was cooled to 0 °C and treated with 140 g of sodium hydroxide pellets keeping the temperature under 35 °C. The mixture was treated with 140 ml of water and extracted four times with 175-ml portions of methylene chloride. The combined extracts were dried over magnesium sulfate and evaporated to a thick crystalline slurry. The residue was flushed twice with 50 ml of ether and filtered at 0–5 °C and the product dried at 35 °C in vacuo yielding 28.5 (70%) of *S*-**1**, mp 83.5–85 °C, $[\alpha]_D$ −30.3° (1 N aqueous HCl), equiv wt 150 (calcd, 147).

This material was identical in all respects with that prepared from (*R*)-glyceraldehyde.

(*S*)-(−)-3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-(*N*-morpholino)-1,2,5-thiadiazole (2) Hemimaleate Salt. Method A. A mixture of 20.57 g (0.100 mol) of 3-(*N*-morpholino)-4-chloro-1,2,5-thiadiazole and 14.72 g (0.100 mol) of (*S*)-(−)-3-*tert*-butylamino-1,2-propanediol (1) in 50 ml of anhydrous *tert*-butyl alcohol was heated to reflux under nitrogen. Then 100 ml of 1 M potassium *tert*-butoxide in *tert*-butyl alcohol was added in 10-ml portions 10 min apart. After the last addition the mixture was refluxed for an additional 10 min, cooled to 60 °C, and treated with 50 ml of 6 N hydrochloric acid with cooling. An additional 50 ml of water was introduced and the *tert*-butyl alcohol evaporated in vacuo, leaving an oil–water residue. The mixture was extracted twice with 35 ml of methylene chloride and the combined organic phases back-extracted twice with 50 ml of 4 N hydrochloric acid. The acid layers were rendered alkaline with excess potassium carbonate and extracted twice with 50 ml of ether. The ether layers were washed twice with 20 ml of water, dried over magnesium sulfate, and evaporated in vacuo to an oil, 13.7 g. This oil was dissolved in 50 ml of tetrahydrofuran, treated with 1.5 g of Merck charcoal, and filtered, and the cake was washed with 20 ml of fresh tetrahydrofuran. To this solution was added a solution of 5.0 g (0.043 mol) of maleic acid in 25 ml of tetrahydrofuran. The mixture was seeded and aged for 1 h at 25 °C. The resulting salt was filtered, washed with 5 ml of tetrahydrofuran, and dried at 50 °C in vacuo, yielding 7.3 g (13%) of **2** hemimaleate, mp 195–198 °C. The product was recrystallized from 60 ml of ethanol (0.5 g charcoal treatment), mp 198.5–199.5 °C dec (lit.[1] mp 201–202 °C), $[\alpha]_{405}$ −11.52° (*c* 4, 1 N aqueous HCl).

The NMR (1.0 N DCl/D_2O) showed a singlet at δ 1.5 ppm [$-C(CH_3)_3$], a doublet at 3.25 ppm ($-CH_2N-$), one-half of a symmetrical pair of multiplets at 3.6 ppm ($-CH_2NCH_2-$), the second half at 3.9 ppm ($-CH_2OCH_2-$), a broad multiplet at 4.5 ppm (−OCH−), a broad singlet at 4.6 ppm ($-CH_2O-$), and a sharp singlet at 6.5 ppm (HC=CH). Anal. Calcd for $C_{17}H_{28}N_4O_7S$: C, 47.21; H, 6.53; N, 12.95; S, 7.41. Found: C, 47.30; H, 6.59; N, 12.78; S, 7.55.

Method B. A mixture of 11.3 ml of 0.885 M potassium *tert*-butoxide in *tert*-butyl alcohol (10 mmol), 2.35 g (10 mmol) of (*S*)-(−)-2-phenyl-3-*tert*-butyl-5-hydroxymethyloxazolidine (8), and 2.05 g (10 mmol) of 3-chloro-4-morpholino-1,2,5-thiadiazole was stirred at 25 °C for 16 h. The solvent was evaporated in vacuo and the residue treated with 20 ml of 1.0 N hydrochloric acid at 60 °C for 1 h. The mixture was cooled to 25 °C and extracted twice with 10 ml of ether. The aqueous layer was made alkaline with excess potassium carbonate and extracted twice with 70 ml of ether. These ether extracts were dried over magnesium sulfate and evaporated to an oil residue of 1.80 g (57%) of the desired free base. This material was dissolved in 10 ml of tetrahydrofuran and treated with 0.7 g (6 mmol) of maleic acid, producing 2.17 g (50%) of **2** hemimaleate, mp 199–201 °C, $[\alpha]_{405}$ −11.9° (*c* 4, 1 N HCl).

The mother liquor from which **2** had been crystallized was concentrated in vacuo to a gummy residue. This residue was partitioned between 40 ml of 5% aqueous sodium bicarbonate and 40 ml of ether. After drying over magnesium sulfate, evaporation of the ether in vacuo gave 6.0 g of a tan oil which was chromatographed on 400 g of Merck neutral alumina. Elution with glyme–THF (1:1) provided 1.9 g of crude **3** which was recrystallized from *n*-hexane affording pale yellow needles, mp 120–121.5 °C. The mass spectrum indicated a molecular ion of 316; NMR (Me_2SO-d_6) showed a multiplet at δ 4.8 ppm (−OCH), poorly resolved doublet at 3.7 ppm ($-CH_2OH$), multiplet at 3.45 ppm ($-CH_2N$, plus morpholino), and a singlet at 1.0 ppm [$-C(CH_3)_3$]. Addition of D_2O did not alter the splitting pattern of the single methine proton, indicating that it was not α to a slowly exchanging active proton. Anal. Calcd for $C_{13}H_{24}N_4O_3S$: C, 49.35; H, 7.65; N, 17.71; S, 10.13. Found: C, 49.53; H, 7.63; N, 17.84; S, 10.24.

Method C. A mixture of 0.92 g (2.5 mmol) of (*S*)-(−)-3-*tert*-butylammonium-1,2-epoxypropane *d*(10)-camphorsulfonate, 0.52 g (2.5 mmol) of the sodium salt of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (from NaOMe in MeOH), plus 0.467 g (2.5 mmol) of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole in 2 ml of dimethyl sulfoxide was aged for 4 days at room temperature. The solution was quenched into 35 ml of distilled water and the aqueous solution brought to pH 9 with sodium carbonate. The aqueous solution was then extracted three times with 40 ml of methylene chloride, and these extracts back extracted with 20 ml of water. After drying over magnesium sulfate, evaporation of the methylene chloride left a tan oil. This oil was dissolved in 8 ml of tetrahydrofuran and was added to a solution of 0.29 g (2.5 mmol) of maleic acic in 3 ml of tetrahydrofuran. After aging for 1 h at room temperature, the precipitate was isolated and dried in vacuo. This afforded 0.63 g (58.5%) of **2** hemimaleate, mp 183–193 °C. Recrystallization from 4 ml of absolute ethanol gave 0.35 g (32.5%), mp 197–198 °C, $[\alpha]_{405}$ −11.49° (c 4, 1 N HCl).

(*S*)-(−)-2-Phenyl-3-*tert*-butyl-5-hydroxymethyloxazolidine (8). A mixture of 7.5 g (0.051 mol) of (*S*)-(−)-3-*tert*-butylamino-1,2-propanediol and 10 ml (0.999 mol) of benzaldehyde was heated to 150 °C. Water plus benzaldehyde distilled from the reaction as fresh benzaldehyde was added to maintain constant volume. After 30 min distillation of volatiles ceased and the mixture was cooled to 30 °C. The excess benzaldehyde was distilled at 0.5 mm. Four fractions were collected: (1) bp 115–117 °C (0.2 g); (2) bp 117–120 °C (0.5 g); (3) bp 120–122 °C (5.3 g of **8**, 85% pure by VPC); (4) bp 122–124 °C (4.0 g of **8**, 93% pure by VPC). The combined yield of fractions 3 and 4 was 77%. The NMR spectrum ($CDCl_3$) (both enantiomers) exhibited a doublet at δ 1.05 ppm [$-C(CH_3)_3$], a singlet at 2.4 ppm (−OH), a doublet at 5.5 ppm (aminal methine), and a multiplet at 7.4 ppm (Ph). The remaining potons form a complex group of multiplets between 2.7 and 4.3 ppm.

(*S*)-(−)-1,2-Dihydroxy-3-*tert*-butylaminopropane 1-*p*-Toluenesulfonate. A solution of 4.0 g (0.027 mol) of (*S*)-(−)-3-*tert*-butylamino-1,2-propanediol and 3.14 g (0.027 mol) of pyridine hydrochloride in 8 ml of pyridine was treated with 5.31 g (0.027 mol) of *p*-toluenesulfonyl chloride. The mixture was stirred for 0.5 h at 25–30 °C and poured into 50 ml of cold water. The solution was treated with 1.92 g (0.014 mol) of potassium carbonate and the pyridine was evaporated at 55–60 °C in vacuo. The aqueous residue was treated with 4.5 g (0.033 mol) of potassium carbonate and the mixture extracted with 50 ml of methylene chloride. Evaporation of the magnesium sulfate dried extract gave a residue of 6.2 g (75%) of the desired tosylate, mp 91–93 °C.

The NMR ($CDCl_3$) exhibited a singlet at δ 1.08 ppm [$-C(CH_3)_3$], a singlet at 2.45 ppm ($-CH_3$), a complex multiplet centered at 2.6 ppm (NCH_2), a singlet at 3.3 ppm (NH, OH), a multiplet centered at 4.0 ppm (CH_2O, OCH), and an A_2B_2 pattern at 7.25 and 7.75 ppm.

(*S*)-(−)-3-*tert*-Butylammonium-1,2-epoxypropane (5) *d*(10)-Camphorsulfonate Salt. A solution of 2.0 g (6.6 mmol) of the above tosylate in 30 ml of benzene was treated with 0.39 g (7.3 mmol) of sodium methoxide. This mixture was aged for 2.5 h at room temperature and was then filtered, the insolubles being washed with 10 ml of benzene. This solution was then treated with a solution of 1.62 g (7 mmol) of *d*(10)-camphorsulfonic acid in 10 ml of acetone. The solution was seeded and evaporated to a volume of 20 ml under a stream of nitrogen. The resulting precipitate was isolated by filtration and dried in vacuo, yielding 0.95 g (38.5%) of the *d*(10)-camphorsulfonate of **5**, mp 141–142 °C. Anal. Calcd for $C_{17}H_{31}NO_5S$: C, 56.47; H, 8.64; N, 3.87. Found: C, 56.44; H, 8.50; N, 3.80. The NMR (Me_2SO-d_6) showed two singlets at δ 0.76 and 1.05 ppm (C_7 geminal CH_3's of camphorsulfonic acid), a singlet at 1.29 ppm [$-C(CH_3)_3$], a multiplet centered at 1.30 ppm (C_5 CH_2 of camphorsulfonic acid), a multiplet centered at 1.85 ppm (C_6 CH_2 plus one H from C_3 CH_2 of camphorsulfonic acid), a multiplet centered at 2.19 ppm (C_4 CH of camphorsulfonic acid), an AB pattern centered at 2.67 ppm ($-CH_2SO_3^-$), a multiplet centered at 2.60 ppm (one proton from C_3CH_2 of camphorsulfonic acid), a multiplet centered at 2.84 ppm (terminal epoxide), a multiplet centered at 3.30 ppm (substituted epoxide and $CH_2N<$), and a broad singlet at 8.92 ppm ($-SO_3H$, −NH−).

Equilibration of Compounds 2 and 3. Demonstration of the Instability of 2 and 3 toward Strong Base. A solution of 0.316 g (1.0 mmol) of **2** base was prepared in 2.0 ml of anhydrous *tert*-butyl alcohol. To this was added 1.12 ml of 0.89 N potassium *tert*-butoxide (1 mmol) in *tert*-butyl alcohol and the mixture digested at ambient temperature. Samples were taken at intervals and after silylation were analyzed by VPC. After 20 min the presence of **3** was detected. Likewise, when pure **3** was treated with potassium *tert*-butoxide at room temperature approximately 18% of **2** was detected in 20 min.

Both **2** and **3** were quantitatively converted into **4** when these compounds were treated with 1.5 molar equiv of potassium *tert*-butoxide in refluxing *tert*-butyl alcohol for 3 h.

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Registry No.—**1**, 30315-46-9; **2** hemimaleate, 33305-95-2; **3**, 59697-06-2; **4**, 30165-97-0; **5** *d*-(10)-camphorsulfonate, 30315-52-7; **6**, 1707-77-3; **7**, 59697-07-3; **8**, 59697-08-4; 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole, 30165-96-9; 3,4-dichloro-1,2,5-thiadiazole, 5728-20-1; morpholine, 110-91-8; *tert*-butylamine, 75-64-9; (*R*)-glyceraldehyde, 453-17-8; 3-hydroxy-4-(*n*-morpholino)-1,2,5-thiadiazole sodium salt, 59697-09-5; benzaldehyde, 100-52-7; (*S*)-(−)-1,2-dihydroxy-3-*tert*-butylaminopropane 1-*p*-toluenesulfonate,

30315-51-6; *p*-toluenesulfenyl chloride, 98-59-9; *d*-(10)-camphorsulfonic acid, 3144-16-9.

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Synthesis of C-Nucleosides. 13.[1] *s*-Triazolo[4,3-*a*]- and -[1,5-*a*]pyridine Derivatives

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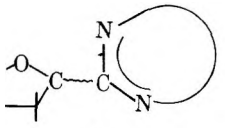
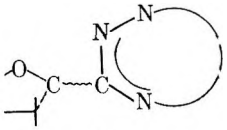
s-Triazolo[4,3-*a*]- and -[1,5-*a*]pyridine C-nucleosides are obtained in one step from 2-pyridylhydrazines and ribofuranosyl thioformimidate. The structures of these compounds are determined with ultraviolet, ^1H and ^{13}C NMR, mass, and circular dichroism spectra.

Glycosyl thioformimidates have proved in our hands to be convenient intermediates for the total synthesis of C-nucleosides. Their condensation with α or ortho aminonitrile derivatives, for instance, gave nucleosides of type 1 (imidazoles, purines, pyrazolopyrimidines)[2] in one step. We decided then to study the feasibility of using the same thioimidates to prepare heterocycles of type **2**, i.e. 1,2,4-triazoles[3] and fused triazoles.



1



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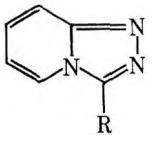
Representative of this new class of heterocycles is the triazolo[4,3-*a*]pyridine **3**. This structure is of particular in-



3

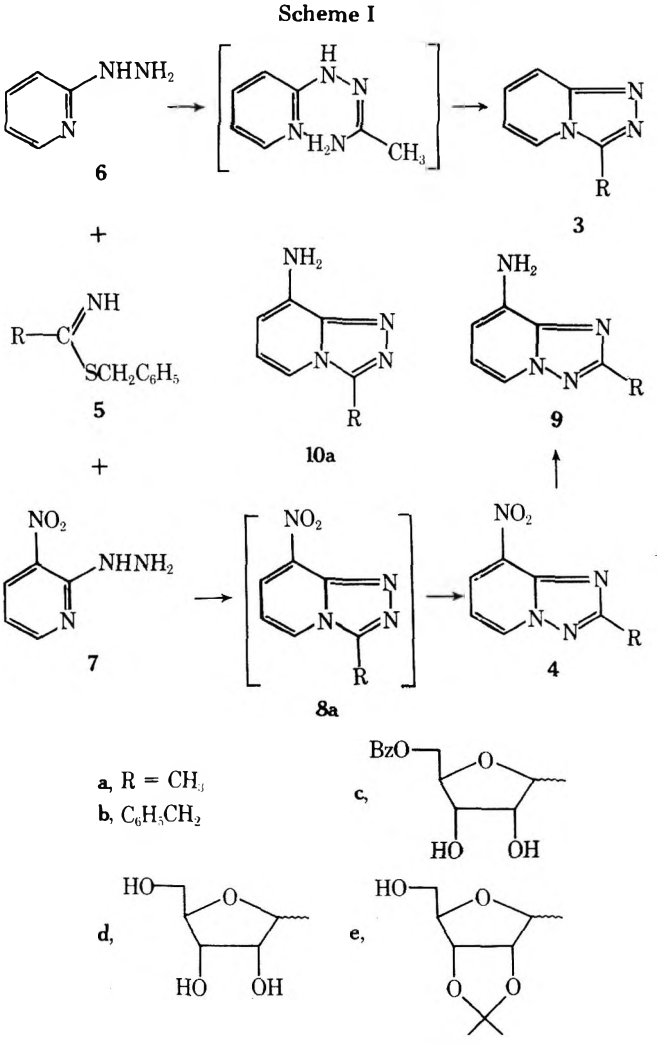
terest since on one hand it contains the 1,2,4-triazole moiety of ribavirine, and on the other hand it may be regarded as an unusual deaza analogue of formycines. C-Nucleosides containing a bridgehead nitrogen atom are unknown.[17] Their synthesis was undertaken in view of their possible biological activities.

3-Alkyl and aryl *s*-triazolo[4,3-*a*]pyridines **3** have been synthesized by cyclization of 2-pyridylhydrazines with carboxylic acid derivatives: anhydrides,[4] chlorides,[5,6] ortho esters,[5] or from the 2-pyridylhydrazone of aromatic aldehydes.[6-8] When the 2-pyridylhydrazine is substituted with an electron-withdrawing NO_2 group in position 3, the ring closure with ortho esters gives the expected 3-alkyl-8-nitro-*s*-triazolo[4,3-*a*]pyridines **3** which isomerized easily into *s*-triazolo[1,5-*a*]pyridines **4**.[9]

Results

In order to develop a reaction that could be extended to carbohydrate chemistry, we condense benzyl thioacetimidate (**5a**) (Scheme I) with 2-pyridylhydrazine (**6**): with 10% of pyridine in chloroform at room temperature, the reaction

Scheme I



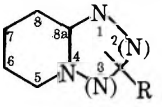
yields the noncyclized intermediate acetamidrazone whereas using reflux in pyridine, the yield of cyclization goes up to 79% of 3-methyl-*s*-triazolo[4,3-*a*]pyridine (**3a**), previously described.[4] In the same conditions, benzyl phenylthioacetim-

† Research chemist of INSERM, deceased on September 14, 1975.

Table I. Ultraviolet Absorption Spectral Data

Compd	s-Triazolo[4,3-a]pyridine, λ_{max} (ϵ) in H_2O				Compd	s-Triazolo[1,5-a]pyridine, λ_{max} (ϵ) in H_2O	
3a	267 (3 300)	286 (3300)			4a	230 (14 600)	330 (6 400)
3b	268 (4 300)	287 (3600)			4b	230 (16 400)	326 (6 000)
β-3c	263 (4 600)	271 (5300)	280 (4500)	295 (3 400)	4c	243 (9 800)	328 (5 200)
α-3c	265 (4 100)	271 (4800)	280 (3900)	296 (3 000)			
β-3d	265 (4 400)	270 (4700)	280 (4000)		4d	235 (13 800)	328 (5 500)
α-3d	261 (3 600)	272 (4500)	280 (3800)				
8a	225 (14 000)	360 (4300)					
10a	225 (12 700)	297 (11 600)			9a	270 (10 400)	294 (6 800)
					9b	272 (10 400)	294 (7 200)
					9c	280 (9 700)	299 (6 900)
					9d	275 (9 000)	295 (6 000)

Table II. ^{13}C Chemical Shifts of Quaternary Carbons (ppm from Me_4Si)



Compd	C-2	C-3	C-8	C-8a
10a		145.4_7	136.1_5	145.7_6
β-3d		149.6_4		144.5_5
9a	162.1_2		136.8_8	145.1_1
9d	162.6_0		136.5_7	143.6_5
4d	166.6_9		135.5_0	144.3_9

idate (**5b**) yields 48% of 3-benzyl-s-triazolo[4,3-a]pyridine (**3b**).

The reaction proceeds differently between 3-nitro-2-pyridylhydrazine (**7**) and thioimidate **5a:** instead of the expected 8-nitro-s-triazolo[4,3-a]pyridine (**8a**),[9] we obtain the isomerized heterocycle, i.e., the triazolo[1,5-a]pyridine **4a.** The structure of **4a**[9,10] is established on the basis of its spectral characteristics (uv, ^{13}C NMR), and also by comparison with authentic samples prepared according to the literature. 2-Benzyl-8-nitro-s-triazolo[1,5-a]pyridine (**4b**) is obtained in the same way (65%) from **5b** and **7.**

The structural assignment is made once again after reduction of the nitro heterocycles over palladium on charcoal. The s-triazolo[1,5-a]pyridine **4a** is then hydrogenated into **9a,**[10] which is different from the s-triazolo[4,3-a]pyridine **10a**[9] obtained from **8a.** The spectral data show that amino benzyl derivative **9b** belongs also to the s-triazolo[1,5-a]pyridine series.

The condensation of benzyl 5-O-benzoyl-D-ribofuranosyl thioformimidate (**5c**) with **6** gives a mixture of s-triazolo[4,3-a]pyridines α- and β-**3c** (63%) which was separated on silica gel chromatography (β/α 90/10). The benzoyl group is quantitatively removed with methanolic ammonia at room temperature giving 3-D-ribofuranosyl-s-triazolo[4,3-a]pyridines α- and β-**3d.**

The cyclization of **5c** with 3-nitro-2 pyridylhydrazine (**7**) leads to 58% of the β anomer of the s-triazolo[1,5-a]pyridine **4c;** we have not isolated the α anomer among the by-products obtained from the chromatographic fractions (<2%). Compound **4c** is debenzoylated into 2-β-D-ribofuranosyl-8-nitro-s-triazolo[1,5-a]pyridine (**4d**). The catalytic reduction of **4c** gives the corresponding 8-amino derivative **9c** which is converted into 2-β-D-ribofuranosyl-8-amino-s-triazolo[1,5-a]pyridine (**9d**).

The isopropylidene derivatives **3e, 4e,** and **9e** are prepared for configuration assignment using ^1H NMR.

Discussion

As observed previously,[2c] the condensation reactions of the ribofuranosyl thioformimidate **5c** give a mixture of anomers with the β anomer strongly predominant (**3c**) or exclusive (**4c**).

The main problem with the reported synthetic sequences is to ascertain (1) the structure of the heterocycles, i.e., s-triazolo[4,3-a]pyridine **3** or s-triazolo[1,5-a]pyridine **4;** (2) the structure and configuration of the nucleosides. These structural assignments are built mainly on uv spectra, ^1H and ^{13}C NMR, mass spectra, and circular dichroism.

1. Structure of the Heterocycles. A first structural determination of the heterocycles **3** and **4** is easily made with the uv spectra, owing to the authentic samples **3a, 8a, 10a** (s-triazolo[4,3-a]pyridine) and **4a, 9a** (s-triazolo[1,5-a]pyridine), the structure of which having been previously established with numerous correlations.[5,9,10] Table I shows that the two series exhibit absorption maxima at different wavelengths.

^{13}C NMR spectra allow one to assign unambiguously the two series of compounds s-triazolo[4,3-a]pyridine of type **3** and s-triazolo[1,5-a]pyridine of type **4** (Table II). As a matter of fact, the chemical shift of a carbon nucleus at position 2 is about 15–20 ppm downfield as compared to that of a carbon at position 3, in similar heterocycles.[11] This fact is due to the presence of the bridgehead nitrogen at position 4 which does not induce a low-field shift for a neighboring carbon as large as that due to a cyclic nitrogen bearing a lone pair of electrons. It has been recently used successfully[12] for similar assignments among s-triazolo[4,3-a]- and s-triazolo[1,5-a]pyrimidines.

Table III gives the ^1H NMR spectra of the model compounds.

Table III. ^1H NMR (Chemical Shifts in ppm from Me_4Si) in Me_2SO-d_6 (5×10^{-3} M) at 34° of s-Triazolopyridine Model Compounds

Compd	H_5	H_6	H_7	H_8	NH_2	R = CH_3	$C_6H_5CH_2$	
3a	8.35	6.96	7.33	7.71		2.68		
3b	8.34	6.93	7.33	7.76			7.29	4.55
4a	9.30	7.34	8.63			2.58		
4b	9.32	7.35	8.63				7.33	4.29
8a	8.81	7.19	8.40			2.76		
9a	7.99	6.81	6.53		5.80	2.43		
9b	8.03	6.83	6.53		5.80		7.30	4.13
10a	7.55	6.71	6.22		5.90	2.61		

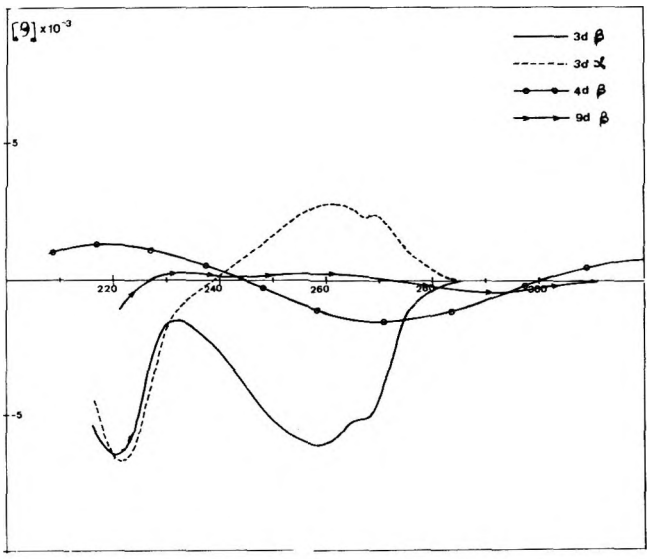


Figure 1. CD spectra of nucleosides in water.

2. Structure and Configuration of the Nucleosides. The structures of the nucleosides are confirmed by the mass spectra: all the ribonucleosides show the molecular ion M and the characteristic peaks of a furanose at M − 30. The C–C bond is established by the reduced intensity of ions at B + 2H and the abundant ions arising from the fragmentation of O–$C_{1'}$, $C_{2'}$–$C_{3'}$ bonds and O–$C_{4'}$, $C_{1'}$–$C_{2'}$ bonds:[2c] the major peak is at B + 30 for s-triazolo[4,3-*a*]pyridines **3d** and at B + 44 for *s*-triazolo[1,5-*a*]pyridines **4d** and **9d.** In a couple of anomers such as **3d,** the configuration is based on the relative intensities of ions at M − 30:[2c] the β anomer exhibits a higher intensity than the α anomer.

The circular dichroism spectra (Figure 1) give opposite Cotton effects for α-**3d** and β-**3d.** The *s*-triazolo[1,5-*a*]pyridines present very weak Cotton effects. This may be explained by the orientation of the base with regard to the sugar: molecular models show that the *s*-triazolo[1,5-*a*]pyridines should have more rotational mobility around the glycosyl bond than their [4,3-*a*]triazolo isomers.

The possibility of assignment of the anomeric configuration by ^{1}H NMR is dependent upon the nature of the compounds. In the C-nucleosides of type **3** (Table IV) the α and β anomers are clearly distinguished by the difference in the chemical shift of the H-1′ proton[13] and in the $J_{1',2'}$ coupling constant (Table VI) for the unsubstituted nucleosides **3d.** The difference in chemical shift values for the methyl resonances in the isopropylidene derivatives[14] **3e,** and especially **4e** (since only one anomer has been isolated), is indicative of the configuration: $\Delta\delta CH_3$ <0.15 for α anomer; $\Delta\delta CH_3$ >0.15 for β anomer. The last effect is presumably due to different ring current effects from the base and to steric hindrance as observed for the H-5 resonances. Proton chemical shift and coupling constant values in the compounds of type **3,** as well as in the other series of C-nucleosides (types **4** and **9,** Table V), are, however, depending on several structural parameters. Besides the anomer configuration, the position of ribose substitution and the syn-trans conformation of the gylcosidic bond govern the NMR properties. The full analysis of these phenomena is beyond the scope of the present paper.

Experimental Section

Melting points were determined with a Kofler microscope and were uncorrected. Ultraviolet spectra were recorded with a Perkin-Elmer 237 or a *Cary 118C. NMR* spectra were obtained using a Varian XL-100 with tetramethylsilane as internal reference. Mass spectra were obtained with a Varian CH-7 or MS-9. Optical activities were measured with a Perkin-Elmer 241 MC polarimeter and circular dichroism spectra were recorded with a Roussel-Jouan II-185 dichrograph. Chromatographic columns were packed with Silicar 100 mesh grade I; 0.25 mm thick TLC plates were prepared with Merck Kieselgel $HF_{254+366}$ and visualized with an uv light at 254 nm.

3-Methyl-*s*-triazolo[4,3-*a*]pyridine (3a). A solution of 5.5 g (50 mmol) of 2-pyridylhydrazine (**6**) and 10.1 g (50 mmol) of benzyl thioacetimidate (**5a**)[15] in 90 ml of pyridine was stirred for 2 h at room temperature and refluxed for an additional 1 h. The residue of evaporation was recrystallized with benzene–cyclohexane (1/1) to yield 5.3 g (79%) of **3a,** mp 132 °C (lit.[4] mp 134 °C).

2-Pyridyl-N_2-acetamidrazone Hydrochloride. Hydrazine **6** (5.5 g, 50 mmol) was added to a solution of 10.1 g (50 mmol) of **5a** in 100 ml of chloroform and 7.9 g (100 mmol) of pyridine. The solution was kept at room temperature for 20 h; the precipitate was filtered and washed with hot chloroform, 9 g (96%), mp 170 °C.

Anal. Calcd for $C_7H_{11}N_4Cl$ (186.5): C, 45.04; H, 5.89; N, 30.02; Cl, 19.03. Found: C, 44.93; H, 5.82; N, 29.81; Cl, 19.12.

3-Benzyl-*s*-triazolo[4,3-*a*]pyridine (3b). The same procedure as for **3a** was followed, 2.2 g (20 mmol) of **6** and 5.6 g (20 mmol) of **5b.**[16] The residue was treated with carbon black and recrystallized from benzene, 2 g (48%), mp 165–166 °C.

Anal. Calcd for $C_{13}H_{11}N_3$ (209): C, 74.62; H, 5.30; N, 20.08. Found: C, 74.53; H, 5.45; N, 19.81.

2-Methyl-8-nitro-*s*-triazolo[1,5-a]pyridine (4a). The condensation as above with 3.1 g (20 mmol) of 3-nitro-2-pyridylhydrazine (**7**) and **5a** gave 82% of **4a,** mp 195–196 °C (benzene).[9,10]

***2-Benzyl-8-nitro-s-triazolo[1,5-a]pyridine* (4b).** The same procedure with 4.62 g (30 mmol) of **7** and 8.3 g (30 mmol) of **5b** gave 4.95 g (65%) of **4b,** mp 137–143 °C (cyclohexane).

Table IV. ^{1}H NMR of *s*-Triazolo[4,3-*a*]pyridine C-Nucleosides

Compd	H_5	H_6	H_7	H_8	$H_{1'}$	$H_{2'}$	$H_{3'}$	$H_{4'}$	$H_{5'a}$	$H_{5'b}$	CH_3,	C_6H_5
α-3c	8.53	6.92	7.36	7.73	5.70			4.60–4.30			*o*	8.02
											m,p	7.60
β-3c	8.42	6.84	7.31	7.70	5.37	4.85		4.45–4.25			*o,m,p*	7.50
α-3d	8.50	6.89	7.35	7.71	5.58	4.24	4.21	4.05	3.68	3.50		
β-3d	8.69	6.96	7.39	7.78	5.21	4.55	4.08	3.95	3.57	3.51		
α-3e	8.59	6.97	7.37	7.74	5.81	5.07	4.91	4.33	3.62		1.34	1.22
β-3e	8.54	7.00	7.41	7.78	5.53	5.58	4.85	4.12	3.17		1.53	1.36

Table V. ^{1}H NMR of *s*-Triazolo[1,5-*a*]pyridine C-Nucleosides

Compd	H_5	H_6	H_7	NH_2	$H_{1'}$	$H_{2'}$	$H_{3'}$	$H_{4'}$	$H_{5'a}$	$H_{5'b}$	CH_3, C_6H_5	
4c	9.26	7.38	8.66		5.03			4.55–4.20			*o*	7.95
											m,p	7.50
4d	9.37	7.41	8.69		4.94	4.33	4.09	3.93	3.62	3.51		
4e	9.38	6.43	8.50		5.16		4.83	4.17	3.53	3.47	1.54	1.35
9c	8.01	6.88	6.58	5.81	4.91			4.55–4.15			*o*	7.95
											m,p	7.50
9d	8.07	6.88	6.59	5.83	4.81	4.31	4.04	3.86	3.57	3.47		
9e	8.08	6.91	6.60	5.91	5.00	5.15	4.77	4.07	3.50	3.40	1.52	1.33

Table VI. Coupling Constants (Hz)

Compd	$J_{5,6}$	$J_{5,7}$	$J_{5,8}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$
3a	6.9	1.2	1.1	6.5	1.2	9.2						
3b	7.0	1.2	1.2	6.5	1.2	9.3						
4a	6.8	1.3		8.0								
4b	6.7	1.2		8.0								
8a	7.0	1.0		7.5								
9a	6.6	1.1		7.6								
9b	6.5	1.2		7.6								
10a	6.6	0.8		7.2								
α-3c	7.2	1.2	1.2	6.5	1.2	9.4	3.0					
β-3c	7.0	1.2	1.2	6.5	1.2	9.2	3.8	4.0				
α-3d	7.0	1.2	1.1	6.5	1.1	9.3	3.5	3.5	7.6	2.5	4.4	12.0
β-3d	7.0	1.0	1.2	6.5	1.1	9.3	6.9	5.2	4.0	3.2	4.0	12.0
α-3e	7.2	1.2	1.2	6.5	1.1	9.4	4.2	6.3	0.7	5.0		
β-3e	7.2	1.2	1.0	6.4	1.0	9.4	3.8	5.8	1.5	5.6		
4c	6.7	1.2		7.9			3.7					
4d	6.8	1.2		8.0			5.2	4.8	5.1	4.0	5.2	11.7
4e	6.8	1.1		6.8				5.9	2.8	5.7		
9c	6.6	1.1		7.6			3.8					
9d	6.5	1.0		7.5			5.4	5.2	5.0	4.5	5.5	11.8
9e	6.7	1.1		7.5			3.9	6.2	2.9	5.8		

Anal. Calcd for $C_{13}H_{10}N_4O_2$ (254): C, 61.41; H, 3.96; N, 22.04. Found: C, 61.70; H, 3.92; N, 22.30.

2-Benzyl-8-amino-s-triazolo[1,5-a]pyridine (9b). 4b (2.54 g, 10 mmol) was hydrogenated in 100 ml of ethanol at room temperature and atmospheric pressure over Pd/C (0.5 g, 30%). The solution was filtered and evaporated into a residue which was recrystallized with cyclohexane, 1.12 g (50%), mp 97–98 °C.

Anal. Calcd for $C_{13}H_{12}N_4$ (224): C, 69.62; H, 5.39; N, 24.99. Found: C, 69.57; H, 5.34; N, 24.93.

Compounds **8a, 10a,** and **9a** were prepared according to the literature.[9,10]

3-(5′-O-Benzoyl-α- and -β-D-ribofuranosyl)-s-triazolo[4,3-a]pyrine (3c). A solution of 7.41 g (17.5 mmol) of thioformimidate **5c**[2b] and 1.91 g (17.5 mmol) of **6** in 70 ml of pyridine was heated at reflux for 15 h. The solution was evaporated, and the residue was dissolved in aqueous methanol and neutralized with NaOH (1 N).

Evaporation to dryness and column chromatography (200 g, 44 × 4 cm) (EtOAc–EtOH, 9/1) gave **β-3c** and **α-3c.**

(a) **β-3c** (3.56 g, 57%), mp 60 °C, R_f 0.78 ($CHCl_3$–EtOH, 25/4).

Anal. Calcd for $C_{18}H_{17}N_3O_5$ (355): C, 60.84; H, 4.82; N, 11.83. Found: C, 60.86; H, 5.15; N, 12.11.

MS M·+ *m/e* 355; $[\alpha]^{25}D$ − 162° (c 0.39, DMF); CD $[\theta]_{239}$ −17 000, $[\theta]_{250}$ −11 500, $[\theta]_{261}$ −13 000, $[\theta]_{270}$ −8000, $[\theta]_{283}$ 0, $[\theta]_{290}$ −600.

(b) **α-3c** (0.40 g, 6%), mp 90 °C; R_f 0.67 ($CHCl_3$–EtOH, 25/4).

Anal. Calcd for $C_{18}H_{17}N_3O_5$ (355): C, 60.84; H, 4.82; N, 11.83. Found: C, 60.55; H, 5.02; N, 11.60.

MS M·+ *m/e* 355; $[\alpha]^{25}D$ = −9° (*c* 0.22, DMF); CD $[\theta]_{237}$ −7000, $[\theta]_{253}$ 0, $[\theta]_{272}$ +2500, $[\theta]_{286}$ +2000, $[\theta]_{321}$ 0.

3β-D-Ribofuranosyl-s-triazolo[4,3-a]pyridine (β-3d). The debenzoylation of **β-3c** with methanolic ammonia at room temperature during 72 h gave quantitatively **β-3d,** mp 198–200 °C (MeOH), R_f 0.36 ($CHCl_3$–EtOH, 5/1).

Anal. Calcd for $C_{11}H_{13}N_3O_4$ (251): C, 52.58; H, 5.22; N, 16.73. Found: C, 52.39; H, 5.51; N, 16.97.

MS M·+ *m/e* 251 (8%), 234 (2%) M − 17, 221 (20%) M − 30, 162 (96%) B + 44, 148 (100%) B + 30, 120 (21%) B + 2; $[\alpha]^{25}D$ −114° (c 0.51, H_2O); CD $[\theta]_{221}$ −6500, $[\theta]_{232}$ −1500, $[\theta]_{259}$ −6000, $[\theta]_{265}$ −5200, $[\theta]_{285}$ 0.

3α-D-Ribofuranosyl-s-triazolo[4,3-a]pyridine (α-3d). As above, **α-3c** gave **α-3d,** mp 100 °C, R_f 0.24 ($CHCl_3$–EtOH, 5/1).

Anal. Calcd for $C_{11}H_{13}N_3O_4$ (251): C, 52.58; H, 5.22; N, 16.73. Found: C, 51.90; H, 5.69; N, 16.25.

MS M·+ *m/e* 251 (10%), 234 (1%) M − 17, 221 (2%) M − 30, 162 (66%) B + 44, 148 (100%) B + 30, 120 (13%) B + 2; CD $[\theta]_{222}$ −6700, $[\theta]_{239}$ 0, $[\theta]_{261}$ +2900, $[\theta]_{269}$ +2500, $[\theta]_{285}$ 0; $[\alpha]^{25}D$ −15° (*c* 0.08, H_2O).

2-(5′-O-Benzoyl-β-D-ribofuranosyl)-8-nitro-s-triazolo-[1,5-a]pyridine (4c). A solution of 5.75 g (13.6 mmol) of **5c** and 2.1 g (13.6 mmol) of **7** in 60 ml of pyridine was heated at reflux for 15 h. The same procedure as for **3c** gave after column chromatography ($CHCl_3$–EtOH, 96/4) 3.17 g of **4c,** mp 133–135 °C (EtOH), R_f 0.41 ($CHCl_3$–EtOH, 10/1).

Anal. Calcd for $C_{18}H_{16}N_4O_7$ (400): C, 54.00; H, 4.03; N, 14.00. Found: C, 54.21; H, 4.21; N, 14.14.

MS M·+ *m/e* 400; $[\alpha]^{25}D$ −28° (c 0.51, DMF); CD $[\theta]_{230}$ −9000, $[\theta]_{236}$ 0, $[\theta]_{250}$ −2700, $[\theta]_{278}$ −520, $[\theta]_{300}$ −1900.

2β-D-Ribofuranosyl-8-nitro-s-triazolo[1,5-a]pyridine (4d). A solution of methanolic ammonia of **4c** gave quantitatively after 72 h **4d,** mp 194–195 °C (EtOH), R_f 0.25 ($CHCl_3$–EtOH, 10/1).

Anal. Calcd for $C_{11}H_{12}N_4O_6$ (296): C, 44.59; H, 4.05; N, 18.91. Found: C, 44.95; H, 4.25; N_i 18.67.

MS M·+ *m/e* 296 (1%), 278 (3%) M − 18, 265 (3%) M − 31, 207 (100%) B + 44, 193 (53%) B + 30, 165 (2%) B + 2; $[\alpha]^{25}D$ −42° (c 0.49, H_2O); CD $[\theta]_{218}$ +1300, $[\theta]_{245}$ 0, $[\theta]_{268}$ −1500, $[\theta]_{300}$ 0.

2-(5′-O-Benzoyl-β-D-ribofuranosyl)-8-amino-s-triazolo-[1,5-a]pyridine (9c). A methanolic solution of 1 g of **4c** was hydrogenated over Pd/C (10%) at room temperature and atmospheric pressure. After filtration, the solvent was evaporated and the residue chromatographed on silica gel (EtOAc–EtOH, 95/5) to yield 0.70 g (76%) of **9c,** mp 70 °C, R_f 0.69 ($CHCl_3$–EtOH, 5/1).

Anal. Calcd for $C_{18}H_{18}N_4O_5$ (370): C, 58.37; H, 4.90; N, 15.13. Found: C, 58.03; H, 5.39; N, 14.89.

MS M·+ *m/e* 370; $[\alpha]^{25}D$ −16° (*c* 0.50, DMF); CD $[\theta]_{222}$ −11 500, $[\theta]_{250}$ 0, $[\theta]_{278}$ −15 000, $[\theta]_{300}$ 0.

2β-D-Ribofuranosyl-8-amino-s-triazolo[1,5-a]pyridine (9d). The debenzoylation during 1 week of **9c** gave **9d,** mp 65 °C, R_f 0.33 ($CHCl_3$–EtOH, 5/1).

Anal. Calcd for $C_{11}H_{14}N_4O_4$ (266): C, 49.62; H, 5.30; N, 21.04. Found: C, 49.87; H, 5.69; N, 20.88.

MS M·+ *m/e* 266 (13%), 249 (3%) M − 17, 236 (6%) M − 30, 177 (100%) B + 44, 163 (32%) B + 30, 135 (8%) B + 2; $[\alpha]^{25}D$ −34° (c 0.49, H_2O); CD $[\theta]_{227}$ 0, $[\theta]_{230}$ +260, $[\theta]_{260}$ +250, $[\theta]_{273}$ 0, $[\theta]_{293}$ −450.

A general procedure was used for the 2′,3′-O-isopropylidene nucleosides.[2b]

β-3e, R_f 0.70 ($CHCl_3$–EtOH, 25/4) (foam).

Anal. Calcd for $C_{14}H_{17}N_3O_4$ (291): C, 57.73; H, 5.88; N, 14.43. Found: C, 57.38; H, 6.34; N, 14.06.

α-3e, R_f 0.55 ($CHCl_3$–EtOH, 25/4) (foam).

Anal. Calcd for $C_{14}H_{17}N_3O_4$ (291): C, 57.73; H, 5.88; N, 14.43. Found: C, 57.48; H, 5.80; N, 14.54.

4e, mp 163 °C, R_f 0.90 ($CHCl_3$–EtOH, 10/1).

Anal. Calcd for $C_{14}H_{16}N_4O_6$ (336): C, 50.00; H, 4.80; N, 16.66. Found: C, 50.39; H, 5.05; N, 16.31.

9e, mp 60 °C R_f 0.61 ($CHCl_3$–EtOH, 10/1) (foam).

Registry No.—**3a,** 1004-65-5; **3b,** 59696-86-5; **α-3c,** 59696-87-6; **β-3c,** 59696-88-7; **α-3d,** 59696-89-8; **β-3d,** 59696-90-1; **α-3e,** 59696-91-2; **β-3e,** 59696-92-3; **4a,** 7169-91-7; **4b,** 59696-93-4; **4c,** 59696-94-5; **4d,** 59696-95-6; **4e,** 59696-96-7; **5a,** 59696-97-8; **5b,** 53331-09-2; **5c,** 50908-31-1; **6,** 4930-98-7; **7,** 15367-16-5; **8a,** 31040-10-5; **9a,** 7169-93-9; **9b,** 59696-98-9; **9c,** 59696-99-0; **9d,** 59697-00-6; **9e,** 59697-01-7; **10a,** 31040-12-7; 2-pyridyl-N_2-acetamidrazone HCl, 59697-02-8.

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6-Oxa Analogues of Pyrimidines and Pyrimidine Nucleosides. Synthesis of 5-Amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one, 2-β-D-Ribofuranosyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione, and Related Derivatives

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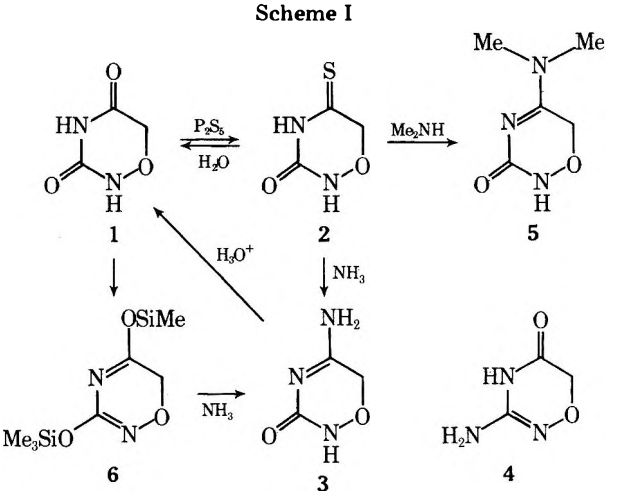
Treatment of 6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**1**, 6-oxadihydrouracil) with phosphorus pentasulfide in dioxane gave 6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**2**, 4-thio-6-oxadihydrouracil). Amination of **2** with ammonia in dioxane gave 5-amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**3**, 6-oxadihydrocytosine). Treatment of **2** with dimethylamine in dioxane afforded 5-dimethylamino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**5**). The stannic chloride catalyzed condensation of 3,5-bis(trimethylsilyloxy)-6*H*-1,2,4-oxadiazine (**6**) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**7a**) or 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**7b**) gave the corresponding blocked 6-oxadihydrouridines 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8a**) and 2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8b**). 2-β-D-Ribofuranosyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8c**, 6-oxadihydrouridine) was obtained by the removal of the acetyl blocking groups of **8b** with methanolic hydrogen chloride. Thiation of **8a** with phosphorus pentasulfide in dioxane afforded 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**12**), which upon treatment with dimethylamine in dioxane gave 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-dimethylamino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**13**). The stannic chloride catalyzed condensation of 3-trimethylsilyloxy-5-dimethylamino-6*H*-1,2,4-oxadiazine (**14**) with **7a** also afforded **13**. The ^{13}C NMR spectra of several of the above 6*H*-1,2,4-oxadiazin-3(2*H*)-ones are reported and have been utilized to support structural assignments.

6*H*-1,2,4-Oxadiazine-3,5(2*H*,4*H*)-dione (**1**) and 6-methyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione, 6-oxa analogues of uracil and thymine, respectively, have previously been synthesized.[1] These analogues are actually isosteres of 5,6-dihydrouracil and 5,6-dihydrothymine in which the 6-methylene group has been replaced by an oxygen such that these compounds can be considered as 6-oxadihydrouracil (**1**) and 6-oxadihydrothymine. It has been shown, however, that 6-oxadihydrouracil (**1**) is an apparent competitive antagonist of uracil, and not of dihydrouracil, in bacterial systems.[2] In an effort to further investigate the chemical and biochemical properties of the 6*H*-1,2,4-oxadiazin-3(2*H*)-one ring system, we have synthesized the 6-oxa analogues of 4-thiouracil, cytosine, and *N*,*N*-dimethylcytosine as well as the 6-oxa analogue of uridine, the first 6*H*-1,2,4-oxadiazine nucleoside.

Reaction of 6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**1**) with phosphorus pentasulfide in refluxing, anhydrous dioxane afforded 6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**2**, 4-thio-6-oxadihydrouracil) in 55% yield. Elemental analysis established that **2** was a monothio derivative of **1**. The shift in the uv maximum from 220 nm (ε 1250) to 272 nm (ε 15 900) upon thiation was similar to that found upon thiation of 5,6-dihydrouracils.[3] That the 6*H*-1,2,4-oxadiazine ring had remained intact was shown by the almost quantitative reconversion of **2** to **1** by boiling water. Thiation of **1** was expected to give the 5-thio derivative in analogy to the thiation of 5,6-dihydrouracils.[3] Unequivocal assignment of the structure of 6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**2**) is based on subsequent transformation of **2** to 5-amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**3**) as described below.

Scheme I



Reaction of 6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**2**) with ammonia in dioxane at room temperature resulted in conversion to 5-amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**3**, 6-oxadihydrocytosine) in 90% yield. The highly reactive nature of the thio group of **2** is analogous to that found for 1-alkyl-

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4-thio-5,6-dihydrouracils.[4] The shift in the uv maximum from 220 nm (ε 1250) to 228 nm (ε 13 200) upon amination and the much lower frequency (1620 cm^{-1}) of the C-3 carbonyl absorption in the ir spectrum of **3** as compared to that of **1** (1745 and 1710^{-1} cm) is indicative of the conjugation of the C-3 carbonyl with the 4,5 double bond of **3**. A similar shift is seen upon comparison of 5,6-dihydrouracil and 5,6-dihydrocytosine.[4]

Deamination of 5-amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**3**) to 6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**1**) by treatment with dilute acid at room temperature confirmed that the 6*H*-1,2,4-oxadiazine ring had remained intact during amination. The 5-amino rather than the 3-amino structure was assigned to **3** since this product was shown to be different from an authentic sample of the known 3-amino-6*H*-1,2,4-oxadiazin-5(4*H*)-one (**4**)[1] by comparison of ir, uv, and ^{1}H NMR spectra as well as melting point and TLC. Since 5-amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**3**) was derived from 6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**2**), the assignment of **2** as the 5-thio derivative is thereby firmly established.

Reaction of 6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**2**) with dimethylamine in dioxane at room temperature resulted in conversion to 5-dimethylamino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**5**) in 87% yield.

It was also found that 6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**1**) could be converted in 20% yield to 5-amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**3**) by conversion in situ to 3,5-bis(trimethylsilyloxy)-6*H*-1,2,4-oxadiazine (**6**) and subsequent reaction with ammonia.[6,7]

The ^{13}C NMR spectra of several 6*H*-1,2,4-oxadiazin-3(2*H*)-ones have been obtained and the chemical shifts are summarized in Table II. The relative ordering of the C-3 and C-5 carbons was assigned by comparing the chemical shifts of 6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**1**) with those of the anion formed by LiOH in Me_2SO-d_6. Since the negative charge is expected to be localized at the oxygen atom of the C-3 carbonyl, the C-3 resonances of **1** and the corresponding anion should differ more than the C-5 resonances. The observed shift difference of 11.9 ppm for the C-3 carbons and the 2.8-ppm difference for the C-5 carbons strongly supports the assignment of C-3 and C-5 as indicated in Table II. Additional confirmation for the assignment of the C-3 and C-5 carbons of **1** was obtained by comparison with the ^{13}C NMR spectra of uridine,[8] where the resonance for the C-4 carbon occurs downfield from the C-2 carbon.

The significant downfield shift observed in the C-5 resonance (33.6 ppm) of 6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**2**) confirms that thiation had occurred at C-5. Similar downfield shifts upon substitution of sulfur for oxygen have been observed for the thiopyrimidine nucleosides.[8] In the ^{13}C NMR spectrum of 5-amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**3**), the C-5 resonance occurs downfield from the C-3 resonance, analogous to the ^{13}C NMR spectrum of cytidine[8] where the C-4 resonance occurs downfield from the C-2 resonance.

After 5-amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**3**) was heated in deuterium oxide for 24 h at 55 °C (necessary for complete dissolution), the ^{1}H NMR spectrum indicated incorporation of deuterium at the C-6 position. Some hydrolysis to 6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**1**) had occurred as indicated by TLC and the appearance in the ^{1}H NMR spectrum of a signal for the C-6 protons of **1**. Under the same conditions the C-6 protons of **1** did not exchange. In pH 7.5 Tris buffer at room temperature, **3** slowly under went hydrolysis ($t_{1/2}$ = 5 days) to **1**. The facile hydrolysis of 5-amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**3**) to 6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**1**) and the exchange of the C-6 protons of **3** with deuterium oxide are analogous to the results found for 5,6-dihydrocytosine.[4] The similarity of the amino group of **3** with that of 5,6-dihydrocytosine is indicated by the similarity of the pK_a values of these two compounds. The pK_a of **3** is 6.1 while that of 5,6-dihydrocytosine is 6.3.[4]

Table I. Properties of 6*H*-1,2,4-Oxadiazin-3(2*H*)-ones

Compd	pK_a	Uv (EtOH), λ_{max}, nm ($\epsilon \times 10^{-3}$)	Ir, cm^{-1} [a]
1	7.6	220 (1.25)	3170; 3070; 1745; 1710
2	7.1	274 (15.9)	3190; 1720
3	6.1	228 (13.2)	3250; 1620
4		234 (7.78)	3200; 3120; 1660; 1620
5		245 (16.4)	3110; 1645
8a		230 (44.1)	3240; 1730
8b		217 (1.65)	3210; 3100; 1760; 1725
8c	8.7	219 (1.80)	3360; 1710
10	9.1	225 (1.64)	3170; 3070; 1725
11	7.8	*b*	3250; 1735; 1680
12		276 (22.0)	3230; 3180; 1745; 1715
		229 (40.9)	
13		250 (21.9)	1735; 1675
		231 (46.3)	

[a] KBr. [b] End absorption only.

We next investigated the synthesis of 2-β-D-ribofuranosyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8c**, 6-oxadihydrouridine). Reaction of 6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**1**) in refluxing dioxane with hexamethyldisilazane (HMDS) in the presence of ammonium sulfate afforded 3,5-bis(trimethylsilyloxy)-6*H*-1,2,4-oxadiazine (**6**), which without further purification was condensed in 1,2-dichloroethane with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**7a**) and 1 equiv of stannic chloride[9] to afford a 68% yield of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8a**), the only nucleoside product detected by TLC. The ^{1}H NMR signal for the anomeric proton of **8a** appeared as a singlet, and coupling constants of less than 1.0 Hz establish the β configuration[10] for ribonucleosides. It was also possible to prepare **8a** by the reaction of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**9**) in acetonitrile with **6**, with the sodium salt of **1**, or by the reaction of **9** with **1** in nitromethane in the presence of mercuric cyanide.[11] In these cases, however, the yield of **8a** was considerably reduced.

Treatment of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8a**) with sodium methoxide in methanol gave a different product than that obtained by the treatment with methanolic ammonia. In neither case was the desired 2-β-D-ribofuranosyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8c**) obtained. While the benzoyl groups were removed in each case, ring opening probably had occurred as noted by the lack of uv absorbance of the resulting products, which were not further investigated.

As the 6*H*-1,2,4-oxadiazine ring of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8a**) was unstable to the above basic deblocking conditions, and since the acetyl blocking groups of a ribonucleoside can be removed by the use of acidic conditions,[12] 2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5-(2*H*,4*H*)-dione (**8b**) was synthesized from 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**7b**) and **6** in 86% yield using the same conditions as for the synthesis of **8a**. Treatment of 2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5-(2*H*,4*H*)-dione (**8b**) with anhydrous methanolic hydrogen chloride afforded 2-β-D-ribofuranosyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8c**, 6-oxadihydrouridine) in 79% yield. Support for the assignment of the site of ribosylation as N-2 rather than N-4 is based on a comparison of the pK_a of 6-oxadihydrouridine (**8c**) with that of 2-methyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**10**)[5] and 4-methyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**11**)[5] (Table I). The value of 8.7

Table II. ^{13}C Chemical Shifts of Some 6*H*-1,2,4-Oxadiazin-3(2*H*)-ones

Compd	Chemical shift, ppm[a]			
	C-3	C-5	C-6	NCH_3
1	155.7	169.4	69.3	
Anion of 1	167.6	172.2	67.6	
2	151.4	203.0	75.9	
3	162.4	174.8	64.2	
8b	153.1	168.9	70.4	
10	155.2	169.2	69.7	35.0
11	155.8	168.2	69.8	25.5

[a] Chemical shifts are measured from Me_2SO-d_6, and are converted to Me_4Si scale using the relationship δ Me_4Si = δ Me_2SO-d_6 + 39.5 ppm.

found for the pK_a of **8c** is much closer to the value of 9.1 found for the pK_a of the 2-methyl derivative **10** than the value of 7.8 found for the pK_a of the 4-methyl derivative **11**. Proof for the assignment of the site of ribosylation was possible from subsequent transformations.

Comparison of the ^{13}C NMR spectra of 2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8b**), **10**, and **11** (Table II) indicates that the site of ribosylation cannot be assigned on the basis of these data. The substitution of a methyl group or a β-D-ribofuranosyl moiety for the proton at the N-2 or N-4 position of 6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**1**) has little effect on the carbon-13 chemical shift values of the C-3 or C-5 carbons. This suggests that the structures of these compounds are essentially unchanged upon substitution of the NH proton and that the keto form predominates in both cases.

In aromatic heterocycles, N-substitution has been observed to produce a significant upfield shift in the ^{13}C NMR signal of the carbon α to the substituted nitrogen and a downfield shift in the signal of the carbon β to that nitrogen[13] when the neutral species is compared with the corresponding anion. Owing to the lack of aromaticity in these compounds, the negative charge of the anion is not delocalized around the ring and the corresponding substitution shifts are therefore not observed.

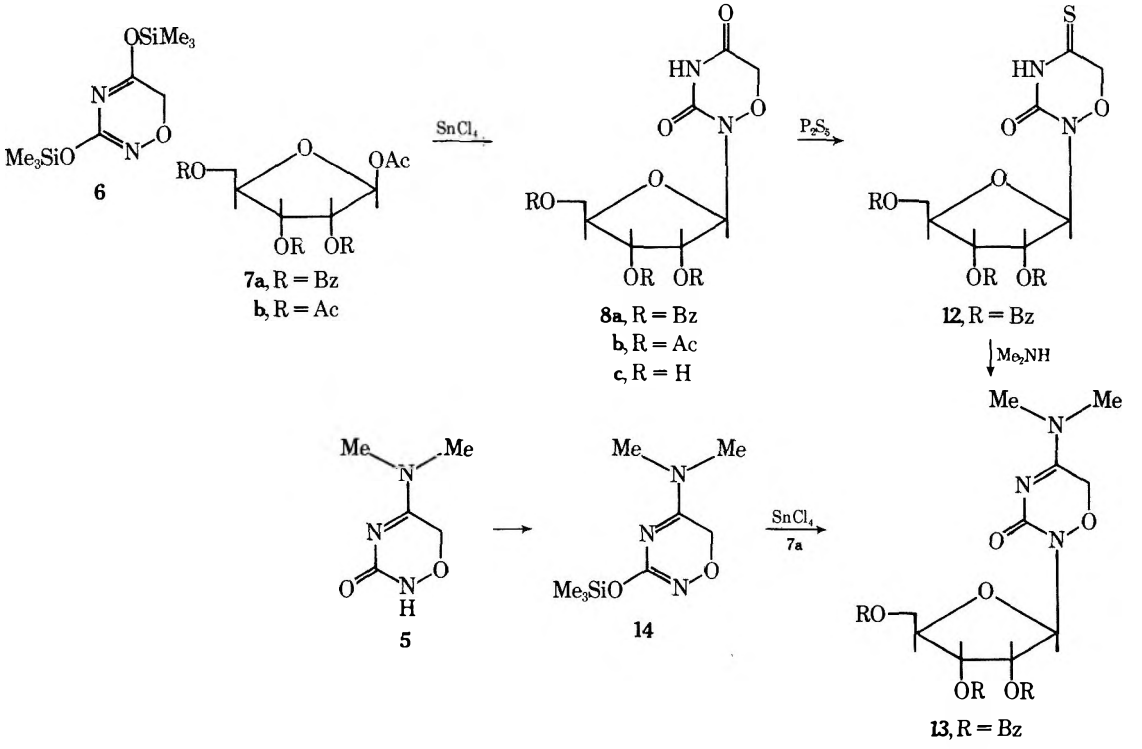
It is interesting to note that the ^{13}C chemical shift of the *N*-methyl carbon of 2-methyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**10**) occurs considerably more downfield than that of 4-methyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**11**). In order to see if this β effect of a carbonyl group on an *N*-methyl carbon is of a general nature, we investigated the ^{13}C NMR spectrum of 1,3-dimethyluracil, which had been previously reported without assignment of the *N*-methyl carbons.[14] By examining the proton coupled ^{13}C NMR spectrum of 1,3-dimethyluracil in Me_2SO-d_6 it was possible to assign the resonance at 36.8 ppm to the N-1 methyl carbon and the resonance at 27.5 ppm to the N-3 methyl carbon based on the small vicinal coupling (5 Hz) of the C-6 proton to the N-1 methyl carbon. Therefore, the ^{13}C chemical shift of the N-3 methyl carbon of 1,3-dimethyluracil, which is adjacent to two carbonyl groups, also occurs at a considerably higher field than that of the N-1 methyl carbon, which is adjacent to only one carbonyl group.

In an effort to provide further proof for the site of ribosylation of 2β-D-ribofuranosyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8c**), we undertook the synthesis of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**12**) and 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-dimethylamino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**13**).

Thiation of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8a**) with phosphorus pentasulfide in anhydrous, refluxing dioxane afforded 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**12**) in 45% yield. Elemental analysis established that **12** was a monothio derivative of **8a** and, as seen upon thiation of 6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**1**), the uv maxima of **12**, 229 nm (ε 40 900) and 276 (22 000), had shifted as compared to the uv maximum of 230 nm (ε 44 100) for **8a**.

The ^1H NMR signal for the anomeric proton of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazin-3-(2*H*)-one-5(4*H*)-thione (**12**) appeared at 6.18 ppm while that

Scheme II



of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8a**) appeared at 6.12 ppm. The anisotropic effect of a thione group adjacent to the site of glycosylation causes a large shift of the ^{1}H NMR signal for the anomeric proton to lower field.[10,15,16] If **12** were the 3-thio rather than the 5-thio derivative, the ^{1}H NMR signal of the anomeric proton of **12** would be expected to appear at a much lower field than that of **8a**. The same would be true if **12** were the N-4 isomer, as then the site of glycosylation would be adjacent to both a carbonyl and a thione group. This indicates that **12** is the 5-thio rather than the 3-thio derivative, and, also, that both **8a** and **12** are the N-2 rather than the N-4 ribonucleosides.

Treatment of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**12**) with sodium methoxide in methanol gave a complex reaction mixture, which was not further investigated. Presumably the 6*H*-1,2,4-oxadiazine ring of **12** is unstable to basic deblocking conditions, as found for **8a**. Treatment of certain thio analogues of 5,6-dihydrouracil and their methyl derivatives with sodium methoxide in methanol also resulted in ring opening.[17]

Reaction of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**12**) with dimethylamine in dioxane at room temperature afforded 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-dimethylamino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**13**) in 53% yield. It was also possible to prepare **13**, in 61% yield, by condensation in 1,2-dichloroethane of 3-trimethylsilyloxy-5-dimethylamino-6*H*-1,2,4-oxadiazine (**14**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**7a**) and 1 equiv of stannic chloride.[9] Silyl derivative **14** was prepared by treatment of 5-dimethylamino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**5**) in refluxing dioxane with HMDS in the presence of ammonium sulfate, and, after removal of solvents, was used without further purification.

The synthesis of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-dimethylamino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**13**) from 5-dimethylamino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**5**) firmly establishes **13** as the N-2 ribonucleoside. As 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazin-3-(2*H*)-one-5(4*H*)-thione (**12**) was converted to **13** and 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8a**) was converted to **12**, the assigned structures for **8a** and **12** thus received further support.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Specific rotations were measured in a 1-dm tube with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 60 MHz on a Hitachi Perkin-Elmer R-20A spectrometer in Me_2SO-d_6 using DSS as an internal standard. The ^{13}C NMR spectra were obtained on a Bruker HX-90 NMR spectrometer operating at 22.62 MHz in the Fourier transform mode at a probe temperature of 35 °C. A Fabri-Tek 1074 signal averager with 4096 word memory was used for data accumulation and a PDP-8/e computer for data processing. Solutions (1.0 M) were prepared in Me_2SO-d_6 and were studied in 10-mm tubes. Ultraviolet spectra (uv, $\epsilon \times 10^{-3}$) were recorded on a Cary Model 15 spectrophotometer and infrared spectra (ir) on a Perkin-Elmer 257 spectrophotometer (KBr pellets). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The pK_a determinations were performed on a Radiometer automatic potentiometric titrator. Evaporations were carried out under reduced pressure below 40 °C. Detection of components on silica gel (ICN, Woelm F254) was by ultraviolet light and with anisaldehyde spray followed by heating.

6*H*-1,2,4-Oxadiazin-3(2*H*)-one-5(4*H*)-thione (2). A solution of 23.2 g (200 mmol) of **1** and 23.2 g (100 mmol) of purified P_2S_5 in 1000 ml of dry dioxane was refluxed for 2 h. After cooling, the reaction mixture was filtered and the filtrate concentrated in vacuo to about 300 ml. Silica gel (80 g) was added and the solvent removed in vacuo. The residue was applied to an 800-g silica gel dry column (2.75 in. nylon tubing) followed by 200 g of W200 alumina. The column was eluted with 2000 ml of 6:4 CH_2Cl_2–Et_2O and 5000 ml of 1:1 CH_2Cl_2–Et_2O, fractions of 500 ml being collected. Fractions 2–9 were combined and after removal of solvent in vacuo the crude product was recrystallized from CH_3CN to give 10.77 g. Recrystallization from CH_3CN gave the analytical sample: mp 153.5–154.5 °C; NMR (Me_2SO-d_6) δ 4.68 (s, 2, CH_2), 11.4 (br s, 1, NH), 13.6 (br s, 1, NH).

Anal. Calcd for $C_3H_4N_2O_2S$ (132.141): C, 27.27; H, 3.05; N, 21.20; S, 24.26. Found: C, 27.47; H, 3.06; N, 21.14; S, 24.39.

Workup of the mother liquor afforded 3.83 g of additional product for a total yield of 14.60 g (55.3%).

5-Amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (3). A. Dry ammonia was bubbled into a solution of 1.33 g (10 mmol) of **2** in 50 ml of dry dioxane for 2.5 h. The yellow suspension was filtered and the filter cake washed with dry dioxane (2 × 10 ml). After washing well with $CHCl_3$ there remained 1.039 g of white solid (90.3%). Recrystallization from MeOH followed by two recrystallizations from EtOH gave the analytical sample: mp 151–152 °C; NMR (Me_2SO-d_6) δ 4.33 (s, 2, CH_2), 7.9 (broad s, 1, NH), 9.1 (broad s, 2, NH_2).

Anal. Calcd for $C_3H_5N_3O_2$ (115.092): C, 31.31; H, 4.38; N, 36.51. Found: C, 31.20; H, 4.18; N, 36.40.

B. Ammonia was bubbled into a solution of 10 ml of HMDS and 50 ml of dry dioxane for 30 min at room temperature. This solution was then transferred to a bomb containing 1.16 g (10 mmol) of **1** and 100 mg of ammonium sulfate. The bomb was heated on a steam bath for 15 h. After cooling, the contents of the bomb were removed and the bomb washed well with $CHCl_3$. The solvents were removed in vacuo and the residue dried at the vacuum pump for 30 min. The residue was then suspended in EtOAc and filtered, and the solid was washed with EtOAc to give 0.235 g (20.4%) of slightly impure **3a** as determined by comparison with the TLC, uv, and ir spectrum of the material prepared by method A above.

EtOH was added to the EtOAc filtrate and solvents were then removed in vacuo. EtOH was added to the residue and then removed in vacuo to afford a dark brown solid residue, which was shown by TLC (7:3 $CHCl_3$–MeOH) to only contain more **3** as well as unreacted **1**.

5-Dimethylamino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (5). Dimethylamine was bubbled into a solution of 0.375 g (2.8 mmol) of **2** in 11 ml of dry dioxane for 5 min. After stirring at room temperature for 50 min, the resulting precipitate was filtered and washed with a little dioxane and then washed well with ether to give 0.350 g (87.3%) of white solid. Recrystallization from EtOH gave the analytical sample: mp 176–177 °C; NMR (Me_2SO-d_6) δ 3.03 and 3.08 (s, 6, NMe_2), 4.60 (s, 2, CH_2), 9.61 (broad s, 1, NH).

Anal. Calcd for $C_5H_9N_3O_2$ (143.146): C, 41.95; H, 6.34; N, 29.36. Found: C, 42.24; H, 6.63; N, 29.60.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5-(2*H*,4*H*)-dione (8a). A solution of 2.55 g (22 mmol) of **1** (powdered and dried for 1 day in vacuo over P_2O_5 at 80 °C), 220 mg of ammonium sulfate, and 20 ml of HMDS in 100 ml of dry dioxane was refluxed for 18 h. After cooling, dioxane and HMDS were removed in vacuo and the residue was then dried at the vacuum pump for 1 h. The semisolid residue was taken up in 200 ml of dry 1,2-dichloroethane (dried by a Woelm W200 basic alumina column and then stored overnight over 4A molecular sieves) after which 10 g of 4A molecular sieves and 10.08 g (20 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (powdered and dried for 1 day in vacuo over P_2O_5 at 80 °C) were added. The flask was flushed with dry nitrogen and stoppered with a rubber septum. After $SnCl_4$ (2.3 ml, 20 mmol) was added via a syringe, the reaction mixture was stirred at room temperature for 22 h. The reaction mixture was then poured into 100 ml of saturated aqueous $NaHCO_3$ solution. After stirring well, Celite was added followed by filtration through a Celite pad. After the filter cake was washed well with CH_2Cl_2, the organic phase was washed with 50 ml of saturated aqueous NaCl solution and then dried over Na_2SO_4. Removal of the solvent in vacuo gave 9.60 g of a yellowish foam. Recrystallization from 250 ml of EtOH gave 6.846 g of white needles. A second recrystallization from EtOH gave the analytical sample: mp 174–174.5 °C; $[\alpha]^{25}D$ −38.3° (c 1.0, $CHCl_3$); NMR (Me_2SO-d_6) δ 4.50 (s, 2, CH_2), 6.12 (s, 1, $H_{1'}$).

Anal. Calcd for $C_{29}H_{24}N_2O_{10}$ (560.515): C, 62.14; H, 4.32; N, 5.00. Found: C, 62.23; H, 4.52; N, 4.76.

The mother liquor was removed in vacuo and the residue chromatographed on 300 g of dry column silica gel, eluting with 9:1 $CHCl_3$–EtOAc to give 0.763 g more product for a combined yield of 7.609 g (67.8%).

2-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (8b). A solution of 6.38 g (55 mmol) of **1**

(powdered and dried in vacuo at 60 °C for 6 h), 500 mg of ammonium sulfate, and 50 ml of HMDS in 250 ml of dry dioxane was refluxed for 15 h. After cooling, dioxane and HMDS were removed in vacuo and the residue was dried at the vacuum pump for 1 h. The semisolid residue was taken up in 350 ml of dry 1,2-dichloroethane after which 35 g of 4A molecular sieves and 16.0 g (50 mmol) of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (powdered and dried in vacuo at 80 °C for 15 h) were added. The flask was flushed with nitrogen and stoppered with a rubber septum. After $SnCl_4$ (5.8 ml, 50 mmol) was added via a syringe, the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then poured into 250 ml of saturated aqueous $NaHCO_3$. After stirring well, Celite was added followed by filtration through a Celite pad. After the filter cake was washed well with $CHCl_3$, the organic phase was washed with 200 ml of saturated aqueous NaCl solution and then dried over $MgSO_4$. Removal of the solvent in vacuo followed by drying of the residue in vacuo for 15 h and then a further drying in vacuo over P_2O_5 for 24 h gave 16.1 g (86.0%) of a white glass, which was shown by TLC (85:15 $CHCl_3$–Me_2CO) to contain only minor impurities. Chromatography of a portion of the above on silica gel, eluting with 99:1 $CHCl_3$–MeOH, afforded an analytical sample: mp 45 °C; $[\alpha]^{25}D$ −24.3° (*c* 1.2, $CHCl_3$); NMR (Me_2SO-d_6) δ 4.71 (s, 2, CH_2), 5.80 (d, J = 4 Hz, 1, $H_{1'}$).

Anal. Calcd for $C_{14}H_{18}N_2O_{10}\cdot H_2O$ (392.321); C, 42.86; H, 5.14; N, 7.14. Found: C, 42.81; H, 5.36; N, 6.95.

2β-D-Ribofuranosyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (8c). A solution of 1.51 g (3.8 mmol) of **8b** in 75 ml of anhydrous 0.1 M MeOH–HCl was refrigerated for 25 h in a stoppered flask. The reaction mixture was neutralized with IR-45(OH) resin, and the resin was filtered and washed with MeOH. Removal of the MeOH in vacuo followed by drying the residue overnight in vacuo afforded 0.75 g (79.6%) of slightly impure **13** as a syrup. A homogeneous sample of **13** was obtained by preparative TLC on silica gel (7:3 $CHCl_3$–MeOH). The product was extracted from the silica gel with MeOH. Removal of the MeOH in vacuo gave a slightly yellowish syrup which was taken up in water, treated with charcoal, filtered through Celite, and then lyophilized to give a white solid: mp 180 °C dec; $[\alpha]^{25}D$ −14.2° (*c* 1.0, H_2O); NMR (Me_2SO-d_6) δ 4.63 (s, 2, CH_2), 5.52 (d, J = 5 Hz, 1, $H_{1'}$), 6.92 (br s, 1, NH).

Anal. Calcd for $C_8H_{12}N_2O_7\cdot H_2O$ (266.209): C, 36.09; H, 5.30; N, 10.52. Found: C, 36.60; H, 5.43; N, 10.43.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(1*H*)-thione (12). A solution of 1.122 g (2.0 mmol) of **8a** and 0.266 g (1.2 mmol) of P_2S_5 in 20 ml of dry dioxane was refluxed for 2 h. After cooling, the reaction mixture was filtered and the dioxane removed in vacuo to give 1.566 g of a yellow foam. Chromatography on silica gel (50 g), eluting with 98:2 CH_2Cl_2–Et_2O, gave 0.519 g (45.0%) of yellow solid. Two recrystallizations from EtOH gave the analytical sample: mp 186.5–187.5 °C; $[\alpha]^{25}D$ −113.7° (*c* 1.0, $CHCl_3$); NMR (Me_2SO-d_6) δ 4.72 (s, 2, CH_2), 6.18 (s, 1, $H_{1'}$).

Anal. Calcd for $C_{29}H_{24}N_2O_9S$ (576.580): C, 60.41; H, 4.20; N, 4.86; S, 5.56. Found: C, 60.63; H, 4.49; N, 5.03; S, 5.60.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-dimethylamino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (13). A. A solution of 0.430 g (3.0 mmol) of **5**, 30 mg of ammonium sulfate, and 4.3 ml of HMDS in 37 ml of dry dioxane was refluxed for 15 h. After cooling, dioxane and HMDS were removed in vacuo and the residue was then dried at the vacuum pump for 1 h. The semisolid residue was taken up in 30 ml of dry 1,2-dichloroethane after which 3 g of 4A molecular sieves and 1.526 g (3.0 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose were added. The flask was then flushed with nitrogen and stoppered with a rubber septum. After $SnCl_4$ (0.4 ml, 3.0 mmol) was added, the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then poured into 15 ml of saturated aqueous $NaHCO_3$. After stirring well, Celite was added followed by filtration through a Celite pad. After the filter cake was washed well with CH_2Cl_2, the organic phase was washed with 25 ml of saturated aqueous NaCl solution and then dried over Na_2SO_4. Removal of the solvent in vacuo gave 1.627 g of solid residue. Dry column chromatography on 100 g of dry column silica gel, eluting with 150 ml of 99:5 CH_2Cl_2–MeOH, gave 1.081 g (61.3%) of white solid. Two recrystallizations from EtOH gave the analytical sample: mp 185–186 °C; $[\alpha]^{25}D$ −56.4° (*c* 1.0, $CHCl_3$); NMR (Me_2SO-d_6) δ 2.94, 3.19 (s, 6, NMe_2), 4.63 (s, 2, CH_2), 6.44 (d, J = 5 Hz, 1, H_1).

Anal. Calcd for $C_{31}H_{29}N_3O_9$ (587.585): C, 63.37; H, 4.97; N, 7.15. Found: C, 63.19; H, 4.67; N, 7.17.

B. Dimethylamine was bubbled into a solution of 0.179 g (0.3 mmol) of **12** in 7 ml of dry dioxane for 5 min. After stirring at room temperature for 12 min longer, dioxane was removed in vacuo. Preparative TLC of the residue on silica gel, eluting with 95:5 $CHCl_3$–MeOH, gave 0.094 g (53.3%) of a white solid, which was the same as the product obtained in A by comparison of TLC, melting point, ir, and NMR.

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Registry No.—**1**, 5766-95-0; **1** anion, 59696-54-7; **2**, 59696-55-8; **3**, 59696-56-9; **4**, 5767-01-1; **5**, 59696-57-0; **8a**, 59696-58-1; **8b**, 59696-59-2; **8c**, 59696-60-5; **10**, 5767-08-8; **11**, 5767-15-7; **12**, 59696-61-6; **13**, 59696-62-7; P_2S_5, 1314-80-3; dimethylamine, 124-40-3; 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, 6974-32-9; 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose, 13035-61-5.

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Nucleosides. 101. Conformationally Restricted Analogues of Pyrimidine Nucleosides. 1. Synthesis of 6,5′(S)- and 6,5′(R)-Cyclouridine[1]

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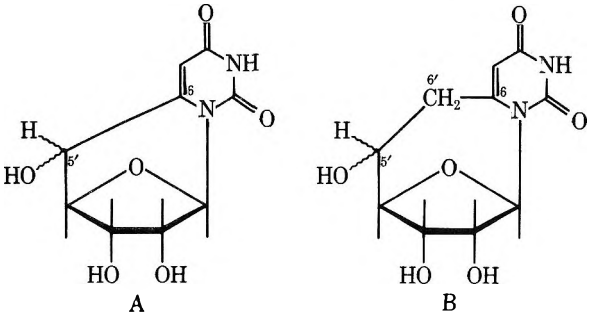
Methods are described for the synthesis of the 5′(S) and 5′(R) epimers of 6,5′-cyclouridine, conformationally restricted nucleosides that simulate the anti:gauche-trans and anti:trans-gauche conformers of uridine. The previously reported 2′,3′-O-isopropylidene-5-hydroxy-6,5′(S)-cyclouridine serves as starting material for both epimers. Mesylation of the phenolic 5-hydroxyl group, followed by desulfonyloxylation with hydrogen and palladium–charcoal in the presence of triethylamine, affords 2′,3′-O-isopropylidene-6,5′(S)-cyclouridine. Deblocking with 80% acetic acid then gives 6,5′(S)-cyclouridine. Both the 5′-mesyl and 5′-acetyl esters of 2′,3′-O-isopropylidene-6,5′(S)-cyclouridine undergo base-catalyzed epimerization at C-5′ to give equilibrium mixtures of the 5′(S) and 5′(R) esters. Separation of 5′-O-acetyl-2′,3′-O-isopropylidene-6,5′(R)-cyclouridine from its 5′(S) isomer, followed by removal of protecting groups under acidic conditions, affords a convenient route to 6,5′(R)-cyclouridine. NMR experiments in pyridine-d_6 containing D_2O indicate that the 5′-epimerization reactions involve carbanion intermediates.

A knowledge of the conformations of enzyme-bound nucleosides and nucleotides would be invaluable for gaining insight into enzyme mechanisms and the nature of active sites, and could serve eventually as a basis for the design of nucleoside antimetabolites having enhanced affinity and specificity for their target enzymes. In order to explore the relationship between conformation[2] and biological activity[3] in the pyrimidine nucleoside series, we have undertaken the synthesis of conformationally restricted compounds of the types illustrated by the uridine analogues A and B in Scheme I. These

Scheme I

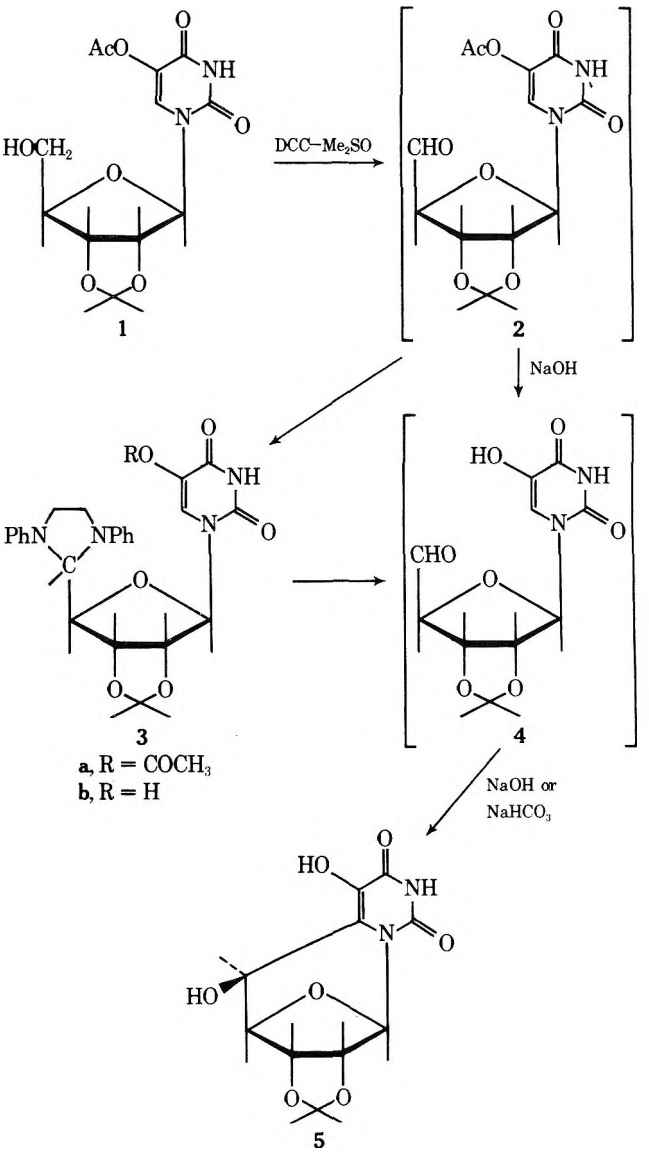


nucleosides, and the corresponding nucleotides, are suitable conformational probes for the following reasons. Both the 6,5′-cyclo (A) and methylene-bridged (B) types retain the full complement of hydrogen-bonding sites of their unrestricted analogues. Both types are constrained within the anti range, a desirable feature because previous studies have shown that conformationally abnormal, syn nucleosides do not, in general, substitute for their anti counterparts in enzyme-catalyzed reactions.[3a,b,4] Further, since nucleosides of types A and B are asymmetric at C-5′, each can exist as pairs of D-allo (5′R) and L-talo (5′S) isomers. The orientations of the 5′-hydroxyl (or 5′-phosphate) groups in these epimeric pairs correspond approximately to the gauche-trans and trans-gauche $C_{4'}$, $C_{5'}$ rotamers of ordinary nucleosides,[2,5] and the behavior of each epimer in enzyme-catalyzed reactions may allow a general assessment of the importance of this conformational feature.

In this paper we describe the synthesis of both the 5′(R) and 5′(S) isomers of 6,5′-cyclouridine (A)[6] by procedures that we plan to extend to the synthesis of other nucleosides of type A, and to the methylene-bridged types B.

The basic procedure for the synthesis of 6,5′-cyclopyrimidine nucleosides was developed in this laboratory by Rabi and Fox.[7] This method (Scheme II) depends on the fact that 5-hydroxyuracils are susceptible to electrophilic substitution at C-6,[8] and can, for example, undergo base-catalyzed hydroxymethylation at this position.[9] When the 5′-aldehyde (4)

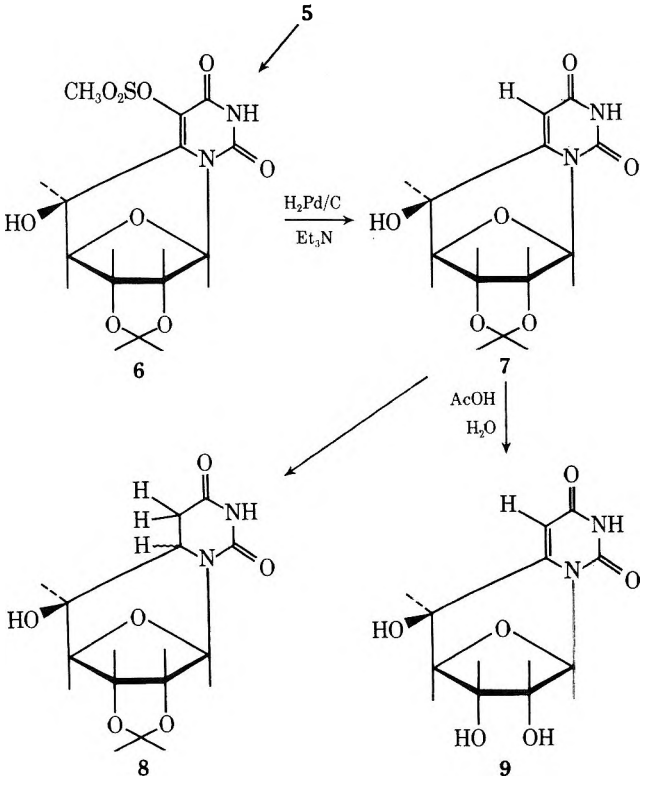
Scheme II



derived from 5-hydroxyuridine is treated with sodium bicarbonate, hydroxyalkylation proceeds in an intramolecular manner to afford the 6,5′(*S*)-cyclonucleoside **5**.[7] In the original work, the 5′-aldehydonucleoside **2** resulting from Me_2SO–DCC oxidation of 5-acetoxy-2′,3′-*O*-isopropylideneuridine (**1**) was converted into **5** via the 5′-imidazolidine derivatives **3a** and **3b**. We have simplified this procedure by treating reaction mixtures containing **2** with excess sodium hydroxide, thereby generating **4** which spontaneously cyclizes to give **5** directly in 40% yield. The ring closure **4** → **5**, whether catalyzed by sodium hydroxide or sodium bicarbonate, affords only the 5′-*S* isomer of **5**; none of the 5′-*R* isomer has been detected. Therefore, for conversion of **5** into the isomeric 6,5′-cyclouridines, methods were required for epimerization at C-5′, as well as for removal of the pyrimidine 5-hydroxyl group.

The procedure shown in Scheme III for the removal of the

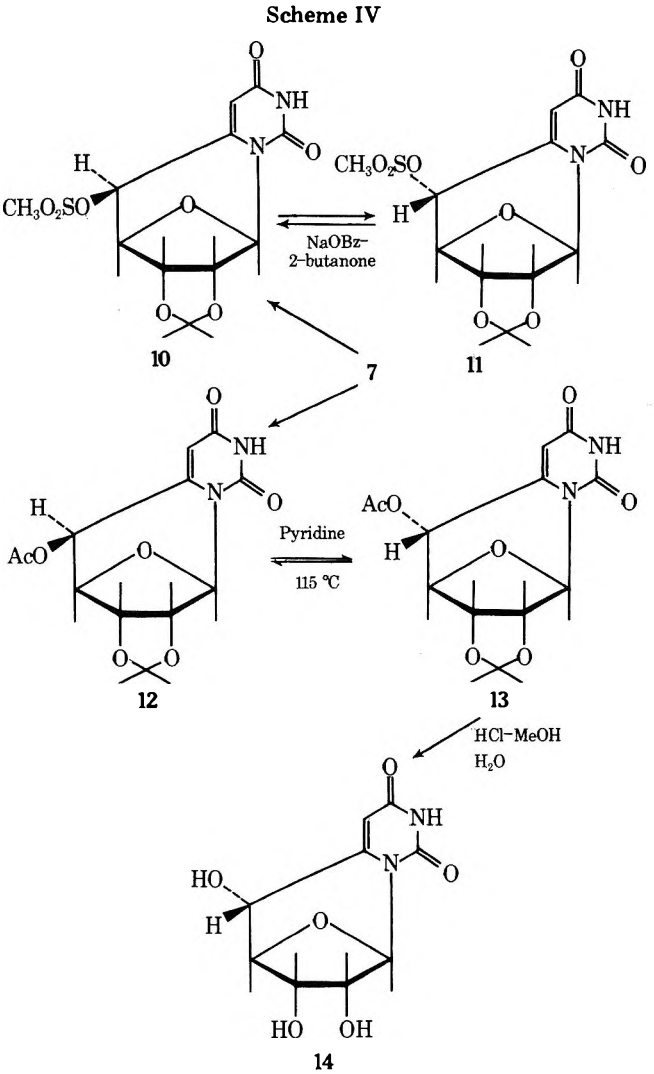
Scheme III



pyrimidine 5-hydroxyl group of **5** is an extension of the method developed by Clauss and Jensen[10] for the deoxygenation of phenols, namely the hydrogenolysis of phenol sulfonic esters in the presence of a base. In our case, the required 5-methanesulfonyl ester **6** was prepared by selective esterification of **5** in pyridine. The presence of a 5′-hydroxyl signal in the NMR spectrum of **6** (δ 6.29, $J_{5',5'OH}$ = 6.4 Hz), together with a uv spectrum appropriate for a 5-O-substituted 5-hydroxyuridine, confirms that esterification takes place at the 5 position of **5** as expected. Hydrogenation of **6** in the presence of palladium–carbon catalyst and an equivalent amount of triethylamine affords 2′,3′-*O*-isopropylidene-6,5′(*S*)-cyclouridine (**7**) in ~57% yield.[11] The structure of **7** was evident from the NMR spectrum, in which H-5 (δ 5.69) appears as a narrow doublet, coupled (1.7 Hz) to the 5′ proton appearing at δ 4.69. The chemical shift of the single 5′ proton and the 5′-hydroxyl signal at δ 6.54 confirm that reduction of the allylic 5′ position does not occur under these conditions. However, the desulfonyloxylation reaction **6** → **7** has to be monitored carefully because the product (**7**) undergoes further reduction to give the 5,6-dihydronucleoside **8**. The NMR spectrum of **8** (H-6, δ 3.40; H-5a, 2.96; H-5b, 2.65) shows a single isomer, although the various coupling constants do not allow an unequivocal assignment of the configuration at C-6. The relative rates of the reactions **6** → **7** and **7** → **8** are such that a clear-cut change in the rate of hydrogen uptake is not observed. Consequently, preparations of **7** invariably contained small amounts of **8**. This contaminant is not separable by chromatography, but can be removed by careful recrystallization of **7**. In practice, the use of impure **7** for further reactions posed no problems. For example, hydrolysis of **7** containing about 10% of **8** in refluxing 80% acetic acid affords the desired 6,5′(*S*)-cyclouridine (**9**), which is readily obtained in a high state of purity.

An obvious method for inverting the C-5′ configuration of these 6,5′-cyclonucleosides would be displacement of a 5′-sulfonyl ester by an oxygen nucleophile, under conditions that favor an SN2 mechanism. Accordingly, the 5′-mesyl ester **10** (Scheme IV) was prepared from **7** and refluxed in 2-butanone

Scheme IV



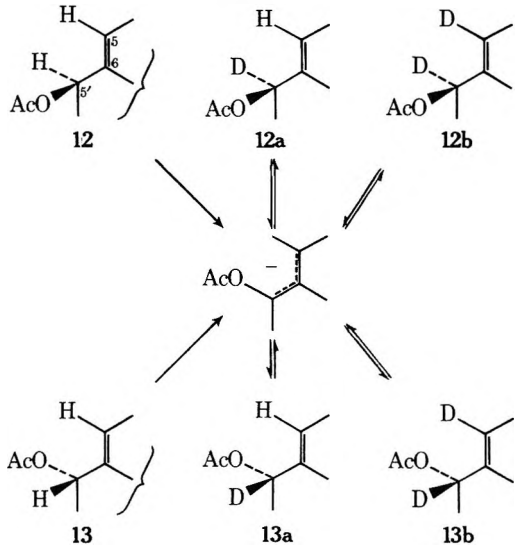
with sodium benzoate. This treatment results in the gradual appearance of material that migrates on TLC plates with a mobility very close to that of starting material **10**, although the reaction apparently does not go to completion. The NMR spectrum of this mixture, after removal of sodium benzoate, shows that the 5′-mesyl group is not displaced by benzoate ion under these rather mild conditions, but that epimerization at C-5′ had nevertheless taken place. This conclusion follows from the presence of NMR signals assignable to the 5′(*R*) mesyl ester **11**. The NMR spectrum of **11** obtained after fractional crystallization shows a value of <1 Hz for the H-4′, H-5′ coupling constant. This value is diagnostic of the 5′(*R*)

configuration because the 4′,5′ dihedral angle approaches 90°, and is quite different from the $J_{4',5'}$ value of 6.4 Hz noted for the 5′(S) isomer **10**, where the dihedral angle is ~30°. The 5′(S) mesyl ester **10** is itself stable in refluxing 2-butanone, but rapidly equilibrates with the 5′(R) isomer **11** on addition of triethylamine. This finding is consistent with benzoate ion acting as a base in the epimerization **10** → **11**, although it does not exclude the possibility of salt effects promoting a carbonium-ion mechanism. However, the results described below indicate that the epimerization most likely involves carbanionic intermediates.

We have not attempted to hydrolyze the 5′-mesyl group of **11** because the strongly basic conditions required would probably lead to equilibration of the S and R isomers, with the subsequent formation of both forms of 6,5′-cyclouridine. Instead, we have prepared the 5′-acetyl ester **12**, where all the blocking groups are acid labile, and studied the 5′ epimerization induced by treatment with refluxing pyridine. Compound **12** epimerizes slowly under these conditions, giving a **12** (S):**13** (R) ratio of ~2:1 at 24 h.[12] The isomers **12** and **13** are separable by silica gel chromatography, and again, assignment of the 5′(R) configuration to **13** rests on a $J_{4',5'}$ value of 0.8 Hz, as compared with a value of 6.5 Hz for **12**. Removal of the 5′-acetyl group of **13** by treatment with 30% hydrogen chloride in methanol, followed by the addition of water for the hydrolysis of the 2′,3′-*O*-isopropylidene group, affords 6,5′(R)-cyclouridine (**14**) in excellent yield. None of the 5′(S) isomer **9** was formed in this process, showing that **13** is not susceptible to acid-catalyzed isomerization to **12** prior to hydrolysis under these conditions.

Evidence that the mechanism of the above 5′-epimerization reactions involves carbanion intermediates comes from an NMR study of the interconversion of **12** and **13** in pyridine-d_6 containing 5% D_2O (Scheme V). At 80 °C, both the C-5 and

Scheme V



C-5′ hydrogens of the S isomer **12** undergo exchange for deuterium, with the rate of exchange at the allylic C-5′ position exceeding that of the pyrimidine C-5 position. Thus H-5′ had undergone 80% exchange at 30 min whereas H-5 was exchanged to the extent of 40%; at 2 h, H-5′ was exchanged completely, as compared with 60% exchange for H-5. At this stage the NMR spectrum shows a mixture of **12a** and **12b**; that is, exchange of H-5′ for deuterium proceeds with retention of configuration and greatly exceeds the rate of racemization. With further heating, where the deuterium exchange reactions become invisible, increasing amounts of the R isomer **13b** are observed, together with traces of **13a**. The S:R ratio reaches an equilibrium value of 2:1 at 40 h. These results indicate that **12** forms a resonance stabilized carbanion that can undergo deuteration at C-5 and C-5′;[13] and that because of asymmetric ion solvation, or the steric effects promoted by the asymmetry of the rest of the molecule, deuteration from the rear side of C-5′ (retention) predominates over deuteration from the front side (inversion). When the R isomer **13** is heated at 80 °C in pyridine-d_6–D_2O, the initial formation of **13a** and **13b** (exchange with retention) was *not* observed. Instead, **13** is converted gradually into a mixture of S isomers containing **12b** with traces of **12a**. This result can be accounted for in two ways. The R isomer **13** could undergo isoinversion[14]—that is, inversion without exchange for deuterium—to give the S isomer **12** directly, which would then undergo exchange at C-5 and C-5′ with predominant retention of configuration, as seen above. Alternatively, the carbanion derived from **13**, being formally the same as that derived from **12**, would on the basis of the above results undergo deuteration preferentially from the rear side (inversion) to give **12a**, and eventually **12b**. In either case, **12b** would be expected to reequilibrate with **13b**, and indeed, a substantial decrease in the integration value of H-5 and H-5′ of **13** is seen at 40 h, reflecting the presence of **13b**. The equilibrium S:R ratio of 2:1 at 40 h is the same as that observed when starting from the S isomer **12**.

The extensive studies by Cram and associates[14] on the stereochemistry of carbanion reactions have shown that the extent of inversion, retention, or racemization is very sensitive to changes in the base–solvent combination. It is therefore quite likely that different reaction conditions would lead to increased amounts of the R isomer (**13**) in the equilibrium with **12**. Similar base-catalyzed epimerizations should greatly facilitate the synthesis of other 6,5′-cyclopyrimidine nucleosides, and may find application in the 8,5′-cyclopurine nucleoside series. Studies of the chemistry of the R and S cyclouridines, and their behavior with some of the enzymes of pyrimidine nucleoside metabolism, are currently under investigation.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The nuclear magnetic resonance spectra were determined on a JEOL PFT-100 spectrometer operating in the Fourier transform mode (EC-100 computer), with internal deuterium field-frequency lock. Values given for coupling constants (hertz) and chemical shifts (δ) are first order, and the resolution resulting from various combinations of spectral widths and computer data points is noted for each spectrum. Tetramethylsilane was used as internal standard. Ultraviolet spectra were measured on a Cary Model 15 spectrometer. Thin layer chromatography was performed on microscope slides coated with silica gel GF_{254} (Merck); separated materials were detected with ultraviolet light and by spraying with 10% v/v sulfuric acid in ethanol followed by charring. Evaporations were carried out in vacuo with bath temperatures kept below 45 °C. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

5-Hydroxy-2′,3′-*O*-isopropylidene-6,5′(*S*)-cyclouridine (5). Pyridine (5 ml) and trifluoroacetic acid (2.5 ml) were added to a solution of 5-acetoxy-2′,3′-*O*-isopropylideneuridine (**1**, 17.1 g, 50 mmol) in dry dimethyl sulfoxide (200 ml) containing dicyclohexylcarbodiimide (40 g). The mixture was stirred at room temperature for 15 h, and then diluted with 25 ml of water. The precipitated dicyclohexylurea was collected after cooling and washed with acetone. The filtrate was concentrated to dryness at 35–40 °C (bath) in a rotary evaporator (oil pump) equipped with a Dewar condenser cooled with 2-propanol–dry ice, and the resulting syrup was dissolved in dichloromethane. Residual dicyclohexylurea was removed and the syrup remaining after evaporation of solvent was dissolved and shaken in a mixture of 500 ml of 50% methanol and 110 ml of 1 N NaOH. The solution was kept at room temperature for 30 min and then neutralized with 1 N acetic acid (~60 ml) to pH ~6. Solids were removed by filtration through a pad of Celite and the filtrate was clarified, where necessary, by storage overnight. The solution was decanted from precipitated, oily material and evaporated to remove methanol. After a final filtration (where needed), the clear aqueous solution was extracted with ethyl

acetate (5 × 200 ml), and the combined extracts were dried (Na_2SO_4) and then concentrated to give syrupy **5** (5.45 g) that crystallized spontaneously. A further 600 mg of **5** was obtained from a second series of ethyl acetate extractions, and the combined mother liquors and washings afforded 490 mg, bringing the total yield to 6.54 g (44%). In similar runs the yields ranged from 5.0 g (33%) to 6.79 g (46%). This product on occasion contains traces of dicyclohexylurea but is suitable for further reactions. Material obtained after recrystallization from ethanol was identical (melting point, uv, NMR, TLC) with authentic[7] **5**.

2',3'-*O*-Isopropylidene-5-mesyloxy-6,5'(*S*)-cyclouridine (6). A solution of methanesulfonyl chloride (5.73 ml, 74 mmol) in benzene (30 ml) was added dropwise (~1 h) to a stirred, ice-cold solution of **5** (4.4 g, 14.8 mmol) in pyridine (40 ml). Stirring was continued for an additional 1 h before ice was added to hydrolyze excess methanesulfonyl chloride. After a further 30 min, the volume was reduced to ~5 ml, water (20 ml) was added, and the mixture was extracted with ethyl acetate (3 × 150 ml). The combined extracts were dried (Na_2SO_4) and evaporated to dryness. The resulting syrup crystallized from ethanol (10 ml), affording 3.2 g of **6**. An additional 1 g of material (total yield 75%) was obtained on concentration of the mother liquor. A sample recrystallized from ethanol had mp 145 °C (sinters), 230–234 °C (effervescence), 257 °C dec; uv, pH 1 λ_{max} 265 nm, λ_{min} 228; pH 13 λ_{max} 264, λ_{min} 230; NMR (Me_2SO-d_6, res 0.3 Hz) exchangeable protons at δ 12.01 (1, broad s, N^3 H), 6.29 (1, d, 5'-OH, $J_{5',5'OH}$ = 6.4 Hz); Me_2SO-d_6 + D_2O (res 0.19 Hz), 5.88 (1, s, H-1'), 5.11 (1, d, H-2'), 5.06 (1, d, H-5'), 4.79 (1, d, H-3'), 4.52 (1, d, H-4'), 3.47 (3, s, mesyl CH_3), 1.41 (3, s) and 1.29 (3, s, isopropylidene methyls), $J_{1',2'}$ = 0, $J_{2',3'}$ = 5.8, $J_{3',4'}$ = 0, $J_{4',5'}$ = 7.2 Hz.

Anal. Calcd for $C_{13}H_{16}N_2O_9S$·0.5H_2O: C, 40.52; H, 4.45; N, 7.27. Found: C, 40.54; H, 4.27; N, 7.09.

2',3'-*O*-isopropylidene-6,5'(*S*)-cyclouridine (7). A suspension of 10% palladium on carbon (1 g) in water (10 ml) was added to a solution of **6** (3.0 g, 8 mmol) and triethylamine (1.09 ml, 8 mmol) in methanol (50 ml). The mixture was shaken under a hydrogen atmosphere in a Parr apparatus for ~170 min (variable), at which time hydrogen uptake reached ~12 mmol. The catalyst was removed and the filtrate concentrated to give a colorless syrup. Crystallization from ~20 ml of hot water afforded 1.28 g (57%) of **7** contaminated with small (and variable) amounts of **8**. A further recrystallization gave material with mp 290–291 °C dec; uv, pH 1 λ_{max} 268 nm, λ_{min} 234; pH 13 λ_{max} 269, λ_{min} 243; NMR (Me_2SO-d_6, res 0.3 Hz) exchangeable protons at δ 11.36 (1, broad s, N^3 H) and 6.54 (1, d, 5'-OH, $J_{5'5'OH}$ = 5.8 Hz); in Me_2SO-d_6 + D_2O res 0.09 Hz), 5.90 (1, s, H-1'), 5.69 (1, d, H-5), 4.90 (1, d, H-2'), 4.73 (1, d, H-3'), 4.43 (1, d, H-4'), 4.69 (1, dd, H-5'), 1.40 (3, s), and 1.26 (3, s, isopropylidene methyls), $J_{1',2'}$ = 0, $J_{2',3'}$ = 5.9, $J_{3',4'}$ = 0, $J_{4',5'}$ = 6.3, $J_{5',5}$ = 1.7 Hz.

Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.07; H, 5.00; N, 9.93. Found: C, 51.23; H, 5.22; N, 9.92.

The aqueous phase from the above reaction contains starting material (**6**), small amounts of **7**, and substantial amounts of **8**. Separation of **6** from **7** and **8** can be effected by chromatography on silica gel 60 (Merck, 70–230 mesh) using heptane–ethyl acetate (1:2 v/v), but this procedure does not separate **7** from **8**. Compound **7** containing small amounts of **8** can be purified by recrystallization from ethyl acetate–petroleum ether (bp 30–60 °C) mixtures.

5,6-Dihydro-2',3'-*O*-isopropylidene-6,5'(*S*)-cyclouridine (8). A mixture of **7** and **8** (500 mg), obtained from a reaction similar to that described above, was dissolved in 50% methanol (50 ml) containing triethylamine (0.16 ml). The mixture was reduced in the presence of 10% palladium on carbon catalyst (500 mg) on a Parr apparatus for 5 h. Catalyst and solvents were removed, and the resulting residue was recrystallized from 95% ethanol to give pure, non-uv-absorbing **8**: mp 238–239 °C; NMR (acetone-d_6, res 0.3 Hz), exchangeable protons at δ 9.25 (1, broad s, N^3 H) and 5.14 (1, broad d, 5'-OH, $J_{5',5'OH}$ ~ 4.6 Hz); acetone-d_6 + D_2O (res 0.15 Hz), 5.86 (1, s, H-1'), 4.97 and 4.79 (2, AB system, H-2' and H-3'), 4.28 (1, d, H-4'), 3.67 (1, dd, H-5'), 3.40 (1, eight-line m, H-6), 2.96 and 2.65 (2, two four-line m, H-5a and H-5b), 1.44 (3, s) and 1.34 (3, s, isopropylidene methyls), $J_{1',2'}$ = 0, $J_{2',3'}$ = 5.7, $J_{3',4'}$ = 0, $J_{4',5'}$ = 4.3, $J_{5',6}$ = 9.1, $J_{5a,6}$ = 4.6, $J_{5b,6}$ = 11.5, $J_{5a,5b}$ = 16.8 Hz.

Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.55; H, 5.49; N, 9.84.

6,5'(*S*)-Cyclouridine (9). A solution of **7** (800 mg, 2.8 mmol) in 80% acetic acid (25 ml) was refluxed for 5 h, at which time TLC (ethyl acetate) indicated that the hydrolysis was complete. The solution was evaporated to dryness and two 15-ml portions of ethanol were evaporated from the residue. Recrystallization from 20% ethanol afforded pure **9** (590 mg, 87%): mp 293–294 °C; uv pH 1 λ_{max} 268 nm (ϵ 10 750), λ_{min} 233 (1700); pH 10.8 λ_{max} 268 (8530), λ_{min} 243 (4190); NMR (Me_2SO-d_6, res 0.09 Hz) δ 11.27 (1, broad s, NH, exchanges), 6.44 (1, d, 5'-OH, exchanges), 5.74 (1, s, H-1'), 5.64 (1, d, broadened by unresolved N^3 H coupling, H-5), 5.35 (1, d, 3'-OH, exchanges), 5.23 (1, d, 2'-OH, exchanges), 4.61 (1, six-line m, H-5'), 4.31 and 4.22 (2, m, H-2' and H-4'), 4.02 (1, three lines, H-3'), $J_{1',2'}$ = 0, $J_{2',3'}$ = 6.1, $J_{3',4'}$ = 0, $J_{4',5'}$ = 6.0, $J_{5'5}$ = 1.6, $J_{5',5'OH}$ = 6.1, $J_{3',3'OH}$ = 5.3, $J_{2',2'OH}$ = 6.8 Hz.

Anal. Calcd for $C_9H_{10}N_2O_6$: C, 44.63; H, 4.16; N, 11.57. Found: C, 44.45; H, 4.19; N, 11.55.

2',3'-*O*-Isopropylidene-5'-*O*-mesyl-6,5'(*S*)-cyclouridine (10). A solution of **7** (500 mg, 2.07 mmol) and methanesulfonyl chloride (1.35 ml) in pyridine (20 ml) was stirred at room temperature until TLC (ethyl acetate) indicated disappearance of starting material (~4 h). Water (10 ml) was added to the mixture, and solvents were removed by evaporation. The residue was partitioned between water (10 ml) and ethyl acetate (3 × 50 ml), and the organic phase was dried (Na_2SO_4) and then concentrated to dryness. Two recrystallizations from ethanol afforded **10** (495 mg, 66%): mp 260 °C (sinters), 264–265 °C dec; uv λ_{max} pH 1 268 nm, λ_{min} 233, pH 10.8 λ_{max} 268, λ_{min} 243; NMR (Me_2SO-d_6, res 0.3 Hz), exchangeable proton at 11.6 (1, broad s, N^3 H), Me_2SO-d_6 + D_2O (res 0.3 Hz), 5.95 (1, s, H-1'), 5.87 (1, dd, H-5'), 5.74 (1, d, H-5), 4.91 (1, d, H-2'), 4.83 (1, d, H-3'), 4.71 (1, d, H-4'), 3.56 (3, s, mesyl CH_3), 1.41 (3, s), and 1.28 (3, s, isopropylidene methyls); $J_{1',2'}$ = 0, $J_{2',3'}$ = 5.5, $J_{3',4'}$ = 0, $J_{4',5'}$ = 6.4, $J_{5',5}$ = 1.5 Hz.

Anal. Calcd for $C_{13}H_{16}N_2O_8S$: C, 43.33; H, 4.48; N, 7.77. Found: C, 43.16; H, 4.68, N, 7.75.

5'-*O*-Acetyl-2',3'-*O*-isopropylidene-6,5'(*S*)-cyclouridine (12). A solution of **7** (760 mg, 2.7 mmol) and acetic anhydride (0.51 ml, 5.4 mmol) in pyridine (10 ml) was stirred at room temperature for 4 h. Water (10 ml) was added and stirring continued for an additional 1 h before concentration to dryness. The residue was recrystallized from ethanol, and then from ethyl acetate–petroleum ether, to give pure **12** (610 mg, 70%): mp 220 °C (sinters), 227–228 °C; uv, pH 1 λ_{max} 267 nm, λ_{min} 235; NMR (Me_2SO-d_6, res 0.15 Hz) δ 11.49 (1, d, N^3 H, exchanges), 5.95 (1, s, H-1'), 5.79 (1, dd, H-5'), 5.67 (1, three lines, H-5), 4.86 (2, s, H-2' and H-3'), 4.60 (d, H-4'), 2.19 (3, s, OAc), 1.40 (3, s), and 1.27 (3, s, isopropylidene methyls), $J_{1',2'}$ = $J_{3',4'}$ = 0, $J_{4',5'}$ = 6.5, $J_{5,N^3\text{-}H}$ = 1.5, $J_{5,5'}$ = 1.5 Hz. In Me_2SO-d_6 + D_2O, H-2' and H-3' give an AB system at δ 4.90 and 4.82, with $J_{2',3'}$ = 5.8 Hz.

Anal. Calcd for $C_{14}H_{16}N_2O_7$: C, 51.85; H, 4.97; N, 8.64. Found: C, 51.92; H, 5.03; N, 8.61.

2',3'-*O*-Isopropylidene-5'-*O*-mesyl-6,5'(*R*)-cyclouridine (11). **A.** Sodium benzoate (75 mg, 0.52 mmol) was added to a solution of **10** (150 mg, 0.42 mmol) in 2-butanone (10 ml), and the mixture was heated to reflux with stirring. TLC (EtOAc–petroleum ether, 3:1 v/v) showed the formation of a slower moving component (**11**) that did not increase in concentration after ~5 h. The mixture was filtered and the filtrate was concentrated to dryness. The residue was partitioned between water and chloroform, and the organic phase was dried and concentrated to afford a crystalline mixture containing approximately equal amounts (NMR) of **10** and **11**. Attempts to separate these isomers by thick layer chromatography were unsuccessful because the mixture crystallized at the origin when applied to the plates. Recrystallization of the mixture from ethanol afforded several crops of **10**, crops containing both components, and finally moderately pure **11**. Recrystallization (EtOH) afforded ~40 mg of chromatographically pure **11**: mp 255–258 °C dec; uv, pH 1 λ_{max} 271 nm, λ_{min} 235.5; pH 10.8 λ_{max} 271, λ_{min} 241; NMR (Me_2SO-d_6, res 0.15 Hz) δ 11.64 (1, broad s, N^3 H, exchanges), 5.98 (1, s, H-1'), 5.78 (1, s, broadened by unresolved $J_{5,5'}$, H-5), 5.56 (1, s, broadened by unresolved $J_{4',5'}$, H-5'), 4.87 (1, d, H-2'), 4.76 and 4.73 (2, H-3' d overlapped by H-4's), 3.46 (3, s, mesyl CH_3), 1.41 (3, s), and 1.26 (3, s, isopropylidene methyls); $J_{1',2'}$ = $J_{3',4'}$ = 0, $J_{2',3'}$ = 5.6, $J_{4',5'} \simeq J_{5',5} < 1$ Hz.

Anal. Calcd for $C_{13}H_{16}N_2O_8S$: C, 43.33; H, 4.48; N, 7.77. Found: C, 43.52; H, 4.48; N, 7.71.

B. A solution of **10** (200 mg) in 2-butanone (10 ml) containing triethylamine (0.2 ml) was refluxed for 4 h. Removal of solvent afforded a solid residue with an NMR spectrum identical with that of the **10**:**11** mixture obtained above.

5'-*O*-Acetyl-2',3'-*O*-isopropylidene-6,5'(*R*)-cyclouridine (13). A solution of **12** (900 mg) in pyridine (20 ml) was protected from moisture and refluxed for 24 h. The pale brown solution was then evaporated to dryness and residual pyridine was removed by codistillation with aqeous ethanol and then ethanol. The NMR spectrum of the residue in Me_2SO-d_6 showed a **12**:**13** ratio of 2:1. A solution of the residue in chloroform was applied to a column of silica gel G (Merck, 200 g, 4.5 × 40 cm) that had been packed under air pressure in benzene–ether[15] (1:1). The column was eluted with the same solvent pair, using air pressure to achieve a reasonable flow rate. Combination of the appropriate fractions afforded 402 mg of **12** (eluted from the

column first) and 226 mg of **13**. Attempts to recover **13** by fractional crystallization of fractions containing both **12** and **13** were unsuccessful. Chromatographically pure **13** (multiple development in ethyl acetate–benzene, 2:3) showed mp 240 °C (sinters), 248–251 °C; uv, pH 1 λ_{max} 271 nm, λ_{min} 236; NMR (Me_2SO-d_6, res 0.07 Hz) δ 11.55 (1, broad s, N^3 H, exchanges), 5.96 (1, s, H-1′), 5.70 (1, d, broadened by unresolved J_{5,N^3H}, H-5), 5.54 (1, three lines, H-5′), 4.92 (1, d, H-2′), 4.71 (1, d, H-3′), 4.54 (1, broadened s, H-4′), 2.10 (3, s, OAc), 1.40 (3, s), and 1.27 (3, s, isopropylidene methyls); $J_{1',2'} = 0$, $J_{2',3'} = 5.6$, $J_{3',4'} = 0$, $J_{4',5'} = J_{5',5} = 0.8$ Hz.

Anal. Calcd for $C_{14}H_{16}N_2O_7$: C, 51.85; H, 4.97; N, 8.64. Found: C, 51.64; H, 4.94; N, 8.48.

The NMR study of the interconversions of the 5′(*S*)-acetyl compound **12** and 5′(*R*)-acetyl compound **13** was performed as follows.

Each isomer (5 mg) was dissolved in 0.4 ml of pyridine-d_6 containing 5% D_2O. Spectra were recorded immediately and at various intervals after heating at 80 °C in an oil bath. Each spectrum was determined at 1250 Hz width using five 90 ° (23 μs) pulses with 15-s repetition time. The results are described in the text.

6,5′(*R*)-Cyclouridine (14). Compound **13** (100 mg, 0.31 mmol) was suspended in 30% hydrogen chloride in methanol (5 ml) and the mixture was stirred at room temperature. Solution was complete within 5 min, and TLC (EtOAc) showed complete loss of the 5′-acetyl group of **13** at 2 h. Water (0.5 ml) was added and the solution was stored until TLC showed hydrolysis of the 2′,3′-*O*-isopropylidene group to be complete (~5 h, total). The clear solution was concentrated to dryness and the residue was dried by repeated coevaporation of ethanol. The crystalline residue was suspended in ether, collected, and washed liberally with ether. This material (69 mg, 92%) is chromatographically pure and can be recrystallized with good recovery from water: mp 265 °C (sinters), 284–285 °C dec; uv, pH 1 λ_{max} 272 nm (ε 10 250), λ_{min} 235 (1450); pH 10.8 λ_{max} 272 (8100), λ_{min} 244 (4000); NMR (Me_2SO-d_6, res 0.15 Hz) δ 11.33 (1, broad s N^3 H exchanges), 6.17 (1, d, 5′-OH, exchanges), 5.76 (1, s, H-1′), 5.59 (1, d, H-5), 5.36 (1, d, 2′(3′)-OH exchanges), 5.18 (1, d, 3′(2′)-OH, exchanges), 4.24 (1, d, broadened by unresolved couplings, H-5′), 4.18 (1, s, broadened by unresolved couplings, H-4′), 4.0 (2, six-line m, H-2′ and H-3′), $J_{1',2'} = 0$, $J_{5',5'\text{-OH}} = 6.1$, $J_{2'(3'),2'(3')\text{OH}} = 5.5$, $J_{3'(2'),3'(2')\text{-OH}} = 5.8$, $J_{5,N^3\text{-H}} = 1.7$ Hz, $J_{4',5'}$ unresolved, $J_{5'5}$ unresolved. In Me_2SO-d_6 + D_2O, H-2′ and H-3′ given an AB system at δ 4.05 and 3.97 with $J_{2',3'} = 6.1$ Hz.

Anal. Calcd for $C_9H_{10}N_2O_6$: C, 44.63; H, 4.16; N, 11.57. Found: C, 44.58; H, 4.23; N, 11.52.

Registry No.—**1**, 36507-00-3; **5**, 36507-05-8; **6**, 59686-57-6; **7**, 59686-58-7; **8**, 59686-59-8; **9**, 59686-60-1; **10**, 59686-61-2; **11**, 59728-00-6; **12**, 59686-62-3; **13**, 59728-01-7; **14**, 59728-02-8; methanesulfonyl chloride, 124-63-0; acetic anhydride 108-24-7.

References and Notes

(1) This investigation was supported in part by funds from the American Cancer Society (Grant CH-38) and from the National Institutes of Health, U.S. Public Health Service (Grant 17085).

(2) For recent reviews on nucleoside and nucleotide conformation see (a) The Jerusalem Symposia on Quantum Chemistry and Biology, "Conformation of Biological Molecules and Polymers", Vol. V, E. D. Bergman and B. Pullman, Ed., Academic Press, New York, N.Y., 1973; (b) "Basic Principles in Nucleic Acid Chemistry", P. O. P. T'so, Academic Press, New York, N.Y., 1974; (c) M. Sundaralingham, *Ann. N.Y. Acad. Sci.*, **255**, 3 (1975).

(3) Reviews that stress the relationship between nucleoside–nucleotide conformation and biological activity include (a) D. C. Ward and E. Reich, *Annu. Rep. Med. Chem.* (1969); (b) W. Saenger, *Angew. Chem., Int. Ed. Engl.*, **12**, 591 (1972). Recent papers suggesting a relationship between conformation and the biological activities of 8-azaadenylic acid,[3c] 6-thiopurine ribonucleoside 5′-phosphate,[3d] and poly(formycin B)-poly(C) complexes[3e] are (c) C-H. Lee, F. E. Evans, and R. H. Sarma, *J. Biol. Chem.*, **250**, 1290 (1975); (d) F. E. Evans and R. H. Sarma, *J. Am. Chem. Soc.*, **97**, 3215 (1975); (e) P. T. Torrence, E. DeClercq, J. A. Waters, and B. Witkop, *Biochem. Biophys. Res. Commun.*, **62**, 658 (1975).

(4) (a) A. Holy, R. W. Bald, and F. Sorm, *Collect. Czech. Chem. Commun.*, **37**, 592 (1972); (b) A. Holy and R. W. Bald, *ibid.*, **36**, 2809 (1971); (c) A. M. Kapuler and E. Reich, *Biochemistry*, **10**, 4050 (1971); (d) A. M. Kapuler, C. Monny, and A. M. Michelson, *Biochem. Biophys. Acta*, **217**, 18 (1970); (e) J. Zemlicka, *J. Am. Chem. Soc.*, **97**, 5896 (1975).

(5) The D-allo (5′*R*) isomers simulate the gauche-trans conformation—that is, the 5′-OH group is gauche with respect to the sugar-ring oxygen and trans with respect to C-3′ in a Newman projection along the $C_{4'}$–$C_{5'}$ bond. The opposite case, namely trans-gauche, is simulated by the L-talo (5′*S*) isomers. In most nucleotides, both in solution and in the solid state, the gauche-gauche conformation predominates (5′-OH group gauche with respect to *both* C-3′ and the ring oxygen), but interestingly, the available low-resolution x-ray structures of nucleotide–enzyme complexes show gauche-trans and trans-gauche conformers. See ref 2c and references cited therein.

(6) These compounds are the pyrimidine counterparts of 8,5′-cycloadenosine, an anti purine cyclonucleoside with a similarly restricted range of sugar conformations. One of the 5′ epimers (unseparable) of the corresponding 8,5′-cycloadenylic acid participated efficiently in a variety of enzyme-catalyzed reactions that normally require adenylic acid. See A. Hampton, P. J. Harper, and T. Sakai, *Biochemistry*, **11**, 4965 (1972).

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(11) We assume that the desulfonyloxylation of **6** involves C–O bond cleavage to give **7** directly, but it is possible that the reaction proceeds by reduction of the 5,6 double bond of **6**, followed by base-catalyzed elimination of methanesulfonic acid from the resulting 5-mesyloxy-5,6-dihydrouracil nucleoside. Indeed, we have previously used a similar reduction–elimination procedure to prepare 1,3-dimethyl-6-propyluracil from 1,3-dimethyl-5-mesyloxy-6-propyluracil.[9] The only other example of reductive removal of a pyrimidine-5-hydroxyl group of which we are aware involves hydrogenolysis of uracil-5-(1-phenyltetrazoyl) ether.[9]

(12) Although the 5′(*S*)-acetyl compound **12** and the 5′(*S*)-mesyl ester **10** are prepared in pyridine, the conditions used are too mild (4 h, room temperature) to result in any appreciable 5′ epimerization. For similar reasons, the 6,5′(*S*)-cyclonucleoside **7** does not epimerize during its preparation in the presence of triethylamine; in addition, ionization of the 5′-hydroxyl group would probably inhibit epimerization.

(13) N_3 H will also be ionized under these conditions.

(14) (a) D. J. Cram, "Organic Chemistry", Vol. 4, A. T. Bloomquist, Ed., Academic Press, New York, N.Y., 1965; (b) D. J. Cram and J. M. Cram, *Intra-Sci. Chem. Rep.*, **7**, 1 (1973).

(15) Mallinckrodt USP grade ether, containing a maximum ethanol content of 3.5%.

Introduction of an Azide Group into Some Uridine Derivatives via 2′,3′-Benzoxonium and 2′,3′-Azidonium Intermediates

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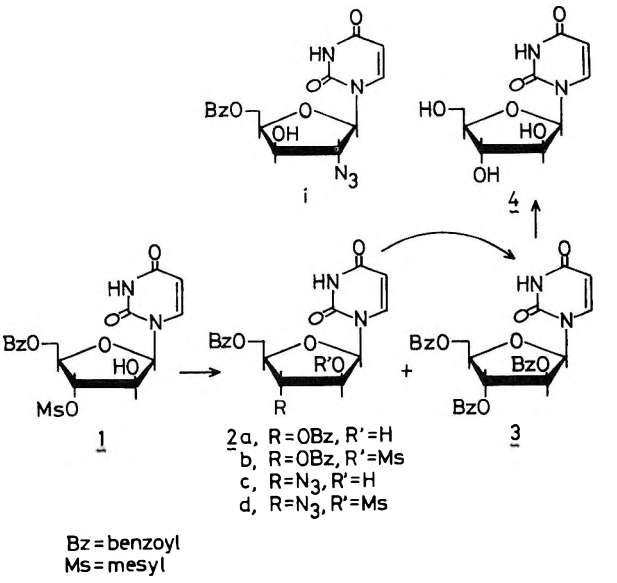
With a view to probing the reactions of supposed 2′,3′-benzoxonium (**5**) and 2′,3′-azidonium (**19**) intermediates with azide ion, their precursors, **2b** and **2d**, were synthesized. **2b** with azide ion gave 1-(2′-azido-2′-deoxy-3′,5′-di-*O*-benzoyl-β-D-ribofuranosyl)uracil (**7**) and its 3′-debenzoylated analogue (**8**). These were converted to the known compounds, **11a,b.** Treatment of 1-(2′-azido-2′-deoxy-5′-*O*-benzoyl-3′-*O*-mesyl-β-D-ribofuranosyl)uracil (**12**), obtained from **8**, with potassium *tert*-butoxide and sodium *p*-chlorobenzoate gave 1-(2′-azido-5′-*O*-benzoyl-2′,3′-dideoxy-β-D-glyceropent-2′-enofuranosyl)uracil (**14**) and 1-(5′-*O*-benzoyl-2′-*O*-*p*-chlorobenzoyl-3′-deoxy-2′,3′-imino-β-D-arabinofuranosyl)uracil (**15**), respectively. **2d** with azide ion gave 5′-*O*-benzoyl-2′,3′-dideoxy-2′,3′-diazidouridine (**21a**), which was converted to **21b** and the corresponding diamino compound (**22c**). 5′-*O*-Benzoyl-2′,3′-dideoxy-2′,3′-diamino compound (**22a**) obtained from **21a** was converted to a cyclic urea (**23**) for structural assignments of **21** and **22.** Some mechanistic comments are also presented.

Among the many known routes for the synthesis of amino nucleosides or their precursors, reactions of modified nucleosides with azide ion have attracted our recent concern, largely through the multiple aspects of an azide reaction[1] which would uniquely modify natural nucleosides.[2,25] In the pyrimidine series, nucleophilic ring openings of 2,2′-,[3] 2,3′-anhydro,[4] and 2′,3′-epoxy nucleosides[5] with amines and/or azide salts have been explored. However, we lack appropriate methods for introducing an "up" amino group into pyrimidine nucleosides[6] although in the adenine series up-side amination through an azide has been achieved in a few cases.[7] With respect to this point, a 2′,3′-ribo benzoxonium (Scheme II, **5**) or the corresponding azidonium cation intermediate (Scheme IV, **19**) deserves investigation as a possible acceptor of azide ion, since it is established that **5** can accept external benzoate anion at $C_{2'}$[8] or $C_{3'}$[9] from the "up" side, accompanied by a intramolecular reaction leading to a 2,2′-anhydro nucleoside. On the other hand, azidonium chemistry as a logical extension remains as yet to be explored in the nucleoside area, and appeared to assure a direct route to 2′,3′-diamino sugar nucleosides. Syntheses of this type of compounds were once proposed by Baker et al.[10] but have not yet been described. This paper describes the results of a synthetic study carried out using 1-(3′,5′-di-*O*-benzoyl-2′-*O*-mesyl-β-D-arabinofuranosyl)uracil (**2b**) and 1-(3′-azido-3′-deoxy-5′-benzoyl-2′-*O*-mesyl-β-D-arabinofuranosyl)uracil (**2d**) as precursors for the obligatory intermediates, **5** as well as **19.**

Syntheses of the Substrates, 2b and 2d, for Azide Reactions. 1-(3′,5′-Di-*O*-benzoyl-β-D-arabinofuranosyl)uracil (**2a**) was obtained from 1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (**1**)[5] by the known method.[8] This time, a minor by-product, 1-(2′,3′,5′-tri-*O*-benzoyl-β-D-arabinofuranosyl)uracil (**3**), was isolated by chromatography. The structure of **3** was based upon analysis, spectroscopic data (see Experimental Section and Table I), and deprotection to spongouridine (**4**). Appearance of an NH resonance at 9.10 ppm in its NMR spectrum excluded N-benzoylation. This compound has proved to be formed by reaction between **2a** and sodium benzoate.[11]

Similarly, treatment of **1** with a 2:1 mixture of sodium azide and ammonium chloride gave a TLC-homogeneous foam, the NMR spectrum of which exhibited two kinds of anomeric proton signals at 6.15 (¾ H, d, J = 3.9 Hz) and 5.83 ppm (¼ H, s), a H_5 signal at 5.90 ppm (d, $J_{5,6}$ = 8.0 Hz), and a $C_{5'}$-methylene signal at 4.2 ppm as a broad singlet. The resonances of the other sugar protons merged into a complex multiplet at a range of 4.4–5.0 ppm. This product was hence concluded to be a 4:1 mixture of 1-(3′-azido-3′-deoxy-5′-*O*-benzoyl-β-D-arabinofuranosyl)uracil (**2c**) and its xylo isomer (i), and was directly used for the next step. In this reaction, intermediacy of an 2′,3′-epoxy compound[5] was evidenced by TLC in a separate, time-controlled experiment. Mesylation of impure **2c** gave 1-(3′-azido-3′-deoxy-5′-*O*-benzoyl-2′-*O*-mesyl-β-D-arabinofuranosyl)uracil (**2d**) as crystals. These substrates were fully characterized spectroscopically.

Scheme I



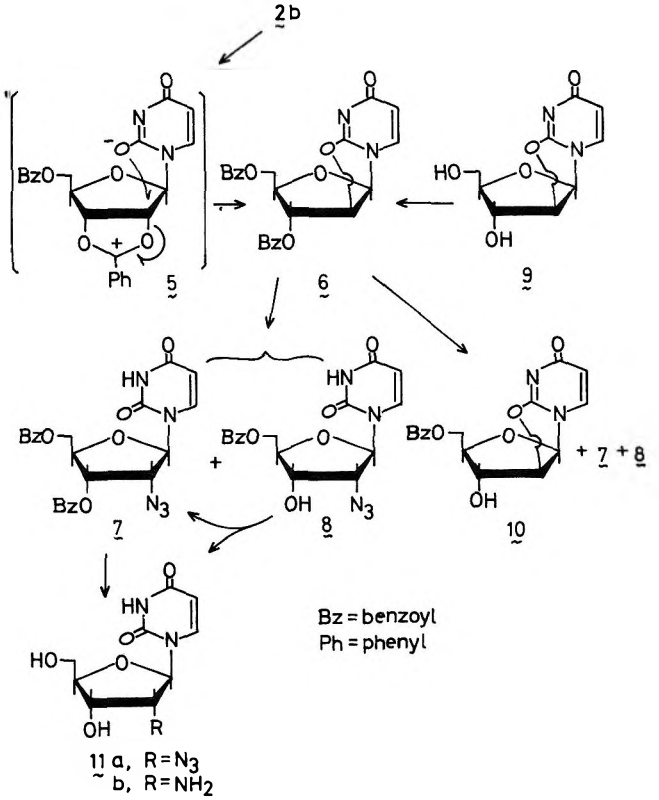
Reaction of 1-(3′,5′-Di-*O*-benzoyl-2′-*O*-mesyl-β-D-arabinofuranosyl)uracil (2b) with Azide Ion. After many trial experiments using sodium azide alone, sodium azide–ammonium chloride mixture in various molar ratios, and several temperature conditions, we chose the use of a large excess of a 3:2 mixture of sodium azide and ammonium chloride, and a reaction temperature of 120 °C. In all cases two primary products were detected by thin layer chromatography, and elongation of time or raising the temperature above 120 °C frequently caused deglycosidation and formation of a couple of secondary products, presumably by thermal decomposition of the introduced azide function.[12] It is to be noted that the use of a one to one mixture of the reagents at 120 °C retarded the reaction and consequently caused considerable deglycosidation in spite of the higher solubility in DMF of ammonium azide.[2] Thus, the selected reaction conditions described in this paper gave only the two primary products, 1-(2′-azido-2′-deoxy-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil (**8**) and 1-(2′-azido-2′-deoxy-3′,5′-di-*O*-benzoyl-

Table I. NMR Spectra of Uridine Derivatives[a-c]

Registry no.	Compd	$C_{5'}H$	$C_{4'}H$	$C_{3'}H$	$C_{2'}H$	$C_{1'}H$	C_5H	N_3H
4348-69-0	**3**[d]	4.82 (m)	4.50 (m)	5.60 (dd) $J_{2',3'}$ = 1.8 Hz $J_{3',4'} \simeq$ 3.0 Hz	5.82 (dd) $J_{1',2'}$ = 4.2 Hz $J_{2',3'}$ = 1.8 Hz	6.45 (d) $J_{1',2'}$ = 4.2 Hz	5.52 (dd) $J_{5,6}$ = 8.0 Hz $J_{5,NH}$ = 1.6 Hz	9.10 (br s)
59686-41-8	**2d**[f]	4.47–4.75 (m)		4.16 (m)	5.31 (dd) $J_{1',2'}$ = 5.0 Hz $J_{2',3'}$ = 4.0 Hz	6.16 (d) $J_{1',2'}$ = 5.0 Hz	5.58 (d) $J_{5,6}$ = 8.0 Hz	10.86 (br s)
26889-44-1	**7**[d]	4.54–4.88 (m)		5.50 (t) $J_{2',3'} = J_{3',4'}$ = 8.0 Hz	4.38 (dd) $J_{1',2'}$ = 4.5 Hz $J_{2',3'}$ = 6.0 Hz	5.96 (d) $J_{1',2'}$ = 4.5 Hz	5.54 (d) $J_{5,6}$ = 8.0 Hz	8.91 (br s)
59686-42-9	**8**[f]	4.20–4.75 (m)				5.77 (d) $J_{1',2'}$ = 4.3 Hz	5.52 (d) $J_{5,6}$ = 8.0 Hz	9.03 (br s)
31616-01-0	**6**[e]	4.36 (m)	4.81 (m)	5.74 (m) J = 6.0 and ca. 1.5 Hz		6.46 (d) $J_{1',2'}$ = 6.0 Hz	5.87 (d) $J_{5,6}$ = 8.0 Hz	
24877-18-7	**10**[e]		4.11–4.60 (m)		5.35 (d) $J_{1',2'}$ = 6.0 Hz	6.37 (d) $J_{1',2'}$ = 6.0 Hz	5.95 (d) $J_{5,6}$ = 8.0 Hz	
59686-43-0	**12**[d]	4.40–4.72 (m) (including $H_{2'}$)		5.33 (t) $J_{2',3'} = J_{3',4'}$ = 6.2 Hz		5.68 (d) $J_{1',2'}$ = 3.7 Hz	5.55 (d) $J_{5,6}$ = 8.0 Hz	9.57 (br s)
59686-44-1	**14**[d]	4.57 (t) $J_{1',5'}$ = 3.5 Hz	5.18 (o) $J_{4',5'} = J_{3',4'}$ = 3.5 Hz $J_{1',4'}$ = 1.6 Hz	6.82 (dd) $J_{1',3'}$ = 1.6 Hz $J_{3',4'}$ = 3.5 Hz		5.83 (t) $J_{1',3'} = J_{1',4'}$ = 1.6 Hz	5.38 (d) $J_{5,6}$ = 8.0 Hz	9.42 (br s)
59686-45-2	**21a**[f]	4.20–4.28 (m)				5.67 (d) $J_{1',2'}$ = 2.1 Hz	5.50 (d) $J_{5,6}$ = 8.0 Hz	10.77 (br s)
59686-46-3	**22a**[e]	3.10–3.65 (m) (in amino envelope)	4.0 (m)	4.50 (t) J = 5.2 and 3.0 Hz		5.65 (br s)	5.44 (d) $J_{5,6}$ = 8.0 Hz	*g*
59686-47-4	**24**[e]	3.80–4.20 (m)		4.55 (d) J = 5.3 Hz		6.10 (d) $J_{1',2'}$ = 5.3 Hz	5.42 (d) $J_{5,6}$ = 8.0 Hz	*g*

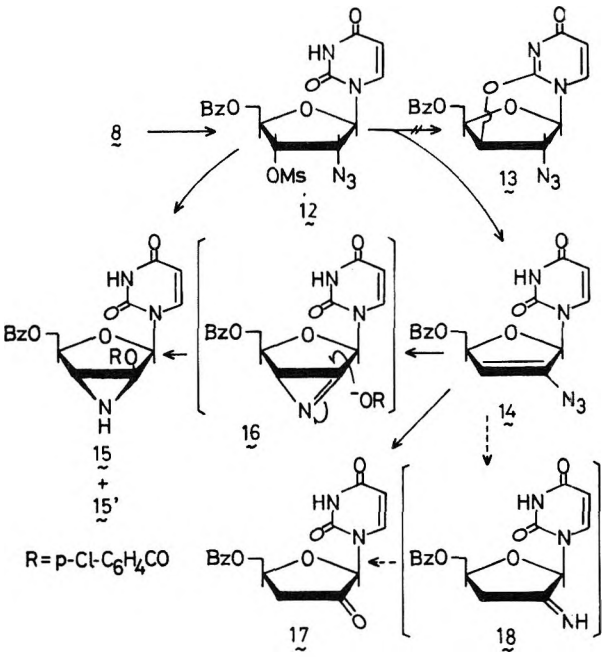
[a] The spectra of **3**, **7**, and **22a** were measured at 100 MHz, the others at 60 MHz. [b] (s) = singlet, (d) = doublet, (dd) = doublet of doublets, (t) = triplet, (o) = octet, (m) = multiplet. All these terms are used to refer to the apparent forms of splittings for the sake of visualization. Thus, for example, the t and dd for H_3, denote a similar ABX type resonance. [c] In most cases H_6 signals were overlayed on the benzoyl envelope and hence were omitted. [d] In $CDCl_3$. [e] In Me_2SO-d_6. [f] In a mixture of $CDCl_3$ and Me_2SO-d_6. [g] Did not appear clearly.

Scheme II

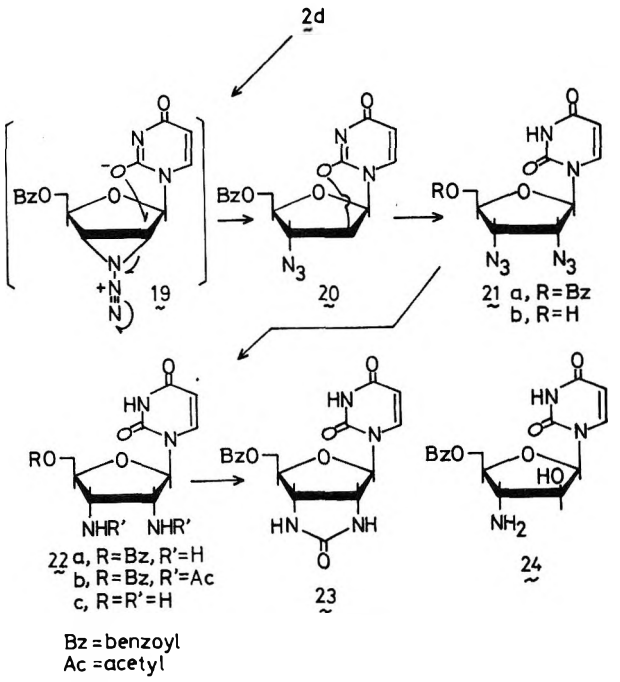


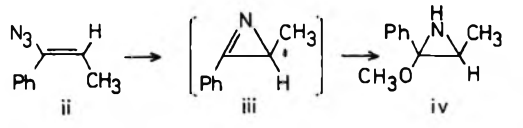
β-D-ribofuranosyl)uracil (**7**), in 53 and 16% yield, respectively, at the stage the starting material disappeared. Crystalline **7** exhibited uridine absorptions and well-resolved nuclear magnetic resonances[13] (see Table I). The resonance at 5.50 ppm was assigned to the benzoyloxy-deshielded $H_{3'}$, which interacted with 2′ and 4′ protons with the same coupling constant, 6.0 Hz, while the doublet of doublets at 4.38 ppm was reasonably assigned to the azido-shielded 2′ proton. However, these data failed to assign configurations at $C_{2'}$ and $C_{3'}$, since a survey of literature values[14] for $H_{1'}$–$H_{2'}$ coupling constants permits no definitive discrimination between ribo and arabino configurations. This situation also holds for all the compounds described in this paper. Nevertheless, the melting point, 156–157 °C, and the general resonance pattern strongly suggested its identity with a described substance,[3] and the structure was established by comparison with an authentic sample kindly provided by Dr. Moffatt.[15] The minor variations of the spectroscopic data would be explainable in terms of instrumental differences. The structure of noncrystalline **8** was confirmed by its conversion into **7** and conclusively by the experiments depicted in Scheme III. The ill-resolved NMR spectrum failed to locate the benzoyl group at this stage. Thus, the exclusive formation of the ribonucleosides, **7** and **8**, requires 2,2′-anhydro-1-(3′,5′-di-*O*-benzoyl-β-D-arabinofuranosyl)uracil (**6**), as the sole second intermediate. Since in our case no trace of **6** was detected by TLC, the molecules of **6** seem to have been intercepted as they formed and, accordingly, the major rate-determining step appears to be generation of the benzoxonium intermediate, **5**. Evidence for the intermediacy of **6** was obtained starting from an authentic preparation of **6** which was conveniently synthesized from 2,2′-anhydro-β-D-arabinofuranosyluracil (**9**).[3] Reaction of **6** with a 3:2 mixture of sodium azide and ammonium chloride under similar conditions gave **8** in a similar yield (60%) and

Scheme III



Scheme IV





a negligible amount of **7**, while the use of a 1:1 mixture afforded 2,2′-anhydro-1-(5′-*O*-benzoyl-β-D-arabinofuranosyl)uracil (**10**, 43%), **8** (18%), and **7** (15%). The structure of **10** was clear on the basis of analysis and spectroscopic data (see Experimental Section and Table I). The location of the benzoyloxy group was confirmed by the rather deshielded chemical shift of the $C_{5'}$ protons at the range of 4.11–4.60 ppm. Reasons for the formation of **10** and also of **8** are uncertain at present. It was consistently observed that **8** appeared slightly later than **7**, usually after a reaction time of 40–60 min, while **7** was detected after 20–30 min and persisted until the end of the reaction. Thus, an explanation for the genesis of **8** (**7** and/or **10**) requires another scrupulous study. Deprotection of **7** and **8** gave 2′-azido-2′-deoxyuridine (**11a**)[3] as a syrup, which was directly reduced to 2′-amino-2′-deoxyuridine (**11b**).[3] Attempted crystallization of **11b** was unsuccessful in our case.

At an earlier stage, we attempted to convert **8** into a 2,2′- or 2,3′-anhydro compound (**13**) for its structural elucidation, since it was expected that such a rigid system would give more convincing spectroscopic information, especially with respect to NMR spectroscopy. Accordingly, **8** was mesylated to 1-(2′-azido-2′-deoxy-5′-*O*-benzoyl-3′-*O*-mesyl-β-D-ribofuranosyl)uracil (**12**), the NMR spectrum of which showed the mesyl-deshielded 3′-proton signal at 5.33 ppm as a tripletlike ABX pattern (Table I). The absence of coupling of $H_{3'}$ with the anomeric proton firmly established the location of the hydroxyl in **8**. Treatment of **12** with potassium *tert*-butoxide caused no cyclization, but gave exclusively 1-(2′-azido-5′-*O*-benzoyl-2′,3′-dideoxy-β-D-glyceropent-2′-enofuranosyl)-uracil (**14**) as a syrup. Although **14** is rather unstable as is usual with common vinyl azides and therefore its repeated elemental analysis has failed to offer reasonable values, sufficient structural informations were given by NMR spectroscopy. Thus, in the spectrum of **14**, the $H_{4'}$ signal appeared at 5.18 ppm as an octetlike multiplet, $H_{1'}$ at 5.83 ppm (tripletlike long-range couplings), and $H_{3'}$ at 6.82 ppm (dd). These resonance patterns characteristic for 2′-substituted didehydro nucleosides have already been documented by us.[16] Heating **12** with sodium *p*-chlorobenzoate in DMF gave 1-(5′-*O*-benzoyl-2′-*O*-*p*-chlorobenzoyl-3′-deoxy-2′,3′-imino-β-D-arabinofuranosyl)uracil (**15**) and an unknown compound (**15′**). The structure of **15** was confirmed by 100-MHz NMR spectroscopy[13] (see Experimental Section). Thus, the broad, two-proton singlet at 3.30 ppm collapsed, on D_2O addition, to a one-proton doublet at 3.33 ppm with a small coupling constant (1.2 Hz). This should be assigned to an aziridine proton somewhat deshielded by one or both of the ester functions.[17] Appearance of the $H_{1'}$ signal as a singlet and the small $H_{3'}$–$H_{4'}$ coupling constant substantiate the proposed structure (**15**) with a "down" 2′,3′-imino function, in which the dihedral angle between $H_{3'}$ and $H_{4'}$ is quite close to 90°.[18] The formation of **15** is explainable by the reaction sequence **12** → **14** → **16** → **15**. This was also verified by a separate, tiny scale experiment using **14** and sodium *p*-chlorobenzoate.[23] In this case, **15** was detected by TLC as one of the two major products. Synthesis of analogous 2-methoxy-2-phenyl-3-methylaziridine (iv) from a vinyl azide (ii) via an azirine (iii) has been recorded by Hassner et al.[19]

Several trials of one-step reduction of **14** to a 2′-amino-2′,3′-dideoxynucleoside have been unsuccessful. Specifically, atmospheric pressure hydrogenation of **14** in the presence of palladium on charcoal gave 5′-*O*-benzoyl-3′-deoxy-2′-ketouridine (**17**),[16b] which must have resulted by hydrolysis of an intervening imine (**18**) during the reduction or the workup procedure.

Reaction of 1-(3′-Azido-3′-deoxy-5′-*O*-benzoyl-2′-*O*-mesyl-β-D-arabinofuranosyl)uracil (2d) with Azide Ion. Several trial experiments, conducted on small scales, revealed that the use of excess sodium azide at a temperature between 115 and 120 °C is preferable to the use of sodium azide–ammonium chloride mixtures to suppress deglycosidation to a minimum. Thus, reaction of **2d** with 4 molar equiv of sodium azide gave 1-(2′,3′-dideoxy-2′,3′-diazido-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil (**21a**) in 59% yield. Although a certain degree of deglycosidation was inevitable, no other notable side reactions were observed, provided purity of the starting material and the temperature condition just below 120 °C were

assured. The configurations of the azide groups could not be assigned by available spectroscopic methods but were finally established chemically. **21a** was deprotected to 1-(2′,3′-dideoxy-2′,3′-diazido-β-D-ribofuranosyl)uracil (**21b**), a syrup, which was directly hydrogenated to 1-(2′,3′-dideoxy-2′,3′-diamino-β-D-ribofuranosyl)uracil (**22c**). On the other hand, similar reduction of **21a** gave crystalline 1-(2′,3′-dideoxy-2′,3′-diamino-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil (**22a**) in a modest yield. To establish cis stereochemistry for the two amino groups, **22a** was heated with acetic anhydride merely to give 1-(2′,3′-dideoxy-2′,3′-diacetamido-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil (**22b**), but not a 2′,3′-cyclic acetamidine. However, **22a** with diphenyl carbonate provided the desired product, 1-(2′,3′-dideoxy-2′,3′-diamino-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil 2′,3′-carbonate (**23**), which was characterized by analysis, uv, and mass spectroscopy (see Experimental Section). If azide ion attacks **19** from the "up" side, there should be formed one or both of the two possible trans isomers (xylo and arabino derivatives), while there are no obvious, mechanistic reasons to support a cis lyxo configuration. In addition, a possibility of benzoyloxy rearrangement to $C_{2'}$ or $C_{3'}$ with concomitant introduction of an azide group at $C_{5'}$ is excluded, since in the NMR spectrum of **21a** the resonance of the $C_{5'}$ methylene occurred at an usually observed, ester-deshielded position, while those of the azido-shielded $H_{2'}$ and $H_{3'}$ were extensively shifted upfield to merge with $C_{4'}$ and $C_{5'}$ protons (Table I).

Circular dichroism spectra[20] of **22a** and 1-(3′-amino-3′-deoxy-5′-*O*-benzoyl-β-D-arabinofuranosyl)uracil (**24**) obtained from **2c** were measured and compared with the described values for uridine and spongouridine.[21] Although the arabino type amino nucleoside, **24**, exhibited an intense positive Cotton effect at 267 nm comparable with spongouridine, the corresponding molar ellipticity of **22a** is located between that of uridine and spongouridine, thus excluding direct configurational assignment at $C_{2'}$.

Thus, as in the case of the reaction of **2b**, a 2,2′-anhydro nucleoside, **20**, must have intervened and been immediately intercepted by azide ion. In both cases, it is highly improbable that azide ion directly attacks **2b** and **2d** from the bottom side extruding the leaving group at the secondary carbon atom.[22] This seems to be verified by the above observation that the reactions were retarded by the use of less basic ammonium azide,[2] which might have retarded production of the second intermediates (**6** and **20**). Although the desired "up" side introduction of an azide group was completely excluded, this work has introduced the new and important species, **14** and **15**, which would supply a variety of new entries into the chemistry of nucleosides. Moreover, synthesis of **21a** represents a successful synthetic use of neighboring group participation by an azide group and suggests interesting extensions to purine ribonucleoside derivatives.

Experimental Section[24]

Reaction of 1-(5′-*O*-Benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (1) with Sodium Benzoate. Synthesis of 2a, 3, and 4. A mixture of **1** (2.89 g, 6.79 mmol) and sodium benzoate (2.77 g, 19.22 mmol) in *N*,*N*-dimethylformamide (DMF, 48 ml) was stirred at 120–125 °C for 2 h. After cooling, the solvent was evaporated off and the residue thoroughly digested with ice–water (30 ml). The precipitate was collected by suction, dissolved in chloroform (100 ml), and dried over sodium sulfate and the solution evaporated to a gum, which was applied on a silica gel column (18 × 3 cm) and eluted with solvent B. The first, practically homogeneous fraction was recrystallized from a mixture of methanol and chloroform to give 360 mg (9.5%) of **3**: mp 203–205 °C; λ_{max} (MeOH) 235 nm (ε 48 900) and 259 (13 300).

Anal. Calcd for $C_{30}H_{24}N_2O_9$: C, 64.74; H, 4.35; N, 5.03. Found: C, 64.92; H, 4.49; N, 4.89.

A suspension of **3** (0.265 g, 0.477 mmol) in a mixture of methanol (12 ml) and concentrated ammonia (3 ml) was stirred at room temperature for 2 h, and the resulting solution left at room temperature for 38 h. The mixture was evaporated, and the residue coevaporated with ethanol several times and triturated with ethyl acetate (2 ml). The insoluble solid was collected, redissolved in ethanol (2 ml), treated with Norit, and again evaporated to give a syrup, which crystallized on scratching with ethanol. The ethyl acetate solution gave another crop. The combined product was recrystallized to give 93 mg (80%) of **4**, mp 219–222 °C (lit.[9a] 213–216 °C), identical with an authentic specimen in terms of infrared and ultraviolet spectroscopy.

The second fraction gave 2.04 g (66.5%) of **2a**, identical in all respects with an authentic sample.[8]

Reaction of 2a with Sodium Benzoate. A mixture of **2a** (0.2 g, 0.443 mmol) and sodium benzoate (159 mg, 1.12 mmol) in DMF (3 ml) was stirred at 120–125 °C for 2 h. The mixture was worked up similarly with the reaction between **1** and sodium benzoate to afford 35 mg (14%) of **3** and the starting material in unspecified yield after column chromatography using silica gel (14 × 1.5 cm) and solvent C. Increasing the amount of the basic catalyst did not significantly change the yield of **3**.

1-(3′-Azido-3′-deoxy-5′-*O*-benzoyl-β-D-arabinofuranosyl)uracil (2c). A mixture of **1** (1 g, 2.35 mmol), sodium azide (925 mg, 14.1 mmol), and ammonium chloride (380 mg, 7.1 mmol) in DMF (25 ml) was stirred at 105–110 °C for 1 h. After cooling, the inorganic materials were filtered off and the filtrate evaporated. The residue was quickly digested with a small amount of ice–water, neutralized with acetic acid, and partitioned between ethyl acetate (50 ml) and water (10 ml). The separated ethyl acetate solution was dried over sodium sulfate and evaporated to a practically homogeneous (in terms of TLC using solvent A, B, E, and F) foam (**2c** + i, total yield 0.774 g, 88%; NMR spectroscopically estimated yield of **2c** was ca. 66%), which was clearly distinguished from the starting material and intermediary 2′,3′-epoxy nucleoside[5] by TLC: ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 226 nm (ε 15 600) and 260 (10 300).

This product excluded crystallization or separation by available techniques, and hence was directly used for the next step.

1-(3′-Azido-3′-deoxy-5′-*O*-benzoyl-2′-*O*-mesyl-β-D-arabinofuranosyl)uracil (2d). To a solution of the above obtained mixture of **2c** and i (1.1 g, 2.95 mmol) (estimated amount of **2c** was 825 mg, 2.21 mmol) in pyridine (10 ml) was added at 0 °C methanesulfonyl chloride (0.37 ml, 4.4 mmol). The mixture was left at room temperature for 18 h, treated with methanol (3 ml) for 30 min, and evaporated. The pasty residue was dissolved in methanol (10 ml) and poured into ice–water (200 ml) under vigorous stirring. The precipitate was collected by suction, dissolved in ethyl acetate, and dried over sodium sulfate. After the solvent was evaporated, the residue was triturated with a small volume of solvent B to give crystals, which were collected. The filtrate was concentrated and again treated with the same solvent mixture to give another crop. The same procedure was repeated until the filtrate gave no more crystals. The final crop was obtained by silica gel column chromatography using the same solvent mixture. The combined product was recrystallized from a mixture of methanol and acetone to afford **2d** as granules of mp 160–162 °C: yield 64–68% (based on the estimated amount of **2c**); ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 231 nm (ε 15 700) and 259 (10 300).

Anal. Calcd for $C_{17}H_{17}N_5O_8S$: C, 45.24; H, 3.80; N, 15.52. Found: C, 45.16; H, 3.82; N, 15.30.

Reaction of 1-(3′,5′-Di-*O*-benzoyl-2′-*O*-mesyl-β-D-arabinofuranosyl)uracil (2b) with a Mixture of Sodium Azide and Ammonium Chloride (3:2, Molar Ratio). A mixture of **2b** (1.06 g, 2.0 mmol), sodium azide (390 mg, 6.0 mmol), and ammonium chloride (215 mg, 4.0 mmol) in DMF (15 ml) was stirred at 120 °C for 2 h. Further sodium azide (390 mg, 6.0 mmol) and ammonium chloride (215 mg, 4.0 mmol) were added, and the reaction was continued for another 2 h at the same temperature. After cooling, the inorganic materials were filtered off and the filtrate evaporated. The residue was taken into acetone (30 ml), neutralized with acetic acid, and filtered, and the filtrate was evaporated to a gum, which was shown by TLC (solvent E) to be a mixture of two products, the faster moving being the minor. The total was applied on a silica gel column (20 × 2 cm) and eluted with solvent B to give, from the faster moving fraction, a homogeneous syrup (**7**, 150 mg, 15.7%), which crystallized on prolonged drying at 50 °C and then at room temperature under high vacuum. A portion was recrystallized from a mixture of methanol and *n*-hexane to needles: mp 156–157 °C (lit.[3] 153–154 °C); ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 234 nm (ε 30 200) and 258 (12 500).

Anal. Calcd for $C_{23}H_{19}N_5O_7$: C, 57.86; H, 4.01; N, 14.67. Found: C, 58.02; H, 4.12; N, 14.49.

This sample was identified with an authentic sample[3] by mixed fusion, infrared, and ultraviolet spectroscopy.

The succeeding eluents gave 395 mg (53%) of **8** as a practically pure

foam, a portion of which was further purified by TLC using silica gel and solvent A for spectroscopic measurements and analysis: ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 231 nm (ϵ 14 200) and 261 (8800).

Anal. Calcd for $C_{16}H_{15}N_5O_6$: C, 51.47; H, 4.05; N, 18.76. Found: C, 51.73; H, 4.22; N, 18.49.

To a cooled solution of 8 (20 mg, 0.054 mmol) in pyridine (1 ml) was added benzoyl chloride (0.008 ml, 0.064 mmol). The mixture was left at 0 °C overnight, treated with 1 drop of water for 1 h at room temperature, and evaporated to a gum, which was taken into chloroform (10 ml) and dried over sodium sulfate. After evaporation of the solvent, the residue was heated in 95% pyridine (1 ml) at 95 °C for 1 h. After the solvent was evaporated off, the residue was repeatedly coevaporated with ethanol and applied on a silica gel column (1 × 13 cm). Elution with solvent B gave 20 mg (78%) of 7 as a syrup, which was brought to crystals by seeding, mp 157–159 °C, identical with the above obtained 7 in terms of mixed fusion, infrared, and ultraviolet spectroscopy.

2,2′-Anhydro-1-(3′,5′-di-*O*-benzoyl-β-D-arabinofuranosyl)uracil (6). To a stirred suspension of 9[3] (1.50 g, 6.63 mmol) in a mixture of DMF (25 ml) and pyridine (25 ml) was added benzoyl chloride (1.8 ml, 15.45 mmol). The mixture was stirred at room temperature overnight, treated with water (2 ml) for 30 min, and evaporated to give a solid residue, which was digested with ice–water (20 ml) and collected by suction. Recrystallization from acetonitrile gave 2.11 g (73%) of **6**: mp 275–277 °C (lit.[9a] 260–262 °C): λ_{max} (MeOH) 227 nm (ϵ 42 400) and 252 (11 000, sh).

Anal. Calcd for $C_{23}H_{18}N_2O_7$: C, 63.59; H, 4.17; N, 6.45. Found: C, 63.34; H, 4.37; N, 6.56.

Reaction of 2,2′-Anhydro-1-(3′,5′-di-*O*-benzoyl-β-D-arabinofuranosyl)uracil (6) with Azide Ion. Method A. A mixture of **6** (1.25 g, 2.88 mmol), sodium azide (565 mg, 8.64 mmol), and ammonium chloride (310 mg, 5.76 mmol) in DMF (20 ml) was stirred at 110–120 °C for 10 h. After cooling, the inorganic materials were filtered off and the filtrate evaporated to give a syrupy residue, which was partitioned between ethyl acetate (100 ml) and water (20 ml). The ethyl acetate extract was worked up as usual and applied on a silica gel column. Elution with solvent B gave 640 mg (60%) of 8 as a homogeneous foam, identified with an authentic sample of 8 by infrared and ultraviolet spectroscopy. A negligible amount of **7** was also obtained from the faster moving fractions.

Method B. A mixture of **6** (220 mg, 0.51 mmol), sodium azide (165 mg, 2.50 mmol), and ammonium chloride (135 mg, 2.50 mmol) in DMF (4 ml) was stirred at 110 °C for 26 h. TLC (silica gel and solvent F, twice developed) indicated the disappearance of the starting material and formation of three products. After cooling, the insolubles were filtered off and the filtrate evaporated to a paste, which was partitioned between chloroform (50 ml) and water (15 ml). The separated chloroform layer was worked up as usual and chromatographed on a silica gel column (2 × 15 cm) using solvent B to give 35 mg (15%) of **7** and 35 mg (18%) of **8**. These were identified with the above obtained authentic samples in all respects.

On the other hand, concentration of the aqueous layer afforded a crystalline precipitate, which was collected and recrystallized from methanol to give 75 mg (43%) of **10** as colorless needles: mp 201–202.5 °C; λ_{max} (MeOH) 227 nm (ϵ 21 700) and 251 (8500, inflection).

Anal. Calcd for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 9.25. Found: C, 58.01; H, 4.24; N, 8.97.

1-(2′-Azido-2′-deoxy-β-D-ribofuranosyl)uracil (11a). Compound **7** (350 mg, 0.94 mmol) in a mixture of methanol (6 ml) and concentrated ammonium hydroxide (2 ml) was stirred at room temperature overnight. The mixture was evaporated and the residue repeatedly coevaporated with ethanol and then chromatographed on a silica gel plate (20 × 20 cm, 2 mm thick) using solvent F. Elution of the main band with acetone gave 170 mg (67%) of a homogeneous syrup, ir (KBr) νN_3 2120 cm^{-1}. This substance, obtainable also from **8**, resisted crystallization, and was hence directly used for the next step.

1-(2′-Amino-2′-deoxy-β-D-ribofuranosyl)uracil (11b). Compound **11a** (170 mg, 0.63 mmol) with 10% palladium on charcoal (70 mg) in methanol (30 ml) was stirred under hydrogen (1 atm) at room temperature overnight. The catalyst was filtered off and the filtrate evaporated to a syrup, which resisted crystallization. The total was dissolved in ethanol (5 ml), acidified with saturated hydrogen chloride solution in dioxane (0.5 ml), and then evaporated to give a crystalline solid, which was recrystallized from methanol to afford 100 mg (57%) of the hydrochloride of **11b**: mp 245–247 °C; λ_{max} (MeOH) 260 nm (ϵ 9350); mass spectrum *m/e* 244 $(M - HCl + H)^+$, 243 $(M - HCl)^+$, 132 $(M - HCl - base)^+$, 131 $(M - HCl - uracil)^+$, 112 (uracil).

Anal. Calcd for $C_9H_{13}N_3O_5 \cdot HCl$: C, 38.65; H, 5.05; N, 15.02. Found: C, 38.82; H, 5.06; N, 14.94.

1-(2′-Azido-2′-deoxy-5′-*O*-benzoyl-3′-*O*-mesyl-β-D-ribofuranosyl)uracil (12). To a stirred ice-cold solution of **8** (640 mg, 1.72 mmol) in pyridine (8 ml) was added methanesulfonyl chloride (0.16 ml, 2.06 mmol). The mixture was left at 0 °C overnight, treated with methanol (2 ml) at room temperature for 30 min, and evaporated. The residue was partitioned between ethyl acetate (60 ml) and water (20 ml). The separated ethyl acetate layer was worked up as usual and chromatographed on a silica gel column (20 × 2.5 cm) using solvent B to give 600 mg (77%) of **12** as a homogeneous foam. A portion of this product was further purified by TLC using the same solvent mixture for analysis: ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 229 nm (ϵ 14 500) and 257 (10 100).

Anal. Calcd for $C_{17}H_{17}N_5O_8S$: C, 45.24; H, 3.80; N, 15.52. Found: C, 45.55; H, 4.05; N, 15.24.

1-(2′-Azido-5′-*O*-benzoyl-2′,3′-dideoxy-β-D-glyceropent-2′-enofuranosyl)uracil (14). Potassium *tert*-butoxide (630 mg, 5.62 mmol) was added in portions to an ice-cold, stirred solution of **12** (1.01 g, 2.24 mmol) in dry tetrahydrofuran (THF, 15 ml). The mixture was stirred at 0 °C for 40 min, left at −20 °C overnight, and carefully neutralized with acetic acid. The mixture was evaporated below 35 °C and the residue partitioned between ethyl acetate (60 ml) and water (20 ml). The separated organic layer was dried over sodium sulfate and evaporated and the obtained paste was chromatographed on a silica gel column (2.5 × 13 cm) with use of solvent B to give 520 mg (64%) of **14** as a homogeneous foam: ir (KBr) νN_3 2130 cm^{-1}; λ_{max} (MeOH) 230 nm (ϵ 21 200) and 258 (13 600, sh).

Reaction of 12 with Sodium *p*-Chlorobenzoate. A mixture of **12** (600 mg, 1.43 mmol) and sodium *p*-chlorobenzoate (355 mg, 1.98 mmol) in DMF (10 ml) was stirred at 90 °C for 2.5 h. Additional sodium *p*-chlorobenzoate (355 mg, 1.98 mmol) was added and the reaction continued for another 2 h. TLC at this stage, using silica gel and solvent A and E, indicated two main products in approximately equal amounts and no starting material. The mixture was evaporated and the residue digested with ice–water (15 ml) to give a precipitate, which was collected by suction, dried, and chromatographed on a silica gel column (1.6 × 22 cm) using solvent D. The first, crystalline fraction gave 115 mg (16.7%) of **15** as colorless needles of mp 170–172 °C after recrystallization from methanol: λ_{max} (MeOH) 237 nm (ϵ 31 700) and 261 (15 300); NMR (Me_2SO-d_6) δ 3.30 (2 H, br s, NH and $H_{3'}$, reduced to one proton d at 3.33 ppm on D_2O addition, $J_{3',4'}$ = 1.2 Hz, $H_{3'}$), 4.44–4.58 (2 H, br d, J = 4.2 Hz, 5′-CH_2), 4.58–4.77 (1 H, broad complex multiplet, $H_{4'}$), 5.67 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 6.44 (1 H, s, $H_{1'}$), 7.40–7.70 (5 H, m, aryl protons), 7.85–8.10 (5 H, m, H_6 and aryl protons), and 11.30 (1 H, br s, N_3H, D_2O exchangeable).

Anal. Calcd for $C_{23}H_{18}N_3O_7Cl$: C, 57.09; H, 3.75; N, 8.68. Found: C, 57.10; H, 3.97; N, 8.65.

The second fraction gave 180 mg of TLC-homogeneous syrup (**15′**), the infrared spectrum of which exhibited a weak absorption at 2130 cm^{-1} suggesting contamination by **14**. Rechromatography did not result in further purification.

Catalytic Reduction of 14. A solution of **14** (205 mg, 0.58 mmol) in methanol (25 ml) containing 10% palladium on charcoal (50 mg) was stirred under hydrogen (1 atm) for 6 h at room temperature. The catalyst was filtered off and the filtrate evaporated to a gum, which was applied on a silica gel column (1 × 15 cm) and eluted with solvent B to give 100 mg (55%) of **17** after recrystallization from methanol, mp 192–194 °C. Identity with an authentic sample[16b] was confirmed by mixed fusion, infrared, and ultraviolet spectroscopy.

1-(2′,3′-Dideoxy-2′,3′-diazido-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil (21a). A mixture of **2d** (660 mg, 1.46 mmol) and sodium azide (380 mg, 5.8 mmol) in DMF (7 ml) was stirred at 115–120 °C for 4.5 h. TLC using silica gel, solvent A and/or E revealed that almost all the starting material was consumed and a faster moving substance formed with a slight amount of uracil. The mixture was evaporated, digested with a small volume of ice–water, neutralized with acetic acid, and partitioned between ethyl acetate (70 ml) and water (20 ml). The ethyl acetate solution was dried over sodium sulfate and evaporated to give a glass, which crystallized on standing overnight with a few drops of methanol. The crystals were collected and the mother liquor evaporated to a tar, which was chromatographed on a silica gel column (1.5 × 20 cm) using solvent B to give another crop. The combined crops were recrystallized from methanol to afford 310 mg (59%) of **21a**: mp 166–167 °C; ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 228 nm (ϵ 16 900) and 259 (11 300).

Anal. Calcd for $C_{16}H_{14}N_8O_5$: C, 48.24; H, 3.54; N, 28.13. Found: C, 48.19; H, 3.70; N, 27.97.

1-(2′,3′-Dideoxy-2′,3′-diazido-β-D-ribofuranosyl)uracil (21b). Compound **21a** (400 mg, 1.01 mmol) in a mixture (16 ml) of methanol and concentrated ammonium hydroxide (3:1) was stirred at room temperature overnight. After the solvent was evaporated, the residue

was repeatedly coevaporated with ethanol to remove residual water, charged on a silica gel plate (20 × 20 cm, 2 mm thick), and developed with solvent G. Elution of the main band gave 210 mg (71%) of **21b** as a homogeneous foam. This compound resisted crystallization and was hence directly used for the next step.

1-(2′,3′-Dideoxy-2′,3′-diamino-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil (22a). A mixture of **21a** (517 mg, 1.3 mmol) in methanol (100 ml) was stirred in a hydrogen atmosphere with 10% palladium on charcoal (150 mg) overnight. The mixture was filtered to give a glass, which crystallized from a mixture of ethanol and methanol. Recrystallization from ethanol gave 200 mg (44%) of **22a** as needles: mp 103–105 °C; λ_{max} (MeOH) 224 nm (ε 16 400) and 261 (11 000); CD (MeOH) Cotton effects θ (nm) −11 900 (240) and +14 900 (267).

Anal. Calcd for $C_{16}H_{18}N_4O_5$: C, 55.48; H, 5.24; N, 16.18. Found: C, 55.57; H, 5.32; N, 16.01.

1-(2′,3′-Dideoxy-2′,3′-diacetamido-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil (22b). A mixture of **22a** (90 mg, 0.26 mmol) and acetic anhydride (2 ml) was heated at 100 °C for 1 h and then cooled with ice–water. Methanol (2 ml) was added and the total was left at 0 °C for 1 h and then at room temperature for a couple of hours. Evaporation of the solvent gave a syrup, which crystallized on scratching with a few drops of ethyl acetate. Recrystallization from a mixture of methanol and ethanol gave 70 mg (62.5%) of **22b**: mp 160–162 °C; λ_{max} (MeOH) 224 nm (ε 16 600) and 259 (11 300).

Anal. Calcd for $C_{20}H_{22}N_4O_7 \cdot CH_3OH$: C, 54.53; H, 5.62; N, 12.11. Found: C, 54.28; H, 5.55; N, 12.36.

1-(2′,3′-Dideoxy-2′,3′-diamino-β-D-ribofuranosyl)uracil (22c). A solution of **21b** (200 mg, 0.8 mmol) in ethanol (50 ml) was stirred in a hydrogen atmosphere with 10% palladium on charcoal (100 mg) for 5 h. The mixture was filtered and evaporated to a glass, which was charged on a silica gel plate (20 × 10 cm) and developed twice with solvent E to remove small amounts of faster moving impurities. Elution of the main band with ethanol and evaporation of the solvent gave a homogeneous glass, which resisted crystallization. The total was dissolved in dry methanol (7 ml), treated with Norit, concentrated to ca. 3 ml, and precipitated into vigorously stirred dry ether (30 ml). The precipitate was collected by centrifugation and dried at 50 °C under high vacuum to give a rather hygroscopic foam, yield 66 mg (40%), λ_{max} (MeOH) 260 nm (ε 9100).

Anal. Calcd for $C_9H_{14}N_4O_4$: C, 44.62; H, 5.83; N, 23.13. Found: C, 44.62; H, 5.57; N, 22.85.

1-(2′,3′-Dideoxy-2′,3′-diamino-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil 2′,3′-Carbonate (23). A mixture of **22a** (100 mg, 0.29 mmol) and diphenyl carbonate (80 mg, 0.37 mmol) in DMF (8 ml) was stirred at 125–130 °C for 4 h. An aliquot was withdrawn, evaporated, and examined by TLC (silica gel, solvent G) to show no starting material and two other faster moving spots, one of which being that of diphenyl carbonate. The mixture was evaporated, charged on a silica gel plate (20 × 20 cm, 2 mm thick), and developed with solvent G. The desired portion was eluted with ethanol and the solvent evaporated off to leave an amorphous powder, which was dissolved in methanol (2 ml) and treated with Norit. The methanol solution was concentrated to a minimum volume and left at room temperature for a couple of days to effect very slow crystallization: mp 250–252 °C; yield 20%; λ_{max} (MeOH) 226 nm (ε 14 800) and 259 (11 000); mass spectrum *m/e* 261 (M − uracilyl)$^+$, 262 (M − uracilyl + H)$^+$, 111 (uracilyl)$^+$ and 112 (uracil)$^+$.

Anal. Calcd for $C_{17}H_{16}N_4O_6$: C, 54.84; H, 4.33; N, 15.05. Found: C, 54.57; H, 4.62; N, 14.85.

1-(3′-Amino-3′-deoxy-5′-*O*-benzoyl-β-D-arabinofuranosyl)uracil (24). A mixture of the above obtained impure **2c** (0.2 g) and 10% palladium on charcoal (100 mg) in ethanol (30 ml) was stirred in a hydrogen atmosphere overnight. After the usual workup and preparative TLC (silica gel and solvent F), 0.1 g (ca. 66% based on pure **2c**) of **24** was obtained as fine needles: mp 238–239 °C (MeOH); λ_{max} (MeOH) 227 nm (ε 20 800) and 262 (14 500); CD (MeOH) Cotton effects θ (nm) −11 100 (238) and +22 400 (267).

Anal. Calcd for $C_{16}H_{17}N_3O_6$: C, 55.33; H, 4.93; N, 12.10. Found: C, 55.15; H, 5.02; N, 11.85.

Registry No.—**1**, 55263-52-0; **2a**, 55263-53-1; **2b**, 18743-34-5; **2c**, 58540-97-9; **9**, 3736-77-4; **11a**, 26929-65-7; **11b**, 26889-39-4; **15**, 59710-47-3; **17**, 38359-55-6; **21b**, 59686-48-5; **22b**, 59686-49-6; **22c**, 59686-50-9; **23**, 59686-51-0; i, 59686-52-1; sodium benzoate, 532-32-1; sodium azide, 26628-22-8; methanesulfonyl chloride, 124-63-0; benzoyl chloride, 98-88-4; sodium *p*-chlorobenzoate, 3686-66-6; acetic anhydride, 108-24-7; diphenyl carbonate, 102-09-0.

References and Notes

(1) S. Patai, Ed., "The Chemistry of Azido Group", Interscience, New York, N.Y., 1970.
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(5) J. F. Codington, R. Fecher, and J. J. Fox, *J. Org. Chem.*, **27**, 163 (1962).
(6) In a pyrimidine nucleoside with a "down" 2′,3′-epoxy function, intramolecular nucleophilic displacement by 2 oxygen preferably occurs to give an 2,2′-anhydro nucleoside: (a) M. Hirata, T. Kobayashi, and T. Naito, *Chem. Pharm. Bull.*, **17**, 1188 (1969); (b) T. Ueda and S. Shibuya, *ibid.*, **22**, 930 (1974).
(7) (a) E. J. Reist, D. F. Calkins, and L. Goodman, *J. Org. Chem.*, **32**, 2538 (1967); (b) M. J. Robins, Y. Fouron, and R. Mengel, *ibid.*, **39**, 1564 (1973).
(8) T. Sasaki, K. Minamoto, and H. Suzuki, *J. Carbohydr., Nucleosides, Nucleotides*, **1**, 337 (1974).
(9) (a) J. F. Codington, R. Fecher, and J. J. Fox, *J. Am. Chem. Soc.*, **82**, 2794 (1960); (b) J. J. Fox and K. A. Watanabe, *Chem. Pharm. Bull.*, **17**, 211 (1969).
(10) B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1047 (1964).
(11) That compound 3 forms by a base-catalyzed disproportionation mechanism from two molecules of **2a** was evidenced in separate experiments, which will be described elsewhere.
(12) A trial experiment has shown that a sample of 5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneuridine smoothly decomposes at 115–120 °C during several hours to give highly insoluble polymer-like products.
(13) The measurement was carried out at 100 MHz by Takeda Chemical Industries, Co., Ltd., for which we are grateful.
(14) $J_{1',2'}$ values shown by compounds with or without an azide group seem to vary extensively between 3 and 7 Hz, depending upon the differences of substituents or protecting groups, irrespective of the configurations. For example, see ref 3 and 7*a*.
(15) We thank Dr. Moffatt for a generous gift of authentic samples of **8** and **12b**.
(16) (a) T. Sasaki, K. Minamoto, and S. Tanizawa, *J. Org. Chem.*, **38**, 2896 (1973); (b) T. Sasaki, K. Minamoto, and K. Hattori, *ibid.*, **38**, 1283 (1973).
(17) An appropriate literature analogue is not available for comparison.
(18) A structure with an "up" 2′,3′-imino group requires ca. 20° as $H_{3'}$–$H_{4'}$ dihedral angle. In addition, the presence of NH and absence of any olefinic proton preclude a valence isomer with a six-membered ring.
(19) A. Hassner and F. W. Fowler, *J. Am. Chem. Soc.*, **90**, 2869 (1968).
(20) We are indebted to Dr. H. Ogura and his group, Kitazato University, Tokyo, for the measurements, for which a JASCO Model J-20 recording spectropolarimeter was used.
(21) Uridine, θ −4000 (240 nm) and +9200 (267 nm); spongouridine, θ −6500 (235 nm) and +22 000 (266 nm) [D. W. Miles, W. H. Inskeep, M. J. Robins, M. W. Winkley, R. K. Robins, and H. Eyring, *J. Am. Chem. Soc.*, **92**, 3872 (1970)].
(22) Considerable efforts may have been devoted to exploration of such direct (without neighboring group participation) substitutions at $C_{2'}$ and $C_{3'}$ in nucleosides, but there seems to have been no successful case.
(23) This reagent is more soluble in DMF than sodium benzoate.
(24) The general methods used are similar to those described earlier.[2] Melting points were obtained on a Yanagimoto micromelting point apparatus and are not corrected. All evaporations were conducted in vacuo at or below 40 °C. Solvent mixtures used for column and thin layer chromatography are as follows: $CHCl_3$/EtOAc, 1:1 (v/v) (solvent A), 3:1 (B), 4:1 (C), 5:1 (D); $CHCl_3$/MeOH, 9:1 (v/v) (E); 20% EtOH/benzene, F; 30% EtOH/benzene, G. These are designated as solvent A, B, C, etc., in all cases.
(25) **Note Added in Proof.** In a very recent issue of this journal, Robins et al. corrected the mechanism for the conversion[2] of $O^2 \rightarrow 2'$-anhydro-1-(5-*O*-benzoyl-3-*O*-methanesulfonyl-β-D-arabinofuranosyl)uracil to the corresponding $N^3 \rightarrow 3'$-anhydro-2-amino-1-(5-*O*-benzoyl-3-deoxy-β-D-lyxofuranosyl)-4-pyrimidinone [*J. Org. Chem.*, **41**, 1886 (1976)].

Synthesis of Sesquiterpene Antitumor Lactones. 6.[1] *cis*-8a-Vinyloctahydro-3*H*-2-benzopyran-3,7-dione, a Precursor to Vernolepin

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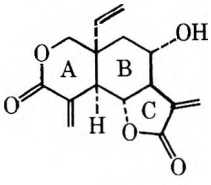
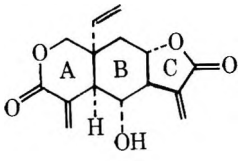
Received March 24, 1976

An efficient six-stage synthesis of bicyclic keto lactone **5**, a valuable intermediate for conversion into analogues of the sesquiterpene antitumor lactone vernolepin, has been developed.

The sesquiterpene antitumor lactone vernolepin (**1**)[2] and its congener vernomenin (**2**) have elicited considerable synthetic attention. Several groups have reported interesting syntheses of the prototype α-methylenevalerolactone **3**,[3-6] which has been shown to possess mildly cytotoxic properties,[4b] and we have applied the Norton cyclocarbonylation process[7] to a synthesis of the prototype α-methylenebutyrolactone **4**.[1]



1



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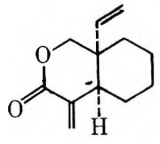

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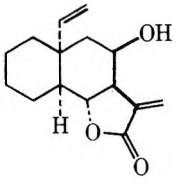
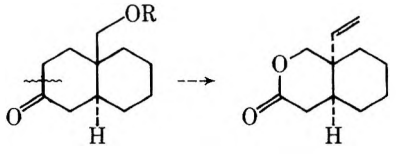
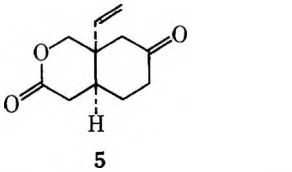


4

Grieco[8] and Danishefsky[9] have recently reported total syntheses which yield vernolepin and vernomenin in ratios of 3:1 and 2:1, respectively.

To date, most of the synthetic approaches have involved elaboration of the cis-fused δ-valerolactone system by scission of the C_2–C_3 bond of an angularly functionalized *trans*-bicyclo[4.4.0]decane. In this paper, we report a completely different approach to this problem in the synthesis of keto lactone **5**, a promising intermediate for further elaboration into natural products **1** and **2**, as well as analogues of these interesting compounds.

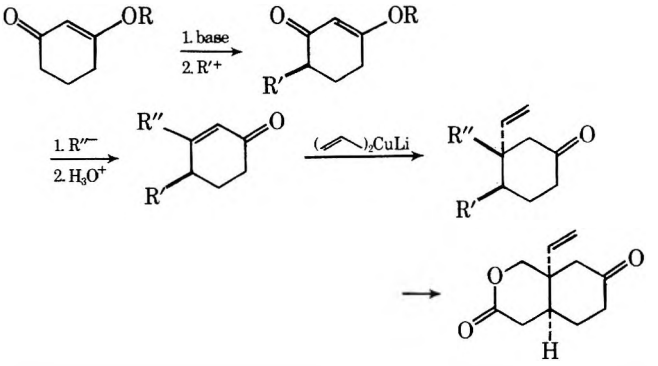


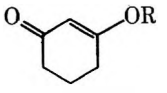


5

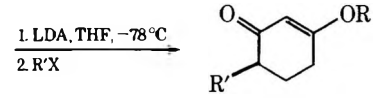
Our basic synthetic plan is outlined below, where R′ is a synthon for an acetic acid unit, $-CH_2COOH$, and R″ is a synthon for a hydroxymethyl unit, $-CH_2OH$. In our plan, R′ would be added as an electrophile and R″ as a nucleophile.

As a starting material for our work, we have used the 1,3-cyclohexanedione enol ethers **6**[10] and **7**.[11] Alkylation of the kinetic enolate, following the procedure of Danheiser and Stork,[12] with a variety of alkyl halides affords compounds **8**–**12** in yields of 55, 99, 98,[12] 81, and 90%, respectively. Each of the R′ groups are, in principle, convertible to acetic acid side chains by either hydrolysis or oxidation.





6, R = CH_2CH_3
7, R = $CH_2CH(CH_3)_2$



8, R = $CH_2CH(CH_3)_2$; R′ = $CH_2CO_2C_2H_5$
9, R = CH_2CH_3; R′ = $CH_2CO_2C(CH_3)_3$
10, R = $CH_2CH(CH_3)_2$; R′ = $CH_2CH{=}CH_2$
11, R = CH_2CH_3; R′ = $CH_2CH{=}CHCH_3$
12, R = CH_2CH_3; R′ = $CH_2CH{=}C(CH_3)_2$

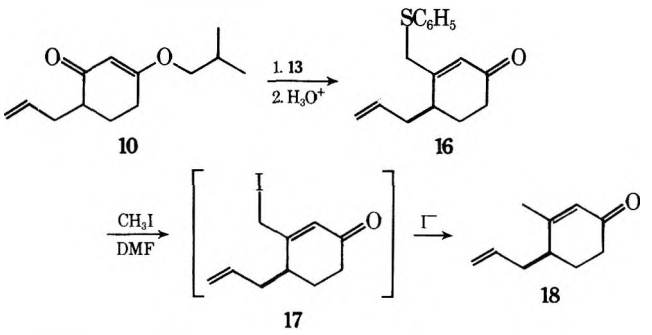
As masked hydroxymethyl groups, we initially explored the use of phenylthiomethyllithium (**13**),[13] methylthiomethyllithium (**14**),[14] and methoxymethylmagnesium chloride (**15**).[15]

$C_6H_5SCH_2Li$	CH_3SCH_2Li	CH_3OCH_2MgCl
13	**14**	**15**

We soon discovered that organometallic reagents **13**–**15** are not suitable for the introduction of a one-carbon unit into compounds **8** or **9**. For example, treatment of keto ester **8** with lithium reagent **13** gave only recovered starting material, even under conditions which have been used for the reaction of compound **13** with other esters and ketones.[13b] It may be that keto ester **8** undergoes exclusive enolization, due to the inductive effect of the second carbonyl group. On the other hand, Grignard reagents such as **15** react indiscriminately at both carbonyl groups, even with *tert*-butyl ester **9**.

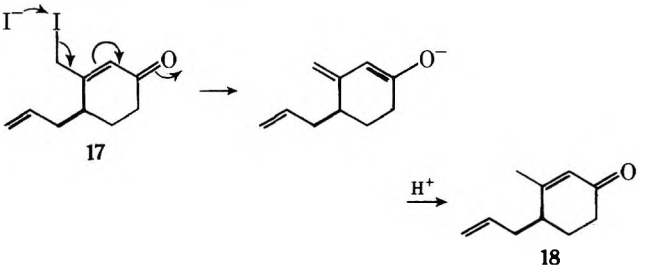
Therefore, we turned our attention to allylated enol ether **10**. This material reacts smoothly with phenylthiomethyllithium (**13**) to give sulfide **16**, after hydrolysis of the initial adduct with dilute aqueous acid. However, an attempt to re-

place the phenylthio group by iodo, following Corey's procedure (CH_3I, NaI in DMF or DMA),[16] gave enone **18** in nearly



10 16 17 18

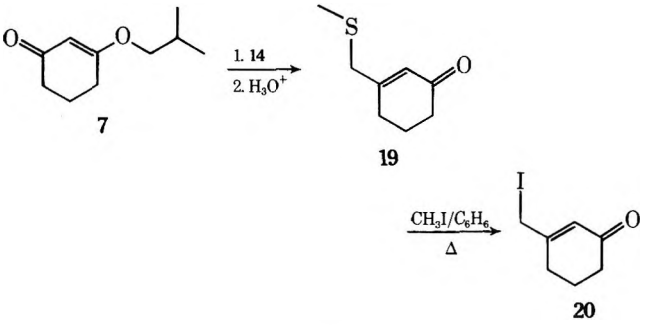
quantitative yield. Presumably, iodide **17** is an intermediate in the conversion of **16** to **18**. It is probably deiodinated by iodide ion by the following process:



17 18

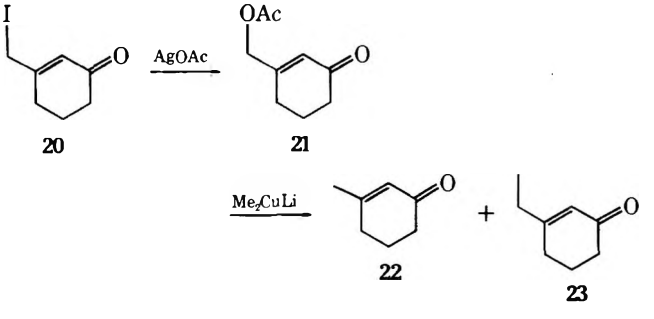
However, even the iodide produced in the initial methylation reaction is sufficient to reduce **17**, for the same result is obtained when sodium iodide is omitted from the reaction mixture.

We reasoned that if we could cause the conversion of **16** to **17** to occur more rapidly, relative to the annoying reduction of **17**, we might realize the selective synthesis of this compound. Since the rate-limiting step in the conversion of **16** to **17** is probably methylation of the sulfur, we turned to the more basic methylthio group. As a model, enol ether **7** was allowed to react with methylthiomethyllithium (**14**) to obtain sulfide **19**. Our anticipation was realized when we found that iodide **20** is produced in yields of up to 90% by refluxing sulfide **19** in a 1:1 mixture of methyl iodide and benzene for 20 h.



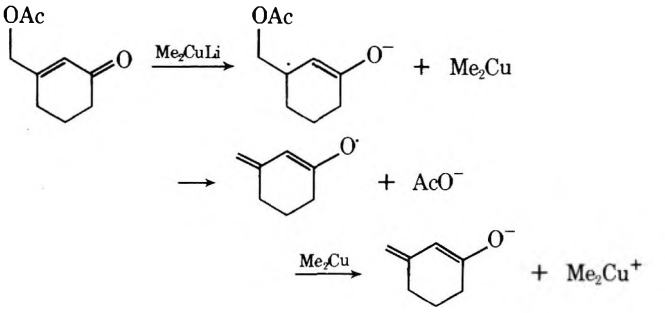
7 19 20

Treatment of iodide **20** with silver acetate yields acetate **21**. Unfortunately, this material reacts with lithium dimethylcuprate (a model for our planned vinylation process) to yield mainly the reduced enone **22**, accompanied by approximately



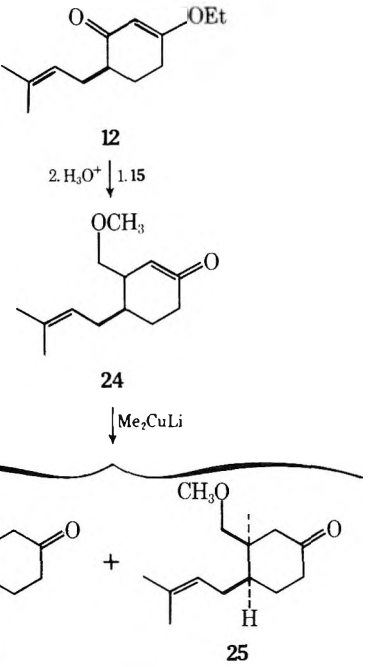
20 21 22 23

15% of enone **23**. Reductive removal of the acetoxy group in this reaction is not surprising, since such a good leaving group should be expelled rather readily from the radical anion supposed to be an intermediate in this reaction:[17]



Similar reductions have subsequently been reported.[18]

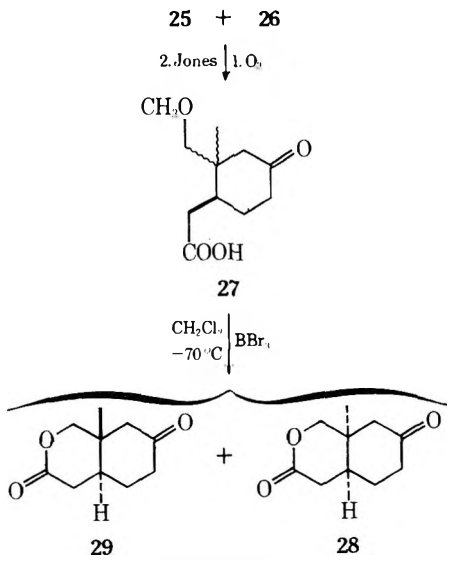
It seemed that replacing the acetoxy group by a poorer leaving group, such as alkoxy, might alleviate this problem. However, because of the delicate nature of the desulfurization reaction and low yields encountered in displacements of the allylic iodide **20**, we turned to a more direct method of introducing the desired alkoxymethyl group. Methoxymethylmagnesium chloride proved to be admirably suited for this purpose. Treatment of compound **12** with this reagent in methylal for several hours at room temperature, followed by hydrolysis with dilute acid, affords enone ether **24** in 80% yield.



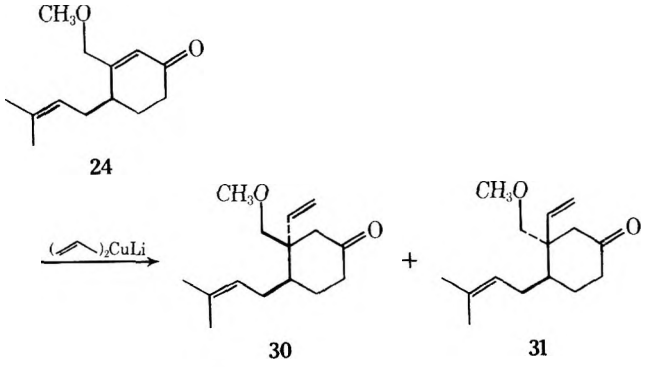
12 24 26 25

Enone **24** does indeed react smoothly with lithium dimethylcuprate, giving a 92:8 ratio of ketones **25** and **26** in 94% yield; no reductive removal of the methoxy group is observed.[19] The stereoselectivity observed in the addition of lithium dimethylcuprate to **24** was expected on the basis of analogy to the reaction of 3,4-dimethylcyclohex-2-en-1-one with lithium divinylcuprate, which affords the adduct with the vinyl trans to the C-3 methyl in greater than 95% yield.[21]

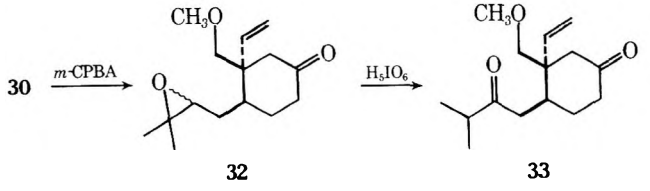
Compounds **25** and **26** provided us with an excellent opportunity to test our proposed elaboration of the two functionalized side chains into the desired δ-lactone. Treatment of the diastereomeric mixture with ozone in methylene chloride at −78 °C followed by Jones oxidation[22] of the ozonide affords a mixture of diastereomeric acids (**27**) in 55% yield. Treatment of the crude acid mixture with boron tribromide in methylene chloride at −70 °C affords lactones **28** and **29** (86:14 ratio) in 90% yield.



With a method for construction of the δ-lactone in hand, we turned to introduction of the potential angular vinyl group. Enone **24** reacts smoothly with lithium divinylcuprate, affording adducts **30** and **31** in a ratio of 94:6 (76% yield).

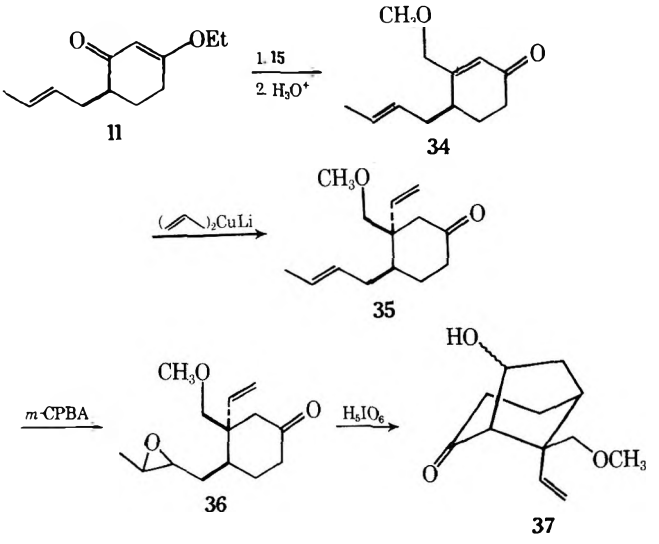


However, numerous attempts to achieve selective fission of the trisubstituted double bond in this attractive intermediate were unsuccessful. For example, selective ozonization could not be achieved. Compound **30** does react selectively with *m*-chloroperoxybenzoic acid to yield oxirane **32** (a diastereomeric mixture), but attempts at cleavage to an aldehyde met with failure, due to the propensity of **32** to rearrange to the isomeric isopropyl ketone **33**.

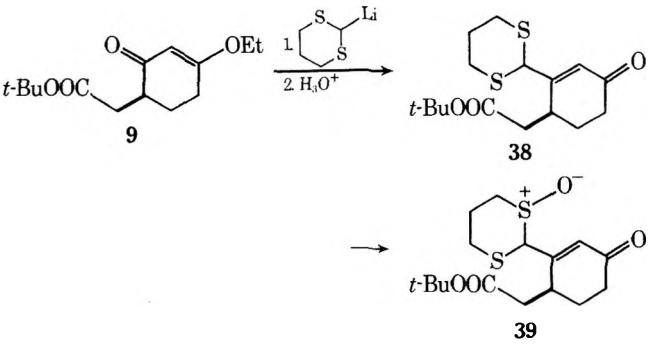


In an attempt to thwart this annoying rearrangement, we prepared oxirane **36**, via intermediates **34** and **35**. This oxirane does undergo the desired periodic acid cleavage, but the only product which may be isolated from the reaction is the bicyclic aldol **37**.

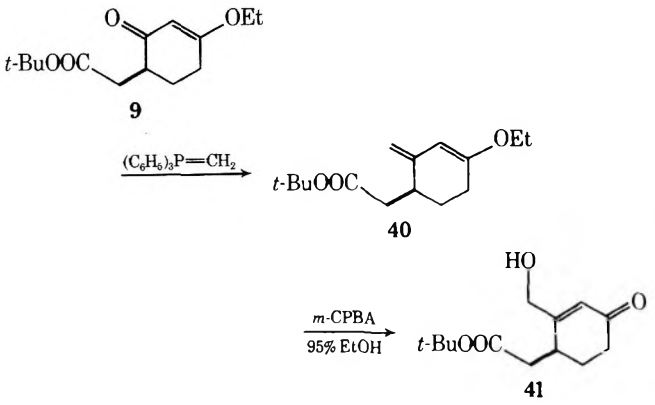
Because of these unexpected problems with conversion of the allyl side chains to the desired acetic acid side chain, we again turned our attention to precursors **8** and **9**, in which the carboxy group is already present. Continuing our search for a functionalized one-carbon nucleophile which would add selectively to the ketone carbonyl of one of these keto esters, we examined the reaction of *tert*-butyl ester **9** with 2-lithio-1,3-dithiane.[23] We were gratified to find that selective addition does occur, affording dithiane **38** in 51% yield after acidic hydrolysis and chromatographic purification. However, we



were unable to hydrolyze dithiane **38** or the monosulfoxide **39** under a variety of conditions.[24]



The hydroxymethyl problem was eventually solved in a most straightforward and elegant manner when we found that keto ester **9** reacts with methylenetriphenylphosphorane cleanly and in high yield to afford dienyl ether **40**. Furthermore, we were pleased to find that this material is readily oxidized by *m*-chloroperoxybenzoic acid in 95% ethanol[25,26] to give the desired hydroxymethyl derivative **41**. The overall yield for the two-stage conversion of **9** to **41** is 65–77%.



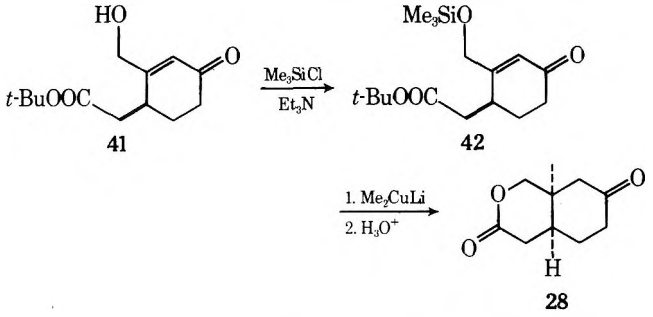
With the hydroxymethyl group in place and the acetic acid side chain protected as the *tert*-butyl ester, it remained only to introduce the angular vinyl group and close the δ-lactone to achieve our goal of keto lactone **5**. After a few unsuccessful attempts to carry out cuprate additions on the unprotected alcohol, it became clear that the hydroxy group must be temporarily blocked. Because of our earlier experience in the reaction of enone ester **21** with cuprates, we decided to protect this function as the trimethylsilyl ether. This is easily accomplished by treatment of compound **41** with trimethylsilyl

Table I. ^{1}H NMR Parameters of Keto Lactone 5

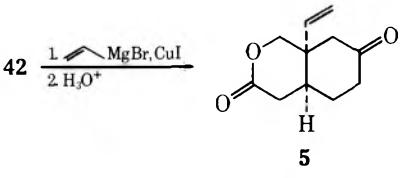
δ, ppm	Assignment	Multiplicity	J, Hz
1.78[a]	H_6	Multiplet (AB of ABXYZ)	$J_{6,7}$ = 14.2 $J_{6,9}$ = 9 $J_{6,5}$ = 9 $J_{6,8}$ = 5.3
2.095[a]	H_7		$J_{7,9}$ = 5.3 $J_{7,5}$ = 5.3 $J_{7,8}$ = 6.5
2.26–2.46	H_5, H_8, H_9	Multiplet	
2.48[b]	H_{10}, H_{11}	AB $\Delta\nu$ = 18.2[c]	$J_{10,11}$ = 15.4
2.54[a] 2.82[a]	H_3, H_4	AB of ABX	$J_{3,4}$ = 17.5 $J_{3,5}$ = 7.1 $J_{4,5}$ = 6.5
4.11[b]	H_1, H_2	AB $\Delta\nu$ = 75.2[c]	$J_{1,2}$ = 11.9
5.25[a]	H_{14}	ABC	$J_{12,13}$ = 11
5.29[a]	H_{13}		$J_{12,14}$ = 18
5.72[a]	H_{12}		$J_{13,14}$ = 0

[a] Center of multiplet, not chemical shift. [b] Geometric center of the AB pattern. [c] $\Delta\nu$ is the difference between the chemical shifts of A and B in hertz.

chloride and triethylamine in ether. In one preliminary experiment, enone **42** was treated with lithium dimethylcuprate

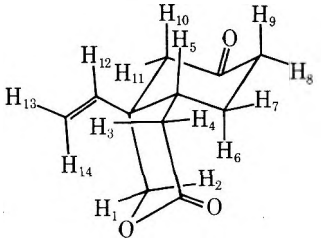


in ether. After hydrolysis of the crude product with sulfuric acid in aqueous 1,2-dimethoxyethane and chromatographic purification, lactone **28** was obtained in 22% yield. This angularly methylated keto lactone was spectrally identical with a specimen prepared earlier by a different route (vide supra). Treatment of enone **42** with vinylmagnesium bromide in the presence of 50 mol % CuI, followed by acidic hydrolysis of the crude product, affords the angularly vinylated keto lactone **5** in 60–85% yield from silyl ether **42**. The stereoselectivity



observed in the cuprate additions to **42** is impressive. High-resolution ^{1}H NMR analysis of compound **5** reveals that it contains at most 2.5% of the trans isomer.

An analysis of the coupling constants obtained from the 360-MHz ^{1}H NMR spectrum of **5** reveals that it exists predominantly in the "nonsteroid" conformation. The spectral parameters are summarized in Table I. The most enlightening



values are the nearly equal values of $J_{3,5}$ and $J_{4,5}$. In the steroid conformation, one of these couplings would be diaxial and the other axial–equatorial.

In summary, we have achieved a viable synthesis of bicyclic keto lactone **5**, an attractive intermediate for conversion to the natural products vernolepin and vernomenin and analogues thereof. The synthetic route developed is short (six steps from the readily available keto ether **6**) and efficient (about 40% overall yield). Furthermore, the reactions involved are easily adaptable to large-scale work (we have prepared approximately 100 g of keto lactone **5**).

Experimental Section

Melting points and boiling points are uncorrected. The ^{1}H NMR spectra were determined on a Varian T-60 NMR spectrometer or on a Bruker HXS-360 (Stanford Magnetic Resonance Laboratory). Infrared spectra were determined on a Perkin-Elmer 137 infrared spectrophotometer. Analytical and preparative gas–liquid phase chromatography was performed using 0.125-in. stainless steel columns (5 ft, 5% SE-30, and 10 ft, 10% FFAP). Low-resolution mass spectra were obtained on a AEI MS-12 mass spectrometer, and high-resolution mass spectra on a CEC 21-110 mass spectrometer. Microanalyses were performed by the University of California Microanalytical Laboratory.

***tert*-Butyl 2-(4-Ethoxy-2-oxocyclohex-3-enyl)acetate (9).** A solution of enol ether **6** (140 g, 1.0 mol) in THF (250 ml) was added dropwise to a −70 °C solution of LDA (1.2 mol) in THF (100 ml) over 30 min. The resulting solution was stirred for 45 min and a solution of *tert*-butyl bromoacetate (205 g, 1.05 mol) in THF (100 ml) was added over 30 min. The solution was allowed to warm to room temperature and water (5 ml) was added. The mixture was evaporated and the residue was taken into ether, washed with water and brine, dried, and evaporated to 252 g (99%) of light yellow powder. This material was sufficiently pure for use in the next reaction (NMR identical with that of purified material; one spot on TLC, R_f 0.6, ether). Further purification may be effected by recrystallization at −78 °C from petroleum ether: mp 68.5–70.5 °C; ir ($CDCl_3$) 1733, 1664, 1613, 1190 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3 H), 1.53 (s, 9 H), 3.96 (quartet, 2 H), 5.38 (s, 1 H).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.14; H, 8.51.

***tert*-Butyl 2-(2-Methylene-4-ethoxycyclohex-3-enyl)acetate (40).** Methyltriphenylphosphonium bromide (53.5 g, 150 mmol) was added to a solution of sodium dimsylate (from 150 mmol of sodium hydride) in 150 ml of dimethyl sulfoxide. The mixture was stirred for several minutes, followed by addition of enol ether **9** (25.4 g, 100 mmol) in dimethyl sulfoxide (25 ml). After 3 h at room temperature, the reaction was quenched by addition of water (300 ml) and petroleum ether (300 ml). After filtration, the aqueous phase was extracted with petroleum ether and the combined organic layers were washed with water and brine, dried, and evaporated to 22.0 g (85%) of **40** as a colorless liquid: ir (film) 1733, 1639, 1186, 1143 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.12 (t, 3 H), 1.44 (s, 9 H), 1.73 (m, 2 H), 3.77 (quartet, 2 H), 4.53 (s, 2 H), 5.18 (s, 1 H); mass spectrum *m/e* (rel intensity) 252 (31), 196 (52), 195 (29), 151 (100), 123 (59), 57 (68); exact mass 252.1731 (calcd for $C_{15}H_{24}O_3$, 252.1725).

***tert*-Butyl 2-(2-(Hydroxymethyl)-4-oxocyclohex-2-enyl)-acetate (41).** A solution of enol ether **40** (32.0 g, 127 mmol) in 95% ethanol (225 ml) was added at once to a stirred solution of *m*-chloroperbenzoic acid (198 mmol) in 95% ethanol (700 ml). The temperature of the mixture increased to 38 °C, then the mixture was stirred for 2 h at ambient temperature. Sodium thiosulfate (35.0 g) and sodium bicarbonate (25.0 g) in water (125 ml) were added and the mixture was stirred for 45 min. Most of the solvent (800 ml) was evaporated at reduced pressure and the residue was taken into water (1000 ml) and extracted with ether (3 × 300 ml). The ether was washed with brine, dried, and evaporated to 27.5 g (90.2%) of alcohol **41** as a light yellow oil. This material was somewhat unstable and was used without further purification: ir (film) 3676, 1727, 1675, 1149 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9 H), 4.27 (s, 2 H), 4.53 (s, 1 H), 6.13 (s, 1 H); mass spectrum *m/e* 226.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.06; H, 8.35.

***tert*-Butyl 2-(2-(Trimethylsiloxymethyl)-4-oxocyclohex-2-enyl)acetate (42).** Triethylamine (34.9 g, 343 mmol) and trimethylsilyl chloride (37.0 g, 343 mmol) were added to a solution of alcohol **41** (46.0 g, 191.6 mmol) in ether (250 ml). After 2 h at room temperature, the mixture was filtered and evaporated. The residue was taken

into petroleum ether, filtered again, and evaporated to 54.0 g (90.8%) of silyl ether **42**, a colorless oil. Owing to its hydrolytic instability, this material was used without further purification: ir (film) 1730, 1678, 1248, 1148 cm^{-1}; ^1H NMR (CCl_4) δ 0.24 (s, 9 H), 1.55 (s, 9 H), 4.38 (s, 2 H), 6.08 (s, 1 H).

***cis*-8a-Vinyloctahydro-3*H*-2-benzopyran-3,7-dione (5).** A solution of vinylmagnesium bromide was prepared from magnesium (8.3 g, 342 mmol) and vinyl bromide (40.2 g, 376 mmol) in THF (650 ml) and cooled to −5 °C. Cuprous iodide (32.5 g, 171 mmol) was added and the resulting jet-black solution was stirred at −5 °C for 3 min, then rapidly cooled to −70 °C. A solution of enone **42** (33.3 g, 107 mmol) in THF (100 ml) was added slowly and the mixture was stirred for 1 h at −70 °C, then allowed to warm to 0 °C. Sulfuric acid (13 ml) and water (40 ml) were cautiously added and the mixture was suction filtered. The filtrate was evaporated and the residue was extracted with chloroform. The combined extracts were evaporated and the residue was dissolved in glyme (500 ml) and 10% sulfuric acid (300 ml). This solution was refluxed for 4 h and the glyme was removed by rotary evaporation. The aqueous residue was extracted with chloroform and the combined extracts were washed with 5% sodium bicarbonate and brine, then dried ($MgSO_4$). The chloroform was evaporated to yield 17.8 g (85.8%) of keto lactone **5** as tan crystals. Recrystallization from ethyl acetate gave an analytical sample: mp 104–105 °C; ir ($CDCl_3$) 1739, 1718, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (AB quartet, J = 15.4 Hz, 2 H), 4.11 (AB quartet, J = 12 Hz, 2 H), 5.25–5.72 (ABC pattern, 3 H), see Table I for complete spectral data; mass spectrum *m/e* (rel intensity) 194 (6), 165 (6), 164 (39), 162 (9), 147 (11), 136 (14), 122 (79), 94 (38), 80 (50), 79 (100); exact mass 194.0943 (calcd for $C_{11}H_{14}O_3$, 194.0939).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.88; H, 7.01.

Acknowledgments. This work was supported by the U.S. Public Health Service (Grant CA-12617). We thank Dr. Woodrow Conover of the Stanford Magnetic Resonance Laboratory for instructing us in the use of the HXS-360 spectrometer, and Mr. Sam L. Woo for technical assistance.

Registry No.—**5,** 59711-44-3; **6,** 5323-87-5; **7,** 29941-87-5; **8,** 58775-58-9; **9,** 58775-59-0; **10,** 40649-34-1; **11,** 59711-45-4; **12,** 58775-55-6; **13,** 13307-75-0; **14,** 10415-47-1; **15,** 107-30-2; **16,** 58775-62-5; **18,** 58775-63-6; **19,** 58775-64-7; **20,** 58775-65-8; **21,** 50557-37-4; **24,** 59711-46-5; **25,** 59711-47-6; **26,** 59711-48-7; **27** (isomer A), 59711-49-8; **27** (isomer B), 59711-50-1; **28,** 59711-51-2; **29,** 59711-52-3; **30,** 59711-53-4; **31,** 59711-54-5; **32** (isomer A), 59711-55-6; **32** (isomer B), 59751-85-8; **33,** 59711-56-7; **34,** 59711-57-8; **35,** 59711-58-9; **36,** 59711-59-0; **38,** 59711-60-3; **39,** 59711-61-4; **40,** 59711-62-5; **41,** 59711-63-6; **42,** 59711-64-7; *tert*-butyl bromoacetate, 5292-43-3; methyltriphenylphosphonium bromide, 1779-49-3; trimethylsilyl chloride, 75-77-4; vinyl bromide, 593-60-2; ethyl bromoacetate, 105-36-2; 1-bromo-2-butene, 4784-77-4; prenyl bromide, 870-63-3; lithium dimethylcuprate, 15681-48-8; lithium divinylcuprate, 22903-99-7; periodic acid, 27803-33-4; 1,3-dithiane, 505-23-7.

Supplementary Material Available. The following experimental procedures: (1) ethyl 2-(4-isobutoxy-2-oxocyclohex-2-enyl)acetate (8); (2) 3-ethoxy-6-(2-butenyl)cyclohex-2-en-1-one (**11**); (3) 3-ethoxy-6-(3-methyl-2-butenyl)cyclohex-2-en-1-one (**12**); (4) 3-phenylthiomethyl-4-(2-propenyl)cyclohex-2-en-1-one (**16**); (5) 3-methyl-2-(2-propenyl)cyclohex-2-en-1-one (**18**); (6) 3-methylthiomethylcyclohex-2-en-1-one (**19**); (7) 3-acetoxymethylcyclohex-2-en-1-one (**21**); (8) reaction of **21** with lithium dimethylcuprate; (9) 3-methoxymethyl-4-(3-methyl-2-butenyl)cyclohex-2-en-1-one (**24**); (10) *cis*-3-methoxymethyl-4-(3-methyl-2-butenyl)-3-methylcyclohexanone (**25**); (11) 2-methoxymethyl-2-methylcyclohexan-4-onylacetic acid (**27**); (12) *cis*-8a-methyloctahydro-3*H*-2-benzopyran-3,7-dione (**28**); (13) *cis*-3-methoxymethyl-4-(3-methyl-2-butenyl)-3-vinylcyclohexanone (**30**); (14) *cis*-3-methoxymethyl-4-(3-methyl-2,3-oxidobutyl)-3-vinylcyclohexanone (**32**); (15) reaction of **32** with periodic acid; (16) 3-methoxymethyl-4-(2-butenyl)cyclohex-2-en-1-one (**34**); (17) *cis*-3-methoxymethyl-4-(2-butenyl)-3-vinylcyclohexanone (**35**); (18) *cis*-3-methoxymethyl-4-(2,3-oxidobutyl)-3-vinylcyclohexanone (**36**); (19) reaction of **36** with periodic acid; (20) *tert*-butyl 2-[2-(2,6-dithianyl)-4-oxocyclohex-2-enyl]acetate (**38**); (21) *tert*-butyl 2-[2-(2-oxo-2,6-dithianyl)-4-oxocyclohex-2-enyl]acetate (**39**).

References and Notes

(1) For part 5, see C. H. Chavdarian, S. L. Woo, R. D. Clark, and C. H. Heathcock, *Tetrahedron Lett.*, 1759 (1976).
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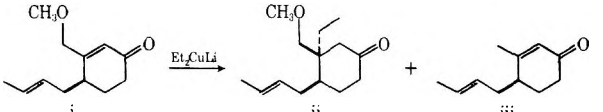
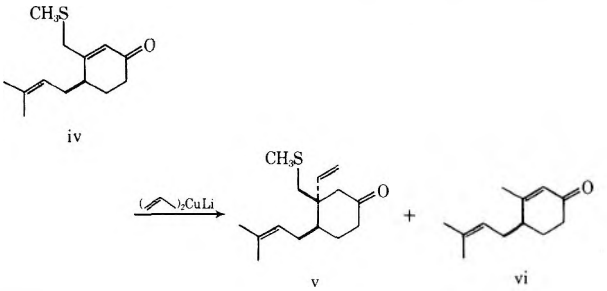
(19) Although we observe no reductive removal of the methoxy group in this reaction, this result is apparently not general. For example, a similar reaction of lithium diethylcuprate with enone ether i affords adduct ii and the



reduced product iii in a ratio of 3:2. An identical product mixture is obtained in the CuI-catalyzed addition of ethylmagnesium bromide to enone i. A similar result is obtained from the reaction of enone sulfide iv with lithium divinylcuprate. Adduct v and enone vi are obtained in a ratio of 3:1.[20]



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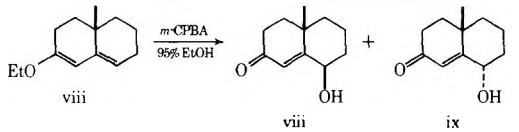
(26) The Kirk and Wiles procedure for the oxidation of enol ethers is a remarkably general and useful process, which does not seem to have received the attention it deserves. We have also used the reaction for the



high-yield conversion of dienyl ether vii to γ-hydroxy enones viii and ix.[27]
(27) E. G. Del Mar, unpublished results.

Synthesis of Pyrido[2,3-*d*]pyrimidine-2,4-diones

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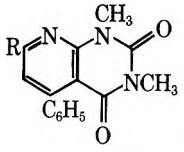
Received March 16, 1976

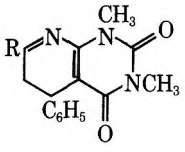
Pyrido[2,3-*d*]pyrimidine-2,4-diones were prepared by the acid- and base-catalyzed condensation of 6-amino-1,3-dimethyluracil with α,β-unsaturated carbonyl compounds. The reaction was carried out successfully with benzalacetophenone, benzalpinacolone, benzalacetone, cinnamaldehyde, crotonaldehyde, methyl vinyl ketone, and 3-penten-2-one. The intermediate dihydropyridine was isolated only in the condensation with benzalpinacolone in acetic acid. In all other examples air oxidation probably occurred and formed the pyridine. Disproportionation of the dihydropyridine to the pyridine and tetrahydropyridine occurred to a minor extent with the product from benzalacetophenone.

The reaction of 6-amino-1,3-dimethyluracil with α,β-unsaturated carbonyl compounds was investigated under a variety of conditions as a method for the preparation of pyrido[2,3-*d*]pyrimidine-2,4-diones. Condensations of this type have been reported only with dibenzoylethylene.[1]

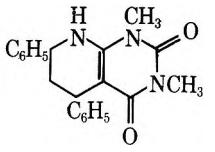
The condensation reaction with benzalacetophenone and benzalpinacolone in the presence of sodium ethoxide gave good yields of the corresponding pyrido[2,3-*d*]pyrimidine-2,4-diones (**1a, 1b**), and poor yields of the desired pyridines



1a, R = C_6H_5
b, R = $C(CH_3)_3$
c, R = H



2a, R = C_6H_5
b, R = $C(CH_3)_3$

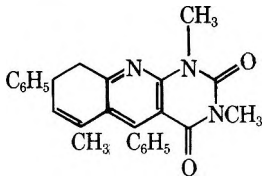


3

with methyl vinyl ketone, 3-penten-2-one, and benzalacetone.

The expected intermediate **2** from the first two examples was not isolated but is apparently oxidized by air to the pyridines **1a** and **1b**. Disproportionation of **2a** to the pyridine **1a** and the tetrahydro derivative **3** is a minor reaction and was observed only with the phenyl derivative **2a**. Proofs for the structures were the NMR and ir spectra and elemental analyses.

Benzalacetone using sodium ethoxide as the condensing agent gave as the main product **4** which results from the con-



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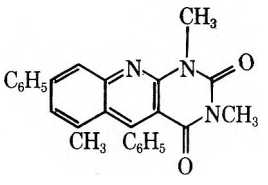

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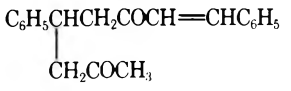
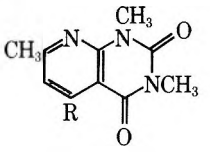
densation of the amine with the dimer of benzalacetone resulting from a Michael addition of benzalacetone to itself. This



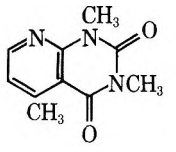
compound (**4**) was converted by sulfur to the quinoline derivative **5**. The NMR and mass spectral data were in agreement with these formulations.

Methyl vinyl ketone, 3-penten-2-one, and benzalacetone were converted to the corresponding pyridines **6** in better yields than those obtained using sodium ethoxide by heating with the amine in acetic acid at 100 °C.

The acetic acid method was also suitable for the preparation of the 5-phenyl derivative **1c** from cinnamaldehyde but was



6a, R = H
b, R = CH_3
c, R = C_6H_5



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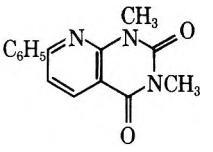


8

not a general method for the preparation of pyridopyrimidines since it gave the dihydro derivative **2b** as the main product when benzalpinacolone was used. The structure was demonstrated by dehydrogenation with chloranil to the corresponding pyridine **1b**. The NMR spectrum was likewise in agreement with this formulation and showed 12 lines for the ABX system involving the hydrogens on the 5 and 6 carbons.

The dihydro derivative **2b** is stable to air oxidation in acetic acid in contrast to the dihydro derivative of **6b**. The reaction of 6-amino-1,3-dimethyluracil with 3-penten-2-one in acetic acid under nitrogen gave a mixture of compounds which, by TLC analysis on silica gel using chloroform as the solvent, contained the pyridine **6b** and two other compounds. Attempts to isolate and characterize these compounds by chromatography and fractional crystallization from methanol were not successful. Evidence for the presence of the dihydro derivative was obtained by heating the mixture further in acetic acid exposed to air; the yield of the pyridine **6b** obtained was twice that present in the original mixture.

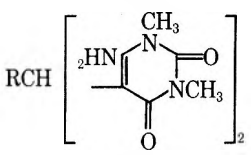
The use of trifluoroacetic acid as a solvent in the condensation reaction was investigated only with benzalacetone and gave **4** as the product instead of the pyridopyrimidine **6c**. Further studies using this acid were therefore not pursued.

Hydrochloric acid as a condensing agent was also studied using crotonaldehyde and cinnamaldehyde. This acid had been used successfully[2] for the conversion of crotonaldehyde and 5-amino-1,3-dimethyluracil to the pyrido[3,2-*d*]pyrimidine. The product formed from 6-amino-1,3-dimethyluracil and crotonaldehyde was the 1,3,5-trimethyl derivative **7**. This formulation was based on the NMR spectrum; the coupling constant for the 6,7 hydrogens was 5 Hz in contrast to a coupling constant of 8 Hz for the 5,6 hydrogens in the 1,3,7-trimethyl derivative **6a**. The related hydrogens in 4-methylquinoline (5 Hz) and 2-methylquinoline (8 Hz) show similar coupling constants. Further evidences for these structures were the ^{13}C NMR spectra. The chemical shift for the 7-methyl group in **6a** (25.15 ppm) was further downfield than that for the 5-methyl group in **7** (22.40 ppm). The tetramethyl derivative **6b** gave shifts of 22.13 and 24.57 ppm for these two groups.

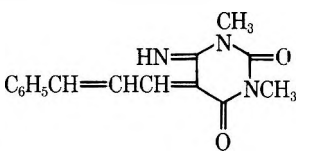
Cinnamaldehyde under these conditions gave the 5-phenyl derivative **1c** in a smaller yield than that obtained using acetic

acid. The reaction in hydrochloric acid was accompanied by a considerable amount of tar.

The condensation of 6-amino-1,3-dimethyluracil with benzalacetophenone, benzalacetone, and cinnamaldehyde in ethanol under neutral conditions was also investigated since the amine reacts with dibenzoylethylene under these conditions and forms a pyrrolo[2,3-*d*]pyrimidine-2,4-dione.[1] No reaction occurred, however, between the amine and either benzalacetophenone or benzalacetone in alcohol at reflux for 24 h. The corresponding reaction with cinnamaldehyde gave **9a**. This aldehyde behaved differently if heated with the



9a, R = $C_6H_5CH{=}CH$
b, R = C_6H_5



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amine at 250 °C in the absence of a solvent and formed the 7-phenyl derivative **8**. The structure assignment was based on its NMR spectrum. The coupling constant for the 5,6 hydrogens was 9 Hz in contrast to a coupling constant of 5 Hz for the 6,7 hydrogens in **1c**. In addition the phenyl group in **8** showed the characteristic splitting found for benzylidene structures. The cinnamylidene derivative **9a** is probably a precursor for the 7-phenyl derivative **8**. The loss of 6-amino-1,3-dimethyluracil by a reverse Michael reaction would form the 5-cinnamylidene derivative of the amine **10**. Cyclization of **10** followed by air oxidation would form **8**.

The formation of the pyridines must occur by a 1,4 addition of the amine at the 5 position to the unsaturated carbonyl system followed by cyclization and air oxidation. Such an involvement of the enamine structure was demonstrated by the behavior of 6-amino-1,3-dimethyluracil with benzaldehyde; the condensative at 190 °C or in acetic acid gave **9b**.

Experimental Section

Melting points are not corrected. Infrared spectra were recorded on a Perkin-Elmer Model 137B spectrophotometer. NMR spectra were obtained with Varian A-60 and Bruker HX-90E nuclear magnetic resonance spectrometers. Mass spectra were obtained with a Hitachi RMU6E spectrometer.

Condensation of Benzalacetophenone with 6-Amino-1,3-dimethyluracil. A solution of benzalacetophenone (2.08 g), 6-amino-1,3-dimethyluracil (1.55 g), and sodium ethoxide (0.68 g) in absolute ethanol (118 ml) was heated at reflux for 17 h. The solution on cooling gave 1.81 g (53%) of 1,3-dimethyl-5,7-diphenylpyrido[2,3-*d*]pyrimidine-2,4-dione (**1a**), mp 250–255 °C. Two crystallizations gave a sample melting at 250–252 °C: ir (Nujol) 5.87, 6.01 μ (C=O); NMR (CF_3COOH) δ 3.53 (s, 3 H, NCH_3), 4.08 (s, 3 H, NCH_3), 7.2–8.0 (m, 11 H, 2 C_6H_5, CH).

Anal. Calcd for $C_{21}H_{17}O_2N_3$: C, 73.47; H, 4.96; N, 12.24. Found: C, 73.48; H, 5.03; N, 12.43.

Concentration of the filtrate gave 0.26 g of solid which from its infrared spectrum proved to be a mixture of **1a** and its tetrahydro derivative (**3**). The resulting filtrate was evaporated to dryness and the solid obtained was extracted with benzene. The benzene extract was discarded and the remaining solid was treated with water and filtered, yield 0.67 g. Two crystallizations from ethanol gave the tetrahydro derivative (**3**) melting at 262–264 °C: ir (Nujol) 3.23 (NH), 6.03 μ (C=O); NMR ($CDCl_3$) 1.7–3.2 (m, 2 H, CH_2), 3.12 (s, 3 H, NCH_3), 3.33 (s, 3 H, NCH_3), 3.8–4.5 (m, 2 H, 2CH), 4.93 (broad s, 1 H, NH), 7.1 (s, 5, C_6H_5), 7.28 (s, 5, C_6H_5).

Anal. Calcd for $C_{21}H_{21}O_2N_3$: C, 72.83; H, 6.07; N, 12.14. Found: C, 72.89; H, 5.84; N, 12.29.

1,3-Dimethyl-7-*tert*-butyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4-dione (1b). Benzalpinacolone under similar conditions to those given for the preparation of **1a** gave an 81% yield of **1b** melting at 120–128 °C. Two recrystallizations from ethanol gave a sample melting at 139–142 °C: ir (Nujol) 5.75, 6.02 μ (C=O); NMR ($CDCl_3$) δ 1.43 [s, 9, $C(CH_3)_3$], 3.35 (s, 3, NCH_3), 3.78 (s, 3, NCH_3), 7.07 (s, 1, CH), 7.20–7.53 (m, 5, C_6H_5).

Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.56; H, 6.50; N, 13.00. Found: C, 70.89; H, 6.56; N, 13.21.

1,3,7-Trimethylpyrido[2,3-*d*]pyrimidine-2,4-dione (6a). A solution of methyl vinyl ketone (4 ml) and 6-amino-1,3-dimethyluracil (7.7 g) in acetic acid (100 ml) was heated on a steam bath for 21 h. Removal of the acetic acid under reduced pressure followed by the addition of water gave 1.92 g (18.7%) of a solid melting at 153–158 °C. Sublimation followed by two crystallizations from ethanol gave white crystals melting at 157.5–159 °C: ir (Nujol) 5.86, 5.98 μ (C=O); NMR ($CDCl_3$) δ 2.60 (s, 3, CH_3), 3.43 (s, 3, NCH_3), 3.64 (s, 3, NCH_3), 7.03 [d, 1, 6-H (J = 8 Hz)], 8.20 [d, 1, 5-H (J = 8 Hz)], 25.15 (7-CH_3), 28.27 (1-CH_3), 29.25 (3-CH_3); *m/e* 205.

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.54; H, 5.37; N, 20.49. Found: C, 58.41; H, 5.62; N, 20.59.

Using sodium ethoxide as the reagent in ethanol gave only trace amounts of this compound.

1,3,5,7-Tetramethylpyrido[2,3-*d*]pyrimidine-2,4-dione (6b). 3-Penten-2-one using the directions given for the preparation of **6a** gave a 61% yield of a solid melting at 155–165 °C. Sublimation under reduced pressure followed by crystallization from ethanol gave white crystals of **6b** melting at 178–180 °C: ir (Nujol) 5.89, 6.02 μ (C=O); NMR ($CDCl_3$) δ 2.52 (s, 3 H, 7-CH_3), 2.73 (s, 3 H, 5-CH_3), 3.40 (s, 3 H, NCH_3), 3.64 (s, 3 H, NCH_3), 6.79 (s, 1 H, 6-H), 22.29 (5-CH_3), 24.73 (7-CH_3), 28.21 (1-CH_3), 29.93 (3-CH_3).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.27; H, 5.94; N, 19.17. Found: C, 60.19; H, 5.42; N, 19.55.

Fractional crystallization of the compounds present in the alcohol filtrate from ethyl acetate gave 0.165 g of a sample melting at 188–193 °C. The NMR spectrum indicated that this sample was probably a mixture of the dihydro and tetrahydro derivative of **6b**. The amount obtained was insufficient to allow further separation and characterization.

The same reaction when carried out under nitrogen gave a 58% yield of a solid which, when chromatographed upon silica gel using chloroform, gave three distinct bands. The first of these was the pyridine **6b** and amounted to 35% of the total product. The second band upon workup also gave the pyridine **6b**. The third fraction gave an oil which could not be obtained crystalline.

Fractional crystallization from methanol gave fractions which always contained the pyridine **6b**.

The above mixture (1 g) when heated in acetic acid (15 ml) at 100 °C in air for 18 h gave 0.7 g of the pyridine **6b**.

The use of sodium ethoxide as a condensing agent gave a 19% yield of **6b**.

5-Phenyl-1,3,7-trimethylpyrido[2,3-*d*]pyrimidine-2,4-dione (6c). A solution of the amine (1.55 g) and benzalacetone (1.46 g) in acetic acid (50 ml) was heated at reflux for 17 h. Removal of the acetic acid followed by the addition of water gave a gum which when triturated with ethanol gave a solid (0.23 g, 8%) melting at 170–173 °C. Crystallization from ethanol gave a sample melting at 185–187 °C. Purification by sublimation followed by crystallization from methanol gave white crystals melting at 187–189 °C: ir (Nujol) 5.87, 6.02 μ (CO); NMR ($CDCl_3$) δ 2.60 (s, 3 H, 7-CH_3), 3.33 (s, 3 H, NCH_3), 3.75 (s, 3 H, NCH_3), 6.89 (s, 1 H, 6-H), 7.1–7.6 (m, 5 H, C_6H_5).

Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.32; H, 5.33; N, 14.95. Found: C, 68.45; H, 5.79; N, 15.03.

The ethanol filtrate upon evaporation gave a solid which upon sublimation under reduced pressure gave 0.33 g (12%) of **6c**.

5-Phenyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4-dione (1c). **A.** The amine (3.1 g) and cinnamaldehyde (2.5 ml) were heated in acetic acid (50 ml) on a steam bath for 21 h. Removal of the acetic acid followed by addition of water gave a gum which was dissolved in hot ethanol. The pale brown solid (0.68 g, 12.8%) obtained melted at 171–178 °C. Sublimation under reduced pressure followed by recrystallization from ethanol gave white crystals melting at 184–186 °C: ir (Nujol) 5.84, 5.93 μ (CO); NMR ($CDCl_3$) δ 3.34 (s, 3, CH_3N), 3.73 (s, 3, CH_3N), 6.99 [d, 1, 6-H (J = 5 Hz)], 7.08–7.62 (m, 5, C_6H_5), 8.62 [d, 1, 7-H (J = 5 Hz)].

Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.42; H, 4.87; N, 15.73. Found: C, 66.96; H, 4.85; N, 15.58.

An additional 1.0 g (19%) of **1c** was obtained by vacuum sublimation of the tarry materials obtained from the ethanol filtrate.

B. The amine (2.0 g) and cinnamaldehyde (2 ml) were heated at reflux in 6 N hydrochloric acid (40 ml) for 30 min. The resulting solution was decanted from the tar formed, poured into water, and neutralized with ammonia. The resulting solid (0.55 g, 16%) melting at 140–170 °C was recrystallized from ethanol, mp 182–184 °C. The ir spectrum was identical with that of **1c** formed using acetic acid as a solvent. The tar from this preparation when heated in a sublimator under reduced pressure gave an additional 0.33 g (5%) of **1c**.

5-Phenyl-7-*tert*-butyl-5,6-dihydropyrido[2,3-*d*]pyrimidine-2,4-dione (2b). The amine (3.1 g) and benzalpinacolone (3.76 g) were heated in acetic acid (100 ml) on a steam bath for 23 h. Removal of the acetic acid followed by the addition of water gave a waxy solid (5.32 g). Trituration with ethanol gave a white solid (3.35 g, 51%) melting at 210–215 °C. Recrystallization from ethyl acetate gave white crystals melting at 215–219 °C: ir (Nujol) 5.90, 6.07 μ (CO); NMR ($CDCl_3$) δ 1.0 [s, 9, $(CH_3)_3C$], 2.32, 2.61 [2, d, 1, B-H (J_{BX} = 9 Hz)], 2.87, 3.15 [2 d, 1, A-H (J_{AX} = 2 Hz)], 3.37 (s, 3, NCH_3), 3.63 (s, 3, NCH_3), 4.16, 4.31 [2 d, 1, X-H (J_{AX} = 2 Hz)], 6.93–7.5 (m, 5, C_6H_5).

Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.15; H, 7.08; N, 12.92. Found: C, 69.85; H, 7.43; N, 12.74.

The dihydropyridine **2b** (0.162 g) and chloranil (0.14 g) in benzene (10 ml) were heated at reflux for 24 h. The resulting solution was cooled and the hydroquinone (0.044 g) which crystallized was filtered. The benzene filtrate was evaporated to dryness. Addition of ethanol gave 0.03 g of **1b** melting at 136–139 °C.

1,3,5-Trimethylpyrido[2,3-*d*]pyrimidine-2,4-dione (7). The amine (7.75 g) and crotonaldehyde (5 ml) were treated with 6 N hydrochloric acid (77.5 ml) using the directions given for 5-amino-1,3-dimethyluracil.[2] The resulting solution was filtered from the tar and the hydrochloric acid was removed under reduced pressure. Treatment with water and basification with ammonium hydroxide was followed by extraction with methylene chloride. Removal of the solvent gave an oil which was dissolved in hot ethanol. Cooling gave crystals (1.52 g, 14%) melting at 130–142 °C. An additional 0.16 g (1.5%) was obtained by concentration of the aclohol filtrate. Sublimation under reduced pressure gave a sample melting at 159–160.5 °C: ir (Nujol) 5.88, 6.05 μ (CO); NMR ($CDCl_3$) δ 2.79 (s, 3, CH_3), 3.42 (s, 3, NCH_3), 3.66 (s, 3, NCH_3), 6.97 [d, 1, 6-H (J = 5 Hz)], 8.42 [d, 1, 7-H (J = 5 Hz)], 22.40 (7-CH_3).

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.54; H, 5.37; N, 20.49. Found: C, 58.75; H, 5.49; N, 20.93.

The tar obtained in this preparation when heated in a sublimator under vacuum gave an additional 0.87 g (8.5%) of **7**. The residue from this sublimation was a white solid (1.59 g) melting at 319–315 °C. The insolubility of this compound in organic solvents prevented the elucidation of its structure.

7-Phenylpyrido[2,3-*d*]pyrimidine-2,4-dione (8). A mixture of the amine (2.0 g) and cinnamaldehyde (2 ml) was heated at 250 °C under nitrogen for 30 min. The red glass obtained was dissolved in hot ethanol and the resulting solution upon cooling gave a solid (0.88 g, 25%) melting at 178–183 °C. Sublimation (vacuum) followed by two recrystallizations from ethanol gave white crystals melting at 186–187.5 °C: ir (Nujol) 5.85, 6.01 μ (CO); NMR ($CDCl_3$) δ 3.44 (s, 3, NCH_3), 3.76 (s, 3, NCH_3), 7.32–7.63 (m, 3, *m,p*-ArH), 7.60 [d. 1, 6-H (J = 9 Hz)], 7.92–8.28 (m, 2, o-ArH), 8.46 [d, 1, 7-H (J = 9 Hz)].

Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.42; H, 4.87; N, 15.73. Found: C, 67.37; H, 5.03; N, 15.85.

Condensation of Benzalacetone with 6-Amino-1,3-dimethyluracil. A. A solution of amine (1.55 g), benzalacetone (1.46 g), and sodium ethoxide (0.68 g) in absolute ethanol (130 ml) was heated at reflux for 23 h. Removal of the ethanol followed by the addition of water gave a solid (2.23 g) melting at 140–170 °C. Treatment with methanol gave a solid (0.48 g, 12%) melting at 193–198 °C. Recrystallization from methanol gave pale yellow crystals of **4** melting at 197–199 °C: ir (Nujol) 5.87, 6.05 μ (CO); NMR ($CDCl_3$) δ 1.85 (s, 3, CH_3), 1.95–3.05 (m, 2 H, CH_2), 3.27 (s, 3, NCH_3), 3.79 (s, 3, NCH_3), 3.83–3.86 (m, 1, CH), 6.31 [d, 1, =CH (J = 5.8 Hz)], 6.47–6.83 (m, 3, aromatic H), 6.83–7.62 (m, 7 H, aromatic); *m/e* 409.

Anal. Calcd for $C_{26}H_{23}N_3O_2$: C, 75.91; H, 6.08; N, 10.21. Found: C, 75.64; H, 5.70; N, 10.11.

The methanol filtrate was evaporated to dryness and the residue was sublimed under reduced pressure. The solid (0.72 g) obtained, upon fractional crystallization from ethanol, gave **4** (0.05 g) and **6c** (0.31 g).

B. The amine (1.55 g) and benzalacetone (1.46 g) were dissolved in trifluoroacetic acid (10 ml) and the solution was allowed to stand for 65 h at room temperature. Addition of water to the solution followed by extraction with methylene chloride gave a solid which after recrystallization from ethanol gave **4** (0.91 g, 22% melting at 191–196 °C.

1,3,6-Trimethyl-5,8-diphenyl-1,2,3,4-tetrahydropyrimido[4,5-*b*]quinoline-2,4-dione (5). The dihydro compound **4** (0.82 g) was heated with sulfur (0.064 g) at 225–230 °C until the evolution of hydrogen sulfide ceased. The resulting product was dissolved in benzene and chromatographed upon silica gel using benzene as an eluent. Removal of the benzene gave **5** (0.55 g) melting at 198–203 °C. Sublimation under reduced pressure followed by two crystallizations from ethyl acetate gave pale yellow crystals melting at 207–209 °C: ir (Nujol) 5.84, 5.98 μ (CO); NMR ($CDCl_3$) δ 2.55 (s, 3, 9-CH_3), 3.31 (s, 3, NCH_3), 3.72 (s, 3, NCH_3), 6.6–7.25 (m, 11, aromatic H's and 8-H), 7.87 [broad s (meta coupling), 1, 6-H]; *m/e* 407.

Anal. Calcd for $C_{26}H_{21}O_2N_3$: C, 76.85; H, 4.93; N, 10.34. Found: C, 76.72; H, 5.18; N, 10.24.

3-Phenyl-1,1-bis(6-amino-1,3-dimethyluracil-5)-2-propene (9a). The amine (1.55 g) and cinnamaldehyde (1.25 ml) were heated under reflux in absolute ethanol (100 ml) under nitrogen for 24 h. Removal of the solvent followed by the addition of methanol gave 1.33 g (31%) of **9a.** Two crystallizations from methanol gave a sample which melted partially at 202 °C, resolidified completely at 208 °C, and then melted at 281 °C with gas evolution: ir (Nujol) 2.90, 3.07 (NH_2), 3.2 (CH=CH), 5.91, 6.01 (C=O), 10.2 μ (CH=CH); NMR (Me_2SO-d_6) δ 3.22 [s, 6, 2 N (CH_3)$_2$], 3.42 [s, 6, 2 N (CH_3)$_2$], 5.08 (m, 1, >CH), 6.1–6.66 (m, 2, CH=CH), 7.33 (s, 5, C_6H_5), 7.48 [s, 4, 2 NH_2 (exchanges with D_2O)].

Anal. Calcd for $C_{21}H_{24}N_6O_4$: C, 59.43; H, 5.66; N, 19.81. Found: C, 59.52; H, 5.66; N, 19.91.

Phenylbis(6-amino-1,3-dimethyluracil-5)methane (9b). A. The amine (1.0 g) and benzaldehyde (1 ml) were heated at 190 °C for 30 min. Trituration of the product with methanol gave a solid (1.0 g, 39%) which after recrystallization from methanol gave white crystals of **9b:** mp softens at 283 °C and melts at 289 °C with decomposition; ir (Nujol) 2.92, 3.11 (NH_2), 5.92, 6.06 μ (CO); NMR (Me_2SO-d_6) δ 3.24 (s, 6, 2 NCH_3), 3.40 (s, 6, 2 NCH_3), 5.70 (s, 1, CH), 7.24 (s, 5, C_6H_5), 7.52 [s, 4, 2 NH_2 (exchanges with D_2O)].

Anal. Calcd for $C_{19}H_{22}N_6O_4$: C, 57.29; H, 5.53; N, 21.11. Found: C, 57.26; H, 5.82; N, 20.98.

B. The amine (1.55 g) and benzaldehyde (1 ml) were heated in acetic acid (40 ml) at 100 °C for 16 h. Removal of the acetic acid followed by the addition of methanol gave 1.24 g (31%) of **9b.**

Registry No.—**1a,** 59796-99-5; **1b,** 59797-00-1; **1c,** 59797-01-2; **2b,** 59797-02-3; **3,** 59797-03-4; **4,** 59797-04-5; **5,** 59797-05-6; **6a,** 59797-06-7; **6b,** 59797-07-8; **6c,** 59797-08-9; **7,** 59797-09-0; **8,** 17789-35-4; **9a,** 59797-10-3; **9b,** 13191-76-9; benzalacetophenone, 94-41-7; 6-amino-1,3-dimethyluracil, 6642-31-5; benzalpinacolone, 538-44-3; methyl vinyl ketone, 78-94-4; 3-penten-2-one, 625-33-2; benzalacetone, 122-57-6; cinnamaldehyde, 104-55-2; chloranil, 118-75-2; crotonaldehyde, 4170-30-3; 5-amino-1,3-dimethyluracil, 49738-24-1.

References and Notes

(1) Y. Tamura, T. Sakaguchi, T. Kawasaki, and Y. Kita, *Heterocycles*, **3**, 183 (1975). This publication appeared while the present study was under investigation.
(2) W. J. Irwin and D. G. Wibberley, *J. Chem. Soc. C*, 1745 (1967).

Reaction between 6-Azidoazolopyridazines or 2-Azidopyrido[1,2-*a*]pyrimid-4-one and Some Secondary Aliphatic Amines

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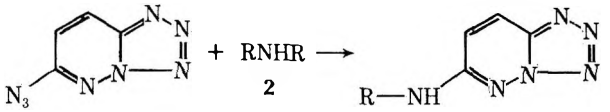
Azidoazoloazines react thermally or photochemically with secondary aliphatic amines to give N- and C-alkylated aminomethyleneamino derivatives. It is proposed that the reaction proceeds via an intermediate imine or enamine with subsequent cycloaddition of the azide. Decomposition of the formed triazoline can take place by several routes to give a mixture of reaction products. 2-Azidopyrido[1,2-*a*]pyrimid-4-one reacts in general in a different manner. Here, the amine is added to the carbonyl bond, the pyrimidine part of the bicycle is cleaved, and finally the azido group is isomerized into a tetrazole ring.

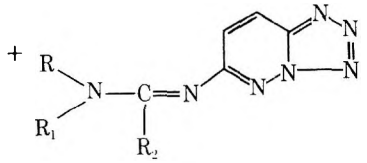
We have previously reported the unusual reaction between a heterocyclic azide and diethylamine.[1,2] To gain more insight into the mechanism of this transformation, we have now studied thermal and photochemical reactions between some higher secondary aliphatic amines and azidoazolopyridazines or 2-azidopyrido[1,2-*a*]pyrimid-4-one.

6-Azidotetrazolo[1,5-*b*]pyridazine (**1**) reacted with dipropylamine (**2a**) under reflux for 50 h to give a mixture of the corresponding amine (**3a**), the *N,N*-dipropylaminomethyleneamino derivative (**4a**), and its ethyl derivative (**4b**). A similar, but easier transformation took place with diisobu-



1 + RNHR (**2**) → **3**

R	R
a, *n*-Pr	a, H
b, *i*-Pr	b, $COCHMe_2$
c, Me_2CHCH_2	c, NEt_2
d, $Me_2CHCH_2CH_2$	
e, Et	



4

R	R_1	R_2
a, *n*-Pr	*n*-Pr	H
b, *n*-Pr	*n*-Pr	Et
c, H	*i*-Pr	Me
d, H	Me_2CHCH_2	*i*-Pr
e, Me_2CHCH_2	Me_2CHCH_2	*i*-Pr
f, $Me_2CHCH_2CH_2$	$Me_2CHCH_2CH_2$	H
g, $Me_2CHCH_2CH_2$	$Me_2CHCH_2CH_2$	Me_2CHCH_2
h, H	Et	H
i, Me_2CHCH_2	Me_2CHCH_2	H
j, Et	Et	H

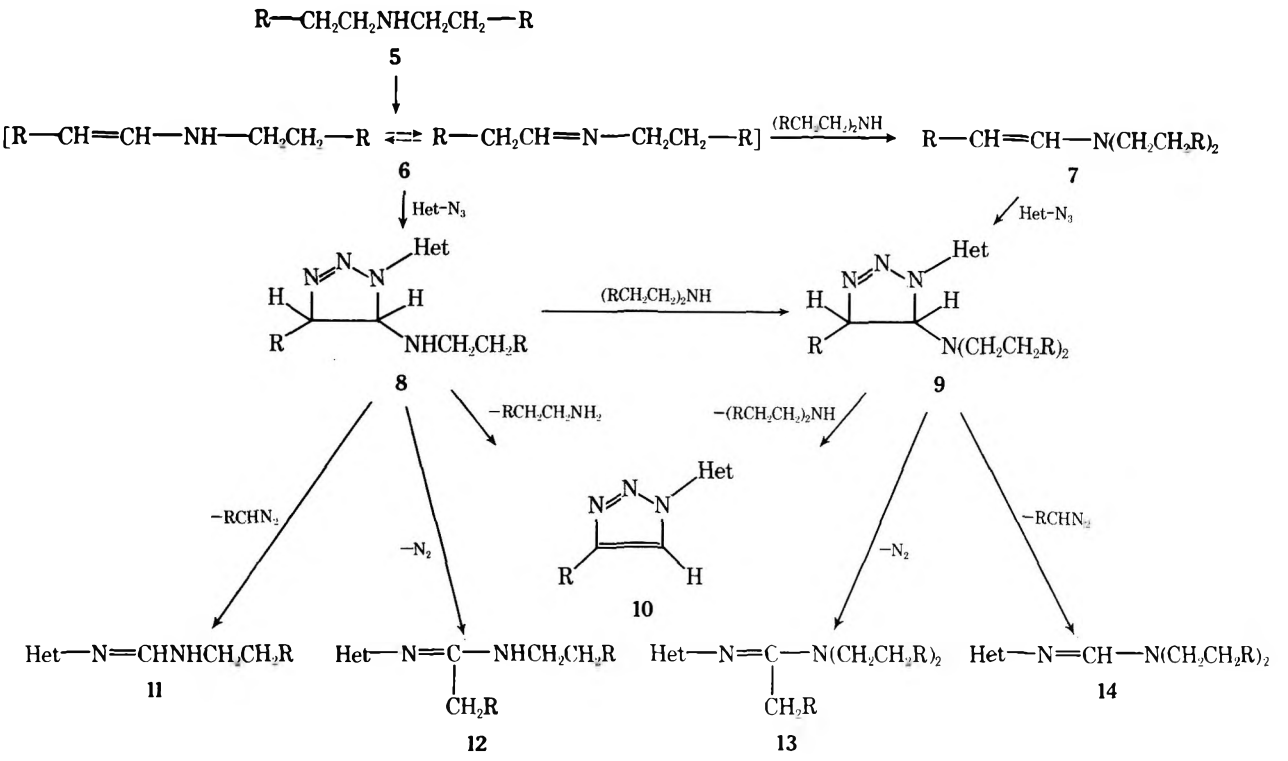
tylamine (**2c**) or diisopentylamine (**2d**) (6 h and 40 min, respectively) to give unusual products (**4d** and **4e**, or **4f** and **4g**, respectively). Diisopropylamine (**2b**) was very unreactive and only after 285 h at reflux a small amount of the *N*-alkylaminoalkyleneamino derivative (**4c**) could be isolated with much of **3a**. In this manner, in all cases, besides the heterocyclic amine as the major product, also di- or trisubstituted amidines were formed.

The above-mentioned results are best explained in terms of an intermediate imine or enamine (**6**), formed by dehydrogenation of the secondary aliphatic amine (**5**). Cycloaddition of the azide on the so-formed double bond[3,4] results in the formation of an unstable triazoline (**8**) which then decomposes in several ways. Elimination of the amine generates the triazole (**10**), whereas elimination of a diazoalkane affords compound **11** or elimination of nitrogen gives the alkylated compound (**12**). It can be anticipated that the *N,N*-dialkylamino derivatives **13** or **14** can be formed in a similar manner. Recently, we have shown that from the decomposition of a substituted triazole, resulting from the reaction between a heterocyclic azide and a 1,3-dicarbonyl compound, under mild reaction conditions a diazo compound is generated and detected.[5] Fragmentation of this type was observed earlier[6] and is operative in several other reactions.[7] No attempts have been made to detect diazoalkanes in our present experiments.

The *N,N*-dialkylamino side chain present in **13** and **14** could be formed in a transamination step from **6** to **7** or from **8** to **9**; the triazoline could then decompose to give either **10** or **13** or **14**. It was established in a separate experiment that the final products are not transaminated. Compound **4d** could not be transformed into **4e** with diisobutylamine under the same reaction conditions as employed for the reaction between **1** and **2c**. The transamination step must therefore occur at an earlier stage, either a conversion of **6** to **7** or **8** to **9**.

For a successful transformation, however, it is necessary that in the first step an unsaturated amine (**6**) be formed. Dehydrogenation of secondary amines can be carried out by a variety of reagents or catalytically.[8] There are no examples of dehydrogenation of a secondary aliphatic amine in the presence of an azide, but there are reports that some amides or amines can act as organic hydrogen abstractors.[9,10] Moreover, partial thermal decomposition of the azide in the reaction mixture gives a nitrenoid species which can abstract hydrogen. In a separate experiment we have treated ethylideneethylamine[11] (**15**) with the azide (**1**) and the reaction proceeded smoothly at room temperature to give the same mixture of products as observed previously in thermal decomposition of the same azide in diethylamine.[1] In a further experiment, a mixture of ethylideneethylamine and diisobutylamine was left to stand at room temperature for several days. The azide (**1**) was added to this reaction mixture and a vigorous reaction was observed. In addition to compound **3a**, the *N,N*-dialkylamino derivative (**4i**) was isolated and identified. This indicates that the ethylamine part of ethylideneethylamine was substituted with the higher secondary amine and that decomposition followed a reaction path similar to the conversion of **9** to **14**.

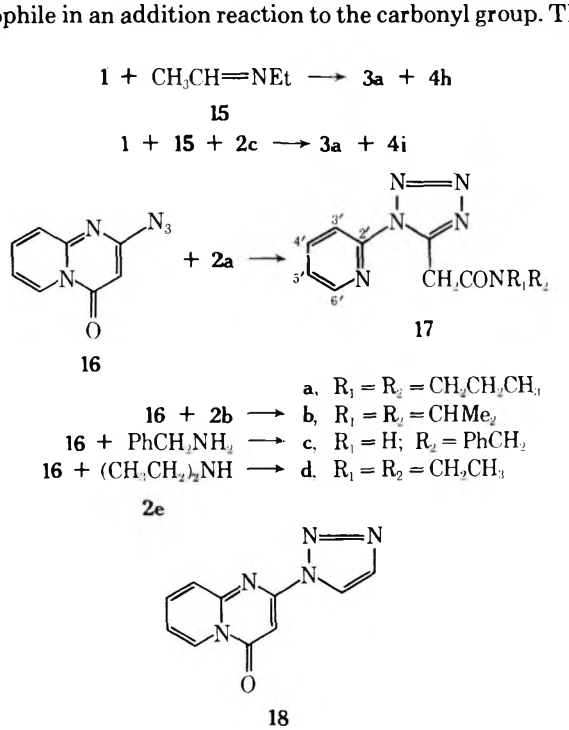
Furthermore, triethylamine reacts thermally in a similar manner as demonstrated previously[1] with diethylamine. Apparently dealkylation must take place during the conver-



sion. This process must be very slow since even after 25 days only partial conversion could be observed. There are known several methods for dealkylation of tertiary amines,[12] but none of them is plausible to explain our results. Heterocyclic amines, which result as the major product from the above reactions, are formed by thermal decomposition of the azides into nitrenes[13] which abstract hydrogens from the solvent, i.e., the secondary amines.

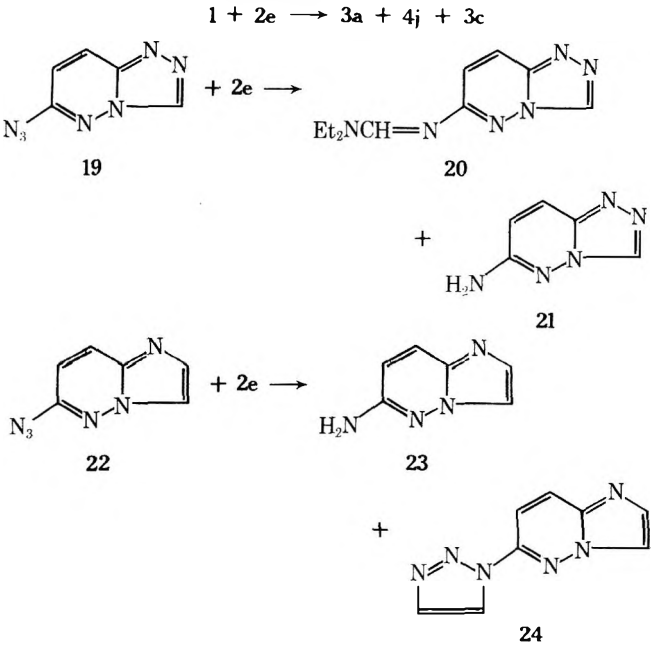
Compound **4d** could be hydrolyzed in 20% acetic acid to give the amide **2b**, in contrast to our previous observations[1] that hydrolysis of similar products afforded the heterocyclic amine (**3a**).

With 2-azidopyrido[1,2-*a*]pyrimid-4-one (**16**), thermal reactions with dipropylamine or diisopropylamine afforded the pyridyltetrazoles **17a** or **17b**. The formation of only these derivatives indicates that in this case the amine acts as nucleophile in an addition reaction to the carbonyl group. This



is followed by ring opening of the pyrimidine part and simultaneous formation of the tetrazole ring. Thus, the nucleophilic addition is faster than the formation of an unsaturated amine and addition of the azide to the formed double bond. This is similar to our previous findings when stronger nucleophiles were employed.[14] Diethylamine reacted partly in the same manner to give **17d**, but in addition compound **18** could be isolated and identified.

Moreover, we have found that the investigated azides react with secondary amines photochemically in almost the same manner as thermally. However, these reactions are less complex, but afford sometimes different reaction products than thermal reactions, since they are performed under less drastic reaction conditions. The azide (**1**) when irradiated at room temperature in the presence of diethylamine for 24 h afforded



in addition to compounds **4j** and **3c** the amine **3a** as the main product. Compound **3c**, however, was not isolated from a thermal decomposition and its formation in a photochemical

Table I [d]

Reaction components (quantity)	Time, h	Products and yield	Mp, °C	Solvent for crystn	R_f	Formula	Mass spectrum M^+, m/e	Solvent	^1H NMR data Chemical shifts (δ) and coupling constants (J)
1 (1 g) + **2a** (40 ml)	50	**3a** (104 mg, 12%)	(ref 24)						
		4a (92 mg, 6%)	58	MeOH, hexane	0.27[a]	$C_{11}H_{17}N_7$	247	CD_3OD	7.27 (d, H_7), 8.15 (d, H_8), 8.48 (s, CH=N), $J_{7,8}$ = 9.7 Hz
		4b (185 mg, 11%)	bp 208–209		0.41[a]	$C_{13}H_{21}N_7$	275	$CDCl_3$	7.02 (d, H_7), 7.94 (d, H_8), $J_{7,8}$ = 10.0 Hz
1 (2 g) + **2b** (30 ml)	285	**3a** (1.43 g, 85%)							
		4c (62 mg, 2.3%)	129	$CHCl_3$ and hexane	0.17[b]	$C_9H_{13}N_7$	219	Me_2SO-d_6	7.24 (d, H_7), 8.38 (d, H_8), 1.20 (d, $CHMe_2$), 4.13 (m, $CHMe_2$), 2.15 (s, –N=C–CH_3), $J_{7,8}$ = 9.8, $J_{i\text{-Pr}}$ = 6.5 Hz
1 (1 g) + **2c** (10 ml)	6.25	**3a** (275 mg, 33%)							
		4d (200 mg, 12%)	112–113	$CHCl_3$ and petroleum ether,[c] MeOH and H_2O	0.59[a]	$C_{12}H_{19}N_7$	261	Me_2SO-d_6	7.27 (d, H_7), 8.44 (d, H_8), $J_{7,8}$ = 10.0 Hz
		4e (120 mg, 6%)	168–169	$CHCl_3$ and petroleum ether,[c] $CHCl_3$ and hexane	0.67[a]	$C_{16}H_{27}N_7$	317	$CDCl_3$	7.04 (d, H_7), 7.98 (d, H_8), 3.12 (septuplet, $CHMe_2$), $J_{7,8}$ = 10.0, $J_{i\text{-Pr}}$ = 7.2 Hz
1 (1 g) + **2d** (6 ml)	0.66	**3a** (480 mg, 57%)							
		4f (32 mg, 1.7%)	92–96	$CHCl_3$ and petroleum ether[c]	0.50[a]	$C_{15}H_{25}N_7$	303	$CDCl_3$	7.23 (d, H_7), 8.09 (d, H_8), 8.60 (s, CH=N), $J_{7,8}$ = 9.5 Hz
		4g (100 mg, 4.5%)	bp 230–231		0.70[a]	$C_{19}H_{33}N_7$	359	CD_3OD	7.20 (d, H_7), 8.22 (d, H_8), $J_{7,8}$ = 9.7 Hz
16 (1 g) + **2a** (25 ml)	170	**17a** (956 mg, 62%)	135–136	MeOH and H_2O (1:2)	0.58[b]	$C_{14}H_{20}N_6O$	288	Me_2SO-d_6	8.05 (m, $H_{3'}$, $H_{4'}$), 7.55 (m, $H_{5'}$), 8.52 (m, $H_{6'}$)
16 (1 g) + **2b** (50 ml)	185	**17b** (975 mg, 63%)	137–138	MeOH and H_2O (1:2)	0.33[a]	$C_{14}H_{20}N_6O$	288	Me_2SO-d_6	7.96 (m, $H_{3'}$, $H_{4'}$), 7.45 (m, $H_{5'}$), 8.45 (m, $H_{6'}$), 5.83 and 6.60 (septuplet, $CHMe_2$), $J_{i\text{-Pr}}$ = 6.9 Hz
16 (0.5 g) + $PhCH_2NH_2$ (1 ml)	1	**17c** (750 mg, 95%)	163–164	EtOH		$C_{15}H_{14}N_6O$	266 (M^+-N_2)	Me_2SO-d_6	8.45 (m, $H_{6'}$), 7.9–8.2 (m, $H_{3'}$, $H_{4'}$), 7.55 (m, $H_{5'}$), 7.18 (s, C_6H_5)

[a] $CHCl_3$. [b] $CHCl_3$–MeOH, 50:1. [c] Petroleum ether, bp 40–60 °C. [d] Satisfactory analytical data were obtained for all compounds listed.

process can be interpreted via an intermediate nitrene, generated from the azide, and secondary amine. This is similar to the observed formation of a substituted hydrazine in a photochemical decomposition of an aromatic azide in the presence of dimethylamine[15,16] and such insertions are also known with some heteroaromatic azides.[17,18] In a similar manner as **1** the azide **19** afforded a mixture of **20** and **21**, but in the case of 6-azidoimidazo[1,2-*b*]pyridazine (**22**) it was possible to isolate from the reaction mixture besides the amine (**23**) also the triazole (**24**). The isolation and identification of this triazole as well as that of **18** supports the above proposed mechanism of formation of intermediates like **8** or **9**. Compound **24** is a 1-substituted triazole and is apparently photostable, although it has been observed that only 2-substituted 1,2,3-triazoles are photostable and others easily eliminate nitrogen.[19–23]

This is probably not the case with compound **18**, since in a photochemical reaction of compound **16** with diethylamine only **17d** was isolated and no **18** could be detected, which contrasts with the corresponding thermal transformation.

Experimental Section

Melting points were determined on a Kofler apparatus. Spectral data were obtained from a JEOL C-60HL spectrometer and Hitachi Perkin-Elmer RMU-6L mass spectrometer. Photochemical reactions were carried out in a Rayonet photoreactor RPR-100 at 300 nm.

General Procedure for Thermal Reaction between 6-Azidotetrazolo[1,5-*b*]pyridazine and an Aliphatic Secondary Amine. A mixture of the azide (1) and secondary amine was heated under reflux (boiling point of the particular secondary amine). At the end of the reaction, the mixture was evaporated in vacuo to dryness, $CHCl_3$ (40–50 ml) was added, and compound **3a** was filtered off. The filtrate was chromatographed by TLC (DC-Fertigplatten Kieselgel F_{254}, 0.5 mm). The separated compounds were eluted and crystallized. The reaction conditions, melting points of the products, yields, NMR, and other data are presented in Table I.

***N*-(Tetrazolo[1,5-*b*]pyridazinyl-6)isobutyramide (3b).** A solution of compound **4d** (50 mg) in diluted acetic acid (1:4, 3 ml) was heated under reflux for 2 h. The reaction mixture was evaporated to dryness and the residue was crystallized from $CHCl_3$ and petroleum ether (bp 40–60 °C): mp 176–179 °C (yield 26 mg, 66%); NMR (CD_3OD) δ 8.66 and 8.45 (d, H_7 H_8), 2.75 (septuplet, $CHMe_2$), $J_{7,8}$ = 10.5, J_{CHMe_2} = 6.8 Hz; mass spectrum $M^{\cdot+}$ 206.091475 (calcd for $C_8H_{10}N_6O$, 206.091603).

Reaction between 1 and Ethylideneethylamine. Compound **1** (1 g) was added portionwise to ethylideneethylamine (**15**)[11] (3 ml, containing 30% ethylamine). After the vigorous reaction had subsided, the reaction mixture was left to stand at room temperature for 1 h. The mixture was evaporated to dryness, $CHCl_3$ (20 ml) was added, and the product was filtered off and washed with $CHCl_3$ (15 ml). The compound was identified as **3a**.[24] The filtrate was chromatographed by TLC, $CHCl_3$ as solvent. The strongly fluorescent compound with R_f 0.5 was eluted and compound **4h** (31 mg, 3%) was obtained and identified.[1]

Synthesis of Compound 4i. A mixture of ethylideneethylamine (**15**, 1.5 ml, containing 30% ethylamine) and diisobutylamine (1.5 ml) was left at room temperature in a sealed vessel for 4 days. To this mixture compound **1** (1 g) was added portionwise. After the vigorous reaction had subsided, the reaction mixture was left at room temperature for 1 h and evaporated to dryness. $CHCl_3$ (20 ml) was added and compound **3a** (220 mg, 26%) was filtered off. The filtrate was purified by TLC and after the strongly fluorescent product with R_f 0.42 was eluted, it was identified as compound **4i**: mp 93–96 °C (37 mg, 2% yield) (from $CHCl_3$ and petroleum ether, bp 40–60 °C); mass spectrum $M^{\cdot+}$ 275.185839 (calcd for $C_{13}H_{21}N_7$, 275.185834); NMR ($CDCl_3$) δ 7.25 (d, H_7), 8.12 (d, H_8), 8.65 (s, CH=N), 2.0 ($CHMe_2$), $J_{7,8}$ = 9.5, $J_{i\text{-}Pr}$ = 7.0 Hz.

Reaction between 2-Azidopyrido[1,2-*a*]pyrimid-4-one (16) and Diethylamine. A mixture of compound **16**[14] (0.5 g) and diethylamine (100 ml) was heated under reflux for 115 h. The reaction mixture was evaporated to dryness, ethanol (15 ml) was added, and the product was filtered off. The compound was purified by crystallization from aqueous ethanol and identified as **18**: mp 232–233 °C (yield 80 mg, 14%); NMR (DMF-d_7) δ 6.89 (s, H_3), 9.0 (m, H_6), 8.18–7.22 (m, H_7, H_8, H_9), 7.82 (d, $H_{4'}$), 8.67 (d, $H_{5'}$), $J_{4',5'}$ = 1.3 Hz; mass spectrum $M^{\cdot+}$ 213.

Anal. Calcd for $C_{10}H_7N_5O$: C, 56.33; H, 3.31; N, 32.85. Found: C, 56.07; H, 3.52; N, 32.63.

The filtrate was evaporated to dryness, $CHCl_3$ (3 ml) was added, and the solution was treated with charcoal and after 30 min was filtered and poured into hexane (15 ml). The separated product **17d** was crystallized three times from $CHCl_3$ and hexane, mp 88–90 °C (320 mg, 46%), mass spectrum $M^{\cdot+}$ 260.

Anal. Calcd for $C_{12}H_{16}N_6O$: C, 55.37; H, 6.20; N, 32.29. Found: C, 54.98; H, 6.35; N, 32.60.

Reactions of **16** with other amines were performed in a similar manner and the products **17a**, **17b**, and **17c** are presented in Table I.

Photochemical Reaction between 1 and Diethylamine. A mixture of compound **1** (0.8 g) and diethylamine (24 ml) was irradiated in a photoreactor for 24 h at room temperature. The reaction mixture was evaporated in vacuo to dryness, $CHCl_3$ (24 ml) was added, and the separated product was filtered off. It was identified as **3a** (230 mg, 34%). The filtrate was purified by TLC (DC-Fertigplatten Al_2O_3 F_{254} T, 1.5 mm, $CHCl_3$ as solvent). The compound with R_f 0.82 was identified as **4j**[1] (182 mg, 17%) and the other compound with R_f 0.55 was crystallized from $CHCl_3$ and hexane and identified as **3c**: mp 88–92 °C (32 mg, 3%); NMR ($CDCl_3$) δ 7.67 (d, H_7), 8.22 (d, H_8), $J_{7,8}$ = 10.4 Hz; mass spectrum $M^{\cdot+}$ 207.

Anal. Calcd for $C_8H_{13}N_7$: C, 46.36; H, 6.32; N, 47.32. Found: C, 46.31; H, 6.03; N, 47.59.

In a similar manner compound **19** (0.5 g) was irradiated in the presence of **2e** (110 h) to give a mixture of **20**[1] (85 mg, 13%), **21** (25 mg, 6%), and starting compound **19** (25 mg). When compound **22** (2 g) was irradiated in the presence of **2e** for 62 h, compounds **23** (145 mg, 9%) and **24**[1] (54 mg, 2%) were isolated and identified.

Photochemical Reaction of 16 with 2e. A mixture of the azide **16** (0.34 g) and diethylamine (10 ml) was irradiated for 110 h (at 300, 254, or 350 nm) at room temperature. After evaporation to dryness the residue was dissolved in $CHCl_3$ and purified by TLC (DC-Fertigplatten Al_2O_3 F_{254} T, 1.5 mm, $CHCl_3$ as solvent. The compound with R_f 0.53 was eluted and crystallized from $CHCl_3$ and hexane and identified as **17d** (160 mg, 34%).

Acknowledgment. We thank the B. Kidric Fund for partial support of this work.

Registry No.—**1**, 14393-79-4; **2a**, 142-84-7; **2b**, 108-18-9; **2c**, 110-96-3; **2d**, 544-00-3; **2e**, 109-89-7; **3a**, 19195-43-8; **3b**, 59711-30-7; **3c**, 59711-31-8; **4a**, 59711-32-9; **4b**, 59711-33-0; **4c**, 59711-34-1; **4d**, 59711-35-2; **4e**, 59711-36-3; **4f**, 59711-37-4; **4g**, 59711-38-5; **4i**, 59711-39-6; **15**, 1190-79-0; **16**, 55395-31-8; **17a**, 59711-40-9; **17b**, 59711-41-0; **17c**, 59711-42-1; **17d**, 55395-34-1; **18**, 59711-43-2; **19**, 14393-80-7; **22**, 13526-73-3; $PhCH_2NH_2$, 100-46-9.

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Heterocyclic Studies. 44. Thermal Rearrangement of 2-Acyl-1,2-diazabicycloheptenones

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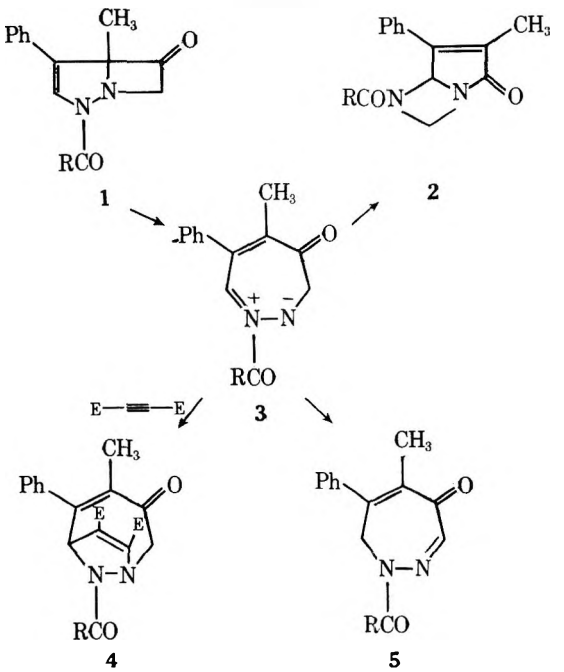
1-Acyl-2-(alkoxymethyl)tetrahydropyridazinones **8** are obtained from the bicyclic ketones **1** on heating in alcohol or alcohol–benzene mixtures and are suggested to arise by trapping of the intermediate **10**. A pathway from **10** to the bicyclic pyrrolinones **2** is suggested (Scheme II).

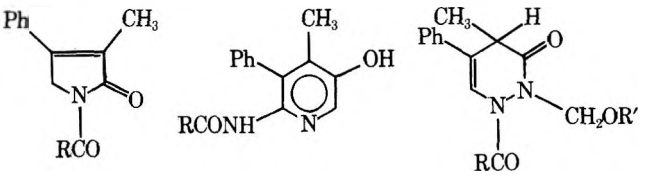
Some years ago we reported the transformation of the bicyclic ketones **1**, on warming, to the isomeric bicyclic pyrrolinones **2**.[3] It was subsequently found that the 1-acyl-1,7-dihydrodiazepinone **5a** is a minor product accompanying **2a**, and that heating **1** in the presence of acetylenedicarboxylic ester gives the adducts **4**.[4] The formation of **4** and **5** clearly point to the acyldiazepinium betaine **3** as an initial intermediate in the thermal reaction of **1**. We now present information about further steps in the unusual rearrangement to **2**.

Scheme I



a, R = CH_3
b, R = C_6H_5

A clue to the pathway from **1** to **2** was obtained from a study of the reactions of the bicyclic ketones with alcohols. In methanol, **1a** and **1b** are converted to mixtures of the acylpyrrolinones **6** and 3-hydroxypyridines **7** as described in an earlier paper.[5] However, when the benzoyl ketone **1b** was heated in benzene containing 10% methanol, the major product in the mixture was different from those obtained in either solvent alone; the NMR spectrum indicated the presence of $CH_3OCH_2N<$ and $CH_3CH<$ groups.[6] A homologous product was then isolated as a crystalline solid from the reaction of **1b** in refluxing absolute ethanol, and the tetrahydropyridazinone structure **8b** (R′ = Et) was established by crystallographic analysis. The pyridine **7b** is a minor product in the reaction of **1b** in ethanol, but is formed in progressively larger amount, together with pyrrolinone **6b**, as the reaction temperature is lowered to 50 °C, or when traces of water are

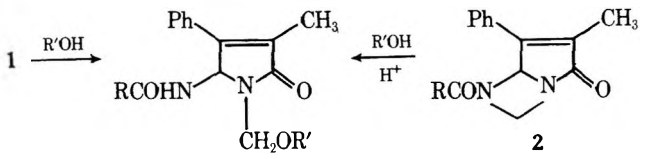


6 **7** **8**

a, R = CH_3
b, R = C_6H_5

present. Thus, even in 99% ethanol at 70 °C for 1 h, the product was a mixture of **7b** and (ca. 10%) **6b**, and contained little if any pyridazinone **8b**.

In isopropyl alcohol, the pyridazinone **8b** (R′ = *i*-Pr) was isolated as the major product from **1b** at 50 °C, but as the temperature was increased to 80 °C, another compound was formed in progressively larger amount. This substance was isolated by chromatography and identified as the 1-isopropoxymethyl pyrrolinone **9b** (R′ = *i*-Pr). Finally, the reaction



9 **2**

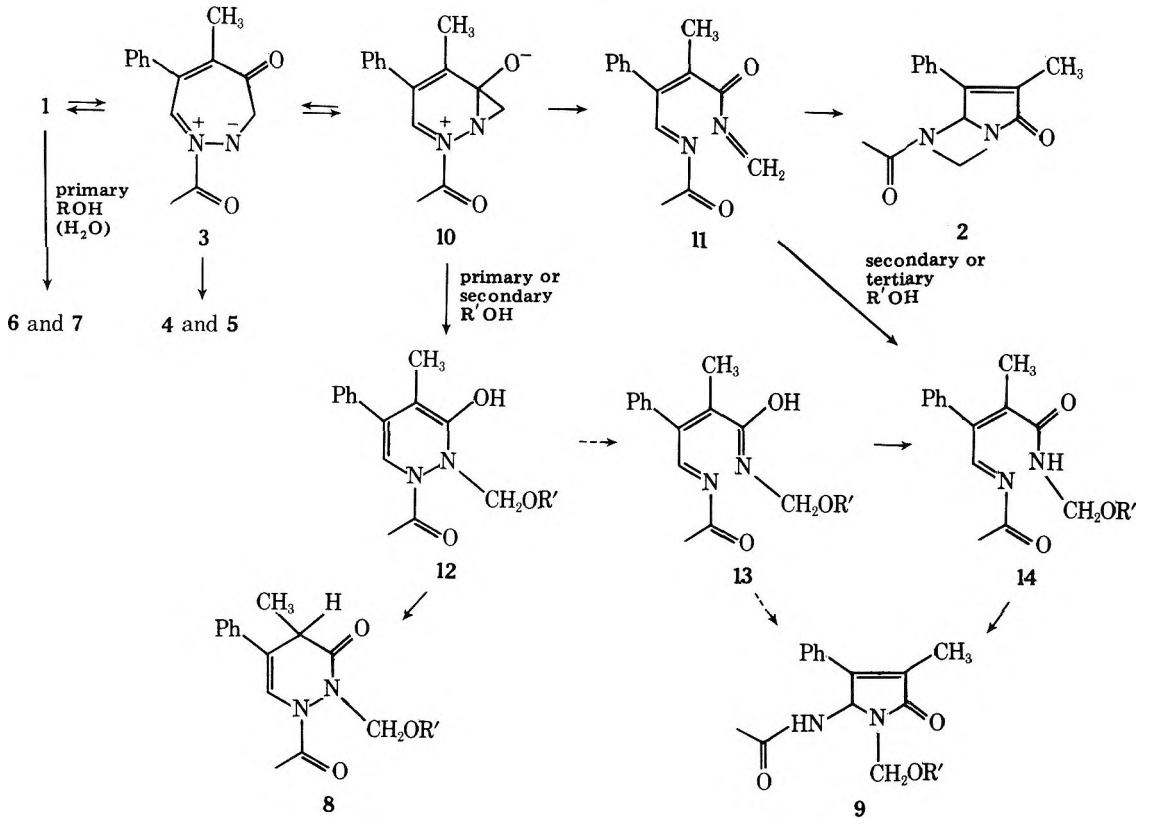
a, R = CH_3
b, R = C_6H_5

of **1b** in *tert*-butyl alcohol gave the pyrrolinone **9b** (R′ = *t*-Bu) as the principal product at 50 °C, with a minor amount of the pyridazinone **8b** (R′ = *t*-Bu). At 80 °C, only a trace of **8b** was present, and **9b** was isolated by direct crystallization.

The alkoxymethylpyrrolinones **9** were identified by comparison with samples prepared by alcoholysis of the bicyclic pyrrolinone **2**. This reaction, which was a key step in the structure elucidation of **2**,[3] occurs slowly on heating **2** in alcohols and very rapidly in the presence of acid. It was supposed initially that the pyrrolinones **9b**, R′ = *i*-Pr and *t*-Bu, arose in the reactions of **1b** by ring opening of the bicyclic pyrrolinone **2b**. However, this process was shown not to be the major source of the alkoxymethylpyrrolinone from **1b** in *tert*-butyl alcohol, since the reaction of **2b** with *tert*-butyl alcohol is much slower than that of **1b** under the same conditions. After a mixture of **1b** and **2b** was heated in *tert*-butyl alcohol solution at 60 °C for 24 h, the NMR spectrum showed nearly complete reaction of **1b**, with formation of **9b**, and only minor loss of **2b**.

Qualitatively similar behavior was observed with the acetyl ketone **1a** in alcohols, but the reaction mixtures were complicated by the presence of the dihydrodiazepinone **5a**. (In the thermal reactions of **1a** and **1b** in benzene, **5a** and **5b** amount to about 35 and 10% of the product, respectively.[4])

Scheme II



In refluxing isopropyl alcohol, the acetyl ketone **1a** was converted to the pyridazinone **8a** (R′ = *i*-Pr) and 15–20% of **5a**; **8a** was not obtained in crystalline form and was characterized only by NMR. The reaction mixture from **1a** in refluxing *tert*-butyl alcohol was complex, and probably contained **8a** and **9a** (R′ = *t*-Bu). In benzene containing 10% *tert*-butyl alcohol, NMR showed a mixture of **2a**, **5a**, and **9a** (R′ = *t*-Bu). The mixture was not separated; **9a** (R′ = *t*-Bu) was identified by the correspondence of eight distinctive NMR peaks with those of a sample prepared from **2a**.

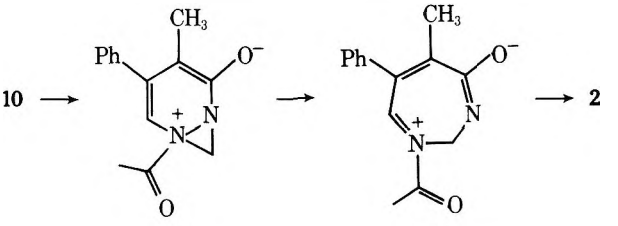
Discussion

The succession of products obtained from the ketones **1** with alcohols of decreasing nucleophilic power suggests the trapping of a series of increasingly reactive intermediates which lead eventually, if not intercepted, to the rearrangement product **2**. One sequence that seems consistent with the data is shown in Scheme II.

In the most polar media, methanol and aqueous ethanol, the ketones undergo reactions at 50–60 °C or below that are more rapid than the ring opening to **3**. These reactions, which will be described in more detail in a later paper, lead to the previously described products **6** and **7**. At 50 °C and above, reactions proceeding via **3** become progressively more important, particularly in less polar media.

Compounds **4** and **5** (Scheme I) provide evidence for the initial intermediate **3**, formed by 6π electrocyclic ring opening of **1**. A second bicyclic valence isomer available from **3** is **10**. Nucleophilic attack by primary or secondary alcohols at the three-membered ring of **10** would lead, via the enol **12**, to the pyridazinone **8**. In the absence of a reactive nucleophile, collapse of **10** could give the acyclic intermediate **11**. The CON=CH_2 system of **11** would be highly electrophilic, perhaps sufficiently so to undergo addition of sterically hindered alcohols, giving **14** and thence the pyrrolinones **8**. Finally, when generated in an unreactive medium, recyclization of **11** would give the end product **2**.

Several alternatives to the steps in Scheme II can be considered. Thus an acyclic enol **13**, which could arise by ring opening of **12**, would provide another plausible path to **9**. In an attempt to test this possibility, the pyridazinone **8b** (R′ = Et) was heated under reaction conditions in which **9** is formed from **1**, but no reaction was observed. An alternative pathway from **10** to **2** involves intermediates **15** and **16**, but further



comment on these or other possibilities is not justified by the present data. The sequence involving intermediates **10** and **11** provides a rational basis for the products observed, and is clearly an improvement over our earlier speculations on the formation of **2**.[3]

Crystallography. Crystals of **8b** (R′ = Et) are orthorhombic, space group $P2_12_12_1$, with a = 13.911 (25), b = 14.184 (12), c = 19.630 (16), and Z = 8. The intensity data were collected on a Hilger-Watts diffractometer (θ–2θ scans, Ni-filtered Cu Kα radiation, pulse height discrimination). The size of the crystal used for data collection was 0.1 × 0.3 × 0.5 mm. Of the 2976 reflections with $\theta < 57°$, 2346 had intensities which were significantly greater than background. The structure was solved by a multiple solution procedure.[7] The first E map calculated revealed all of the atoms of one molecule and half of the atoms of the other molecule in the asymmetric unit. The remaining atoms were found on an electron density map based on these atoms. Full-matrix least squares was used for the initial refinement in which all atoms had isotropic temperature factors. For the anisotropic refinement, block diagonal least squares was used in which the matrix was partitioned into two blocks. A difference map calculated at the conclusion

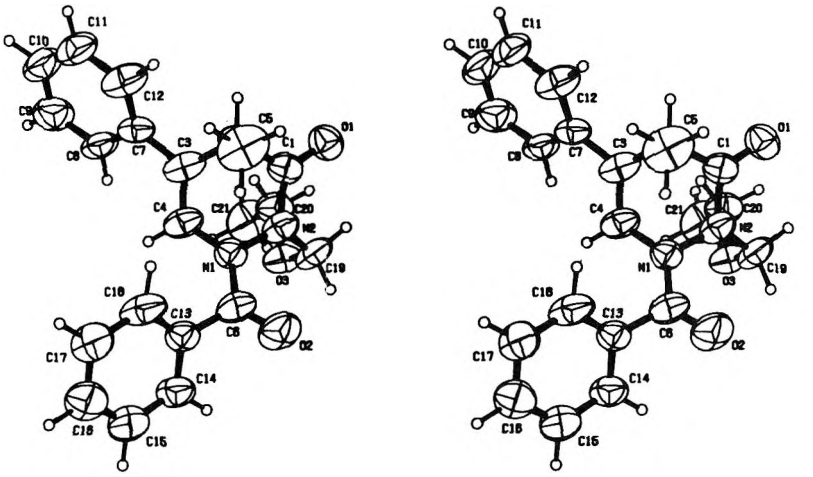


Figure 1. ORTEP projection of **8b** (R′ = Et).

of the anisotropic refinement of the heavier atoms had peaks at reasonable positions for many of the hydrogen atoms. In the final refinement anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms, which were held fixed at their calculated positions. The final unweighted and weighted discrepancy indices are $R = 0.088$ and $wR = 0.099$ for the 2346 observed reflections. The final difference map has no peaks greater than ±0.5 eÅ^{-3}. The final atomic coordinates are tabulated in supplementary pages (see paragraph at end of paper regarding supplementary material). A stereoscopic view of the structure is shown in Figure 1. There are two independent molecules in the unit cell. One molecule (primed) is related to the other (unprimed) by a noncrystallographic pseudoglide plane.

$$x' = x - (0.006 \pm 0.007)$$
$$y' = y + (0.270 \pm 0.007)$$
$$z' = -z - (0.011 \pm 0.010)$$

The relatively high R values are attributed to the fact that a suitable single crystal was not available. The specimen used for data collection was cut from a multiple crystal, and may not have been a true single crystal. Despite the high R values, the correctness of structure **8b** (R′ = Et) is supported by several lines of evidence. All bond lengths (std dev 0.015 Å) and bond angles (std dev 1.0°) are consistent with the structure. Prominent peaks were found for the hydrogen atoms at C(2) and C(4) in both independent molecules. Finally, the R factors for the isotropic refinement of two other trial structures were higher than those for structure **3**. The results of the three isotropic refinements were (a) N(1), N(2), N(1)′, N(2)′ as nitrogens, $R = 0.166$, $wR = 0.181$; (b) N(1), C(4), N(1)′, C(4)′, as nitrogens and N(2), N(2)′ as carbons, $R = 0.169$, $wR = 0.183$; (c) N(2), C(4), N(2)′, C(4)′ as nitrogens and N(1), N(1)′ as carbons, $R = 0.171$, $wR = 0.185$.

Experimental Section

NMR spectra designated FT 90 MHz were recorded on a Bruker HFX 90 instrument; other NMR spectra were obtained with Perkin-Elmer R-12B or Varian A-60A spectrometers.

1-Benzoyl-2-ethoxymethyl-4-methyl-5-phenyl-1,2,3,4-tetrahydropyridazin-3-one (8b, R′ = Et). A solution of 3.0 g of **1b** in 15 ml of absolute ethanol was refluxed for 7.5 h and then evaporated to a yellow gum; the NMR spectrum indicated the presence of mainly **8b** and a minor amount of **7b**. The gum crystallized after addition of ether to give 1.1 g of colorless solid; an additional 0.4 g of solid was obtained on further crystallization from ethanol. Recrystallization from aqueous ethanol gave slender rods: mp 110–112 °C; δ ($CDCl_3$) (90 MHz FT) 1.14 (t, J = 7.0 Hz), 1.51 (d, J = 7.3 Hz), 3.44 (q, J = 7.0 Hz), 3.72 (dd, J = 1.2, 7.3 Hz) [H-4], 4.99 (d, J = 11 Hz) and 5.58 (d, J = 11 Hz) [AB NCH_2O], 7.19–7.69 ppm (m).

Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 8.00. Found: C, 71.73; H, 6.32; N, 8.02.

A sample crystallized slowly from ethanol at 38–30 °C and was used for crystallographic analysis.

Isopropoxymethylpyridazinone 8b (R′ = *i*-Pr). A solution of 160 mg of **1b** in 15 ml of 2-propanol was kept in a 50 °C bath for 4 days and evaporated to a yellow syrup which crystallized after standing for 12 h. Recrystallization from 2-propanol plus water gave 69 mg of **7b** (R = *i*-Pr) as colorless crystals: mp 123–124 °C; δ ($CDCl_3$) (90 MHz FT) 1.09 (d, J = 6.1 Hz) and 1.14 (d, J = 6.0 Hz) [nonequivalent isopropyl CH_3 groups], 1.52 (d, J = 7.2 Hz), 3.57 (septet, J = 6.1 Hz), 3.70 (dd, J = 1.3 and 7.3 Hz) [H-4], 4.95 (d), and 5.64 (d, J = 11 Hz) [NCH_2O], 7.2–7.69 ppm (m).

Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.98; H, 6.29; N, 7.83.

5-Benzamido-1-isopropoxymethyl-3-methyl-4-phenyl-3-pyrrolin-2-one (9b, R′ = *i*-Pr). The bicyclic pyrrolinone **2b** (50 mg) was suspended in 1 ml of 2-propanol and 1 drop of concentrated HCl was added. The solid rapidly dissolved; after 2 min, 3 ml of water was added. The resulting crystalline solid was collected and recrystallized from 2-propanol to give 300 mg of **9b** (R′ = *i*-Pr) as colorless needles: mp 176–117 °C; δ ($CDCl_3$) 1.15 [d, J = 5.9 Hz, $(CH_3)_2CH$–], 2.10 (s, CH_3), 3.75 (septet, J = 5.9 Hz), 4.75 (d, J = 10 Hz), and 5.03 (d, J = 10 Hz) [NCH_2O], 6.7–7.2 (m, H-5 and NH), 7.2–8.0 ppm (m).

Anal. Calcd for $C_{22}H_{24}O_3N_2$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.63; H, 6.81; N, 7.78.

9b (R′ = *i*-Pr) from 1b. A solution of 300 mg of **1b** in 15 ml of 2-propanol was refluxed for 7 h and then evaporated to a yellow syrup. The NMR spectrum showed a mixture of **8b** and **9b** in a ratio of 2:1. A portion of this syrup was chromatographed on a 20 × 20 cm silica gel plate with $CHCl_3$ as eluent. The pyridazinone **8b** was present in a band just below the solvent front. A central band containing **9b** was scraped from the plate and extracted to give 30 mg of **9b** as colorless needles, mp 173–175 °C.

***tert*-Butoxymethylpyrrolinone 9b, R′ = *t*-Bu.**[8] A solution of 1.0 g of **2b** in 50 ml of *tert*-butyl alcohol was refluxed for 6 h. After evaporation of the alcohol, the residual yellow oil crystallized on addition of ether. Recrystallization from ether gave 610 mg of white needles of **9b** (R′ = *t*-Bu): mp 171–172 °C; ν^{KBr} 3400, 1725, 1660 cm^{-1}; δ ($CDCl_3$) 1.21 (s, *t*-Bu), 2.11 (d, J = 0.6 Hz, 3-CH_3), 4.80 (J = 9 Hz) and 5.00 (J = 9 Hz) [AB NCH_2O], 6.85 and 6.95 (multiplets, H-5 and NH), 7.27–7.95 ppm (m, 10).

Anal. Calcd for $C_{23}H_{26}O_3N_2$: C, 72.99; H, 6.93. Found: C, 72.95; H, 6.83.

Reaction of Acetyl Ketone 1a in Isopropyl Alcohol. Following the general procedure used to examine the products from **1a** and **1b** by NMR, a solution of 35 mg of **1a** in 1.5 ml of *i*-PrOH was refluxed (16 h) and evaporated to an oil in vacuo. CCl_4 was added and evaporated three times and the NMR spectrum in $CDCl_3$ was then recorded. Peaks for **8a** (R = *i*-Pr): δ 1.10 (d, J = 6.2 Hz) and 1.15 (d, J = 6.2 Hz) [nonequivalent isopropyl CH_3], 1.40 (d, J = 7.5 Hz), 3.76 (center of symmetrical six-line multiplet), 5.07 (d, J = 11 Hz), 5.70 (d, J = 11 Hz) [AB NCH_2O], 7.55 (s, aryl). Peaks for **5a:** δ 1.95 (s), 2.48 (s), 5.00 (s). The ratio of peak heights indicated a ratio of **8a**/**5a** of ~8:1.

***tert*-Butoxymethylpyrrolinone 9a (R′ = *t*-Bu).** A sample of **2a**[4] was prepared by refluxing a solution of 210 mg of bicyclic ketone **1a** in toluene for 50 min. After evaporation, crystals of **5a** were obtained from the yellow oil by treatment with ether. After removal of two crops

of **5a**, the residual oil, 126 mg, which could not be crystallized, had the NMR spectrum of **2a**[4] [δ 1.90 (d, J = 1.5 Hz), 2.10 (s), 5.10 (d, J = 10 Hz), 5.88 (m), 5.92 (d, J = 10 Hz), 7.5–7.9 (m)] with only a trace of **5a**. A solution of this oil in 2 ml of *tert*-butyl alcohol was heated for 16 h at 70 °C and was then evaporated. Crystals formed slowly from ether. Repeated recrystallization from ether gave colorless needles of **9a** (R′ = *t*-Bu): mp 177–178 °C; δ 1.30 (s, *t*-Bu), 2.0 (d, J ~0.4 Hz, 3-CH_3), 2.11 (d, $COCH_3$), 4.80 (d, J = 9.5 Hz) and 5.05 (d, J = 9.5 Hz) [$-OCH_2N$], 6.1 and 6.9 (both apparent doublets, NH and H-5, 7.6 (s, C_6H_5).

Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.38; H, 7.66; N, 8.88.

Registry No.—**1a**, 5109-37-5; **1b**, 5109-45-5; **2a**, 36004-91-8; **2b**, 10137-20-9; **5a**, 36004-94-1; **8a** (R′ = *i*-Pr), 59729-10-1; **8b** (R′ = Et), 59729-11-2; **8b** (R′ = *i*-Pr), 59729-12-3; **9a** (R′ = *t*-Bu), 59729-13-4; **9b** (R′ = *i*-Pr), 59729-14-5; **9b** (R′ = *t*-Bu), 59729-15-6.

Supplementary Material Available. Table of atomic coordinates (5 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Visiting professor at University of Delaware from University of the Witwatersrand, Johannesburg, South Africa.
(2) Hoffmann-La Roche Inc.
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(8) This experiment was carried out by C. M. Kopay.

A Symmetrical Diazaditwistane. 2,9-Dicyano-5,11-dimethyl-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane

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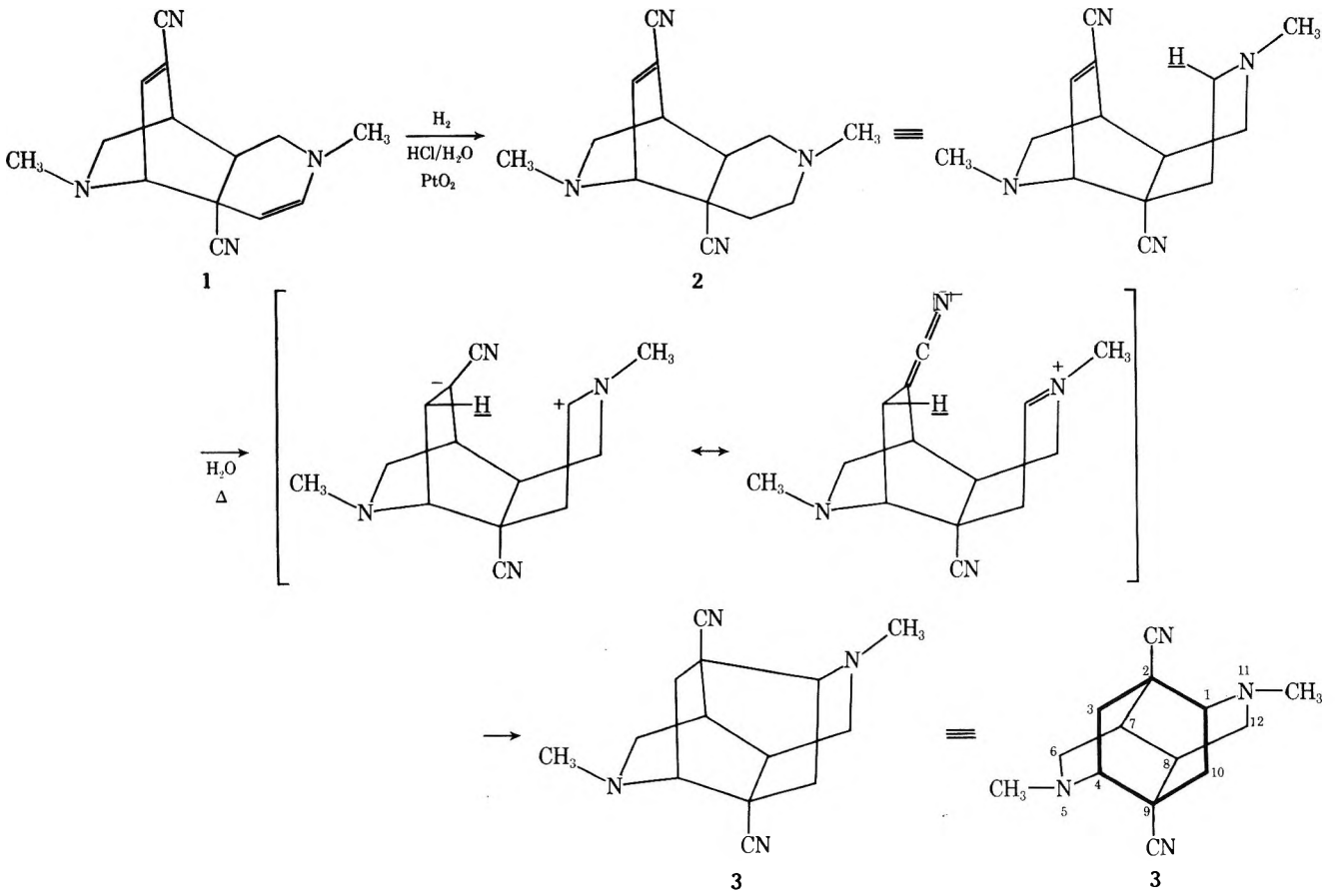
The facile synthesis of 2,9-dicyano-5,11-dimethyl-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (**3**), a unique and symmetric diazaditwistane, from *endo*-7,11-dicyano-4,9-dimethyl-4,9-diazatricyclo[6.2.2.0^{2,7}]dodeca-11-ene (**2**) via an intramolecular hydride transfer is reported. Spectral evidence and deuterium labeling studies confirming the structure of **3** and its mode of formation are presented.

In connection with studies directed toward the development of bioactive molecules with functional groups in unique and fixed three-dimensional relationships, an examination of the chemistry of Diels–Alder adduct **1** and its reduction product **2**, both of which have been recently prepared by Liberatore, Casini, and Carelli,[1] was begun. During the course of these studies, we have discovered that **2**, when heated in polar, protic solvents, undergoes a facile rearrangement to afford **3** (2,9-dicyano-5,11-dimethyl-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane), which is a substituted, diaza analogue of the recently reported ditwistane system.[2] Formation of **3** was first noted when **2** was refluxed in water. It was isolated in 55% yield by filtration and shown to be isomeric with **2** by means of mass spectral and elemental analyses. Subsequent large-scale preparations of **3** in 81% yield have been carried out in methanol at 150 °C. The ir spectrum of **3** displayed one band at 2240 cm^{-1} ($CHCl_3$) indicative of saturated nitrile, and no double bond stretching absorptions were present in the spectrum. The ^1H and ^{13}C NMR spectra of **3** provided the basis for its structural assignment. In 1 N DCl the ^1H NMR spectrum revealed nine protons distributed in a ratio of 2:1:3:1:1:1, starting from high field, none of which occurred in the vinyl region. Since mass spectral and elemental analyses confirmed a molecular formula of $C_{14}H_{18}N_4$ for **3**, we concluded that it must be highly symmetrical in nature. The proton spectrum is summarized in Table I. The *N*-methyl resonance appeared as a singlet at 3.08 ppm, and the remainder of the proton spectrum could be interpreted by a first-order analysis, with second-order effects contributing to line broadening. The presence of the following groups was indicated: CH_3N, $NCHCH_2$, and NCH_2CH. The ^{13}C NMR spectrum, summarized in Table II, suggested the presence of seven types of carbon atoms. In addition to the five already indicated, a nitrile carbon and a carbon attached to four other carbons were detected. Assignments were confirmed by off-resonance decoupling experiments. The highly symmetrical nature was again indicated in this spectrum. Based on the accumulated data, structure **3** has been assigned to the new product. It contains a C_2 axis of symmetry and exists as an enantiomeric pair. Resolution of **3** has been achieved via its dibenzoyl-D-tartrate salt. Details of this procedure are reported in the Experimental Section.

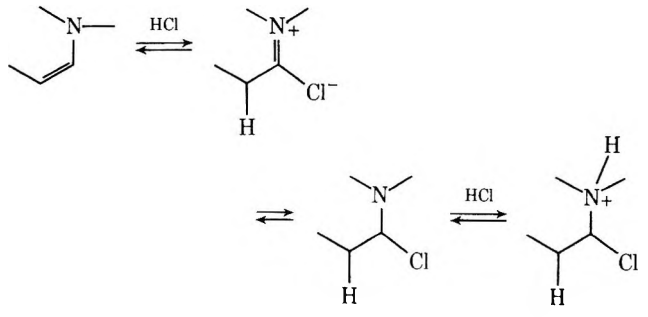
A reasonable reaction path for the formation of **3** involves an intramolecular hydride transfer in **2** as indicated, which proceeds through a dipolar transition state or through a discrete zwitterionic intermediate, which subsequently affords **3**. The proposed reaction path requires that the piperidine ring in **2** adopt a boatlike conformation prior to hydride transfer. Models suggest that this, the subsequent hydride transfer, and the final ring closure involve no severe distortions of the molecular framework. The latter two transformations occur over six-atom frameworks. This and the ability of the substituents to stabilize the developing charges in the intermediate or transition state account for facility of the reaction.

Consistent with the proposed intramolecular reaction path, no deuterium incorporation resulted when the reaction was run in D_2O. Also, it was noted that the reaction proceeded at comparable rates in water (100 °C), methanol (150 °C), and ethylene glycol (160 °C), much more slowly in 1-butanol (118 °C), hardly at all in *tert*-butyl alcohol (150 °C) and dimethyl sulfoxide (150 °C), and not at all in diglyme (125 °C) and xylene (140 °C). The requirement for a polar, protic solvent is consistent with the proposed ionic nature of the reaction path. In acetic acid (115 °C) and 50% aqueous acetic acid (105 °C) the reaction proceeded at one-quarter of its rate in water, suggesting that acid catalysis does not facilitate the reaction. Although we have not been able to find a direct analogy for this specific type of hydride-transfer reaction in the literature,



compound **2** contains all of the fundamental elements required for a hydride-transfer reaction as noted by Deno, Peterson, and Saines[4] in their review on this general class of reactions. The facilitation of intramolecular hydride-transfer reactions due to steric proximity in bridged, polycyclic systems has been noted by Prelog and Traynham in their review of transannular hydride shifts.[5]

To provide further support for the proposed reaction path for the formation of **3**, the sequence was reexamined in a deuterated series. Compound **1** was reduced in DCl/D_2O over PtO_2 using deuterium gas. It has been previously established that enamines in aqueous acid protonate at their β carbon and are in equilibrium with their iminium forms. This results in a net exchange of the β protons in deuterated media. It has also been shown that when the acids used have a nucleophilic anion, addition of that anion to the imine occurs.[6] Thus, the equilibria involved for an enamine in aqueous HCl, neglecting hydrolysis which is slow for cyclic enamines, can be represented as follows:



Given the complex nature of this series of equilibria, the a priori prediction of the resultant species upon reduction of **1** in a deuterated system is not possible. However, incorporation of three deuterium atoms in the product is expected: two at the β carbon via exchange and one at the α carbon via reduction. Examination of the mass spectrum of the reduction product of **1** in the deuterated system revealed 88% of d_3 species, 6% of d_2, 2% of d_1, and 4% of d_0. Support for these results was obtained by comparison of the ^{13}C spectra of **2** and its trideuterio analogue. In the ^{13}C spectrum of the trideuterio analogue the high-field resonance at 27.6 ppm due to a C–CH_2–C group was absent, having been replaced by a C–CD_2–C group. In addition the NCH_2– group at 49.0 ppm in **2** had become a triplet at 48.5 ppm since it was now a CHD group in the trideuterio analogue. Up to this point the stereochemistry at the α carbon in the trideuterio analogue has not been specified. This became possible by a comparison of the ^1H NMR spectra of the protio and deuterio compounds. The ^1H NMR spectrum of **2** shows a sextet corresponding to one proton at approximately 3.0 ppm ($CDCl_3$), due to a single proton in one of the NCH_2 groups. Only two other of the NCH protons in **2** are further downfield. Referring to structure **2a**, H_x, which is a methine geminal to nitrogen and also allylic, occurs as a doublet (δ 3.60 ppm, J = 6.0 Hz) and H_y, which is geminal to nitrogen and in the deshielding regions of the nitrogen lone pair and the cyano group,[1,7] occurs as a quartet (δ 3.42 ppm, J = 10, 2.0 Hz). The remainder of the protons on carbon adjacent to a nitrogen atom occur as a complex multiplet at 2.2–2.7 ppm. In the trideuterio analogue the sextet at 3.0 ppm has become a broadened singlet, and the high-field methylene on the β carbon in **2a**, which occurs as a multiplet at 1.7 ppm in **2**, is completely absent. Thus, the sextet at 3.0 ppm in **2** must be due to one of the protons on the α carbon of the original enamine group. The sum of the splittings in this pattern is observed to be 28 Hz. The magnitude of the geminal splitting should be on the order of 12 Hz,[3] leaving the sum of the vicinal couplings at approximately 16 Hz. This is consistent only with an essentially axial orientation of the methylenic proton exhibiting this multiplet.[8] Assuming that pseudochair conformations will be more stable for the flexible six-membered ring in **2** than the corresponding boat conformations, conformations **2a** and **2b** can be drawn for **2**, and the sextet observed in its spectrum could arise from H_a in either

Table I. ^{1}H NMR Spectrum of 3[a]

Chem shift,[b] mult	J, Hz	Area	Assignment
2.71, d	2.7	2	$-CH_2CHN<$
2.91, d	2.7	1	$>CHCH_2N<$
3.08, s		3	$>NCH_3$
3.67, d[c]	13.5	1	$>N-\overset{H}{\underset{H}{C}}-CH<$
3.91, q[c]	13.5, 3.5	1	
4.38, t	2.9	1	$>NCHCH_2-$

[a] Spectrum taken in 1 N DCl/D_2O with DSS standard. [b] δ, ppm. [c] The multiplets at 3.67 and 3.91 ppm are in accord with a methylene attached to nitrogen coupled to a methine in which one dihedral angle approaches 90° giving a vanishingly small splitting and the other is such that a moderate splitting results.[3] This, based on molecular models, is in accord with 3.

Table II. ^{13}C NMR Spectrum of 3[a]

Chem shift[b]	Multiplicity[c]	Assignment
22.5	t	OCH_2C
35.0	s	$C(C)_4$
36.4	d	$CCHC$
41.6	q	$>NCH_3$
50.9	t	$>NCH_2C$
59.6	d	$>NCH(C)_2$
122.9	s	$-CN$

[a] Spectrum taken in $CDCl_3$. [b] δ, ppm, Me_4Si internal reference. [c] Observed with off-resonance proton decoupling.

case. However, in conformation **2a** H_a would experience a deshielding effect because of its position relative to the cyano group, whereas in conformation **2b** H_a would experience a shielding effect because of its position relative to the π lobes of the double bond.[7] Since H_a is downfield relative to the bulk of protons similar to it in **2**, conformation **2a** must obtain. Returning to the trideuterio analogue, since the sextet in **2a** has become a broadened singlet attributed to the same proton, the structure and conformation for the trideuterio analogue must be represented by **4a**. Integration of this broadened singlet accounted for only 0.7 H. Since the mass spectral analysis confirmed the labeled reduction product as principally a trideuterio species and its ^{1}H and ^{13}C spectra showed only involvement of the α- and β-carbon atoms of the original enamine, the remaining 0.3 H in the labeled species must be represented by structure **4b**. H_e in **4b** was not specifically observed in the labeled product mixture since it occurs with the bulk of the protons on carbon bound to nitrogen. In summary, therefore, reduction of **1** in the deuterated system affords approximately a 7:3 mixture of trideuterio compounds **4a** and **4b**.

The labeled mixture **4a** and **4b** was rearranged in water as before. No loss of deuterium occurred during the rearrangement. Examination of the ^{1}H NMR spectrum of the rear-

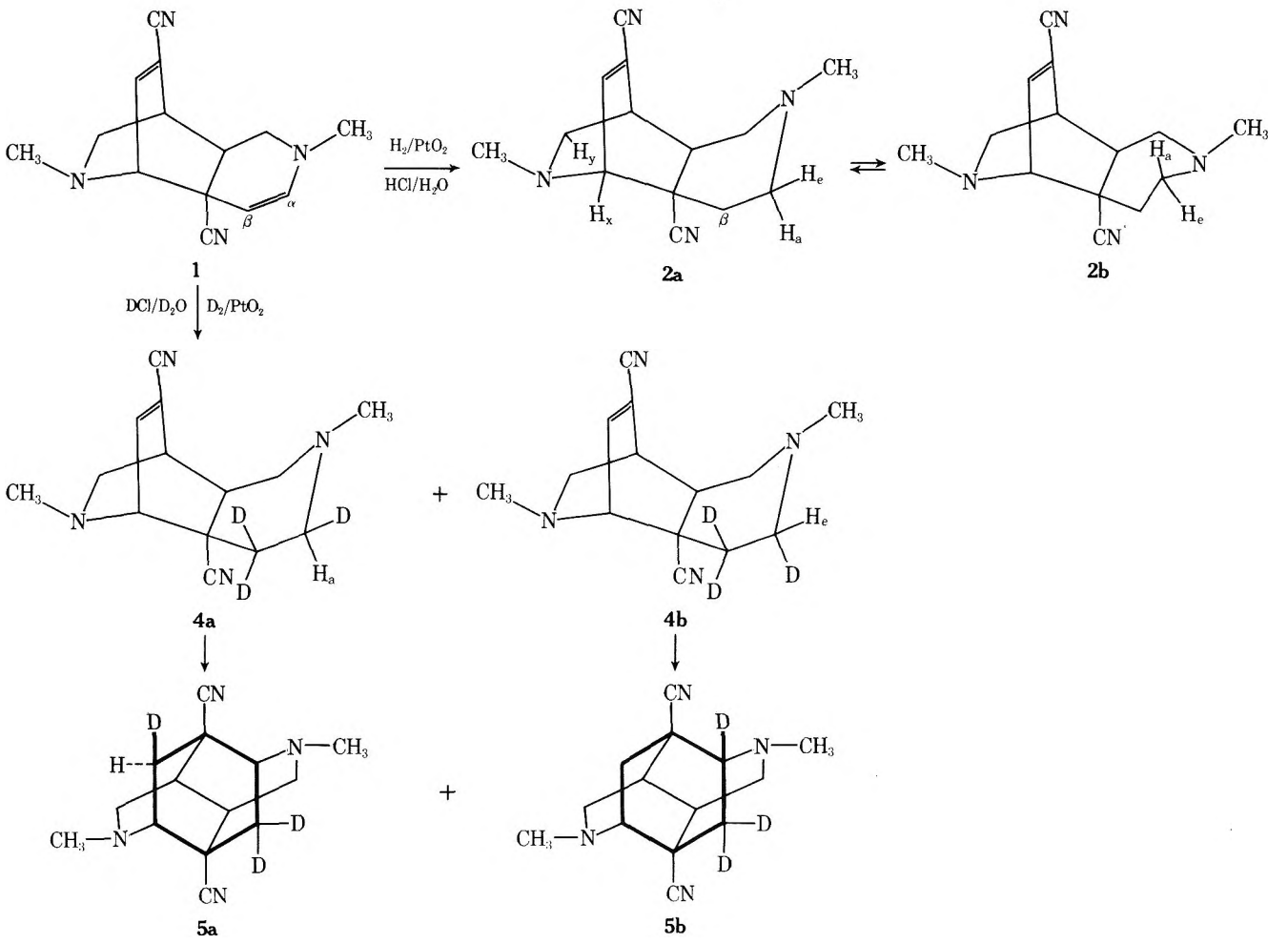


Table III. Proton Areas for the 5a–5b Mixture[a]

Group	NCH	NCH_2	NCH_3	CCH	CCH_2
Observed for 3	2	4	6	2	4
Predicted for 5a–5b	1.7	4	6	2	1.3
Observed for 5a–5b	1.6	4	6	2	1.4

[a] Area measurement errors are estimated to be correct to ±0.1 H.

ranged product mixture (**5a** and **5b**) afforded relative areas for the various protons in accord with the proposed hydride transfer reaction path based on **4a** and **4b** being a 7:3 mixture. These results are summarized in Table III. Also, the ^{13}C NMR spectrum of the **5a–5b** mixture was in accord with the presence of the following groups: NCHCHD, $NCHCD_2$, $NCHCH_2$, and $NCDCD_2$.

In summary, we believe that sufficient evidence exists to establish diazaditwistane **3** as the product resulting from the rearrangement of **2** via an intramolecular hydride transfer and ring closure. To our knowledge this represents the first report of the synthesis of a symmetrical diazaditwistane.[9] In addition to being a symmetrical diaza analogue of a unique, rigid polycyclic system, diazaditwistane **3** has other unusual structural features. It can be viewed as a fusing of two piperidine rings. Because of the nature of the system, each nitrile exists simultaneously in a 1–3 and a 1–4 relationship to piperidine ring nitrogens.

Although **3** is a stable system, the functionality at positions 2, 5, 9, and 11 can be readily and extensively varied. Subsequent papers will present the chemistry which has been developed from **3**, and the biology which has resulted from that chemistry.[10]

Experimental Section

Melting points are uncorrected. Infrared spectra were taken with a Perkin-Elmer IR 257 spectrophotometer. ^1H NMR spectra were taken with a JEOL C60HL spectrometer and carbon-13 spectra were taken with a Varian CFT 20 spectrometer. Rotations were determined on a Zeiss photoelectric polarimeter using a 1-dm tube. We wish to thank Ms. Emily J. Maitheny, Mr. Robert A. Reamer, Mr. Jack L. Smith, Mr. Richard C. Zerfing, Mr. Richard N. Boos, and Mr. Jack P. Gilbert for assistance in obtaining the spectral and analytical data.

***endo*-7,11-Dicyano-4,9-dimethyl-4,9-diazatricyclo[6.2.2.-$0^{2,7}$]dodeca-5,11-diene (1).**[1,11] Under nitrogen 366 g (9.15 mol) of NaOH and 9.5 l. of CH_3OH were charged with stirring to a 12-l. flask. After 10 min the clear solution was cooled to 10 °C and 200 g (5.28 mol) of $NaBH_4$ was charged. Cooling was continued and at −18 °C 1326 g (5.39 mol) of 1-methyl-4-cyanopyridinium iodide[12] was charged over 15 min keeping the temperature between −15 and −20 °C. The mixture was stirred at −20 to 0 °C for 2.5 h. The precipitate was filtered, washed with 4 × 600 ml of cold CH_3OH, and dried at 40 °C (1 mm) overnight to yield 541 g (2.25 mol, 83%) of **1** as a yellow solid, mp 173–176 °C (lit.[1] 175 °C).

***endo*-7,11-Dicyano-4,9-dimethyl-4,9-diazatricyclo[6.2.2.-$0^{2,7}$]dodec-11-ene (2).** In 1.5 l. of 2.5 N HCl was dissolved 360 g (1.5 mol) of **1** and 1.50 g of PtO_2 catalyst was added. This was hydrogenated at an initial pressure of 40 psi and theoretical hydrogen uptake was complete in 2.5 h. Catalyst was removed by filtration through Supercel which was washed twice with 2 × 100 ml of 2.5 N HCl. Benzene (2.0 l.) was added to the filtrate followed by the addition of 165 g of NaOH in 500 ml of H_2O with stirring and cooling. After separation, the aqueous phase was extracted with 3 × 1 l. of benzene, and the combined benzene extracts were dried over Na_2SO_4, filtered, and vacuum concentrated to a crystalline mass. This was slurried with 1500 ml of ether and filtered, and the filtrate was washed with 2 × 300 ml of ether and dried under vacuum to afford 306 g (1.27 mol, 84%) of **2**, mp 139–143 °C. This material was of sufficient purity for subsequent preparative work. An analytical sample was prepared by recrystallization from 2-propanol: mp 145–147 °C (lit.[1] 148 °C); mass spectrum molecular ion at *m/e* 242.

Anal. Calcd for $C_{14}H_{18}N_4$: C, 69.39; H, 7.49; N, 23.12. Found: C, 69.19; H, 7.77; N, 22.91.

2,9-Dicyano-5,11-dimethyl-5,11-diazatetracyclo[6.2.2.$0^{2,7}$.-$0^{4,9}$]dodecane (3). Procedure A. A slurry of 242 g (1.0 mol) of **2** in 2.42 l. of water was refluxed for 3 h. During the course of the reaction much of the starting material went into solution; however, product crystallized before complete dissolution occurred. The resulting slurry was cooled to 5 °C, filtered, washed with 3 × 400 ml of water, and dried at 50 °C under vacuum to yield 134 g (0.55 mol, 55%) of **3**: mp 206–209 °C; TLC (98/2 $CHCl_3/CH_3OH$, silica gel) single spot at R_f 0.5; spectral data recorded in the text.

Anal. Calcd for $C_{14}H_{18}N_4$: C, 69.39; H, 7.49; N, 23.12. Found: C, 69.43; H, 7.34; N, 22.99.

Procedure B. In an autoclave 157 g (0.65 mol) of **2** in 1.57 l. of methanol was heated at 150 °C for 6 h. The resulting mixture was concentrated to remove 1.4 l. of methanol. The precipitate was then filtered, washed with 4 × 100 ml of 2-propanol, and dried at 50 °C under vacuum to afford 127 g (0.525 mol, 81%) of **3**, mp 205–209 °C. This material was identical with that previously prepared.

Resolutions. A solution of 12.12 g (50.0 mmol) of racemic **3** in 500 ml of refluxing methanol was treated with a hot solution of 18.7 g (52.5 mmol) of dibenzoyl-D-tartaric acid in 200 ml of methanol. On cooling granular crystals formed first and after 1 h flocculent crystals started to separate. The mixture was warmed to dissolve the latter and filtered, and the solid was washed with methanol and dried to yield 12.25 g of granular crystals of the monosalt of the (−) isomer of **3**. On aging for 24 h the filtrate yielded a flocculent crystal mass which was filtered, washed with methanol, and dried to yield 8.7 g of the monosalt of the (+) isomer. The granular salt of the (−) isomer was twice recrystallized from 40 volumes of methanol and converted to the free base by distribution between 60 ml of saturated $NaHCO_3$ solution and 150 ml of methylene chloride. After separation and evaporation of the methylene chloride there was obtained 3.40 g (56%) of the (−) isomer of **3**: mp 249–253 °C; $[\alpha]_{578}$ −220.8, $[\alpha]_{546}$ −250.6, $[\alpha]_{436}$ −426.0, $[\alpha]_{405}$ −509.0, $[\alpha]_{365}$ −660.2 (*c* 0.52, CH_2Cl_2). The flocculent salt of the (+) isomer was twice recrystallized from 30 volumes of methanol and converted to the free base as above to yield 2.06 g (36%) of the (+) isomer of **3**: mp 249–253 °C; $[\alpha]_{578}$ +223.1, $[\alpha]_{546}$ +254.1, $[\alpha]_{436}$ +431.6, $[\alpha]_{405}$ +517.1, $[\alpha]_{365}$ +666.3 (*c* 0.53, CH_2Cl_2).

4a and 4b. To a solution of 1.92 g (8.0 mmol) of **1** in 16 ml of 2.5 N DCl (97% D) was added 10 mg of PtO_2 and the mixture reduced with D_2 gas at 25 °C (40 psi) until 8.0 mmol of D_2 was taken up. The mixture was filtered, and the filtrate was adjusted to pH 12 with 2.5 N NaOH, resulting in some crystal formation. The mixture was extracted with 3 × 20 ml of benzene, which was dried over $MgSO_4$, filtered, and concentrated to dryness, and the residue was recrystallized from 7 ml of 2-propanol to afford 1.70 g (7.1 mmol, 88%) of **4a** and **4b**: mp 137–140 °C; 88% d_3, 6% d_2, 2% d_1, and 4% d_0 by mass spectral analysis.

Anal. Calcd for $C_{14}D_3H_{15}N_4$:[11] C, 68.53; H, 7.49; N, 22.83. Found: C, 68.81; H, 7.65; N, 22.65.

5a and 5b. A 1.0-g sample of the labeled **4a–4b** mixture was slurried in 10 ml of water and refluxed for 2.5 h. The resulting precipitate was filtered, washed with 2 × 1 ml of cold water, and dried at 64 °C (1 mm) to afford 0.47 g of the **5a–5b** trideuterio mixture: mp 206–208 °C; 87% d_3, 7% d_2, 2% d_1, and 4% d_0 by mass spectral analysis; spectral data recorded in text.

Anal. Calcd for $C_{14}D_3H_{15}N_4$:[13] C, 68.53; H, 7.49; N, 22.83. Found: C, 68.60; H, 7.42; N, 22.54.

Registry No.—**1**, 33422-84-3; **2**, 59711-05-6; (±)-**3**, 59711-06-7; (−)-**3**, 59711-07-8; (+)-**3**, 59711-08-9; **4a**, 59751-82-5; **4b**, 59751-83-6; **5a**, 59751-84-7; **5b**, 59711-09-0; 1-methyl-4-cyanopyridinium iodide, 1194-04-3; dibenzoyl-D-tartaric acid, 2743-38-6.

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Reaction of 2,4-Dinitrohalobenzenes with Imidazole in Nonpolar Aprotic Solvents[1]

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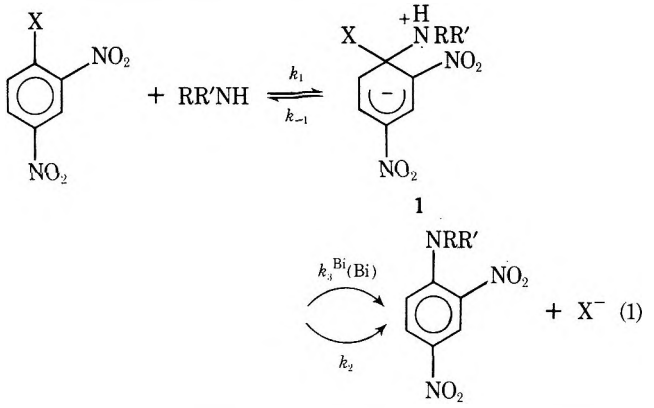
The reactions of 1-chloro-2,4-dinitrobenzene and 1-fluoro-2,4-dinitrobenzene with imidazole in benzene or chloroform were studied. It was found that the reaction of both substrates is general base catalyzed. For 1-chloro-2,4-dinitrobenzene the ratio of the catalyzed to the uncatalyzed rate coefficient (k_3^B/k_2) is 200 M^{-1} for the imidazole and 253 M^{-1} for Dabco in chloroform. The implication of base catalysis in this reaction is discussed.

The reaction of activated aromatic substrates with amines is often base catalyzed.[2] This observation has been rationalized in terms of the intermediate complex mechanism for which eq 1 is representative.



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Base catalysis is experimentally observable when the product-forming steps k_2 and $k_3^{Bi}(Bi)$ are slower than the reversion of the intermediate **1** to reactants ($k_2 + \Sigma k_3^{Bi}(Bi) < k_{-1}$).

When the ratio $k_2/k_{-1} \ll 1$, base catalysis is usually observable;[2a] thus whether a given reaction is base catalyzed or not can be influenced by the factors which decrease k_2 and/or enhance k_{-1}.

With chloride as leaving group there are only a few examples where base catalysis has been unequivocally demonstrated and these are cases where the amine is weakly basic which tends to decrease the k_2/k_{-1} ratio by increasing k_{-1}. A case in point is the reaction of *p*-anisidine with 1-chloro-2,4-dinitrobenzene[3] in benzene solution.

Base catalysis in the reaction of 1-chloro-2,4-dinitrobenzene with piperidine and aniline in acetone was claimed by Hirst and Bankole,[4] but these results could not be reproduced in our hands.[5]

The reaction of imidazole with picryl chloride was shown to be catalyzed by imidazole and Dabco in chloroform.[6] Also Pietra[7] found that the reaction of 1-chloro-2,4-dinitrobenzene with imidazole is mildly accelerated by imidazole, but he did not regard this acceleration as base catalysis.

We became interested in the reaction of imidazole because we think that its behavior is important in regard to the mechanism of the k_2 step.

Base catalysis is usually recognized when a change to a better catalyst brings about stronger catalysis.[2a] Thus we investigated the reaction of 1-chloro-2,4-dinitrobenzene with imidazole in benzene and chloroform in the presence of Dabco and pyridine, in order to see whether the reactions are base catalyzed or not. We also report kinetic data on the reaction of 1-fluoro-2,4-dinitrobenzene with imidazole in chloroform catalyzed by imidazole and Dabco to compare these results with those of 1-chloro-2,4-dinitrobenzene.

Results and Discussion

1-Chloro-2,4-dinitrobenzene. In Table I the kinetic results for the reaction of the aforementioned substrate with imidazole with or without added other bases are displayed.

For the imidazole catalyzed reaction the three points at lower concentration compare well with those reported by Pietra[7] under the same experimental conditions, but the agreement is not as good at higher concentration. The ratio of the third- to the second-order rate constant is even lower in our case. The response of k_A to the base concentration is linear. For the reaction of imidazole with 1-chloro-2,4-dinitrobenzene in the presence of Dabco or pyridine the rate seems to level off at high base concentration (Table I).

The kinetic expression derived with reference to the mechanism depicted in eq 1, by means of the usual steady-state approximation, is represented in eq 2 where k_A is the observed second-order rate constant and the summation includes all the bases present in the solution including the nucleophile.

$$\frac{\text{rate}}{(\text{ArX})(\text{HNRR}')} = k_A = \frac{k_1\left[k_2 + \sum_i k_3^{Bi}(Bi)\right]}{k_{-1} + k_2 + \sum_i k_3^{Bi}(Bi)} \quad (2)$$

Linear dependence of the second-order rate constant k_A on the base concentration means that

$$k_2 + \sum_i k_3^{Bi}(Bi) \ll k_{-1}$$

which simplifies eq 2 to eq 3.

$$k_A = k_1\frac{k_2}{k_{-1}} + k_1\frac{\sum_i k_3^{Bi}(Bi)}{k_{-1}} \quad (3)$$

Table I. Reaction of 1-Chloro-2,4-dinitrobenzene with Imidazole in Benzene at (100 ± 0.2) °C[a]

A. Catalyzed by Imidazole

Imidazole, M	$k_\psi \times 10^5$, s^{-1}	$k_A \times 10^4$, $M^{-1} s^{-1}$
0.00694	0.224	3.23
0.0117	0.431	3.68
0.0135	0.518	3.84
0.0176	0.698	3.94
0.0236	1.12	4.77
0.0297	1.55	5.25

B. Catalyzed by Dabco[b]

Dabco, M	$k_\psi \times 10^5$, s^{-1}	$k_A \times 10^4$, $M^{-1} s^{-1}$
0.0214	1.27	5.80
0.0435	1.60	7.30
0.0710	1.92	8.75
0.0886	2.24	10.2 ± 0.8
0.120	2.18	10.8 ± 0.7
0.170	2.86	13.1 ± 0.6
0.201	3.31	15.1 ± 0.5
0.270[c]	3.03	13.8 ± 0.5
0.271	3.10	14.1 ± 0.6
0.101[d]	4.44	12.6 ± 0.4
0.151[d]	4.98	14.1
0.202[d]	5.67	16.1

C. Catalyzed by Pyridine[b]

Pyridine, M	$k_\psi \times 10^5$, s^{-1}	$k_A \times 10^4$, $M^{-1} s^{-1}$
0.0993	1.42	6.51 ± 0.3
0.199	1.97	8.99 ± 0.3
0.398	2.22	10.1 ± 0.7

[a] $(S_0) = 5.28–5.4 \times 10^{-4}$ M; average deviation is given when rate constants are average of two or three determinations. [b] $(\text{Imidazole})_0 = 2.19 \times 10^{-2}$. [c] $(S)_0 = 2.90 \times 10^{-4}$ M. [d] $(\text{Imidazole})_0 = 0.353 \times 10^{-1}$ M.

Curvilinear dependence of k_A vs. base concentration means that

$$k_{-1} \simeq k_2 + \sum_i k_3^{Bi}(Bi)$$

i.e. in this case k_1 is partially rate determining. The leveling off of the rate occurs when $k_A = k_1$, i.e., the plateau value (k_1) must be independent of the base catalyst. However, the data displayed in Table I part B and C seem to indicate that the rate levels off at lower value for pyridine than for Dabco, although the limited number of data concerning pyridine catalysis does not allow speculation about possible reasons.[8]

The low solubility of imidazole in benzene prevented us from doing accurate determinations at higher concentration than those reported here; thus we decided to change to chloroform, which is a better solvent for imidazole.

The reaction of imidazole with 1-chloro-2,4-dinitrobenzene in chloroform is accelerated by imidazole and Dabco (Table II). The second-order rate constant k_A is curvilinearly dependent on both bases concentration (Figures 1 and 2).

We have treated our data as follows.[9] In the absence of Dabco or pyridine and assuming that $k_{-1} \gg k_2$ (justified later), which permits one to neglect k_2, eq 2 can be inverted to give eq 4.

$$\frac{1}{k_A} = \frac{1}{k_1} + \frac{k_{-1}}{k_1 k_3^{Im}(Im)} \qquad (4)$$

Table II. Reaction of Imidazole with 1-Chloro-2,4-dinitrobenzene in Chloroform at (69 ± 0.1) °C[a]

A. Catalyzed by Imidazole

Imidazole, M	$k_\psi \times 10^5$, s^{-1}	$k_A \times 10^4$, $M^{-1} s^{-1}$
0.0201	0.120	0.596 ± 0.03
0.0398	0.415	1.04 ± 0.08
0.0602	0.818	1.36 ± 0.08
0.0699	1.02	1.48 ± 0.03
0.0803	1.28	1.59 ± 0.06
0.0941	1.49	1.58 ± 0.05
0.110	1.89	1.72 ± 0.06
0.130	2.38	1.83 ± 0.05
0.140	2.71	1.94 ± 0.04
0.152	3.16	2.07 ± 0.04

B. Catalyzed by Dabco[b]

Dabco, M	$k_\psi \times 10^5$, s^{-1}	$k_A \times 10^4$, $M^{-1} s^{-1}$
0.0126	0.873	1.46
0.0220	0.977	1.63
0.0300	0.956	1.60
0.0518	1.07	1.79
0.0681	1.12	1.87
0.100	1.27	2.13
0.130	1.26	2.12
0.150	1.42	2.34
0.180	1.43	2.40
0.200	1.41	2.36
0.240	1.47	2.46

[a] $(\text{Substrate})_0 = 5.03 \times 10^{-4}$ M; average deviation is given when rate constants are average of two or three determinations. [b] $(\text{Imidazole})_0 = 0.0598$ M.

A plot ("inversion plot") of k_A^{-1} vs. $(Im)^{-1}$ (not shown) yields a straight line from which $k_1 = 3.03 \times 10^{-4}$ $M^{-1} s^{-1}$ and $k_3^{Im}/k_{-1} = 12.3$ M^{-1} were determined.

An alternative form of eq 2, again in absence of Dabco or pyridine but without neglecting k_2, is eq 5.

$$\frac{k_A}{k_1 - k_A} = \frac{k_2}{k_{-1}} + \frac{k_3^{Im}}{k_{-1}}(Im) \qquad (5)$$

Plotting the left-hand side of eq 5 vs. (Im) yields $k_2/k_{-1} = 0.06$, and $k_3^{Im}/k_{-1} = 12.0$ M^{-1}. This latter value is in excellent agreement with k_3^{Im}/k_{-1} determined from eq 4. This and the low value of k_2/k_{-1} (0.06) justifies the assumption $k_2 \ll k_{-1}$ which underlies eq 4. In fact, the curve of k_A vs. (Im) calculated on the basis of the obtained k_1, k_2/k_{-1}, and k_3^{Im}/k_{-1} values describes the experimental data very well.

To calculate k_3^D/k_{-1} for Dabco catalysis we use again eq 5 including now the term $k_3^{Im}(Im)/k_{-1}$ in the intercept since the experiments (Table IIB) were carried out at constant imidazole concentration.

It is not possible in this case to draw a similar "inversion plot" as for the imidazole-catalyzed reactions because there were no experimental conditions accessible where $k_3^{Im}(Im) + k_2 \ll k_{-1}$.

From the slope of the plot of $k_A/(k_1 - k_A)$ vs. Dabco concentration, k_3^D/k_{-1} is reckoned as 15.2 M^{-1}. Dabco is only a slightly better catalyst than imidazole. The ratio k_3^B/k_2 is 200 M^{-1} for imidazole and 253 M^{-1} for Dabco; these values are well above the limit proposed by Bunnett[10] in order to decide whether an acceleration should be considered as genuine base catalysis.

Notably, the ratios k_3^B/k_2 are much higher than those re-

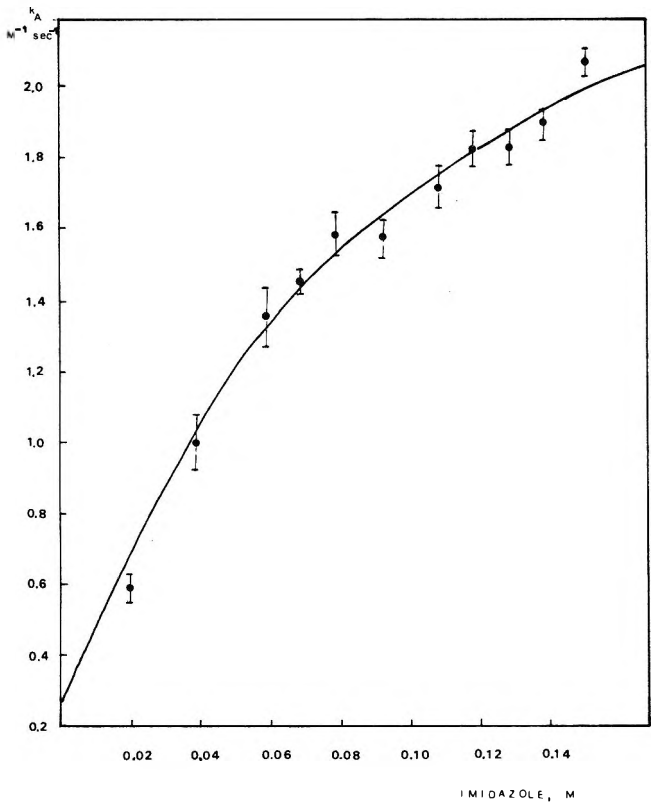


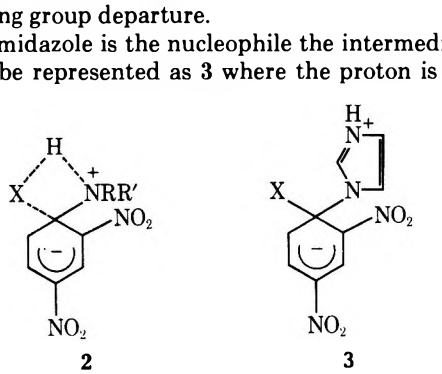
Figure 1. Second-order rate constant for the reaction of 1-chloro-2,4-dinitrobenzene with imidazole in chloroform as a function of imidazole concentration. Data from Table IIA. The solid line is calculated from eq 2 with $k_1 = 3.03 \times 10^{-4}$ M^{-1} s^{-1}, $k_2/k_{-1} = 0.06$, and $k_3^{Im}/k_{-1} = 12$ M^{-1}.

ported for other reactions of several amines with 1-chloro-2,4-dinitrobenzene in chloroform (between 0.2 and 4.6).[11] The small acceleration in these latter reactions is probably not due to genuine base catalysis[2a] and in those reactions k_2/k_{-1} is probably $\gg 1$.

The fact that for the imidazole reaction base catalysis is observed but not for most other reactions of 1-chloro-2,4-dinitrobenzene with amines is a consecuence of an unusually small k_2/k_{-1} ratio.

The factors affecting k_{-1} have been discussed recently.[12] It appears to us that steric effects in the intermediate together with a relatively low basicity of imidazole ($pK_a = 7$) certainly play a role in increasing k_{-1} but it may not be the only factor affecting the ratio k_2/k_{-1}. It has been suggested that the transition state for the k_2 step may be represented as in **2**[2a,12] where the proton is transferred to the leaving group in concert with leaving group departure.

When imidazole is the nucleophile the intermediate may probably be represented as **3** where the proton is not at a



2 **3**

bonding distance to the leaving group as in **2**. If **3** is the intermediate, the proton is not available for intramolecular assistance to the leaving group departure; k_2 is thus decreased.

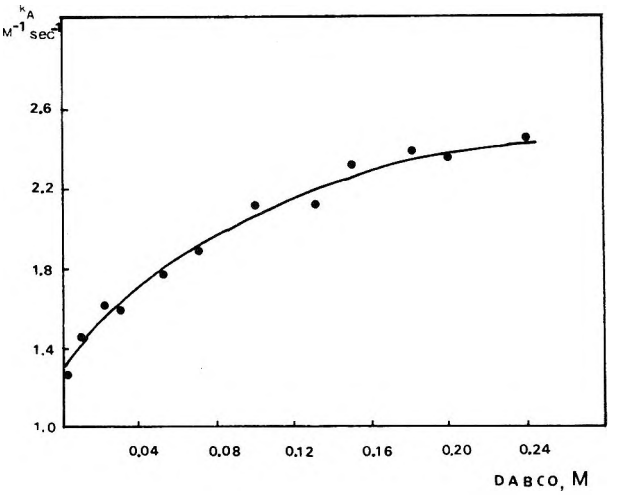


Figure 2. Second-order rate constant for the reaction of 1-chloro-2,4-dinitrobenzene with imidazole in chloroform as a function of Dabco concentration. Data from Table IIB. The solid line is calculated from eq 2 with $k_1 = 3.03 \times 10^{-4}$ M^{-1} s^{-1}, $k_2/k_{-1} = 0.06$, $k_3^{Im}/k_{-1} = 12$ M^{-1}, and $k_3^{D}/k_{-1} = 15.2$ M^{-1}.

Table III. Reaction of 1-Fluoro-2,4-dinitrobenzene with Imidazole in Chloroform at (52.5 ± 0.1) °C[a]

A. Catalyzed by Imidazole[a]

Imidazole, M	$k_\psi \times 10^4$, s^{-1}	$k_A \times 10^2$, M^{-1} s^{-1}
0.0025	0.335	1.34
0.0050	0.737	1.47
0.0200	9.06	4.53
0.0402	28.2	7.01
0.0600	50.7	8.45 ± 0.1
0.0798	82.0	10.3 ± 0.6
0.100	124	12.4 ± 0.5
0.120	151	12.6 ± 0.4
0.140	190	13.6 ± 0.5

B. Catalyzed by Dabco[a,b]

Dabco, M	$k_\psi \times 10^4$, s^{-1}	$k_A \times 10^2$, M^{-1s-1}
0.040	17.4	8.70
0.060	19.7	9.87
0.080	23.5	11.8
0.100	26.3	13.2
0.120	29.7	14.9
0.140	34.0	17.0
0.160	32.8	16.4
0.180	36.0	18.0
0.200	38.0	19.0

[a] $(S)_0 = 5 \times 10^{-6}$; average deviation is given when rate constant are average of two or three determinations. [b] (Imidazole) = 0.02 M.

Since it is known that k_2/k_{-1} decreases with decreasing polarity of the solvent, it is expected that this ratio in benzene be at least as low as in chloroform; thus the rate acceleration observed in benzene may be interpreted as base catalysis, although there seems to be a complicating effect which prevents further analysis of the data.

1-Fluoro-2,4-dinitrobenzene. The reaction of 1-fluoro-2,4-dinitrobenzene with imidazole is catalyzed by imidazole (Table IIIA) and Dabco (Table IIIB); k_1 and the ratios k_2/k_{-1}, k_3^{Im}/k_{-1}, and k_3^{D}/k_{-1} were reckoned as 0.25, 0.039, 9.45 M^{-1}, and 11 M^{-1}, respectively, from eq 4 and 5. However, the rate

constants determined at high imidazole concentration are not very accurate because the rate of reaction is too fast at this high concentration and difficult to measure with our experimental technique; thus we regard the value of k_1 as only approximate and so of course the other parameters which are calculated from it.

Experimental Section

Materials. Benzene (Erba) was shaken repeatedly with sulfuric acid to remove thiophene[13] and distilled before use from Na wire. Chloroform (Erba) was obtained free of ethanol by washing it several times with water; it was dried with $CaCl_2$ and stored in the refrigerator under N_2 in the dark. We noted that when this care was not taken the solutions of 1-chloro-2,4-dinitrobenzene or imidazole in this solvent turned yellow. The purified chloroform was used at most over 10 days. 1-Fluoro-2,4-dinitrobenzene (Merck) was distilled under vacuum. 1-Chloro-2,4-dinitrobenzene (Merck) was twice recrystallized from absolute ethanol. Dabco was sublimed at 40 °C (10 Torr). Pyridine was left over potassium hydroxide for 2 days and distilled under N_2 from KOH before use. Imidazole was recrystallized several times from benzene and then sublimed under vacuum. *N*-2,4-Dinitrophenylimidazole was prepared from 5 mmol (340 mg) of imidazole dissolved in 2 ml of dry benzene and 1-chloro-2,4-dinitrobenzene (2.5 mmol). The solution was boiled for 30 min and the benzene was evaporated. This yellow residue was recrystallized several times from methanol, yield 60%, mp 141–142.5 °C (lit.[14] 146–148 °C). During the synthesis and workup, the product was protected from light.

Kinetics. The product *N*-2,4-dinitrophenylimidazole has no absorption maximum in the spectral region available for examination in benzene or chloroform. Moreover, at the wavelength useful for examination (where the difference in the extinction coefficient of starting material and product is higher) the extinction coefficient of the *N*-2,4-dinitrophenylimidazole is quite low (ca. 2500 M^{-1} cm^{-1}); thus the total change in optical density over the reaction is also low. Thus we decided to monitor the concentration of 1-chloro-2,4-dinitrobenzene making use of its fast reaction with piperidine. In all the reactions in benzene or chloroform with imidazole with or without other bases added, the sealed ampule technique was utilized. The reactions at low base concentration were followed over ca. 10% conversion; after the desired time the ampule was cooled to room temperature and 1.0 ml of its contents was added to about 8 ml of benzene or chloroform contained in a 10-ml volumetric flask. Then 0.2 ml of piperidine was added and the flask diluted to the mark. After about 10 min all the 1-chloro-2,4-dinitrobenzene has reacted and the optical density of the product, *N*-2,4-dinitrophenylpiperidine, formed was measured at its maximum (380 nm). *N*-2,4-Dinitrophenylimidazole does not react with piperidine under these conditions during about 1 h. The rate constant was reckoned as 2.3 times the slope of the plot of log *A* vs. time. All the reactions were carried out under pseudo-first-order conditions. The reactions of 1-fluoro-2,4-dinitrobenzene with imidazole were carried out in the thermostated cell of the spectrophotometer.[15]

Acknowledgment. We thank Professor Claude F. Bernasconi for criticism of the manuscript.

Registry No.—Imidazole, 288-32-4; 1-chloro-2,4-dinitrobenzene, 97-00-7; 1-fluoro-2,4-dinitrobenzene, 70-34-8.

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The Acid-Catalyzed Nitramine Rearrangement. 8. Solvent Viscosity Effects[1,2]

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The rearrangement of *N*-nitro-*N*-methylaniline in methanol–glycerol mixtures of various compositions and viscosities was studied. In the presence of hydroquinone (which eliminates the intermolecular portion of the rearrangement), the yields of nitroanilines and the ortho to para isomer ratio increased with viscosity. The enhanced yield is explained by the lessened tendency of the intermediate solvent caged particles to dissociate in the higher viscosity solvents. The greater ortho to para isomer ratio must be caused by solvent interference to the migration of the nitro group within the solvent cage to the more distant para position. This hindrance increases with solvent viscosity. Rearrangement in the absence of hydroquinone scavenger yields similar results although more nitrated product is formed. The data can be quantitatively accounted for in terms of the mechanism shown in Chart II. This mechanism postulates a solvent viscosity effect within the solvent cage.

The outcome of the nitramine rearrangement frequently appears to be affected by the nature of the solvent. For example, the isomerization of *N*,2,4-trinitro-*N*-methylaniline proceeded normally in 80 or 96% sulfuric acid to yield 2,4,6-trinitro-*N*-methylaniline.[3] However, only the denitrated product, 2,4-dinitro-*N*-methylaniline, was formed from the same nitramine in 1:1 sulfuric acid–acetic acid mixture or in hot dilute hydrochloric acid. Rearrangement of 2,4,6-tribromo-*N*-nitroaniline in aqueous acids produced the expected mixture of isomeric nitrodibromoanilines.[4] Different products, 2,4,6-tribromobenzenediazonium ion and a quinoneanil, were formed when the medium was changed to acetic acid–sulfuric acid. Rearrangement of *N*-nitroaniline is also affected by the solvent.[5] Decreasing the molarity of the acid catalyst lowered the yield of nitrated products from 95% to 60% and changed the ortho–para ratio from 19.0 to 3.5. Similar behavior was noted in the rearrangements of *N*-nitro-1-naphthylamine and *N*-nitro-*N*-methyl-1-naphthylamine.[6]

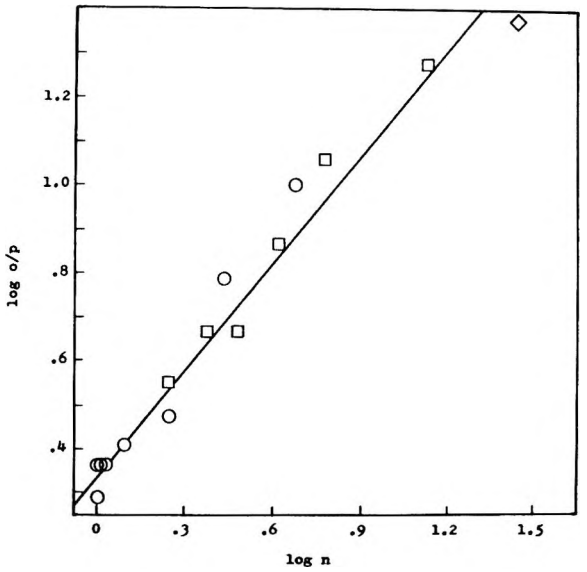


Figure 1. Ratio of percent o-nitroaniline to percent *p*-nitroaniline (*o*-/*p*-) from rearrangement of *N*-nitroaniline in acid media of different viscosities. □, H_2SO_4; ○, $HClO_4$; and ◇, H_3PO_4. Equation of the curve: o-/*p*- = $(\eta + 0.4)/(0.008\eta + 0.6)$.

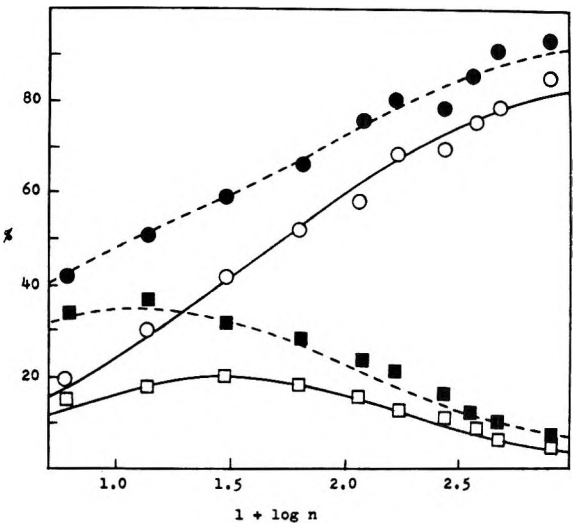


Figure 2. Yields of *o*- and *p*-nitro-*N*-methylanilines in methanol–glycerol solutions of various viscosities: ● and ■, ortho and para isomer, respectively, in the absence of hydroquinone scavenger; ○ and □, ortho and para isomer, respectively, in the presence of hydroquinone scavenger. Curves were calculated from the kinetics of the mechanism of Chart II using the relative rate constants in Table I.

Results and Discussion

The influence of acid concentration on the isomer ratio obtained from *N*-nitroaniline has been attributed to the effect of the acid medium's base strength on proton loss from the ortho and para σ-bonded intermediates.[5] Analysis of the results shows that the change in the ortho–para ratio cannot be interpreted in terms of the base strength of the solvent. The suggested proton abstraction[5] would be similar to that in an A-2 type mechanism.[7] Both the Zucker–Hammett hypothesis[7] and the Bunnett equation[8] require that the logarithm of the ortho–para ratio for such a process have a linear relationship to the logarithm of water activity in the various media. However, a plot of these two quantities shows a great deal of scatter (correlation coefficient $r = 0.75$). A graph of the logarithm of the isomer ratio vs. H_0 is of similar quality ($r = 0.73$).

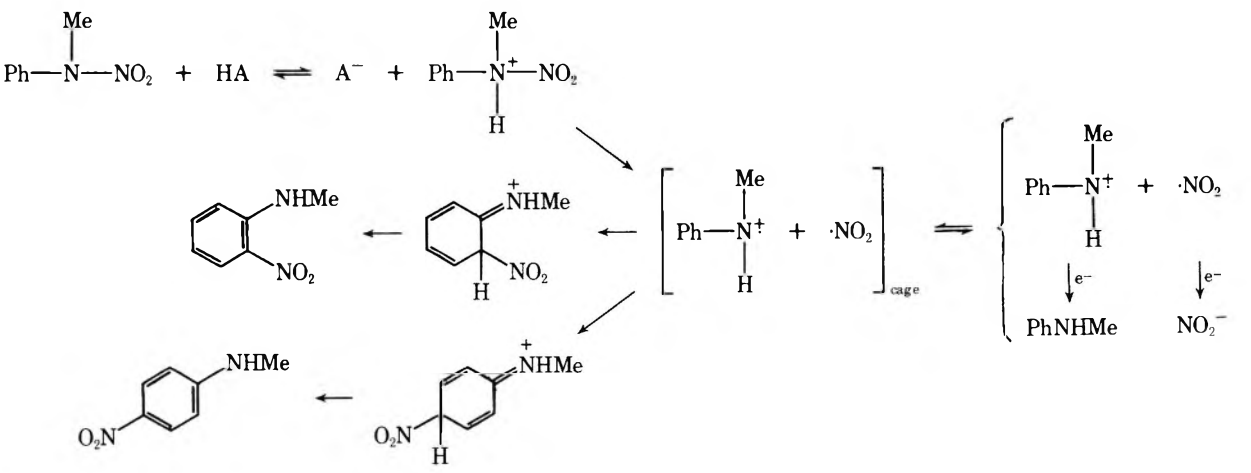
Previous studies[2a-g] of the aromatic nitramine rearrangement have shown that it involves the decomposition of the protonated nitramine to form a pair of caged radicals which may either dissociate to free radicals or recombine to yield nitrated products (Chart I). It would be expected that the competition between these latter processes would be affected by the solvent property known as viscosity. Viscosity increases should strengthen the solvent cage, hinder dissociation, and thus favor recombination. High-viscosity solvents should improve the yields of nitrated products. In fact, the yield of *o*- and *p*-nitroaniline from *N*-nitroaniline did increase from 60 to 95% as the concentration, and the viscosity, of the catalyzing acid was increased.[5]

Interestingly, although the observed ratios of products from *N*-nitroaniline cannot be correlated with the acidities or basicities of the acid media, a plot of these isomer ratios vs. the viscosities of the acid solutions provides a smooth curve even though three different acids were involved (Figure 1, correlation coefficient $r = 0.98$).[9]

These limited correlations suggested a more thorough investigation in which solvent viscosity was changed while other properties of the medium were kept almost constant. For this purpose, the rearrangement of *N*-nitro-*N*-methylaniline in a series of methanol–glycerol solutions of varying composition was chosen for study. Methanol and glycerol have very similar polarities as indicated by their *Z* values (83.6 and 85.3 kcal/mol, respectively), but very different viscosities (0.55 and 954 cP, respectively). Rearrangements were carried out both with and without the addition of hydroquinone as a scavenger. The results are shown graphically in Figure 2.

The data obtained in presence of hydroquinone are the most revealing and the least ambiguous. Hydroquinone eliminates the intermolecular portion of the rearrangement so that the

Chart I



yield of nitrated material is a measure of the extent of the intramolecular (cage) process. Figure 2 shows that the total yield of nitroanilines increases as the medium viscosity becomes greater. A higher viscosity does not change the rate of geminate recombination of the anilinium radicals and nitrogen dioxide within the solvent cage to form nitrated anilines, but does decrease the rate of escape of these species from the cage. The liberated free radicals react with hydroquinone, are reduced, and do not recombine. Therefore, they do not contribute to the yield of nitroaniline. Since this latter unproductive side reaction (diffusion from the cage and reduction) is disfavored in higher viscosity solvents, the yields of nitroaniline rise with increasing viscosity.

There is a marked change in the ortho to para isomer ratio as the viscosity is changed. An increase in viscosity of 135-fold causes a 14-fold enhancement of the ortho to para ratio—the increment being the greatest in the high viscosity range. It appears that high viscosity not only interferes with the diffusion of particles out of the solvent cage, but also hinders the movement of those particles with respect to each other in the cage. In very low viscosity solvents, the ortho to para ratio will be dictated mainly by electronic, steric, and statistical factors. However, as the viscosity increases, the movement of the caged particles will become more restricted. Since the ortho position is closer to the origin of the nitro group than is the para position, the opportunity for the nitrogen dioxide radical to approach the para position before reaction occurs at the nearer ortho position of the anilinium radical is decreased. As a result the relative amount of ortho isomer increases with the viscosity.[10]

The rearrangement of *N*-nitro-*N*-methylaniline in methanol–glycerol mixtures in the *absence* of hydroquinone yielded similar results (Figure 2). In these experiments, there was a smaller decrease in the yields of nitroanilines as the viscosity was reduced because the intermolecular portion of the rearrangement is not eliminated. The behavior of the ortho to para isomer ratio was much the same as that observed in the presence of hydroquinone, but less dramatic (a change of 11-fold over a viscosity range of 0.61–80.5 cP). This latter result is in agreement with the suggested course of the reaction since recombination of the dissociated free radicals which occurs in the absence of hydroquinone would not be expected to discriminate between the ortho and para positions as severely as intracage recombination.[1g]

Table I. Relative Rate Constants [a] for the Mechanism of Chart II

MeOH–glycerol	H_2O–glycerol
$k_3 = 7.1k_7$	$k_3 = 7.7k_7$
$k_4 = 16k_{15} - 8.1k_9$	$k_4 = 5.4k_{15} - 8.7k_9$
$k_5 = 4.0k_{15}$	$k_5 = 3.0k_{15}$
$k_6 = 5.1k_{16}$	$k_6 = 5.6k_{16}$
$k_8 < 0.3\sqrt{k_{13}k_{14}}$ [b]	$k_8 < 0.1\sqrt{k_{13}k_{14}}$ [b]
$k_{10} = 7.5\sqrt{k_{13}k_{14}}$ [b]	$k_{10} = 3.1\sqrt{k_{13}k_{14}}$ [b]
$k_{11} < 0.2k_{16}$	$k_{11} < 0.3k_{16}$
$k_{12} = 2.5\sqrt{k_{13}k_{14}}$ [b]	$k_{12} = 1.9\sqrt{k_{13}k_{14}}$ [b]

[a] The rate constants of steps 3–14 are for unit viscosity (1 cP). Rate constants at other viscosities (k_i') are obtained by dividing the listed rate constants by viscosity (k_i/η). [b] In the presence of hydroquinone scavenger, k_{13} and k_{14} will both be very much larger than k_8, k_{10}, and k_{12}.

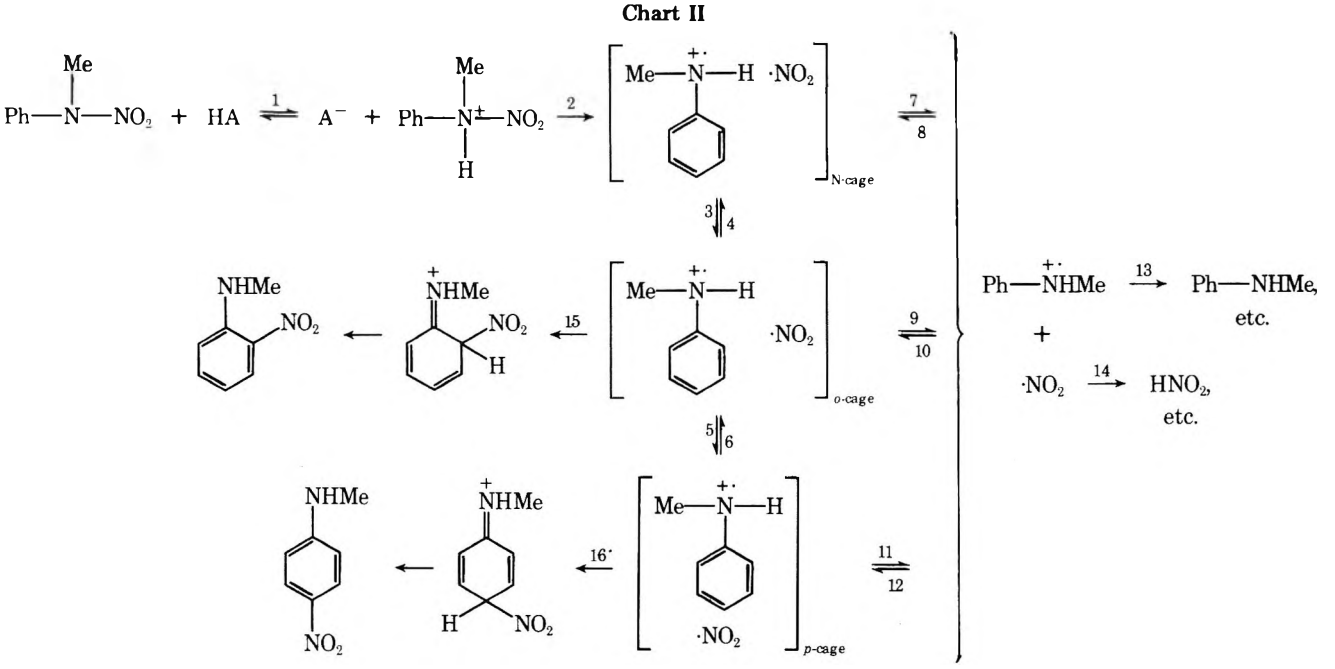
These conclusions were put on a more quantitative basis by use of the mechanism shown in Chart II. The mechanism supposes three more or less distinct cage species—one formed directly from the protonated nitramine with the NO_2 radical close to the amino nitrogen (N-cage), one that collapses to the ortho isomer with nitrogen dioxide in the region of the ortho positions (o-cage), and one that yields the para compound with the free nitro group in proximity to the para position. Application of steady-state kinetic methods to this scheme permitted the derivation of expressions for the percentage of each product in terms of the rate constants for each step and power terms involving the viscosity of the medium. The rate constants for steps 3–14 were assumed to have the following dependence on viscosity:

$$k_i' = k_i/\eta = \text{rate constant of step } i$$

Substitution of the experimental isomer yields in these equations allowed the evaluation of the relative rate constants (Table I). The theoretical curves defined by these rates parameters are those drawn in Figure 2.

Some interpretation of the relative values of the rate constants in Table I is possible. The smallness of k_8 is probably due to the fact that the positive nitrogen atom in the *N*-methylanilinium radical binds solvent so strongly that the NO_2 radical cannot easily diffuse back to reform the N-cage species. If this is so, it seems likely that k_4, which involves a

Chart II



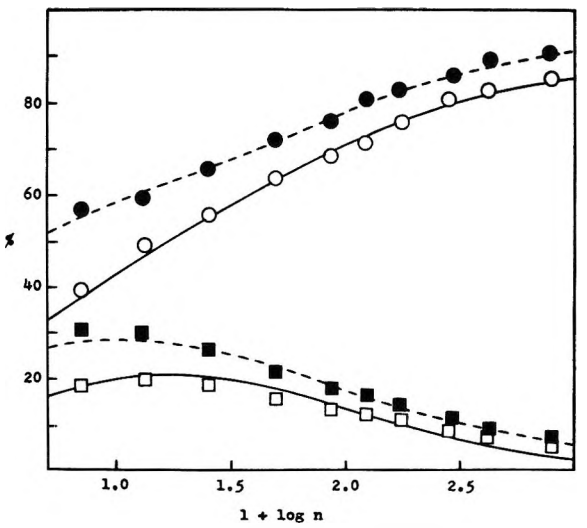


Figure 3. Yields of *o*- and *p*-nitro-*N*-methylanilines in water–glycerol solutions of various viscosities: ● and ■, ortho and para isomer, respectively, in the absence of hydroquinone scavenger; ○ and □, ortho and para isomer, respectively, in the presence of hydroquinone scavenger. Curves were calculated from the kinetics of the mechanism of Chart II using the relative rate constants in Table I.

similar, but intracage, diffusion to reform the N-cage, would also be small and perhaps negligible so that $16k_{15} - 8.1k_9 = k_4 \simeq 0$ or $k_9 \simeq 2k_{15}$. This last relationship permits a comparison of the rate of an intracage diffusion process (k_5) with the rate of a diffusion out of the cage (k_9). Since $k_5 = 4k_{15}$ and $k_9 = 2k_{15}$, diffusion within the cage is somewhat faster, but of the same order of magnitude as diffusion from the cage. This result is not surprising in view of the fact that the aniline ring shields one side of the NO_2 radical from contact with the impeding solvent in the intracage diffusion.[11] It is also interesting to note that the rates of most of the intracage diffusion processes are faster than the rates of radical recombination at unit viscosity (e.g., $k_5 = 4k_{15}$ and $k_6 = 5k_{16}$).[11] Finally, the smallness of k_{11} (dissociation of the *p*-cage) may be due to the fact that the para position is sufficiently distant from the positive amino nitrogen so that the solvent structure making properties of the hydrophobic aromatic residue may become predominant.[12] This increase in solvent structure will strengthen the attractions between solvent molecules in this region and thus make it more difficult for the two radicals in the *p*-cage species to separate.

A set of experiments similar to those described above were carried out using water–glycerol mixtures. The findings are summarized in Figure 3 and Table I. The close correspondence of these results with those obtained in methanol–glycerol media indicates that solvent polarity is of little importance in determining the yields and isomer ratios in water, methanol, glycerol, or their mixtures.

This research yields two important conclusions. First, the influence of solvent viscosity on the composition of the product from the aromatic nitramine rearrangement is most readily interpreted in terms of a mechanism involving a solvent-caged intermediate. Therefore, the results support the previously proposed "cation radical" mechanism for this isomerization. Secondly, and more generally applicable, the effect of solvent viscosity on processes occurring within the solvent cage has been shown to be significant in determining the outcome of chemical reactions.

Experimental Section

***N*-, *o*-, and *p*-Nitro-*N*-methylanilines.** These substances were available from previous investigations.[2b]

Perchloric Acid Solutions. Sufficient 60% perchloric acid was added to pure methanol or pure glycerol to yield solutions approximately 0.5 M in acid. These solutions were titrated with standard sodium hydroxide solution to determine their exact concentrations.[13]

Rearrangement of *N*-Nitro-*N*-methylaniline in Methanol–Glycerol Solutions. Appropriate quantities of 0.481 M perchloric acid in glycerol and 0.485 M perchloric acid in methanol were combined to give a solution of the desired viscosity. About 49 ml of this methanol–glycerol solution was thermostated (40.0 ± 0.2 °C) in a 50.0-ml volumetric flask. The volume was adjusted to 50.0 ml by addition of the methanol–glycerol solution. A 1.00-ml aliquot of 0.0210 M *N*-nitro-*N*-methylaniline in dioxane was added and the mixture was shaken thoroughly and kept at 40.0 ± 0.2 °C for 2 h. It was then cooled and about 5 ml[14] of the solution was transferred to a 25.0-ml volumetric flask. A 5.0-ml aliquot of 5% sulfamic acid was added and the mixture was heated at 90 °C for 30 min to destroy nitrous acid. After the solution was cooled to room temperature, it was diluted to 25.0 ml with acetate buffer (15.0 g of sodium acetate trihydrate, 50.0 ml of water, and 50.0 ml of glacial acetic acid).

Aliquots (1 ml) of dioxane, 0.0130 M *n*-nitro-*N*-methylaniline in dioxane, and 0.00660 M *p*-nitro-*N*-methylaniline in dioxane were treated in a similar way. The final solution from the dioxane run was used as a spectral blank for the other three solutions. Absorbances were determined at 390, 410, 430, 450, and 470 nm and the method of least squares was used to calculate the concentrations of *o*- and *p*-nitro-*N*-methylanilines that best reproduced the optical densities at the five wavelengths.

Rearrangement solutions containing hydroquinone were prepared in the same way as described above except that 20 mg of hydroquinone was weighed into the reaction flask before addition of the methanol–glycerol solution. The nitramine, each of the standard substances, and dioxane alone were treated with the hydroquinone-containing solutions and the final absorbances were used to calculate the product distribution.

Rearrangement of *N*-Nitro-*N*-methylaniline in Water–Glycerol Solutions. Acid solutions of different viscosities were made up by combining 0.485 M aqueous perchloric acid with 0.489 M perchloric acid in glycerol. Aliquots of the *N*-, *o*-, and *p*-nitro-*N*-methylaniline solutions and of dioxane were heated at 40.0 ± 0.2 °C with these solutions as described above and then treated in the same way. Runs were also made in the presence of hydroquinone using the previous procedure.

Viscosity Measurements. The viscosities of the methanol–glycerol and water–glycerol reaction mixtures were determined using an Ostwald viscometer and the falling sphere method. Both procedures were calibrated using distilled water and 60% aqueous sucrose solution at 40.0 °C (the temperature of all measurements).

Registry No.—*N*-Nitro-*N*-methylaniline, 7119-93-9; o-nitro-*N*-methylaniline, 612-28-2; *p*-nitro-*N*-methylaniline, 100-15-2.

References and Notes

(1) This work was supported by Grants GP-1970 and GP-8996 from the National Science Foundation.
(2) Previous papers in this series: (a) W. N. White, J. R. Klink, D. Lazdins, C. Hathaway, J. T. Golden, and H. S. White, *J. Am. Chem. Soc.*, **83**, 2024 (1961); (b) W. N. White, D. Lazdins, and H. S. White, *ibid.*, **86**, 1517 (1964); (c) W. N. White, C. Hathaway, and D. Huston, *J. Org. Chem.*, **35**, 737 (1970); (d) W. N. White and J. R. Klink, *ibid.*, **35**, 965 (1970); (e) W. N. White, J. T. Golden, and D. Lazdins, *ibid.*, **35**, 2048 (1970); (f) W. N. White and H. S. White, *ibid.*, **35**, 1803 (1970); (g) W. N. White and J. T. Golden, *ibid.*, **35**, 2759 (1970).
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(9) The results reported in this study also yield a linear relation between the logarithm of the ortho/para ratio and the logarithm of viscosity for viscosities up to 25 cP.
(10) (a) An effect of medium rigidity (viscosity) on product distribution was postulated by J. M. McBride [cf. A. B. Jaffe, K. J. Skinner, and J. M. McBride, *J. Am. Chem. Soc.*, **94**, 8510 (1972); J. M. McBride, *ibid.*, **93**, 6302 (1971); and related papers] to explain the behavior of geminate radicals in various media. (b) R. C. Neuman, Jr. [*Acc. Chem. Res.*, **5**, 381 (1972)] has interpreted these results in terms of pressure effects on the rotational motions of radicals within the solvent cage.
(11) These findings are similar to those observed by F. D. Greene, M. A. Berwick, and J. C. Stowell, *J. Am. Chem. Soc.*, **92**, 867 (1970), and J. P. Engstrom and F. D. Greene, *J. Org. Chem.*, **37**, 968 (1972), for quite different systems

assuming that intracage rotation is similar to intracage diffusion.

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(13) The viscosity of the glycerol solution precluded volume measurements by pipetting. Instead, quantities of the solution were weighed out and the density (estimated by means of a pycnometer) was used to calculate the volume.

(14) The solution was weighed and its volume was determined using the density. A pycnometer was utilized to measure the density of the reaction mixture.

Chlorination of Anilines. Bimolecular Acid-Catalyzed Rearrangement of *N*-Chloroanilines

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N-Chloroanilines undergo an acid-catalyzed rearrangement in nonpolar solvents to yield a mixture of o-chloro-, *p*-chloro-, and 2,4-dichloroanilines. The ratio of the yield of the *o*- to that of the *p*-chloroaniline is much higher than would be predicted for a statistically controlled electrophilic aromatic substitution. Although current theories of electrophilic rearrangements attribute such high ortho:para ratios to intramolecular processes, our search could find no conclusive evidence for an intramolecular pathway in these rearrangements. On the contrary, our results show that the highest ortho:para ratios are observed only when the conditions are ideal for an intermolecular transfer of chlorine.

N-Chloroanilines have been shown in our earlier report to be intermediates in the chlorination of anilines.[2] Further, studies by Gassman and co-workers have also shown that these compounds are quite stable and can be isolated.[3] They also reported a detailed study of para-substituted *N*-chloroanilines in buffered ethanol solution which showed that 4-ethoxycyclohexadienone imines were formed with rates of solvolysis which correlated with Brown's σ^+ with ρ of -6.35.[4] This product and kinetic behavior indicated that in the absence of strong acid the rearrangement was proceeding by way of the electron-deficient nitrenium ion. With acid present, these authors found evidence for two competing mechanisms, one which proceeded through the nitrenium ion and another through the electron-deficient chloronium ion.

We observed in our earlier work[2] that the rearrangement of *N*-chloroanilines produced an unusually high ratio of ortho to para chlorinated products, and decided to search for an explanation for these unusual results. The literature shows that one other reaction, the acid-catalyzed rearrangement of *N*-nitroaniline, yields exclusively the ortho-substituted product, and there seems to be general agreement that this rearrangement takes place by an intramolecular mechanism.[5-7] There is much evidence in the literature which suggests that the rearrangement of a *N*-chloroaniline under acid catalysis should be similar to the rearrangement of *N*-nitroaniline. First, the most commonly accepted theory of the *N*-nitroaniline rearrangement is an intramolecular process proceeding by way of a π complex intermediate.[5,7] Evidence for the existence of π complexes[8] has been well established. Secondly, many similarities have been observed between chlorination and nitration.[10,11] Finally there are precedents in the literature for assuming that a high ortho:para ratio of products in the chlorination of anilines is evidence for an intramolecular process.[12,13] Neale and co-workers[12] have claimed that the higher than predicted yields of o-chloroaniline observed in the chlorination of aniline with *N*-chlorosuccinimide were caused by the formation of the *N*-chloroaniline which then rearranged by an intramolecular process to yield the ortho-substituted product. This view was accepted by Kovacic in his review on *N*-halo compounds.[13]

Because of these precedents our efforts were directed to determine whether there was any evidence other than the high selectivity for ortho substitution to support an intramolecular mechanism for the *N*-chloroaniline rearrangement. In the course of this study many new and interesting discoveries have been made about the chemistry of *N*-chloroanilines which are presented in this paper, but no evidence has been found to support an intramolecular mechanism for the acid-catalyzed rearrangement.

Results

The products of the rearrangement of *N*-chloroanilines in aprotic, nonpolar solvents were generally found to be o-chloro-, *p*-chloro-, 2,4-dichloroaniline, and appreciable quantities of the parent aniline. In samples in which the rearrangement was allowed to go to completion the ortho:para ratio was always much greater than 2.0. The results of some typical rearrangements are shown in Table I, which shows an ortho:para ratio of 7.1 for *N*-methylaniline and 19.3 for *N*-*tert*-butylaniline if the dichlorinated products are discounted. When the ortho:para ratio was determined at various points in the rearrangement of *N*-chloro-*N*-methylaniline (1), a steady increase was observed over the course of the rearrangement. These results are shown in Table II.

Kinetic studies of the rearrangement showed that it was an acid-catalyzed reaction. Solutions of both 1 and *N*-chloro-*N*-*tert*-butylaniline (2) behaved very erratically when no attempt was made to control the amount of acid with which they came in contact. Further, the rate of the rearrangement could be increased by the addition of small concentrations of acids or could be decreased by treatment of the glass containers to reduce the acidity of their surfaces. The kinetic behavior of 1 was also complicated by the spontaneous elimination of HCl to form the Schiff base $PhN{=}CH_2$. The HCl which was formed by this reaction caused an acceleration of the rate of rearrangement which could be eliminated by stirring the solution with finely powdered sodium carbonate as shown in Figure 1. No similar acceleration was observed for 2 which cannot undergo β-elimination of HCl.

A rapid exchange of chlorine was observed when a small

Table I. Products of the Rearrangement of *N*-Chloroanilines in Carbon Tetrachloride Solution at 25.0 °C

	Yield, %			
N-Chloroaniline	PhNHR	o-Cl	*p*-Cl	2,4-Di-Cl
N-Methyl-[a]	10.9	66.4	9.4	10.3
N-*tert*-Butyl-[b]	5.0	83.2	6.9	5.0
N-*tert*-Butyl-[c]	3.2	89.0	4.6	2.8
N-*tert*-Butyl-[d]	2.6	84.0	5.3	3.1

[a] 0.020 M in untreated glass vessel at 25 °C. [b] Catalyzed by glass surface at 43 °C (in a polyethylene bottle no reaction took place within minutes). [c] Catalyzed by HCl (0.01 M) at 43 °C. [d] Catalyzed by trichloroacetic acid (0.01 M) at 43 °C.

Table II. Ortho:Para Ratios and Yields of Dichloro Product in the Rearrangement of 1 in Carbon Tetrachloride Solution at 25 °C

N-Chloroaniline Rearranged, %	2,4-Dichloro-aniline, %	Ortho:para ratio[a]
43	4.3	3.3
56	5.9	4.6
87	10.1	5.5
100	10.5	7.0

[a] This ratio contains no correction for the disubstituted product.

quantity of trichloroacetic acid was added to a solution of **2** and *p*-chloro-*N*-*tert*-butylaniline (**3**) in carbon tetrachloride. Table III shows that in the absence of acid no exchange took place, and that after the addition of the acid, equilibrium was established before 1% of the rearrangement had taken place. This experiment also showed that *p*,*N*-dichloro-*N*-*tert*-butylaniline was formed readily under the conditions of the rearrangement, but in a similar experiment with **2** and *o*-chloro-*N*-*tert*-butylaniline no evidence could be found for *o*,*N*-dichloro-*N*-*tert*-butylaniline.

In Table IV are shown the results of an experiment in which **2** was allowed to rearrange in a solution containing *N*,*N*-dimethylaniline (**5**). As can be seen, **5** was readily chlorinated to yield the *o*-chloro product but no measurable quantity of the *p*-chloro product of either of the anilines was observed.

The rates of rearrangement of chloroanilines **1** and **2** were increased by the addition of their corresponding anilines. Plots of the log of concentration of these chloroanilines against time gave straight lines which are shown in Figures 2 and 3. From

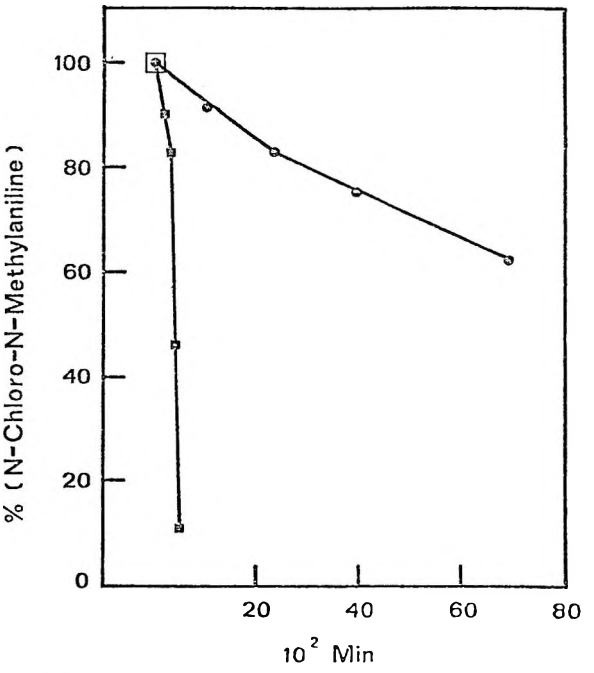

Figure 1. Percent of *N*-Chloro-*N*-methylaniline, 0.020 M in carbon tetrachloride, vs. time (■) in a glass vessel (●) stirred with sodium carbonate in a glass vessel.

the slopes of these lines first-order rate constants for the initial rates were calculated using the rate law, rate = k_1[PhNHR][PhNClR]. These pseudo-first-order rate constants, shown in Table V, appear from the analysis of columns A and B to be proportional to the total concentration of aromatic molecules and not to the concentration of the added anilines. The products of these rearrangements are also presented in Table V which shows a very large range in the ortho:para ratio for *N*-methylaniline while the ratio for the *tert*-butylaniline is always very high.

Discussion

Two outstanding features of the rearrangement of *N*-chloroanilines in the absence of added anilines are the formation of dichlorinated anilines and an ortho:para ratio which is always greater than 2.0. Such high ortho:para ratios have been assumed to be evidence for an intramolecular rearrangement.[5,6,7,12] Yet the formation of dichlorinated product requires the presence of some type of intermolecular process. Therefore, it seemed necessary to examine the nature of the rearrangement more closely.

Evidence that the rearrangement was not a simple intra-

Table III. The Chlorine Exchange Reaction (1). Products and Reactants (%) in the Chlorination of *p*-Chloro-*N*-*tert*-Butylaniline by *N*-Chloro-*N*-*tert*-butylaniline (0.95 M in Carbon Tetrachloride at 43 °C)

Time, 10^3 s	PhNClR[a]	PhNHR	*o*-ClPhNHR	*p*-ClPhNClR	*p*-ClPhNHR	2,4-Cl_2PhNHR	K_{eq}[b]
0.00	74.0	0.0	1.0	0.0	24.0	0.0	
1.74[c]	74.0	0.0	1.0	0.0	24.0	0.0	
3.24	62.0	11.0	1.0	11.0	15.0	0.0	0.13
5.28	57.0	16.0	2.0	16.0	9.0	0.0	0.50
6.48	56.0	16.0	3.0	16.0	9.0	0.0	0.51
8.70	54.0	16.0	4.0	16.0	9.0	0.0	0.53
14.58	51.0	16.0	7.0	16.0	9.0	0.0	0.56
72.18	31.0	15.0	29.0	12.0	11.0	3.4	0.53
97.98	26.0	15.0	34.0	10.0	10.0	4.0	0.58
116.70	20.0	15.0	38.0	11.0	12.0	4.0	0.69
185.40	16.0	13.0	44.0	8.0	14.0	5.0	0.46

[a] R = *tert*-butyl. [b] K_{eq} = [*p*-ClPhNClR][PhNHR]/[PhNClR][*p*-ClPhNHR]. [c] Trichloroacetic acid, 20 μl of 0.2 M, was added after this point.

Table IV. Molar Quantities of Products and Reactants at Intervals in the Trichloroacetic Acid (0.0025 M) Catalyzed Reaction of *N*-Chloro-*N*-*tert*-butylaniline (0.25 M) and *N,N*-Dimethylaniline (0.34 M) at 43 °C in Carbon Tetrachloride

Time, s × 10^{-3}	Ph-NHR′[a]	*o*-ClPh-NHR′	Ph-NClR′	Ph-NR_2[b]	*o*-ClPh-NR_2
0.00	0.63	0.44	8.89	12.1	0.45
0.30	0.89	0.48	8.63	14.2	0.89
1.02	1.17	0.67	8.10	12.9	1.23
1.38	1.17	0.68	8.15	12.5	1.24
1.98	1.34	0.77	7.88	12.5	1.34
2.82	1.64	0.93	7.50	12.4	1.67
3.54	1.67	0.92	7.45	12.1	1.64
4.98	1.79	1.00	7.13	11.7	1.75
5.76	1.94	1.14	6.92	11.8	1.90
8.52	2.22	1.38	6.40	11.4	2.14
10.08	2.28	1.53	6.20	11.0	2.24
11.04	2.35	1.65	6.00	11.2	2.35
12.84	2.62	1.85	5.51	10.6	2.53
15.90	2.86	2.16	4.97	10.6	2.74
18.12	3.06	2.41	4.50	10.4	2.86
21.96	3.22	2.83	3.87	10.2	3.05
25.68	3.46	3.20	3.32	10.4	3.36
28.62	3.58	3.54	2.88	9.9	3.40
Final	4.40	5.63	0	9.3	4.27

[a] R′ = *tert*-butyl. [b] R = methyl.

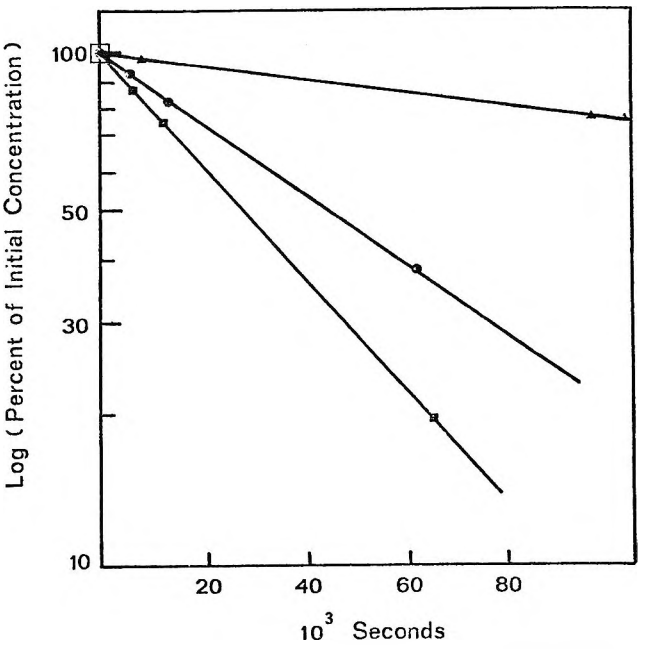

Figure 2. Log of percent of initial concentration of *N*-chloroaniline vs. time in the rearrangement of *N*-chloro-*N*-methylaniline in hexane at 25 °C with the ratio of parent aniline to *N*-chloroaniline as indicated: (▲) zero, (●) 8.0, (■) 16.0.

Table V. First-Order Rate Constants[a] (k_1) and Ortho:Para Ratios for the Rearrangement of *N*-Chloroanilines with Added Anilines in Carbon Tetrachloride and Their Dependence on the Concentration of Anilines

PhNHR[b]	PhNClR[b]	R	$k_1 \times 10^6$, s	*A*[c]	*B*[d]	o-/*p*-
0	0.02	CH_3	1.1		55	2.9
0.16	0.02	CH_3	5.6	35	31	3.9
0.32	0.02	CH_3	9.6	30	28	11.5
0	0.40	$C(CH_3)_3$	4.8		12	16.0
0.04	0.40	$C(CH_3)_3$	4.2	105	9.5	16.0
0.10	0.40	$C(CH_3)_3$	5.5	55	11	13.0
0.59	0.40	$C(CH_3)_3$	12.2	21	12.3	13.0

[a] 25 °C for *N*-chloro-*N*-methylaniline and 43 °C for *N*-chloro-*N*-*tert*-butylaniline. [b] Concentration in moles per liter as determined by NMR anaalysis of the reaction mixture. [c] $10^6 k_1/[\text{PhNHR}] = A$. [d] $10^6 k_1/([\text{PhNClR}] + [\text{PhNHR}]) = B$.

molecular process was provided by the changing ortho:para ratio shown in Table II. If the rearrangement was a clean intramolecular process of the type proposed for *N*-nitroaniline,[5] one would expect the product ratio to be constant at all stages of the rearrangement. This was not observed. There was a steady increase in the ortho:para ratio as the rearrangement progressed which is shown in Table II. A unimolecular process involving only a protonated *N*-chloroaniline could not yield this result.

The data discussed thus far do not rule out the possibility that the transfer of chlorine from the nitrogen to the carbon of the aromatic ring is an intramolecular process. Such a transfer could account for the products in Table I if the rearrangement were preceded by an exchange of chlorine between the anilines in solution such as

$$\text{PhNClR} + \text{Ph′NHR} \rightleftharpoons \text{PhNHR} + \text{Ph′NClR} \quad (1)$$

Since this exchange reaction takes place as is shown in Table III, the presence of dichlorinated products and the increasing ortho:para ratio in Table II cannot be used as conclusive evidence for either the intra- or the intermolecular pathway.

If there was an intramolecular mechanism, it might be detected by carrying out the rearrangement in the presence of an aniline which would not be expected undergo the nitrogen chlorination shown in eq 1. Since **5** is at least as reactive as **3** to electrophilic aromatic substitution, the absence of its chlorinated products in a rearranging sample of **2** would be evidence for an intramolecular process. The data in Table IV show, however, that **5** is readily chlorinated by **2** and that the ortho:para ratios for both the chlorinating and substrate anilines are very much higher than would have been predicted for a statistically controlled process. The unusually high selectivity for the ortho position in both anilines strongly suggests that the carbon chlorination took place by the same mechanism. And although this result does not prove an intermolecular transfer from nitrogen to carbon, it makes speculation about this possibility quite plausible.

Evidence that the nitrogen to carbon transfer of chlorine might be an intermolecular process is provided in Figures 2 and 3, and by Table V. They show that the rate of rearrangement is increased by the added anilines and that the ortho:para ratio increases for *N*-methylaniline whenever there is a significant quantity of free aniline present. As can be seen in eq 2, the chlorine exchange reaction can produce no change in the composition of an aniline and its *N*-chloro derivative because the products are identical with the reactants.

$$\text{PhNHR} + \text{PhNClR} \rightleftharpoons \text{PhNClR} + \text{PhNHR} \quad (2)$$

If the rearrangement were intramolecular its rate would depend on the concentration of PhNClR and should not be affected by the addition of PhNHR. Thus the increase in the rate is most probably caused by an intermolecular transfer of chlorine from nitrogen to carbon, since it is under these conditions that unusually high yields of ortho chloroanilines are observed.

The increase in rate discussed above could also have been caused by an increase in the polarity of the medium. Two pieces of data would seem to contradict this proposition. The first is that at the end of the rearrangement shown in Table II the ortho:para ratio was higher than at the beginning. The experimental data show that the last 13% of the rearrangement yielded almost exclusively the ortho product. Since the

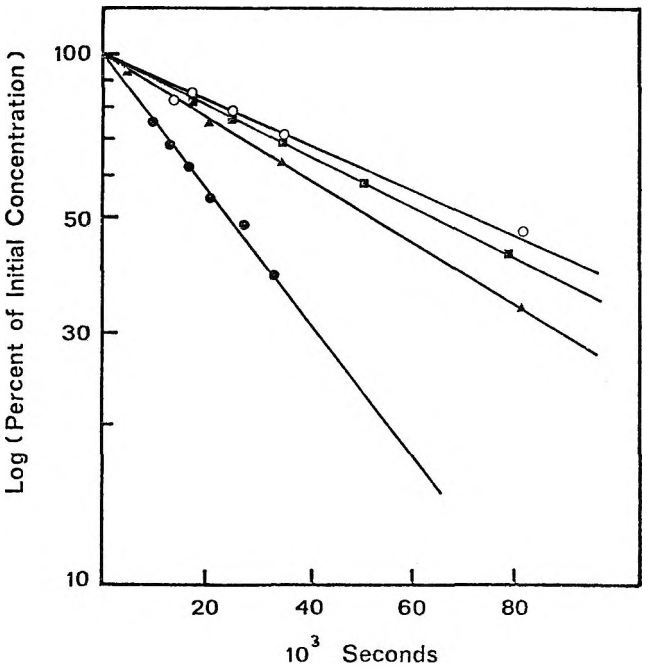

Figure 3. Log of percent of initial concentration of *N*-chloro-*tert*-butylaniline vs. time in the rearrangement of *N*-chloro-*N*-*tert*-butylaniline in carbon tetrachloride at 42 °C with the ratio of parent aniline to *N*-chloroaniline as indicated: (■) zero, (○) 0.10, (▲) 0.25, (●) 1.48.

number of aromatic molecules remained constant over the course of the rearrangement, it is unlikely that there was a significant change in the polarity of the medium yet a change in the product ratio took place. This change in the ortho:para ratio could be caused by the increase in the concentration of the parent aniline which was generated by the formation of dichlorinated products. Secondly, the results of the chlorination of dimethylaniline presented in Table IV show that both anilines are chlorinated and that in the completely rearranged mixture there are no *p*-chloroanilines. This essentially infinite ortho:para ratio for *tert*-butylaniline should be contrasted to the data in Table I which show that in the absence of added aniline a significant quantity of para product is always formed. The similarity of product ratio between added dimethyl- and parent aniline also suggests that the rate enhancement produced by the parent aniline could have been caused by an intermolecular transfer of chlorine from nitrogen to carbon.

Summary and Conclusion

We have shown that the rearrangement of *N*-chloroanilines is a complex mixture of reactions and not a single reaction as that proposed for the rearrangement of *N*-nitroaniline.[5] We have shown also that the high ortho:para ratios observed in the rearrangement are enhanced by the addition of dimethylaniline, and when there is a significant quantity of the parent aniline the product formed is almost exclusively ortho. These experiments were designed primarily to find evidence to support the proposition that the high ortho:para ratios were produced by an intramolecular reaction. We had expected that if the rearrangement were intramolecular, the product ratio over the course of the rearrangement would be reasonably constant, but the ortho product became increasingly favored as the rearrangement progressed. We had expected that if there was a clean intramolecular pathway that none or only very little of the dimethylaniline would have been chlorinated. This was not observed. We had expected to find no change in rate or product distribution on the addition of the parent aniline, but both an increase in rate and an increase in the ortho:para ratio were observed. This absence of any clear-cut

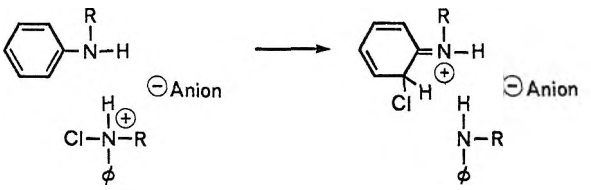

Figure 4. Reactants and σ complex intermediate in the ortho chlorination of an aniline molecule by a *N*-chloroanilinium ion.

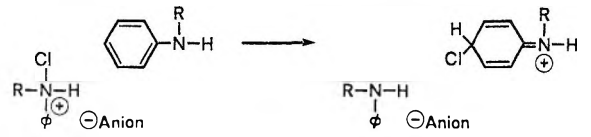

Figure 5. Reactants and σ complex intermediate in the para chlorination of an aniline molecule by a *N*-chloroanilinium ion.

evidence for the intramolecular reaction prompted us to examine whether a plausible explanation could be presented in terms of an intermolecular transfer of chlorine from the nitrogen of a chloroaniline to the aromatic carbon of an aniline molecule.

First, the changing ortho:para ratios as the rearrangement progresses could have been caused by chlorination of one chloroaniline molecule by another at the very early stages of the rearrangement. This chlorination should take place predominantly in the para position because, as we have shown, *p*,*N*-dichloroanilines form very readily whereas there is no evidence for the *o*,*N*-dichloroaniline. This is further supported by the data in Table V which show that the rate of rearrangement shows a better dependence on the total aromatic than on the free aniline concentration.

Second, the data from the dimethylamiline experiment and the added aniline experiment could be explained by an intermolecular transfer which favors ortho substitution because of differences in the charge separation in the intermediates leading to ortho and para substitution. It has been shown that for reactions which require varying degrees of charge separation in the transition state the one which can proceed with the minimum separation of charge would be favored in solvents of low polarity.[14,15] Figures 4 and 5 show possible arrangements of the reactants for the intermolecular transfer of chlorine to the ortho and para positions of aniline molecules. Since the reaction is acid catalyzed, the most likely chlorinating agent would be a protonated *N*-chloroaniline closely associated with the anion of the acid. It can be seen that the developing charge in para substitution would be much further removed from the anion than would be the case in ortho substitution. An alternate explanation could be provided by an expansion of Kovacic's concept of a linear coordination mechanism. In such a mechanism, the protonated *N*-chloroaniline would be positioned by this coordination effect near the most basic site of an aniline molecule, i.e., near the nitrogen atom, as shown in Figure 4. The geometry of such a complex would be ideal for the transfer of the chlorine to the ortho position of the aniline molecule. This explanation focuses on the greater stability of the ortho chlorination transition state by using a reactant-like transition state model, whereas the charge separation explanation uses a product-like transition state model. It is possible that a combination of both of these effects operate in this case.

Finally, although there is no clear-cut evidence in any one of the experiments to say that the rearrangement is unambiguously intermolecular, it seems fair to say that the grounds for the speculation that it is intramolecular are the high ortho:para ratios which could equally be explained by an intermolecular process as described above. Further, it seems that

taken as a group the data provide good circumstantial evidence for an intermolecular process.

Experimental Section

***N*-Methylaniline (6).** The commercially available yellow oil was mixed with 1% by weight of lithium aluminum hydride and distilled under a nitrogen atmosphere to give an almost colorless product better than 99% pure by vapor phase chromatography.

***p*-Chloro-*N*-methylaniline (7).** A 38.3-g sample of *p*-chloroaniline (Eastman Yellow Label) mixed with 47.7 g of trimethyl orthoformate (Fischer Scientific, practical) and with 1.2 g of concentrated sulfuric acid was heated under reflux for 0.5 h. The mixture was distilled to yield 42 g of *p*-chloro-*N*-formyl-*N*-methylaniline, bp 166–170 °C (20 mm), lit.[16] 165–170 °C (20 mm). The amide was hydrolyzed by heating under reflux with 120 ml of 3 M sulfuric acid for 4 h. The reaction mixture was extracted with ether, made basic with NaOH, and extracted again with ether. The second ether extract was dried over sodium carbonate and distilled to yield 22.2 g (53%) of **7**: bp 120 °C (20 mm), lit.[4] bp 120 °C (20 mm); n^{20}D 1.5816, lit.[2] n^{25}D 1.5779; NMR (CCl_4) τ 7.30 (s, 3), 6.50 (s, 1), 2.73–3.80 (symmetrical m, 4).

***o*-Chloro-*N*-methylaniline (8).** *N*-Formyl-*N*-methyl-*o*-chloroaniline was prepared as described for aniline **7**. The reaction product was dissolved in ether and extracted with two 50-ml portions of 1 M sulfuric acid. The ether was evaporated and the residue was hydrolyzed as described for aniline **7** to yield 32.0 g of **8** (76%): bp 106 °C (20 mm); n^{24}D 1.5784, lit.[4] n^{25}D 1.5784; NMR (CCl_4) τ 7.65 (s, 3), 6.06 (s, 1), 2.66–3.66 (m, 4).

2,4-Dichloro-*N*-methylaniline (9). A 4.05-g sample of 2,4-dichloroaniline (Eastman White Label) was heated under reflux for 0.5 h with 2.55 g of 90% formic acid. The mixture was dissolved in 50 ml of ether, stirred over sodium carbonate, filtered, and concentrated to 15 ml. On standing, it crystallized to give 4.0 g (86%) of *N*-formyl-2,4-dichloroaniline (mp 159–160 °C). This was dissolved in 50 ml of tetrahydrofuran and heated under reflux for 4 h with 1.0 g of lithium aluminum hydride. After evaporation of the solvent, the residue was dissolved in hydrochloric acid and extracted with ether. The aqueous layer was made basic and extracted with ether which was then dried over sodium carbonate and distilled to yield 2.4 g of a product which was found to be a 1:5 mixture of **7** and **9** by vapor phase chromatography. A pure sample of **9** was obtained by vapor phase chromatography: n^{20}D 1.5945; NMR (CCl_4) τ 7.20 (s, 3), 5.80 (s, 1), 2.20–3.70 (m, 3).

Anal. Calcd for $C_7H_7Cl_2N$: C, 47.74; H, 4.01. Found: C, 47.74; H, 4.12.

Attempts to prepare **8** by a similar reduction of the formyl derivative gave **6** as the principle product.

***N*-*tert*-Butylaniline (10).** To 175 g of *tert*-butylamine (Eastman Yellow Label) and 7.8 g of sodamide which had been heated under reflux for 24 h was added 32 g of bromobenzene, and the mixture was heated again for another 72 h. Unreacted butylamine was removed by distillation. The residue, dissolved in 100 ml of 6 N hydrochloric acid, was extracted with ether which was dried over sodium carbonate and distilled to yield 11.0 g (40%) of **10**: bp 105 °C (22 mm); lit.[17] bp 97 °C (19 mm); n(^{24}D 1.5250, lit.[17] n^{24}D 1.5246; NMR (0.2 M, CCl_4) τ 8.78 (s, 9), 6.65 (s, 1), 2.80–3.66 (m, 5).

***p*-Chloro-*N*-*tert*-butylaniline (3).** A 2.98-g sample of **10** was heated under reflux for 1 h with 2.66 g of *N*-chlorosuccinimide in 50 ml of benzene. The solution was extracted with water, dried over sodium carbonate, add concentrated to a volume of 5.0 ml. The products were separated by vapor phase chromatography to give 1.2 g (32%) of **3**: n^{24}D 1.5425, lit.[16] n^{24}D 1.5416; NMR (1.2 M, CCl_4) τ 8.70 (s, 9), 6.68 (s, 1), 3.22 (symmetrical m, 4).

***o*-Chloro-*N*-*tert*-butylaniline (4).** The chlorination mixture from which **3** was extracted gave also by preparative gas chromatography 1.8 g (50%) of **4**: n^{24}D 1.5350, lit.[16] n^{24}D 1.5346; NMR (0.80 M, CCl_4) τ 8.66 (s, 9), 5.83 (s, 1), 2.80–3.70 (m, 4) [lit.[16] NMR τ 8.63 (s, 9), 5.83 (s, 1), 2.70–3.60 (m, 4)].

2,4-Dichloro-*N*-*tert*-butylaniline (11). In 50 ml of benzene, 0.92 g of **3** was stirred for 0.5 h at 25 °C with 5.0 g of calcium hypochlorite which had been moistened with 0.5 ml of water. The mixture was filtered. The filtrate was mixed with 1.0 ml of 0.1 N trichloroacetic acid in benzene and held at 43 °C for 48 h. Evaporation of the benzene left **11**, better than 98% pure. It was purified further by gas chromatography: n^{20}D 1.5524; NMR (2.0 M CCl_4) τ 8.60 (s, 9), 5.90 (s, 1), 2.72–3.33 (m, 3).

Anal. Calcd for $C_{10}H_{13}Cl_2N$: C, 55.07; H, 5.95. Found: C, 55.33; H, 6.05.

***N*-Chloro-*N*-methylaniline (1). Method A.** A 1.075-g sample of **6** in 500 ml of carbon tetrachloride at 0 °C was mixed with 10.0 g of calcium hypochlorite which had been moistened with 1.0 ml of water. The mixture was stirred for 15 min, vacuum filtered on a Buchner funnel with genuine Whatman filter paper no. 1, and readjusted to 500 ml with carbon tetrachloride. Titration[2] of an aliquot immediately after filtering showed a 99% yield of **1**.

Method B. A 0.268-g sample of **6** was mixed with 0.58 g of *N*-chlorobenzanilide and 2.0 g of finely powdered sodium carbonate in 125 ml of benzene at 25 °C. The mixture was stirred for 25 h, filtered as in method A, and titrated to give a 99% yield of **1**. The residue, dissolved in water and filtered, gave 0.48 g (96%) of benzanilide (mp 161–162 °C).

***N*-Chloro-*N*-*tert*-butylaniline (2).** A 1.49-g sample of **10** was chlorinated by method A of *N*-chloro-*N*-methylaniline to give a 99+% yield by titration of **2**: NMR (0.40 M, CCl_4) τ 8.80 (s, 9), 2.50–3.00 (m, 5).

Method C. To a 1.49-g sample of **10** in 25 ml of carbon tetrachloride were added 1.362 g of *N*-chlorosuccinimide (Aldrich, 98+% purity) and 2.0 g of finely powdered sodium carbonate. The mixture was stirred for 18 h at 25 °C in a polyethylene flask and filtered to give a 99+% yield of **2** having the same NMR spectrum as the sample obtained by method A.

Rearrangement of 1 in an Untreated Glass Vessel at 25 °C. A 0.020 M solution of **1** in carbon tetrachloride was kept in a glass vessel at 0 °C, and 5.00-ml aliquots were removed at intervals for titration. The titrated samples were made basic with sodium hydroxide and the anilines were extracted from them with hexane and analyzed by vapor phase chromatography. The products obtained from these samples are shown below. A plot of percent of positive chlorine vs. time is shown in Figure 1.

	Yield of products, %			
Sample no.	**6**	**7**	**8**	**9**
1		7.9	25.8	4.5
2	44.7	8.9	41.3	5.9
3	22.1	10.3	56.5	10.1
4	10.9	9.4	66.4	10.3

Rearrangement of 1 over Sodium Carbonate in an Untreated Glass Vessel at 25 °C. A 200-ml sample of a 0.02 M solution of **1** in carbon tetrachloride at 25 °C was placed in a 500-ml glass flask and stirred very vigorously with 10 g of finely powdered sodium carbonate. Aliquots of the solution were removed at intervals and titrated for positive chlorine.[2] A plot of the data is shown in Figure 1. A sample, titrated at the end of 115 h of stirring, was made basic with sodium hydroxide, and the anilines were extracted with hexane and analyzed by vapor phase chromatography. The products observed were aniline, 6.2%; **6**, 60.4%; **7**, 3.6%; **8**, 12.9%; **9**, 1.2%.

Rearrangement of 2 in Carbon Tetrachloride at 43 °C Catalyzed by Glass Surface. Samples (1.00 ml) of a 0.40 M solution of **2** in carbon tetrachloride (calcium hypochlorite preparation) were placed in glass tubes which were prepared by soaking in a chromic acid bath for 1 h, then washing with water and baking at 180 °C for 12 h. They were degassed by repeatedly freezing and thawing at 0.01 mm pressure, sealed, and placed in constant-temperature baths at 43 °C. Samples were removed at intervals and titrated for positive halogen with standard thiosulfate.[2] A 20% decrease in concentration was observed in 5.90×10^3 s.

The products obtained by NMR analysis of the samples after all of the **2** had reacted were as follows.

Products	Water-washed glass vessels	Catalyzed	Trichloroacetic acid catalyzed
10	5.0	3.2	2.6
4	83.2	89.0	84.0
3	6.9	4.6	5.3
11	5.0	2.8	3.1

Rearrangement of 2 in Carbon Tetrachloride Solution at 43 °C Catalyzed by Hydrochloric and Trichloroacetic Acids. Samples of 3.33 M solution of **2** in carbon tetrachloride, 0.20 ml each, were placed in NMR sample tubes. To one tube was added 0.2 ml of 0.19 N HCl in carbon tetrachloride; to the other tube was added 0.2 ml of 0.019 N trichloroacetic acid in carbon tetrachloride. Spectra were taken at intervals in the course of the rearrangement from which the concentrations of reactants and products were determined. The rates of rearrangements were quite similar with both samples showing a

change to 50% in approximately 25×10^3 s.

Reaction of 2 with 3 in Carbon Tetrachloride at 43 °C. To a 0.40-ml sample of a 0.40 M solution of **2** in carbon tetrachloride, 12 μl of **3** was added. The sample was placed in an NMR sample tube which had been washed with water and baked dry. It was then placed in a constant-temperature bath at 43 °C. The products were identified by the position of the *tert*-butyl resonance signal of the various anilines and were determined quantitatively by peak height analysis. The results are presented in Table III.

Reaction of 2 with 5 at 43 °C Catalyzed by Trichloroacetic Acid. To 1.0 ml of a 0.40 M solution of *N*-chloro-*N*-*tert*-butylaniline in carbon tetrachloride was added 0.654 g (0.540 mmol) of **5**. The sample was placed in NMR sample tubes which had been washed with a dilute (ca. 0.5%) solution of sodium carbonate and baked dry. To the tube was added 20 μl of 0.2 M trichloroacetic acid in carbon tetrachloride. Spectra of the mixtures were taken at intervals, and the relative molar ratio of products and reactants were calculated. The results are recorded in Table IV. Para-chlorinated anilines accounted for less than 2% of the total product.

Rearrangement of 1 with 6 over Sodium Carbonate at 25 °C. An 0.02 M solution of **1** was prepared in hexane by method A. Three samples, 200 ml each, of this solution were stirred over 4.0 g of finely powdered sodium carbonate. To sample A was added 3.43 g (32.0 mmol) of **6**, and to sample B was added 6.86 g (64.0 mmol) of the same. Sample C was an 0.02 M solution of **1** and sodium carbonate. Aliquots of A, B, and C, 10.14 ml each, were transferred to a solution of potassium iodide in 50% acetic acid and titrated with standard sodium thiosulfate solution. The results are shown in Figure 2.

Effect of Glass Surfaces on the Rate of Rearrangement of 2. Samples of a 0.10 M solution of **2**, 1.00 ml each, in carbon tetrachloride were placed in glass tubes which were prepared in the following manner: 8-mm o.d. Pyrex tubing was sealed off in 6-in. lengths and constricted 4 in. from the bottom. They were kept in a chromic acid bath for 1 h, then washed exhaustively with water, and finally with a 5% sodium carbonate solution. Some of the tubes were washed with distilled water to remove all sodium carbonate. Both sets of tubes were then baked for 12 h at 180 °C. The samples of this solution of **2** were degassed by freezing and thawing four times at 0.01 mm pressure; they were then sealed at the same pressure and placed in a 43 °C constant-temperature bath. Tubes were removed at intervals, and their contents were transferred to a mixture of potassium iodide in 50% acetic acid, for titration with standard sodium thiosulfate solution. The results are shown below.

Water-washed tubes		Sodium carbonate washed tubes	
Time, h	Concn, %	Time, h	Concn, %
0.0	100	0.0	100
3.5	85	3.5	98
14.0	30	29.0	99
23.0	18	52.0	99

Rearrangement of 2 with 10 in Carbon Tetrachloride at 43 °C. A 4.0-ml sample of a 0.40 M solution of **2** and 40 μl of 0.2 M trichloroacetic acid was prepared in carbon tetrachloride. Aliquots, 1.00 ml each, were added to NMR sample tubes which had been washed with 20% nitric acid in sulfuric acid, then with water, and finally with a dilute solution of sodium carbonate (ca. 0.2% solution) and baked for 12 h at 180 °C. Samples of **10** were added to these tubes in the following order: tube A, none; tube B, approximately 5.0 μl; tube C, approximately 12.0 μl; tube D, approximately 30.0 μl. The exact quantities were determined by integration of the NMR spectra of the mixtures and are shown in Table V. The course of the rearrangement was followed by scanning the region of the spectrum between 0 and 100 Hz downfield from Me_4Si. The results are shown in Figure 3. First-order rate constants calculated from the results of this experiment are shown in Table V.

Rearrangement of 2 with 4 in Carbon Tetrachloride at 43 °C. A sample of **4**, 0.0524 g (0.350 mmol), was added to 0.20 ml of 1.90 M solution of **2** in carbon tetrachloride and the volume made up to 0.40 ml with the solvent. The sample was placed in an NMR sample tube which had been washed with water and baked dry. It was kept in a constant-temperature bath at 43 °C and removed at intervals for NMR spectra to be taken. Resonance signals were observed for *tert*-butyl protons at −1.6, 3.0, 5.0, 7.4, and 9.4 Hz from that of the *tert*-butyl resonance of **2** indicating the presence of these anilines, respectively: *p*,*N*-dichloro-*N*-*tert*-butylaniline, **3**, **4**, **10**, and **11**. There were no other peaks present which could be attributed to *o*,*N*-dichloro-*N*-*tert*-butylaniline. After all positive chlorine had been used up the products observed on analysis by NMR were **4**, 85.5%; **3**, 6.3%; **11**, 4.0%; **10**, 4.0%. Under the conditions of the analysis, an absorption corresponding to less than 0.5% of the total mixture could have been identified.

Registry No.—**1**, 4707-14-6; **2**, 22020-91-3; **3**, 48131-06-2; **4**, 939-36-6; **5**, 121-69-7; **6**, 100-61-8; **7**, 932-96-7; **8**, 57218-02-7; **9**, 35113-88-3; **10**, 937-33-7; **11**, 38370-52-4; *p*-chloroaniline, 106-47-8; trimethyl orthoformate, 149-73-5; *p*-chloro-*N*-formyl-*N*-methylaniline, 26772-93-0; *o*-chloroaniline, 95-51-2; *N*-formyl-*N*-methyl-*o*-chloroaniline, 14924-76-6; 2,4-dichloroaniline, 554-00-7; *N*-formyl-2,4-dichloroaniline, 22923-00-8; *tert*-butylamine, 75-64-9; bromobenzene, 108-86-1; *N*-chlorobenzanilide, 5014-47-1; benzanilide, 93-98-1; *N*-chlorosuccinimide, 128-09-6; *N*-chloroaniline, 24613-03-4.

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Use of the Kinetic Isotope Effect as a Test for Homogeneous Unimolecular Gas Phase Reactions in Thermolytic Processes

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Experiments are described employing the kinetic isotope effect to discriminate between homogeneous and heterogeneous surface catalyzed reactions. Advantage is taken of the differences in isotope effect expected between the nonequilibrium statistical weight isotope effect (NESWIE) observed at low pressures and the conventional isotope effect observed at higher pressures for molecules containing up to approximately 15 atoms. No change in isotope effect as a function of pressure is expected for surface-catalyzed processes. The k_H/k_D ratio for the thermal decomposition of diketene to ketene in a flow system is reported. At low pressures a value of k_H/k_D of 0.91 was obtained while at pressures of 140 mm, k_H/k_D was found to be 1.04 at 420 °C.

Interest in the study of thermolytic gas phase reactions has increased dramatically in the past decade.[1-4] This renaissance has been prompted to a large part by recent advances in theory[2,3] and technology of thermolytic processes.[4] One of the inherent difficulties in studying many thermolytic reactions in the gas phase at constant volume is the variety of secondary reactions which may follow the primary process. This complexity is often overcome by reducing the residence time of the reactants and products in the furnace by using flow methods. This has proven quite successful for the synthesis of many interesting and reactive molecules.[4] Flow methods, however, have not been extensively used by organic chemists to obtain mechanistic information. This can be attributed in part to a variety of obstacles associated with obtaining quantitative kinetic data.[5]

Surface effects in the pyrolysis of organic molecules in the gas phase are often not well understood. Their role may range from a means of energizing molecules to catalyzing specific processes which may or may not also occur homogeneously. Although several methods are routinely used to test for surface effects in static systems, these methods are generally not applicable to flow systems.[6] In flow systems, thermal activation by the surface can become the primary process of activating molecules, particularly in flash vacuum thermolysis. Differentiation between thermal activation and catalysis by the surface is thus further obscured. Mechanistic deductions from flash vacuum thermolysis, such as orbital symmetry considerations, do not require quantitative kinetic data. They do require the demonstration of unimolecularity.[7] Competitive kinetic isotope measurements to be described below afford a means of testing for the unimolecularity of a reaction, when run in a flow system.

One of the best tests for a homogeneous gas phase reaction is the falloff of the unimolecular rate constant, k_{uni}, with decreasing pressure [M].[8] At sufficiently low pressures, $k_2 > k_{-1}[M]$, the rate-determining step in the reaction of small molecules can become energization of the molecule (a molecule, A*, with sufficient internal energy to react, but randomly localized among the available quantum states, e.g., rotation, vibration). The efficiency of energization under these conditions is dependent upon the density of quantum states available. Isotopic substitution, specifically by deuterium, leads to an increase in the density of vibrational levels available. This results from the lower fundamental vibrational frequencies of R-D as compared to the R-H bond. Under conditions of low pressure an inverse isotope effect can result ($k_H/k_D < 1$). The magnitude of this effect depends upon the number of isotopic substitutions and can be much larger than conventional isotope effects measured at higher pressures. Furthermore, this effect is roughly independent of the position of isotopic substitution in the molecule. This inverse isotope effect has been observed in a number of constant volume experiments and has been termed a nonequilibrium statistical weight isotope effect (NESWIE).[8,28]

$$A + M \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} A^* + M$$

$$A^* \xrightarrow{k_2} A^{\ddagger} \rightarrow \text{products}$$

$$k_{uni} = \frac{k_2 k_1 [M]}{k_{-1}[M] + k_2}$$

M = any collision partner (e.g., the wall, A, or carrier gas)

The pressure dependence of the kinetic isotope effect can be used to discriminate between a homogeneous and heterogeneous process in the following way. In a competition experiment between appropriately deuterated and undeuterated reactant, relative reaction rates can be determined by the k_H/k_D ratios. This ratio, regardless of the value, should remain invariant to the pressure of a carrier gas for a heterogeneous process, but would be expected to vary for a homogeneous process. This obtains because activation and catalysis of a heterogeneous process can occur simultaneously on the surface whereas the rate-determining step in a homogeneous process can be changed from energization of the molecule at low pressure (possibly on the surface) to collapse of the activated complex at higher carrier gas pressures. The converse of this is not necessarily true. Invariance of the kinetic isotope effect as a function of pressure is not a sufficient condition for a heterogeneous process.[9]

An interesting situation arises in the case where an observed chemical transformation involves a series of consecutive reactions. In this instance it is possible to have sequential homogeneous and heterogeneous processes. If the intermediate(s) in the transformation are thermodynamically accessible, the short contact times involved enhance the probability that they will be trapped. Otherwise, the information conveyed by the pressure dependence of the kinetic isotope effect relates only to the rate-determining step in the series. As an example of the limiting case of a multistep reaction, consider a reaction involving an intermediate which experiences small but comparable barriers for return to reactant and conversion to products.[10] In this instance the reaction would be expected to exhibit a pressure-dependent kinetic isotope effect respective only of the process (homogeneous or heterogeneous) which led to its formation. This conclusion is based on the condition that the intermediate, once formed, is energized with respect to all the barriers along the reaction coordinate and hence does not require additional collision induced energization.[17]

The thermolysis of diketene was chosen to demonstrate how

Table I. Low-Pressure Kinetic Isotope Effect for Diketene Thermolysis[a]

Run no.	Temp, °C	Diketene[c] vapor pressure, mm	No. of passes[d]	Fraction reacted (f)	R_{Dk^0}	R_{Dk^f}	R_{K^f}	F_{DkD}	F_{DkH}	k_H/k_D (from ketene)[b]	k_H/k_D (from diketene)[b]
1	510	1.6	5	0.787	1.03	1.246		0.806	0.770		0.88 (0.88)
2	510	1	5	0.61	1.05	1.18		0.631	0.592		0.88 (0.88)
3	510	1	1	0.125	1.05		0.944	0.132	0.119	0.89 (0.89)	
4	510	8	1	0.084	1.05		0.923	0.0896	0.0786	0.87 (0.87)	
5	478	8	1	0.04	1.05		0.960	0.0210	0.0192	0.91 (0.91)	
6	420	1	1	0.0358	1.05		0.970	0.0372	0.0345	0.92 (0.92)	
7	410	1.6	2	0.018	1.05		0.954	0.0191	0.0174	0.91 (0.91)	

[a] For definitions of the symbols used in these tables and a description of Experimental conditons, see Experimental Section. [b] Estimated error ±0.03; isotope effects in parentheses are values calculated for reactions run at constant volume.[23] [c] Vapor pressures obtained by immersing samples in baths of appropriate temperature.[25] [d] Approximate residence time in oven, ~0.1 s/pass.

Table II. High-Pressure Kinetic Isotope Effect for Diketene Thermolysis[a]

Run no.	Temp, °C	Diketene[c] vapor pressure, mm	Carrier[d] gas, mm	Fraction reacted (f)	R_{Dk^0}	R_{Dk^f}	R_{K^f}	F_{DkD}	F_{DkH}	k_H/k_D (from ketene)[b]	k_H/k_D (from diketene)[b]
8	420	8	N_2, 295	0.929	1.026	0.888		0.914	0.925		1.06 (1.06)
9	420	8	N_2, 140	0.852	1.026	0.931		0.860	0.873		1.06 (1.06)
10	420	8	N_2, 137	0.919	1.026	0.931		0.916	0.923		1.04 (1.04)
11	345	8	N_2, 146	0.224	1.026		1.075	0.219	0.229	1.06 (1.05)	
12	520	8	N_2, 100	0.858	1.067	1.016		0.854	0.861		1.03 (1.03)
13	520	8	N_2, 72	0.844	1.067	1.005		0.839	0.849		1.04 (1.03)
14	420	8	Ar, 140	0.741	1.067	1.026		0.736	0.746		1.03 (1.03)
15	420	8	He, 140	0.852	1.020	0.949		0.846	0.857		1.05 (1.04)
16[e]	420	8	N_2, 141	0.68							
17[e]	420	1.6	N_2, 138	0.63							

[a–c] See Table I. [d] Flow rates varied from 0.24 to 0.5 ml/s giving rise to calculated contact times of 1–8 s. [e] Flow rate 0.5 ml/s.

the pressure dependence of the kinetic isotope effect could be used to test for a homogeneous reaction. This substrate was selected for a variety of reasons. Earlier work of Rice and Greenburg cast some doubt as to whether the dimerization of ketene could occur homogeneously in the gas phase.[18] Furthermore despite the industrial importance of diketene, relatively little concerning the mechanism of its formation has appeared in the literature.[19,20] Finally, as is typical of many other organic reactions, diketene is converted to a variety of products in a static system;[21] a quantitative conversion to ketene occurs in a flow system at 500 °C.[19]

Experimental Section

The thermolysis of diketene was performed in a 1-cm diameter quartz tube at temperatures between 410 and 520 °C with and without a carrier gas. Prior to each experiment the vacuum of the system was reduced to approximately 1 μm. In order to obtain reasonable conversion to products in the absence of carrier gas, it was necessary at some temperatures to recycle the reactant. The temperatures reported in Tables I and II were controlled to ±15 °C. The carrier gas was passed through a liquid nitrogen trap before use. In a typical experiment approximately 50 mg of a mixture consisting of equal molar amounts of diketene and perdeuteriodiketene were thermolyzed. Ketene and diketene were trapped at liquid nitrogen temperatures, separated at dry ice–acetone temperatures, and analyzed. The isotopic ratios were measured on an AEI MS 12 mass spectrometer at 70 eV by analyzing the parent ion of the reactants at high conversion and mass analysis of the products at low conversion. Analysis of dideuterioketene was complicated by traces of carbon dioxide. Consequently, the ketene mixture was allowed to react with a threefold excess of methanol prior to analysis and thus analyzed as methyl acetate.

Calculations. The isotope effects were calculated from the following equation derived by Benton for flow systems conducted at constant pressure assuming plug flow and negligible diffusion.[22]

$$k_H/k_D = \frac{2\left[\ln \frac{1}{1 - F_{DkH}}\right] - F_{DkH}}{2\left[\ln \frac{1}{1 - F_{DkD}}\right] - F_{DkD}}$$

The term F_{Dk} refers to the fraction of reacted diketene at time t and the superscripts refer to deuterated and undeuterated species and are included in Tables I and II. For comparison, the isotope effects calculated for reactions occurring at constant volume are also included in Tables I and II in parentheses. The following equations were used.[23] For isotopic analysis of residual diketene (DK)

$$k_H/k_D - 1 = \frac{\log A}{\log [(1 - f)B]}$$

$$\text{where } A = R_{Dk^t}/R_{Dk^0};\ B = \frac{1 + R_{Dk^0}}{1 + R_{Dk^t}};\ 1 - f_{Dk} = \frac{[Dk^t_H] + [Dk^t_D]}{[Dk^0_H] + [Dk^0_D]}$$

and for initially formed ketene (K)

$$k_H/k_D - 1 = \frac{\log \left[1 + C\left(\frac{D}{1 - D}\right)\right]}{\log [1 - D]}$$

$$\text{where } C = \frac{R_{Dk^0} - R_{K^t}}{R_{Dk^0}};\ D = f_K\left[\frac{1 + R_{Dk^0}}{1 + R_{K^t}}\right];$$

$$f_K = \frac{[K^t_D]}{2[Dk^0_D]} \frac{(1 + R_{k^t})}{(1 + R_{Dk^0})}$$

The terms used in these two equations, R_{Dk^0}, R_{Dk^t}, R_{K^t}, f, refer to the initial ratios of diketene to perdeuteriodiketene, diketene to perdeuteriodiketene at time t, ketene to dideuterioketene at time t, and the fraction of reaction at time t as defined, respectively.

Ketene and Diketene. Ketene and dideuterioketene were prepared from the corresponding anhydrides (Aldrich Chemical Co., Milwaukee, Wis.) by thermolysis in an evacuated hot tube at 500 °C. The acetic acid was trapped at dry ice–acetone temperatures and the ketene was trapped in liquid nitrogen. The isotopic purity of dideuterioketene exceeded 99% as analyzed by mass spectroscopy. Diketene was prepared by allowing a sealed tube of ketene to stand at −10 °C overnight. The diketene was isolated by bulb to bulb distillation on a vacuum line. NMR analysis suggested a purity in excess of 95%. Upon pyrolysis, better than 95% of the theoretical amount of ketene could be recovered.

Results

The experimental results for the thermolysis of diketene are shown in Tables I and II. Table I lists the results of ex-

periments performed under a variety of experimental conditions in the absence of carrier gas while the results obtained with carrier gas are reproduced in Table II. In both cases the isotope effects calculated were not sensitive to whether the equations for constant volume (static system) or constant pressure (flow) were used. Entries 16 and 17 in Table II were performed with unlabeled diketene and are included to demonstrate that the thermolysis of diketene is first order and is consistent with earlier reports.[19] Thermolysis of diketene at different concentrations but otherwise similar conditions of flow and pressure gave, within experimental error, the same fractional conversion. The fraction of reaction would be expected to increase for a zero-order reaction and to decrease for second or higher order reactions as the concentration of diketene decreased. The isotope effects measured at both high and low pressures do not seem particularly sensitive to temperature and hence it can be concluded that the changes in the kinetic isotope effect reflected in Tables I and II are not due to the failure of diketene to achieve thermal equilibrium when passed through without a carrier gas. It is believed that the isotope effect measured at high pressure is real (>1) but it is not presently known how it would compare to the isotope effect measured at the same temperature in a constant volume experiment. Comparison of runs 8 and 9 in Table II suggests that the high-pressure region has been reached at 140 mm pressure. Runs 10, 14, and 15 demonstrate the invariance of k_H/k_D to carrier gas. Finally, the isotope effect observed at low pressure can be contrasted to that observed under similar conditions at higher pressure. These results clearly indicate a pressure dependence on the observed isotope effect.[27]

The normal secondary deuterium isotope effect ($k_H/k_D > 1$) measured at high pressures is consistent with the results expected for a carbon atom undergoing an $sp^3 \rightarrow sp^2$ interconversion during the rate-determining step. This suggests that carbon–carbon bond breaking is involved during the slow step of diketene thermolysis. The low-pressure inverse isotope effect is exactly what is expected on the basis of the NESWIE.[26]

Advantages of this method of testing for homogeneous reactions include the fact the the experimental apparatus is easy to construct, precise temperature control is not essential, and flow rates need not be accurately reproducible. Although quartz tubes were used in these experiments, there are no limitations to the type of material that can be used. Furthermore, the magnitude of the NESWIE effect is dependent primarily on the number of isotopic substitutions, and not necessarily on how close they are to the reaction site. Thus deuterium substitution remote from the reaction site would be expected to give a NESWIE effect at low pressures and a $k_H/k_D = 1$ at higher pressures.[8]

The major limitation to this method of ascertaining the homogeneous character of a reaction is that the falloff region is not always experimentally accessible. The largest molecule whose falloff region has been experimentally investigated has contained approximately 15 atoms.[8,24] Furthermore, the pressures at which the falloff is accessable decreases rapidly with increasing molecule size.[8,26] However, this method may be applicable to slightly larger molecules since it is not necessary to obtain the limiting low-pressure NESWIE to apply this method. All that is needed to demonstrate the NESWIE is a change in the limiting high-pressure value of k_H/k_D at constant temperature as the pressure is decreased.

Registry No.—Ketene, 463-51-4; dideuterioketene, 4789-21-3; acetic anhydride, 108-24-7; diketene, 674-82-8.

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(9) A referee suggested the possibility of a reaction occurring partially at the surface and partially in the gas phase. The effect of carrier gas might be to compete for active sites and at high pressure the carrier might essentially quench the surface-catalyzed process, thus leading to a possible change in isotope effect. it should be pointed out that in spite of the unlikelihood of generating the same product(s) by two different but competing mechanisms with similar $\Delta F^{\ddagger}$, the conclusions reached by changes in the competitive kinetic isotope effect are not invalidated. The results simply suggest that the reaction is occurring homogeneously and that the surface is not necessary for reaction.

(10) A diradical has been suggested as such an intermediate. Consider a surface-catalyzed ring opening to give a singlet diradical which then diffuses off the surface. If the diradical is not energized with respect to product formation, a pressure-dependent kinetic isotope effect could be observed because the second step will show a pressure dependence typical of a homogeneous process, while the recombination reaction, which must be surface catalyzed (principle of microscopic reversibility), will not. Competition between these two processes as a function of pressure may lead to changes in isotopic discrimination. Activation energies for the recombination of two radicals are very small providing that there is no spin barrier.[11] Recent theoretical and experimental results suggests similar recombination barriers for diradicals. In some cases the barriers may be vanishingly small.[12] Catalysis by a surface becomes a moot point if the activation energies of the homogeneous reaction simply reflect the thermodynamic bond strengths involved. Nevertheless, should a reaction involve sequential heterogeneous and homogeneous steps as described above for the diradical, and small barrier separating intermediate from products relative to the total barrier separating reactant from product assures an operating temperature sufficiently high that the pressure at which the unimolecular rate constant for the homogeneous step begins to decline will be anomalously high.[13] Comparison of the falloff pressure (in this case the pressure region in which the KIE is variable) to that expected for the corresponding hypothetical homogeneous unimolecular process permits a distinction between the two possibilities. This conclusion is based on the experimental observation that for two competing reactions at low pressure, the reaction with the lower activation energy is furthest into the falloff region.[13,14] A theoretical relation between the change in falloff pressure and temperature is given by Slater's theory.[13,15]

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Reactions of Hydroperoxy Radicals. Comparison of Reactivity with Organic Peroxy Radicals

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1,4-Cyclohexadiene, which oxidizes with the hydroperoxy radical as a chain carrier, has been cooxidized with butadiene, tetralin, and tetramethylethylene at 50 °C. The relative reactivities of 1,4-cyclohexadiene, butadiene, and tetralin toward the hydroperoxy radical are 1.0:0.23:0.18, while toward the butadiene and tetralin peroxy radicals they are 1.0:0.041:0.012 and 1.0:0.033:0.015, respectively. Thus the hydroperoxy radical is significantly less selective than the organic peroxy radicals generated from butadiene and tetralin. The cooxidation of 1,4-cyclohexadiene with tetramethylethylene indicates that the hydroperoxy radical has a greater tendency to form the tetramethylethylene epoxide than does the tetramethylethylene peroxy radical. This effect is due to a higher tendency of the hydroperoxy radical to add to the olefin to form the β-peroxyalkyl radical, although the rearrangement of this adduct to form the epoxide is somewhat slower than that of the β-alkylperoxyalkyl radical.

Earlier studies[1-3] have shown that cyclic olefins, conjugated olefins, and aralkanes generally have the same relative reactivity (±20%) toward the various corresponding peroxy radicals. For these peroxy radicals, the organic portions are sufficiently removed from the free valences so that they have little inductive or steric effect on reactivity. However, in one case where steric interference should be maximized,[2] the selectivities for the two peroxy radicals vary by a factor of 2 toward the same two hydrocarbons. This paper gives the reactivities of several hydrocarbons toward the hydroperoxy radical, the simplest of all peroxy radicals, and compares them with reactivities toward typical organic peroxy radicals.

We have shown that oxygen abstracts a hydrogen from the cyclohexadienyl radical in the main propagation step in the oxidation of 1,4-cyclohexadiene.[4] The propagation cycle is

$$HO_2\cdot + C_6H_8 \rightarrow H_2O_2 + C_6H_7\cdot \quad (1)$$

$$C_6H_7\cdot + O_2 \rightarrow C_6H_6 + HO_2\cdot \quad (2)$$

Thus cooxidation of 1,4-cyclohexadiene with a second hydrocarbon (RH) will involve the following propagation reactions:

$$HO_2\cdot + C_6H_8 \rightarrow H_2O_2 + C_6H_7\cdot \quad (3)$$

$$HO_2\cdot + RH \rightarrow H_2O_2 + R\cdot \quad (4)$$

$$RO_2\cdot + RH \rightarrow RO_2H + R\cdot \quad (5)$$

$$RO_2\cdot + 1,4\text{-}C_6H_8 \rightarrow RO_2H + C_6H_7\cdot \quad (6)$$

From the consumption of each reactant (measured by disappearance of reactant or formation of products), the two reactivity ratios, $r_{HO_2\cdot} = k_3/k_4$ and $r_{RO_2\cdot} = k_5/k_6$, are determined by using standard copolymerization and analysis techniques.[1] Thus if the two parent hydrocarbons have different relative reactivities toward each peroxy radical, then $r_{HO_2\cdot} \neq 1/r_{RO_2\cdot}$.

Experimental Section

Reactions were carried out using vacuum line procedures. All hydrocarbons were purchased through common commercial channels. 1,4-Cyclohexadiene (>99.8%), tetralin (>99.8%), tetramethylethylene (98.4%), and chlorobenzene (>99.9%) were passed through silica gel, stored over calcium hydride, and distilled into the reaction vessel as needed. Butadiene (99.88%) was stored as a gas in the vacuum line after distillation from −78 °C, and was measured as a gas in a standard bulb of the vacuum line. Other compounds that were liquids at room temperature were measured as liquids in calibrated tubes in the vacuum line. All reactions were carried out in a water bath at 50 (±0.1) °C. Gas–liquid mixing maintained by a Burell wrist-action shaker (330 cycles/min) and a Vibro Mixer (7500 cycles/min) gave identical results. The analyses of H_2O_2 and H_2O at the completion of the reaction were described previously.[4]

Results

Cooxidations of 1,4-Cyclohexadiene and 1,3-Butadiene. Table I summarizes data for the cooxidation of 1,4-cyclohexadiene and 1,3-butadiene. The consumption of 1,4-cyclohexadiene was measured by formation of benzene, since reactions 3 and 6 are followed immediately by reaction 2. Less water (after reduction of H_2O_2) than benzene is formed because many of the hydroperoxy radicals add to butadiene. The amounts of hydrogen peroxide detected (not reported) are less than the water found after decomposition of hydrogen peroxide; therefore some decomposition

$$H_2O_2 \rightarrow H_2O + \tfrac{1}{2}O_2 \quad (7)$$

occurs during the reaction as was observed previously.[4] The oxygen consumption is corrected for this decomposition by adding one-half the value of water present at the end of the reaction.

The consumption of butadiene is measured in four different ways. The first method is by measuring the difference in the butadiene before and after reaction; this entails separating butadiene from the reaction mixture, then measuring it as a gas in the standard bulb of the vacuum line. The efficiency of the separation was checked by GLC and correction made when necessary. The second procedure requires an assumption that 1 mol of oxygen is consumed for each mole of hydrocarbon consumed. Thus

$$\Delta 1,4\text{-}C_6H_8 + \Delta\text{hydrocarbon} = \Delta O_2 \text{ (corrected)} \quad (8)$$

This equation is valid when chain lengths are long. Since we have measured the consumptions of oxygen (corrected) and 1,4-cyclohexadiene, the butadiene consumption is obtained

Table I. Cooxidations of Butadiene (B) and 1,4-Cyclohexadiene (C) At 50 °C with 0.01 M ABN and 3–4 Atm Oxygen

C_{av}, M	B_{av}, M	Liq vol, ml	Time, h	ΔC, mmol	ΔH_2O,[a] mmol	ΔO_2, mmol	ΔO_2 cor, mmol	ΔC,[b] mmol: Direct	ΔO_2,[c] C_6H_6	Residue, by NMR	Residue, titration	Weighted average
0.38	10.5	1.03	5.02	0.088	0.031	0.231	0.245	0.156	0.157	0.166	0.162	0.16
0.91	9.40	0.962	4.63	0.257	0.081	0.453	0.493	0.248	0.236		0.273	0.25
0.96	9.09	0.962	5.29	0.385	0.120	0.721	0.735	0.367	0.350	0.403	0.384	0.38
1.08	8.69	0.907	0.97	0.037		0.075		0.046			0.035	0.036
3.22	6.37	0.929	3.17	0.648	0.318	0.877	0.970	0.233	0.322	0.245	0.237	0.24

[a] Water present after decomposition of H_2O_2. [b] See text for different methods of determining ΔC_4H_6. [c] Correction equals ½ H_2O added to oxygen consumption.

Table II. Cooxidations of 1,4-Cyclohexadiene (C) with Tetralin (T) at 50 °C with 0.01 M ABN and 1–3 Atm Oxygen

Expt	C_{av}, M	T_{av}, M	Liq vol, ml	Time, h	ΔO_2, mmol	ΔC,[a] mmol	H_2O_2, mmol	H_2O,[b] mmol	$C_{10}H_{11}OH$, mmol	ΔT,[c] mmol
36	0.95	6.54	2.04	2.00	0.115	0.102	0.019	0.086	0.056	0.056
34	0.130	7.11	2.93	5.92	0.109	0.040	0.0105	0.029[d]	0.066	0.084
35	0.054	7.25	3.93	3.45	0.114	0.034	0.007	0.032	0.083	0.096

[a] Measured by benzene formed. [b] H_2O before H_2O_2 analysis. [c] ΔT = ΔO_2 (corrected) − ΔC. [d] No direct measurement, estimated from ΔC − ΔH_2O_2.

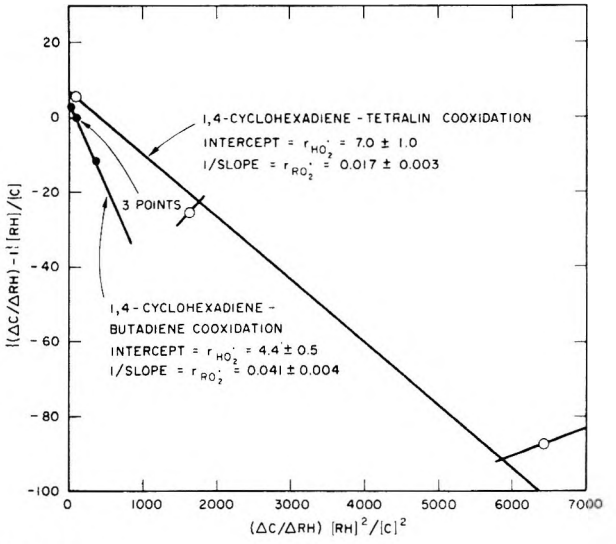


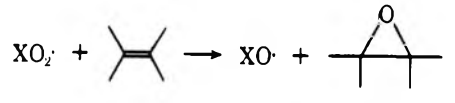
Figure 1.

by difference. The third method makes use of the weight of residue and the ratio of butadiene and hydroperoxy groups in residue as determined by NMR.[4] A fourth method entails subtracting the amount of peroxide oxygen by iodometric titration[4] from the total weight of the residue. A Fineman and Ross analysis (Figure 1) using the weighted average for butadiene consumption and other data in Table I gives $r_{HO_2\cdot}$ = 4.4 ± 0.5 and $r_{RO_2\cdot}$ = 0.041 ± 0.004, ($r_{HO_2\cdot}$)($r_{RO_2\cdot}$) = 0.18 ± 0.04, significantly less than the unity expected if both radicals have the same selectivity.

Cooxidations with Tetralin. The amount of tetralin consumed in cooxidation with 1,4-cyclohexadiene was found by determining the tetralin product (generally 97% 1-tetralol and 3% 1-tetralone) by GLC analysis of a reaction mixture after reduction with triphenylphosphine and by use of eq 8. Initial experiments carried to higher conversions than those shown in Table II indicated that the consumed tetralin could not be accounted for as the corresponding alcohol or ketone after hydroperoxide reduction with triphenylphosphine. The average rates of oxidation were also larger than those observed in Table II. However, by carrying out the reactions to relatively low conversions, the two measures of tetralin consumption gave satisfactory agreement. These data are given in Table II. Under the conditions of these experiments (low conversions), the tetralol formation is a slightly better measurement of tetralin consumption and has been used in the Fineman and Ross analysis[1] of the data (Figure 1). The analysis gives the values of $r_{HO_2\cdot}$ and $r_{C_{10}H_{11}O_2\cdot}$ in this system as 7.0 ± 1.0 and 0.017 ± 0.001, respectively. Thus ($r_{HO_2\cdot}$)·($r_{C_{10}H_{11}O_2\cdot}$) = 0.12 ± 0.02, which is also significantly less than the unity expected if the two peroxy radicals had the same selectivity.

Cooxidations with Tetramethylethylene. Table III summarizes some oxidations of tetramethylethylene (TM) with and without 1,4-cyclohexadiene. Each reaction mixture was separated into volatile and nonvolatile fractions; the former was analyzed for H_2O_2 and H_2O, titrated for hyroperoxide,[6] and finally analyzed for epoxide and acetone by GLC. The residue was then analyzed for peroxide,[5] and the remainder was assumed to be tetramethylethylene. This procedure is similar to that used by Van Sickle et al.,[7] and our data for pure tetramethylethylene agree with those data; our yield of epoxide is 14%, while Van Sickle's data predict 18% under our conditions. The yields of tetramethylethylene oxide in the cooxidation are two to three times greater than for tetramethylene alone. In experiments 33, 34, and 24, where the ratios of reactants are about the same, the yields of epoxide vary from 44 to 26% as the oxygen pressure is increased from 0.8 to 3.0 atm. The corresponding yields from neat hydrocarbon are 25 to 16% over the same pressure range.[7]

For each molecule of epoxide in the products, one alkoxy or hydroxy radical is formed by the reaction



(9)

Because these radicals, as well as both peroxy radicals, are consuming both hydrocarbons, we are unable to evaluate accurately reactivity ratios. However, in the reactions where $HO_2\cdot$ is the major radical, tetramethylethylene is about one-fourth as reactive as 1,4-cyclohexadiene after correcting for concentration differences.

Table III. Cooxidations of 1,4-Cyclohexadiene (C) with Tetramethylethylene (TM) at 50 °C with 0.1 M ABN

Expt	C_0, M	TM_0, M	Liq vol, ml	Av O_2, atm	Time, h	ΔO_2, mmol	ΔC, mmol	Epoxide, mmol (% ΔTM)[a]	Volatile ^-O_2H, mmol (% ΔTM)[a]	Residue, mg	TM in residue,[b] mmol (% ΔTM)[a]
25	2.63	6.11	1.08	1.8	3.76	0.862	0.532	0.175 (30)	0.085 (15)	38.4	0.310 (54)
33	0.98	7.39	1.06	3.0	3.72	0.262	0.109	0.042 (24)	0.005 (3)	16.0	0.125 (73)
34	0.97	7.39	1.07	0.8	3.76	0.253	0.135	0.078 (44)	0.018 (10)	10.6	0.078 (44)
24	0.93	7.42	1.00	2.4	2.94	0.186	0.084	0.046 (38)	0.000 (0)	10.1	0.072 (59)
23	0	8.12	1.924	2.6	5.55	0.192		0.027 (14)	0.084 (44)	7.8	0.067 (35)

[a] ΔTM determined from epoxide + RO_2H + residue plus 0.0014 to 0.005 mmol acetone for the cooxidations and 0.030 mmol for expt 23. [b] Assuming that all residue is TM except for titratable peroxide; if small amounts of nonperoxidic oxygen are present, these values may be slightly high.

Table IV. Relative and Absolute Reactivities of Some Hydrocarbons toward the Corresponding Peroxy Radicals at 50 °C[a]

Registry no.	Hydrocarbon	Relative reactivity[a] $HO_2\cdot$	$\sim C_4H_6O_2\cdot$	$C_{10}H_{11}O_2\cdot$
628-41-1	1,4-Cyclohexadiene	1.0[b] (4200[c])	1.0[b] (~2900)	1.0[b] (1130)
106-99-0	1,3-Butadiene	0.23 (970)	0.041 (~120[c])	0.037 (42)
119-64-2	Tetralin	0.14 (590)	0.012 (~35)	0.017 (19.2[c])
563-79-1	Tetramethylethylene	0.25 (1050		

[a] Values in parentheses are propagation rate constants in $(M\ s)^{-1}$ units. [b] Assumed. [c] Reference 11. [d] The value for butadiene homopropagation is not known but is approximated by value for styrene (ref 3), since butadiene and styrene have similar relative reactivities toward peroxy radicals (1).

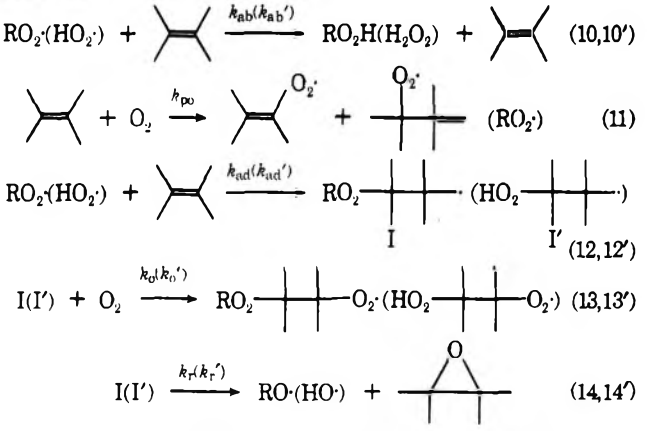
Discussion

Selectivity of Hydroperoxy Radicals in Cooxidation. Table IV summarizes the relative reactivities of butadiene, tetralin, and cyclohexadiene toward the corresponding peroxy radicals and shows that the hydroperoxy radical is less selective than peroxy radicals from tetralin or butadiene. Limited data for tetramethylethylene are included. The absolute propagation constants (calculated from appropriate relative reactivities and homopropagation constants) included in Table IV show that this reduction in selectivity corresponds with an increase in reactivity. The absolute rate constants decrease with increasing steric complexity of the peroxy radicals,[8]

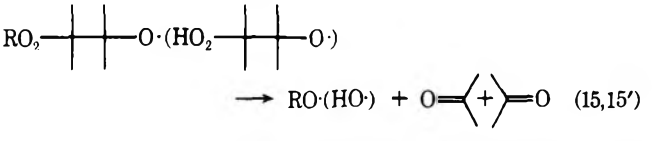
$$HO_2\cdot > \sim C_4H_6O_2\cdot > C_{10}H_{11}O_2\cdot$$

consistent with the trend observed by Howard and Ingold[9] that tertiary peroxy radicals abstract hydrogen and add to carbon–carbon double bonds more slowly than secondary or primary peroxy radicals. However, the large differences between the rate constants for hydroperoxy radicals and hydrocarbon peroxy radicals suggest that an inductive effect must be important. The reactivity increase parallels the increase in electron-withdrawing ability of the R group of RO_2.[10]

Selectivity in Addition and Abstraction. Table III shows that more addition products (epoxide and residue) are formed from tetramethylethylene in the presence of cyclohexadiene than in its absence. Thus the hydroperoxy radical has a greater tendency toward addition to the carbon–carbon double bond relative to hydrogen abstraction than do the peroxy radicals formed from tetramethylethylene. Product-producing reactions are



where reactions of $RO_2\cdot$ and $HO_2\cdot$ radicals are designated by unprimed and primed notations, respectively. The peroxy radical formed in reaction 13 or 13′ can react like $RO_2\cdot$. If it reacts by hydrogen abstraction, a stable material appears as residue. If it adds (reaction 12) and reaction 14 occurs, the resulting RO· radical is capable of decomposing to acetone and another RO· radical as in reaction 15.



In the oxidation of tetramethylethylene, the reacted olefin consumed by addition corresponds to the sum of epoxide, acetone, and one-half the residue, assuming that the residue is largely dimeric, $C_6H_{11}O_2C(CH_3)_2C(CH_3)_2O_2H$. Thus the data from experiment 23 in Table III give a value of 0.40 for the fraction of olefin consumed by addition (f_a), in agreement with the previously reported value of 0.42.[7] In the cooxidation experiments, the residue, from peroxide analyses, appears to be of the structure $HO_2C(CH_3)_2C(CH_3)_2O_2H$; thus the fraction of addition, the sum of epoxide, one-half the acetone, and all the residue, is approximately 0.9. Both hydroperoxy and tetramethylethylene peroxy radicals participate in the cooxidation experiments, so that the fraction of addition by hydroperoxy alone on tetramethylethylene (f_a') must be slightly larger than 0.9. Since for alkylperoxy radicals $f_a = k_{ad}/(k_{ad} + k_{ab}) = 0.40$ and for hydroperoxy radicals $f_a' = k_{ad}'/(k_{ad}' + k_{ab}')$

$\simeq 0.9$, the simpler ratios are $k_{ad}/k_{ab} \simeq 0.7$ and $k_{ad}'/k_{ab}' \simeq 9$; thus the hydroperoxy radical gives more addition with nonconjugated carbon–carbon double bonds (relative to hydrogen abstraction) than alkylperoxy radicals.

Epoxide Formation. In the oxidation of neat tetramethylethylene the kinetic expression for the mole ratio of olefin consumed to epoxide formed is given by the expression[6]

$$\frac{-d[TM]}{d[E]} = \frac{1 + f_a + [O_2]k_o/k_r}{f_a} \quad (16)$$

If we assume that tetramethylethylene in the cooxidations is attacked only by hydroperoxy radicals, a similar expression is obtained:

$$\frac{-d[TM]}{d[E]} = \frac{f_a' + [O_2]k_o'/k_a'}{f_a'} \quad (17)$$

Since $-d[TM]/d[E]$, f_a', and $[O_2]$ are known, the ratio k_o'/k_r' is evaluated as ~90 l./mol. The reported value of k_o/k_r is 32 l./mol, while from experiment 23 (Table III) and eq 26, a value of 50 l./mol is obtained. Since k_o' should be essentially the same as k_o, $k_r/k_r' = 1.5$–2.0. This difference is consistent with 5 kcal/mol weaker oxygen–oxygen bonds in dialkyl peroxides than in hydroperoxides.[12] Reaction 14 and 14′ are both exothermic and only a small portion of difference in heats is seen in the rate constants (about 0.5 kcal/mol) if all the difference is in the activation energy.

Registry No.—Hydroperoxy radical, 14691-59-9.

References and Notes

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(9) From our data for the oxidations of butadiene (ref 5), the butadiene peroxy radical has the formula $Y(O_2C_4H_6)_xO_2$, where the end group Y is either a fragment from the initiator, a hydrogen atom, or a fragment corresponding to the cooxidant. In the oxidation of butadiene by itself, *x* averages about 30, but in the cooxidations it is generally of the order of 1–3 owing to extensive reaction of the other hydrocarbon by hydrogen abstraction. The C_4H_6 units in the final product are present as both 1,2 addition units and trans 1,4 addition units in approximately equal amounts. Thus butadiene peroxy radical comprises both primary and secondary allylperoxy radicals and is somewhat less sterically hindered than tetralin peroxy radical, which is a secondary benzylic peroxy radical.
(10) J. A. Howard in "Free Radicals", Vol. II, J. K. Kochi, Ed., Wiley-Interscience, New York, N.Y., 1973, p 24.
(11) D. G. Hendry, T. Mill, L. Piszkiewicz, J. A. Howard, and H. K. Eigenman, *J. Phys. Chem. Ref. Data*, **3**, 937 (1974).
(12) The O–O bond strength in alkyl peroxides is about 37 kcal/mol, while for hydroperoxides it is about 42 kcal/mol: S. W. Benson, *J. Chem. Phys.*, **40**, 1007 (1964).

Multi-Bond Fragmentation of *tert*-Butyl 2-Methyl-2-*tert*-butylperoxyperpropanoate

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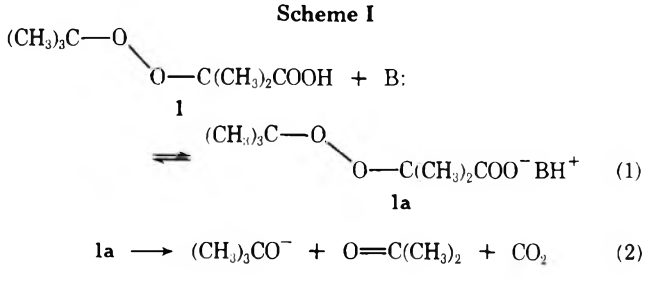
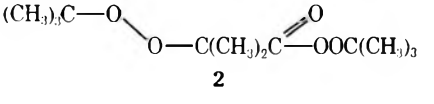
A kinetic study of the thermolysis of *tert*-butyl 2-methyl-2-*tert*-butylperoxyperpropanoate (**2**) and a model perester, *tert*-butyl 2-methoxy-2-methylperpropanoate (**5**), is presented. The decompositions follow first-order kinetics in the presence of styrene, where the activation parameters for **2** are $E_a = 18.8 \pm 0.4$ kcal/mol, $\Delta H^{\ddagger} = 18.2 \pm 0.4$ kcal/mol, log $A = 10.4$, and $\Delta S^{\ddagger} = -13.0 \pm 1.5$ eu. Activation parameters for **5** are $E_a = 20.6 \pm 0.2$ kcal/mol, $\Delta H^{\ddagger} = 20.1 \pm 0.2$ kcal/mol, log $A = 12.8$, and $\Delta S^{\ddagger} = 2.7 \pm 1.0$ eu. Products from the thermolysis of **2** in benzene are (in 100 mmol/mmol **2**) acetone (169), *tert*-butyl alcohol (102), and *tert*-butyl peroxide (9.5). Attempts to trap the radical $(CH_3)_3COOC(CH_3)_2$, which could be generated by two-bond homolysis of **2**, were unsuccessful. CIDNP signals were not observed for the potential reaction of this radical with a *tert*-butoxy radical in or out of the solvent cage. However, CIDNP signals were not observed either in the thermolysis of **5**. Correlations of several peresters in $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ vs. $\Delta H_r°$ plots were made in order to differentiate between two- and three-bond homolysis processes for **2**. Although the analysis is not unambiguous, the results tend to favor a three-bond homolysis for **2**. Excited state acetone is not produced by thermolysis of **2**, which is consistent with the maximum heat of reaction (−21.9 kcal/mol).

Previously we reported the base-catalyzed decomposition of 2-methyl-2-*tert*-butylperoxypropanoic acid (**1**). This reaction was most conveniently explained as a concerted fragmentation of the carboxylate anion (**1a**).[1]

Scheme I



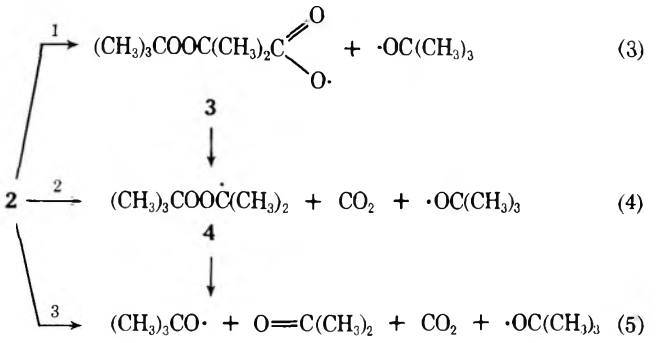
We now report an analogous free-radical decomposition in this peroxide system, namely, the thermolysis of *tert*-butyl 2-methyl-2-*tert*-butylperoxyperpropanoate (**2**). Three uni-



2

molecular homolytic reaction paths may be considered for perester **2** (Scheme II). As one proceeds from process 1 to 2 to 3, homolysis of one to two to three bonds occurs in the rate-determining step. A kinetic and product study, along with radical trapping experiments, are employed here in an attempt to differentiate between these three processes.

Scheme II

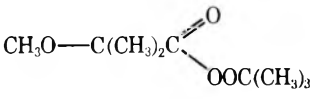


Results

Products. The products observed from the decomposition of **2** in benzene are given in Table I. Unexpectedly, no toluene was observed with an estimated detectability level of 10^{-2} mmol/mmol **2**. In an attempt to provide evidence for the fragment radical **4** in Scheme II, a GLC analysis for cumyl *tert*-butyl peroxide was made for the thermolysis of **2** in benzene. Cumyl *tert*-butyl peroxide, which could result from solvent trapping of **4**, was not detected. By comparison to an authentic sample of this peroxide, as little as a 1% yield should be easily detectable. Another attempt was made to trap **4** by decomposing the perester **2** in toluene. The expected product from this trapping experiment, *tert*-butyl isopropyl peroxide, was not detected within the 1% yield limit by comparison to an authentic sample. A final attempt to trap **4** by decomposing **2** in carbon tetrachloride was made, where 2-chloro-2-*tert*-butylperoxypropane is the expected product. No products were observed at the expected retention time corresponding to this peroxide.

Kinetic Studies. The effect of temperature on the rate of thermolysis of perester **2** is given in Table II. The decomposition of **2** proved to be first order in the presence of 0.218 M styrene, which was added as a precautionary measure to avoid induced decomposition. Not only were good first-order plots obtained, but in addition the first-order rate coefficient was unaffected by an 11-fold change in the initial concentration of **2**. The latter check is seen by comparing the rate coefficients at 19 and 20 °C. A small correction of these data to the same temperature places the rate coefficients to within 0.7% of each other. From the data in Table II, activation parameters for the thermolysis of **2** in benzene with probable error are E_a = 18.8 ± 0.4 kcal/mol, $\Delta H^{\ddagger}$ = 18.2 ± 0.4 kcal/mol, log A = 10.4, and $\Delta S^{\ddagger}$ = −13.0 ± 1.5 eu.

As a model for **2**, where the alkyl peroxide bond is replaced with an ether linkage, the thermolysis of *tert*-butyl 2-methoxy-2-methylperpropanoate (**5**) in chlorobenzene was



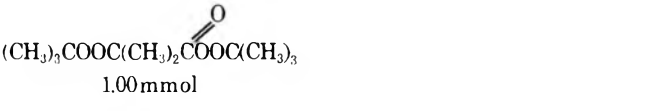
5

studied. The results of this kinetic study are given in Table III. Good first-order plots were obtained with **5** and changing the concentration of the free-radical trap, styrene, from 0.262 M to 1.33 M while the perester concentration was varied from 0.059 M to 0.119 M did not alter the rate coefficient within experimental error. From Table III, activation parameters for **5** are calculated to be E_a = 20.6 ± 0.2 kcal/mol, $\Delta H^{\ddagger}$ = 20.1 ± 0.2 kcal/mol, log A = 12.8, and $\Delta S^{\ddagger}$ = −1.9 ± 0.9 eu. These values compare favorably with those reported by another laboratory ($\Delta H^{\ddagger}$ = 20.8 ± 0.4 kcal/mol, $\Delta S^{\ddagger}$ = 2.7 ± 1.0 eu)[2] where a different experimental method was employed.

Discussion

From data of Table I, a 96% (= [(169 + 102 + 2(9.5))/300] × 10^2) product balance is obtained for the thermolysis of perester **2** in benzene at 40 °C. The product balance is based on a summation of the yields of acetone, *tert*-butyl alcohol, and *tert*-butyl peroxide.

Irrespective of the rate-determining step for thermolysis of **2** (cf. Scheme II), decomposition of **2** can be written as proceeding to the stage as shown in eq 6. Thus, 1.00 mmol of acetone will result from 1.00 mmol of **2**, according to eq 6. Based on the experimental data of Table I and the scheme below along with eq 6, a calculated yield of *tert*-butyl alcohol



can be compared to the experimental value. Agreement between calculated and observed yields of *tert*-butyl alcohol is satisfactory and serves to support the overall mode of thermolysis of **2**. Presumably, the benzene solvent is the hydrogen atom source (RH) for the *tert*-butoxy radicals in eq 8.[3] It should be noted that the product studies were measured in the absence of a free-radical scavenger. Although this allows for a more reliable product balance, it does increase the possibility of induced decomposition of the perester. Relevant to this

Table I. Product Analysis of the Thermolysis of *tert*-Butyl 2-Methyl-2-*tert*-butylperoxyperpropanoate (2)[a] in Benzene at 40.0 °C[b]

	Products, 100 mmol/mmol **2**		
Run	Acetone	*tert*-Butyl alcohol	*tert*-Butyl peroxide
1	169	100	9.8
2	168	104	9.3
Av	169	102	9.5

[a] 2.53 × 10^{-2} M. [b] After 10 half-lives. No styrene present.

Table II. Effect of Temperature on the Rate of Thermolysis of *tert*-Butyl 2-Methyl-2-*tert*-butylperoxyperpropanoate (2) in Benzene[a]

Temp, °C	{2}, M	$10^4 k$,[b] s^{-1}
42.0	0.1597	24.3 ± 0.8
32.0	0.1432	7.98 ± 0.18
30.0	0.1644	6.94 ± 0.09
20.0	0.0163	2.05 ± 0.05
19.0	0.1752	1.99 ± 0.05
11.0	0.1769	0.983 ± 0.029
9.0	0.1726	0.666 ± 0.010

[a] With 0.218 M styrene. [b] Least-squares fit with probable error.

Table III. Effect of Temperature on the Thermolysis of *tert*-Butyl 2-Methoxy-2-methylperpropanoate (5) in Chlorobenzene

Temp, °C	{5}, *M*	{Styrene}, M	$10^4 k$,[a] s^{-1}
15.0	0.059	0.262	12.8 ± 0.6
15.0	0.119	1.33	12.0 ± 0.5
7.0	0.119	1.38	4.39 ± 0.11
6.0	0.119	1.47	7.72 ± 0.09
0.0	0.074	0.468	1.77 ± 0.02
−1.0	0.107	0.351	1.67 ± 0.03
−7.0	0.082	0.253	0.673 ± 0.009
−14.0	0.120	0.328	0.205 ± 0.009

[a] Least-squares fit with probable error.

$$2(CH_3)_3CO\cdot \xrightarrow{k_f} \underbrace{2O{=}C(CH_3)_2 + 2\dot{C}H_3}_{0.69\text{mmol}\,(=1.69_{obsd}-1.00)} \quad (7)$$

$$2(CH_3)_3CO\cdot \xrightarrow[R\text{-}H]{k_a} 2(CH_3)_3COH \quad (8)$$

calcd (2.00 − 0.69 − 2(0.095)) = 1.12mmol
obsd 1.02 mmol

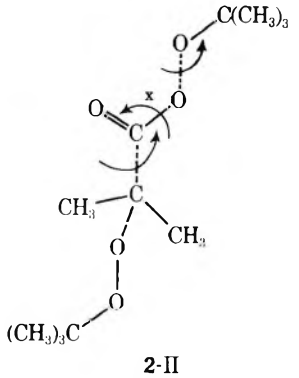
$$2(CH_3)_3CO\cdot \xrightarrow{k_c} (CH_3)_3COOC(CH_3)_3 \quad (9)$$

obsd 0.095 mmol

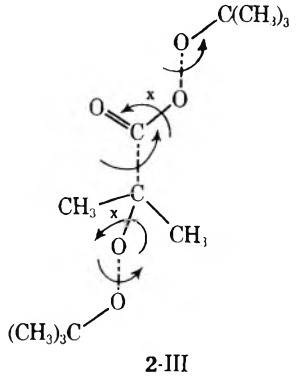
point is the fate of the methyl radicals produced in eq 7. At considerably higher temperatures than used here, methyl radicals produce toluene in benzene solution.[3] The lack of toluene from the thermolysis of **2** at 40 °C in benzene could be attributed to hydrogen atom abstraction from **2** by methyl radicals. Alternatively, reactions other than toluene formation may be more favorable for methyl radicals at this lower temperature. At this time we cannot distinguish between these two possible explanations for the lack of toluene. The above scheme is simply formulated in terms of free *tert*-butoxy radicals combining to give *tert*-butyl peroxide (eq 9). We have not investigated this aspect of the reaction, but it is likely that *tert*-butyl peroxide could be formed in a cage reaction.[4]

Considering Scheme II, it appears that one-bond homolysis (eq 3) can be eliminated with some certainty. The most restrictive differentiation of one-bond vs. multi-bond homolysis of peresters, based on the enthalpy of activation, is given by Pryor and Smith.[5] Here it is proposed that peresters with $\Delta H^{\ddagger}$ greater than 33 kcal/mol decompose by one-bond homolysis, while those with $\Delta H^{\ddagger}$ less than 27 kcal/mol decompose by multi-bond homolysis. Since $\Delta H^{\ddagger}$ = 18.2 kcal/mol for thermolysis of **2**, a multi-bond homolysis process is clearly indicated.

The problem of differentiating between the two- and three-bond homolyses in Scheme II (eq 4 and 5) is considerably more difficult. In their classic paper, Bartlett and Hiatt[6] noted a linear relationship between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for a series of peresters.[7] The number of bond rotations that were frozen in the activated complex were also correlated with this plot. Such a correlation could then potentially distinguish between the two- and three-bond homolysis routes for **2**. It is seen from the activated complexes for two-bond (**2**-II) and three-bond (**2**-III) homolyses that one and two bonds, respectively, are



2-II



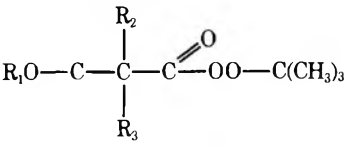
2-III

restricted in their rotation. With regard to the $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ plot, perester **2** is well correlated. With an experimental $\Delta H^{\ddagger}$ value of 18.2 kcal/mol, $\Delta S^{\ddagger}$ is calculated[7] to be −11 eu, compared to the experimental value of −13 eu. These values of $\Delta S^{\ddagger}$ are within experimental error. Since perester **2** has to our knowledge the lowest reported $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values, the Bartlett–Hiatt plot[6] does not extent to these values. However, it seems clear that this plot would predict at least three bond rotations frozen in the activated complex. Since at most only two bonds are frozen in the activated complex for **2** (cf. **2**-III), the Bartlett–Hiatt plot does not allow a choice to be made between **2**-II and **2**-III. Similarly three bonds are expected to be frozen in the activated complex for perester **5**, whereas only one bond is frozen based on a two-bond homolysis. This lack of a quantitative correlation of frozen bond rotations with activation parameters was previously noted by Pryor and Smith.[5] One possible explanation for the apparent increased number of restricted rotations for **2** and **5**, as predicted by the Bartlett–Hiatt correlation, is increased solvation of the activated complex relative to the reactant. This ordering of solvent would be expected for an activated complex with significant polar character. Thus, the ordering of the activated complex is reflected in both restricted bond rotations and solvation.

Table IV. Activation Parameters for *tert*-Butyl α-Alkoxy and α-Aryloxy Peresters 6

R_1	R_2	R_3	Solvent	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	Ref
CH_3	CH_3	CH_3	C_6H_5Cl	20.1	−1.9	This work
C_6H_5	H	H	$C_6H_5C_2H_5$	27	4	9
$C_6H_5CH_2$	H	H	$C_6H_5C_2H_5$	24	2	9
CH_3	H	H	$C_6H_5C_2H_5$	25	4	9
C_2H_5	H	H	$C_6H_5C_2H_5$	25	3.5	9
i-C_3H_7	H	H	$C_6H_5C_2H_5$	24	2	9
4-CH_3O-C_6H_4	H	H	$C_6H_5C_2H_5$	25	−1	9

Another approach to a Bartlett–Hiatt correlation is to use peresters of similar structure where solvation effects may be more uniform. As a model series for **2**, α-alkoxy or α-aryloxy peresters **6** may be considered where only one bond rotation



6

is restricted in the activated complex. Activation parameters for peresters of type **6** are given in Table IV. Activation parameters are not included where thermolyses were carried out with neat samples and where induced decomposition is likely. A least-squares correlation of the data in Table IV gives $\Delta S^{\ddagger}$ (eu) = (−20.44 ± 3.46) + (0.939 ± 0.142)$\Delta H^{\ddagger}$ (kcal/mol) with r = 0.957, where the last entry in Table IV deviates significantly from the plot and it is excluded. With $\Delta H^{\ddagger}$ = 18.2 kcal/mol for **2**, the above equation gives $\Delta S^{\ddagger}$ = −3.35 ± 2.58 eu. This calculated value of $\Delta S^{\ddagger}$, based on one frozen bond in the activated complex, may be compared to the experimental $\Delta S^{\ddagger}$ value for **2** of −13 eu. Providing that peresters of type **6** are good models for **2**, this may suggest that an additional bond rotation is frozen in **2** (cf. **2**-III). Considering the inherent problems in the $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ correlation, this conclusion can only be tentative.

Another approach was used to differentiate between the two- and three-bond homolysis routes for **2**. Here the heat of reaction ($\Delta H_r°$) was calculated for various perester thermolyses where one- and two-bond mechanisms were operative. It was hoped that a linear Polanyi plot[10] would be established between $\Delta H^{\ddagger}$ for the peresters and $\Delta H_r°$. If so, the $\Delta H_r°$ values for a two- and three-bond homolysis of **2** could be calculated to see which value best fits the Polanyi plot. Thus a decision could be made for two- vs. three-bond homolysis with **2**. Table V presents the literature values of $\Delta H^{\ddagger}$ along with the calculated[11] $\Delta H_r°$ values and in Figure 1 these data are plotted. In addition, two points are included for **2**, which correspond to a two-bond ($\Delta H_r°$ = 0.3 kcal/mol) and a

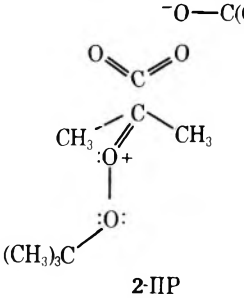
Table V. Experimental Enthalpies of Activation ($\Delta H^{\ddagger}$)[12] and Calculated Heats of Reaction ($\Delta H_r°$)[11] for the Thermolysis of Peresters[a]

Registry no.	Code no.	R in $RCO_3C(CH_3)_3$	$\Delta H^{\ddagger}$, kcal/mol	$\Delta H_r°$, kcal/mol	Homolysis type[b]
5970-01-2	1	CH_3OCH_2	24.8	19.1	2
5789-99-1	2	$C_2H_5OCH_2$	24.5	19.1	2
5790-02-3	3	$(CH_3)_2CHOCH_2$	23.6	19.1	2
7062-83-1	4	$C_6H_5CH_2OCH_2$	24.3	19.1	2
5789-77-5	5	$C_6H_5OCH_2$	27	19.1	2
6104-79-6	6	p-$CH_3OC_6H_4OCH_2$	25	19.1	2
29610-77-3	7	C_2H_5OCO	26.9	11.7	2
55695-98-2	8	$C_6H_5CH_2OCO$	26.6	11.7	2
59710-68-8	9	p-$CH_3OC_6H_4CH_2OCO$	26.2	11.5	2
107-71-1	10	CH_3	36.9	35.5	1
3990-94-1	11	$C_6H_5CH(CH_3)CH_2$	35.2	35.5	1
16474-36-5	12	$CH_3(CH_2)_7CH_2$	35.3	35.5	1
15076-84-3	13	$CH_3CH{=}CHCH_2$	25.8	6.7	2
59710-69-9	14	$C_6H_5CH{=}CHCH_2$	23.5	−4.3	2
3377-89-7	15	$C_6H_5CH_2$	28.1	8.1	2
17066-26-1	16	$CH_3C{\equiv}CCH_2$	29.8	17.1	2
614-45-9	17	C_6H_5	33.5	35.5	1
17066-27-2	18	$CH_3C{\equiv}CCH(CH_3)$	28.0	12.1	2
59710-70-2	19	$C_6H_5CH(CH{=}CH_2)$	23.0	−8.5	2
13144-32-6	20	$(C_6H_5)_2CH$	25.0	−2.8	2
927-07-1	21	$(CH_3)_3C$	30.0	15.2	2
22426-34-2	22	$CH_3(CH_2)_2C(CH_3)_2$	25.2	15.3	2
22426-33-1	23	$(CH_3CH_2)_3C$	24.7	15.3	2
24161-29-3	24	$C_6H_5C(CH_3)_2$	26.1	3.0	2
30893-89-1	25	$CH_3OC(CH_3)_2$	20.8	0.3	2
59710-71-3	26	$CH_3(CH_2)_{12}$	35.0	35.5	1
3990-91-8	27	$C_6H_{11}C(CH_3)_2CH_2$	35.2	35.5	1
2123-93-5	28	$C_6H_5CH_2CH_2$	35	35.5	1
3990-83-8	29	$C_6H_5C(CH_3)_2CH_2$	34.6	35.5	1
7482-68-0	30	$C_6H_5OCH_2CH_2$	34	35.5	1
7446-49-3	31	$C_6H_5O(CH_2)_3$	33	35.5	1
7446-56-2	32	$CH_3OCH(CH_3)CH_2$	33	35.5	1
17066-28-3	33	$C_6H_5C{\equiv}CCH_2$	28.9	17.1	2
17066-29-4	34	$C_6H_5C{\equiv}CCH(CH_3)$	26.7	2.1	2

[a] Peresters where decompositions were performed on neat samples were not included owing to the likelihood of induced decomposition. [b] Number of bonds ruptured in the rate-determining step.

three-bond ($\Delta H_r° = -21.9$ kcal/mol) process. A qualitative survey of Figure 1 reveals that two types of peresters show unusually lower $\Delta H^{\ddagger}$ values compared to the bulk of the peresters. These are peresters with unusually large steric effects[13] (code no. 22 and 23) and those with an α-alkoxy or α-aryloxy substituents (code no. 1–6 and 25). Excluding these peresters as well as *tert*-butyl peracetate (code no. 10), a least-squares fit gives a satisfactory[15] correlation ($r = 0.975$), where $\Delta H^{\ddagger} = (0.263 \pm 0.013)\Delta H_r° + 24.94 \pm 0.31$. With the exception of the α-phenoxy substituted perester (code no. 5), the α-alkoxy and α-aryloxy substituted peresters crudely form a line which parallels the bulk of the peresters. A least-squares fit gives a satisfactory correlation ($r = 0.951$), where $\Delta H^{\ddagger} = (0.194 \pm 0.032)\Delta H_r° + 20.74 \pm 0.55$ for these α-alkoxy and α-aryloxy peresters. With this equation and the $\Delta H^{\ddagger}$ value (18.2 kcal/mol) for **2**, a $\Delta H_r°$ value of -13.1 ± 2.6 kcal/mol is calculated, which is intermediate between the $\Delta H_r°$ values calculated for two-bond (0.3 kcal/mol) and three-bond (−21.9 kcal/mol) homolysis of **2**. A similar calculation with the correlation equation for the bulk of the peresters gives $\Delta H_r° = -25.6 \pm 1.4$ kcal/mol, which is clearly in better agreement with the calculated $\Delta H_r°$ value for three-bond rather than two-bond homolysis of **2**.

The question is now whether the bulk of the peresters or the α-alkoxy and α-aryloxy peresters provide a better model for the thermolysis of **2**. To answer this question, one must account for the origin of the lower $\Delta H^{\ddagger}$ values for α-alkoxy and α-aryloxy peresters as seen in Figure 1. The most reasonable explanation for this appears to be polar effects in the activated complex. Such effects are well documented;[2,8,16] however, polar contributions are not included in the calculation of $\Delta H_r°$. These polar contributions would make $\Delta H_r°$ more negative so as to more closely fit the correlation line of the bulk of the peresters, where polar effects are not as pronounced. Now one may ask if two-bond homolysis of **2** is characterized by large polar effects in the activated complex, as evidenced with α-alkoxy and α-aryloxy peresters, or with lesser polar effects associated with the bulk of the peresters. Examination of one of the polar canonical structures for the activated complex of **2** (i.e., **2**-IIP) suggests that polar effects should be of lesser importance here than in α-alkoxy or α-aryloxy peresters. In **2**-IIP the strongly electron-withdrawing *tert*-butoxy portion of the intact peroxide bond should destabilize the polar structure. Thus, the bulk of the peresters, where polar effects are less pronounced, would provide a better model for the thermolysis of **2**. However, the $\Delta H_r°$ value for two-bond homolysis of **2** is poorly correlated with the bulk of the per-



2-IIP

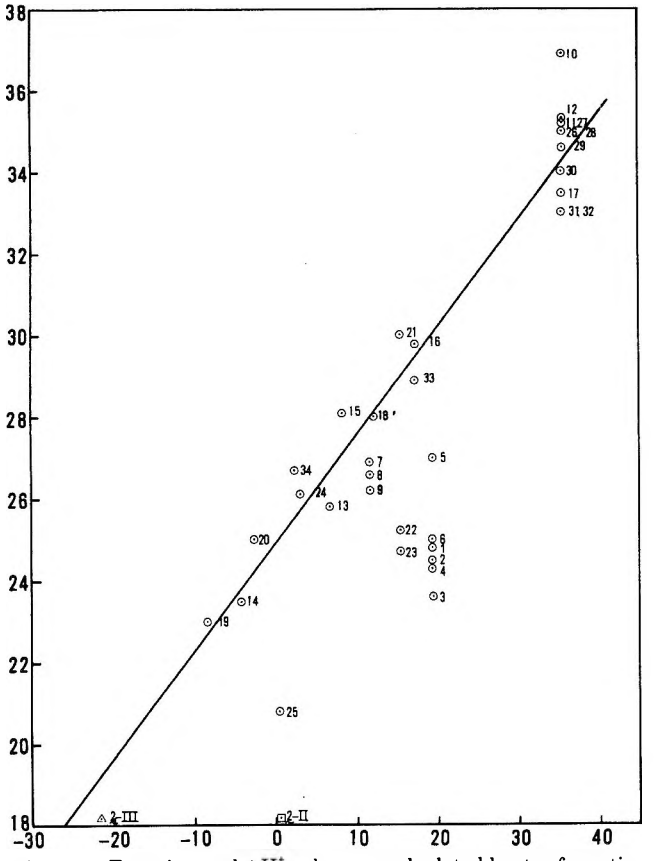


Figure 1. Experimental $\Delta H^{\ddagger}$ values vs. calculated heats of reaction ($\Delta H_r°$) for peresters in Table V. The correlation line is for the bulk of the peresters and excludes code no. 1–6, 10, 22, 23, 25, and **2**. Points shown as □ and △ correspond to ΔH_r values for two- and three-bond homolysis, respectively.

esters. Yet the $\Delta H_r°$ value for three-bond homolysis of **2** is reasonably well correlated by the bulk of the peresters. This analysis of the $\Delta H^{\ddagger}$ vs. $\Delta H_r°$ correlation then suggests that **2** is better represented by a three-bond homolysis process.

Experiments designed to trap the fragment radical **4** and thus to provide evidence for the two-bond homolysis process were unsuccessful. Products expected from trapping of **4** by solvent (cumyl *tert*-butyl peroxide), or hydrogen atom abstraction (isopropyl *tert*-butyl peroxide), or chlorine atom abstraction (2-*tert*-butylperoxy-2-chloropropane) were not detected from the thermolysis of **2**. Although these results are consistent with a three-bond homolysis process, the unimolecular rate of decomposition of **4** may be fast vs. the bimolecular trapping reactions. The unimolecular rate for decomposition of **4** is unknown, but a rapid decomposition seems reasonable based on the exothermicity of the reaction (−34.3 kcal/mol).

Product analysis from thermolysis of *tert*-butyl isopropoxyperacetate showed that the fragment radical $(CH_3)_2CHOCH_2$ was trapped by the *tert*-butoxy radical to give $(CH_3)_2CHOCH_2OC(CH_3)_2$.[2] If the fragment radical **4**, resulting from two-bond homolysis of **2**, was trapped by the *tert*-butoxy radical in or out of the solvent cage, then a CIDNP signal would be expected.[17] No CIDNP signals were detected during the thermolysis of either perester **2** or **5**. Unfortunately, this leaves the CIDNP method of detecting radical **4** in doubt under our experimental conditions, since the model perester **5** did not show CIDNP signals.

In summary, an analysis of the data for thermolysis of **2** tends to favor a three-bond homolysis process. Although the arguments for a three-bond homolysis appear reasonable, the two-bond process cannot be rigorously excluded. Presently it does appear that **2** is the best candidate to date for a perester that undergoes a three-bond homolysis.[8]

In conjunction with our interests in the chemical production of excited state molecules,[18] we attempted to measure light emission during the thermolysis of **2**. No light emission was noted from **2**, which is consistent with the maximum exothermicity of the reaction (i.e., three-bond homolysis, where $\Delta H_r° = -21.9$ kcal/mol). The decomposition would have to be exothermic by at least 80 kcal/mol to produce triplet acetone.[19]

Experimental Section[20]

Materials. *tert*-Butyl hydroperoxide-90 (Lucidol) was purified by azeotropic distillation and then by vacuum distillation.[6] Pyridine (Matheson Coleman and Bell) was fractionally distilled from barium oxide, bp 111–114 °C (lit.[21] bp 115.5 °C). Thionyl chloride (MCB) was purified[22] by refluxing with triethylphosphite, and then by fractional distillation. Thiophene-free, reagent-grade benzene (MCB) was distilled from calcium hydride and a heart cut was collected, bp 79.8–80.1 °C (lit.[23] bp 80.1 °C). The solvent was stored over Drierite and under nitrogen. Chlorobenzene (MCB) was dried over calcium hydride and then over phosphorus pentoxide. The dried solvent was then fractionally distilled and a heart cut was collected, bp 131.0–131.5 °C (lit.[24] bp 132 °C). The purified solvent was stored over Drierite and under nitrogen. Stabilized styrene (MCB) was distilled and a heart cut was collected, bp 35–36 °C (10 mm) [lit.[25] 145–146 °C (760 mm)]. Cumyl *tert*-butyl peroxide[26] and isopropyl *tert*-butyl peroxide[1] were prepared by previously reported procedures.

2-Methyl-2-*tert*-butylperoxypropanoic Acid. This acid was prepared according to a previously reported method.[1] The acid was purified by sublimation at 1 mm pressure (bath 70 °C) and dried in a vacuum desiccator over phorphorus pentoxide, mp 62.0–64.0 °C (lit.[1] mp 62.0–63.5 °C). The NMR spectrum showed the following absorptions: $(CH_3)_3C$ 1.23, s, 9; $C(CH_3)_2$ 1.43, s, 6; and COOH 11.6, s, 1.

2-Methyl-2-*tert*-butylperoxypropanoyl Chloride. An aluminum foil wrapped flask was charged with 1 ml (1.65 g, 13.9 mmol) of purified thionyl chloride and then 1.57 g (8.92 mmol) of 2-methyl-2-*tert*-butylperoxypropanoic acid in 3 ml of methylene chloride was added dropwise with magnetic stirring. The system was protected from moisture with a calcium chloride drying tube and the solution was stirred for 22 h at room temperature.

Thionyl chloride and methylene chloride were distilled at room temperature (4 mm). Flash distillation of the residue at room temperature (2 mm) into an isopropyl alcohol/dry ice cooled receiver gave 0.99 g (58% yield) of the acid chloride. The NMR spectrum of the acid chloride showed the following absorptions: $(CH_3)_3C$ 1.25, s, 9; and $C(CH_3)_2$ 1.48, s, 6.

***tert*-Butyl 2-Methyl-2-*tert*-butylperoxyperpropanoate (2).** An aluminum foil wrapped flask was charged with 0.30 g (1.5 mmol) of 2-methyl-2-*tert*-butylperoxypropanoyl chloride and 2 ml of carbon tetrachloride. The flask was cooled to −24 °C in a carbon tetrachloride/dry ice bath. To the cold solution, 0.17 g (2.1 mmol) of purified pyridine was slowly added dropwise over 5 min with shaking. After precipitation was complete, 0.18 g (2.0 mmol) of purified *tert*-butyl hydroperoxide was slowly added dropwise over 20 min with shaking. During the additions, the reaction flask was swept with a slow stream of nitrogen.

After the additions were completed, the reaction mixture was stored in a freezer (−20 °C) for 3 h and then rapidly filtered through a sintered glass funnel and into a receiver which was cooled in a carbon tetrachloride/dry ice bath. The precipitate was washed with 0.5 ml of cold carbon tetrachloride. The filtrate was washed once with 0.5 ml of 10% (w/v) cold sulfuric acid, once with 0.5 ml of 10% (w/v) cold sodium carbonate, and once with 0.5 ml of cold water. The filtrate was then dried over Drierite for 1 h at −20 °C and finally distilled. The distilling flask was placed in an ice bath and the receiver was immersed in an isopropyl alcohol/dry ice bath. After pumping for 20 min at 4 mm pressure to remove the carbon tetrachloride, 3 ml of benzene was immediately added and the solution was frozen in an isopropyl alcohol/dry ice bath until it was used. The approximate yield, by NMR, was 33%. The NMR spectrum of **2** showed the following absorptions: *gem*-dimethyl protons 1.42, s, 6; *tert*-butylperoxy protons 1.22, s, 9; and *tert*-butyl perester protons 1.28, s, 9.

2-Methoxy-2-methylpropanoic Acid. This acid was prepared according to the procedure of Weizmann, Sulzbacher, and Bergmann,[27] bp 100.0–100.5 °C (22 mm) [lit.[27] bp 98.0–99.0 °C (20 mm)], yield 74%. The NMR spectrum showed the following absorptions: $C(CH_3)_2$ 1.42, s, 6; CH_3O 3.28, s, 3; and COOH 11.6, s, 1.

2-Methoxy-2-methylpropanoyl Chloride. A flask was charged with 2 ml (3.3 g, 28 mmol) of thionyl chloride and 2.40 g (20.3 mmol) of 2-methoxy-2-methylpropanoic acid in 3 ml of methylene chloride was added dropwise with magnetic stirring. The flask was protected from moisture with a calcium chloride drying tube and the solution was stirred for 3 h at room temperature. Thionyl chloride and methylene chloride were distilled at room temperature (4 mm). Flash distillation of the residue at 2 mm pressure (bath 40 °C) gave 1.13 g (41% yield) of the acid chloride. The NMR spectrum showed the following absorptions: $C(CH_3)_2$ 1.48, s, 6; and CH_3O 3.30, s, 3.

***tert*-Butyl 2-Methoxy-2-methylperpropanoate (5).** An aluminum foil wrapped flask was charged with 1.0 g (7.3 mmol) of 2-methoxy-2-methylpropanoyl chloride and 2 ml of Freon-11. The flask was cooled in an isopropyl alcohol/dry ice bath (−78 °C) and then 0.79 g (10 mmol) of purified pyridine was added dropwise over 5 min with shaking. After precipitation was complete, 0.86 g (9.6 mmol) of purified *tert*-butyl hydroperoxide was slowly added dropwise with shaking. During the additions, the flask was swept with a slow stream of nitrogen.

After the additions were completed, the reaction mixture was stored in an isopropyl alcohol/dry ice bath for 3 h. The precipitate was rapidly filtered through a sintered glass funnel and the filtrate was cooled in an isopropyl alcohol/dry ice bath. The precipitate was washed with 3 ml of cold Freon-11. The filtrate was then rapidly washed once with 0.5 ml of 10% (w/v) cold sulfuric acid, once with 0.5 ml of 10% (w/v) cold sodium carbonate solution, and once with 0.5 ml of cold water. The organic phase was dried over Drierite in an isopropyl alcohol/dry ice bath and then the Freon-11 was distilled at room temperature (40 mm) until about 1 ml of solution remained. Now 5 ml of chlorobenzene was added and distillation was continued to remove the Freon-11 [room temperature (5 mm)]. The solution was stored in an isopropyl alcohol/dry ice bath until it was used. The percent yield (10%) was obtained by NMR analysis in comparison to a known amount of methylene chloride. The NMR spectrum showed the following absorptions: $C(CH_3)_2$ 1.40, s, 6; CH_3O 3.20, s, 3; and $(CH_3)_3C$ 1.23, s, 9.

Kinetic Methods. NMR sample tubes were prepared by using 0.8 ml of the thawed stock solution of the perester, 20 μl of methylene chloride, and 20 μl of styrene. The contents were mixed by shaking and frozen until they were to be used. Kinetic data were obtained from thermolysis of **2** by following the appearance of the acetone absorption and from **5** by following the disappearance of the methoxy absorption of **5**, both relative to the methylene chloride absorption. The initial concentration of **2** was obtained by measuring the *gem*-dimethyl protons of **2** relative to the methylene chloride absorption, where the concentration of the latter was known. Similarly, the methoxy protons were used to determine the initial concentration of **5**. Areas of the absorptions were measured with a planimeter. The NMR probe temperature was measured before and after the kinetic measurement with a thermometer which was inserted into the probe. The NMR tube was left in the NMR probe during the entire kinetic measurement (2–3 half-lives). An infinity point was measured after about 10 half-lives. Both the first-order rate coefficients and the activation parameters were obtained by means of a least-squares computer program.

Product Analyses. Initial concentrations of the perester were determined by NMR relative to a known concentration of methylene chloride. The solution was degassed in three freeze–thaw cycles on a vacuum line at 2×10^{-4} mm pressure. The sample was then heated for 3 h in an oil bath at 40 °C. An internal standard was introduced by means of a μl syringe and the sample was subjected to GLC analysis on a 20% polypropylene glycol on Chromosorb W column (5 ft × 0.125 in.), column temperature 150 °C, and flow rate 20 ml nitrogen/min. The yield of products was calculated by reference to a standard mixture which contained the internal standard (typically ethylbenzene) and the reaction products. A chart speed of 4 in./min was used and the retention times for acetone, *tert*-butyl alcohol, *tert*-butyl peroxide, and ethylbenzene were 0.7, 1.0, 1.3, and 3.0 min, respectively.

In the trapping experiments, cumyl *tert*-butyl peroxide was analyzed on a 3% SE-30 on Varaport-30 column (5 ft × 0.125 in.) with a column temperature of 70 °C, injector temperature 95 °C, and a flow rate of 22 ml/min. The $t_{1/2}$ and t_∞ reaction mixtures showed no GLC peaks with a retention time greater than that of benzene (8 min). The retention time of cumyl *tert*-butyl peroxide was 26 min. It was estimated that a 1% yield of this peroxide could be detected. Analyses for isopropyl *tert*-butyl peroxide and 2-chloro-2-*tert*-butylperoxypropane were carried out with an XF-96 column under the following conditions: column temperature 25 °C, injector 75 °C, and flow rate 25 ml/min. The retention time for 2-chloro-2-*tert*-butylperoxypropane was estimated to be greater than that for benzene and approximately the same as that of di-*tert*-butyl peroxide. No peaks were observed between benzene (14 min) and di-*tert*-butyl peroxide (33 min) or greater than 33 min. It was estimated that a 1% yield of isopropyl *tert*-butyl peroxide or 2-chloro-2-*tert*-butylperoxypropane could be detected.

Light Emission. Light emission measurements were obtained with a Hamamatsu R374 head-on photomultiplier tube as previously described.[18d] Measurements were made with nondegassed benzene solutions of **2** in the presence and absence of 9,10-diphenylanthracene at 26–28 °C.

CIDNP. An NMR tube containing 0.2 M **5** was placed in the preheated probe (18 °C, $t_{1/2}$ = 9 min) of a JEOL PS-100 spectrometer operating with an external H_2O lock. A repetitive scan from 1.0 to 2.5 ppm with a sweep time of 100 s was run through 3 half-lives of the perester decomposition. A second repetitive scan was made from 2.5 to 4.0 ppm with a fresh sample of **5**. No enhanced absorption or emission was observed. The same procedure was repeated with perester **2**, where the probe temperature was 35 °C ($t_{1/2}$ = 11 min). Again, no CIDNP signals were observed.

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Registry No.—2, 59710-72-4; 2-methyl-2-*tert*-butylperoxypropanoic acid, 59710-73-5; 2-methyl-2-*tert*-butylperoxypropanoyl-chloride, 59710-74-6; thionyl chloride, 7719-09-7; *tert*-butyl hydroperoxide, 75-91-2; 2-methoxy-2-methylpropanoic acid, 13836-62-9; 2-methoxy-2-methylpropanoyl chloride, 56680-82-1.

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Lead Tetraacetate Oxidation of 2-Methyl-2-*tert*-butylperoxypropanoic Acid

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A product and kinetic study of the lead tetraacetate (LTA) oxidation of 2-methyl-2-*tert*-butylperoxypropanoic acid (1) was made in benzene solution. The products from the oxidation of 1 (per mmol of 1) are 1.32 mmol of acetone, 0.70 mmol of *tert*-butyl alcohol, and 0.39 mmol of toluene. In the presence of LTA and sodium chloride the products are (per mmol of 1) 1.45 mmol of acetone, 0.53 mmol of *tert*-butyl alcohol, and 0.39 mmol of toluene. Attempted trapping experiments with LTA/sodium chloride or with LTA/carbon tetrachloride did not reveal the presence of the possible radical intermediate $(CH_3)_3COO\dot{C}(CH_3)_2$ (3). Relative rates for the LTA oxidation of pivalic acid, 1, and 2-methoxy-2-methylpropanoic acid at 80 °C are 1.00:14.2:534, respectively. Oxidation of 1 to *tert*-butoxy radical, acetone, and carbon dioxide in a concerted manner could not be clearly differentiated from a stepwise oxidation to radical 3 and carbon dioxide. However, if the latter process was operative, radical 3 was extremely short lived and it approached its vibrational lifetime. A direct two-electron oxidation of 1 by LTA was eliminated by the product studies.

The ionic base catalyzed fragmentation of 2-methyl-2-*tert*-butylperoxypropanoic acid (1) and the analogous free-radical fragmentation of the perester 2 were reported previously.[1,2] A concerted fragmentation of the anion of 1 to carbon dioxide, acetone, and *tert*-butoxide was clearly the most acceptable mechanism.[1] In the homolytic decomposition of 2, a concerted fragmentation involving the simultaneous rupture of three bonds appeared most consistent with the data. However, a two-bond homolysis process could not be rigorously excluded.[2]

$(CH_3)_3COOC(CH_3)_2CO_2H$ (1) $(CH_3)_3COOC(CH_3)_2CO_3C(CH_3)_3$ (2)

We now report the lead tetraacetate (LTA) oxidation of 1. Most carboxylic acids undergo a free-radical decomposition with LTA, which involves lead(IV) and lead(III) species.[3] By this mechanism, acid 1 could undergo decarboxylation to the radical 3, which could subsequently undergo fragmentation

$(CH_3)_3COO\dot{C}(CH_3)_2$ (3)

to acetone and *tert*-butoxy radical. Alternatively, further oxidation of 3 could give the acetate 4 and/or olefin 5. The

$(CH_3)_3COO-C(CH_3)_2OAc$ (4) $(CH_3)_3COO-C(CH_3)=CH_2$ (5)

olefin 5 possesses a labile peroxide bond and would suffer further decomposition. Alternatively, a concerted oxidative decarboxylation of 1 could occur to give carbon dioxide, acetone, and *tert*-butoxy radical directly. In addition, a two-electron oxidation of 1 should be considered.

A product and kinetic study of the LTA oxidation of 1 is presented with the hope of sorting out these possible mechanisms. Particular attention is given to the question of a homolytic concerted fragmentation process as opposed to a stepwise process involving radical 3. These results are compared to those obtained with perester 2. Rates of the LTA oxidation of pivalic acid and 2-methoxy-2-methylpropanoic acid are presented for comparison to 1.

Results

Products. The yield of condensable products with and without added sodium chloride which result from the LTA oxidation of acid 1 in benzene are given in Table I. GLC analysis for cumyl *tert*-butyl peroxide was made, since this would be an expected product if radical 3 or the corresponding carbonium ion were trapped by the benzene solvent. This peroxide was not observed and it was estimated that a 1% yield could be observed. GLC analyses were made for 2-chloro-2-*tert*-butylperoxypropane in the oxidation of 1 with LTA and added sodium chloride and also in the oxidation of 1 with LTA in carbon tetrachloride solvent. No evidence for the chloroperoxide could be found in either of these attempted trapping experiments. Finally, di-*tert*-butyl peroxide was not observed in the oxidation of 1 and no other products were observed other than acetone, *tert*-butyl alcohol, and toluene by GLC analysis.

Kinetics. The rate of oxidation of 1 and pivalic acid (6) were measured at 80.01 °C. The rate of oxidation of 2-methoxy-2-methylpropanoic acid (7) was too fast to conveniently measure at 80 °C, so rates were measured from 30 to 70 °C and a rate coefficient at 80 °C was obtained from the activation parameters. These data are given in Tables II and III. The relative rates of oxidation of 6:1:7 at 80 °C are 1.00:14.2:534, respectively.

Discussion

The product balance for the LTA oxidation of 1 appears to be satisfactory. The *tert*-butyl group in 1 is accounted for per mmol of 1 as 0.70 mmol of *tert*-butyl alcohol and 0.39 mmol of toluene. There is then an "excess" of 0.09 mmol (9%) in the *tert*-butyl group product balance. Although lead(IV) tetraacetate is stable under the reaction conditions, it is possible that an intermediate lead(III) triacetate (where 1 does not occupy a ligand site) decomposes to give methyl radicals and thus increases the yield of toluene. One millimole of acetone should result from the *gem*-dimethyl portion of 1 (per mmol of 1). The additional 0.32 mmol of acetone, to give a total of 1.32 mmol of acetone, would most reasonably arise from fragmentation of a *tert*-butoxy radical generated from 1. This is in good agreement with 1.00 mmol of *tert*-butoxy radical from 1 giving the observed 0.70 mmol of *tert*-butyl alcohol and 0.30 mmol of acetone plus 0.30 mmol of methyl radicals.

The fate of the proposed *tert*-butoxy radical, produced from the LTA oxidation of 1, can be compared to the *tert*-butoxy radicals which arise from the perester 2[2] in benzene solvent. By an analysis of the products from 2, 1.00 mmol of *tert*-butoxy radical yields 0.60 mmol of *tert*-butyl alcohol and 0.40 mmol of acetone. This is in fair agreement with the results from the LTA oxidation of 1, i.e., 0.70 mmol of *tert*-butyl alcohol and 0.32 mmol of acetone per mmol of 1. From this analysis of the product balance of LTA oxidation of 1, it then

Table I. Product Analysis from the Reaction of Lead Tetraacetate [a] with 2-Methyl-2-*tert*-butylperoxypropanoic Acid (1) [b] in Benzene at 80.01 °C [c]

Run no.	Products, mmol/mmol 1		
	Acetone	*tert*-Butyl alcohol	Toluene
1[d]	1.56	0.53	0.39
2[d]	1.35	0.53	0.38
Av	1.45	0.53	0.39
3	1.33	0.71	0.39
4	1.30	0.68	0.38
Av	1.32	0.70	0.39

[a] 4.25×10^{-2} M. [b] 1.56×10^{-2} M. [c] After 10 half-lives. [d] With added NaCl (saturated solution).

Table II. Rate Coefficients for the Lead Tetraacetate Oxidation of 2-Methyl-2-*tert*-butylperoxypropanoic Acid (1) and Pivalic Acid (6) in Benzene at 80.01 °C

Run no.	Acid	[Acid], M × 10^2	[LTA], M × 10^3	$10^5 k$,[a] s^{-1}
1	1	4.26	4.48	109 ± 2
2	1	4.25	4.46	103 ± 5
3	1	4.21	5.57	105 ± 3
Av	1	4.24	4.50	106 ± 3
4	6	4.37	4.16	8.00 ± 0.41
5	6	4.14	4.68	6.67 ± 0.34
6	6	4.26	4.47	8.12 ± 0.69
7	6	4.22	4.49	7.15 ± 0.59
Av	6	4.25	4.43	7.49 ± 0.51

[a] Least-squares fit with probable error.

Table III. Rate Coefficients for the Lead Tetraacetate Oxidation of 2-Methoxy-2-methylpropanoic Acid (7) in Benzene as a Function of Temperature

Temp, °C	[7], M × 10^2	[LTA], M × 10^3	$10^3 k$,[a] s^{-1}
30.00	4.20	4.52	0.129 ± 0.003
39.98	4.31	4.60	0.456 ± 0.006
50.01	4.30	4.55	1.88 ± 0.02
60.02	4.27	4.50	4.49 ± 0.10
69.96	4.24	4.54	15.4 ± 0.8
80.00	Av 4.26 ± 0.04	Av 4.54 ± 0.03	Est 40.0[b]

[a] Least-squares fit with probable error. [b] Estimated from the activation parameters obtained from these data: $E_a = 24.5 \pm 0.8$ kcal/mol, log $A = 13.77 \pm 0.55$, $r = 0.9985$.

appears that *tert*-butoxy radicals are intermediates in this oxidation.

It is interesting that no di-*tert*-butyl peroxide is observed in the LTA oxidation of **1**, whereas 0.095 mmol of di-*tert*-butyl peroxide is produced per mmol of perester **2**. This apparent dichotomy is most reasonably explained by a predominant or exclusive cage production of di-*tert*-butyl peroxide from **2**. Two *tert*-butoxy radicals may be initially produced in a solvent cage from **2**, while this is not possible from the LTA oxidation of **1**. The concept of predominant or exclusive cage recombination of *tert*-butoxy radicals from **2** is consistent with a similar proposal based on the thermolysis of di-*tert*-butyl peroxyoxalate.[4]

Another significant difference between the LTA oxidation of **1** and the thermolysis of perester **2** in benzene is seen in the yield of toluene. One millimole of *tert*-butoxy radical, produced from the LTA oxidation of **1**, yields 0.39 mmol of toluene. In contrast, no toluene was observed in the perester decomposition where 2.00 mmol of *tert*-butoxy radicals are produced per mmol of **2**. The origin of this difference in toluene yields is uncertain at this time. As mentioned in the previous paper,[2] the lack of toluene produced from the perester **2** in benzene could be an artifact due to hydrogen atom abstraction from **2** by methyl radicals which circumvents toluene formation. Alternatively, the rather low temperature (40 °C) used for the thermolysis of **2** could be responsible for the lack of toluene. At the temperature used for the LTA oxidation of **1** in benzene (80 °C), addition of methyl radicals to benzene seems reasonable.[5]

From the above considerations, Scheme I may be proposed

Scheme I

$(CH_3)_3COOC(CH_3)_2CO_2H + Pb^{IV}(OAc)_4$

1

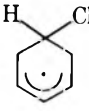
$\rightleftharpoons (CH_3)_3COOC(CH_3)_2CO_2Pb^{IV}(OAc)_3 + HOAc$ (1)

8

$8 \longrightarrow (CH_3)_3CO\cdot + CH_3COCH_3 + CO_2 + Pb^{III}(OAc)_3$ (2)

$(CH_3)_3CO\cdot \xrightarrow{RH} (CH_3)_3COH$ (3)

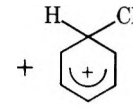
$(CH_3)_3CO\cdot \longrightarrow CH_3COCH_3 + \dot{C}H_3$ (4)

$\dot{C}H_3 + C_6H_6 \longrightarrow$  (5)

9

$9 + 8 \longrightarrow (CH_3)_3COOC(CH_3)_2CO_2Pb^{III}(OAC)_2$

10

 (6)

11

$11 + OAc^- \longrightarrow C_6H_5CH_3 + HOAc$ (7)

$10 \longrightarrow (CH_3)_3CO\cdot + CH_3COCH_3 + CO_2 + Pb^{II}(OAc)_2$ (8)

$10 + R'\cdot \longrightarrow Pb^{II} + [R'^+]$ (9)

for the LTA oxidation of **1**. The mechanism is similar to that proposed for other carboxylic acids;[3] where eq 1 and 2 are the initiation steps, eq 3–8 include the propagation steps, and eq 9 is the possible termination step. In eq 9, R·′ may be radical **9** or a solvent-derived radical as formed in eq 3. Not included is the oxidation of the solvent-derived radical by **8**. The mechanism differs from that proposed for most carboxylic acids in that the radical initially formed in the chain reaction **8** (*tert*-butoxy radical) is not oxidized. Instead, radical **9** is oxidized in another chain-carrying step (eq 6). Oxidation of *tert*-butoxy radicals by LTA has been shown to be slow.[6] In addition, our observed high yield of *tert*-butyl alcohol is inconsistent with a facile oxidation of *tert*-butoxy radicals by lead(IV).

Rather than a concerted three-bond homolysis mechanism as given in Scheme I, a two-bond homolysis process can be considered as outlined in Scheme II. The *tert*-butoxy radical, produced in eq 15, can then enter the reaction sequence as shown in Scheme I. The product balance is inconsistent with the oxidation of radical **3**, where significant amounts of acetates **4** and **13** are expected. In addition, trapping experiments with sodium chloride or with carbon tetrachloride failed, which indicates that the lifetime of **3** is insufficient for it to be the chain-carrying radical. With these observations, Scheme II can be eliminated from consideration.

A variation of Scheme II needs to be considered where radical **3** is initially produced, but suffers fragmentation prior

Scheme II

$$8 \longrightarrow (CH_3)_3COO\dot{C}(CH_3)_2 + CO_2 + Pb^{III}(OAc)_3 \quad (10)$$

3

$$3 + 8 \longrightarrow (CH_3)_3COO\overset{+}{C}(CH_3)_2 + (CH_3)_3COOC(CH_3)_2CO_2Pb^{III}(OAc)_2 + OAc^- \quad (11)$$

10

$$3 + 8 \longrightarrow (CH_3)_3COOC(CH_3)=CH_2 + \mathbf{10} + HOAc \quad (12)$$

5

$$\mathbf{10} \longrightarrow \mathbf{3} + CO_2 + Pb^{II}(OAc)_2 \quad (13)$$

$$(CH_3)_3COO\overset{+}{C}(CH_3)_2 \xrightarrow[(-H^+)]{HOAc} (CH_3)_3COOC(CH_3)_2OAc \quad (14)$$

4

$$5 \longrightarrow (CH_3)_3CO\cdot + \left[O-C(CH_2)(CH_3) \leftrightarrow O=C(CH_2)(CH_3) \right] \quad (15)$$

12

$$\mathbf{12} + 8 \xrightarrow[(-H^+)]{HOAc} CH_3COCH_2OAc + \mathbf{10} \quad (16)$$

13

$$\mathbf{10} + R'\cdot \longrightarrow Pb^{II} + [R'^+] \quad (9)$$

to oxidation as shown in eq 17. The *tert*-butoxy radicals produced in Scheme III then enter the reaction sequence as

Scheme III

$$8 \longrightarrow (CH_3)_3COOC(CH_3)_2 + CO_2 + Pb^{III}(OAc)_3 \quad (10)$$

3

$$3 \longrightarrow (CH_3)_3CO\cdot + CH_3COCH_3 \quad (17)$$

shown in Scheme I. Providing that **3** undergoes rapid fragmentation, the product and trapping studies do not allow a distinction to be made between Schemes I and III. A crude estimate of the lifetime (τ) of radical **3** can be made if Scheme III is operative. The relative velocities for oxidation of **3** in eq 11 (v_{ox}) vs. fragmentation of **3** in eq 17 (v_f) is given by $v_f/v_{ox} = k_f/k_{ox}[Pb(IV)]$. Oxidation of radicals to give relatively stable carbonium ions as in eq 11 approach diffusion-controlled processes.[3] With the diffusion-controlled rate coefficient in benzene at 25 °C[7] of $1.6 \times 10^{10} M^{-1} s^{-1}$, $[Pb(IV)] = 4 \times 10^{-2}$ M (cf. Table I), and assuming 1% oxidation occurs undetected so that $v_f/v_{ox} = 10^2$, $k_f = 6 \times 10^{10}\ s^{-1}$ or $\tau = 2 \times 10^{-11}$ s. For Scheme *III* to be operative, it appears that radical **3** would be extremely short lived and, in fact, approaches its vibrational lifetime.

Finally, a two-electron oxidation of **1** by LTA can be considered. This mode of oxidation appears most reasonable for α-hydroxycarboxylic acids.[3] Oxidation to give a *tert*-butoxy cation seems unlikely; however, a simultaneous methyl group migration to give carbonium ion **14** can be considered as shown in Scheme IV. This scheme conflicts with the product analyses

Scheme IV

$$(CH_3)_3COOC(CH_3)_2CO_2Pb^{IV}(OAc)_3 \longrightarrow (CH_3)_2\overset{+}{C}OCH_3 + CH_3COCH_3 + CO_2 + Pb^{II}(OAc)_2 + OAc^- \quad (18)$$

8 **14**

$$\mathbf{14} \xrightarrow[(-H^+)]{HOAc} (CH_3)_2C(OAc)(OCH_3) \quad (19)$$

and it can be eliminated on that basis. Although acetone is predicted by Scheme IV, the observed high yield of *tert*-butyl alcohol cannot be accommodated.

Kinetics. The propagation steps for the LTA oxidation of most carboxylic acids are given by eq 20 and 21, where $[R^+]$

$$R\cdot + RCO_2Pb^{IV}(OAc)_3 \longrightarrow [R^+] + RCO_2Pb^{III}(OAc)_2 + OAc^- \quad (20)$$

$$RCO_2Pb^{III}(OAc)_2 \longrightarrow R\cdot + CO_2 + Pb^{II}(OAc)_2 \quad (21)$$

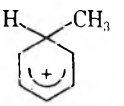
may or may not be a free carbonium ion.[3] The rate of oxidative decarboxylation by LTA is found to be more facile as the carbonium ion stability of $[R^+]$ increases.[3] The relative rates of LTA oxidation of the carboxylic acids studied here increase in the order **6** (1.00) < **1** (14.2) < **7** (534) at 80 °C. This appears to correspond to the relative stabilities of the carbonium ion which is associated with the acid in the chain process. Based on the most likely mechanisms for the LTA oxidation of **1** (Schemes I or III), the order of reactivity of **6** < **1** < **7** indicates

$$(CH_3)_3CCO_2H \sim (CH_3)_3\overset{+}{C} \qquad CH_3OC(CH_3)_2CO_2H \sim CH_3O\overset{+}{C}(CH_3)_2$$

6 **7**

$$(CH_3)_3COOC(CH_3)_2CO_2H \sim$$

1



11

that the methyl radical is not oxidized in the chain process. Instead methyl adds to benzene and the resulting radical **9** is oxidized. If the methyl radical were directly oxidized by lead(IV), the expected reactivity order would be **1** < **6** < **7**. A similar argument eliminates the oxidation of the *tert*-butoxy radical, which is in agreement with the product studies.

In summary, the LTA oxidation of **1** can be explained by Schemes I or III, but not by Schemes II or IV. A clear choice cannot be made between Schemes I and III. However, if Scheme III is operative, radical **3** must be extremely short lived where the *maximum* lifetime approaches its vibrational lifetime.

Experimental Section[8]

Materials. Thiophene-free, reagent grade benzene was fractionally distilled from calcium hydride and a heart cut was collected, bp 79.8–80.1 °C (lit.[9] bp 80.1 °C). The distilled benzene was purged with purified nitrogen for 20 min and then stored under nitrogen. Water-pumped nitrogen (99.7% pure) was purified by bubbling it through Fieser's solution[10] and then through concentrated sulfuric acid. Pivalic acid (Matheson Coleman and Bell) was dried in a vacuum desiccator over phosphorus pentoxide, mp 34.0–35.0 °C (lit.[9] mp 35.5 °C). The NMR spectrum showed the following absorptions: $(CH_3)_3C$ 1.25, s, 9; and CO_2H 12.5, s, 1. Lead tetraacetate (Alpha Inorganics or G. Frederick Smith Co.) was purified by the procedure of Kochi[11] where the crystalline solid was dried by suction on a Büchner funnel under a nitrogen atmosphere.

2-Methyl-2-*tert*-butylperoxypropanoic Acid (1). This acid was prepared according to a previously described procedure.[1] The acid was sublimed at 1 mm (bath 70 °C) and dried over phosphorus pentoxide, mp 62.0–64.0 °C (lit.[1] mp 62.0–63.5 °C). The NMR spectrum showed the following absorptions: $(CH_3)_3C$ 1.23, s, 9; $(CH_3)_2C$ 1.43, s, 6; and CO_2H 11.6, s, 1.

2-Methoxy-2-methylpropanoic Acid (7). This acid was synthesized according to the procedure of Weizmann, Sulzbacher, and Bergmann:[12] bp 100.0–100.5 °C (22 mm) [lit.[12] bp 98.0–99.0 °C (20 mm)]; 74% yield; NMR spectrum $(CH_3)_2C$ 1.42, s, 6; CH_3O 3.28, s, 3; and CO_2H 11.6, s, 1.

Product Analysis. Product studies were made with triply degassed benzene solutions, where the initial concentrations of lead tetraacetate and **1** were 4.25×10^{-2} and 1.56×10^{-2} M, respectively. The degassing was carried out on a vacuum line where the pressure was 10^{-4} mm and the tubes were protected from light throughout the degassing, heating, and analysis by aluminum foil wrapping. The degassed sample was heated for 2.5 h (approximately 10 half-lives) at 70.0 °C in an oil bath

and stored in a freezer (−20 °C) until it was analyzed. Analysis was obtained by GLC with ethylbenzene as the internal standard. Yields of products were obtained by comparison to a standard mixture which contained the internal standard and authentic samples of the products. Peak areas were determined with a planimeter. The GLC analysis was carried out with a 20% polypropylene glycol on Chromosorb W column (5 ft × 0.125 in.) under the following conditions: injector 95 °C, column 150 °C, detector 160 °C, nitrogen carrier gas 20 ml/min, chart speed 4 in./min, and sample size 0.5 μl. The retention times for acetone, *tert*-butyl alcohol, toluene, and ethylbenzene were 0.7, 1.0, 2.0, and 3.0 min, respectively.

To check for products resulting from trapping of radical **3**, reactions were carried out through one half-life ($t_{1/2}$) and through 10 half-lives (t_∞). The analysis for cumyl *tert*-butyl peroxide was made by GLC on a 3% SE-30 on Varaport-30 column (5 ft × 0.125 in.) under the following conditions: injector 95 °C, column 70 °C, detector 75 °C, nitrogen carrier gas 22 ml/min, and sample size 0.5 μl. Neither the $t_{1/2}$ nor the t_∞ reaction mixtures showed GLC peaks with a retention time greater than that of benzene (8 min). The retention time of cumyl *tert*-butyl peroxide was 26 min. It was estimated that at least a 1% yield of this peroxide could have been detected.

Analysis for 2-chloro-2-*tert*-butylperoxypropane, which is a possible trapping product from radical **3** in the presence of sodium chloride or carbon tetrachloride solvent, was made with a 15% XF-96 (5 ft × 0.125 in.) on Chromosorb W column. The conditions for trapping **3** with sodium chloride/LTA in benzene were injector 75 °C, column 25 °C, detector 125 °C, nitrogen carrier gas 25 ml/min, and 0.5-μl sample size. It was estimated that the retention time for the chloroperoxide would be somewhat greater than that of di-*tert*-butyl peroxide, based on expected boiling points. No product peaks were observed after benzene (14 min). Under these conditions, di-*tert*-butyl peroxide was found to have a retention time of 33 min. The GLC conditions for analysis of the chloroperoxide from the LTA oxidation of **1** in carbon tetrachloride were injector 110 °C, column 30 °C, detector 90 °C, nitrogen carrier gas 20 ml/min, and sample size 0.5 μl. No product peaks with retention times greater than that of carbon tetrachloride (11 min) were observed.

Kinetic Method. All glassware was dried at 140 °C in an oven for 12 h and then cooled in a vacuum desiccator over silica gel or in a stream of dry nitrogen. The reaction vessel consisted of a 150-ml round-bottomed flask, to which was sealed a condenser and a long stoppered tube into which a pipet could be placed to withdraw aliquots. The reaction vessel, wrapped with aluminum foil, was flushed with purified nitrogen and placed in a constant-temperature bath controlled to ±0.01 °C. A benzene solution of LTA was thermally equilibrated (at least 20 min) in the reaction vessel and then a thermally equilibrated benzene solution of the carboxylic acid was added. The timer was started and 10-ml aliquots were periodically withdrawn. An infinity aliquot was withdrawn after 10 half-lives. The aliquots were added to 10 ml of a potassium iodide solution, which were contained in nitrogen-swept 250-ml Erlenmeyer flasks. The potassium iodide solution was prepared from 15 g of potassium iodide, 25 g of sodium acetate, and 10 g of sodium carbonate per 100 ml of doubly distilled water solution. After the reaction solution aliquot was added to the potassium iodide solution, 20 ml of acetic acid was added, and the flask was swept with nitrogen and allowed to stand in the dark for 20 min. Now 150 ml of water was added, and if a precipitate formed, 0.5 g of sodium carbonate was added. The solution was then titrated with 0.0100 N standardized (with standard sodium dichromate solution) thiosulfate solution to a straw yellow–colorless end point.

The data were processed with a least-squares first-order computer program. The activation parameters for carboxylic acid **7** were obtained by a least-squares computer program as well.

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Registry No.—**1**, 16424-69-4; **6**, 75-98-9; **7**, 13836-62-9; lead tetraacetate, 546-67-8.

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Phosphorus-Containing Products from the Reaction of Propargyl Alcohols with Phosphorus Trihalides. 4. Alkyl Substituent Effects on Oxaphospholene Formation[1,2]

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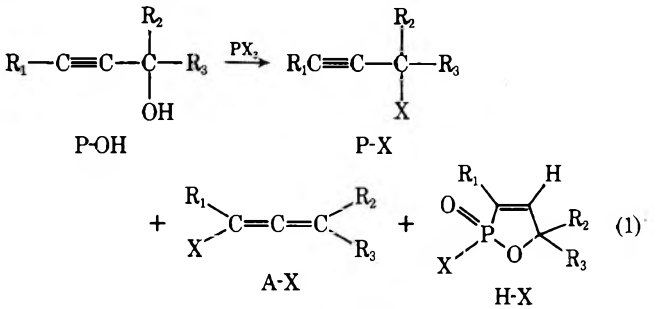
The reactions of eight propargyl alcohols ($R_1C{\equiv}C{-}CR_2R_3OH$) with one or more molar equivalents of phosphorus trichloride have been examined in detail. Each of the alcohols reacts immediately to give the corresponding propargyl dichlorophosphite. If the hydrogen chloride formed during this reaction is efficiently *removed* (not neutralized), the phosphites [except when $R_1 = R_2 = C(CH_3)_3$ and $R_3 = C(CH_3)_3$ or CH_3] rearrange to allenic phosphonyl dichlorides, hydrolysis of which gives crystalline allenic phosphonic acids. These [except when $R_1 = R_2 = R_3 = H$ and $R_1 = R_2 = C(CH_3)_3$; $R_3 = H$] undergo acid-catalyzed cyclization to the novel oxaphospholenes. The relative rates of both the rearrangement and the cyclization follow the order $R_1 = H, R_2 + R_3 = (CH_2)_4 > R_1 = H, R_2 + R_3 = (CH_2)_5 > R_1 = H, R_2 = R_3 = CH_3 > R_1 = C(CH_3)_3, R_2 = R_3 = CH_3 \gg R_1 = R_2 = C(CH_3)_3, R_3 = H > R_1 = R_2 = R_3 = H$. The isolated percent yields of allenic phosphonic acid from propargyl alcohol, and oxaphospholene from phosphonic acid for the above series are 40, 36; 60, 38; 45, 85; 32, 69; 68, 0; 66, 0, respectively. The mechanisms of these reactions as gauged by their response to substituent effects are discussed. The ^1H NMR spectra of these compounds are also described.

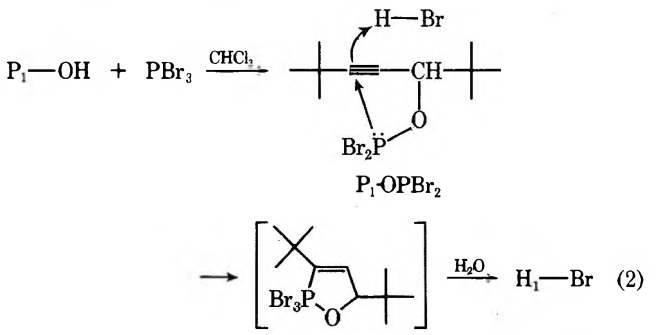
During the preparation of 3-bromo-2,2,6,6-tetramethyl-4-heptyne (P_1-Br) and its allenic isomer (A_1-Br) from the reaction of the corresponding propargyl alcohol (P_1-OH) with phosphorus tribromide (PTB) in chloroform, we isolated in

ca. 10% yield a crystalline side product to which we assigned[3] heterocyclic structure H_1-Br. We proposed[3] that the heterocycle resulted from acid-promoted cyclization of intermediate dibromophosphite P_1-$OPBr_2$:[4]



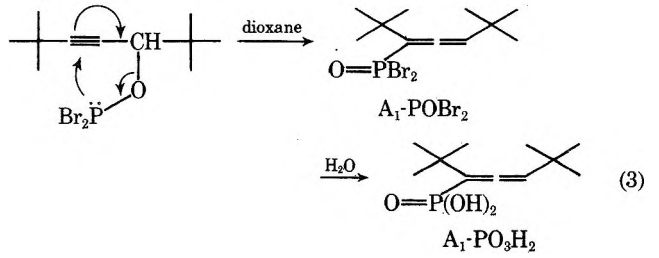
P-OH P-X A-X H-X (1)

1, $R_1 = R_2 = C(CH_3)_3$; $R_3 = H$
2, $R_1 = R_2 = C(CH_3)_3$; $R_3 = CH_3$
3, $R_1 = R_2 = R_3 = C(CH_3)_3$
4, $R_1 = H$; $R_2 = R_3 = CH_3$
5, $R_1 = H$; $R_2 + R_3 = (CH_2)_5$
6, $R_1 = H$; $R_2 + R_3 = (CH_2)_4$
7, $R_1 = C(CH_3)_3$; $R_2 = R_3 = CH_3$
8, $R_1 = R_2 = R_3 = H$



P_1-$OPBr_2$ (2)

In subsequent work[5] this mechanism gained support from the direct observation of intermediates P_1-$OPBr_2$ by low-temperature ^1H NMR, and the fact that changing the solvent to the more basic dioxane diverted the intermediate via a [3,2] sigmatropic shift to allenic phosphonic acid A_1-PO_3H_2.[6] Phosphorus trichloride (PTC) provided comparable results.[5]



A_1-$POBr_2$ A_1-PO_3H_2 (3)

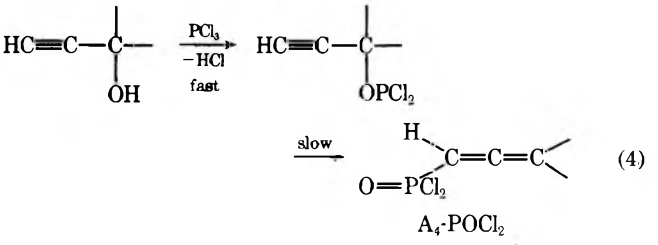
Further hydrolysis of H_1-Br led to H_1-OH, whose structure was confirmed[5] by x-ray crystallographic analysis. Significantly, isomers H_1-OH and A_1-PO_3H_2 could *not* be interconverted under acidic, basic, thermal, or electron impact conditions.

We have now extended this work to seven other propargyl alcohols to assess the effect of alkyl substitution on the formation of phosphorus-containing products. These results not only establish the generality of these reactions but also shed new light on the mechanism of heterocycle formation.

Results

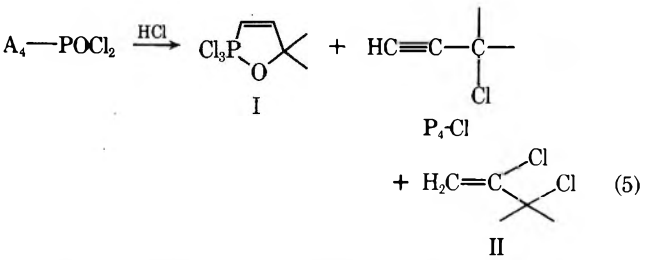
Our initial approach in this study was to incorporate substituents that would minimize formation of propargyl and allenic halides, thereby rendering formation of phosphorus-containing products more competitive. We first examined P_2-OH and P_3-OH, where the methine hydrogen in P_1-OH had been replaced by a methyl and *tert*-butyl group, respectively. These preliminary results proved disappointing; no phosphorus-containing compounds could be isolated, only the simple substitution products and those arising from addition and elimination of HX. (Subsequent work on these compounds is described more fully below.) However, preliminary studies with P_4-OH encouraged us to examine it in detail.

When equimolar amounts of P_4-OH and PTC (in methylene chloride or deuteriochloroform) were combined at 25 °C, ^1H NMR revealed that the original absorptions [δ 1.55 (s, 6 H), 2.45 (s, 1 H), 3.08 (s, 1 H, OH)] had shifted to δ 1.57, 2.45, and 2.75, respectively.[7] Over the next 37 min (at 35 °C), these absorptions were completely replaced by those of a single new species [δ 1.95 (d of d, J_{HH} = 3, J_{PH} = 12 Hz, 6 H), 5.95 (d of septet, J_{HH} = 3, J_{PH} = 28.5 Hz, 1 H)], to which we assign structure A_4-$POCl_2$. An infrared spectrum of this compound exhibited strong bands at 1955 (C=C=C) and 1270 cm^{-1} (P=O), confirming the assignment.



A_4-$POCl_2$ (4)

During the following 5 days (at 25 °C), the allenic proton absorptions decreased by ca. 80%, and were replaced by peaks characteristic[3,5] of the oxaphospholene skeleton[8] [δ 1.57 (s, 6 H), 6.40 (d of d, J_{HH} = 8.5, J_{PH} = 39 Hz, 1 H), 7.21 (d of d, J_{HH} = 8.5, J_{PH} = 56 Hz, 1 H)]. We assign these to I, the unhydrolyzed precursor[4] of H_4-OH. The spectrum also showed the presence of P_4-Cl [δ 1.84 (s, 6 H), 2.70 (s, 1 H)] and addition product II [δ 1.71 (s, 6 H), 6.31 (AB quartet, 2 H)]. The ratio of these three products was 6:1:2, respectively, and this remained constant over the next 5 days (at 25 °C).



I P_4-Cl II (5)

This result is extremely significant, for it proves that, at least in the case of P_4-OH, the oxaphospholene arises via the allenic intermediate, *not* directly from P_4-$OPCl_2$ as previously suggested for P_1-OH.[3,5] This represented the first observation of an allenic phosphonyl compound cyclizing to an oxaphospholene.

Repetition of this reaction on the preparative scale proved frustratingly complex, until it was discovered that removing the hydrogen chloride formed in the first step (reaction 4) with a stream of nitrogen afforded A_4-$POCl_2$ (a liquid with phosgenelike odor) in 84% yield, the reaction requiring 2 h at 25 °C. *The entire success of this step, and the similar ones described later, rests on the efficient removal of the hydrogen chloride.* Simple neutralization leaves Cl^- in the medium to react with the dichlorophosphite giving undesired propargyl and allenic chlorides. Because PTC has bp 76 °C, an excess must generally be used to compensate for that which evaporates into the nitrogen stream.

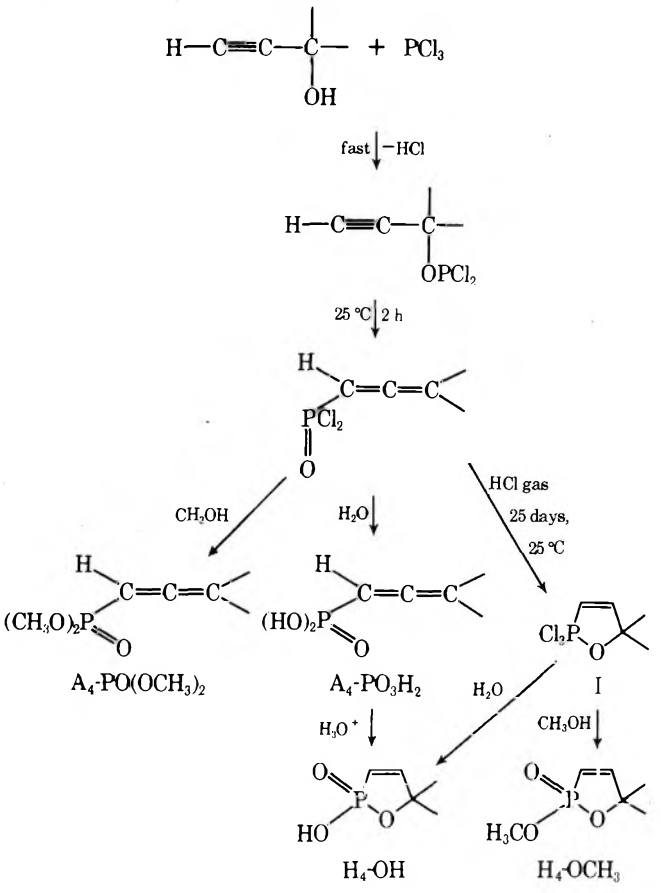
Although A_4-$POCl_2$ underwent uncomplicated methanolysis to give A_4-$PO(OCH_3)_2$ in 64% overall yield, attempts to hydrolyze the former compound under a variety of conditions

gave A_4-PO_3H_2 contaminated inseparably with varying amounts of H_4-OH. It was eventually found that *partial* neutralization of the hydrogen chloride formed during *hydrolysis* gave stable crystalline A_4-PO_3H_2 in 45% overall yield.

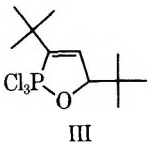
Confirming the occurrence of reaction 5, and the partial isomerization during hydrolysis (vide supra), A_4-PO_3H_2 was found to cyclize cleanly in 2 M aqueous hydrochloric acid to H_4-OH (85% yield), with a half-life of 10.3 h at 66 °C.

Although the above sequence provided a convenient method for the preparation of H_1-OH, we wished to repeat reaction 5 on the preparative scale. Indeed, passage of dry gaseous hydrogen chloride through a methylene chloride solution of A_4-$POCl_2$ for 25 days (25 °C) gave the same product mixture as seen in the ^1H NMR experiment. Hydrolysis or methanolysis of this mixture gave H_4-OH or H_4-OCH_3. These results are summarized in Scheme I.

Scheme I



Armed with these results, we reexamined the reaction of P_1-OH with PTC.[5] When equimolar amounts of the reactants in deuteriochloroform were combined at 25 °C, the ^1H NMR spectrum showed only P_1-$OPCl_2$ [δ 1.01 (s, 9 H), 1.24 (s, 9 H), 4.87 (d, J_{PH} = 12.5 Hz, 1 H)], analogous to P_1-$OPBr_2$.[5] Over the next 27 h, 50 times slower than for P_4-$OPCl_2$, these absorptions were replaced by those of four products, A_1-$POCl_2$ [δ 1.17 (s), 1.36 (s), 5.82 (d, J_{PH} = 17.5 Hz)]; III [δ 1.03 (s), 1.36 (s), 4.78 (d of d, J_{HH} = 1.8, J_{PH} = 6 Hz), 6.82 (d of d, J_{HH} = 1.8, J_{PH} = 54 Hz)];[4] P_1-Cl^3 [δ 1.09 (s), 1.23 (s), 4.33 (s)] and A_1-Cl^3 [δ 1.17 (s), 1.24 (s), 6.59 (s)], in the ratio 4:2:2:1. This remained unchanged after 22 h (25 °C).



III

Table I. Half-Lives of Acid-Catalyzed Cyclization of Allenic Phosphonic Acids

Reactant	$t_{1/2}$, min: Aq acetonitrile,[a] 65 °C	Aq dioxane,[b] 64 °C
A_6-PO_3H_2	40	30
A_5-PO_3H_2	200	90
A_4-PO_3H_2	250	180
A_7-PO_3H_2		2000
A_1-PO_3H_2	∞	∞
A_8-PO_3H_2	∞	∞

[a] Ca. 30 mg of reactant dissolved in 0.35 ml of solvent consisting of CD_3CH, D_2O, and concentrated HCl in volume ratio 5:1.2:1. When attempts were made to cyclize A_1- and A_8-PO_3H_2 at 95 °C in ~50% aqueous acetonitrile containing ~20% (v/v) perchloric acid, crystalline ammonium perchlorate precipitated slowly. [b] Ca. 45 mg of reactant dissolved in 0.34 ml of solvent consisting of dioxane-d_8, D_2O, and concentrated HCl in the volume ratio 1.2:1.2:1.

Repetition on the preparative scale, removing the hydrogen chloride with nitrogen, gave A_1-$POCl_2$ quantitatively, and hydrolysis afforded A_1-PO_3H_2 in 68% overall yield (four times greater than before[5]). Passage of gaseous hydrogen chloride through a methylene chloride solution of A_1-$POCl_2$ gave a complex mixture of products from which only A_1-PO_3H_2 could be isolated. Most importantly, A_1-PO_3H_2 could not be made to cyclize, even when heated to 90 °C for 11 days (2 M hydrochloric acid in 80% aqueous diglyme).

Thus, the rearrangement of P_1-$OPCl_2$ to A_1-$POCl_2$ is about $1/50$ as fast as the rearrangement of P_4-$OPCl_2$, and the cyclization of A_1-PO_3H_2 must be infinitely slower than for A_4-PO_3H_2, suggesting that both reactions respond similarly to substituent changes. Since neither A_1-PO_3H_2 nor A_1-$POCl_2$ could be made to cyclize, the originally observed H_1-Br^3 and H_1-Cl^5 must arise (inefficiently) from P_1-OPX_2, not via allenic phosphonyl compounds, and the best entry into the H_1 system continues to be the original one.[3]

Cyclic alcohols P_5-OH and P_6-OH behaved very similarly to P_4-OH. Both reacted with PTC to produce the phosphonyl dichlorides A_5-$POCl_2$ (91% after 2 h at 25 °C) and A_6-$POCl_2$ (68% after 1.5 h at 25 °C). These could be hydrolyzed to phosphonic acids A_5-PO_3H (68%) and A_6-PO_3H_2 (58%). The latter pair of compounds underwent acid-catalyzed cyclization in a number of solvents, as did A_4-PO_3H_2. These rearrangements were readily followed by ^1H NMR, and they seemed to proceed quantitatively. However, the darkening of the reaction solution (especially in the case of A_6-PO_3H_2) and the relatively low isolated yields (H_5-OH, 38%; H_6-OH, 36%) suggested that other reactions may have competed. At any rate, the relative rates of cyclization (by ^1H NMR) are given in Table I.

To determine if R_1 played any role in the rearrangement and cyclization reactions, P_7-OH,[10] with the methyl groups of P_4-OH and the *tert*-butyl group of P_1-OH, was examined. Preliminary investigation by ^1H NMR showed that the only significant product was P_7-Cl,[10] suggesting that the *tert*-butyl group hindered the [3,2] sigmatropic shift, thus favoring attack by external halide. However, when addition was carried out over 2.6 h at 0 °C with a copious nitrogen flow, A_7-$POCl_2$ could be isolated in 47% yield, along with P_7-Cl. The rearrangement of P_7-$OPCl_2$ required about 8 h, longer than P_4-$OPCl_2$, but shorter than P_1-$OPCl_2$. Hydrolysis led in 32% overall yield to A_7-PO_3H_2, which in turn underwent acid-catalyzed cyclization to H_7-OH (quantitative by ^1H NMR, 69% isolated yield). Most interesting, however, was that this cyclization was only *ca.* one-tenth as fast as that of A_4-PO_3H_2

(Table I), confirming the retarding effect of $R_1 = C(CH_3)_3$ on both reactions.

Alcohol P_2-OH[11] (vide supra) was next reexamined in detail. Its reaction with PTC led after 3 h at 25 °C to a mixture of P_2-Cl and elimination product IV in approximately equal

IV

amounts, together with a trace of A_2-$POCl_2$. The latter was in too small an amount to allow isolation of A_2-PO_3H_2. When P_3-OH[12] was allowed to react with PTC, A_3-Cl could be isolated in 92% yield and no phosphorus-containing products could be detected. The results with these two compounds suggest that if R_2 and R_3 are sterically repulsive enough, ionization of the $-OPCl_2$ group takes place to allow rehybridization ($sp^3 \rightarrow sp^2$) and reduction in nonbonded interaction. The resulting carbonium ions then suffer attack by Cl^- (or elimination of an α hydrogen in the case of P_2^+) in preference to the attack by the bulkier $O{=}PCl_2^-$. This can be taken as evidence that the propargyl phosphite → allenic phosphonyl rearrangement is a concerted sigmatropic shift and does not occur via an SN1′ ion-pair mechanism.

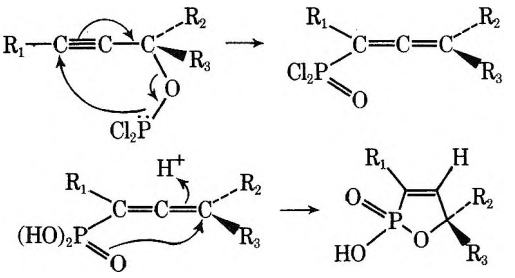
Finally, propargyl alcohol (P_8-OH) itself was examined. Preliminary NMR analysis showed that although formation of P_8-$OPCl_2$ was immediate, its rearrangement to A_8-$POCl_2$ was very slow. On the preparative scale, the reaction gave initially a 72% yield of P_8-$OPCl_2$ [δ 2.62 (t, J_{HH} = 2.6 Hz, 1 H), 4.83 (d of d, J_{HH} = 2.6, J_{PH} = 8.0 Hz, 2 H); 3280, 2120 cm^{-1}]. This material rearranged to A_8-$POCl_2$ [δ 5.51 (d of d, J_{PH} = 18, J_{HH} = 6.6 Hz, 2 H), 6.02 (d of t, J_{PH} = 22, J_{HH} = 6.6 Hz, 1 H),[8] 1940, 1260 cm^{-1}], but the reaction required 10 h at 60 °C, approximately one-fifth as fast as P_1-$OPCl_2$ (vide supra). Hydrolysis led to A_8-PO_3H_2 (66% yield based on P_8-OH) as a slowly crystallizing oil which could not be further purified. Methanolysis gave A_8-$PO(OCH_3)_2$ as a readily distilled liquid. Most importantly, a solution of A_8-PO_3H_2 in acidic aqueous dioxane was heated to 94 °C for 46 h, and although there was some decomposition (evidenced by darkening), ^1H NMR showed only starting material. No absorptions attributable to H_8-OH (vide infra) were observed. Thus, A_1- and A_8-PO_3H_2 were the only two of six allenic phosphonic acids that failed to cyclize, even under harsh conditions.

Discussion

All eight propargyl alcohols examined in this study reacted with PTC instantaneously at 0 or 25 °C to give the corresponding propargyl dichlorophosphites. When the hydrogen chloride formed during this reaction was efficiently *removed* with a stream of nitrogen, the dichlorophosphites rearranged more slowly to the isomeric allenic phosphonyl dichlorides. Exceptions were P_2- and P_3-$OPCl_2$, where steric repulsion between R_2 and R_3 accelerated ionization of the $-OPCl_2$ group at the expense of rearrangement. Compound P_8-$OPCl_2$ was so slow to rearrange that it could be isolated.

Hydrolysis of the phosphonyl dichlorides gave the allenic phosphonic acids as crystalline solids in yields ranging from 32 to 68%. With the exception of A_1- and A_8-PO_3H_2, these compounds underwent acid-catalyzed cyclization to highly crystalline oxaphospholenes, indicating the greater stability of the latter. This reaction could be conveniently monitored by ^1H NMR, and it generally appeared to take place quantitatively, although isolated yields ranged from 35 to 85%. This represents the first general syntheses of allenic phosphonic acids and oxaphospholenes. These compounds are moderately to highly soluble in polar organic media, and relatively insoluble in nonpolar media.

The relative rates of dichlorophosphite → allenic phosphonyl dichloride seemed to parallel the rate of cyclization: system 6 > 5 > 4 > 7 ≫ 1 > 8. This may seem somewhat paradoxical, because substituent interaction between R_1, R_2, and R_3 which would accelerate the first reaction should inhibit the



second one. In the cases where these reactions occur spontaneously, they must be exoergic, and thus have early (reactant-like) transition states by Hammond's postulate. The first reaction should be accelerated by sterically small R_1, and by fairly large R_2 and R_3 which, by virtue of their interaction, decrease the ≡C–C–O angle and favor sp^2 hybridization at the initially saturated carbon. However, if R_2 and R_3 are too large (vide supra) ionization of $-OPCl_2$ occurs more readily than the sigmatropic shift. These expectations agree essentially with the observations except that P_6-OH, with $R_2 + R_3$ constituting a five-membered ring, might be expected to be *slower* than P_5- and P_4-OH.

If the second reaction is stepwise, protonation of the double bond followed by nucleophilic ring closure, its rate should reflect the stability of the intermediate carbonium ion. Thus, $R_2 = R_3$ = alkyl (to give a tertiary carbonium ion) should be faster that R_2 = alkyl, R_3 = H, faster than $R_2 = R_3$ = H, as observed. Here, partial relief of angle strain during rehybridization might explain the relative rates A_6-$PO_3H_2 > A_5 > A_4$.

Probably the strangest finding was that $R_1 = C(CH_3)_3$ *decelerates* cyclization by a factor of 10 compared to R_1 = H. The R_1–C–P angle in H_1-OH (125°[5]) suggests that cyclization might be *facilitated* by large R_1. Perhaps, however, if $R_1 = C(CH_3)_3$ the angle is too large in the allenic precursor. Whatever its source, the deceleration by $R_1 = C(CH_3)_3$, coupled with the lack of sufficient carbonium ion stabilization by $R_2 = C(CH_3)_3$, R_3 = H, renders A_1-PO_3H_2 extremely unreactive toward cyclization. To support these various conclusions, system 8 ($R_1 = R_2 = R_3$ = H) not only rearranges slowest of all compounds in this study, but it also fails to cyclize even in 25% perchloric acid at 94 °C.

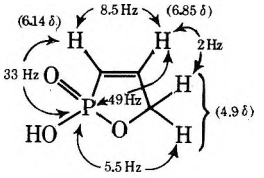
Further work on the generality of these reactions, as well as the chemistry of the oxaphospholenes and allenic phosphonic acids, is underway.

NMR Spectra of Allenic Phosphonic Acids and Oxophospholenes.[8] Several interesting observations can be made regarding the ^1H NMR spectra of the compounds in this study. Compounds H_4-OH and H_7-OH show singlets for the *gem*-dimethyl groups, even though the methyls may be diastereotopic by virtue of the phosphorus substituents. We have explained this type of observation[5] as being due to extremely rapid exchange of the acidic proton between the oxygens on phosphorus. In support of this, it was observed that H_4-OCH_3, where the configuration of phosphorus is fixed, gives rise to two methyl singlets separated by 2.5 Hz.

The two-bond (geminal) P–H coupling in compounds $A_{4,5,6}$-$POCl_2$ averages 28 ± 1 Hz (22 Hz in A_8-$POCl_2$), but it drops to 6 ± 2 Hz in $A_{4,5,6,8}$-PO_3H_2. Similarly, the five-bond P–H coupling in $A_{4,7}$-$POCl_2$ (12 Hz) drops to 7 ± 1 Hz when the Cl groups are hydrolyzed, and the four-bond constant in A_8-$POCl_2$ (18 Hz) drops to 13.4 Hz. Thus, the electronegativity of the phosphorus substituent strongly influences the mag-

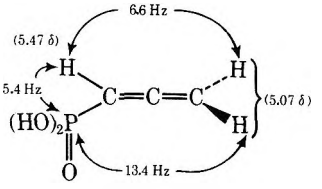
nitude of both short- and long-range coupling interactions.

The predicted chemical shifts and coupling constants for the unsubstituted oxaphospholene H_8-OH (as yet unknown), based on the data for $H_{1,4,5,6,7}$-OH, are given below.



Note that $^3J_{PH}$ always exceeds $^2J_{PH}$ and that $^2J_{PH}$ for the oxaphospholenes always exceeds ^2J for the isomeric allenic phosphonic acids, presumably a consequence of the smaller H–C–P angle in the latter compounds.

The ^{1}H NMR data for isolated A_8-PO_3H_2 are given below.



Experimental Section

General. The instrumentation and techniques were as described previously.[3,5] Except as noted, all reagents were commercially available. Microanalyses[13] were performed by Chemalytics, Tempe, Ariz. PTC was freshly distilled; all solvents were dried over molecular sieve.

Reaction of P_4-OH with PTC. With a small gas dispersion tube, dry nitrogen (200 ml/min) was passed through a solution of 3.45 g (25 mmol) of PTC in 25 ml of CH_2Cl_2, maintained at 25 °C in a water bath. Over 14 min a solution of 2.10 g (25 mmol) of P_4-OH in 25 ml of CH_2Cl_2 was added dropwise. With nitrogen flow continuing, the solution was stirred for 2.0 h. Rotary evaporation (10 mm, 35 °C) left 3.87 g (21 mmol, 84%) of A_4-$POCl_2$ as a colorless liquid. Its spectra are described in the text. This material was added dropwise over 30 min to 15 ml of water at 0 °C. During the addition sodium bicarbonate (exactly 1.76 g, 21 mmol) was added portionwise. The mixture was warmed to 35 °C, 5 ml of water was added, and it was swirled until homogeneous. Complete evaporation of solvent ($P \rightarrow 0.1$ mm, $T <$ 35 °C) left a colorless solid which was treated with 30 ml of hot acetone. After filtration (mass NaCl 1.14 g), evaporation left 3.03 g of crude A_4-PO_3H. Two recrystallizations from $CHCl_3$ gave 1.65 g (45% overall) with mp 101.5–103.0 °C. Prolonged heating during recrystallization causes rearrangement, rendering purification impossible. Acid A_4-PO_3H_2 was highly soluble in water and acetone. ^{1}H NMR (acetone-d_6) δ 1.75 (dd, J_{HH} = 3.5, J_{PH} = 7.5 Hz, 6 H), 5.33 (overlapping d of septet, J_{HH} = 3.5, J_{PH} = 5.4 Hz, 1 H), 11.07 (s, 2 H); ir (mull) 3500–1800 (v br), 1960 (m), 1470 (s), 1370 cm^{-1} (s); MS (70 eV) *m/e* 148 (molecular ion and base).

Anal. Calcd for $C_5H_9O_3P$: C, 40.55; H, 6.13. Found: C, 40.55; H, 6.05.

Methanolysis of A_4-$POCl_2$. A solution of 3.90 g of A_4-$POCl_2$ in 18 ml of CH_2Cl_2 was added dropwise over 10 min to 20 ml of anhydrous CH_3OH at 0 °C. The solution was stirred for 2 h at 25 °C, then rotary evaporated and distilled to give 2.80 g (76%) of A_4-$PO(OCH_3)_2$: bp 48–51 °C (0.09 mm); ^{1}H NMR (CCl_4) δ 1.80 (dd, J_{PH} = 7.3, J_{HH} = 3.5 Hz, 6 H), 3.85 (d, J_{PH} = 11 Hz, 6 H), 5.09 (d of septet, J_{P-H} = 7.8, J_{HH} = 3.5 Hz, 1 h); ir (CCl_4) 1970 (sh), 1260 cm^{-1} (vs); MS (20 eV) *m/e* 176 (mi), 81 (base). A satisfactory elemental analysis could not be obtained.[18]

Rearrangement of A_4-PO_3H_2 to H_4-OH. A 456-mg sample of the allenic acid was dissolved in 1.00 ml of water, 249 mg of concentrated HCl was added, and this solution was heated to 67 °C for 43.5 h. (A ^{1}H NMR kinetic study showed that the rearrangement was clean, giving only H_4-OH, with a half-life of 10.3 h.) Upon cooling to room temperature the slightly colored solution deposited two crops totalling 387 mg (85%), mp 156.0–157.5 °C. Spectral data for H_4-OH: ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 6 H), 6.17 (d of d, J_{PH} = 33, J_{HH} = 8.5 Hz, 1 H), 7.13 (d of d, J_{PH} = 48.5, J_{HH} = 8.5 Hz, 1 H), 11.20 (s, 1 H); ^{31}P (CHCl) δ −41.9 (d of d, J = 48.5, 33 Hz); ir ($CHCl_3$) 3000–2600 (br), 3010 (m), 2950 (s), 1600 (s), 1330 (s), 1210 cm^{-1} (s); MS (70 eV) *m/e* 148 (mi), 81 (base).

Anal. Calcd for $C_5H_9O_3P$: C, 40.55; H, 6.13; P, 20.91. Found: C, 40.83; H, 6.16; P, 21.27.

Direct Preparation of H_4-OH. A 1.59-g sample of A_4-$POCl_2$ was hydrolyzed with half-neutralization (vide supra), and this solution was heated to 66.5 °C for 40 h. The resulting solution was decanted to remove a dark, insoluble oil, rotary evaporated (to 0.1 mm), and the residue recrystallized from water to give 0.86 g (68%) of H_4-OH. This represents a 22% (absolute) increase compared to the route via isolated A_4-PO_3H_2.

Reaction of A_4-$POCl_2$ with HCl. Dry gaseous HCl was passed through a stirred solution of 7.40 g (40 mmol) of A_4-$POCl_2$ in 50 ml of CH_2Cl_2 for 25 days at room temperature, replenishing solvent as necessary. At this point ^{1}H NMR indicated 90% conversion to heterocycle. Rotary evaporation left 6.62 g of a brown crystallizing oil. Half of this material was dissolved in 15 ml of dioxane and added to 20 ml of 60% aqueous dioxane at 0 °C. This solution was stirred for 3 h at 25 °C, rotary evaporated to dryness, and recrystallized from water to give 1.78 g (60% from A_4-$POCl_2$) of H_4-OH. This route to H_4-OH, however, considerably less convenient and more costly than the route via A_4-PO_3H_2 (vide supra).

The other half (3.31 g) was dissolved in 20 ml of CH_2Cl_2 and added to 10 ml of anhydrous methanol at 0 °C. After stirring for 2.5 h at room temperature, rotary evaporation left 3.03 g of a green oil. Short-path distillation at 0.05 mm gave 2.11 g of impure H_4-OCH_3 (bp 56–58 °C). The main impurity was A_4-$PO(OCH_3)_2$ (vide supra). A second short-path distillation at 0.70 mm provided 800 mg of 95% H_4-OCH_3, bp 81–83 °C. Larger scale preparations with spinning band distillation would provide higher purity and better recovery. ^{1}H NMR data for H_4-OCH_3 (CCl_4): δ 1.46 (s, 3 H), 1.50 (s, 3 H), 3.71 (d, J_{PH} = 12 Hz, 6 H), 6.07 (d of d, J_{HH} = 8.5, J_{PH} = 32.5 Hz, 1 H), 7.19 (d of d, J_{HH} = 8.5, J_{PH} = 47.5 Hz, 1 H).

Reaction of P_5-OH with PTC. Using the same procedure as described for P_4-OH, 2.48 g (20 mmol) of P_5-OH was reacted with 2.94 g (21 mmol) of PTC. Addition (10 min, 23 °C) was followed by stirring (130 min, 24 °C) and rotary evaporation left 4.09 g (91%) of crude A_5-$POCl_2$ (ir 1955 cm^{-1}; ^{1}H NMR δ 5.86, d of quintet, J_{PH} = 29, J_{H-H} ~ 2 Hz). This was added dropwise over 10 min to 25 ml of 50% aqueous dioxane at 0 °C. This was accompanied by portionwise addition of 1.55 g of sodium bicarbonate. Exhaustive rotary evaporation ($T <$ 30 °C, $P <$ 0.05 mm) left 4.14 g of colorless solid. The product was taken up in 2 × 20 ml of hot dioxane, filtered (giving 1.01 g of sodium chloride), and again rotary evaporated to dryness to give 3.22 g of crude A_5-PO_3H_2. Two recrystallizations from 35 ml of acetonitrile gave 2.26 g (60% based on P_5-OH) with mp 138–139 °C; ^{1}H NMR (acetone-d_6) δ 1.62 (s, $\Delta\nu_{1/2}$ = 10 Hz, 6 H), 2.20 (m, 4 H), 5.31 (heptet, 1 H), 6.80 (s, 2 H, exchanges fairly rapidly with solvent); ir (KBr disk) 3000–2700 (br), 2925 (s), 2845 (s), 1970 (m), 1130 (vs), 1005 (vs), 955 cm^{-1} (vs); mass spectrum (70 eV) *m/e* 188 (mi), 133 (base).

Anal. Calcd for $C_8H_{13}O_3P$: C, 51.06; H, 6.91; P, 16.49. Found: C, 51.25; H, 6.87; P, 16.54.

Isolation of H_5-OH. NMR experiments described in the text indicated that A_5-PO_3H_2 rearranged cleanly to H_5-OH under a variety of conditions. However, isolated yields were well below quantitative. The highest isolated yields were obtained as follows. A_5-PO_3H_2 (1.467 g) was dissolved in 30 ml of 50% aqueous dioxane and 6 ml of concentrated HCl. The solution was heated to 63 °C for 25 h, at which point ^{1}H NMR showed only H_5-OH. The golden solution was rotary evaporated (0.1 mm, 25 °C) to dryness, dissolved in 20 ml of acetone, and again evaporated to dryness (0.1 mm overnight). The remaining dark oil (1.65 g) was dissolved in 3 ml of acetone, cooled, the vessel scratched, and the mixture allowed to stand at −25 °C overnight. The resulting two crops (0.72 g) were recrystallized from acetone to give 0.55 g (38%): mp 151–152.5 °C; ^{1}H NMR ($DCCl_3$) δ 1.68 (s, $\Delta\nu_{1/2}$ = 4 Hz, 10 H), 6.14 (dd, J_{HH} = 8.5, J_{PH} = 32.5 Hz, 1 H), 6.95 (dd, J_{HH} = 8.5, J_{PH} = 47.5 Hz, 1 H), 11.65 (s, 1 H); ^{31}P NMR ($HCCl_3$, external H_3PO_4) δ −43.4 (dd, J = 32 and 47 Hz); ir ($CHCl_3$) 3000–2600 (br), 3000 (w), 2940 (s), 2860 (m), 1600 (m), 1460 (m), 1330 (m), 1210 (s), 1000 (s), 955 (s), 910 (m), 860 (m), 750 cm^{-1} (vs); MS (70 eV) *m/e* 188 (mi), 133 (base).

Anal. Calcd for $C_8H_{13}O_3P$: C, 51.06; H, 6.91; P, 16.49. Found: C, 50.85; H, 6.94; P, 16.40.

Direct Preparation of H_5-OH. Crude A_5-$POCl_2$ (4.00 g) was dissolved in 25 ml of 50% aqueous dioxane and 2 ml of concentrated HCl, and the solution heated to 64 °C for 89 h. Workup as above and two recrystallizations from acetone gave 1.16 g (35%) of H_5-OH. This exceeds the yield via isolated A_5-PO_3H_2 (25% overall).

Reaction of P_6-OH with PTC. Using the same procedure as with P_4-OH and P_5-OH, 2.78 g (25.3 mmol) of the alcohol was reacted with 3.58 g (26 mmol) of PTC, both in 40 ml of CH_2Cl_2. Addition (50 min,

23 °C),[14] stirring (85 min, 24 °C), and rotary evaporation gave 3.63 g (68%) of crude A_6-$POCl_2$ (ir 1950 cm^{-1}; ^1H NMR d of quintet, J_{PH} = 28 Hz). This was added over 10 min to 20 ml of 50% aqueous dioxane (0 °C) along with 1.45 g of sodium bicarbonate. Exhaustive rotary evaporation (0.1 mm) gave 3.61 g of solid which was treated with 35 ml of hot dioxane, filtered (mass NaCl = 0.97 g), and concentrated, and the residue was recrystallized from acetone to give 2.07 g of A_6-PO_3H_2 (40% from P_6-OH): mp 142–143 °C dec; ^1H NMR (dioxane-d_8, D_2O) δ 1.70 (m, 4 H), 2.50 (m, 4 H), 4.80 (s, 1 H as HOD), 5.37 (apparent septet, 1 H); ir (KBr) 3000–2600 (br), 2950 (s), 1960 (m), 1125 (vs), 1000 (vs), 960 cm^{-1} (vs); MS (70 eV) *m/e* 174 (mi), 148 (base).

Anal. Calcd for $C_7H_{11}O_3P$: C, 48.28; H, 6.32. Found: C, 48.58; H, 6.22.

Isolation of H_6-OH. As with H_5-OH, isolated yields were always considerably lower than theoretical, although NMR indicated clean conversion. A solution of 503 mg of A_6-PO_3H_2 in 10 ml of 50% aqueous dioxane and 2.0 ml of concentrated HCl was heated to 62 °C for 4.0 hr. (When carried out for 22 h at 45 °C, the cyclization gives slightly lower yields.) The dark brown solution was rotary evaporated (0.1 mm, 25 °C) to dryness, and the resulting dark oil (530 mg) dissolved in 1.5 ml of hot acetone. The solution was seeded or the vessel vigorously scratched, and then placed at −25 °C. Two crops were collected (235 mg), redissolved in 3 ml of hot dioxane, treated with Norite, filtered, and evaporated. Recrystallization from acetone gave two crops (181 mg, 36%) of H_6-OH: mp 159.5–161 °C; ^1H NMR ($CDCl_3$) δ 1.90 (s, $\Delta\nu_{1/2}$ = 3 Hz, 8 H), 6.10 (dd, J_{HH} = 8.5, J_{PH} = 32 Hz, 1 H), 6.94 (dd, J_{HH} = 8.5, J_{PH} = 47.5 Hz, 1 H), 12.03 (s, 1 H); ^{31}P NMR ($CHCl_3$, external H_3PO_4) δ −43.9 (dd, *J* = 32, 47 Hz); ir ($CHCl_3$) 3000–2600 (br), 3010(s), 2965 (s), 2870 (m), 1600 (s), 1350 (s), 1205 (vs), 1000 (vs), 975 cm^{-1} (vs); MS (70 eV) *m/e* 174 (mi), 146 (base).

Anal. Calcd for $C_7H_{11}O_3P$: C, 48.28; H, 6.32; P, 17.82. Found: C, 48.37; H, 6.28; P, 18.47.

Reaction of P_7-OH with PTC. The usual procedure was used with 2.80 g (20 mmol) of P_7-OH and 4.50 g (33 mmol) of PTC in a total of 40 ml of CCl_4. Addition period: 2.6 h at 0 °C; stir for 5.5 h at 25 °C.[14] Rotary evaporation (10 mm, 25 °C) left 2.84 g of a mixture comprised of 80% A_7-$POCl_2$ [δ (CCl_4) (s, 9 H), 1.85 (d, J_{PH} = 11.5 Hz, 6 H); ir 1950, 1260 cm^{-1}] and 10% P_7-Cl[15] [δ 1.22 (s, 9 H), 1.78 (s, 6 H); ir 2225 cm^{-1}].

The mixture was dissolved in 10 ml of dioxane and the solution was added dropwise to 10 ml of water at 0 °C over 15 min. Rotary evaporation to dryness (0.1 mm overnight) left 2.30 g of the crude product which was recrystallized slowly from CH_3CN to give 1.30 g (32%) of material with mp 175–176 °C.

Spectral data: ^1H NMR (acetone-d_6) δ 1.23 (s, 9 H), 1.73 (d, *J* = 6.4 Hz, 6 H), 8.15 (s, 2 H); ir (acetone-d_6) 3600–2000 (br), 2940, 1945, 1225, 1190, 1000 cm^{-1}; MS (20 eV) *m/e* 204 (mi), 148 (base).

Anal. Calcd for $C_9H_{17}O_3P$: C, 52.93; H, 8.39. Found: C, 52.71; H, 8.50.

Rearrangement of A_7-PO_3H_2. The allenic phosphonic acid (380 mg) was dissolved in 10 ml of 50% aqueous dioxane and 2.0 ml of concentrated HCl and the solution heated to 88 °C for 10 h (4 half-lives). The yellow solution was rotary evaporated to dryness (0.1 min, 40 °C), leaving ~400 mg of crude H_7-OH. This was recrystallized from acetone/heptane (3/2 v/v) to give 260 mg (69%), mp 235–236 °C.

Spectral data: ^1H NMR ($CDCl_3$) δ 1.29 (s, 9 H), 1.46 (s, 6 H), 6.50 (d, J_{PH} = 47 Hz, 1 H), 12.2 (s, 1 H); ir ($CDCl_3$) 3300–1900 (very broad), 2990, 1470, 1380, 1305, 1280, 1230 (vs), 1165, 1000, 840 cm^{-1}; MS (30 eV) *m/e* 204 (mi), 189 (base).

Anal. Calcd for $C_9H_{17}O_3P$: C, 52.93; H, 8.39. Found: C, 52.71; H, 8.63.

Reaction of P_2-OH with PTC. The usual procedure was used with 2.73 g (15 mmol) of the alcohol[11] and 6.18 g (45 mmol) of PTC in a total of 200 ml of CH_2Cl_2. Addition time: 220 min at 0 °C, stir for 3.5 h at 25 °C. Rotary evaporation and centrifugation to remove a highly unstable oily solid[14] gave 2.32 g of a mixture of IV, P_2-Cl, and A_2-POCl in the ratio 5:5:1. The first two of these could be separated by preparative TLC (silica gel, pentane). Spectral data: IV, ^1H NMR (CCl_4) δ 1.10 (s, 9 H), 1.25 (s, 9 H), 5.08 (s, 2 H); ir (CCl_4) 2210, 1670, 1600 cm^{-1}; uv (cyclohexane) λ_{max} 222 nm (ε 1230), 232 (1045); MS (70 eV) *m/e* 164 (mi), 57 (100); P_2-Cl, ^1H NMR (CCl_4) δ 1.15 (s, 9 H), 1.20 (s, 9 H), 1.73 (s, 3 H); MS (70 eV) virtually superimposable on that of IV, no molecular ion; A_2-$POCl_2$, ^1H NMR (CC_4) δ 1.15 (s), 1.30 (s), 1.83 (d, *J* = 11 Hz); ir (CCl_4) 1950, 1280 cm^{-1}. Attempts to hydrolyze this mixture and recover A_2-PO_3H_2 were unsuccessful.

Reaction of P_3-OH with PTC. The usual conditions were employed with 0.70 g (5.0 mmol) of PTC and 1.12 g (5.0 mmol) of P_3-OH[12] in a total of 15 ml of CH_2Cl_2. Addition period: 24 min at 25 °C, stir for 75 min at 30 °C. Rotary evaporation (10 min, 25 °C) left 1.11 g (92%) of A_3-Cl: ^1H NMR (CCl_4) δ 1.15 (s, 9 H), 1.22 (s, 18 H); ir ($CHCl_3$) 2960 (vs), 1940 (m), 1395 (m), 1360 (s), 1240 (s), 1040 (m), 995 (m), 920 cm^{-1} (s); MS (70 eV) *m/e* 242, 244 (mi), 150 (base).

Reaction of Propargyl Alcohol (P_8-OH). In the usual way 2.24 g (40 mmol) of the alcohol in 80 ml of CH_2Cl_2 was added to 16.48 g (120 mmol) of PTC in 80 ml of CH_2Cl_2 over 145 min at 0 °C. After addition, rotary evaporation (10 min, room temperature) left 4.52 g (72%) of P_8-$OPCl_2$, whose spectra are given in the text. This was redissolved in 30 ml of hydrocarbon-stabilized chloroform and heated to 61 °C for 10.5 h. Rotary evaporation left 2.45 g (71%) of crude A_8-$POCl_2$, whose spectra are given in the text.

Hydrolysis of A_8-$POCl_2$. The allene (2.23 g, 1.42 mmol) was added dropwise to 20 ml of 50% aqueous dioxane at 0 °C over 5 min. Rotary evaporation (0.1 min, 40 °C) left 1.58 g (93% based on A_8-$POCl_2$, 66% based on P_8-OH) of a pale yellow oil which crystallized upon standing at −25 °C, mp 43–55 °C. It could not be recrystallized: ^1H NMR (acetone-d_6)[8] δ 5.07 (~dd, $^4J_{PH}$ = 13.4, J_{HH} = 6.6 Hz, ~2 H), 5.47 (~dt, $^2J_{PH}$ = 5.4, J_{HH} = 6.6 Hz, ~1 H), 10.5 (s, 2 H); ir (CH_3CN) 3500–1800 (v broad), 1940 (br), 1210 (br).

Methanolysis of A_8-$POCl_2$. The allene (2.22 g, 1.42 mmol) was added over 15 min to 20 ml of anhydrous methanol at 0 °C. Rotary evaporation (10 mm, 30 °C) left 2.16 g of a pale yellow liquid. Distillation gave 1.26 g (43% based on P_8-OH): bp 46–47 °C (0.08 mm); ^1H NMR (CCl_4) δ 3.70 (d, J_{PH} = 11 Hz, 6 H), 5.03 (~dd, J_{PH} = 12.8, J_{HH} = 6.6 Hz, 2 H), 5.22 (~dt, J_{PH} = 5.6, J_{HH} = 6.6 Hz, 1 H);[8] ir (CCl_4) 3045, 2950, 2840, 1970, 1940,[17] 1470, 1265, 1180, 1040, 835 cm^{-1}; MS (20 eV) *m/e* 148 (mi, 100%), 109 (base). A satisfactory elemental analysis could not be obtained.[18]

Attempted Cyclization of A_8-PO_3H_2. A solution of the allenic acid (40 mg), 0.10 ml of D_2O, 0.10 ml of dioxane, and 0.10 ml of 70% perchloric acid was heated to 94 °C for 46 h. Although the solution had darkened, ^1H NMR showed only solvent and starting material.

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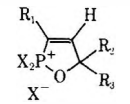
Registry No.—A_2-$POCl_2$, 59474-10-1; A_3-Cl, 37892-65-2; A_4-$POCl_2$, 13337-33-2; A_4-PO_3H_2, 1831-37-4; A_4-$PO(OCH_3)_2$, 17166-43-7; A_5-$POCl_2$, 59474-11-2; A_5-PO_3H_2, 1831-36-3; A_6-$POCl_2$, 59474-12-3; A_6-PO_3H_2, 59474-13-4; A_7-$POCl_2$, 59474-14-5; A_7-PO_3H_2, 59474-15-6; A_8-$POCl_2$, 17166-36-8; A_8-PO_3H_2, 34163-96-7; A_8-$PO(OCH_3)_2$, 18356-17-7; H_4-OH, 59474-16-7; H_4-OCH_3, 59474-17-8; H_5-OH, 59474-18-9; H_6-OH, 59474-19-0; H_7-OH, 59474-20-3; P_2-Cl, 59474-21-4; P_2-OH, 36187-02-7; P_3-OH, 36187-03-8; P_4-OH, 115-19-5; P_5-OH, 78-27-3; P_6-OH, 17356-19-3; P_7-OH, 1522-16-3; P_8-$OPCl_2$, 17166-44-8; P_8-OH, 107-19-7; PTC, 7719-12-2; IV, 59474-22-5.

References and Notes

(1) Part of this work was taken from the Ph.D. Thesis of E.R.K., University of Cincinnati, 1975.
(2) Previous paper in the series: E. R. Kennedy and R. S. Macomber, *J. Org. Chem.*, **39**, 1952 (1974).
(3) R. S. Macomber, *J. Org. Chem.*, **36**, 2713 (1971).
(4) The unhydrolyzed precursors of H–X might exist as salts.[3]



(5) R. C. Elder, L. R. Florian, E. R. Kennedy, and R. S. Macomber, *J. Org. Chem.*, **38**, 4177 (1973).
(6) Several other solvents were found[5] to give inferior results.
(7) During the subsequent reaction the "O–H" absorption moved steadily downfield, reaching δ 4.98 after 4 h (35 °C).
(8) For several of the compounds in this study, the ^1H NMR coupling schemes cannot be uniquely determined by first-order analysis. In such cases, the spectra were simulated (LAOCOON III[9]) to extract the true chemical shifts and coupling constants. Copies of the ^1H NMR spectra of any compound described in this paper will be supplied upon request.
(9) S. Castellano and A. A. Bothner-By, Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University, No. 111.
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(11) A. I. Zehkarova and G. M. Murashov, *Zh. Obshch. Khim.*, **23**, 1981 (1953); *Chem. Abstr.*, **49**, 3783*i* (1955).
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(13) Samples of the oxaphospholenes and allenic phosphonic acids were vacuum dried before analysis.
(14) These reactions also produced an insoluble oily solid. Attempted isolation gave highly unstable materials whose ^1H NMR spectra did not resemble the desired phosphorus-containing products. This accounts in part for the lower yield.
(15) Some P_7-Cl (bp 81 °C, 100 mm)[16] is lost during rotary evaporation.

(16) G. F. Hennion and T. F. Banigan, Jr., J. Am. Chem. Soc., 68, 1202 (1946).
(17) The doublet out-of-phase allene stretch is uncommon, but known: N. B. Colthup, L. H. Daly, and S. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N.Y., 1975, p 237.
(18) Both A_4-$PO(OCH_3)_2$ and A_8-$PO(OCH_3)_2$ gave low values for C, H analysis: A_4, C, 45.27; H, 7.11 (theory, C, 47.23; H, 7.44); A_8, C, 39.18; H, 6.00 (theory, C, 40.54; H, 6.13). Both compounds appeared homogeneous by spectroscopy and chromatography. The low values may be due to facile hydrolysis or hygroscopicity.

α-Substituted Toluenes and 3-Substituted Propenes. Evaluation of Substituent Effects via Carbon-13 Nuclear Magnetic Resonance Spectroscopy

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The ^{13}C NMR shielding effects for 12 α-substituted toluenes and nine 3-substituted propenes have been determined. The substituent effects were analyzed by the Taft σ_I and σ_R and by the Swain–Lupton **F** and **R** parameters. No significant difference was observed between the two methods. In the α-substituted toluenes substantial substituent shifts were observed at C_4 (para to methylene), five bonds removed from the substituent. Excellent correlation between the toluenes and propenes was obtained for the methylene and C_1 carbons. A substantial resonance interaction was found to be important to describe the substituent effects at C_1 in toluene and C_2 in propene.

The correlation of the effects of substituents on carbon-13 shieldings is an important facet of the current research in ^{13}C NMR spectroscopy.[1] Once determined, these substituent effects can, in principle, be used to predict chemical shifts and thus lend valuable aid to the interpretation of complex spectra. Substituent effect studies have also played a significant role in the correlation of chemical and physical properties with molecular structure.[2] From the studies of substituent effects on fluorine-19, proton, and carbon-13 chemical shifts in substituted benzenes, it is apparent that the substituent is capable of altering the electronic structure of the aromatic ring in a predictive fashion.[3] Recently, a significant carbon-13 substituent effect through eight covalent bonds was observed for substituted biphenyls.[4] Similar results have been reported using ^{19}F NMR where the substituent effect was transmitted through an "insulating" methylene cavity.[5]

The nature of the transmission of substituent effects in α-substituted toluenes, particularly the halogenated cases, has been addressed by various methods. It has been shown that α-substitution, even by a nitro group, does not markedly affect the ortho–para directability in these systems.[6] The acidity of α-substituted *p*-toluic acids as a function of the α substituent indicated that a π-inductive mechanism was operating.[7] Other studies, including PES spectra, have attributed the substituent effect to a hyperconjugative mechanism.[8,9] Since it has been established that the carbon-13 chemical shift is sensitive to π-charge density,[3a] it would be of interest to see how the carbon-13 chemical shifts behave with respect to a variety of substituents at the benzylic position. Additionally, it should prove informative to compare the substituent effects obtained from aromatic systems to those of the ethylene derivatives, in this instance 3-substituted propenes.

The use of linear free energy relationships has found great utility in the study of substituent effects in NMR spectroscopy.[3b,c] In general, the contributions to the chemical shift changes induced by the substituent are attributable to either inductive or field and resonance effects.[10] In order to obtain the relative importance of these interactions a two (or more) parameter equation such as eq 1 can be used[11]

$$\Delta\delta = aA + bB + i \qquad (1)$$

where $\Delta\delta$ is the chemical shift difference for a particular carbon in the parent compound vs. the same carbon in the substituted case; A is the inductive and field parameter taken together, and B is the resonance parameter. For the purpose of the study herein two different but equally diagnostic forms of eq 1 will be evaluated: that of Swain and Lupton,[11b] where A = **F** and B = **R**, and that of Taft,[11a] where $A = \sigma_I$ and $B = \sigma_{R^\circ}$. The terms a and b (correlation factors) are determined by a minimization of the difference between the experimental chemical shifts and the chemical shifts calculated on the basis of eq 1. The term i is the intercept of the regression analysis and corresponds to the calculated shift of a particular carbon in the parent system.[12] The percent of contribution for each of the correlation factors can be obtained by the relative magnitudes of the absolute a and b values.[11b]

Results

The ^{13}C NMR spectra were recorded in deuteriochloroform solution, and all chemical shifts were determined from proton decoupled spectra using Me_4Si as internal reference.

The carbon-13 chemical shifts for the α-substituted toluenes are given in Table I. The aromatic assignments were determined as follows. The C_1 carbon (methylene substituted carbon) was readily identified by its low intensity and its singlet nature in the proton coupled spectrum. Likewise the assignment of the C_4 carbon could be easily established via intensity considerations since it is only ca. one-half the area of the other two signals. The $C_{2,6}$ and $C_{3,5}$ carbon shift assignments were more difficult to make, and in those cases where the chemical shifts are close, the assignments given in Table I may be reversed. However, when the $C_{2,6}$ and $C_{3,5}$ carbon shifts are separated by more than ca. 0.5 ppm and no overlap with the C_4 resonance occurs, the assignments could be obtained from inspection of the proton coupled spectrum. The $C_{2,6}$ carbon resonance appears as a broad multiplet owing to two different three-bond couplings (protons meta to $C_{2,6}$), a two-bond coupling (protons ortho to $C_{2,6}$) and a four-bond coupling (from the proton para to $C_{2,6}$), while the $C_{3,5}$ carbon resonance appears as a broad doublet owing to one three-bond, two two-bond, and one four-bond couplings.[13] The assignments, see Table III, for the 3-propenes are straightforward,

Table I. Chemical Shift of Toluene Compounds (ppm Relative to Internal Me_4Si) [a]

Registry no.	X	CH_2	C_1	$C_{2,6}$	$C_{3,5}$	C_4	Other
108-88-3	H	21.3	137.8	129.3	128.5	125.6	
100-41-4	CH_3	29.3	144.1	128.1	128.5	125.9	16.8 (CH_3)
101-81-5	Ph	42.0	141.3	129.0	128.5	126.2	
350-50-5	F[b]	84.9	137.0	127.8[c]	128.7[c]	125.9	
100-44-7	Cl	46.2	137.5	128.6[c]	128.5[c]	128.3	
100-39-0	Br[b]	33.4	137.8	129.0[c]	128.6[c]	129.0	
620-05-3	I	5.9	139.0	128.5	128.5	127.6	
140-29-4	CN	23.4	130.2	129.0	127.7	127.9	118.0 (CN)
622-42-4	NO_2[b]	81.0	130.7	130.7	130.7	129.7	
100-46-9	NH_2	46.4	143.3	127.0	128.4	126.6	
100-51-6	OH	64.9	140.5	127.2	128.6	127.7	
140-11-4	$OCOCH_3$	66.3	136.4	128.4[c]	128.6[c]	128.4	20.9 (CH_3) 170.7 (CO)

[a] Ca. 20% v/v in deuteriochloroform. [b] L. Zetta and G. Gatta, *Org. Magn. Reson.*, **4**, 585 (1972). [c] Shifts in the same row may be reversed.

Table II. Relative Chemical Shifts of Benzyl Substituted Compounds vs. Toluene [a]

X	CH_2	C_1	$C_{2,6}$	$C_{3,5}$	C_4
CH_3	8.0	6.3	−1.2	0.0	0.3
Ph	20.7	3.5	−0.3	0.0	0.6
F[c]	63.6	−0.8	−1.5 (−0.4)[b]	0.4 (−0.7)	0.3
Cl	24.9	−0.3	−0.7 (−0.8)	0.0 (0.1)	2.7
Br	12.1	0.0	−0.3 (−0.7)	0.1 (−0.3)	3.4
I	−15.4	1.2	−0.8	0.0	2.0
CN	2.1	−7.6	−1.4 (−0.3)	0.5 (−0.6)	2.3
NO_2[c]	59.7	−7.1	1.4	2.2	4.1
NH_2	25.1	5.5	−2.3	−0.1	1.0
OH	43.6	2.7	−2.1	0.1	2.1
$OCOCH_3$	45.0	−1.4	−0.9 (−0.7)	0.1 (−0.1)	2.8

[a] Negative sign indicates an upfield shift. [b] Values in parentheses are for alternate assignments. [c] See Table I.

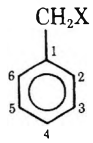
Table III. Chemical Shift Values for Propene Systems (ppm relative to Me_4Si)

Registry no.	X	CH_2=$CHCH_2X$		
		CH_2	C_1	C_2
115-07-1	H[a]	18.7	136.2	115.9
106-98-9	CH_3[c]	26.8 (8.1)[b]	140.2 (4.0)	113.5 (−2.4)
300-57-2	Ph	40.3 (21.6)	137.5 (1.3)	115.7 (−0.2)
107-05-1	Cl	45.3 (25.8)	134.0 (−2.2)	118.4 (2.5)
106-95-6	Br	32.8 (14.1)	134.5 (−1.7)	118.9 (3.0)
109-75-1	CN	21.4 (2.7)	126.5 (−9.7)	119.3 (3.4) (117.2) CN
107-11-9	NH_2	44.6 (25.9)	141.0 (4.8)	112.9 (−3.0)
107-18-6	OH	63.3 (44.6)	137.5 (1.7)	114.9 (−1.0)
591-87-7	$OCOCH_3$	64.7 (46.0)	133.1 (−3.1)	117.8 (1.9)

[a] J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972. [b] Values in parentheses are $\Delta\delta$ values vs. propene. [c] See T. Vonemoto, *J. Magn. Reson.*, **13**, 153 (1974).

and except for propenyl cyanide the shifts compare well with those already reported in the literature.[14] The shift values for propenyl cyanide reported here are consistent with observed substituent effects for this moiety; thus the value reported in ref 14a is in error.

In order to facilitate the discussion of the general trends observed for the substituent effects in the toluene and 3-propene systems, the $\Delta\delta$ values (the difference between the chemical shift of a particular carbon vs. that of the parent system) are given in Tables I and III, respectively. The numbering system used in this study is shown below. On inspection



$H_2\overset{2}{C}=\overset{1}{C}H-CH_2X$

of these data, it is apparent that the $\Delta\delta$ values for the benzylic and allylic methylene carbons vary over a range of ca. 80 ppm. By plotting the respective $\Delta\delta$ values for the methylene carbons in these two systems against each other, an excellent straight line is obtained, see Figure 1, with a correlation coefficient of >0.99 and a slope of 1.02. Good correlation is also found if these methylene $\Delta\delta$ values are plotted vs. the $\Delta\delta$ values obtained for simple aliphatic systems (Figure 2).[14a,15] A plot of the $\Delta\delta$ values vs. group electronegativity[16] does not correlate to a high degree; however, the order of the shifts suggests that the α-substituent effect is primarily inductive in nature.

The C_1 carbon of the toluene and the C_1 carbon of the propene systems are also found to experience similar substituent shifts. A plot (Figure 3) of the carbon shifts for these two systems yields a straight line with a correlation coefficient of 0.98 and a slope of 1.08. The correlation of the substituent

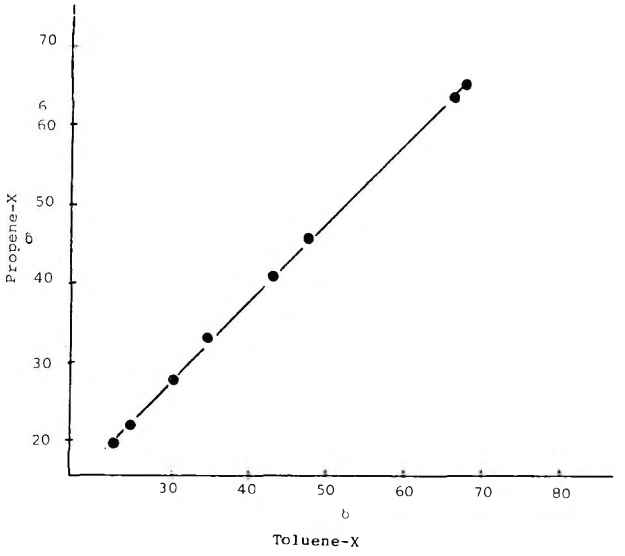


Figure 1. Comparison of the methylene carbon substituent effects for the toluene and propene systems.

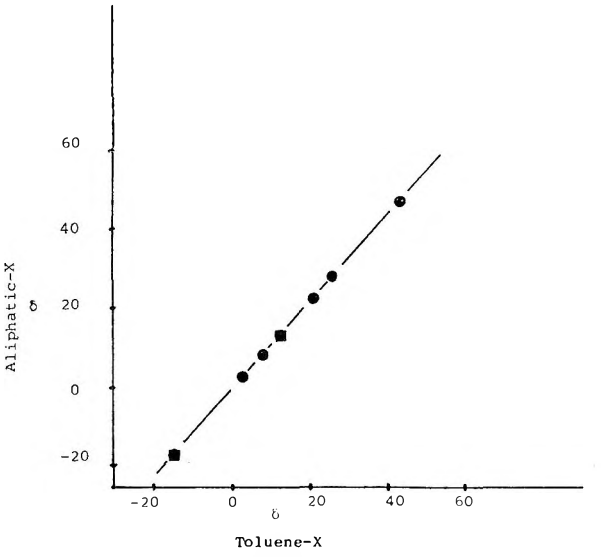


Figure 2. Comparison of the methylene carbon substituent effect for the toluene system with that of similarly substituted aliphatic systems: ●, data from ref 14a; ■, data from ref 15b.

effect at these carbons is not surprising in that the substituent is in the same relative position in space for both systems. Similar results have been obtained on comparison of monosubstituted benzenes with monosubstituted ethylenes.[17]

The remaining carbons which can be directly compared are $C_{2,6}$ (toluene) and C_2 (propene) carbons. A reasonable assumption based upon previous studies concerning aromatic ortho carbon shifts vs. olefinic β carbon shifts is that these carbon substituent shifts should be similar in magnitude and direction. In the benzene vs. ethylene series it was found that the $\Delta\delta$ values in the ethylene system are about twice that in the benzene analogues.[17] However, in the present instance poor correlation was obtained, and this suggests that the mechanism(s) responsible for the substituent shift at these carbons is different. For the propene systems both positive and negative $\Delta\delta$ values are obtained for the C_2 substituent shift, whereas in the toluene system, $C_{2,6}$ is seen generally to have negative values of $\Delta\delta$.

To complete our preliminary inspection of the data concerning the substituent shifts, it is noticed that the $\Delta\delta$ values, except for α-nitrotoluene, for $C_{3,5}$ are negligible while the $\Delta\delta$ values for C_4 are substantial even though this carbon is five bonds removed from the substituent interchange, and transmission of the effect must take place through an "insulating" methylene group.

The above comparison of the substituent shift exerted at C_1 in the toluene and propene systems suggests that a similar mechanism is important in each case for the transfer of the substituent effect. Looking at the data in Table IV, obtained by utilizing eq 1, it is clear that this assumption is correct. Although the absolute magnitudes of a and b are different for the Swain–Lupton and Taft methods, the relative importance of each effect, inductive-field, and resonance, is the same within the experimental error. The difference in magnitude arises from the difference in the initial value of σ_I vs. **F** and σ_{R° vs. **R**. Swain and Lupton found that σ_I and σ_{R° are 0.60**F** and 0.63**R**, respectively. Normalization of the σ_I and σ_{R° regression coefficients by 0.6 yields numbers which compare favorably with the Swain–Lupton treatment. In any case, it is apparent that a large resonance type interaction occurs at C_1.

The analysis of the substituent effects transmitted to the toluene C_4 carbon also indicates some resonance interaction although it is reduced in magnitude. Here σ_R(BA) values, benzoic acid derived, were used as σ_{R° did not give adequate

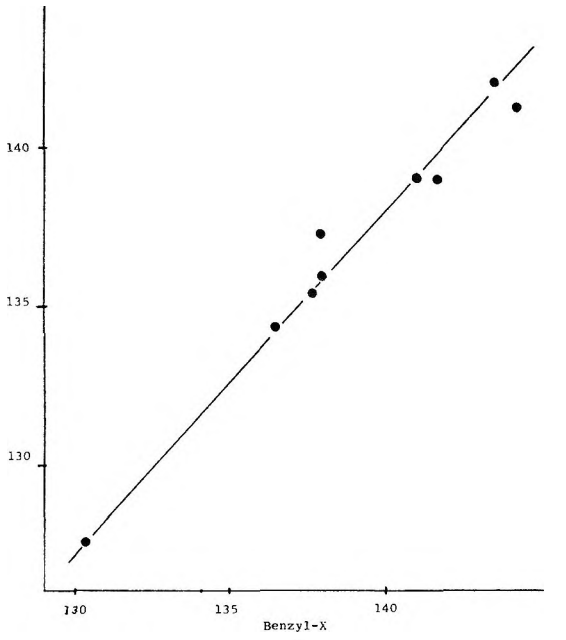
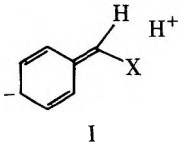


Figure 3. Comparison of the C_1 chemical shift for the toluene-X and propene-X systems.

correlation.[3b] (This may indicate an advantage of the Swain–Lupton treatment as the *search* for values of the resonance parameter which give good correlation is unnecessary.) Since *all* the $\Delta\delta$ values observed at C_4 are positive (downfield shifts) any mechanism that is consistent with the data would logically have to indicate at least a partial positive charge on this carbon owing to a loss of charge density. CNDO calculations bear out this effect in monosubstituted benzenes.[3a] This observation would seem to rule out the hyperconjugative electron release interaction such as I, which is invoked in order to explain the ortho–para directivity of toluene systems,[6] as a major contributor to the observed shift values as it would place a negative charge at C_4—hence induce upfield shifts.



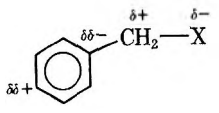
I

Table IV. Results of Linear Regression of $\delta = aA + bB + i$

Position	a	b	c^d	d^d	i	r	Av dev	Range
			Toluene Compounds					
$C_1{}^a$	−7.30	−7.31	−0.81	−0.69	140.3	0.916	1.44	14.0
$C_1{}^b$	−12.65	−11.37	−0.81	−0.68	140.3	0.944	1.30	14.0
$C_4{}^a$	3.63	−1.43	0.93	0.09	125.6	0.964	0.27	4.1
$C_4{}^c$	5.48	−0.71	0.92	0.20	125.7	0.931	0.38	4.1
			Propene Compounds					
$C_1{}^a$	−6.92	−6.99	−0.81	−0.72	137.2	0.961	0.83	11.5
$C_1{}^b$	−12.51	−11.69	−0.83	−0.67	137.3	0.985	0.52	11.5
$C_2{}^a$	5.45	4.28	0.87	0.66	115.2	0.972	0.48	7.7
$C_2{}^b$	9.58	6.26	0.88	0.56	115.2	0.979	0.50	7.7

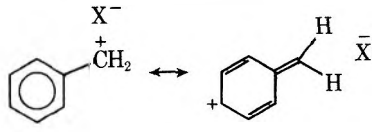
[a] $a\mathbf{F} + b\mathbf{R}$: Swain and Lupton.[11b] [b] $a\sigma_I + b\sigma_{R^\circ}$: Taft.[11a] [c] $a\sigma_I + b\sigma_{R(BA)}$; Taft.[3b] [d] Correlation coefficient (r) of a two-parameter equation A vs. δ and B vs. δ.

As indicated by the relatively good fit of σ_I or **F** alone with the $\Delta\delta$ values observed at C_4, a π-bond polarization mechanism (π-inductive effect) such as II may be dominant.[18] An-



II

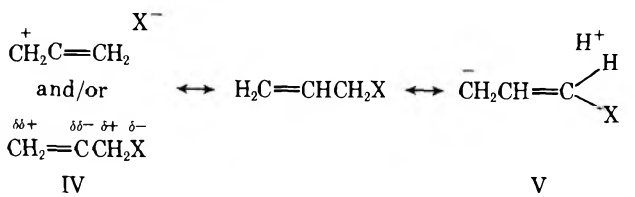
other possible contributor to the transmission of the substituent effect through the "insulating" methylene group involves participation of no-bond resonance forms,[5,19] e.g., III. A recent study concerning the substituent effect of a bromomethyl moiety supports a conjugative electron withdrawal by the C–Br bond.[20] As II and III work in the same direction it is difficult to distinguish between them.



III

The data with respect to the propenyl system can be explained via considerations similar to those for the toluene derivatives. From eq 1, a considerable resonance interaction is observed at both C_1 and C_2. Interestingly, the regression coefficients for C_1 and C_2 are of opposite sign. This trend is readily apparent from the $\Delta\delta$ values in Table III, i.e., those functionalities which exert a positive shift at C_1 exert a negative shift at C_2. These substituents can be grouped as CN, OAc, Br, and Cl (negative shifts at C_1) and CH_3, phenyl, NH_2, and OH (positive shifts at C_1).

A mechanism which is consistent with these data involves resonance contributions of a hyperconjugative nature and inductive polarization (IV) and/or the no-bond resonance form (V). Groups like Br apparently favor IV and groups like NH_2 favor V. The high correlation coefficient obtained for the



IV V

C_2 shift using only inductive and resonance interactions strongly suggests that other mechanisms[10] make at best minor contributions in the propene systems.

This leaves us with the problem of the substituent effect observed at the toluene $C_{2,6}$ carbons. Adequate correlation was not obtained for these carbons using eq 1. Since the substituent shifts are generally upfield a steric interaction may be operative.[1,21] If such a mechanism is important then the order of substituent shift should be inverse to substituent A values, i.e., small A value, larger upfield shift. This order is a consequence of the substituents having smaller A values having more populated states in which the gauche interaction occurs.[1,15] The data in Table II suggest that the steric shift mechanism is not a dominant factor in the $C_{2,6}$ substituent shift. It is possible, then, that the "ortho effect" is important. The utility of the semiempirical Q parameter in assessing this effect has been previously exemplified.[3d,22] It appears from these reports that Q measures a property of the π system and is not a through-space effect. It has been suggested that Q reflects the paramagnetic shielding.[3d] Inclusion of Q into eq 1, using **F** and **R** values, greatly improves the correlation, r = 0.999, $-1.48\mathbf{F}$, $-0.45\mathbf{R}$, and $0.85Q$, av dev 0.03 ppm. The reason for the difference between the C_2 propene carbon and the $C_{2,6}$ toluene carbons remain to be clarified. Further studies are in progress in order to explain this situation.

Experimental Section

All compounds were commercially available and of high purity, as indicated by a lack of significant signals in either the ^1H or ^{13}C NMR, and were used as received. The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a JEOL FX-60 spectrometer system equipped with a Texas Instruments computer with a 24K memory. The spectra were obtained at an observing frequency of 15.00 MHz. Sample concentrations were ca. 20% w/v in deuteriochloroform, in 10 mm o.d. sample tubes. General NMR spectral and instrumental parameters employed were internal deuterium lock to solvent; spectral width of 2500 Hz (166.6 ppm); a pulse width of 4 μs, corresponding to a 36° pulse angle; and a pulse repetition time of 1.8 s. For all decoupled spectra 8K time-domain data points were used while in some cases 16K time-domain data points were used for some of the coupled spectra. All shifts reported are referenced to internal Me_4Si, and are estimated to be accurate to ±0.05 ppm.

Acknowledgments. Grateful acknowledgment is made to the Robert A. Welch Foundation for their financial support of this work and Professor P. D. Bartlett for his encouragement and helpful suggestions.

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The E2C Mechanism in Elimination Reactions. 8. Interaction of Conjugating Substituents with E2C- and E2H-Like Transition States

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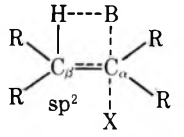
Rates and olefinic products of dehydrotosylation of secondary tosylates under conditions suitable for E2C, E2H, and solvolysis (E1) reactions, respectively, have been measured. The kinetic products are compared with those from equilibration. Quite different proportions of olefins are obtained according to the reaction conditions and this has obvious value for synthetic work. The tosylates studied contain groups, e.g., phenyl, acyl, vinyl, capable of conjugating with the developing double bond in the transition state leading to olefins. The product distribution from E2C-like reactions is not entirely consistent with the concept of a very product- (olefin-) like E2C transition state.

It is generally agreed that the olefin-forming elimination from secondary and tertiary alkyl halides and arenesulfonates induced by halide ions in aprotic solvents proceeds through a product-like transition state which has a large degree of carbon–carbon double bond character I.[1-3] There is little



I

charge at C_α or C_β and the leaving group is only loosely bonded to C_α. Winstein and Parker suggested that the base B is bound to both β hydrogen and C_α in I and describe the mechanism as E2C but there is less agreement on this point.[1,4] A puzzling feature in terms of the product-like E2C transition state has been the similar substituent effect on rate of β-aryl and β-methyl groups,[1,2,5,6] which both strongly enhance the rate of E2C-like eliminations relative to hydrogen. Where there is a choice of elimination pathways, e.g., dehydrotosylation of II, β-phenyl substituents do not appear to dictate the direction of elimination to form an extended conjugated styrene system in preference to the methyl hyperconjugated system. The olefinic products are not close to their equilibrium proportions when phenyl substituents are involved.[6]

$$PhCH_2CH(OTs)CH(CH_3)_2$$

II

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To establish whether these difficulties with our mechanistic interpretation of E2C reactions[1] were general for substituents capable of conjugation with developing double bonds, or were a peculiarity of aryl groups, e.g., steric factors inhibiting coplanarity of the phenyl ring with the developing double bond, we have studied the products of elimination from substrates having β-methyl, β-vinyl, β-acyl, and β-phenyl substituents.

Results and Discussion

We have difficulty in developing a consistent mechanistic description of the rates and proportions of olefinic products from the reactions of NBu_4Br in acetone containing 2,6-lutidine, the reactions of KOBu-*t* in *tert*-butyl alcohol, and the solvolysis in acetone–water of the tosylates shown in Table I. However, very small differences in the energy of transition states or of products can lead to what might at first appear to be rather different proportions of trans to cis olefin or of conjugated to unconjugated olefin. It may not be profitable to try to extend too far our E2C–E2H mechanistic thinking to explain differences in such small effects. Nevertheless, the results in Table I, together with some broad generalizations covering related compounds, could be of value to the organic chemist, anxious to decide between equilibration of olefins with KOBu-*t*/Me_2SO, reactions of tosylates with KOBu-*t*/*t*-BuOH or with NBu_4Br/acetone/lutidine, or solvolysis as a means of obtaining a desired proportion of olefins. For this reason we present the results and make a few very brief generalizations.

The tosylates III, V, and VI in Table I can be dehydrotosylated in two directions as well as giving trans and cis isomers,

Table I. Products [d] of Dehydrotosylation of Secondary Alkyl Tosylates $R_1CH(OTs)R_2$ and Equilibration of Olefins

No.	$R_1CH(OTs)R_2$ R_1	R_2	Mech	Log k [e]	Conjugated [a] / hyperconjugated	Other [b] olefins, %	Trans [c,m] / cis	
III	$PhCH_2$	$CH(CH_3)_2$	E2C [g]	−2.9	0.10	0.8	18	
			Eq [h]		1.8	3.4	130	
			Sol. [i]	−3.3 [f]	0.16	13.3	9	
			E2H [j]	−2.8	37	0.2	60	
IV	CH_3CH_2	$CH(CH_3)_2$	E2C	−2.8	0.043 [a]	2.7	>35	
			Eq		0.092 [a]	<1	6	
			Sol. [k]	>−4 [f]	0.20 [a]	13	>35 [k]	
			E2H	−2.6	0.96 [a]	<1	2	
V	$CH_2{=}CH{-}\underset{CH_3}{\overset{}{CH}}$	$CH(CH_3)_2$	E2C	−2.9	1.0	1.7	1.6	
			Eq		4.0	1.7	1.2	
			Sol.	−2.3 [f]	0.53	2.2	1.0	
			E2H	−3.45	3.5	5.4	2.6	
VI	CH_3COCH_2	$CH(CH_3)_2$	E2C	−2.5	35	0.2	100	
			Eq		110	0.7	200	
			Sol.	−2.7 [f]	20.3	10.4	33	
			E2H	≥1.3	13	0.3	130	
VII	$PhCH_2$	CH_2CH_3	E2C	−4.35	1.6	1	14.5	9.5 [l]
			Eq		15.6	<0.1	52	3.5 [l]
			Sol.	−3.8 [f]	0.50	0.3	5.2	2.2 [l]
			E2H	−2.6	41	<0.1	15	0.6 [l]

[a] Ratio of trans + cis conjugated olefin to trans + cis olefin hyperconjugated with a methyl group. Note that the term conjugated does not apply in compound IV. [b] Percentage of rearranged olefins relative to total of olefinic products, mostly 1-ene. [c] Ratio of trans to cis olefin in the products of dehydrotosylation or equilibration. [d] VPC analysis after extraction of reaction mixture with petroleum ether. Olefins were characterized by synthesis or by preparative VPC, followed by uv and NMR analysis of the separated olefins. [e] k in $M^{-1}\ s^{-1}$ at 75 °C. [f] Initial second-order rate constant from rate of solvolysis assuming second-order reaction with 0.20 M base. [g] Tosylate was 0.02–0.05 M, NBu_4Br was 0.1–0.2 M in acetone containing 0.05–0.1 M 2,6-lutidine. [h] Equilibrated with excess KOBu-t in Me_2SO at 30 °C for 30 min. [i] Solvolysis in 50/50 acetone/water at 75 °C. [j] Tosylate was 0.02–0.05 M, KOBu-t was 0.05–0.10 M, in t-BuOH. [k] A. K. Colter and D. R. McKelvey, *Can. J. Chem.*, **43**, 1282 (1965). [l] Ratio of trans/cis hyperconjugated olefin. [m] Ratio trans/cis of conjugated olefin.

to give olefins having conjugation with a phenyl group (III), a vinyl group (V), and an acyl group (VI), or an olefin hyperconjugated with two methyl groups (III, V, and IV). Two other tosylates are shown: IV, in which dehydrotosylation gives either a trans and cis olefin hyperconjugated with one methyl group or an olefin hyperconjugated with two methyl groups; and VII, in which competition gives trans, cis olefins conjugated with a phenyl group or hyperconjugated with a methyl group.

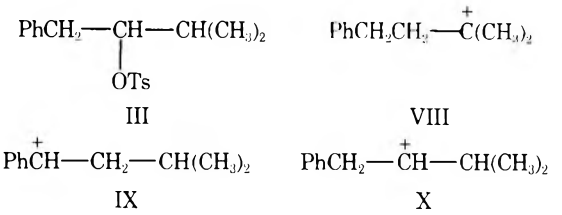
Methyl groups generally stabilize double bonds by hyperconjugation about two-thirds as strongly as do phenyl groups by conjugation[7] and follow additivity rules.[8] The equilibration of the conjugated and unconjugated olefins from III and VII suggests that in Me_2SO, a phenyl group is rather more effective than this, relative to methyl, in stabilizing olefins. By comparing the products of dehydrotosylation from the substrates of Table I via E2C-like, E2H-like, and solvolysis transition states with the products of olefinic equilibration in Me_2SO, information as to the product-like nature of the transition states may be obtained.

Equilibration. Equilibration with KOBu-t/Me_2SO shows that conjugation with a phenyl or a vinyl group (VII and V) is more effective in competition with a hyperconjugative methyl group in stabilizing olefins. Two hyperconjugative methyl groups are more effective than one hyperconjugative methyl group (IV) but are not quite as effective as one conjugative phenyl group (III). A conjugative acyl group (VI) is the most effective of the groups studied in stabilizing olefins. The equilibrium proportions in Me_2SO are consistent with the gas-phase thermodynamic properties of olefins.[7,8] Substituent effects tend to follow additivity rules,[7,8] so our observations may have some general application.

The equilibrium proportion in Me_2SO of trans olefin is higher (sometimes much higher) than that of cis olefin, for all the products studied in this work.

Solvolysis. Solvolysis of these secondary tosylates in 50% acetone–water is likely to be via carbonium ions which to some extent have undergone rearrangement, as shown by the presence of 1-ene in the products. For El elimination from a high-energy carbonium ion, the transition states leading to olefins will be carbonium ion-like. Thus there will be little discrimination of products between trans and cis or conjugated vs. hyperconjugated olefins. Ratios of trans/cis olefins from solvolysis should be nearer to unity than from equilibration and with one exception, such is the case in Table I. The proportion of conjugated to hyperconjugated olefin will depend to some extent on the proportions of rearranged carbonium ions, prior to elimination of a proton from them. With one exception, the ratio of conjugated to hyperconjugated olefin for solvolysis is nearer to unity than for equilibration.

The effect of rearrangements on the solvolysis products of compound III illustrates the problem. Tertiary carbonium ions are slightly more stable than benzylic, than secondary, so that elimination is from a mixture of carbonium ions, VIII–X, with

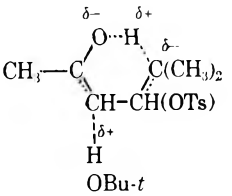


VIII in highest proportion, leading to a large amount of the hyperconjugated olefin and the 1-ene, as is observed.

Clearly interpretation of solvolysis products is a complex matter because of rearrangements and little information which might help us in understanding E2C-like and E2H-like reactions can be obtained. In general, solvolysis is a less clean

way of obtaining high yields of olefins than are E2C or E2H reactions.

E2H Reactions. Dehydrotosylations with KOBu-*t*/*t*-BuOH are generally regarded as E2H-like reactions[1]. Rates of E2H-like reactions are much faster the more acidic the β hydrogen. Bronsted relationships are followed.[5] Thus since vinyl, phenyl, and acyl are more acidifying substituents than methyl, one would expect a high ratio of conjugated to hyperconjugated olefin from E2H-like reactions. Such is the case in Table I. There is, however, one surprising result, in that 7% hyperconjugated olefin is produced from tosylate VI, i.e., two methyl groups compete quite effectively with the very strongly acidifying acyl group in this E2H-like reaction. A potential problem with using the strong base KOBu-*t*/*t*-BuOH is that the products of elimination from VI (particularly the conjugated olefin) decompose slowly in the presence of excess of the *tert*-butoxide ion. However, similar product ratios to those for KOBu-*t*/*t*-BuOH were obtained after 1, 2, and 10 half-lives using the weaker NaOEt/EtOH base system. In the presence of this base the olefins are stable under the reaction conditions. We found no evidence for isomerization toward an equilibrium mixture of olefins under the reaction conditions with either base. An explanation for the high yield of hyperconjugated olefin may be that the carbonyl group is stabilizing the transition state for production of the hyperconjugated olefin via an enolate from as in XI, with return to the keto form



XI

on product isolation. This option is not available to E2C reactions which use very much weaker H bases.

More trans than cis conjugated olefin is produced from the E2H-like reactions of Table I, but more important, the trans/cis proportions for E2H are *less than the equilibrium proportion*, with one exception.

E2C Reactions. E2C-like reactions of NBu_4Br in acetone containing 2,6-lutidine usually give very different proportions of olefins from E2H-like reactions, and from equilibration.[1] This has significance for the synthesis of olefins. The overall rates of dehydrotosylation under E2C conditions are similar ($\log k$ −2.5 to −3) for all tosylates in Table I having R_2 as an isopropyl group, no matter whether R_1 is methyl, phenyl, vinyl, or acyl. The proportion of conjugated to hyperconjugated olefin from E2C-like dehydrotosylation is less than the proportion from equilibration. Thus the E2C-like transition state is not *strongly* product-like in this respect. In general, although more olefin-like, E2C-like transition states lead to less of the conjugated olefin and more of the hyperconjugated olefin than do E2H-like reactions, which are governed by carbanion stability. The one exception is compound VI, where the unexpectedly high proportion of hyperconjugated olefin from the E2H-like reaction has already been commented on (cf. XI).

Proportions of trans to cis olefin from the E2C-like reactions shown in Table I are significantly greater than for solvolysis and greater than unity and this is a feature of most E2C-like reactions. However, the trans/cis ratios are often significantly different from the equilibrium proportions, when substituents capable of conjugation are involved. Sometimes the trans/cis ratio is greater, sometimes less for the E2C-like reaction than for the equilibrium proportion. For formation of a conjugated olefin, the trans/cis ratio is always less from the E2C-like than from the E2H-like reaction.

To summarize, E2C-like conditions often allow us to prepare a significantly different proprotion of olefins from a diastereotropic tosylate than would be obtained from a dehydrotosylation under E2H-like or solvolysis conditions, or from equilibration of olefins. This has advantages in preparative work. The behavior, under E2C-like conditions, of tosylates which contain substituents capable of conjugating with a developing double bond, is not entirely consistent with a very product-like E2C transition state. It may be that conjugating substituents are not able to achieve full conjugation of their π-electron systems with the developing double bond in E2C-like transition states, but we confess ourselves unable to give a completely satisfactory mechanistic explanation for the data in Table I.

Experimental Section

Preparation of Alcohols. 1-Phenyl-3-methyl-2-butanol, 1-phenyl-3-methyl-1-butanol, 1-phenyl-2-butanol, and 1-phenyl-1-butanol were prepared via the Grignard reaction using phenylacetaldehyde or benzaldehyde, and isopropyl bromide or ethyl bromide in the usual manner.[9] The alcohols were purified by spinning band vacuum distillation at 1 mmHg to >95% purity as determined by GC analysis using a 6 ft × 0.125 in. column of Apiezon L at 150 °C. An NMR of the purified alcohols confirmed their structure.

Methyl-2-hydroxy-3-methyl butyl ketone was prepared by slowly adding 2-methylpropionaldehyde dropwise to excess acetone at 5 °C containing 0.5% w/v tetraethylammonium hydroxide. The method was similar to that described by Eccott and Linstead.[10] The alcohol was purified by vacuum distillation (bp 92 °C, 23 mm) and analyzed by GC (Apiezon L at 80°) and NMR to confirm its purity and structure.

2-Methyl-3-hydroxy-4-methyl-5-hexene was prepared by the Grignard reaction with isobutyraldehyde and 1-bromo-2-butene added together to a well-stirred suspension of magnesium in ether. Although allylic bromides can react at either α or γ carbon, 1-bromo-2-butene reacts exclusively at γ carbon.[11] The product is complex because dimerization of the olefin and condensation of the aldehyde occur, and was fractionally distilled at atmospheric pressure and at 13 mmHg. Heptenols boil at 150–180 °C (40–70 °C, 13 mmHg) and a high-boiling aldol condensation product remains. The fraction recovered at 61 °C (13 mm) proved to be the required alcohol (NMR analysis) of 99% purity (GC analysis on Apiezon L at 100 °C). A GC analysis of this alcohol on Carbowax 20M at 60 °C resolved two peaks of equal intensity thought to be different diastereomers. The alcohol possesses two chiral centers.

Preparation of Tosylates. The tosylates were prepared by reacting the corresponding alcohols with a 50% excess of tosyl chloride which had been recrystallized from a 60:40 mixture of light petroleum and ethyl acetate. The reactants were dissolved in cold pyridine and allowed to react overnight. Excess tosyl chloride was removed by slowly adding a theoretical quantity of water and stirring. After 0.5 h, xcess 10% v/v ice-cold hydrochloric acid and ether were added and the tosylate was extracted into the ether layer and worked up in the usual manner. The isolated products were recrystallized or repeatedly oiled out at −70 °C from light petroleum. They were analyzed by ir to confirm the absence of residual alcohol and by NMR to confirm their purity and structure. Melting points were determined on a Kofler block and were found to be (structure; melting point): III, 79.5–80.5 °C; IV, oil; V, oil; VI, oil, ~31 °C; VII, 54–55 °C.

Preparation of Olefins. Conjugated olefins were generally prepared by refluxing the corresponding alcohol with 50% sulfuric acid while hyperconjugated olefins were generally prepared by refluxing the alcohol with iodine catalyst. Boiling points of the pure fraction corresponded to literature values and NMR analyses confirmed their structure. 1-Phenyl-3-methyl-2-butene was prepared independently by a Grignard reaction with bromobenzene and 1-chloro-3-methyl-2-butene. Olefin mixtures were separated and analyzed by GC using a 7 ft × 0.125 in. column of Carbowax 20M at 40–75 °C.

Registry No.—III, 33740-54-4; III alcohol derivative, 705-58-8; IV, 1516-13-8; IV alcohol derivative, 565-67-3; V, 59697-03-9; V alcohol derivative, 53045-65-1; VI, 59697-04-0; VI alcohol derivative, 38836-21-4; VII, 59697-05-1; VII alcohol derivative, 701-70-2; tosyl chloride, 98-59-9.

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Notes

Photochemistry of Organochalcogen Compounds. 2.[1] Photochemical Deselenation of Benzyl Diselenide by Triphenylphosphine

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Although the chemistry of organoselenides is well documented,[2] little is known about their photochemical reactions. By contrast, the photoreactions of many organosulfides have been studied and their mechanisms understood.[3] We have reported recently the first quantitative study on the photolysis of benzyl diselenide (1) in solution.[1] It was found that irradiation of 1 in degassed acetonitrile at wavelengths greater than 280 nm results in formation of elemental selenium and dibenzyl selenide. Photoinduced cleavages of Se–Se and C–Se bonds were proposed as possible primary processes.

Walling and Rabinowitz[4] discovered that trivalent phosphorus compounds convert thiyl radicals into alkyl radicals. This led us to investigate analogous reactions for organoselenides. A recent communication by Cross and Millington[5] on the deselenation of diethyl diselenide by tertiary phosphines prompts us now to report some quantitative details of our studies of photodeselenation of 1 by triphenylphosphine (2).

Irradiation of 1 (2×10^{-2} M) and an excess of 2 (4×10^{-2} M) in degassed acetonitrile at 350 nm for 45 min yields 66.1% of dibenzyl selenide (3), 32.3% of bibenzyl (4), and 65.1% of triphenylphosphine selenide (5).

$$\underset{1}{PhCH_2SeSeCH_2Ph} + \underset{2}{Ph_3P} \xrightarrow[CH_3CN]{h\nu\ (350\ nm)} \underset{3}{PhCH_2SeCH_2Ph} + \underset{4}{PhCH_2CH_2Ph} + \underset{5}{Ph_3PSe}$$

Under these conditions, the formation of elemental selenium is completely suppressed. If molecular oxygen is present, 5 reacts further to produce triphenylphosphine oxide and elemental selenium. The photoproducts were isolated by preparative layer chromatography and identified by comparison with authentic samples prepared by independent syntheses. The progress of the reaction was monitored by NMR as described previously.[1] The methylene protons of 1 (δ 3.81), 3 (δ 3.70), and 4 (δ 2.88) have sufficiently different chemical shifts to permit quantitative analysis. The results are shown in Figure 1. Formation of 5 cannot be monitored by NMR; however, it was demonstrated by GLC that 5 is formed rapidly and reaches constant concentration after about 40 min of irradiation (compare to Figure 1). NMR analyses indicate significant photoreaction in 10 min and complete disappearance of diselenide (1) in 45 min. No detectable reaction occurs in a nonirradiated aliquot of the degassed reaction mixture stored in the dark at room temperature for 7 days.

In contrast to the direct irradiation (quantum yield $\Phi = 0.16$ for disappearance of 1 in benzene at 313 nm),[1] the photodeselenation of 1 by 2 in benzene is remarkably efficient. Table I shows the increase of quantum yield with increasing concentration of 2. The large quantum yields provide strong evidence for a free-radical chain reaction.

For irradiations of 1, in the absence of 2, at 366 nm less than 7% decomposition of 1 was detected after 3 h exposure.[1] This result has been interpreted as evidence for a Se–Se bond cleavage (eq 1) as the major primary process in 1, followed by

$$RSeSeR \xrightarrow{h\nu} 2RSe\cdot \quad (R = PhCH_2) \qquad (1)$$

$$RSeSeR \xrightarrow{h\nu} R\cdot + RSeSe\cdot \longrightarrow RSe\cdot + Se^0 + R\cdot \qquad (2)$$

efficient benzylselenyl radical combination to give 1, or benzylselenyl radical displacement reaction at the Se–Se bond resulting in generation of 1 and an additional benzylselenyl radical.[1] We have no data on the relative importance of combination vs. displacement reactions for benzylselenyl radicals. Sayamol and Knight,[3] however, have reported that displacement reactions play a major role for thiyl radical reactions. Regardless of the relative importance of these reactions for benzylselenyl radicals these processes lead to no photoproduct formation.

The observed photoproducts can be explained on the basis of eq 2.[1] The very low quantum efficiency suggests that benzylselenyl radicals do not dissociate to yield Se^0 and benzyl radicals.

In contrast to these results, irradiation of 1 in the presence of 2 under identical reaction conditions results in total reaction

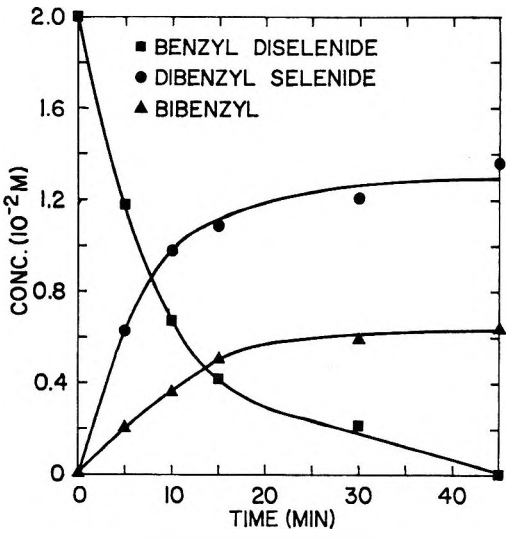


Figure 1. The concentration of reactant and photoproducts plotted vs. photolysis time.

Table I. Quantum Yields for Disappearance of Benzyl Diselenide[a] in the Presence of Triphenylphosphine

No.	Ph_3P, M	$-\Phi_{RSeSeR}$
1	0.000	0.16
2	0.050	1.44
3	0.075	2.66
4	0.100	4.70
5	0.200	6.80

[a] 0.1 M RSeSeR in purified, degassed benzene at 298 K exposed with 313-nm light.

of 1 within 1 h. The major primary photoprocess remains facile Se–Se bond cleavage. It appears that benzylselenyl radicals are trapped by 2 to form triphenylphosphine selenide (5) and benzyl radicals which subsequently react to form all photoproducts observed. The following radical chain mechanism is proposed for the reaction:

$$RSe\cdot + Ph_3P \longrightarrow Ph_3\dot{P}SeR \quad (3)$$

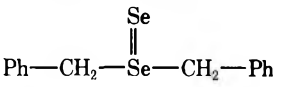
$$RSe\dot{P}Ph_3 \longrightarrow R\cdot + Ph_3PSe \quad (4)$$

$$R\cdot + RSeSeR \longrightarrow RSeR + RSe\cdot \quad (5)$$

$$2R\cdot \longrightarrow R{-}R \quad (6)$$

Our results suggest that benzylselenyl radicals formed in reactions 1 and 2 can attack phosphorus atoms to yield a tetracovalent phosphoranyl radical[4,6] with an expanded valence shell (eq 3). Reactions 3, 4, and 5 are the propagation steps with 5 representing the chain transfer reaction. The relatively stable benzyl radicals produced in 4 combine to yield 4 and terminate the radical chain reaction. This reaction mechanism is analogous to that proposed for thiyl radicals in the presence of trialkyl phosphites.[4]

A reviewer has suggested the possible intermediacy of a structure containing a Se=Se moiety:



We have no spectroscopic evidence for such an intermediate. Furthermore, this intermediate is not consistent with the experimental results. Assuming that this intermediate reacts with Ph_3P to yield $Ph_3P{=}Se$ and dibenzyl selenide, no further free-radical chain mechanisms are possible.[7] Thus, the quantum yield for disappearance of 1 could not exceed unity, and no formation of bibenzyl could occur. We may, therefore, rule out this structure as a possible intermediate in the photochemistry of 1.

Experimental Section

General. Melting points were determined using a Thomas-Hoover apparatus and are not corrected. NMR spectra were obtained with a JEOL C60H instrument using tetramethylsilane as internal standard. Uv spectra were measured on a Cary 15 spectrophotometer. GLC analyses were carried out on a Hewlett-Packard 5750 research chromatograph using a 6 ft × 0.125 in. stainless steel column packed with 10% UCON-98 on 80–100 Chromosorb W and temperature programming. EM precoated silica gel F-254 plates (20 × 20 cm) were used for preparative layer chromatography, with benzene–hexane as eluent.

Materials. Benzyl diselenide and dibenzyl selenide were prepared according to previously reported procedures.[1]

Triphenylphosphine selenide was prepared by adapting the procedure of Nicpon and Meek.[8] The crude product was recrystallized from absolute ethanol, mp 187–188° (lit.[8] 187–188 °C).

Solvents. Thiophene-free reagent grade benzene was further purified by storing the solvent over 4A molecular sieves, filtering, and fractionally distilling. Acetonitrile (Burdick & Jackson spectrographic quality) was purified by passing it through a column of alumina (Woelm, activity 1). Deuterated solvents were commercial spectral grade.

General Irradiation Procedures. Preparative photolyses were carried out in water-cooled Pyrex reactors equipped with dry nitrogen purging and magnetic stirring. Solutions containing benzyl diselenide (2×10^{-2} M) and triphenylphosphine (4×10^{-2} M) were deoxygenated by bubbling nitrogen for 50 min and irradiated under nitrogen atmosphere with eight RUL-3500 Å lamps in a Rayonet RPR-208 photochemical reactor. The progress of the reaction was monitored by NMR as described previously.[1] The photoproducts were isolated by preparative layer chromatography on a precoated silica gel plate and identified by comparison with authentic samples. Yields were calculated by using the NMR and GLC integration data. Quantum yield determinations were carried out in degassed benzene and obtained as previously described.[1]

Acknowledgments. We are grateful to Dr. W. H. H. Günther for encouragement and to Mrs. J. Weaver for some experimental assistance.

Registry No.—1, 1482-82-2; 2, 603-35-0; 3, 1842-38-2; 4, 103-29-7; 5, 3878-44-2.

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Steric Effects in the Base-Catalyzed Hydrolysis of *p*-Nitrophenyl Esters. Relative Behavior of Bridged and Nonbridged Trialkyl Acetates

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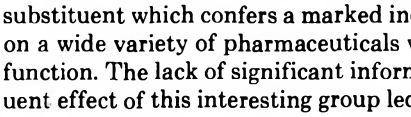
The 1-adamantyl group (1-tricyclo[3.3.1.$3^{3,7}$]decyl) is a substituent which confers a marked increase in lipophilicity on a wide variety of pharmaceuticals without altering their function. The lack of significant information on the substituent effect of this interesting group led us to investigate the base-catalyzed hydrolysis (eq 1) of a series of *p*-nitrophenyl

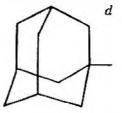
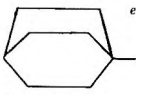


(1)

1

esters (1). In light of Charton's recent findings that alkyl groups do not differ significantly in their electrical effects in base-catalyzed ester hydrolysis,[1] such a study should provide

Table I. Kinetic and Activation Parameters for the Base-Catalyzed Hydrolysis of *p*-Nitrophenyl Alkanoates (1) in 1:1 CH_3CN/0.05 M Aqueous Tris Buffer of pH 9.0

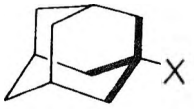
Registry no.	R	Rate constant[a]			Relative rates			$\Delta H^{\ddagger}$[b]	$\Delta S^{\ddagger}$[c]
		23 °C	38 °C	48 °C	23 °C	38 °C	48 °C		
830-03-5	CH_3	3580 ± 30	9910 ± 70	16800 ± 300	4442	3797	3123	11.2	−22.9
1956-06-5	CH_3CH_2	1130 ± 30	3050 ± 30	5840 ± 10	1402	1169	1086	11.8	−22.7
4195-16-8	$(CH_3)_2CH$	892 ± 30	2330 ± 40	4980 ± 60	1107	893	926	12.3	−21.9
4195-17-9	$(CH_3)_3C$	152 ± 3	484 ± 30	907 ± 20	189	185	169	13.0	−23.1
59711-28-3	 [d]	90.5 ± 1.5	244 ± 2	518 ± 20	112	94	96	12.5	−25.7
59711-27-2	 [e]	83.5 ± 3.1	244 ± 12	500 ± 40	104	94	93	13.0	−24.2
59711-26-1	$(C_2H_5)_3C$[f]	0.806[g]	2.61[g]	5.38[g]	1	1	1	13.7	−30.8

[a] $k_2 \times 10^4$, l. mol^{-1} s^{-1}. [b] kcal mol^{-1}. [c] cal mol^{-1} K^{-1}. [d] Mp 130–131 °C. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.66: H, 6.12; N, 4.80. [e] Mp 97–98 °C. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.08. Found: C, 65.08; H, 6.18; N, 4.85. [f] Mp 50–51 °C. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.19; H, 7.35; N, 5.43. [g] These are assigned values which were calculated, by means of the Arrhenius equation, from the experimental rate constants of 1.53 × 10^{-4} at 31 °C and 10.6 × 10^{-4} at 58 °C.

a direct comparison of the steric requirements ("steric effects") of the various alkyl groups. The compounds studied, along with the second-order rate constants and activation parameters, are shown in Table I.

The data clearly indicate a general decrease in the rate of hydrolysis in the order $CH_3 > C_2H_5 > i\text{-Pr} > t\text{-Bu} > 1\text{-Ad} \sim [2.2.2] > Et_3C$. This is certainly a "steric order" of retardation. The 23 and 38 °C rate data for R = CH_3, CH_3CH_2, $(CH_3)_2CH$, $(CH_3)_3C$, and $(C_2H_5)_3C$ have been correlated with Charton's ν constants by means of his modified Taft equation,[1] with correlation coefficients of greater than 0.99[2].

The *t*-Bu/1-Ad rate ratio of approximately 2 is the same as that observed in the $NaBH_4$ reduction of the ketones $RCOCH_3$ in *i*-PrOH over the temperature range 15–45 °C.[3] In combination, these data argue strongly for a greater steric requirement for the 1-adamantyl (2) and 1-bicyclo[2.2.2]octyl (3) groups, even though they might be considered as con-



2

3

strained *tert*-butyl groups. A minor contribution may be due to the greater mass ("ponderal effect") of the 1-adamantyl and 1-bicyclo[2.2.2]octyl groups rather than their relative space filling qualities.[4]

It was originally felt that the rigidity of the adamantyl group (as compared with the libration of the *tert*-butyl group) might result in decreased steric interference to attack at a substituent. This now appears unlikely. In fact, it may be this same rigidity which makes for a more congested transition state. The acyclic analogue is free to "bend back" to diminish this strain (Figure 1). Only when the acyclic group is increased in size to the triethyl carbinyl system 4 is steric retardation due to increased hindrance to attack observed.[5]

4

Figure 1.

Charton, using the above correlations, has calculated a ν value of 1.33 for both the 1-adamantyl and 1-bicyclo[2.2.2]-octyl groups,[2] as compared with values of 1.24 and 2.38 for the $(CH_3)_3C$ and $(C_2H_5)_3C$ groups, respectively. Thus the 1-adamantyl and 1-bicyclo[2.2.2]octyl groups appear to have essentially identical steric requirements, and it may be predicted that the latter might also exhibit interesting effects when substituted on pharmaceuticals.

Experimental Section[6]

Materials. Reagent grade acetonitrile was distilled from P_2O_5. Buffer salts and inorganic acids and bases were of analytical grade. The *p*-nitrophenyl esters of acetic and pivalic acids were obtained in reagent grade quality from Aldrich Chemical Co. The esters remaining were prepared by standard synthetic techniques.

Kinetics. In a typical experiment 3 ml of the 1:1 acetonitrile/0.05 M aqueous Tris buffer of pH 9.0 was placed in a cuvette in a Beckmann DU spectrophotometer equipped with a circulating bath that maintained the desired temperature. The reaction was then initiated by injection of 50 μl of the appropriate ester in acetonitrile. The rate was measured by observing the increase in optical density at 400 nm due to the *p*-nitrophenolate ion. The data thus collected were analyzed by the method of initial rates. Regression analysis of the data (ten points) from each run produced correlation coefficients of better than 0.99. Each rate constant reported in Table I is the unweighted average of at least three separate runs.

Acknowledgments. We thank Professor M. Charton for helpful discussions and analysis of our data. A generous donation of 1-bicyclo[2.2.2]octanecarboxylic acid by Professor C. A. Grob, University of Basle, is acknowledged with pleasure.

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Internal Rotation in Dicyclopropylacetylene

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In organic chemistry, the interactions between groups are generally separated into two broad categories—electronic and steric.[1] This separation, although artificial, works quite well. It is well known that electronic effects can be transmitted through double and triple bonds while steric effects, in the classic sense, are generally assumed not to be. Thus the absence of a rotational barrier in 2-butyne[2] is not surprising despite the fact that the Hamiltonian and the resulting molecular orbitals encompass the entire system, including the two methyl groups. In diarylacetylenes, on the other hand, one might expect a rotational barrier, and the experimental evidence does seem to indicate that certain conformations are preferred.[3] Semiempirical calculations predict, though, that the barrier is small.

Dicyclopropylacetylene has recently been synthesized and some of its reactions studied.[4-7] This system is of interest in the same sense and is sufficiently small to allow ab initio calculations on the rotamers.

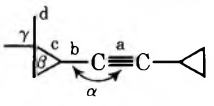
Quantum mechanically, interactions of the cyclopropyl rings with each other and with the alkyne linkage certainly take place, and even a more classic examination would predict some interaction of the cyclopropyl electrons with the triple bond. Consequently, it is of interest to determine whether a rotational barrier actually exists and whether such a barrier, if found, is large or small.

Discussion

The quantum mechanical calculations were all single-determinantal SCF calculations using the 3G basis set of Pople and co-workers.[8]

Table I gives the bond lengths and bond angles. All of the internal cyclopropyl angles β were set equal to 60°, and all external angles γ were set equal to 115°. The cyclopropyl geometries were obtained from the experimental values of cyclopropane and its derivatives,[9-11] the triple bond distance from acetylene and various substituted alkynes.[12-14] The

Table I. Bond Lengths (Angstroms) and Bond Angles (Degrees) for Dicyclopropylacetylene



a	b	c	d	α	β	γ
1.205	1.460	1.515	1.085	180°	60°	115°

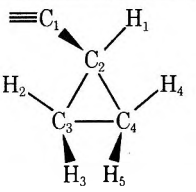
Table II. Geometries Used for Dicyclopropylacetylene

1	2	3	4	5	6	7

Table III. Calculated Energies and Dipole Moments of Geometries 1–7 of Dicyclopropylacetylene

	E	μ
1	−304.92488	0.28
2	−304.92495	0.28
3	−304.92508	0.25
4	−304.92512	0.22
5	−304.92512	0.18
6	−304.92502	0.08
7	−304.92495	0.00

Table IV. The Electronic Density ρ at Each Position in Dicyclopropylacetylene



	C_1	C_2	C_3	C_4	H_1	H_2	H_3	H_4	H_5
ρ	6.06	6.07	6.13	6.13	0.92	0.93	0.92	0.93	0.92

1.46-Å carbon–carbon value for a number of substituted alkynes has been discussed by Costain and Stoicheff[12] and by Dewar.[15] Geometries 1–7 corresponding to dihedral rotations of 0, 34.39389, 68.78778, 90°, 107.196945, 145.60611, and 180° were used (Table II).

Results

The data in Table III give the calculated energies and dipole moments μ of each rotamer. The energy units are hartrees; one hartree equals 627.5 kcal/mol.

In Table IV we present the electronic densities, calculated by a population analysis, at each position in the molecule. The electronic density underwent very little change during the rotation, and we choose geometry **5**. Furthermore, the symmetry of the system requires that only half the molecule be given.

Conclusion

The barrier to internal rotation in dicyclopropylacetylene has been calculated using the 3G basis set. A larger basis set would certainly give a better description of the cyclopropyl rings,[16,17] and in some cases can alter the shape of the reaction coordinate.[18,19] However, in the present case, the 3G result appears reasonable, and although a small barrier is present, for all practical purposes the cyclopropyl rings can be considered as free rotors. The cyclopropyl rings destroy the cylindrical symmetry of the alkyne linkage, yet the interactions do not give rise to a significant barrier to rotation.

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Registry No.—Dicyclopropylacetylene, 27998-49-8.

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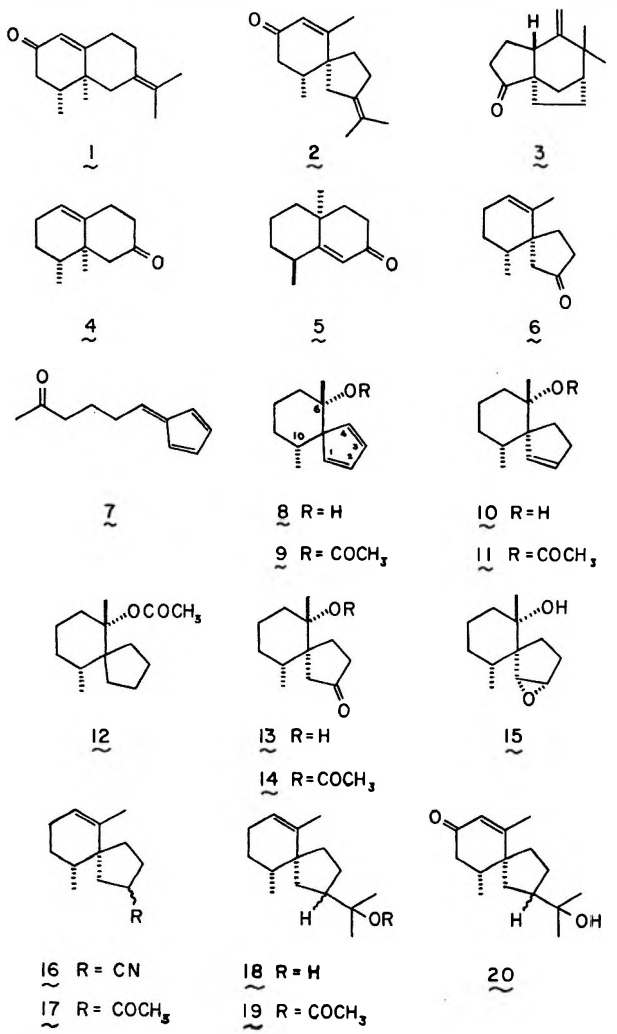
Spirovetivanes from Fulvenes

Summary: Spirovetivanes can be synthesized by adding lithium dimethylcuprate to fulvene **7**, in turn prepared from cyclopentadiene and 5-oxohexanal. No hydroazulene derivatives are formed. Diimide reduction of the diene **9** proceeds with high regiospecificity and the resulting olefin **11** can be transformed to the C_{12} ketone **6**, hinesol **18**, and β-vetivone **2**, all constituents of vetiver oil.

Sir: Commercial vetiver oil [*Vetiveria zizanioides* (L.) Nash] contains the sesquiterpenes α-vetivone (**1**),[1] β-vetivone (**2**),[2] the nor sesquiterpene khusimone (**3**),[3] and minor amounts of the biogenetically related C_{12} compounds **4**,[4] **5**,[4] and **6**.[5] Since the spiroketone **6** appears to play a significant role in the reconstitution of the essential oil[5] we have developed an efficient total synthesis from materials other than β-vetivone (**2**).[6,19]



Condensation of 5-oxohexanal[7] with cyclopentadiene in the presence of diethylamine[8] gave fulvene **7** (uv max (C_2H_5OH) 255 nm, ε 1810) in 70% yield. We reasoned that lithium dimethylcuprate[9] should add to this fulvene to produce the derived lithium cyclopentadienide which should combine with the carbonyl group to form a cyclohexanol in preference to a cycloheptanol. In practice the reaction, when performed in ether solution at −20 °C, produced a single carbinol **8** (80–90%). Efforts to regioselectively reduce one of the two double bonds in **8** or **9** [prepared with CH_3COCl in $C_6H_5N(CH_3)_2$ at 50 °C for 6 h in 78% yield] over a variety of catalysts failed. Similarly, monoepoxides prepared by different methods turned out to be mixtures. Surprisingly, reduction with diimide[10] (hydrazine, 30% hydrogen peroxide, ethanol, 20 °C, 3 days) yielded a single dihydro compound, **11**, mp 35–37 °C (57% after recrystallization) and 5–10% liquid tetrahydroacetate **12**. Dehydration of the alcohols **8**, **10**, and **13** under kinetically controlled conditions afforded mostly exocyclic olefins demanding the presence of an equatorial hydroxy group.[11] The methyl group at C-10 is equatorial also because the chemical shift of its protons depends on the presence or absence of double bonds in the cyclopentane ring (δ 0.78 in **9**, 0.77 in **11**, and 0.87 in **12**), while the singlet caused by the axial C-6 methyl group does not (δ 1.53). Preferential reduction of the syn double bond in the reduction of 7-acetoxynorbornadiene has been attributed to an interaction of diimide and acetoxy group.[12] The much more subtle effect causing the rate enhancement in the reduction of only one of the two double bonds in the diene **9** will only find an explanation after the acetoxy–diimide interaction has been specified in precise structural terms.[13]

Transformation of the olefins **10** and **11** to the ketone **6** was accomplished in two ways. Treatment of the acetate **11** with diborane followed by oxidation with sodium dichromate[14] gave the acetoxy ketone **14**. Pyrolysis at 450 °C, followed by equilibration of endo and exocyclic olefins with *p*-toluenesulfonic acid in boiling benzene, yielded the more stable endocyclic olefin **6** [ir ($CHCl_3$) 1740 cm^{-1}] containing <10% exocyclic isomer (35% from **11**). Spectral and chromatographic properties of racemic ketone **6** agreed with those of optically active material.[15] In an alternate synthesis acetate **11** was hydrolyzed to the alcohol **10** (sodium hydroxide, ethanol, reflux) (95%) which on epoxidation with peracetic acid gave the epoxide **15** (95%) assumed to have the α configuration. Butyllithium in ether at room temperature caused isomerization to the ketone **13** (72%) which was dehydrated to olefin **6** in refluxing benzene containing *p*-toluenesulfonic acid (90%).

To complete syntheses of the C_{15} spirovetivanes, ketone **6** was converted to a mixture of epimeric nitriles **16** in 75% yield with the aid of *p*-toluenesulfonyl isocyanide.[16] Condensation with methylmagnesium bromide provided the methyl ketones **17** (80%) which on treatment with methyllithium gave a 3:2 mixture of epimeric carbinols **18** (90%). Infrared and proton magnetic resonance spectra of the acetate **19** derived from the major epimer with α-oriented hydroxypropyl group were identical with those of authentic hinesol acetate (**19**).[17] Oxidation of the mixture of diastereomeric alcohols **18** with chromium trioxide–pyridine[18] afforded a crystalline mixture of epimeric α,β-unsaturated ketones **20**, mp 114–118 °C (70%). Dehydration with *p*-toluenesulfonic acid in hot benzene furnished racemic β-vetivone (**2**), mp 46–48 °C, identical with natural material.[15] If the dehydration is monitored properly by thin layer chromatography the yield of pure β-vetivone (**2**) is 80%.

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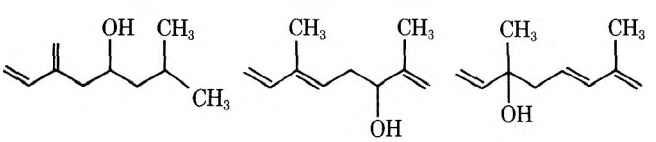
Terpene Synthesis via Pentadienyl Anions

Summary: The introduction of the terminal isoprenoid 1,3-diene unit using pentadienyllithiums is illustrated by the synthesis of monoterpenes from Ho-leaf oil and *Ledum palustre* oil.

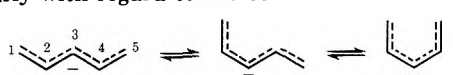
Sir: The formation of terpenes by head-to-tail linking of isoprene units has long been an objective of organic synthesis.[1] Although 1,5-dienes are more common among acyclic terpenes,[2] terpenoids with terminal isoprene residues present as 1,3-dienes of three types occur in nature. For example, tagetol[3] (**1**) is a sex attractant of *Ips confusus*, compound **2**[4] is a volatile constituent of *Ledum palustre* essential oil, and hotrienol[5] (**3**) is a component of Japanese Ho-leaf oil.



1 **2** **3**

We have recently reported[6] a general method for the introduction of terminal isoprenoid 1,3-dienes of type **1**. We now report a convenient method for the stereoselective production of isoprenoid (*E*)-1,3-dienes of the two remaining types.

Pentadienyl anions have been studied for some time,[7] particularly with regard to the conformations in eq 1. The



(1)

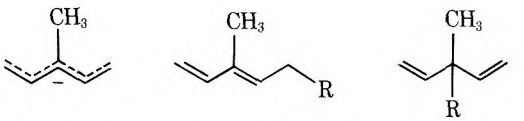
W sickle U

Table I. Reaction of 4 with Electrophiles at 0 °C

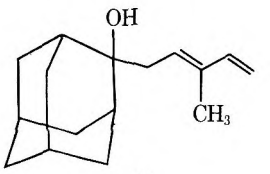
Entry	Electrophile	% 5	% 6
1	H_2O	96[a]	4
2	Adamantanone	75[b]	0
3	Methacrolein	65[b,c]	0
4	$CH_2{=}C(CH_3)(CH_2)_2CHO$	40[b]	60
5	$CH_3(CH_2)_5CHO$	38[b]	48
6	PhCHO	70[b]	30
7	$CH_3(CH_2)_4CH_2I$	38[d]	54
8	$CH_3(CH_2)_4CH_2I$	58[d,e]	34
9	Cyclohexene oxide	28[b]	72

[a] Reference 8. [b] Isolated yields. [c] +9% compound 8. [d] GC yield. [e] With $CuBr{\cdot}SMe_2$ (−78 °C).

three planar conformations, W, sickle, an U have been used to rationalize the sites of protonation in various derivatives. In general the W conformer protonates at C-1 and the U conformer at C-3 (the sickle form is intermediate). A recent ^{13}C NMR determination[8] indicated that 3-methylpentadienyllithium **4** exists almost exclusively as the W form from −80 to +40 °C. Thus protonation of 3-methylpentadienyllithium (**4**) gives 96% **5** (R = H, 95% *E*) and 4% **6** (R = H).

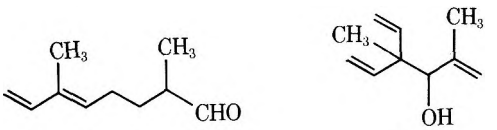


4 **5** **6**



7

Reaction of anion **4** with adamantanone gave **7**[9] (mp 59–61 °C) as the exclusive product (75% yield, >96% *E*). The pentadienyl anion **4** consequently gives us a convenient method for the introduction of the terminal 1,3-diene of type **2**. Reaction of **4** with methacrolein gives the monoterpene **2** in 65% yield. Interestingly, the only other product, isolated in 9% yield, was the conjugate addition product **8** (99% *E*). Since the uncatalyzed 1,4 addition of an organolithium is rather unusual we felt that the copper catalyzed reaction might be very good. Surprisingly, with **4** and 1 equiv of CuI (THF, −78 °C), compound **8** was formed in only 30% yield and the 1,2 adduct **9** *at*



8 **9**

the 3 position was isolated in 25% yield![10] The scope of the reaction of **4** with various electrophiles (Table I) indicates that some exploratory work must be done in order to find optimal conditions for 1,3-diene production.[11]

The synthesis of hotrienol **3**, the last type of terpenoid 1,3-diene, was achieved using 2-methylpentadienyllithium **10**. Compound **10** in contrast to **4** exists as a mixture of con-

10 **11**

formers[7] and consequently yields about a 1:1 mixture of hotrienol 3 and compound 11 on reaction with methyl vinyl ketone. Hotrienol can be isolated by chromatography in 35% yield.[9] This one-step synthesis of hotrienol (3) compares favorably with the published[12] synthesis.

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(10) Compound **9** was never observed in the uncatalyzed reaction, and compound **2** was not detected in the catalyzed reaction. In the presence of $CuBr\text{-}S(CH_3)_2$ only the normal 1,4 adduct **8** is obtained; thus, the origin of compound 9 may involve a RCu species.
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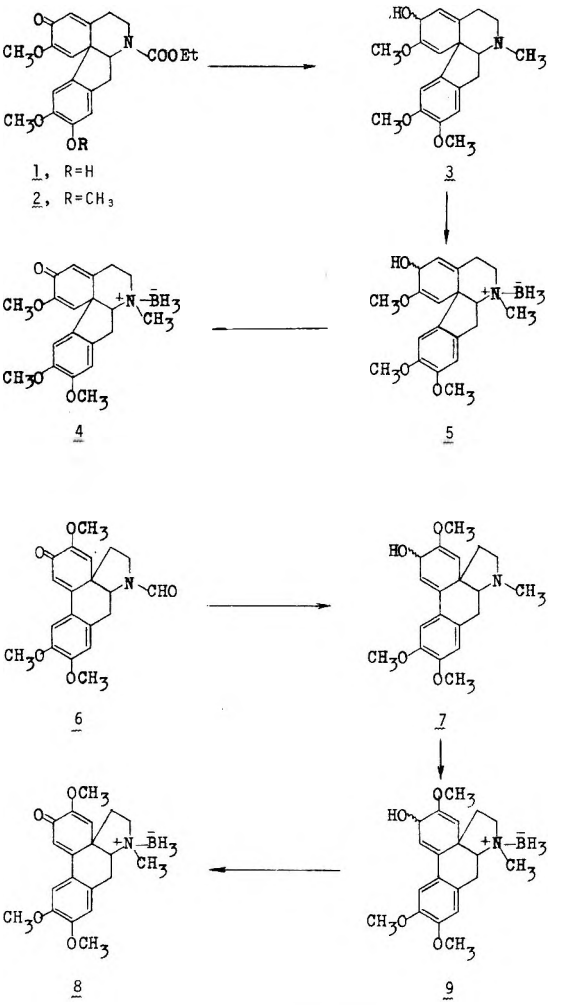
The Synthesis and Chemistry of Elusive Spirodienone Alkaloid Precursors[1]

Summary: *N*-Methylproerythrinadienone and *N*-methylneospirinedienone derivatives, elusive spirodienone intermediates, have been synthesized as borane complexes and shown to be genuine precursors of aporphine and dibenzazonine alkaloids.

Sir: In earlier studies we have shown that spirodienones derived from benzylisoquinolines play important roles in biomimetic syntheses of alkaloids.[2-6] Thus morphinandienones are effective in vitro precursors of aporphine and dibenzazonine alkaloids, and acid-catalyzed rearrangement of morphinandienones to aporphines and dibenzazonines may proceed via the intermediacy of proerythrinadienones and neospirinedienones, respectively.[4,5] The proerythrinadienones have also been proposed as biosynthetic precursors of aporphine[7] and *Erythrina* alkaloids.[8] Attempts to synthesize such spirodienones have failed when the nitrogen atoms were unprotected[8,9] and attempted transformation of *N*-acylproerythrinadienones to aporphines and dibenzazonines has also been unsuccessful.[10] We describe herein the synthesis of the borane complexes[11] of *N*-methylproerythrinadienone (**4**) and *N*-methylneospirinedienone (**8**) derivatives and the first reported laboratory transformation of a proerythrinadienone to an aporphine. In addition, the temperature dependence of rearrangements of these spirodienones is described.

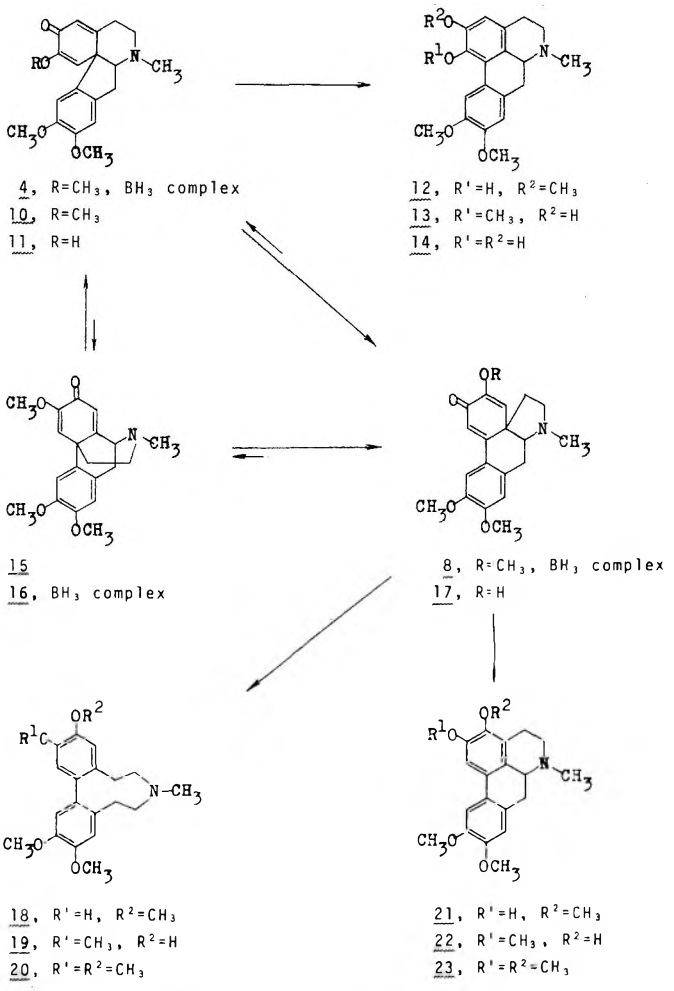
Methylation of (±)-*N*-ethoxycarbonylproerythrinadienone (**1**)[12] with $CH_3I\text{-}K_2CO_3$ in acetone gave **2** (84%, mp 87–89 °C).[13] Reduction of **2** with $LiAlH_4$ in THF gave a mixture of the epimeric dienols (**3**, 73%) which, upon treatment with BH_3–THF followed by MnO_2 oxidation, yielded the (±)-*N*-methylproerythrinadienone–borane complex (**4**, 51% from **3**): mp 135–137 °C ($CHCl_3$–Et_2O); uv λ_{max}^{EtOH}(log ϵ) 286 (3.87), 244 (4.27) nm; ir ($CHCl_3$) 4.21 (B–H), 6.01, 6.11, 6.21 (cyclohexadienone C=O) μ; NMR ($CDCl_3$) δ 6.78, 6.41, 6.16, 5.82 (each s, 4 H, aromatic and olefinic H), 3.88, 3.73, 3.67 (each s, 9 H, 3-OCH_3), 2.71 (s, 3 H, –NCH_3); mass spectrum *m/e* (rel %) 355 (6, M^+), 341 (100), 311 (15). Similarly, (±)-*N*-methylneospirinedienone–borane complex (**8**) was prepared by reduction of (±)-*N*-formylneospirinedienone (**6**)[2] with $LiAlH_4$ to the epimeric dienols (**7**, 72%), treatment of **7** with BH_3–THF to give **9**, and oxidation of **9** with MnO_2 to **8** (47% from **7**): mp



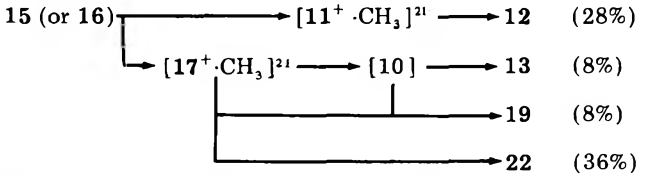
156–158 °C ($CHCl_3$–Et_2O); uv λ_{max}^{EtOH} (log ϵ) 356 (3.92), 290 (4.09), 262 (4.15), 234 (sh, 4.29) nm; ir ($CHCl_3$) 4.20 (B–H), 6.01, 6.10, 6.22 (cyclohexadienone C=O) μ; NMR ($CDCl_3$) δ 6.96, 6.74, 6.34, 6.30 (each s, 4 H, aromatic and olefinic H), 3.92 (s, 6 H, 2-OCH_3), 3.76 (s, 3 H, 1-OCH_3), 2.54 (s, 3 H, –NCH_3); mass spectrum *m/e* (rel %) 355 (7, M^+), 341 (100), 326 (70), 310 (28), 298 (59). Thus the spirodienones postulated earlier[4] as intermediates in the acid-catalyzed rearrangements of morphinandienones to aporphines and dibenzazonines were isolated as borane complexes.

Heating the (±)-*N*-methylproerythrinadienone–borane complex (**4**) in concentrated hydrochloric acid on a steam bath

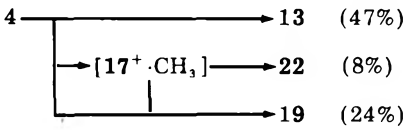
for 1 h gave (±)-predicentrine (**13**) as the hydrochloride (mp 215–217 °C dec[14]) in 75% yield, whereas treatment of **4** with BF_3–Et_2O at room temperature followed by hydrogenation over Pt in methanol afforded (±)-predicentrine (**13**) and erybidine [**19**, mp 176–177 °C (lit.[15] 178–180 °C)] in 44 and 35% yield, respectively. These results represent the first reported laboratory conversions of a proerythrinadienone to an aporphine and support the proposed intermediacy of proerythrinadienones in the acid-catalyzed rearrangement of morphinandienones to aporphines (cf. **15** → [**11**] → **14**)[4] and in the biosynthesis of aporphines in *Dicentra eximia*.[7] When **4** was treated with 1 N NaOH in MeOH followed by $NaBH_4$ reduction, erybidine (**19**) was again obtained (76%). This conversion parallels the biomimetic synthesis of a key *Erythrina* alkaloid precursor[6] and supports the intermediacy of proerythrinadienones in the biosynthesis of *Erythrina* alkaloids in *Erythrina crista galli*.[8] Treatment of **8** with either BF_3–Et_2O at room temperature followed by hydrogenation over Pt in methanol or 1 *N* NaOH in methanol followed by $NaBH_4$ reduction gave **18**[16] (75%, mp 140–142 °C), an isomer of erybidine (**19**). This result supports the proposed intermediacy of *N*-methylneospirinedienones in the acid-catalyzed rearrangement of morphinadienones to dibenzazonines[4,5] and in the $LiAlH_4$ reduction of *N*-formylneospirinedienone dimethyl ketal to *O*-methylerybidine (**20**).[2]



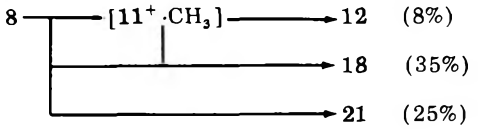
To investigate the temperature dependence of rearrangements of these spirodienones, (±)-*O*-methylflavinantine (**15**)[4,17] was treated with BF_3–Et_2O in benzene under reflux, followed by hydrogenation over Pt in methanol, whereupon four products were obtained: (±)-thalicmidine [**12**, 28%, mp 192–193 °C dec (lit.[18] 192–194 °C dec)], (±)-predicentrine (**13**, 8%), erybidine (**19**, 8%), and an unnatural aporphine, (±)-3-hydroxy-2,9,10-trimethoxyaporphine[19] (**22**, 36%, mp 214–215 °C). At elevated temperature the reaction may thus proceed as shown in the following scheme:



Treatment of (±)-*N*-methylproerythrinadienone–borane complex (**4**) under the same conditions gave (±)-predicentrine (**13**, 47%), erybidine (**19**, 24%), and (±)-3-hydroxy-2,9,10-trimethoxyaporphine (**22**, 8%), presumably via the following scheme:



Finally, the (±)-*N*-methylneospirinedienone–borane complex (**8**), when subjected to the same conditions, yielded (±)-thalicmidine (**12**, 8%), erybidine isomer **18** (35%), and another unnatural aporphine, (±)-2-hydroxy-3,9,10-trimethoxyaporphine[19] (**21**, 25%, mp 210–212 °C dec), presumably via the following scheme:



These observations suggest that the three spirodienones may exist in equilibrium in acidic medium at elevated temperature. It is noteworthy that the conversions from morphinandienones and neospirinedienones to proerythrinadienones and from neospirinedienones to unnatural aporphines have been observed to occur solely at elevated temperature.

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(1) This investigation was supported by grants from the National Cancer Institute (CA-12059) and from Hoffmann-La Roche Inc.
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(4) S. M. Kupchan, and C.-K. Kim, *J. Am. Chem. Soc.*, **97**, 5623 (1975).
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(9) T. Kametani, K. Takahashi, T. Sugahara, M. Koizumi, and K. Fukumoto, *J. Chem. Soc. C*, 1032 (1971).
(10) T. Kametani, K. Takahashi, T. Honda, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.*, **20**, 1793 (1972).
(11) This unique blocking group was particularly convenient because of its sensitivity toward both acids and bases [cf. M. A. Schwartz, B. F. Rose, and B. Vishnuvajjala, *J. Am. Chem. Soc.*, **95**, 612 (1973)].
(12) S. M. Kupchan, C.-K. Kim, and K. Miyano, *J. Chem. Soc., Chem. Commun.*, 91 (1976).
(13) All new compounds were characterized by concordant analytical and spectral data. The structural formulas containing asymmetric atoms refer to racemic mixtures.
(14) T. Kametani, T. Sugahara, H. Yagi, K. Fukumoto, B. R. Pai, and R. Charubala, *J. Chem. Soc. C*, 624 (1970).
(15) K. Ito, H. Furukawa, and H. Tanaka, *Chem. Pharm. Bull.*, **19**, 1509 (1971).
(16) The structure of **18** was confirmed by methylation with diazomethane. Mixture melting point, TLC, and uv, NMR, and mass spectra of the methylated product were identical with those of an authentic sample of *O*-methylerybidine (**20**).[2]
(17) To test whether borane complexes react in the same way as the corresponding free base, rearrangements of morphinandienone–borane complex **16**, prepared by treatment of **15** with BH_3–THF, were examined. Thus treatment of **16** with (a) concentrated hydrochloric acid on the steam bath for 90 min, (b) BF_3–Et_2O at room temperature for 26 h followed by hydrogenation over Pt in methanol, and (c) BF_3–Et_2O in benzene under reflux for 1 h followed by hydrogenation over Pt in methanol gave (a) **14** (78%),

(b) **19** (83%), and (c) **12** (26%), **13** (7%), **19** (9%), and **22** (33%), respectively. These results confirmed the similarity of reactivity of the borane complex and the free base toward acid treatment.

(18) M. Shamma and W. A. Slusarchyk, *Tetrahedron*, **23**, 2563 (1967).
(19) Treatment of **22** or **21** with diazomethane gave (±)-2,3,9,10-tetramethoxyaporphine [**23**, mp 115.5–116 °C (lit.[20] mp 115.5–116.5 °C)].
(20) R. K. Callow, J. M. Gulland, and R. D. Haworth, *J. Chem. Soc.*, 658 (1929).
(21) The methoxonium ions in which the methyl groups are attached to the carbonyl oxygens of **11** or **17** are represented by [11^{+}-CH_3] or [17^{+}-CH_3], respectively.

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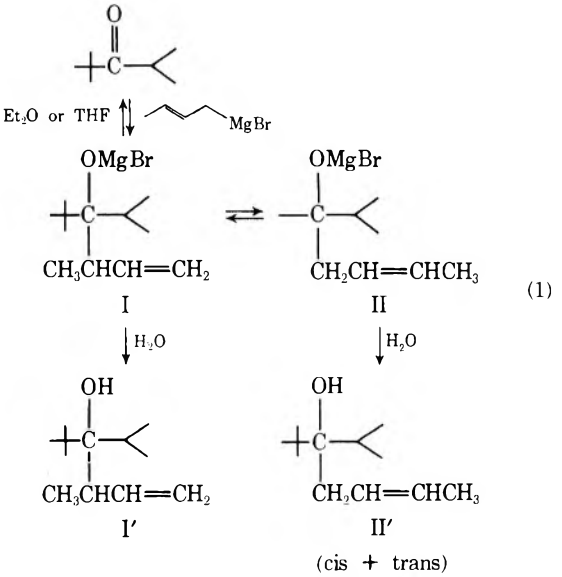
The First Documented Reversible Addition of Allylmagnesium Bromide to a Ketone

Summary: It has been shown for the first time that an *unsubstituted* allylic-type organometallic, allylmagnesium bromide, undergoes reversible additions to ketones forming magnesium salts of allylcarbinols and in the reverse step it is the allyl group which departs cleanly.

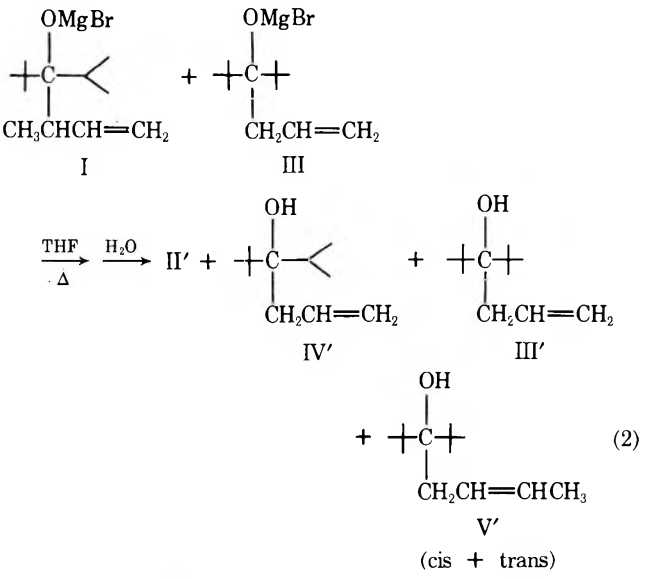
Sir: Previously we[1] reported that crotylmagnesium bromide reacts with *tert*-butyl isopropyl ketone to produce first α-methallylisopropyl-*tert*-butylcarbinol (kinetic product, I′) which then rearranges because of steric crowding to a cis–trans mixture of crotylisopropyl-*tert*-butylcarbinols (thermodynamic products, II′) (eq 1).



(1)

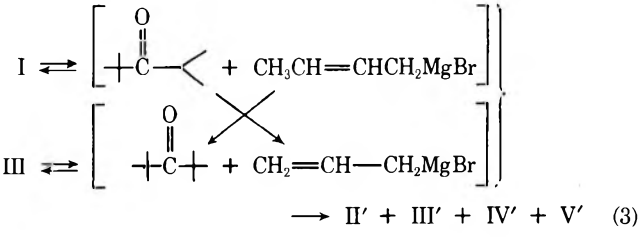
In recent years there have been several disclosures[2–6] of similar reversible additions to carbonyl-containing compounds by *substituted* allylic organometallics, but no one has reported that the parent allyl organometallic (e.g., allylmagnesium bromide) themselves undergo similar reversible additions. This is understandable since such reversibilities would lead to products identical with starting material and hence the reversibilities would go unnoticed.

We are hereby reporting the first documented reversibility of an unsubstituted *allyl* system derived from di-*tert*-butylallylcarbinol. The probe employed for detection of this otherwise disguised reaction was a crossover experiment in conjunction with a protonation reaction to trap the intermediates. The crossover experiment is illustrated by eq 2. The products



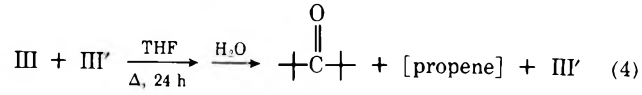
(2)

of the crossover experiment are very illuminating. It is clear that the allyl and butenyl groups have interchanged positions and that the alkoxide (I) rearranged at least in part to the crotyl system (II′). Likewise carbinol III′ but not I′ was detected in the products. The mechanism whereby alkoxides such as I are converted to isomers such as II has never been firmly established although several proposals have been put forth. Whatever the mechanism of these isomerizations might be, one can best accommodate the experimental facts depicted in eq 2 by concluding that *both* starting magnesium salts "come apart" during the course of the transformation. This regenerates the allyl and crotyl Grignard reagents as well as isopropyl *tert*-butyl ketone and di-*tert*-butyl ketone. These four entities then recombine to form the "scrambled" carbinols (eq 3).



(3)

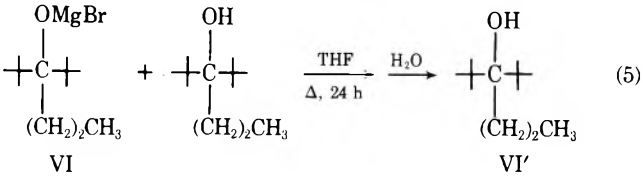
In order to provide further proof that compound III does indeed dissociate as depicted in eq 3, it was refluxed in THF in the presence of an equivalent amount of III′ which can act as a protonating agent. Equation 4 shows the results. The ratio



(4)

of di-*tert*-butyl ketone to recovered carbinol (III′) was 43:57 which is very close to the theoretical 50:50.

When the experiment shown in eq 4 was repeated under identical conditions except that *n*-propyl-di-*tert*-butylcarbinol and its corresponding bromomagnesium salt were used, only recovered carbinol and *no* di-*tert*-butyl ketone were produced (eq 5). The results of these protonation studies



(5)

confirm that, under the mild conditions used, allylic reversal is occurring and that this reversal *requires* a homoallylic species.

In earlier,[7] but related, work, some alkali metal salts of highly branched tertiary alcohols were cleaved thermally, but temperatures in the range of 200–300 °C were required. Significantly in none of these cases did the tertiary alcoholates contain an alkenyl group as in our examples. It is also noteworthy that the rate of *addition* of allylic-type organometallics to ketones is rapid[8] compared with that of other alkyl groups. Since it is now obvious that such additions are reversible, it is not surprising that in the reverse step it is the allylic group which is cleanly removed. Implications of these and related findings will be published later.

Acknowledgment. We wish to thank the National Science Foundation for its financial support of this work.

Supplementary Materials Available. The procedure for the preparation of all starting materials and the experimental details of the crossover study (total, 3 pages). Ordering information is given on any current masthead page.

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(7) H. D. Zook, J. March and D. F. Smith, *J. Am. Chem. Soc.*, **81**, 1617 (1959).
(8) R. A. Benkeser, *Synthesis*, **7**, 347 (1971).

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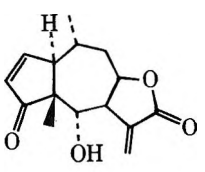
The Stereospecific Synthesis of α-Methylene-γ-butyrolactones of *trans*-1,3-Dihydroxycycloalkanes

Summary: The reactions of 1,1-diethoxy-2-propenyl cuprates with 3,4-epoxycycloalkenes have been found to be largely regiospecific and stereospecific; the product from 1,2 opening of 1,3-cycloheptadiene monoepoxide has been converted to the *trans*-hydroxy-*cis*-butyrolactone of cycloheptane.

Sir: Despite the plurality of synthetic methods[1] for the preparation of α-methylene-γ-butyrolactones fused to cycloalkanes, there is a scarcity of regiospecific and stereospecific methods for construction of α-methylene lactones of 1,3-diols.[2] We wish to report an efficient synthetic scheme for the conversion of cyclic allylic epoxides into the *trans*-hydroxy-*cis*-α-methylene-γ-butyrolactone system found in the antitumor natural product, helenalin (1). The related *cis*-hydroxy-*trans*-α-methylene-γ-butyrolactone found in euparotin (2) is also potentially accessible from the reactions described herein.



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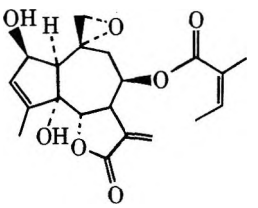
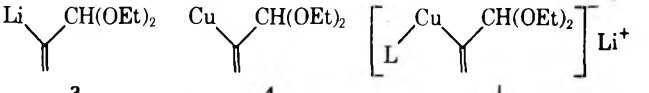


2

As part of our general interest in the synthesis of naturally occurring antitumor agents possessing the α-methylene lactone unit, we have investigated the reactions of various epoxides with organometallic synthons of an acrylate unit. In this paper we report the reactivity of several organocopper reagents (**4–7**)[3] and the corresponding lithio species (**3**),[4] de-



3 **4**

5, L = CH_2=$CCH(OEt)_2$
6, L = *t*-BuC≡C-
7, L = CN

rived from 2-bromo-3,3-diethoxypropene, with several simple epoxides and three activated epoxycycloalkenes.

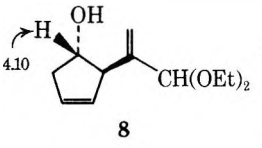
All of the organocopper reagents listed above were prepared from the isopropenyllithium derivative **3**. Copper reagents **5** and **6** have been previously described;[3] the reagent **4** was prepared from the reaction of **3** with 1 equiv of cuprous iodide in THF at −55 °C, while reagent **7** (L = CN) was prepared from cuprous cyanide and **3** in THF at −40 °C.[5]

When reagent **3** was treated with cyclohexene epoxide, propylene oxide, and styrene epoxide under a variety of reaction conditions, including the presence of salts such as anhydrous magnesium bromide, no detectable amounts of alcohol products were found. In the case of the reactive 1,3-cyclohexadiene monoepoxide and 1,3-cycloheptadiene monoepoxide, reagent **3** was once again ineffective, at temperatures up to −40 °C in THF or ether, in opening the epoxide ring.[6]

Previous studies involving the reactions of organocuprates with epoxides have largely focused on the reactions of dialkyl cuprates with simple epoxides and in some cases acyclic vinyl epoxides.[7] The most relevant work to this paper comes from investigations of Rickborn[8] and Weiland and Johnson[9] of 1,3-cyclohexadiene monoepoxide and dialkylcuprates. These workers found that both 1,2 and 1,4 additions of the cuprates occurred to about equal extent and that the stereochemistry of the products with dimethylcopper lithium was exclusively trans.

We have found that the organocopper reagents (**4–7**) undergo the expected 1,2 and 1,4 additions to the monoepoxides of cyclopentadiene, 1,3-cyclohexadiene, and 1,3-cycloheptadiene. More significantly from a synthetic standpoint, the regiospecificity of the addition can be altered to maximize the 1,2 product with trans stereochemistry. Maximum yields of total adducts from the cuprates (**5–7**) were obtained at −40 °C with 1.5–2 equiv of reagent. The effect of ether as the reaction solvent was significant in optimizing the ratio of 1,2 to 1,4 products. Furthermore, the mixed cyanocuprate **7** consistently gave the lowest yields of the adducts with the various unsaturated epoxides. The neutral copper(I) reagent **4** also seemed to be less reactive than reagents **5** and **6** and gave predominately the 1,4 regioisomer from 3,4-epoxycyclohexene. The yields and isomer ratios of the reaction products are summarized in Table I.

The structural assignments of the respective regioisomers were made on the basis of the diagnostic chemical shifts of the protons on carbons bearing the hydroxyl group in key compounds.[10] The regioisomers **8** and **9** from 3,4-epoxycyclo-



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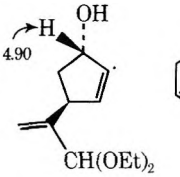

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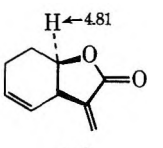


10[2]

Table I. Reactions of Organocopper Reagents (4–7) with 1,3-Cycloalkadiene Monoepoxides

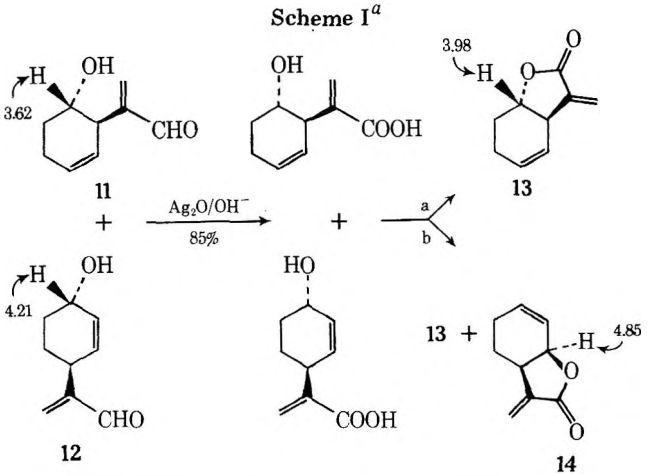
Epoxide	Products[a] [R = CH_2=CCH(OEt)$_2$]	Reagent[b]	% yield[c]	1,2/1,4 ratio[d] (solvent)
		5	87	2.5 (THF)
		6	80	2.0 (THF)
		7	43	1.0 (THF)
		4	71	0.6 (THF)
		5	94	1.5 (THF), 2.7 (Et_2O)
		6	72	1.5 (THF)
		7	50	0.7 (THF)
		4	58	2.7 (THF)
		5	98	2.9 (THF), 4.3 (Et_2O)
		6	70	2.3 (THF)
		7	0	

[a] All products listed in this table and their derivatives gave satisfactory (±0.2%) combustion analyses. Products were either isolated by preparative GLC (5% SE-30 on Chrom P; 5 ft × 0.25 in., vacuum distillation, HPLC, or preparative TLC. [b] With THF as the solvent, the reagents were formed at −40 °C and the reaction mixtures were kept at −40 °C for 5–6 h. When the reactions were carried out in anhydrous ether, the reagent 3 was formed with *tert*-butyllithium at −70 °C. [c] Yields were determined by NMR integration of key absorbances using an internal standard. In all cases, product mixtures after workup were shown to be >95% pure adduct by VPC analysis. [d] The isomer ratios of the cyclopentene epoxide and cyclohexene epoxide were based on NMR analysis of the corresponding aldehydes. The isomer ratio of the cycloheptene epoxide was obtained from NMR analysis of the 1,2 cyclic hemiacetal and 1,4-aldehyde derived from hydrolysis of the initial adducts.

pentene were easily distinguished by the large difference (0.8 ppm) in chemical shifts for the carbinol hydrogens and by decoupling experiments. The trans stereochemistry for **8** and **9** was assumed after both isomers failed to cyclize to the corresponding cyclic acetals or methylene lactones.

The trans stereochemistry was assigned to the initial adducts for 3,4-epoxycyclohexene and their respective hydrolysis products **11** and **12** on the basis of literature precedence for cuprate additions,[8,9] correlation of key NMR chemical shifts, and the chemical transformations outlined in Scheme I. Oxidation of a 1.5:1 mixture of **11** and **12** with silver(I) oxide in base produced the corresponding acrylic acid isomers in 85% yield. Treatment of the mixture of carboxylic acids with dicyclohexylcarbodiimide (DCC) in refluxing chloroform produced the *trans*-1,2-butyrolactone[11] **13** (mp 89–90 °C) which was spectroscopically different from the previously reported[2] cis isomer **10**. When the mixture of carboxylic acids was treated with a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene, the *trans*-lactone **13** was again isolated along with a new unsaturated *cis*-butyrolactone[12] **14**.

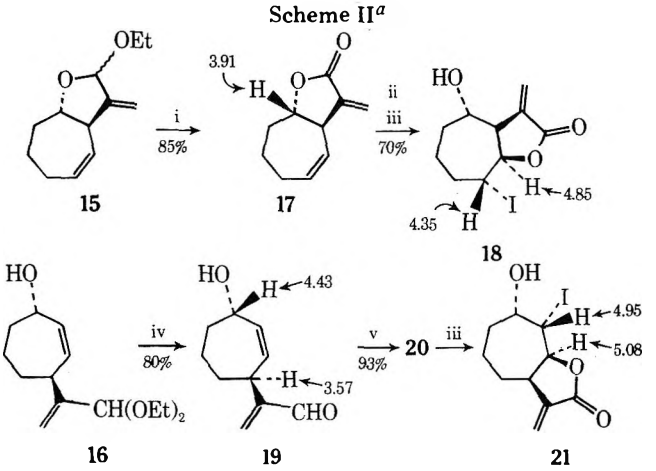
Scheme I[a]



[a] a: DCC, $CHCl_3$, reflux. b: *p*-TosOH, benzene, 13/14 ≅ 1.5.

Upon vacuum distillation of the product mixture from the reaction of 3,4-epoxycycloheptene, the 1,2 adduct cyclizes to the acetal **15** and is easily separated from the 1,4 adduct **16** by distillation.[13] Oxidation of the cyclic acetal **15** with Jones reagent under standard conditions resulted in a 75% yield[14] of crystalline *trans*-lactone[15] **17** (mp 74–75 °C). Conversion of **17** into the hydroxy-*cis*-lactone[15] **18** (mp 137.5–138.5 °C) was achieved in an overall yield of 70% as indicated in Scheme II.

Scheme II[a]



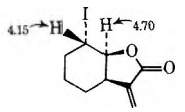
[a] i, Jones reagent at 0 °C. ii: 1 N NaOH. iii: pH 8–9, KI_3. iv: dilute HCl. v: Ag_2O in NaOH.

Hydrolysis of the 1,4 adduct **16** with dilute hydrochloric acid produced the aldehyde **19**, whose NMR spectrum most easily confirmed the 1,4-isomer assignment. Oxidation of **19** to the corresponding acid **20** proceeded in 93% yield, and acid **20** was converted to the iodolactone[16] **21** (mp 133–136 °C), in order to relate the stereochemistry of the free hydroxyl group to the lactone.

The high yield of the initial reaction of **5** with 3,4-epoxycycloheptene and the preponderence of the 1,2 regioisomer (80:20 mixture in ether) render this synthetic approach superior to any existing methodology for construction of α-methylene-γ-butyrolactones of trans 1,3 cyclic diols.

References and Notes

(1) P. A. Grieco, *Synthesis*, 67 (1975), and references therein.
(2) F. E. Ziegler, A. F. Marino, O. A. C. Petroff, and W. Studt, *Tetrahedron Lett.*, 2035 (1974).
(3) J. P. Marino and J. S. Farina, *Tetrahedron Lett.*, 3901 (1975).
(4) J. Ficini and J. C. Depezay, *Tetrahedron Lett.*, 4795 (1969).
(5) The upper limit for the thermal stability of reagents **3–6** has been estimated by us and others[4] to be approximately −40 °C. Reaction mixtures kept above −40 °C for any period of time darkened and the yields of products were diminished.
(6) The 3,4-epoxycyclohexene reaction with reagent **3** at −40 °C yielded about 7% 1,2 adduct. The reaction of **3** with 3,4-epoxycycloheptene failed to yield any adducts at −40 °C for 6–8 h.
(7) G. H. Posner, *Org. React.*, **22**, 253 (1975).
(8) B. Rickborn and J. Starosick, *J. Am. Chem. Soc.*, **93**, 3046 (1971).
(9) D. M. Wieland and C. R. Johnson, *J. Am. Chem. Soc.*, **93**, 3047 (1971).
(10) All of the chemical shifts cited here are given in ppm downfield from internal tetramethylsilane (60 MHz). The specific protons cited as well as the particular compounds were chosen because they were the most informative and definitive in making structural assignments. The multiplicities of the protons cited are not easily described without an actual spectrum but they are consistent with the assigned structures.
(11) The chemical shifts of the methine protons on carbons bearing the lactone oxygen in *cis*-α-methylene butyrolactone of cyclohexane and the corresponding trans isomer are δ 4.46 and 3.65 respectively [J. Marshall and N. Cohen, *J. Org. Chem.*, **30**, 3475 (1965)]. Also see ref 2 for spectral data for compound **10**.
(12) Lactone **14** was independently prepared by dehydrohalogenation of iodolactone i with DBN in benzene at room temperature. The preparation of i has been previously reported by us [J. P. Marino and D. M. Floyd, *J. Am. Chem. Soc.*, **96**, 7138 (1974)].



i

(13) Acetal **15** distilled between 95 and 100 °C (0.05 mmHg).
(14) Yields reported are isolated yields but they have not necessarily been maximized.
(15) The literature (see reference cited in 11) value for the chemical shifts of the lactone methines for *cis*- and *trans*-α-methylene-γ-butyrolactones of the cycloheptane series are δ 4.72 and 4.10, respectively. The absorptions that we have observed for the *trans*-lactone **17** (3.91) and the *cis*-lactone **18** (4.85) are most consistent for the assignments made.
(16) The 60-MHz NMR spectrum of **21** clearly showed coupling constants and chemical shifts for all of the methine hydrogens which were most consistent for the stereochemistry shown. Iodolactone **21** also failed to give an epoxide when treated under basic conditions. The preparation of **21** and analysis of its NMR spectrum were carried out by D. M. Floyd in this laboratory and full details will be published in a full paper.

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Allylic Substitutions with Retention of Stereochemistry

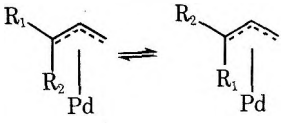
Summary: The "net SN2 displacements" of allylic acetates catalyzed by palladium proceed with complete retention of configuration at the carbon undergoing displacement and without loss of olefin geometry in a trisubstituted double bond.

Sir: The ability to perform displacements with inversion of configuration constitutes one of the most fundamental synthetic reactions in organic chemistry. Alkylations utilizing allylic halides, allylic sulfonate esters, etc., suffer from their high reactivity and consequently make stereochemical control difficult. With cyclohexenyl derivatives, the problems are further confounded by a tendency toward elimination reactions competing with the desired substitution reaction. The use of palladium-catalyzed allylic alkylations,[1,2] which allows use of the configurationally stable and easily handled allylic acetates, overcomes these limitations. Furthermore, these processes proceed with a net retention of configuration in contrast to the usual inversion which is observed in normal alkylations. Surprisingly, even though these reactions presumably involve π-allylpalladium intermediates[3] the stereochemistry of a trisubstituted double bond is retained in the alkylations.

In a previous paper, we suggested that the "net SN2 displacement" catalyzed by palladium(0) complexes proceeded with retention of configuration.[2] In order to establish this point unambiguously, we examined the alkylations of the cis (**1**) and trans (**2**) isomers of 3-acetoxy-5-carbomethoxycyclohexene[4] (see Scheme I). The cis isomer **1** is available by the methanolysis and acetylation of lactone **3**,[5] whereas the trans isomer **2** is available by acetylation of the hydroxy ester which, in turn, was isolated from a cis-trans mixture[6] by selective lactonization of the cis isomer. Whereas **1** was isomerically pure, VPC analysis[7a] of **2** indicated contamination to the extent of 7% by **1**.

Alkylation of **1** with the sodium salt of dimethyl malonate [catalytic amount of $(Ph_3P)_4Pd$, Ph_3P, THF; reflux; 92% yield] gave a single product **4**[4] which was assigned the cis stereochemistry.[8] At 270 MHz, the requisite coupling constants could be determined—$J_{AD} = J_{BD} = J_{CD} = 12.5$ Hz, $J_{BC} = 6.0$, $J_{AC} \sim 5$ Hz—which clearly indicate that both H_A and H_B are pseudoaxial. Alkylation of **2** under identical conditions gave **5**[4] (80% yield) which VPC analysis[7b] indicated was contaminated by **4** to the same extent (7%) that **2** was contaminated by **1**. The trans stereochemistry was indicated by the coupling constants obtainable at 270 MHz—$J_{AC} = 5.7$, $J_{AD} = 4$, $J_{BC} = 10$, $J_{BD} = 4$, $J_{CD} = 13.5$ Hz—which clearly suggest that H_A is pseudoequatorial and H_B is pseudoaxial. The assignment is further confirmed by the base-catalyzed isomerization [$KOC(CH_3)_3$, CH_3OH, reflux] of the less stable trans isomer **5** to the more stable cis isomer **4**. Both isomers were decarbomethoxylated[4] [$(CH_3)_4NOAc$, HMPA, 100 °C, 75% yield] without loss of configurational purity. Compounds of this type have been utilized as intermediates to ibogamine.[9] *Thus, within experimental error, these "net SN2 displacements" of allylic acetates proceed with complete retention of configuration at the carbon undergoing displacement.* Furthermore, no evidence for elimination competing with substitution is seen.

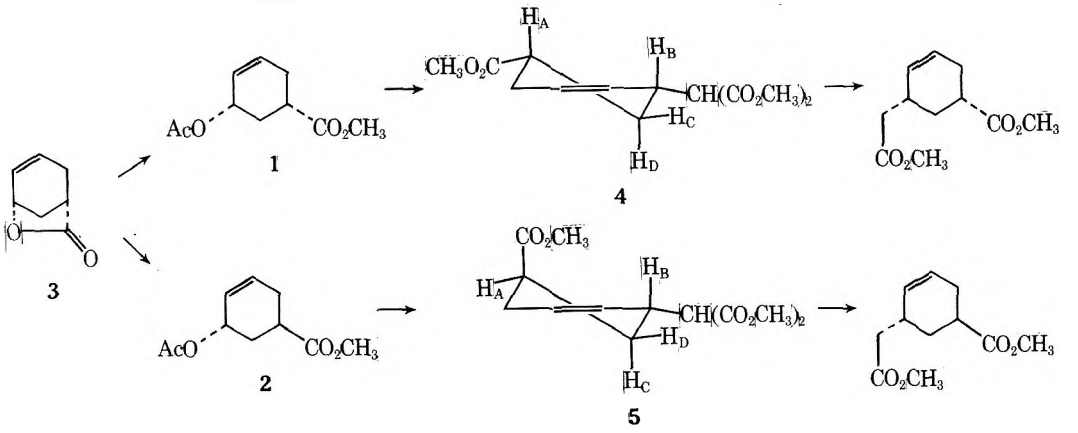
The question of the stereochemical integrity of the double bond in these reactions is crucial for their applications in synthesis. The well-known isomerization of π-allylpalladium complexes[10] makes interconversions of olefin isomers highly



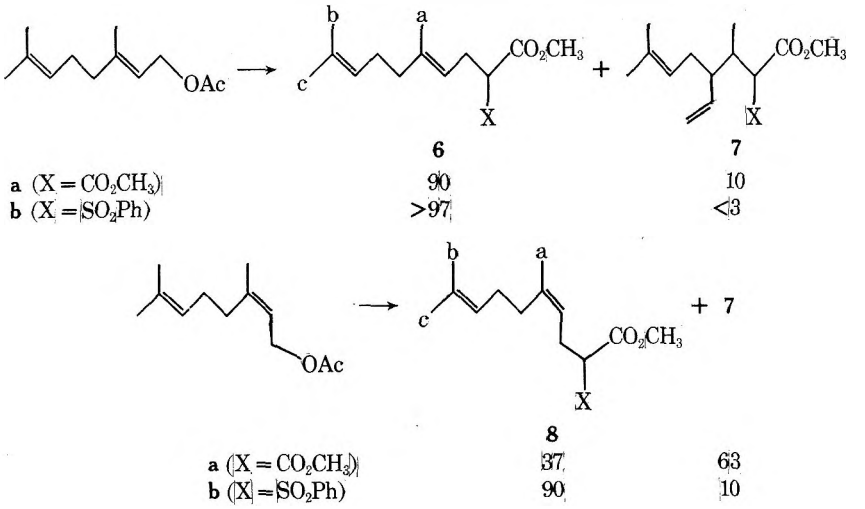
likely. Thus, to probe this question, alkylation of geranyl and neryl acetate was examined (see Scheme II). Alkylation of geranyl acetate with the sodium salt of either dimethyl malonate or methyl phenylsulfonylacetate under conditions identical with the above led to the product of substitution at the primary carbon, i.e., **6a**[4] and **6b**,[4] with complete retention of olefin geometry (VPC[7c] and NMR analysis) in 84–92% isolated yield. The *E* stereochemistry was confirmed by the ^{13}C NMR spectrum which showed a high field absorption for C_a compared (**6a**, δ_{C_a} 15.97, δ_{C_b} 17.63, δ_{C_c} 25.52; **6b**, δ_{C_a} 15.84, δ_{C_b} 17.40, δ_{C_c} 25.39) with the absorption for this methyl carbon in the *Z* isomer (vide infra). Unlike π-allylpalladium complexes from methylenecyclohexanes,[11] this alkylation reaction was insensitive to the nature of the phosphine present. On the other hand, it did show a sensitivity to the nature of the anion in which the sulfonyl anion led to attack only at the primary carbon atom.

Neryl acetate showed an even greater sensitivity to the nature of the anion. Alkylation under the usual conditions

Scheme I. Alkylation of *cis*- and *trans*-3-Acetoxy-5-carbomethoxycyclohexene



Scheme II. Alkylation of Geranyl and Neryl Acetate



	6	7
a (X = CO_2CH_3)	90	10
b (X = SO_2Ph)	>97	<3

	8	
a (X = CO_2CH_3)	37	63
b (X = SO_2Ph)	90	10

gave 7[4] and 8[4] in 74–78% isolated yield. As in the above case, the stereochemistry of the internal olefin derived from attack at the terminal carbon was exclusively *Z* (VPC[7c] and NMR analysis) as indicated by the ^{13}C NMR spectrum (**8a**, δ_{C_a} 23.33, δ_{C_b} 17.53, δ_{C_c} 25.52; **8b**, δ_{C_a} 23.12, δ_{C_b} 17.40, δ_{C_c} 25.32). In contrast to the geranyl case, the major product of the alkylation with malonate was attack at the tertiary carbon atom, whereas switching to the anion of the sulfonyl acetate gave a high regioselectivity for attack at the primary carbon atom.

The completely different product distribution clearly attests to the fact that the alkylation reaction is much faster than the syn–anti isomerization of the π-allylpalladium complexes. Thus, palladium-catalyzed allylic alkylations are kinetically controlled processes. As a result of this fact, stereochemistry is completely retained at both the carbon undergoing substitution and the trisubstituted double bond—obviously of tremendous importance in the application of these processes in syntheses.

Acknowledgment. We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation, and the National Institutes of Health for their support of our programs.

References and Notes

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(2) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **98**, 630 (1976).
(3) While explanations involving σ complexes as intermediates can be invoked, these do not account for the identical product mixtures seen for regioisomeric allylic acetates nor for the reactivity order 1-(1′-acetoxyethyl)cyclopentene > 1-(1′-acetoxyethyl)cycloheptene ≫ 1-(1′-acetoxyethyl)-cyclohexene. The latter parallels the trends observed for palladium-catalyzed carbonylations of olefins [see D. E. James and J. K. Stille, *J. Am. Chem. Soc.*, **98**, 1810 (1976).
(4) All new compounds have been fully characterized by spectral means and elemental composition.
(5) M. Kato, M. Kageyma, R. Tanaka, K. Kuwahara, and A. Yoshikoshi, *J. Org. Chem.*, **40**, 1932 (1975).
(6) A 1:1 mixture of *cis*- and *trans*-3-acetoxy-5-carbomethoxycyclohexenes was obtained by solvolysis of lactone **3** in glacial acetic acid. For easy separation via selective lactonization of *cis*-3-hydroxy-5-carbomethoxy-cyclohexene, the acetate mixture was subjected to methanolysis.
(7) (a) Column: 2.44 m × 0.64 cm 10% UCON polar on 60/80 mesh Chromosorb W at a column temperature of 135 °C. (b) Column: 2.44 m × 0.64 cm 10% XE-60 on 60/80 mesh Chromosorb W at a column temperature of 175 °C. (c) Same as column b but with a column temperature of 155 °C.
(8) In a typical experimental procedure, 229.5 mg (1.27 mmol) of geranyl acetate, 30.4 mg (0.116 mmol) of triphenylphosphine, and 48 mg (0.04 mmol) of tetrakis(triphenylphosphinepalladium) in 2 ml of dry THF were stirred for 15 min. A solution of the sodium salt of methyl phenylsulfonylacetate in 8 ml of dry THF, generated from 948 mg (4.42 mmol) of methyl phenylsulfonylacetate and 168.5 mg of sodium hydride (57% mineral oil dispersion, 4.0 mmol), was added all at once and the resultant mixture refluxed 36 h. The reaction was partitioned between ether and water, and the water layer extracted with additional ether. After drying and evaporation of the solvent in vacuo, the oil was subjected to chromatographic purification on silica gel (2.5:1 hexane–ethyl acetate) to give 345.1 mg (84%) of pure methyl 5,9-dimethyl-2-phenylsulfonyldeca-(*E*)-4,8-diene.
(9) M. E. Kuehne, J. E. Saavedra, and P. J. Reider, Abstracts of the First Chemical Congress of the North American Continent, Mexico City, Mexico, 1975, Orga. 126.
(10) M. Oslinger and J. Powell, *Can. J. Chem.*, **51**, 274 (1973); J. W. Faller, M. T. Tully, and K. J. Laffey, *J. Organometal. Chem.*, **37**, 193 (1972); D. L. Tibbetts and T. L. Brown, *J. Am. Chem. Soc.*, **92**, 3031 (1970); P. W. N. M. van Leeuwen and A. P. Praat, *Chem. Commun.*, 365 (1970); K. Vrieze, A. P. Praat, and P. Cossee, *J. Organometal. Chem.*, **12**, 533 (1968).
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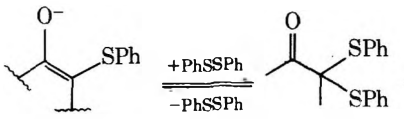
Secosulfenylation of Cyclobutanones

Summary: Treatment of cyclobutanones with sodium methoxide and diphenyl disulfide in refluxing methanol leads to in situ bissulfenylation and ring cleavage.

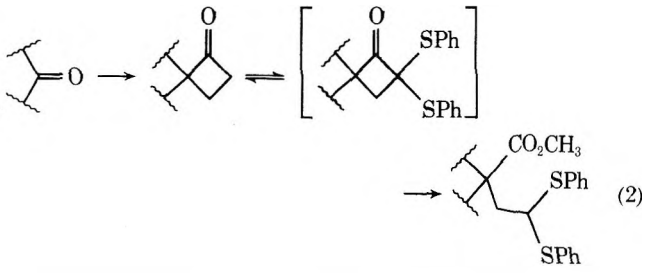
Sir: The increasing number of methods that make cyclobutanones readily available from olefins[1] and carbonyl[2,3] partners enhances the utility of these compounds as synthetic intermediates in the creation of carbon skeletons.[4] Our interest in the replacement of the C–O bonds of a carbonyl group with C–C bonds via cyclobutanone annelation depends critically on the facility of the ring cleavage. While a number of methods exist to achieve a geminal alkylation, all of these are multistep.[5] We wish to report a new single-step chemospecific process that has the added advantage of introducing the acetaldehyde unit masked as a thioacetal.

The procedure evolved from our study of the sulfenylation of ketones[6] in which we found that the enolate of a β-keto sulfide is sulfenylated by diphenyl disulfide but that the byproduct, phenylthiolate, reverses the reaction and the equilibrium represented by eq 1, lies to the left. If, however, the



(1)

product is irreversibly removed, the reaction can be driven to the right. The use of diphenyl disulfide rather than a more reactive sulfenylating agent is necessary to avoid decomposition of the sulfenylating agent under the reaction conditions and to maintain the equilibrium represented by eq 1. Since we had shown that an α,α-bissulfenylated cyclobutanone is readily cleaved by methoxide ion[5b,7] we suspected that we could drive the above equilibrium to the right by ring cleavage in such cases. Equation 2 summarizes the overall sequence and Table I summarizes the specific examples.

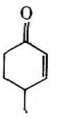
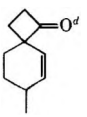
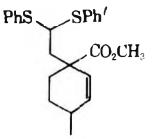
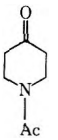
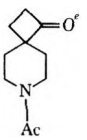
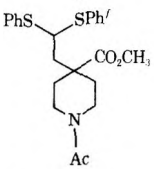
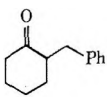
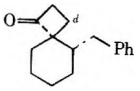
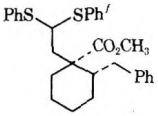
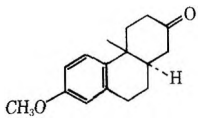
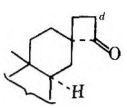
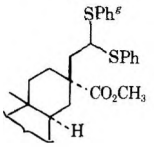


(2)

Typically, the reaction is performed by treating 1 equiv of cyclobutanone with ~3–4 equiv of diphenyl disulfide in methanol containing 3–4 equiv of sodium methoxide at reflux.[8] While the reactions are normally slow (~5 days for completion) at the concentrations utilized (0.1 M in cyclobutanone), they are free of side reactions and generate the product in high purity. The products are characterized by ir bands at ~1730, 1260, 1230, and 1020 cm^{-1} for the ester and NMR absorptions at δ ~3.6 (s) for CO_2CH_3 and 4.2 (t, $J \sim 6$ Hz) for $-CH(SPh)_2$. In the case of compound **1**, it was further characterized by transacetalization (iodine, methanol, reflux) to the methyl acetal which had been previously prepared by an independent route.

The chemospecificity of this net oxidative cleavage is underscored by entries 1, 2, and 4. Particularly noteworthy is the inapplicability of the bromination–ring cleavage approach in the case of entries 1 and 4. The advantage of this approach stems from the versatility that phenyl thioacetals have in synthesis which includes their alkylation,[9] elimination to enol thioethers,[10] and desulfurization. The further advantages of this approach are highlighted by entries 3 and 4 which point out the stereocontrol of this geminal alkylation. Since the spiroannelation is virtually completely stereoselective, so is the overall process.[2] Thus, the combination of spiroannelation and secosulfenylation constitutes a highly efficient two-stage approach to geminal alkylation. The requirement for relatively high ring strain for success for this procedure is illustrated by

Table I. Geminal Alkylation via Secosulfenylation

Entry	Ketone	Spiroannelation method[a]	Cyclobutanone	Product[b]	% yield[c]
1		A		 **1**	80
2		B			61
3		B			74
4		B			70

[a] Method A utilizes 1-lithiocyclopropyl phenyl sulfide.[2a,b] Method B utilizes diphenylsulfonium cyclopropylide.[2c] [b] All new compounds have been characterized spectrally and by elemental compositions. [c] All yields are for isolated pure compounds and have not been optimized. [d] J. Rigby, unpublished results. [e] See ref 5a. [f] Reaction time 5 days. [g] Reaction time 10 days.

the failure to isolate a ring cleavage product from norbornanone under similar conditions.[11]

Acknowledgment. We wish to thank the National Institutes of Health and the National Science Foundation for their generous support of our programs.

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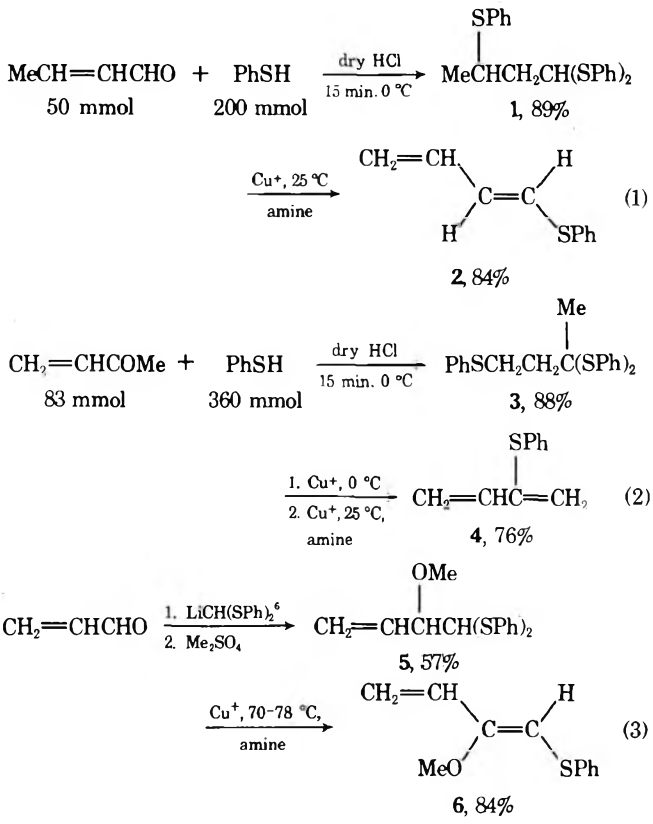
Removal of Sulfur Groups from Molecules by Copper(I). Preparation of Sulfur-Substituted 1,3-Dienes for the Diels–Alder Reaction[1]

Summary: The elimination of thiophenol by copper(I) from readily prepared precursors leads in good yield to several useful phenylthio-subtituted Diels–Alder dienes including (*Z*)-1-phenylthio-2-methoxy-1,3-butadiene which yields a *m*-methoxy adduct with methyl vinyl ketone.

Sir: We wish to report a simple procedure for the preparation of 1,3-dienes which are substituted by phenylthio groups. Because of the great versatility of sulfur in organic compounds, the Diels–Alder adducts of these dienes should be of considerable value in synthesis.

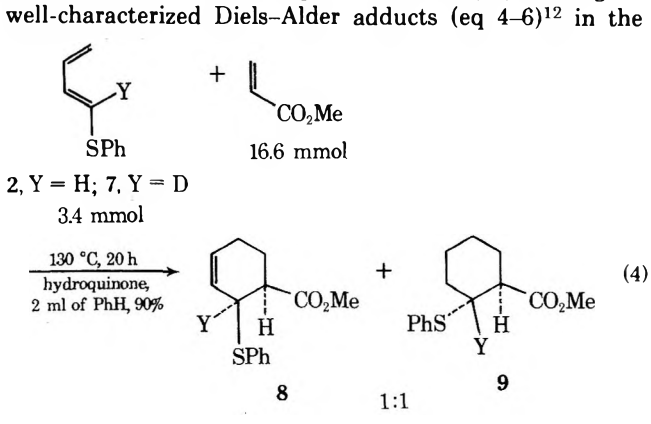
Our procedure consists of the copper(I)-induced removal[2] of one or two thiophenol molecules from readily available diene precursors; eq 1–3 are given as examples.[3,4]

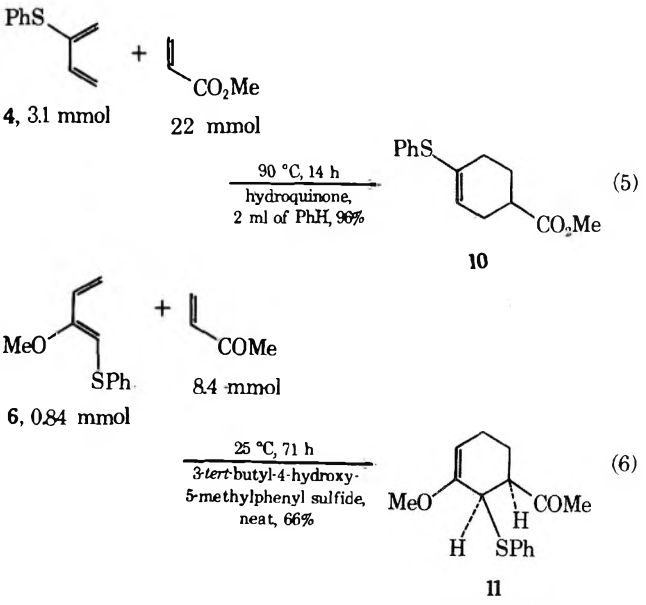


A typical procedure for performing the elimination step follows. A solution of 2.87 mmol of 1,1,3-tris(phenylthio)butane (1) in 2 ml of tetrahydrofuran was added at 0 °C to a solution of 15.5 mmol of the benzene complex of cuprous trifluoromethanesulfonate [Cu_2-$C_6H_6(CF_3SO_3)_2$][7] and 17.6 mmol of diisopropylethylamine dissolved in 120 ml of benzene and the solution was allowed to stir at 25 °C for 14 h. The mixture was passed rapidly through a short silica column, and the light yellow oil which was eluted with ether was submitted to molecular distillation (45–50 °C/0.02 mmHg) in the presence of a small quantity of hydroquinone to give 84% diene as a colorless oil. More concentrated solutions resulted in some polymerization and reduced yields.

As indicated previously,[2] the temperature required for the elimination depends upon the stability of the carbonium ion left after the removal of a thiophenoxide ion. In the case of **1**, the reaction cannot be stopped after the loss of one thiophenol molecule. In the case of **3**, however, the product of loss of one thiophenol molecule, 1,3-bis(phenylthio)-2-butene,[5,8] must be warmed to 25 °C in the presence of cuprous ion in order to convert it to the diene **4**.

The dienes **2** and **6** are stereochemically homogeneous[9] and are assumed to be *E* and *Z*, respectively, on the basis of their ready reactions with dienophiles. Dienes **2**, **4**, and **6** gave well-characterized Diels–Alder adducts (eq 4–6)[12] in the





presence of a trace of radical polymerization inhibitor. The yields in the equations are not optimized and are for purified adducts.

Evans[14] has shown that **2** is capable of condensing with methyl vinyl ketone and maleic anhydride and that its sulfoxide forms useful Diels–Alder adducts with electron-rich dienophiles. In order to demonstrate that the adducts in reaction 4 do not include an allylic rearrangement product[15] of **8** and/or **9**, the C_1 proton of **1** was readily removed (CH_3Li–HMPA) and replaced by deuterium (D_2O); the resulting diene (**7**) gave an adduct lacking NMR peaks for the protons labeled Y in **8** and **9**. The structures of **8** and **9** (Y = H) were confirmed by 250-MHz ^1H NMR decoupling experiments on the mixture.

The structure of **11** was unequivocally established by the same technique. The absorption at 3.83 ppm for the CHS proton appeared as a broad doublet (J = 4.0 Hz) which collapsed to a broad singlet upon irradiation at the frequency of the methine hydrogen adjacent to the carbonyl. The signal for the latter, an eight-line multiplet centered at 2.71 ppm, collapsed to a clean doublet of doublets (J_{ax-ax} = 13 Hz; J_{ax-eq} = 2.5 Hz) upon irradiation at 3.83 ppm. Thus, the acetyl group is equatorial and adjacent to a quasiaxial phenylthio group.

The syntheses herein described of dienes substituted by phenylthio groups are far superior in yield, simplicity, and stereospecificity to any thus far reported.[11,13,14,16] The importance of these dienes lies in their Diels–Alder adducts which bear synthetically manipulatable functionality in fixed regiospecific relationships. Adduct **11** is a striking example in that the potential ketone function is meta to the acetyl group in contrast to the para orientation of the alkoxy groups in adducts of other 2-alkoxybutadienes.[17,18] The exploitation of these now accessible dienes and their adducts is receiving considerable attention in our laboratory and will be described in due course.

Acknowledgment. We thank Dr. Samuel Danishefsky for stimulating suggestions, Mr. Robert Bittner for recording the 250-MHz NMR spectra, Messrs. Vance Bell and Glen Herman for recording the mass spectra, and the National Institutes of Health for support of this work through Grant GM 20707.

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(3) New compounds gave satisfactory spectral and elemental composition data.
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(9) Diene **2** gave a single peak on a support coated (OV-17) open tubular (SCOT) GC column[10] which is capable of almost complete separation of the *E* and *Z*[11] isomers. Diene **6** gave one TLC spot and its ^1H NMR spectrum exhibited a very sharp methyl peak at 3.70 and other absorptions at 4.98–5.60 (8-line multiplet, 2 H, CH_2), 5.78 (s, 1 H, SCH), 5.93–6.43 (quart., 1 H, vinyl), and 7.06–7.50 ppm (m, 5 H, aromatic).
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(19) (a) Andrew Mellon Predoctoral Fellow. (b) Undergraduate Research Participant.

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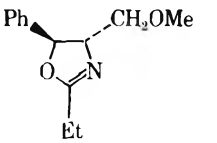
Preparation and Alkylation of a New Chiral Oxazoline from L-Serine

Summary: A new chiral oxazoline was prepared from L-serine, and its alkylation leads to asymmetric induction which is the reverse of that observed for other oxazolines.

Sir: The use of chiral oxazolines in the preparation of optically active α-substituted carboxylic acids has been demonstrated by Meyers. For example, lithiation of **1** followed by treatment



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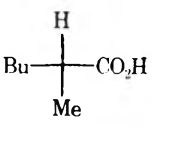
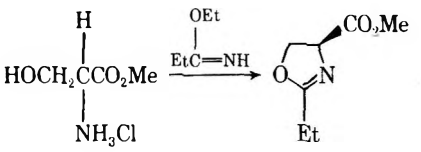


2

with 1-iodobutane gives an alkylated oxazoline which may be converted by acidic hydrolysis into (S)-(+)-2-methylhexanoic acid, **2**, with 78% optical purity.[1] We wish to report the preparation of a new chiral oxazoline related to **1**, along with some unexpected results from preliminary studies of its alkylation and hydrolysis.

The new chiral oxazoline was prepared from the methyl ester hydrochloride, **3**, of L-serine which was converted by sequence **1** through **4** and **5a** to **5b**.[2] Reaction of **3** with ethyl propionimidate[3] in dichloromethane at room temperature for



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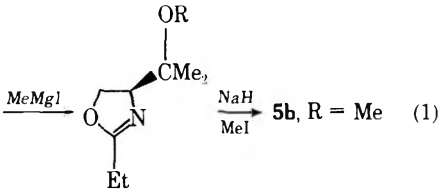


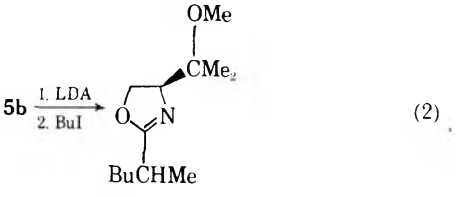
5a, R = H

48 h gave **4**, bp 116–117 °C (24 Torr), $[\alpha]^{26}D$ +163.6° (*c* 6.7, $CHCl_3$), in 90% yield.[4] The ir spectrum of **4** included absorptions at 1740 and 1660 cm^{-1} (C=O and C=N), while the NMR spectrum showed signals at 3.74 (s, 3 H, OMe), 2.32 (q, J = 7, 2 H) and 1.15 (t, J = 7, 3 H) (CH_2CH_3), and overlapping signals at 4.3–4.9 for the three ring protons.

Addition of **4** to 2.2 equiv of methylmagnesium iodide in ether to maintain reflux gave 75% **5a** which was isolated by treatment of the reaction mixture with saturated NH_4Cl and repeated extraction of the slurry with dichloromethane. Spinning band distillation gave a colorless liquid, bp 46 °C (0.1 Torr), $[\alpha]^{25}D$ +84.8° (*c* 8.4, $CHCl_3$). The ir spectrum included the expected broad absorption for OH at 3380 cm^{-1} along with the oxazoline absorption at 1665 cm^{-1}. The NMR spectrum, in addition to the overlapping signals at 3.8–4.3 for the three ring protons and the ethyl quartet and triplet at 2.30 and 1.14, included a broad singlet at 3.02 for OH and two three-proton singlets for the diastereotopic geminal methyl groups at 1.20 and 1.12.

The methyl ether was formed when **5a** in ether was treated with NaH and then stirred with iodomethane at room temperature for 5 days to give 87% **5b**, bp 94 °C (25 Torr), $[\alpha]^{26}D$ +81.7° (*c* 8.8, $CHCl_3$). The ir spectrum included the usual oxazoline absorption at 1665 cm^{-1}, while signals in the NMR appeared at 4.0–4.4 (overlapping, 3 H, ring protons), 3.18 (s, 3 H, OMe), 2.14 (q, J = 7, 2 H) and 1.12 (t, J = 7, 3 H) (CH_2CH_3), and 1.21 (s, 3 H) and 1.00 (s, 3 H) (CMe_2). The mass spectrum included as the base peak a fragment of *m/e* 73.[5]

Alkylation of **5b** was carried out under N_2 by dropwise addition of **5b** in tetrahydrofuran (THF) to a solution containing a 10% excess of lithium diisopropylamide (LDA) (from diisopropylamine and butyllithium) in THF at −78 °C and stirring for 45 min. The resulting solution was cooled to −98 °C (liquid N_2–MeOH), and a solution of 1-iodobutane (10% excess) in THF was added over 2 h. The mixture was warmed to room temperature, washed with saturated brine, and distilled to give 61% **6** (eq 2), bp 60–61 °C (0.1 Torr), $[\alpha]^{26}D$ +72.3° (*c* 9.9, $CHCl_3$). It was found that **6** could be hydrolyzed most conveniently by adding 6.2 g of the oxazoline to 100 ml of 4 N H_2SO_4 and carrying out a direct steam distillation, removing the carboxylic acid as it was formed, and adding water to the pot periodically to maintain relatively constant volume. In this way 88% **2** was obtained after about 90 min, during which 70 ml of distillate was collected. The product was isolated in very pure form (99.4% by GC) after ether extraction from the distillate and distillation as a colorless oil, bp 124–125 °C (30 Torr). The material was identical in the ir with authentic 2-methylhexanoic acid.[6]



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Measurement of the optical activity of **2** obtained as described led, unexpectedly, to a rotation of $[\alpha]^{25}D$ +14.1° (neat), indicating (*S*)-(+)-2-methylhexanoic acid with an optical purity of 75%. Meyers has presented evidence for the alkylation of **1** which indicates that the attack of the alkyl group on the lithio derivative occurs so that the alkyl group approaches from the side of the intermediate on which the ether substituent is located. Since the configuration of the chiral center in **5b** is opposite that of the corresponding center in **1**, then one might have predicted that the acid produced should have the *R* configuration, and the observed results are the opposite of what might have been predicted.

The above results suggest that with the new oxazoline, factors not observed in Meyers' cases, possibly steric influences of the bulky substituent, are operative. Further studies are in progress in order to determine the nature of these effects.

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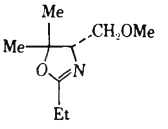
(5) The base peak is assigned as $Me_2C{=}O^+Me$. The prominence of this fragment effectively eliminates the possibility of rearrangement to **7** during the



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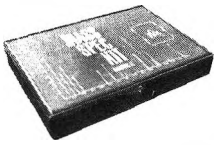

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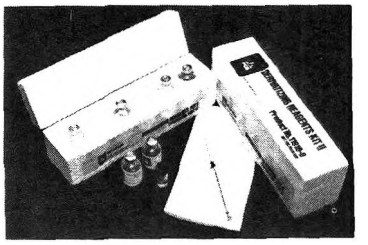

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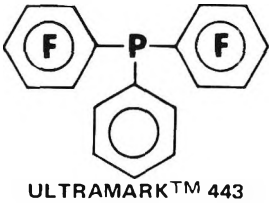

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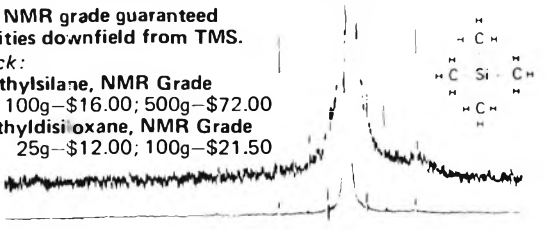

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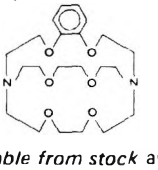

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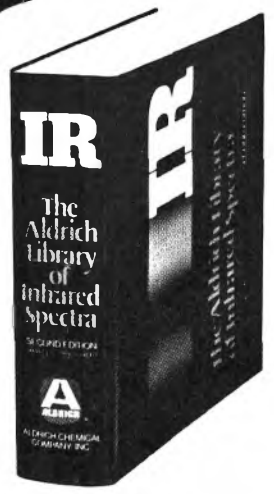

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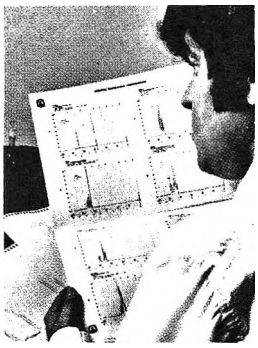

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